

CHAPTER 20

Fibrinolytic (Thrombolytic) Agents

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INTRODUCTION

Rationale

- Acute MI is generally caused by rupture of an atherosclerotic plaque, triggering the formation of an occlusive coronary thrombus.
- The degree and consequences of myocardial necrosis (infarction) will depend on the vessel affected, the proximal site, extent and duration of the occlusion, the extent of other vessel disease and the quality of collateral coronary flow.
- Angiography showed that coronary thrombosis may be a dynamic process, with spontaneous fibrinolysis and restoration of some coronary flow followed by reocclusion occurring over several hours. By 24 hours as many as 50% of presumed originally occluded vessels may be patent.
- To rescue myocardial muscle at risk of undergoing necrosis, rapid restoration of coronary blood flow is essential.
- Clot lysis can be achieved by activating the endogenous fibrinolytic system using plasminogen activating agents. These agents convert plasminogen to plasmin which then degrades fibrin. Fibrin is the major constituent of clots.
- The early establishment of infarct-related coronary artery patency is crucial for patients treated with thrombolytic therapy:
 - Early and sustained restoration of patency had in-hospital mortality of $\leq 5\%$.
 - Initial patency but reoccluded had in-hospital mortality 10%.
 - Failed to reopen at all had a mortality of 17%.

Characteristics of The Ideal Thrombolytic Agent (after Van de Warf, 1999)

- Rapid reperfusion.
- 100% TIMI grade 3 flow (normal flow) reperfusion.
- Administration as an intravenous bolus.
- Fibrin specific.
- Low incidence of systemic bleeding.
- Low incidence of intracranial hemorrhage.
- Resistant to plasminogen activator inhibitor-1 (PAI-1).
- Low reocclusion rate.
- No effect on blood pressure.
- No antigenicity.
- Reasonable cost

** The goal of thrombolytic therapy is to achieve a patent infarct-related artery in the shortest possible time following symptom onset, with the lowest incidence of side-effects.*

Determinant of Efficacy

Regardless of the agent used, the efficacy of thrombolytic therapy is strongly dependent upon:

- The time to therapy.
- The degree of flow obtained.

Time to Therapy

- The survival benefit is greatest when thrombolytic agents are administered within the first four hours after the onset of symptoms, particularly within the first 70 minutes.
- There may be benefit in patients presenting 12 hours after symptoms onset and possibly up to 24 hours, particularly if the patient has ongoing or stuttering chest pain.
- Time from onset of symptoms to fibrinolytic therapy is an important predictor of MI size and patient outcome.
- The efficacy of fibrinolytic agents in lysing thrombus diminishes with passage of time.
- Although most myocardial necrosis occurs early (within the first 90-180 minutes), the advantages of late reperfusion are presumably related to the presence of a patent infarct-related artery, leading to improved ventricular healing, reduced infarct expansion, and greater electrical stability.

Degree of Flow Obtained

- TIMI (Thrombolysis In Myocardial Infarction Trial) flow grade classification:
 1. TIMI 0- absence of any flow.
 2. TIMI 1- faint antegrade flow- incomplete distal filling.
 3. TIMI 2- delayed or sluggish flow with complete distal filling.
 4. TIMI 3- normal flow.
- Normalization (TIMI 3) of flow is seen in only 50 to 60 % of patients.
- Only TIMI 3 has been associated with improved LV function and survival.

Long-term prognosis after thrombolytics

Predictors of increased one year mortality:

1. Demographic: old age (>55)- low weight (≤ 80 kg)- previous MI- previous CABG.
2. Large infarction.
3. Cardiac risk factors: smoking, hypertension, prior cardiovascular disease.

Table (20-1): Comparison of the Advantages of Thrombolytics and Percutaneous Coronary Intervention (PCI)

Thrombolytics	PCI
Quicker time to onset of therapy.	Superior efficacy in clinical trials.
Wider availability, given lack of hospitals performing primary PCI.	Lower risk for bleeding, including intracranial hemorrhage.
Not operator-dependent.	Defines coronary anatomy.
	More patients eligible for PCI than thrombolytics.
	Decreases length of hospital stay.
	Less time-dependent (more useful with delayed patient presentation).

Classification of Fibrinolytic Agents

1. *Non-fibrin-specific agents* (Non-specific fibrinolytics)
 - Streptokinase.
 - Antistreplase.
 - Urokinase.
2. *Fibrin specific fibrinolytics*
 - Recombinant tissue-type plasminogen activator (rt-PA): alteplase.
 - Reteplase (r-PA).
 - Tenecteplase (TNK-tPA).
 - Lanoteplase (n-PA).

Thrombolytic Drugs
<ul style="list-style-type: none"> • Streptokinase • APSAC • Urokinase, scu-PA • Tissue Plasminogen Activator <ul style="list-style-type: none"> - t-PA - rt-PA (alteplase) - r-PA (reteplase) - TNK-rt-PA • 3rd generation agents <ul style="list-style-type: none"> - n-PA (Lanoteplase) - bat-PA (Desmodus rotundus) - Bifunctional molecules conjugating t-PA with monoclonal antibody.

Thrombolytic agents approved by the Food and Drug Administration:

- Streptokinase (Streptase).
- Urokinase (Abbokinase).
- Alteplase (Activase).
- APSAC (Eminase).
- Reteplase (Retevasc).
- TNKase (Tenecteplase).

Mechanism of Action

- The fibrinolytic drugs work by enhancing the conversion of naturally occurring plasminogen within the circulation to the protease enzyme plasmin. They are not direct acting lytics of a thrombus. It is the generated plasmin that digests fibrinogen and fibrin. Plasminogen bound within the thrombus is another target for thrombolytic therapy.
- Fibrin-specific drugs are more efficient at dissolving thrombi and they do not deplete systemic coagulation factors, in contrast to non-fibrin-specific agents.
- This potential advantage of fibrin-specific drugs can increase the risk of reocclusion. The reocclusion rate is twice as high (13%) with the fibrin-specific drug alteplase than with non-fibrin-specific drugs. As a consequence, concomitant treatment with heparin is advised in patients receiving fibrin-specific fibrinolytics.

Thrombolytic Drugs

- Work by enhancing the conversion of naturally occurring plasminogen within the circulation to the protease enzyme plasmin: they are not direct acting lytics of a thrombus; it is the generated plasmin that digest fibrinogen and fibrin.
- Streptokinase activates circulating plasminogen but has poor penetrance into thrombi, the next generation of bioengineered derivatives of naturally occurring (wild-type) tissue plasminogen have enhanced plasminogen activation in the presence of clot-bound thrombin with the potential for more concentrated local rather than systemic plasmin generation and activity. Such thrombolytics are termed "clot-specific".

INDIVIDUAL AGENTS

Streptokinase (SK)

- An indirect fibrinolytic agent that binds to plasminogen, thereby converting plasminogen into a plasmin-like molecule capable of converting plasminogen to plasmin.

- Because streptokinase activates both circulating and fibrin-bound plasminogen to plasmin, it produces systemic plasminemia with resultant depletion of fibrinogen, plasminogen and factors VII and V.
- This systemic lytic state creates a sustained hypocoagulable state that may reduce the risk of rethrombosis.
- Patients who receive streptokinase can develop antistreptococcal antibodies.
- Generation of bradykinin may contribute to the hypotension that occurs in patients receiving streptokinase.
- Patients should not receive a second dose of SK within 1 year of initial therapy; however, many patients receive a second dose without suffering allergic reactions.

Anistreplase (Anisoylated plasminogen streptokinase activator complex- APSAC)

- Anistreplase is a modified SK molecule bound to lys-plasminogen to form an activator complex which has an affinity for fibrin.
- The modified SK undergoes activation after deacylation, a much longer half-life, allowing single bolus dosing.
- Anistreplase failed to improve outcomes compared with streptokinase and with more bleeding complications.

rt-PAs: Alteplase

- rt-PAs are naturally occurring serine proteases that are physiologically identical to the naturally occurring endogenous plasminogen activator in humans.
- Alteplase form have been manufactured commercially.
 - Alteplase: predominantly a single-chain rt-PA molecule.
- Alteplase is not antigenic.
- Fibrin specificity is greater than SK, but it induces mild systemic fibrinogen depletion.
- Due to its short half-life, alteplase requires a continuous infusion.

Tenecteplase: TNK-tPA

- It is a multiple-point mutation of tissue type plasminogen activator (t-PA).
- It has an extended half-life, allowing convenient single-bolus dosing.
- High level of fibrin specificity. It has a more than 14-fold greater fibrin specificity and 80 times greater resistance to inactivation by PAI-1 than does tissue type plasminogen activator.
- It has less systemic fibrinolytic effect.
- When compared as a single bolus tenecteplase with accelerated alteplase, there was equivalent mortality rates and comparable intracerebral hemorrhage rates.

- It leads to faster recanalization compared with alteplase.

Retepase (r-PA)

- Mutation of rt-PA (alteplase) results in half-life twice that of native t-PA permitting double-bolus therapy of 10 U, 30 min apart.
- Fibrinogen depletion with r-PA is greater than that of alteplase but less than that of streptokinase.
- It has lower affinity for fibrin than rt-PA.
- Its main action is similar to that of naturally occurring t-PA.
- When administered as a double bolus 10 U, separated by 30 minutes, it has the same efficacy (mortality rates) as streptokinase (INJECT trial). As with other tissue plasminogen activators, there was a higher total stroke rate for reteplase.

Table (20-2): Fibrinolytic Regimens for AMI*

Fibrinolytic	Initial Treatment	Antithrombin
Streptokinase	1.5 million units in 100 ml 5% dextrose or 0.9% saline over 30-60 min	None or IV heparin for 24-48 hours
Alteplase	15 mg IV bolus, then 90-min infusion of: - 0.75 mg/kg over 30 min (max 50 mg) - 0.50 mg/kg over next hour (max 35 mg) Total dose not to exceed 100 mg	IV heparin for 24-48 hours**
Retepase	10U + 10U IV bolus given 30 minutes apart	IV heparin for 24-48 hours
Tenecteplase	(depending upon body weight) Single IV bolus of: 30 mg if < 60kg 35 mg if 60 kg to < 70 kg 40 mg if 70 kg to < 80 kg 45 mg if 80 mg to < 90 kg 50 mg if \geq 90 kg	IV heparin for 24-48 hours

* From the Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology (2003).

** Monitor a PTT, to keep within 55-70 seconds and to employ weight adjustment normograms (look chapter on heparin).

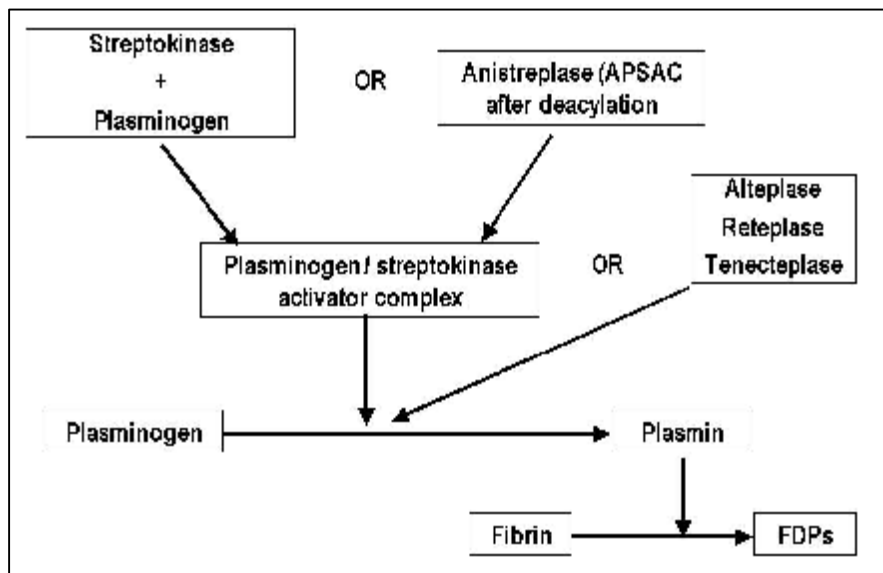


Figure 20-1: Thrombolytic Activation of Plasminogen

INDICATIONS OF THROMBOLYTIC THERAPY

Indications in AMI

- Clinical presentation consistent with myocardial infarction within the previous 12 hours and at least one of:
 - 1 mm ST segment elevation in two or more contiguous limb leads.
 - 2 mm ST segment elevation in two or more contiguous chest leads.
 - New (presumed or known) left bundle branch block.

Consider in patients presenting 12-24 h if chest pain and ST segment elevation are persisting.

Other indications

- Massive pulmonary embolism-accompanied with hypotension or shock.
- Acute ischemic stroke- within 3 hours.

CONTRAINDICATIONS OF THROMBOLYTIC THERAPY*

Absolute contraindications

- Hemorrhagic stroke or stroke of unknown origin at any time.
- Ischemic stroke in preceding 6 months.
- Recent major trauma/ surgery/ head injury within preceding 3 weeks.
- Gastrointestinal bleeding within the last month.

* From the task force on the management of Acute Myocardial Infarction of the European Society of Cardiology (2003).

- Known bleeding disorder.
- Aortic dissection.
- Active internal bleeding.

Relative Contraindications

- Transient ischemic attack in preceding 6 months.
- Oral anticoagulant therapy.
- Pregnancy or within 1 week post-partum.
- Non-compressible vascular punctures.
- Traumatic resuscitation.
- Refractory hypertension (systolic blood pressure >180 mmHg).
- Advanced liver disease.
- Infective endocarditis.
- Active peptic ulcer.

COMPLICATIONS OF THROMBOLYTIC THERAPY

1. Stroke

- Stroke risk is due to intracerebral hemorrhage (ICH).
- Usually occurring within the first 24 hours.
- Resulting in death in about 60% of affected patients.
- Risk of hemorrhagic stroke
 - o After streptokinase < 0.5%.
 - o After a tissue plasminogen activator 0.5-1.0%
- Patients at increased risk of ICH:
 - o Age above 75 years.
 - o Female gender.
 - o Low body weight.
 - o High blood pressure (SBP > 170 mmHg) or pulse pressure on admission.
 - o Prior history of cerebrovascular disease, TIA, dementia.
 - o African descent.

2. Bleeding

- Giving a thrombolytic drug, an antiplatelet and an antithrombin obviously increases the bleeding risk, especially if the PTT is allowed to increase too high.
- Bleeding may occur spontaneously anywhere, more likely in bowel, bladder and at sites of vascular puncture.

3. *Anaphylaxis*

- Occurs rarely in patients treated with a tissue plasminogen activator.
- Occurs in < 2% of patients given streptokinase.
- When patients are given streptokinase, they develop antibodies within 3-4 days. These antibodies can persist for many years.
- Hypotension occurs in < 10% of streptokinase treated patients. Treatment is with temporary cessation of the infusion, fluid replacement and atropine if associated with bradycardia.

LIMITATIONS OF THROMBOLYTIC THERAPY

1. *Failed thrombolysis*

- In about 15% of patients, fibrinolytic agents fail to achieve vessel patency and to restore coronary flow in the culprit artery.
- If the patients remains in pain and the ECG shows persistent ST-segment elevation, then either patency or reperfusion has not been achieved. [ST-segment elevation resolution (i.e. return to the isoelectric line), arbitrary divided into no resolution, $\leq 30\%$ resolution and $\geq 70\%$ resolution correlates with angiographic evidence of patency and subsequent mortality].
- Causes of primary failure of thrombolysis include:
 - Ruptured plaque mechanically prevent penetration of systemically formed plasmin or of intravenously administered thrombolytic drug.
 - Extensive thrombosis spreading from the site of the initial lesion proximally, impairing perfusion of branching collateral vessels.
 - Constituents of the occlusive thrombus may vary, make it less susceptible to digestion by plasmin. Platelet rich thrombi are resistant to fibrinolytic therapy.

2. *Failure to achieve adequate coronary flow (TIMI grade 3)*

- Depending on the agent, only 30% to 60% of patients achieve TIMI grade 3 flow at 90 minutes. The reasons are the same as for failed thrombolysis.

3. *Reocclusion following thrombolysis*

- Incidence
 - Early reocclusion-before hospital discharge in 3-10% of patients.
 - Reocclusion by three months up to 25% of patients.
 - Reocclusion is clinically silent in over 50% of cases.
- In-hospital mortality is significantly higher in patients with reocclusion.

Causes of Reocclusion

- Role of thrombolysis
 - Thrombin bound to fibrin is released into the circulation.
 - Plasmin activated during thrombolysis can activate factors XII and VII, stimulating both intrinsic and extrinsic coagulation pathway activity.
- Plaque ulceration
 - An important risk factor for reocclusion after thrombolysis.
 - Plaque collagen, lipid rich core and tissue factor are exposed to the blood and form highly thrombogenic surface.
 - Angiographic filling defects of irregular lesion are indicative of ulceration.
- High grade residual stenosis results in:
 - Lack of restoration of normal coronary flow
 - Recurrent ischemic events are more likely with delayed or sluggish coronary flow.
 - Slowed flow may promote reocclusion by increasing the residence time of thrombogenic blood constituents.
- Persistent, non occlusive thrombus and ruptured plaque contain large amount of thrombin which increases platelet deposition.

4. Myocyte reperfusion failure

- Even when blood flow to the infarct-related artery is restored, microcirculatory reperfusion can still be absent (no-reflow phenomenon).
- Contrast echo in patients with patent infarct related artery show failure of myocyte perfusion in 25% of patients.
- Causes include: microembolization, capillary damage, endothelial dysfunction, abnormal vasomotor tone.

5. Time dependence

- Fibrinolytics need an average 30-45 minutes to recanalize the infarct related artery.

6. Bleeding complications particularly intracerebral hemorrhage

Rate of ICH averaging 0.5 to 0.9 %, rate of blood transfusion is more than 2%.

7. Long list of contraindications

Not all patients with AMI are eligible for thrombolytic therapy. Up to 40% of patients are ineligible for thrombolytic therapy.

8. Cost

Thrombolytic drugs, particularly the fibrin-specific groups, are very expensive medication.

APPROACHES TO OVERCOME LIMITATIONS OF THROMBOLYTIC THERAPY

- I. Newer thrombolytics.
- II. Adjunctive therapy.
- III. Prehospital fibrinolysis.

<p>Thrombolytic Therapy Overcoming Limitations</p> <ul style="list-style-type: none">•Newer Thrombolytics (Tenecteplase , Reteplase)<ul style="list-style-type: none">-Fibrin specificity-Longer half-life (bolus)•Adjunctive Therapy<ul style="list-style-type: none">-Antiplatelets : GPIIb/IIIa Inhibitors<ul style="list-style-type: none">. Full dose lytics. Half dose lytics-Antithrombins :<ul style="list-style-type: none">. Heparin. Direct thrombin inhibitors-Anticoagulants : Warfarin•Pre-Hospital Fibrinolysis
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I. Newer Thrombolytics

Newer thrombolytics have two advantages

- Longer half-life which allows bolus injection and facilitate drug administration and provide simpler treatment schedules.
- More fibrin specificity which increase efficacy and limit complications.

The two new agents

- Tenecteplase and reteplase have these advantages, they can be given as bolus injection and achieve greater vessel patency in angiographic studies. However, clinical trials did not show superiority of these agents over older therapy (alteplase and streptokinase) regarding improved mortality and incidence of intracerebral hemorrhage.

**NEW BOLUS THROMBOLYTIC AGENTS :
Tenecteplase, Reteplase**

- Easier to administer than TPA.
- Have not reduced mortality.
- Higher risk of intracranial hemorrhage

II. Adjunctive Therapy

- Types
 - Antiplatelets.
 - Antithrombotics.
 - Anticoagulants.
- Rationale for adjunctive therapy
 - Increased prothrombotic state following fibrinolytic therapy due to:
 - a. Release of thrombin from the fibrin-platelet network.
 - b. Platelet activation mediated directly by fibrinolytic agents or increased thrombin generation.
 - c. Release of plasmin from plasminogen, which activates factor V.
- Role of antiplatelets:
 - Platelet rich thrombi are resistant to fibrinolytic therapy.
 - Platelets secrete PAI-1 which inhibits tPA.
 - Platelets form microemboli that may plug the microvasculature.

Adjunctive antiplatelet agents

- Aspirin
- GP IIb/IIIa antagonists.
- Clopidogrel.

Advantages of using adjunctive antiplatelet agents

- a. Accelerate reperfusion.
 - b. Decrease the incidence of reocclusion.
 - c. Improve microvascular reperfusion.
- *Aspirin*
 - o Administration of aspirin alone (160 mg/day) decreases 35 days mortality and reinfarction by 23% in AMI. When combined with streptokinase, it decreases short-term mortality and reinfarction by 42%.
 - o Aspirin is a weak platelet antagonist.

- *GP IIb/IIIa antagonists*
 - o Block the final common pathway to platelet aggregation.
 - o Clinical studies:
 - § GP IIb/IIIa antagonists combined with full doses of fibrinolytics.
 - Increase the speed and the percentage of complete reperfusion indicated by angiographic and continuous ST-segment monitoring.
 - Higher incidence of hemorrhagic complications.
 - A double bolus of abciximab combined with reteplase had the highest TIMI-3 flow percentage at the initial angiographic examination (86% after 90 minutes).
 - No data on long term improvement on mortality.
 - § GP IIb/IIIa antagonists combined with reduced doses of fibrinolytics.
 - An alternative reperfusion strategy, but can not immediately be applied in the clinical setting because of the increased risk of hemorrhage, especially in the elderly.
- *Clopidogrel*
 - o Probably indicated in patients receiving fibrinolytic therapy who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (ACC/AHA Guidelines-2004).
 - o No data concerning the use of ticlopidine or clopidogrel in combination with fibrinolytic agents in AMI.

Adjunctive antithrombin therapy

1. IV-UFH infusion is used routinely with tPA and its derivatives, but its use with streptokinase remains controversial. However, heparin is recommended in patients at high risk of systemic or venous thromboembolism (anterior MI, heart failure, previous embolism, atrial fibrillation, or left ventricular thrombus).
- *Current guidelines recommend heparin administration as follows:*
 - o *Bolus 60 U/kg to a maximum of 4000 U followed by a continuous infusion (12 U/kg/h, maximum 1000 U/h) for a least 48 hours with a target a PTT of 50-70 seconds with frequent monitoring at 3,6,12 and 24 hours after the first dose for additional adjustment.*
 - Use of LMWH requires more clinical studies.
 - Adjunctive treatment with heparin has never been proven to reduce mortality irrespective of fibrinolytic drug used.
 - LMWH

- LMWH should not be used as an alternative to UFH as ancillary therapy in patients over 75 years of age who are receiving fibrinolytic therapy or in patients less than 75 years of age but have significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women). (ACC/AHA Guidelines-2004).

2. Direct thrombin inhibitors

- For patients with known or suspected heparin-induced thrombocytopenia or thrombosis who are receiving fibrinolytic therapy.
- IV hirudin (lepirudin 0.1 mg/kg bolus followed by 0.15 mg/h infusion).

Table (20-3): New Anti-coagulants as Adjuvants to Fibrinolytic Therapy

Study	Fibrinolytic Agents	New Anticoagulant	TIMI-3 flow	
			New treatment	UFH
			<i>90 minutes</i>	
HART-II	rt-PA	Enoxaparin	53%	48%
RENTALYSE	rt-PA	Pentasaccharide	64%	68%
			<i>3-5 days</i>	
AMI-SK	SK	Enoxaparin	70%	58%
ASSENT-PLUS	rt-PA	Dalteparin	69%	63%

^aPlacebo; $p = 0.01$. UFH, unfractionated heparin; rt-PA, recombinant tissue plasminogen activator; SK, streptokinase.

Adjunctive oral anticoagulants

- Following the acute phase, dose adjusted coumadin plus aspirin provides additional benefit after MI, when compared to aspirin alone.
- Anticoagulation intensity with INR 2-3 is recommended. INRs below 2.0 do not improve the outcome following MI.
- Oral direct thrombin inhibitor- ximelagatran is better alternative for coumadin, without the need for monitoring.

Acute Myocardial Infarction-Combination Therapy

- Combined enoxaparin and TNK-tPA: the most attractive pharmacological reperfusion strategy.
- Role of combining GP IIb/IIIa inhibitors and thrombolytic therapy is less certain.
- Combining GP IIb/IIIa inhibitors with SK has been abandoned because of excessive bleeding.

III. Pre-hospital Fibrinolytic Therapy

- Early administration of thrombolytic therapy, ideally at the pre-hospital stage, can significantly reduce mortality compared with in-hospital treatment.
- Most patients fail react rapidly to symptoms, there is delay in the time needed for transportation to the hospital, delay in-hospital initial evaluation and transport to CCU.
- Apparent reduction in treatment delay can be reached if the diagnosis of MI and subsequent initiation of fibrinolytic therapy can be displaced from the hospital to the patient's home.
- The first hour after start of symptoms (chest pain) in MI is the most precious hour (golden hour). Administration of fibrinolytic agent during this hour can save many lives. Patients treated within two hours had a significantly lower mortality rates than those treated within 2-6 hours from symptoms onset..
- Pre-hospital initiation of thrombolytic therapy in patients with AMI by emergency care teams or mobile intensive care units, has been shown to be feasible, safe and beneficial.
- Several large controlled trials have evaluated the effects of early, pre-hospital thrombolysis. The first hour earlier treatment with pre-hospital fibrinolysis was associated with saving approximately 20 lives/1000 patients treated .
- No significant differences in both in-hospital and long-term mortality between patients receiving early pre-hospital thrombolysis and early (<2 hour) primary angioplasty (PCI) following AMI. The mortality rate was lower in the pre-hospital thrombolysis groups, however, there was a lower reinfarction rate in the angioplasty group (CAPTIM trial).

Results of CAPTIM Trial			
	Prehospital Thrombolysis (n=419)	Primary PTCA (n=421)	P
Death (%)	3.8	4.8	0.6
Reinfarction (%)	3.7	1.7	0.13
Urgent PTCA (%)	33.0	4.0	< 0.01

XXIII Congress of the ESC. 2001

- No mortality benefit of primary intervention over thrombolysis in patients when primary angioplasty was performed more than 2-3 hours after arrival at hospital. Current guidelines recommend a door-to-balloon time of 90+30 minutes.

**Prehospital Fibrinolysis
ACC/AHA Guidelines – 2004**

Establishment of a prehospital fibrinolysis protocol is reasonable in 1) settings in which physicians are present in the ambulance or in 2) well-organized emergency medical service systems with full-time paramedics who have 12 leads ECG in the field with transmission capability, paramedic initial and ongoing training in ECG interpretation and STEMI treatment, on line medical command, a medical director with training/experience in STEMI management, and an ongoing continuous quality-improvement program.

FACTORS IN TREATMENT DECISIONS

1. *Elderly patients*

- Accelerated tPA reduced the rates of death and death/disabling stroke in all age groups except the oldest patients (more than 85 years of age).
- Oldest patients (more than 85 years of age): streptokinase with subcutaneous heparin proved to be the best regimen.
- No apparent extra benefit of PCI in the elderly (GUSTO-IIb). After 1 year their mortality was similar to that of patients treated with thrombolytic therapy.

2. *Cardiogenic shock*

- Patients with cardiogenic shock derived no benefit from thrombolytic therapy. (GISSI-1 study).

3. *Late treatment*

- More fibrin-specific agents may have a greater role in this situation.
- Patients treated after 4 hours had a significantly lower 30-day mortality rate with tenecteplase, which is more fibrin specific than tPA.

THROMBOLYTIC AGENTS
Late Treatment – after 4 hours

- Use more fibrin-specific agents.
- Lower 30-days mortality with tenecteplase than TPA (ASSENT-2) in patients treated after 4-hours.

4. *Reinfarction*

- Reinfarction after fibrinolysis occurs in 4% of patients and is associated with a more than 3-fold increase in 30-day mortality.
- When timely revascularization is not available, repeat fibrinolytic therapy is a valuable alternative, repeat fibrinolysis significantly improves outcome.
- Patients with recurrent ischemic-type chest discomfort after initial reperfusion therapy for STEMI should undergo escalation of medical therapy with nitrates and beta-blockers to decrease myocardial oxygen demand and reduce ischemia. Intravenous anticoagulation should be initiated if not already accomplished (ACC/ AHA Guidelines-2004).

5. *Facilitated Percutaneous Revascularization (PCI)*

- Facilitated PCI refers to the administration of a fibrinolytic agent before taking the patient to catheter lab.
- Studies showed a reduction in major cardiac complications in AMI patients undergoing PCI after the combined administration of fibrinolytics and GP IIb/IIIa antagonists in comparison with fibrinolytics alone.
- The rationale is that reperfusion can be obtained sooner than with PCI alone, while PCI allows immediate recanalization if fibrinolysis fails.
- This approach has great potential to overcome the delay before PCI and allows early restoration of TIMI grade 3 flow. However, when assessing the possible benefit of PCI for patients with TIMI-2 flow after fibrinolysis, there was no apparent benefit of angioplasty with

regard to death or recurrent infarction but there was an improvement in LV function at follow-up.

RECOMMENDED STRATEGY FOR ACUTE MI MANAGEMENT

Pre-hospital

- ASA + Clopidogrel
 - Bolus Thrombolytic
 - GP IIb/IIIa Blocker
 - Thrombin inhibitor
- Direct: bivalirudin
Indirect: LMWH heparin

Hospital

- PCI + Intervention if:
 - o Ischemia persists
 - o High risk

REFERENCES AND SUGGESTED READINGS

1. Anand SS, Yusuf S, Pogue J, et al. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction. *Circulation*. 1998; 98:1064-1070
2. Antman EM, de Lemos JA, Braunwald E. Epicardial flow and myocardial reperfusion following abciximab and low-dose thrombolytic therapy for acute myocardial infarction. *Eur Heart J Supplements* 2001; 3(Supl A): A8-A13
3. Antman EM. The re-emergence of anticoagulation in coronary disease. *Euro Heart J Suppl*.2004; 6: (suppl B) B2-B8
4. Berger PB, Steinhubl S. Clinical implications of percutaneous coronary intervention-clopidogrel in unstable angina to prevent recurrent events (PCI-CURE) study: a US perspective. *Circulation*.2002; 106:2284-2287
5. Brouwer MA, van den Bergh P.J.P.C, Aengevaeren WR.M., et al. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction. Results of the antithrombotics in the prevention of reocclusion in coronary thrombolysis (APRICOT)-2 Trial. *Circulation*.2002;106:659-665
6. Connolly DL, Lip, GYH, Chin B SP. ABC of antithrombotic therapy. Antithrombotic strategies in acute coronary syndromes and percutaneous coronary interventions. *BMJ*. 2002; 325:1404-7
7. Dunn CJ, Goa KL. Tenecteplase: a review of its pharmacology and therapeutic efficacy in patients with acute myocardial infarction. *Am J Cardiovasc Drugs*. 2001; 1(1): 51-66
8. Ferguson JJ, Antman EM, Bates ER, et al. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: final results of the National Investigators collaborating on Enoxaparin-3 (NICE-3) study. *Am Heart J* 2003; 146:628-34.
9. Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) Investigators. *Lancet*. 1999; 354: 701-07
10. Knotenbelt C, Brennan PJ, Meade TW, et al. Antithrombotic treatment and the incidence of angina pectoris. *Arch Intern Med*. 2002; 162:881-886
11. Kronenberg HM. Antithrombotic therapy after myocardial infarction. *N Engl J Med*. 2002;347:1019-1024
12. Levine GN, Ali N, Schafer AI. Antithrombotic therapy in patients with acute coronary syndromes. *Arch Intern Med*. 2001; 161:937-948
13. Llevadot J, Giugliano RP, Antman EM, et al. Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA*. 2001; 286:442-449
14. Ohman EM, Harrington RA, Cannon CP, et al. Intravenous thrombolysis in acute myocardial infarction. *CHEST*.2001;119:253S-277S
15. Rourke RA, Hochman JS, Cohen MC, et al. New approaches to diagnosis and management of unstable angina and non-ST-segment elevation myocardial infarction. *Arch Intern Med*. 2001; 161:674-682
16. The assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomized trial in acute myocardial infarction. *Lancet*. 2001; 358: 605-13
17. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease in men at increased risk. *Lancet*. 1998; 351:233-41
18. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease in men at increased risk. *Lancet*. 1998; 351:233-41
19. Van de Werf FJ. The ideal fibrinolytic: can drug design improve clinical results? *Eur Heart J*. 1999; 20: 1452-1458
20. Van de Werf F, Baim DS. Reperfusion for ST-segment elevation myocardial infarction: an overview of current treatment options. *Circulation*. 2002; 105:2813-2816
21. Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomized controlled trial. *Lancet*.2003;362:789-97

22. Wallentin L. Oral direct thrombin inhibition for anticoagulation in coronary artery disease – focus on the ESTEEM trial. *Euro Heart J Suppl.* 2004; 6: (suppl B) B9-B14
23. Weitz JI, Buller HR. Direct thrombin inhibitors in acute coronary syndromes: present and future. *Circulation.* 2002; 105:1004-1011
24. Wong CK, White HD. Medical treatment for acute coronary syndromes. *Curr Opin Cardiol* 2000, 15:441-462
25. Wong GC, Giugliano RP, Antman EM. Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention. *JAMA.* 2003; 289:331-342