



# Fibrinolysis in Acute Myocardial Infarction; State of the Art

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## Abstract

The treatment of ST-Elevation Myocardial Infarction (STEMI) has endured striking expansions over the past three decades. Current practice guidelines are acquainted with the importance of promptly restoring normal coronary blood flow in infarct related artery. In principle, pharmacologic or mechanical strategies might be considered for reperfusion and this is based on multiple randomized controlled trials. National registries for acute myocardial infarction are also important as they offer data that are unique for that specific community or country and could contribute to the optimal use of reperfusion therapies in that region. In this review article we summarize data based on the available studies conducted over the past last 30 years about pharmacologic reperfusion therapy and compare it with primary angioplasty coronary intervention.

**Keywords:** Fibrinolytic agents; Streptokinase; Retapase; Alteplase; Tenecteplase; Acute myocardial infarction

## Abbreviations

GISSI-1 trail: Gruppo Italiano per lo Studio Streptokinasi nell'Infarto Miocardico trail; ISAM study: The Intravenous Streptokinase in Acute Myocardial infarction study; ISIS trail: Second International Study of Infarct Survival trail; EMERAS: Estudio Multicentrico Estreptoquinasa Republicas de America del Sur; GUSTO: Global Use of Strategies to Open Occluded Coronary Arteries; PRIMI Trial: Randomised double-blind trial of recombinant pro-urokinase against streptokinase in acute myocardial infarction trial; TIMI trail: Thrombolysis in Myocardial infarction trail; PAIMS: Plasminogen Activator Italian Multicenter Study; COBALT: Comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction; INJECT trial: International Joint Efficacy Comparison of Thrombolytics trial; COBALT: Continuous Infusion versus Double-Bolus Administration of Alteplase; RAPID: More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction; RAPID-2: Randomized Comparison of Coronary Thrombolysis Achieved With Double-Bolus Reteplase And Front-Loaded, Accelerated Alteplase; ASSENT-1; The Assessment of the Safety and Efficacy of a New Thrombolytic Agent; ENTIRE-TIMI 23: Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction; INTEGRITI: integrilin and tenecteplase in acute myocardial infarction; EXTRACT-TIMI 25 trial: Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction; CAPITAL AMI: Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction; WEST: Which Early ST-elevation myocardial infarction Therapy study; GRACIA-2: Grupo de Análisis de Cardiopatía Isquémica Aguda) Investigators; SESAM Study; the Study in Europe with Saruplase and Alteplase in Myocardial Infarction; COMASS trial: Comparison Trial of Saruplase and Streptokinase trial; GREAT trial: Grampian Region Early Anistreplase Trial; CLARITY trial: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation; TRITON-TIMI 38: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction; COMMIT study: Clopidogrel and Metoprolol in Myocardial Infarction Trial; SPEED study: Patency Enhancement in the Emergency Department study; PARADIGM trial: Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction trail; IMPACT-AMI: Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with integrilin in acute myocardial infarction; INTRO AMI trial: Integrilin and Low-Dose Thrombolysis in Myocardial Infarction trial; INTEGRITI trial: Integrilin and Tenecteplase in Acute Myocardial Infarction; HART II: second trial of Heparin and Aspirin Reperfusion Therapy; BIOMACS II: biochemical markers in acute coronary syndromes; OASIS-6: trial: Organization for

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the Assessment of Strategies for Ischemic Syndromes 6; FRAMI trial: Fragmin in Acute Myocardial Infarction; HIT-III study: the Hirudin for the Improvement of Thrombolysis-3 trial; HERO trial: Hirulog Early Reperfusion/ Occlusion; MITI: Myocardial Infarction Triage and Intervention; TRANSFER-AMI: Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; CARESS-in-AMI: Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction; NRMI-2: National Registry of Myocardial Infarction; DANAM II: Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction; PRAGUE II: Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention; HELIOS: Hellenic Infarction Observation Study; IMPORTANT study: Iwate Myocardial infarction Prospective Observation by Randomized Trial for Analysis of usefulness of intravenous t-PA study; AMIS Plus: Acute Myocardial Infarction and Unstable Angina in Switzerland; DANAMI-2 trial: Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction; GEMÍ: Grupo de Estudios Multicéntrico del Infarto; CARESS-in-AMI: Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction; WIRE Registry: Wielkopolska REgional 2002 Registry; MsAMI: Miyagi Study Group for AMI; FAST-MI; French registry on Acute ST-elevation Myocardial Infarction; Gulf RACE: Gulf registry of acute coronary event; PL-ACS: Polish Acute Coronary Syndrome Registry; OPERA study : Observatoire sur la Prise en charge hospitalière, l'Evolution a' un an et les caractéristiques de patients présentant un infarctus du myocarde avec ou sans onde Q. study; PPRIMM75 registry: Pronóstico del Primer Infarto de Miocardio en Mayores de 75 Años Registry French 2000 registry;USIC: Unité de Soins Intensifs Coronaires; NRMI 2: The National Registry of MI 2; STREAM ;The Strategic Reperfusion Early After Myocardial Infarction study

## Introduction

The field of thrombo-cardiology that deals with steadiness with both thrombotic complications and bleeding risk gained importance in clinical cardiology. Experimentally total coronary occlusion is associated with a radical decrease of coronary blood flow resulting in severe myocardial ischemia. At least 20% of normal coronary blood flow is required to effectively flush the lactate and protons from the purview of ischemic myocardial cells [1-3].

Thrombolytic therapy came as upheaval in the management of Acute Myocardial Infarction (AMI), through dissolving arterial thrombi and attaining reperfusion, in that way reducing infarct size, upholding left ventricular function, and improving morbidity and mortality. Many techniques through which reperfusion can result in improved outcome; different dosing regimens, combinations of different agents, amended adjunctive therapy such as direct antithrombin agents, Low-Molecular-Weight Heparin (LMWH), or glycoprotein IIb/IIIa receptor antagonists (GP IIb/IIIa inhibitors), fibrin specific thrombolytic, agents with extended half-lives authorizing bolus administration [4].

Studies were selected via MEDLINE, PubMed, EMBASE, and Current Contents searches as well as and by reviewing reference lists. In addition, relevant abstracts from the annual meetings of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology were also reviewed. The

studies that evaluated the pharmacokinetics and pharmacodynamics of the various fibrinolytic agents including streptokinase, alteplase, reteplase and tenecteplase were considered in term of the impact of these agents on angiographic and on both short and long-term clinical outcomes. We also reviewed publications of registries of fibrinolytic therapy use among MI patients in registries from around the world. The main aim of this document was to provide systematic review of all available trials and studies over the past 30 years.

## Historical Background of Fibrinolysis

The history of thrombolytic therapy began in 1933 after the identification of filtrates of beta-hemolytic streptococci broth cultures could dissolve a fibrin clot. James Herrick 1912 depicted that MI is related to coronary artery thrombus, he stated, "The hope for the damaged myocardium lies in the direction of securing a supply of blood" [5]. In 1980, DeWood and colleagues reported finding thrombus in the infarct-related arteries of 90% of patients undergoing acute coronary artery surgery in the first few hours after the onset of AMI [6].

The first use of fibrinolytic therapy in patients with AMI was recounted in 1958 [7]. In the early 1960s and 1970s, 24 trials were performed assessing the effectiveness of intravenous streptokinase [8]. In 1969, Chazov administered intracoronary streptokinase in Russia [9] and it is approximately 30 years since Rentrop et al. [10] reported its use, thus restoring interest in reperfusion as a treatment modality for AMI. Since then, several newer fibrinolytic agents were developed, including tissue plasminogen activators (alteplase or reteplase). Furthermore, the development in fibrinolytic agents was accompanied by significant advances in adjunctive therapies including antiplatelet agents as well as the emergence of newer antithrombotic regimens, which are outlined in the current review.

## Pathophysiology of Coronary Occlusion

Experimentally total occlusion of any of the coronaries can result in AMI. Even in the setting of total and fixed coronary occlusion this is not absolute, as certain residual blood flow remains in the ischemic area as this demonstrated subsequent to experimental coronary artery ligation. In addition, there is usually a steady repossession of blood flow to the ischemic myocardium with a 2-fold increase at 96 h contrasted with coronary blood flow directly post occlusion [2,3]. It has been estimated that myocardial viability (the basic cellular functions, mitochondrial and membrane integrity) is maintained at about 20% of total coronary flow.

The human AMI may have a stammering development with alternating occlusion and re-canalization [11]. Angiographic studies indicated that Infarct-Related Artery (IRA) was not totally occluded in nearly 30% of patients presenting within 12 h from the symptom onset. Preservation of residual blood flow in the IRA is associated with a reduction in the infarct size, healthier left ventricular function, and favorable clinical outcome judged with total occlusion. [12-15]. Coronary collateral circulation may be an important alternative that preserves coronary blood flow and preserves viable myocardium after coronary occlusions which is a contributing factor to left ventricular functional recovery following late mechanical reperfusion [16,17]. Positron emission tomography performed within 3 days of the symptom's onset in patients with anterior AMI has shown that viability was maintained in half of infarcted segments [18]. Persistence of viable myocardium has been demonstrated by experimental and clinical studies [17,19,20,21]. The data obtained from experimental

**Table 1:** Fibrinolytic agents; characteristics and properties.

Agent	Source	Molecular Weight, kD	Mutation	Structure	Fibrin Specific	Metabolism	Half-life, min	Mode of Action	Antigenic	Dosing	Other Properties	Hospital Cost/Dose, \$US†
Streptokinase	Group A streptococci	47	-----	-----	-----	Hepatic	18-23	Activator	Yes	1-h infusion		300
Alteplase, duteplase (tPA)	Recombinant, human	63-70	-----	F, E, K, P domains	—	Hepatic	3-8	Direct	No	Bolus, 90 min infusion	↑ γνινιβ vιρβι	2,200
Retepase	Recombinant, human mutant tPA	39	Single-chain deletion	Lacks F, E, K1 domains; has K2, P	+	Renal	15-18	Direct	No	Double bolus	Decreased fibrin binding	2,200
Tenecteplase	Recombinant	-----	Point substitutions	T103N, N117Q, KHHRR 296-299 AAAA	+++	Hepatic	18-20	Direct	No	Single bolus	Resistance to PAI-1	2,200

\*F: Finger Domain; E: Epidermal Growth Factor Domain; K: Kringle Domain; P: Serine Protease Domain; PAI: Plasminogen Activator Inhibitor; NA: Not Available. †Costs list current US prices of usual dose.

**Table 2:** Infarct-Artery Patency before the era of Fibrinolytic Therapy.

Author	Time to patency	Patient No.	Time to treatment, min	Mean Catheterization Time	Patency %	Total pt. no.	Pooled patency
Anderson et al. 1984 [27]	baseline	23	168	-----	9%	352	20%
Chesebro et al. 1987 [28]		289	285	-----	20%		
Timmis et al. 1987 [29]		40	186	-----	28%		
Collen et al. 1984 [30]	1 hr	14	284	45 min	7%	62	15%
Cribier et al. 1986 [31]		23	208	74 min	22%		
Topol et al. 1987 [32]		25	228	68 min	13%		
Verstraete et al. 1985 [33]	90 min	65	198	75-90 min	21%	95% CI, %=11-31	
Guerci et al. 1987 [34]	2-3 hr	66	192	2.5 h	24%	95% CI, %=14-35	
Durand et al. 1987 [35]	24 hr	29	149	35 h	13%	85	21%
Armstrong et al. 1989 [36]		56	180	17 hr	29%		
White et al. 1987 [41]	3-21 days	112	180	21 days	54%	1,027	61%
Bassand et al. 1987 [43]		55	190	21 days	67%		
NHFA 1988 [38]		71	195	5-7 d	41%		
Kennedy et al. 1988 [39]		177	210	10 d	78%		
de Bono 1988 [40]		366	186	10-21 d	78%		
O'Rourke et al. 1988 [42]		71	114	21 days	64%		
Bassand et al. 1989 [37]		119	188	4.1 d	35%		
Armstrong et al. 1989 [36]		56	180	10 days	45%		

studies [1] and mega trials of fibrinolytic therapy [22-25] gave rise to the concept of time dependency of the benefit of the reperfusion therapy in AMI.

## Fibrinolytic Trials

### Trials on streptokinase

**Clinical trials:** Streptokinase was first used in patients with AMI in 1958, an affair that revolted AMI management (Table 1). The initial trials of urokinase and streptokinase were brought out in dosages instituted on a theoretical background. Unfortunately, streptokinase has not been subjected to a factual form of dose ranging angiographic trial [26]. On the other hand, the placebo-controlled trials of streptokinase displayed a noteworthy mortality benefit with intravenous streptokinase. Several trials have reported patency of the IRA at different time points among patients not treated with fibrinolytics [27-44] (Table 2).

The efficacy of streptokinase in term of mortality benefit was appraised in four large, placebo-controlled trials (Table 3)

[22,23,45,46]. The Gruppo Italiano per lo Studio Streptokinasi nell'Infarto Miocardico (GISSI-1) trial (first true mortality trail); an open label, randomized trial of 11,806 patients of which 14% received aspirin and 62% received any heparin. Streptokinase use resulted in 18% reduction in in-hospital mortality (14 days-21 days) (10.7% vs. 13.0%; p=0.002) which is time dependent reduction, decreasing from a 47% reduction in patients treated within 1 h, to 23% for those treated within 3 h, and to 17% for those treated within 6 h of symptom's onset compared with standard therapy. Such reduction was upheld at 12 months (17.2% for streptokinase vs. 19.0% for controls; p=0.008) [22].

The Intravenous Streptokinase in Acute Myocardial infarction study (ISAM) [45] was a double blind, randomized trial of streptokinase vs. placebo in 1,741 patients with STEMI, in this study there was an 11% reduction in 21-day mortality ( P; NS), it is harmonious with the GISSI-1 conclusions. The 2<sup>nd</sup> ISIS trial; a bulky double blind, placebo-controlled study of iv. streptokinase in patients with alleged MI, included 17,187 patients in 417 hospitals worldwide [23]. Physician's clinical suspicion of an AMI was the only entry

**Table 3:** Placebo-Controlled Mortality Trials of Streptokinase.

Variables	GISSI-1 [22]	ISAM 1986 [45]	ISIS-2 1988 [23]	EMERAS 1993 [46]
Patients, No.	11,806	1741	17,187	3568
Dose/duration, h	1.5 MU/l	1.5 MU/l	1.5 MU/l	1.5 MU/l
Enrollment period	2/84-6/85	3/82-3/85	3/85-12/87	1/88-1/91
Placebo blinding	No	Yes	Yes	Yes
Age criteria	All	<75 y	All	All
Symptom duration, h	<12	<6	<24	24-Jun
ECG criteria	ST1 or 2	ST 1	None	None
Aspirin	+/-	Yes	Randomized	Yes
Heparin	+/-	iv	+/-	+/-
Mortality follow-up, d	In-hospital	21	35	35

**Table 4:** Angiographic studies with streptokinase reperfusion therapy.

Author	Time to patency	Patient No.	Strep dose MU	Door needle time	Patency rate %	Pt. no.	Pooled patency
Cribier et al. 1989 [31]	60 min	21	1.5	115 min	52%	224	48%, 95% CI, %=41-56
PRIMI study group 1989 [47]		203	1.5	140 min	48%		
Spann et al. 1982 [61]		43	1.5	60 min	49% recanalization rate		
Rogers et al. 1983 [62]		16	1	45 min	44% recanalization rate		
de Marneffe et al. 1985 [63]		10	1.5	30min	80% recanalization rate		
ECSG-2 ;Verstraete et al. 1985 [48]	90 min	65	1	156 min	55%	789	95% CI, %=48-55
Chesebro et al. 1987 [28]		159	1.5	286 min	43%		
Stack et al. 1988 [49]		216	1.5	180 min	44%		
Lopez-Sendon et al. 1988 [50]		25	1.5	<6 h	60%		
PRIMI study group 1989 [47]		203	1.5	140 min	64%		
Charbonnier et al. 1989 [52]		58	1.5	168 min	51%		
Hogg et al. 1990 [51]		63	1.5	209 min	53%		
Hillis et al. 1985 [59]		34	1.5	60 min	32% recanalization rate		
TIMI-1 Chesebro et al. 1987 [28]		119	1.5	60min	31% recanalization rate		
TEAM-2 1987 [53]		182	1.5	158 min	73%		
Monnier et al. 1987 [54]	11	1.5	135 min	64%			
Golf et al. 1988 [55]	135	1.5	138 min	70			
Six et al. 1990 [26]	56	1.5	150 min	60%			
PRIMI study group 1986 [47]	24hr	203	1.5	140	88%	376	95% CI, %=82-89
Durand et al. 1987 [36]		35	1.5	149 min	82%		
Lopez-Sendon et al. 1988 [50]		25	1.5	<6h	75%		
Hogg et al. 1990 [51]		63	1.5	209	88%		
Ribeiro et al. 1991 [55]		50	1.2	180 min	80%		
White et al. 1987 [41]		107	1.5	180 min	75%	658	95% CI, %=70-78
Bassand et al. 1987 [43]		52	1.5	210 min	68%		
Kennedy et al. 1988 [39]		191	1.5	210 min	69%		
Lopez-Sendon et al. 1988 [50]		25	1.5	<6h	90%		
Magnani BT/ PAIMS 1989 [57]		85	1.5	127min	77%		
White et al. 1989 [59]		135	1.5	150 min	75%		
Cherng et al. 1992 [58]		63	1.5	294 min	57%		

MU=million unit.

criteria (ST-segment elevation or left bundle-branch block on the presenting ECG). Patients randomized in the first 12 h and up to 24 h after symptom’s onset. Patients received either aspirin alone (162.5

mg/d for 1 month) or streptokinase alone (1.5 MU. 1 h) or, both, or neither. There was 25% reduction in 35-day vascular mortality among streptokinase group compared to placebo (9.2% vs. 12.0%; p<

**Table 5:** Alteplase (t-PA) angiographic trials.

Author/year	Time to patency	Patient No.	Alteplase dose	Symptoms-needle time	Patency rate %	Total pt. no.	Overall patency %			
Topol et al. 1987 [78]	60 min	75	1.25 mg/kg/3h	216 min	57	487	57%			
Smalling et al. 1990 [76]		91	1.25 mg/kg/3h	228 min	45					
de Bono 1992 [89]		183	100 mg/3 h	156 min	60					
Carney et al. 1992 [77]		138	00 mg/3 h	168 min	63					
Verstraete et al. 1985 [48]	90 min	64	0.75mg/kg/1.5h	180 min	70	1,648	70%			
Chesebro et al. 1987 [28]		157	80 mg/3 h	287 min	70					
Topol et a 1987 [78]		75	1.25 mg/kg/3 h	216 min	69					
Topol et al. 1987 [84]		142	1 mg/kg/h	190 min	72					
Johns et al. 1988 [82]		68	1 mg/kg/1.5 h	180 min	76					
TIMI-IIA 1988 [79]		133	100 mg/6 h	168 min	75					
Neuhaus et al. 1988 [86]		124	70 mg/1.5 h	<4 h	69					
Topol et al. 1989 [84]		134	1.5 mg/kg/4 h	168 min	79					
Topol et al. 1989 [80]		50	100 mg/3 h	243 min	52					
Smalling et al. 1990 [76]		91	1.25 mg/kg/3 h	228 min	70					
Califf et al. 1991 [81]		95	100 mg/3 h	200 min	71					
Whitlow & Bashore 1991 [83]		206	100 mg/3 h	<6 h	63					
Grines et al. 1991 [85]		107	100 mg/3 h	180 min	64					
Carney et al. 1992 [77]		138	100 mg/3 h	168 min	77					
Topol et al. 1987 [78]		2 to 3 h	75	1.25 mg/kg/3 h	216 min			79	147	73%
Guerci et al. 1987 [34]			72	80-100 mg/3 h	192 min			66		
Neuhaus et al. 1988 [86]	24hr	124	70 mg/1.5 h	<4 h	78	1,782	84%			
TIMI-IIA 1988 [79]		128	100-150 mg/6h	174 min	82					
TIMI-II 1989 [88]		1,366	100 mg	156 min	85					
Anderson et al. 1992 [87]		164	100 mg	168 min	86					
de Bono 1988 [40]	3 to 21 d	367	100 mg/3 h	156 min	87	2,327	80%			
O'Rourke et al. 1988 [42]	-----	74	100 mg/3 h	120 min	81					
NHFA 1988 [38]		73	100 mg/3 h	195 min	70					
TIMI-IIA 1988 [79]		389	100-150 mg/6h	174 min	79					
Neuhaus et al. 1988 [86]		124	70 mg/3 h	<4 h	73					
Bassand et al. 1989 [37]		93	100 mg/3 h	172 min	76					
Magnani 1989 [56]		86	100 mg/3 h	124 min	81					
White et al. 1989 [58]		135	100 mg/3 h	150 min	76					
Rapold et al. 1989 [91]		34	100 mg/3 h	186 min	81					
Thompson et al. 1991 [90]		241	100 mg/3 h	155 min	80					
de Bono et al. 1992 [89]		652	100 mg/3 h	170 min	79					
Cherng et al. 199 [57]		59	100 mg/3 h	312 min	77					

0.001). Aspirin alone resulted in 23% mortality reduction (p<0.001). Aspirin with streptokinase had synergistic effects generated with 42% reduction in vascular mortality (8.0% vs. 13.2%; p<0.001) the most domineering finding. Aspirin use also reduced rates of re-infarction, cardiac arrest, cardiac rupture, and stroke. Patients treated within 6 h of symptoms had meaningfully improved survival; such benefit persevered up to 12 h after symptom's onset, consistent with findings of the GISSI-1 study.

A smaller, south American trial (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) [46]; a double-blind, placebo-controlled trial of streptokinase included only patients presented at least 6 h after but within 24 h of symptom onset. The

35 days mortality did not diverge significantly in the 3,568 patients enrolled between 6 h and 24 h (11.2% for streptokinase vs. 11.8% for placebo).

Steady facts across all above trials: The overall benefit was observed among patients with ST-segment elevation or bundle-branch block regardless of age, sex, blood pressure, heart rate, prior MI, or diabetic status; such benefit was observed in the first 21-42 days and maintained up to 1 year after AMI. In addition, the earlier the treatment was initiated the greater was the benefit [24].

**Angiographic trials:** Many trials [22-24,26,28,32,36,39,41-63] were conducted to evaluate the angiographic findings after treatment

**Table 6:** Trials on Reteplase(r-PA).

Study		Patients, No.	Fibrinolytic Agent	Mortality at 30-35 d, %	Intracranial Hemorrhage, %	Patency % vs. TIMI Grade 3 Flow at 90 min, %
Clinical (mortality) trials	INJECT trial 1995 [98]	3,004	r-PA 10 U plus 10 U	9.02%	0.77%	-----
		3,006	Streptokinase 1.5 MU	9.53%	0.37%	-----
	GUSTO-3 1997 [99]	10,138	r-PA 10 U plus 10 U	7.47%	0.91%	-----
		4,921	Accelerated alteplase	7.24%	0.87%	-----
Angiographic trials	RAPID 1995 [100]	146	r-PA 15 U	-----	-----	63 % vs. 41%
		152	r-PA 10 U plus 5 U	-----	-----	67% vs. 46%
		154	r-PA 10 U plus 10 U	-----	-----	85% vs. 63%
		154	Alteplase 100 mg/3 h	-----	-----	77% vs. 49%
	RAPID II 1996 [101]	169	r-PA 10 U plus 10 U	-----	-----	83% vs. 60%
		155	Alteplase (accelerated)	-----	-----	73% vs. 45%

with streptokinase in STEMI patients; these are summarized in (Table 4).

### Trials on Alteplase (t-PA)

Alteplase can be administered in an accelerated infusion (1.5 h), 50-mg and 100-mg vials reconstituted with sterile water to 1 mg/mL (Table 5). The most common t-PA infusion protocol in AMI is the accelerated infusion of 15 mg IV bolus, followed by 0.75 mg/kg (up to 50 mg) IV over 30 minutes, then 0.5 mg/kg (up to 35 mg) IV over 60 minutes (maximum total dose is 100 mg for patients weighing >67 kg).

**Clinical trials:** The GUSTO-1 trial included 41,021 patients with the primary end point of 30-day mortality embarked to evaluate several fibrinolytic regimens. Used streptokinase in two arms, one with subcutaneous heparin (12,500 U q12h at 4 h) and one with IV heparin. The third arm used accelerated t-PA and IV heparin. The fourth arm was combination fibrinolytic therapy, which involved about two thirds of the typical doses of t-PA and streptokinase with IV heparin. All patients received aspirin, 325 mg/d [25,64]. Accelerated t-PA arm had lower mortality rate (evident as early as 24 h after treatment) compared with each of the other 3 arms. Alteplase reduced major complications including: cardiogenic shock, CHF and ventricular arrhythmias [25]. For each of the streptokinase arms, Intracranial Hemorrhage (ICH) occurred in 0.5% vs. 0.7% of patients treated with accelerated t-PA and 0.9% in combination fibrinolytic therapy. The benefit of accelerated t-PA was seen in all subgroups. The absolute benefit was greater in higher-risk patients [25].

The TIMI-4 trial; a double-blind trial comparing accelerated alteplase, anistreplase and their combinations. All patients received aspirin and IV heparin. Accelerated t-PA achieved a 78% patency rate after only 60 min compared with only 60% for anistreplase or combination fibrinolytic therapy [65]. At 90 min, patency and TIMI grade 3 flow rates both were significantly better in the accelerated t-PA arm. Overall clinical outcomes (composite end point and 1-year survival) were better with t-PA. This result is compatible with the GUSTO-1 trial. The benefit of accelerated t-PA seen in the GUSTO-1 and TIMI-4 trials vs. lack of benefit seen in GISSI-2 and ISIS-3 reflects two factors: the t-PA regimen and the heparin dosing. The former trials used the accelerated t-PA regimen, which resulted in higher rates of early patency compared with the older, 3-h regimen [44] and early, IV heparin use improved late IRA patency. In contrast, the GISSI-2 and ISIS-3 trials used the slower infusion of t-PA or alteplase and delayed sc. heparin, which did not elevate the APTT level until approximately 24 h after the start of treatment. Re-occlusion of an open IRA, which

is associated with a 3-fold increase in mortality, occurred most often during this period. Consequently, sc. heparin regimen cannot prevent such predictor of poor outcomes. The benefits of accelerated t-PA and IV heparin are based on the ability to achieve rapid, sustained IRA patency after AMI. This link between early reperfusion, (TIMI grade 3 flow) and improved survival was established in the GUSTO-1 angiographic sub study [66,68].

The awareness of a double bolus regimen of t-PA [71] had given the rise for COBALT trial (7169 patients), which compared double-bolus vs. accelerated infusion dosing of t-PA. The 30-day mortality rates have had a propensity to be higher in the double-bolus group compared to accelerated-infusion group (7.98% vs. 7.53%), this had questioned the safety of the double-bolus regimen. The rates of hemorrhagic stroke were 1.12% after double-bolus t-PA compared with 0.81% after accelerated infusion of t-PA [72]. However, double-bolus t-PA resulted in TIMI grade 3 flow in only 58% of patients compared with a 66% rate in patients treated with the accelerated, 90-min infusion of t-PA [73].

**Angiographic trials:** Alteplase has been studied in numerous angiographic trials [22-24,26,28,34-59,75-91] (Table 5). The observation in these trials is the 3-h dosing regimen of t-PA resulted in higher 60 min and 90 min patency and TIMI grade 3 flow compared with streptokinase or anistreplase [92]. Neuhaus and colleagues [86] developed an "accelerated" 90-min dosing regimen for t-PA, which achieved higher rates of early reperfusion compared to 3-h regimen of t-PA. Anistreplase treatment or streptokinase treatment [63,64,67,77,86-93] that was associated with lower mortality rates, such result contradicted by the results of the GISSI-2 [96] and the ISIS-3 trial [97]. Such diversity may be attributable to the use of sc. heparin (rather than IV heparin) and the use of alteplase as opposed to t-PA.

The GUSTO-1 angiographic sub study included over 2,400 patients randomized to angiography at 90 min, 180 min, 24 h, or 5 days. The improved patency at 90 min reflected on improved survival at 24 h and 30 days, thus stressing the benefits of rapid reperfusion [68,96].

### Trials of Reteplase (r-PA)

Reteplase; one of the first mutant t-PA molecules had been studied in broad clinical trials, the dosage for optimal therapeutic efficacy ensued with two boluses (10 U 1 10 U) given 30 min apart (Table 1) [97].

**Clinical trials:** The INJECT study compared double-bolus r-PA

**Table 7:** Clinical and angiographic Tenecteplase (TNKase) trials.

Trial (year)	Patients no.	Comparison	Conclusion
<b>Clinical trials</b>			
TIMI 10B 1998 [71]	886	a single bolus 30 or 50 mg TNK-t-PA vs. Front loaded t-PA	TNK-t-PA, as a single 40-mg bolus, achieved rates of TIMI grade 3 flow=90-minute bolus & infusion of t-PA
ASSENT-1 1999 [107]	3235	TNKase ( bolus) vs. front loaded t-PA	▼ doses of IV heparin are associated with ▼ rates of ICH
ASSENT-2 1999 [109]	16,949	TNKase vs. t-PA	TNKase and rt-PA equivalent, ▼ major bleeding with TNKase
ASSENT-3 (2001) [112,113]	6,095	TNKase+enoxaparin vs. abciximab vs. UFHa	enoxaparin & abciximab superior to UFH
ENTIRE-TIMI 23 (2002) [114]	483	TNKase+enoxaparin vs. abciximab vs. UFHa	enoxaparin & abciximab superior to UFH, ▲ bleeding with ABX
ASSENT-3-PLUS 2003 [117]	1,639	TNKase+enoxaparin vs. UFHa, pre-hospital delivery	▼ re-infarction with ENOX, ▲ stroke/intracranial bleed
<b>Angiographic trials</b>			
INTEGRITI trial 2003 [115]	438	eptifibatid e+½ dosage TNKase vs. TNKase monotherapy	TIMI-3 flow, overall patency& ST-segment resolution is similar
CAPITAL-AMI 2005 [120]	170	F-PCIc vs. TNKase	▼ residual ischemia with F-PCI
WEST 2006 [122]	304	TNKase vs. F-PCIc vs. PPCI	TNKase & F-PCI comparable to P-PCI
ASSENT-4 2006 [121]	1,667	F-PCIc vs. PPCI	▲ death/ischemia/bleeding in the F-PCI group
GRACIA-2 2007 [123]	212	TNKase vs. PPCI	▲ reperfusion with TNKased Similar ventricular damage

▼: Decrease; ▼: Increase; PPCI: Primary Percutaneous Coronary Intervention; UFH: Unfractionated Heparin; F: Facilitated

**Table 8:** Clinical Trials of Full-Dose Fibrinolytic Therapy With anti-platelet; agents clopedogril, GP IIb/IIIa Inhibition.

Trial/Year	Patients No.	Primary Treatment	Result
TRITON-TIMI 38 2007[142]	13608 moderate-high-risk ACS patients	Prasugrel (60-mg loading dose and then 10-mg daily maintenance dose) or clopidogrel (300-mg/75-mg) for six to 15 months' Outcomes	▼ the CV death/MI/stroke, ▼ key secondary end points (MI, TVR, and stent thrombosis) vs. clopidogrel
CLARITY-TIMI 28 2005 [143]	3491	-Clopidogrel (300-mg loading dose, followed by 75 mg once daily) or placebo+ fibrinolytic+Wt. adjusted heparin	improves the patency rate of the IRA, ▼ ischemic complications
COMMIT 2005 [144]	45,852	-Clopedogril 75 mg+aspirin 162 mg+slandered fibrinolysis	▼ mortality and major vascular events in hospital
INTEGRITI 2003 [115]	438	-Eptifibatide+TNK +heparin 60 U/kg bolus; 7 U/kg/h infusion	TIMI 3 Flow/ 90 Min=62%,
		-TNKase alone 60 U/kg bolus; 12 U/kg/h infusion	TIMI 3 Flow/ 90 Min=49%
INTRO AMI 2002 [150]	649	-Eptifibatide+tPA+ heparin 60 U/kg bolus; 7 U/kg/h infusion	TIMI 3 Flow/ 90 Min=56%
		-tPA alone+heparin60 U/kg bolus; 7 U/kg/h infusion	TIMI 3 Flow/ 90 Min=40%
GUSTO-V 2001 [116]	16,588	-Retaplaste +heparin vs. retaplaste ½ dose+abciximab	Rates of re-infarction (p<0.0001) &recurrent ischemia no difference in the incidence of nonfatal disabling stroke or any stroke in two groups but not above 75 yr
SPEED 1999 [69]	528	-Abciximab+reteplase+heparin 60 U/kg boluses	TIMI 3 Flow/ 90 Min 61%
		-Abciximab+reteplase+heparin 40 U/kg boluses	TIMI 3 Flow/ 90 Min=51%
		-Reteplaste alone+heparin 70 U/kg boluses	TIMI 3 Flow/ 90 Min=47%
TIMI-14 1999 [70]	888	-t-PA+abciximab+heparin60 U/kg bolus; 7 U/kg/h infusion-t-PA+abciximab +heparin 30 U/kg bolus; 4 U/kg/h infusion-t-PA alone +heparin70 U/kg bolus; 15 U/kg/h infusion	TIMI 3 Flow/ 90 Min=78% TIMI 3 Flow/ 90 Min=69% TIMI 3 Flow/ 90 Min=62%
PARADIGM 1998 [147]	345	-Lamifiban+t-PA or streptokinase	▲ bleeding at highest doses, ▲ST-segment resolution vs. fibrinolytic alone
IMPACT-AMI 1997 [146]	132	Eptifibatide+t-PA	▲ acute TIMI grade 3 flow &faster ECG resolution vs. alteplase
TAMI-8 1993 [145]	68	m7E3+t-PA	▲ angiographic patency
TREAT Study 2018 [151]	3799	Ticagrelor vs. clopedogril in combination with fibrinolytics	fatal (0.16% vs. 0.11%; P=.67) and intracranial bleeding (0.42% vs. 0.37%; P=.82) were similar between the ticagrelor and clopidogrel groups

▼=Decrease, ▲=Increase, IRA=infarct related artery

to streptokinase in reducing mortality. The 35-day mortality rate with r-PA was 9% compared to 9.5% with streptokinase (0.5%; 95% CI, 2 1.98 to 0.96). The study suggested that r-PA is comparable to streptokinase with similar in-hospital stroke rates, bleeding events and recurrent MI but fewer cases of atrial fibrillation, a systole, cardiac shock, heart failure, and hypotension in the r-PA group. Reteplase is clinically safe and simply administered (Table 6) [98].

The GUSTO-III study (15,059 AMI patients presenting within 6 h of symptom's onset) compared double-bolus r-PA with

accelerated t-PA; the primary end point of 30-day mortality rates was accomplished in 7.47% for r-PA group and 7.24% for t-PA -treated patients. r-PA was not superior to t-PA with similar mortality rates in subgroups analysis according to age, infarct location, and registering region, with no differences in regards to the rates of stroke, bleeding, and ICH. Such results is concordant with the hypothesis that at least a 20% absolute increase in TIMI grade 3 flow is required for substantial mortality improvement [99].

**Angiographic trials:** Two angiographic trials [100,101] compared

**Table 9:** Trials of Fibrinolytics with Unfractionated Heparin (UFH) versus Low-Molecular Weight Heparin (LMWH).

Trial/Year	Patients No.	Fibrinolytic Agent	LMWH Group vs. Control Group	Primary Efficacy Outcome	conclusion
OASIS-6 trial 2008 [159]	5436	Predominantly streptokinase	Fundapurinox vs. UFH	30-days death, in-hospital re-infarction.	-Significant ▼ the risk of death, re-MI and severe bleeds
ExTRACT trial (2007) [156,157]	20506	Streptokinase or fibrin specific fibrinolysis	Enoxaparin throughout hospitalization or UFH for at least 48 hrs.	30-days death, in-hospital re MI, in-hospital refractory ischemia	-Significant ▼ in the risk of death & reinfarction at 30 vs. weight adjusted heparin dose, with a significant ▲ in non-cerebral bleeding complications.
ASSENT-3 PLUS 2003 [117]	1,639	TKNase	Enoxaparin 30 mg IV bolus pre-hospital+1 mg/kg sc. bid (up to 7 days) vs. UFH	30-days death, in-hospital re-infarction, in-hospital refractory ischemia	-53% of patients received pre-hospital fibrinolysis within 2 hrs of symptom's onset. -Combination of TKNase+enoxaparin ▼ early ischemic events.
ENTIRE-TIMI 23 2002 [114]	483	full or half-dose TKNase +abciximab	Enoxaparin 30 mg IV bolus+ 1 mg/kg SC bid (up to 8 days) vs. UFH	TIMI 3 flow (60 min)	-Enoxaparin was associated with similar TIMI 3 flow rates as UFH at an early time point
AMI-SK 2002 [153]	496	Streptokinase	Enoxaparin 30 mg IV bolus+1 mg/kg bid (3-8 days) vs. placebo	TIMI 3 flow (5-10 d)	-Triple clinical end-point of death, re-infarction & recurrent angina at 30 days ▼ with enoxaparin 13% vs. placebo 21%, P=0.03
ASSENT-3 2001 [112]	4,075	TKNase	Enoxaparin 30 mg IV bolus plus 1 mg/kg SC bid (up to 7 days) vs. UFH	30-days death, in hospital re infarction, refractory ischemia	Enoxaparin ▼ the risk of in-hospital re-infarction or in-hospital refractory ischemia.
HART II 2001 [157]	400	t-PA	Enoxaparin 30 mg IV bolus plus 1 mg/kg SC bid (3 days) vs. UFH	IRA patency (90 min)	-Enoxaparin=UFH as an adjunct to thrombolysis, with ▲ recanalization rates & ▼ re-occlusion at 5 to 7 days
BIOMACS II 1999 [152]	101	Streptokinase	Dalteparin 100 IU/kg pre streptokinase+120 IU/kg at 12 hrs. vs. placebo	TIMI 3 flow (20-28 h)	▲ Rate of TIMI grade 3 flow in IRA compared to placebo, 68% vs. 51% (p=0.10). Dalteparin had no effects on noninvasive signs of early reperfusion
FRAMI 1997 [160]	776	Streptokinase	Dalteparin 150 IU/kg bid (in hospital) Placebo	LV thrombus+Arterial thromboembolism (9 days)	Dalteparin significantly ▼ LV thrombus formation in anterior AMI, ▲ hemorrhagic risk

TKNase: Tenecteplase; IRA: Infarct Related Artery; UFH: Unfractionated Heparin; LV: Left Ventricular; ▼: Decrease/lowe; ▲: Increase/ higher; ►: Equal/ no difference; Hrs:Hours

t-PA with r-PA, these are summarized in Table 6.

### Trials on Tenecteplase (TNKase)

TNKase has the highest degree of fibrin specificity and binding (Table 1), infers a reduced propensity for major non-cerebral bleeds [102]. Nitrates do not appear to affect TNKase levels, as opposed t-PA levels [103]. Moreover, the inhibition by PAI-1 is reduced 80 times balanced with t-PA. TNKase has powerful antiplatelet properties both *in vitro* and *in vivo* [104] with higher thrombolytic potency compared to t-PA [105].

**Clinical (mortality) trails:** Several trails have tested the use of TNKase (Table 7). TIMI-10A trial, showed a dose-dependent increase in TIMI-3 flow rates in the 5 mg to 50 mg dose range (p=0.032) [106]. While TIMI 10B patency (patency trial) a dose-escalating pilot accomplished coronary TIMI grade-3 flow rates of 55%, 63% and 66% at 90 minutes after 30, 40 and 50 mg bolus injection which is similar to control group, receiving front-loaded t-PA [75].

In ASSENT-1 trial, a total of 3,235 patients were randomized to TNK- t-PA: 1705 received 30 mg, 1457 received 40 mg, and 73 received 50 mg. The 50-mg dose was discontinued and was replaced by 40 mg because of increased bleeding observed in the TIMI-10B study, the phase II angiographic efficacy trial was conducted in parallel with this study. The 30 days stroke rate was 1.5%. ICH rate was 0.77% (0.94% in 30-mg group and 0.62% in the 40-mg group). No strokes seen with 50 mg TNK-tPA. Within 6 hours treatment after symptom's onset: The rates of ICH were 0.56% and 0.58% in 30 & 40 mg TNK-tPA respectively. Death, nonfatal stroke, or severe bleeding complications occurred in a low proportion of patients: 6.4%, 7.4%, and 2.8%, respectively [107,108].

In ASSENT-2 trial all-cause mortality at 30 days was the primary end-point. No differences between TNKase and t-PA in mortality

(6.18% vs. 6.15%) or stroke rates, including ICH (0.93% vs. 0.94%, respectively) [109]. Moreover, there was a decreased rate in non-cerebral bleeding (p=0.0003), major bleeding (p=0.0002) and in the need for blood transfusion (p=0.0002) in the TNKase group were observed among the high-risk population of females of more than 75 years old and who weighed <67 kg (1.14% vs. 3.02%) [110]; such benefits were observed in all major subgroups regardless of age, gender, infarct location, Killip class or diabetes status. TNKase also reduced the rate of CHF. ASSENT-2 trial indicates that single-bolus TNKase is equivalent to the more complex accelerated tPA infusion, in terms of mortality and mortality/stroke combination, with decrease in major bleeding rate even after 1 year [111].

In the ASSENT-3 trial; a total of 6,095 patients with STEMI were treated with full-dose TNKase and Unfractionated Heparin (UFH), full-dose TNKase and enoxaparin, or half-dose TNKase and UFH and the GP IIB-IIIa inhibitor abciximab within 6 hours from the onset of symptoms. Compared with UFH, enoxaparin resulted in reduction in the combination of 30-day mortality plus in-hospital re-infarction and refractory ischemia (p=0.0002). This reduction persisted even with addition of in-hospital ICH or major bleeds. Abciximab increased the rate of thrombocytopenia compared to both enoxaparin and UFH (p=0.0001) and it also increased the cost of treatment [112,113].

The ENTIRE-TIMI 23 trial [114] had very similar design to that of ASSENT-3 with similar result (Table 7). In general, the adjunctive use of enoxaparin with TNKase when compared to UFH reduced the combined incidence of death/ MI at 30 days (p=0.005). Abciximab increased the risk of major bleeding (5.2% vs. 2.4%) but had no effect on the end-point. Major bleeding was also increased when half-dose TNKase was combined with eptifibatide, a small-molecule GP IIB-IIIa inhibitor in the INTEGRITI study [115]. In conjunction

with the GUSTO-V data [116], ASSENT-3, ENTIRE-TIMI- 23 and INTEGRITI specify not to combine GPIIB-IIIa agents with thrombolytic drugs.

Furthermore, in the ASSENT-3-PLUS, enoxaparin tended to reduce the composite of 30-day mortality or in-hospital re-infarction or in-hospital refractory ischemia (14.2% vs. 17.4%,  $p=0.08$ ), with no differences in the efficacy plus safety end-point, also including the rate of ICH or major bleeding ( $p=NS$ ). Enoxaparin increased the rate of total stroke (2.9% vs. 1.3%,  $p=0.026$ ) and (ICH) ( $p=0.047$ ) occurred in the group of patients older than 75 years [117]. Analysis of data from different trial [118,119] will be discussed below.

**Angiographic trials:** Tenecteplase has been assessed in several angiographic trails [115,120-122]; these are summarized in Table 7.

### Trials on other fibrinolytics

Staphylokinase [127-129] and urokinase had undergone relatively sparse clinical trials evaluation [128-132]. Saruplase (scu-PA) studied in human and was equivalent to t-PA [135] and controversial result when compared to streptokinase [47,134-135]. lanoteplase n-PA: A modified t-PA molecule underwent far-reaching assay may be superior to t-PA, in term of patency rate but with higher ICH [136,137]. Anistreplase: home administration of thrombolytic therapy rather than in the hospital decreased mortality from AMI [138]. These fibrinolytics are not in clinical use any more.

**ACC/AHA Practice Guidelines summary for fibrinolytic use 2013:** Fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads (in the absence of contraindications). (Class I, Level of Evidence: A) [139].

Fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB (in the absence of contraindications). (Class I Level of Evidence: A).

In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptom onset within the prior 12 hours and 12-lead ECG findings consistent with a true posterior MI. (Class IIa, Level of Evidence: C).

In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to patients with symptoms of STEMI beginning within the prior 12 hours-24 hours who have continuing ischemic symptoms and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads. (Class IIa, Level of Evidence: B).

Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began more than 24 hours earlier. (Class III Level of Evidence: C).

Fibrinolytic therapy should not be administered to patients whose 12-lead ECG shows only ST-segment depression except if a true posterior MI is suspected. (Class III Level of Evidence: A).

## Fibrinolysis and Adjunctive Therapies

### Fibrinolytics and antiplatelet agents

Persuasive evidence of the effectiveness of aspirin was demonstrated by the ISIS-2 trial, [23] in which the benefits of aspirin and streptokinase were additive (Table 8). The first dose of 150 mg-

325 mg should be chewed (not enteric-coated aspirin because of its slow onset of action) and a lower dose (75 mg-100 mg) given orally daily thereafter. Aspirin can be given intravenously (250 mg-500 mg) if indicated. The benefit of initial aspirin therapy was sustained long-term in the ISIS-2 trial. Consequently, treatment with aspirin at a dose of 75mg to 162 mg should be continued indefinitely. The Antiplatelet Trialists Collaboration [140,141] reported 40 further deaths, re-infarctions, or strokes prevented per 1,000 patients in the first few years of sustained treatment.

Prasugrel, a new thienopyridine has been studied in TRITON-TIMI 38 trial; in which 13 608 moderate- to high-risk ACS patients undergoing PCI which showed prasugrel had greater ischemic event protection than clopidogrel but significantly increased major bleeding risk [142].

Clopidogrel is a thienopyridine derivative, potent platelet inhibitor. In the CLARITY trial, patient's  $\leq 75$  years were treated with a standard fibrinolytic regimen and randomized to 300 mg clopidogrel loading dose followed by 75 mg/ day or placebo on top of aspirin up to a maximum of 8 days including the day of angiography (mean duration 3 days). By 30 days, clopidogrel reduced the odds of the composite end-point of death from cardiovascular causes, recurrent MI, or recurrent ischemia, with 20% reduction for urgent revascularization. The rates of major bleeding and ICH were similar in the two groups [143] (Table 8). In the COMMIT study, 45 852 Chinese patients of any age ( $<1000$  patients aged  $>75$  years) with suspected MI (93% with STEMI) randomized to clopidogrel 75 mg (without loading dose) or placebo in addition to aspirin. Clopidogrel significantly reduced the odds of the composite of death, MI, and stroke [144].

Fibrinolytics and other platelet inhibitors such as gp IIb/IIIa inhibitors were studied in many trials (Table 8); Initial trials were performed with full doses of both agents [145-147], they uniformly showed improvement in the angiographic or ECG measures of reperfusion, but concerns were raised about bleeding risks. Such concern led to the design of trials evaluating the combination of partial-dose fibrinolytic therapy with GP IIb/IIIa inhibitors [69,70]. The dose-finding phase of the TIMI-14 studied 677 patients within 12 h of STEMI symptom's onset. Subjects studied received partial-dose t-PA with abciximab infusion for 12 h or abciximab with streptokinase. The streptokinase study arm was discarded due to unacceptable bleeding risk and a dose-confirmation study [70] with 211 patients assigned to front-loaded alteplase, with heparin (70 U/kg bolus and 15 U/kg/h) or t-PA 50 mg over 60 min with abciximab in addition to either low-dose heparin (60 U/kg bolus, 7 U/kg/h infusion) or very-low-dose heparin (30 U/kg bolus+4 U/kg/h infusion). Combination therapy in TIMI-14 resulted in a historical 76% TIMI-3 flow rate at 90 min compared to the 57% seen with standard t-PA treatment with no difference in the overall major bleeding rate (7%).

PARADIGM trial tested Lamifiban in combination with tissue-plasminogen activator or streptokinase in patients with ST segment elevation presenting within 12 h of symptom's onset, Lamifiban given with thrombolytic therapy was associated with more rapid and complete reperfusion with better ST resolution than placebo [148].

Similarly, the Strategies for Patency Enhancement in the Emergency Department study (SPEED study) (Table 8) randomized 304 patients to full-dose abciximab alone or abciximab and reteplase. The preferred combination of reteplase (5 U+5 U) with abciximab compared to standard dosage (10 U+10 U) of reteplase in 224

**Table 10:** Studies comparing fibrinolysis and primary angioplasty.

Author	Registry	Patient no	Mean age	Result
Armstrong et al. 2013 [176]	STREAM study	1892 STEMI patients within 3 hours of symptom onset	59.7 ± 12.4 in fibrinolysis group 59.6 ± 12.5 in PCI group	-Death, shock, CHF, or re-infarction up to 30 days occurred in 12.4% of fibrinolysis & 14.3% in the primary PCI group (P=0.21). -Emergency angiography required in 36.3% in the fibrinolysis group. More ICH occurred in the fibrinolysis group than in the primary PCI group (1.0% vs. 0.2%, P=0.04; after protocol amendment, 0.5% vs. 0.3%, P=0.45). -The rates of non-intracranial bleeding were similar in the two groups.
Yan AT et al. 2008 Canada [177]	TRANSFER-AMI trial	1200 pts. high-risk STEMI presenting to non-PCI centers PCI vs. FL		-Early routine PCI associated with ▼ rate of death/re-MI at 30 days in the low-intermediate risk stratum (8.1 vs. 2.9%, P<0.001), but a ▲ rate of death/re-MI in the high-risk group (13.8 vs. 27.8%, P=0.025) In hospital mortality 3.6% in PCI gp. & 4.6% in FL gp. MR 30 days & at 6 months=7.2% & 11.3% in PCI gp. & 5.8% & 7.1% in FL gp. respectively.
Pipilis et al. 2010 [178] Greece	HELIOS Registry (a cohort)	PCI n=84, 9.7% & FL n=497, 57.1%	61 ± 12 vs. 62 ± 13	FL with rescue PCI associated with[- ▼ rates of coronary patency & TIMI flow grade 3, -▼ MR, death/MI & hemorrhagic complications at 30 days vs. PPCI in this gp of STEMI pts. with late presentation & delayed treatments. life-threatening hemorrhage=2.9%
Gao RL, et al. 2010 China [179]	multicenter randomized clinical trial	PCI gp n=101; r-Sak gp (n=104); & (rt-PA) gp (n=106)	57.33 ± 9.18	-Patency rate & LVEF in the prior-t-PA gp. ▲ than in the P-PCI gp (69% vs. 17%, P<0.001; 61.6 ± 9.5% vs. 55.0 ± 11.6%, P=0.01). -The MACE-free rate in the prior-t-PA gp. ▼ than PPCI gp. (58.7% vs. 80.9%; P=0.03). -The MACE-free rate in the F-PCI gp. → PPCI gp (73.7% vs. 80.9%; P=0.39), MACE-free rate in the prior-t-PA-alone gp ▼ in the PPCI gp (48.1% vs. 80.9%; P=0.01)
ITOH T et al. 2010 Japan [180]	IMPORTANT study multicenter, prospective, randomized study	101 pts. had Prior t-PA gp. (n=50) & PPCI gp (n=51).	55.8 ± 10.6	-In-hospital MR & re-infarction rate ▼ significantly in Swiss STEMI pts in the last 7 years, parallel to a significant ▲ in the number of PCI+medical therapy. Outcome is not related to the site of admission but to PCI access.
Stolt Steiger V et al. 2009 Switzerland [181]	Swiss prospective national registry data ACS in (AMIS Plus).	12 026 STEMI pts in 68 hospitals.	64 ± 13 years, 73% male	-TT used in only 33% of cases. Death rate 21.2% vs. 2.1 in angioplasty treated pt. major bleeding=2.2%
Soares et al. 2009 Brazil [182]	cohort, observational, prospective	158 pts with STEMI	60.8 yrs. (22-89)	Angioplasty vs. FL; the composite endpoint occurred in 20.1 vs. 26.7% (P=0.007), death in 13.6 vs. 16.4% (P=0.18), I re-infarction in 8.9 vs. 12.3% (P=0.05), stroke in 3.2 vs. 4.7% (P=0.23)
Busk M et al. 2008 Denmark [183]	DANAMI-2 trial	1572 pts with STEMI	63 (54-73) yrs.	MR in TT gp=10.2% (7.6% in men & 18.7% in women, p <0.01). for pts treated with PPCI, was 4.7% (2.5% in men & 13% in women, p <0.01),
Prieto et al. 2008 Chile [184]	GEMI network, from 2001 to 2005	3,255 pts	FL=60 ± 11 in PCI=60 ± 13	-Death, re-infarction, refractory ischemia at 30 days occurred in 4.4%, in the immediate PCI gp vs. 10.7% in the standard care/rescue PCI gp (HR 0.40; 95% CI 0.21-0.76, log rank p=0.004). -Major bleeding ► (3.4% vs 2.3%, p=0.47). Strokes ► (0.7% vs. 1.3%, p=0.50).
Di Mario et al. 2008 [185] France, Italy, & Poland	CARESS-in-AMI trial	600 pts ► PPCI vs. rescue PCI 1/2-dose after FL	75 yrs. or younger	-t-PA in patients under 70 years of age & up to 4 hours from pain onset may be an alternative to an invasive strategy. 25% pts require urgent PCI. -In long-term mortality benefit can be clearly seen only in early PCI Patient.
Grajek et al. 2008 Poland [186]	Wielkopolska Regional 2002 Registry (WIRE Registry)	3780 pts with STEMI	59.1 ± 11.6 yrs. -PCI. 56.1 ± 10.4 yrs. rTPA gp 65.6 ± 11.8 l yrs. SK gp	Hospital MR among pts. treated with FL=10.9% & PCI=5.6% (p=0.01).
Greig et al. 2008 Chile [187]	Chilean National Registry of Acute MI	1,634 STEMI pts 72% ► FL	967 pts, 60 ± 12 yrs., 77% Males.	-At 5 years follow up TT compared to transfer PCI 53% vs. 40%. cumulative all-cause mortality 23 vs. 19% recurrent infarction 19 vs. 12%, stroke 8 vs. 8%, revascularization 51 vs. 34%
Widimsky et al. [189]	The PRAGUE-2 trial	850 STEMI pts. in non cath lab hospitals in 12 h	64 (31-86) yrs.	-PPCI usage ▲ from 16% to almost 60%, the use of FL ▼ from 50.5% to 26.7% in the participating centers. In-hospital MR ▼ from 16% to 9.5%, including pts not receiving RT. PPCI & FL have comparable in-hospital MR when initiated within 2 to 3 hrs. from onset of symptoms, PPCI more effective in acute STEMI of >3 but <12 hours' duration.
Kalla et al. 2006 Austria. [190]	Vienna STEMI Registry	1053 pts. with acute STEMI	60.8 ± 13.0	-In FL; over all Death 7.9%, re-infarction 6.7%, Death or re-infarction 13.5%, Stroke=2.2% PPCI associated 37% ▼ in 30-day mortality [adj. OR, 0.63; 95% CI (0.420-0.84)].
Boersma E et al. 2006 [191]	25 randomized trials analysis testing the efficacy of PPCI vs. FL	7743 pt. / 3383 receive FL	62 (53-71)	

McNamara RL et al. 2006 USA [192]	Retrospective observational study from the National Registry of MI 3 & 4	FL; n=68,439 pts PCI n=33,647 pts	61.7 (13.0) in FL 61.8 (13.2) in PCI	-46% of the pts. in the FL cohort treated within the recommended 30-minute door-to-needle time. -35% of the pts in the PCI cohort treated within 90-minute door-to-balloon time
Rathore et al. 2006 [193]	a randomized controlled trial	47882 AMI pts	76 (70-82) yrs.	-30-day MR ▲ in pts. with ▲ TIMI scores (TIMI score 2: 4.4% vs. TIMI score >8:35.6%, P < .0001 for trend). Overall, after adjusting for all pts. covariates, pts. presenting during off-hours had significantly ▲ in-hospital mortality than pts. presenting during regular hours (OR, 1.07; 95% CI, 1.01-1.14; P=0.02).
Magid DJ et al. 2005 USA [194]	Cohort study 1999-2002.	68 439 pts with STEMI,FL & 33 647 ►PCI)	Age, mean (SD), yrs. 63 ± (13)	In-hospital death=3.3% for pre-hospital FL, 8.0% for in-hospital FL 6.7% for PPCI, 1-year survival=94%, 89%, 89%, respectively
Danchin et al. 2008 [196]	French Nationwide USIC 2000 Registry /FAST MI	1922 AMI pts	median age, 67 yrs; 73% men)	-PPCI was better than TT at; -▼ overall short-term death (7% vs. 9%,p=0-0002), death excluding the SHOCK trial data (5% vs. 7%, p=0-0003), non-fatal re-infarction (3% vs. 7%; p<0-0001), stroke (1% vs. 2%; p=0-0004), & the combined endpoint of death, non-fatal re-infarction, &stroke (8% [253] vs. 14% [442]; p<0-0001). -PPCI was better than TT at long-term follow-up independent of both the type of thrombolytic agent used, and whether or not the patient was transferred for primary PTCA.
Keeley et al. 2003 [197] USA	Meta-analysis of 23 trials	7739thrombolytic-eligible patients with STEMI-to PPCI (n=3872) or TT (n=3867).	short-term: 4-6 weeks long-term; 6-18 months	-▼ Re-infarction by 68% (P=0.001) & stroke by 56% (P<0.015). -▼ In all-cause mortality of 19% (95% CI=3% to 36%; P=0.08) with transfer PPCI.
Dalby et al. 2003 [198]	meta-analysis 6 clinical trials	3750 pts.	-----	30-day in-hospital MR=12.7% for IV-T, 3.7% for IC-T, 4.8% for PPCI, 7.9% for rescue PCI, covariate-adjusted OR (95% CI)=0.38 (0.28-0.52) for PPCI, 0.30 (0.15-0.60) for IC-T, 1.04 (0.51-2.10) for IV-FL & 0.77 (0.46-1.30) in rescue PCI.
Sakurai k et al. 2003 [199] Japan	Registry of Miyagi Study Group for AMI (MsAMI)	3,258 AMI pt.	66.5 yrs.	

PCI: Percutaneous Coronary Intervention; AMI: Acute Myocardial Infarction; PPCI: Primary Percutaneous Coronary Intervention; TT: Thrombolytic Therapy; FL: Fibrinolysis; ACS: Acute Coronary Syndrome; STEMI: ST Elevation Myocardial Infarction; CHF: Congestive Heart Failure; LVEF: left Ventricular Ejection Fraction; RT: Reperfusion Therapy; IC-T: Intracoronary Thrombolysis; F-PCI: Facilitated Percutaneous Coronary Intervention; MR: Mortality Rate; ▼: Decrease/lower; ▲: Increase/higher; ►: Equal; pts.: Patients; gp.: Group; yrs.: Years

additional patients. In this angiographic trial, 60-90 min TIMI-3 flow rates with half-dose reteplase and abciximab, standard reteplase, and abciximab alone were 62%, 47%, and 27%, respectively. Severe bleeding was seen in 9.2% in combination treatment group vs. 3.3% and 3.7% with reteplase and abciximab, respectively. The increased patency rates witnessed with combination therapy directed the idea that treatment with these agents may further decrease mortality [69].

GUSTO-V randomized patients to 1:1 ratio to standard-dose reteplase (10 U+10 U, 30-min apart) or a combination of abciximab (0.25 mg/kg bolus, 0.125 microg/kg/min infusion maximum 10 microg/min) for 12 h with half-dose reteplase (5 U+5 U, 30 min apart). The primary end point of 30-day mortality is similar in both reteplase and combination groups (5.9% vs. 5.6%; p=0.43). With no difference in the incidence of nonfatal disabling stroke or any stroke with double ICH risk in those aged >75 years (p=0.069), with a significant interaction of treatment by age (p=0.033). Rates of re-infarction (and recurrent ischemia were significantly reduced with combination therapy, patients aged <75, anterior infarctions, and late >4 h presenters gained more benefit from combination therapy, with similar 1-year all-cause mortality rate in the reteplase-alone and combination therapy groups [116,149].

The ASSENT-3 trial (described above); the rate of all stroke as well as ICH was similar for combination therapy as compared to standard treatment. Total major, and minor bleeding rates were all significantly higher with combination treatment. No benefit and a tendency toward harm were seen in the elderly [113]. Consequently GUSTO-V and ASSENT-3 findings point out that abciximab combined with half-dose fibrinolytic has a beneficial effect on the end point of re-infarction, with no impact on short (GUSTO-V and

ASSENT-3) or long-term mortality (GUSTO-V). In ASSENT-3, major bleeding with combination therapy in the elderly was noticeably higher than with TNKase therapy alone (13.3% vs. 4.1%). It is preferable not to use combination in patients aged >75 years. Trials with eptifibatide and half-dose fibrinolytic agents; the Integrilin and Low-Dose Thrombolysis in Myocardial Infarction trial (INTRO AMI trial) randomized patients to receive double-bolus eptifibatide with 50-mg t-PA, eptifibatide with 50-mg t-PA, and standard full-dose weight-adjusted t-PA. The 60 min TIMI-3 flow for the 3 groups were 42%, 56%, and 40%, respectively. The median TIMI frame count was significantly lower with combination therapy, with similar rates of major bleeding and ICH [150].

The INTEGRITI trial, the Integrilin and Tenecteplase in Acute Myocardial Infarction phase II angiographic trial (Table7) enrolled 438 patients within 6 h of STEMI symptoms. The combination of eptifibatide with half-dosage tenecteplase (0.27 mg/kg) and UFH (60 U/kg, 7 U/kg/h) was selected after the dose-finding phase. In dose confirmation, this regimen had similar TIMI-3 flow (59% vs. 49%, p= 0.15), overall patency (85% vs. 77%, p=0.17), and ST-segment resolution (71% vs. 61%, p=0.08) as standard TNase monotherapy (0.53 mg/kg). The rate of ICH observed in 0.6% with combination therapy vs. 1.7% with standard therapy [115]. A large, clinically powered trial using eptifibatide with fibrinolytic agents has not yet been accomplished. Other trial on other potent antiplatelet are summarized in (Table 8). A recent randomized found that in patients younger than 75 years with ST-segment elevation myocardial infarction, delayed administration of ticagrelor after fibrinolytic therapy was non-inferior to clopidogrel for TIMI major bleeding at 30 days [151].

**Table 11:** Several observational national studies, sub studies registries and meta-analysis on the fibrinolysis:

Author	Registry	Patient No.	Mean age	Mortality rate
No authors listed 2011 China * [200]	Retrospective study on ACS SEMI	1 307 in-pts with STEMI ACS from 64 hospitals	-----	30.9%-69.4% of the pts received reperfusion therapies. 1.3%-62.7% received P PCI, 46.2% did not receive any form of reperfusion. TT more often used in secondary hospitals compared to tertiary hospitals (36.8% vs.14.6%).
AlHabib et al. in press Gulf RACE II Arab Middle Eastern countries[201]	2nd Gulf Registry of Acute Coronary Events (Gulf RACE-II)a prospective, multinational, multicenter, observational survey	2,465 STEMI pts., 66% 1,586 streptokinase 43% reteplase 44%, tenecteplase 10%, & alteplase 3%. 22.7% no reperfusion	50 (44-57) years	TT (reteplase & tenecteplase) associated with ▲ GRACE risk scores (P<0.001). ▼ mortality at both 1-month (0.8% vs. 1.7% vs. 4.2%; P=0.014) & 1-year (0% vs. 1.7% vs. 3.4%; P=0.044) compared to SK
Awad et al. 2011 Gulf RACE Arab Middle Eastern countries [202]	prospective registry pts ACS in (Kuwait, Oman, UAE, Yemen, Qatar, & Bahrain)	11,151 patients of which 2,619 With STEMI	54.4 " 13 yr.	20% of Gulf RACE hospitals have catheterization facilities, FL was the reperfusion strategy compared to GRACE (78% vs.13%) major bleeding occur in 2.4%, 1.2%, P=0.01 respectively
Anna Polewczyk et al. 2010 Poland [203]	Polish Acute Coronary Syndrome Registry (PL-ACS) retrospective analysis	830 Pt.	75.7 ± 6.3	in-hospital & 6-month mortality tended to be ▼ in the more recent group 18.5% & 23.8%,
Binbrek et al. 2010 UAE [204]	meta-analysis of 6 studies	1,262 pts. With STEMI thrombolysed <6 hrs. of symptoms onset	47 years	30-day mortality (3%), re-infarction (2.5%), stroke (0.4%), or major bleeding (0%) ▼ compared to global experience with recanalization. No major bleeding
Pereira et al. 2009 Brazil [205]	cross-sectional, observational and retrospective study	103 Pt. of acute STEMI	60 ± 12 yrs, M=58.3 ± 10.9 yrs F63.6 ± 13.5	Hospital MR after AMI=17.5%, 66.7% occurred within 48 hours. 58.3% of the pts received thrombolytic with MR=10%
Zubaid et al. 2009 Gulf region / Middle East. [206]	Gulf RACE; a prospective ACS registry	8176 pts with the final diagnosis of ACS	56 years	82% received TT & 10% did not receive any reperfusion. Median door-to-needle time=45 minutes
Danchin et al. 2008 France [207]	French Nationwide USIC 2000 Registry	1922 pts, 9% ► prehospital TTs, 19% ► in-hospital TT, 23% ► PPCI, & 49% no RT.	Prehospital Lysis; 59 ± 13, In-Hospital Lysis; 61 ± 14	Multivariate analysis of predictors of 1-year survival, PHT was associated with a 0.49 relative risk of death (95% CI, 0.24 to 1.00; P<0.05).
Nallamothu et al. 2007. USA [208]	National Registry of Myocardial Infarction USA, cohorts 1994-2003	238, 291 pts.	62.6 (± 13.3)	Utilization of acute RT in ideal pts. improved over the last decade, more than 10% remain untreated
Andrikopoul AAndrikopoulos et al. 2007Greece [209]	HELIOS study, registry of AMI,	1096 STEMI pts.	Mean age 68 ± 13 years, 75% men	In-hospital MR=7.7%. 6-month follow-up period, The 30-day & 6-month MR=10.5% & 14.4% respectively.
Poloński et al. 2007 Poland [210]	Polish Registry of Acute Coronary Syndromes (PL-ACS)	100,193 pts. 31.2% → STEMI	64.0 ± 12.4 years	Reperfusion therapy administered in 63.3% of STEMI pts. (TT 7.8%, P PCI 54.1%, & PCI after TT 1.4%). In-hospital MR in STEMI=9.3%.
G. Montalescot et al. 2007 France [211]	The OPERA registry; prospective, longitudinal cohort study.	1476 pts. STEMI	64+14 years	28.9 of STEMI have FL 1-year MR=9.0% in STEMI pts. Hemorrhagic stroke ► in 0.4 %
Kobayashi H et al. 2006 Japan [212]	retrospective study involved	405 AMI pts.	60 ± 9 yrs. in IV FL. 60 ± 11 in IC-T	Cardiac death 2.4% years for IV thrombolysis 3.2 for ICT=0% cerebral bleeding
Dudek et al. 2006 Poland [213]	Acute Coronary Syndromes Registry of Małopolska 2002-2003	867 STEMI pt.	67.7 ± 10.9 yr.	FL used in 21% of pts. with STEMI. In-hospital MR=14.3% in pts treated with FL as compared to 15.9% in those treated conservatively
Bartolucci et al. 2006 Chile [214]	4,938 pts.	1,631 ► SK, 1,465 pts. ► 1.5 MU in 60 min, 166 pts. with chest pain & ST elevation or LBBB, ►0.5 MU-0.75MU SK within 30min+UFH, 0 to 6 hrs. of symptom	58,56+12,09 in gp 1 58,96+11,42 in gp 2	-The low dose group of pts. had a better reperfusion criteria profile. -No differences between gps. observed in pts. evolution, mortality, maximum Killip classification, post MI HF, ischemic complications, arrhythmias or mechanical complications
Hadi et al. 2005 Qatar [215]	10 years retrospective study	5388 MI pts. 66.3% with STEMI 61.4% received TT	30-80 yrs.	-9.2% (38) vs. 19.5% (231) who did not receive TT (p<0.001).female pts. With TT had ▲ MR ((20.5% vs. 6.1%; p <0.001. TT used in 61.4%, which is still underutilized
Björklund E, et al. 2005 Sweden [216]	Prospective cohort study Swedish Register of Cardiac intensive care on pts 75 Swedish hospitals in 2001-2004	Pre-hospital FL=1690 In-hospital FL n=3685	64 (57-71)in Pre-hospital FL. 67 (58-74) in In-hospital FL	1-year MR=7.2 vs. 11.8% for pre-hospital TT& in-hospital TT
Doyle F et al. 2005 Ireland [217]	in: a national cross-sectional survey	1365 episodes, 935 AMI & 430 ACS pts	mean (SD)=66 (13)	FL given more often in the emergency department in 2003 (48% vs. 2%). achieved faster than TT delivered in intensive/coronary care (35 vs. 60 mins; p <.0001).

Diwedi et al. 2005 India [218]	Double blind, randomized, non-inferiority, multicentric, parallel study.	150 pts	r-SK=52.0 ± 10.3 n-SK=51.6 ± 10.7	Reperfusion occurred in 68.2% (58) & 69.4% (34) pts in r-SK and n-SK gp respectively. Adverse events include fever in 7 (8.5%), hypotension in 3 (3.6%), nausea in 2 (2.4%) pts. Minor bleeding occur in 4 (4.8%) of pts. Paramedic-delivered TT can be done appropriately, safely, & effectively. Time gains are substantial & meet the national targets for early TT in the majority of pts. No major bleeding
Chittari et al. 2005 [219]	Retrospective observational case-control study	54 pt. acute STEMI	-----	
Hanania, et al. 2004 [220] France	French Nationwide USIC 2000 Registry	2320 pts. 83% had (STEMI	median age 68 years, 73% men)	-In-hospital MR=8.7% (5.5% of pts. without & 9.3% with STEMI). multivariate analysis age, Killip class, ▼BP, ▲HR on admission, anterior infarct, STEMI, DM, previous stroke, &no current smoking independently predicted in-hospital MR.
Gupta et al. 2003 [221]	multilevel analysis of patients in ASSENT-2	16 949 pts. with STEMI within 6 h	62 (52,71) yrs.	MR at 30 days ▼ for countries with the highest revascularization rates (5.1% vs. 6.9% vs. 6.5% for the ▼ 2 tertiles, P<0.001). At 1 year, MR ▼ in the highest tertile countries (8.4% vs. 10.6% vs. 9.9%, P=0.001)
Nagao et al. 2002 Japan [222]	FAST trial	195 pts. with (AMI)	TT; 58.5 ± 8.9 TT+intervention; 59.2 ± 9.0	► in 30-day MR or complications. TIMI-3 flow at the initial angiography ▲ with a single bolus of mutant t-PA montepase vs. accelerated infusion of t-PA (60% vs. 32%, p=0.005). comparison of the TT alone (n=83) & TT+intervention (n=112) gps showed significant differences in the time interval from hospital arrival to achievement of TIMI-3 flow
Cundiff et al. 2002 [224] GUSTO investigators 2002 [154]	meta-analysis of 9 randomized placebo-controlled trials GUSTO Angiographic	58,511 pts. 2431 pts.		-Survival advantage of 2% (11.5% vs. 9.6%) in favor of TT. -Iatrogenic deaths from TT complications=1%. -Angiographic data does not support the open-artery hypothesis as the mechanism of benefit of TT
Fu et al. 2001 [225]	Sub study of ASSENT-2	13 100 pts. with STE MI	61 (52-70)	-ST resolution at 24 to 36 hours after FL is influenced by time to treatment & inversely related to 1-year MR. -Time to treatment further differentiates between high & low-risk pts & highlights the importance of ▼ time delay to initiation of FL in AMI
Zaputović et al. (2000) Croatia. [226]	Retrospective cohort study.	366 pts with AMI,	66+/-11 years	-27% received TT. Less frequently applied in older pts., women, & pts. with previous MI. -Reperfusion achieved in 66 (66%) pts. & re-occlusion occurred in 14%. MR after TT ▼ (7% vs. 17%, p=0.015), without fatal outcome in pts. with finally successful TT
Barron et al. 1998 USA [227]	The National Registry of MI 2 (NRM 2) is a prospective, observational, phase IV study	84 663pts eligible for reperfusion therapy	63.860.05 Years	-24% have no RT (7.5% of all pts). multivariate analyses; LBBB, no chest pain at presentation (age 75 years, female sex, &various preexisting CV conditions are independent predictors not to receive FL
Baardman et al. 1996 [228]	The GUSTO Enzyme Sub study	553 pts. AMI	62 years	-Early patency rates (TIMI 2+3)=similar in the 2 SK gp. (53 & 46%). -▲ Patency rates in the combination therapy gp. (87 & 90%).
Lee et al. (1995) USA [230]	analysis of relations between baseline clinical data and 30-day mortality of the GUSTO-I trial	41,021 pts enrolled in GUSTO-I	62 (52,70) yrs.	-Multivariable analysis; age most significant factor influencing 30-day MR with of 1.1% in the <45 years & 20.5% in pts. >75 (P<.0001). -Other factors of ▲ mortality; lower SBP (P<.0001), ▲ Killip class (chi 2=350, P<.0001), ▲ HR (P<.0001), & anterior MI (P<.0001).
Bode et al. 1996 Germany [97]	RAPID II	324 pts AMI	Reteplase; 58yrs Alteplase; 62 yrs	-Patency & complete patency, significantly ▲ in reteplase-treated pts. (reteplase vs. alteplase) -TIMI grade 2 or 3: 81.8% vs. 66.1%, P=.01; TIMI grade 3: 51.2% vs. 37.4%, P<.03). -No differences between reteplase & alteplase in bleedings requiring a transfusion (12.4% vs. 9.7%) or hemorrhagic stroke (1.2% vs.1.9%).
Aguirre et al. 1995 USA [230]	A secondary analysis of TIMI II trial	2634 pts enrolled in the TIMI II trial with a first MI	56.4 yrs	Early mortality & adverse clinical cardiac events in pts not significantly different after a conservative vs. invasive strategy, regardless of infarct type

Simes et al. (1995) Australia [231]	An angiographic sub study within GUSTO-I	41,021 pts in GUSTO-I	-----	-Predicted & observed 30-day MR of the 4 treatments ; SK+ SC UFH, 7.46% vs. 7.28%; SK+iv UFH, 7.26% vs. 7.39%; accelerated TPA, 6.31% vs. 6.37%; & SK +TPA, 6.98% vs. 6.96%.
Zhou L et al. 1992 Japan& China [232]	Retrospective study	408 pt with acute STEMI	64 ± 11 in Japan 58 ± 13in China	-Urokinase (UK: 71.4%) or rt-PA: 28.6%) administered IV85.7% & intracoronary 14.3%) injection.

PCI: Percutaneous Coronary Intervention; AMI: Acute Myocardial Infarction; PPCI: Primary Percutaneous Coronary Intervention; FL: Fibrinolysis; ACS: Acute Coronary Syndrome; STEMI: ST Elevation Myocardial Infarction; LVEF: Left Ventricular Ejection fraction; TT: Thrombolytic Therapy; SK: Streptokinase; MR: Mortality Rate; IC-T: Intracoronary Thrombolysis; UFH: Unfractionated Heparin; RT: Reperfusion Therapy; ▼: Decrease; ▲: Increase; ►: Equal/no Difference  
\* This article was published in Chinese language; information was obtained from the abstract only.

### ACC/AHA Practice Guidelines summary

**Aspirin:** A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 mg-162 mg) should be given indefinitely after STEMI to all patients without a true aspirin allergy. (Class I Level of Evidence: A) [139].

**Thienopyridines:** In patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and for up to 12 months in patients who are not at high risk for bleeding. (Class I Level of Evidence: B).

In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days, and preferably for 7, unless the urgency for revascularization outweighs the risks of excess bleeding. (Class I, Level of Evidence: B).

Clopidogrel is probably indicated in patients receiving fibrinolytic therapy who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. (Class IIa Level of Evidence: C).

**Glycoprotein IIb/IIIa inhibitors:** It is reasonable to start treatment with abciximab as early as possible before primary PCI (with or without stenting) in patients with STEMI. (Class IIa, Level of Evidence: B).

Treatment with tirofiban or eptifibatide may be considered before primary PCI (with or without stenting) in patients with STEMI. (Class IIb, Level of Evidence: C).

Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction (Level of Evidence: A) and other complications of STEMI in selected patients: anterior location of MI, age less than 75 years, and no risk factors for bleeding. In two clinical trials of combination reperfusion, the prevention of reinfarction did not translate into a survival benefit at either 30 days or 1 year.54a (Class IIb Level of Evidence: B).

Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction and other complications of STEMI in selected patients (anterior location of MI, age less than 75 years, and no risk factors for bleeding) in whom an early referral for angiography and PCI (i.e facilitated PCI) is planned. (Class IIb Level of Evidence: C)- Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase should not be given to patients aged greater than 75 years because of an increased risk of ICH. Class III (Level of Evidence: B).

### Fibrinolytics with unfractionated (UFH) vs. low molecular weight heparin (LMWH)

Several trials were performed on the combinations of fibrinolytic and anticoagulant therapies. Patient receiving streptokinase, anistreplase, or alteplase in the ISIS-3 and GISSI-2 trials received adjunctive sc. heparin treatment or no heparin at all. Treatment with sc. heparin, 12,500 IU, was initiated late after clinical presentation (12 h in GISSI-2 and 4 h in ISIS-3). In ISIS-3, an initial in hospital mortality reduction but not at one month was noticed this benefit was tempered by an observed increase in hemorrhagic stroke (0.1-0.2 %) and excess bleeding (3-5/1,000). A combined analysis of the two trials suggested early prevention deaths (5/1,000) (6% vs. 7.3%) but no mortality benefit at 35 days or 6 months. On the other hand an absolute increase in major or severe bleeding of  $3.2 \pm 0.7\%$  with heparin therapy was recorded. Similar clinical outcomes of death and re-infarction was seen with iv. UFH with streptokinase vs. sc. heparin with streptokinase in the GUSTO-I trial with a tendency of higher bleeding and hemorrhagic stroke with iv. UFH. The combination of heparin with t-PA achieved higher angiographic patency with a direct relationship between measured aPTT and infarct artery patency reported with t-PA. The combination of iv. heparin with t-PA resulted in less deaths, re-infarctions, and pulmonary embolism. The large trials with t-PA-GUSTO-I, GUSTO-IIb, TIMI 9B, COBALT, and GUSTO-III all utilized a 5,000-U bolus of adjunctive heparin followed by 1,000 U/h UFH. Newer t-PA derivatives have all been tested in combination with UFH [23,152,153].

The rate of ICH for patients receiving sc. heparin with t-PA in the International Study was 0.4% and 0.72% in the GUSTO-I trial which utilized iv. heparin and t-PA. Higher rates of heparin infusion as well as a higher target aPTT in the GUSTO-IIa and TIMI 9-A studies resulted in a prohibitive increase in ICH that is more striking with streptokinase (3%). Heparin dosages were subsequently decreased in the TIMI-9B and GUSTO-II B trials. Weight-adjusted bolus with a target aPTT of 50s-70s was used in subsequent trial. This approach in TIME-II trial resulted in 0.62% ICH rate. Clinical trials involving UFH had used universal therapeutic aPTT ranges typically 50s-70s regardless of the responsiveness of the thromboplastin reagent in use at the participating institutions. This responsiveness has been shown to have significant variation, similar to that of prothrombin time reagents but tends to correspond to a 0.2 U/mL to 0.5 U/mL anti Xa activity, therapeutic aPTT ranges should be modified for the specific thromboplastin reagent in use and as far as the clinical trials have failed to do so, evidence-based recommendations for use of UFH for cardiac indications are difficult to make [112,116].

Heparin does not improve immediate clot lysis, but coronary patency evaluated in the hours or days following t-PA appeared to be better with iv. heparin [89]. No differences in patency were apparent in patients treated with either sc. or iv. heparin and streptokinase [70].

Heparin infusion after fibrinolytic therapy may be discontinued after 24 h-48 h after which no evidence of administration until discharge prevents re-occlusion after angiographically successful fibrinolysis [90]. Close monitoring of weight adjustment iv. heparin dose may decrease the risk of non-cerebral bleeding [90,112].

The ASSENT-3 trial (largest trial comparing LMWH to UFH after fibrinolysis) in which 7 days standard dose of enoxaparin after TNKase reduced the risk of in-hospital reinfarction /in-hospital refractory ischaemia compared to heparin [112].

Though, in the ASSENT-3 PLUS (n=1639) trial, pre-hospital administration of the same dose of enoxaparin resulted in a significant increase in ICH in elderly patients [104]. In the large ExTRACT trial (Table 9) (n=20,506), a lower dose of enoxaparin was given to patients >75 years and to those with impaired renal function (estimated GFR, 30 mL/min) resulted in a significant reduction in the risk of death and re-infarction at 30 days compared with a weight adjusted heparin dose, but at the cost of a significant increase in non-cerebral bleeding [154,155].

Analysis of data from ASSENT-3, ASSENT-3-PLUS, EXTRACT-TIMI 25 trials is largely confirmed the advantage of using enoxaparin instead of UFH in conjunction with fibrinolytics (discussed below) in reducing the primary efficacy end-point, and better outcome in patient required urgent revascularization (p=0.013) [118,119].

Second Trial of Heparin and Aspirin Reperfusion Therapy (HART II); a non-inferiority (Table 9) studied 400 patients undergoing reperfusion therapy with an accelerated t-PA regimen and aspirin for AMI randomly assigned to (for at least 3 days) enoxaparin or UFH. Patency rates (TIMI flow grade II-III) achieved after 90 minutes of starting therapy of 80.1% and 75.1% respectively. Re-occlusion at 5-7 days from TIMI grade II-III to TIMI 0 or I flow and TIMI grade III to TIMI 0 or I flow, respectively, occurred in 5.9% and 3.1% of the enoxaparin group vs. 9.8% and 9.1% in the UFH group. In HART II: Enoxaparin was at least as effective as UFH as an adjunct to thrombolysis, with a trend toward higher recanalization rates and less re-occlusion at 5 to 7 days [158].

In the large OASIS-6 trial, a low dose of fondaparinux, a synthetic indirect anti-Xa agent, was superior to placebo or heparin in preventing death and re-infarction in 5436 patients who received fibrinolytic therapy. In subgroup analysis fondaparinux was not superior to heparin in preventing death, re-infarction, or major bleeding complications [159].

In FRAMI study; a multicenter, randomized, double blind, placebo-controlled trial investigated the efficacy and safety of dalteparin in the prevention of arterial thromboembolism after AMI of sc. dalteparin (150 IU/kg body weight every 12 h during hospitalization). Thrombolytic therapy and aspirin were administered in 91.5% and 97.6% of patients, respectively; in this trail dalteparin treatment significantly reduced LV thrombus formation but associated with increased hemorrhagic risk (Table 9) [160].

**ACC/AHA Practice guidelines summery:** Patients undergoing percutaneous or surgical revascularization should be given UFH. (Class I .Level of Evidence: C) [139].

UFH should be given intravenously to patients undergoing reperfusion therapy with alteplase, reteplase, or tenecteplase, with dosing as follows: bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per hour (maximum 1000 U/hr)

adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds). {Class I, Level of Evidence: C}.

UFH should be given intravenously to patients treated with nonselective fibrinolytic agents (streptokinase, anistreplase, or urokinase) who are at high risk for systemic emboli (large or anterior MI, atrial fibrillation, previous embolus, or known LV thrombus). (Class I Level of Evidence: B).

Platelet counts should be monitored daily in patients given UFH. (Class I Level of Evidence: C).

It may be reasonable to administer UFH intravenously to patients undergoing reperfusion therapy with streptokinase. (Class IIB, Level of Evidence: B).

LMWH might be considered an acceptable alternative to UFH as ancillary therapy for patients less than 75 years of age who are receiving fibrinolytic therapy, provided that significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women) is not present. Enoxaparin (30 mg IV bolus followed by 1.0 mg/kg subcutaneous injection every 12 hours until hospital discharge) used in combination with full-dose tenecteplase is the most comprehensively studied regimen in patients less than 75 years of age. (Class IIB, Level of Evidence: B).

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. (Class III Level of Evidence: B).

LMWH should not be used as an alternative to UFH as ancillary therapy in patients less than 75 years of age who are receiving fibrinolytic therapy but have significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women). Class III (Level of Evidence: B).

### Fibrinolytics and direct thrombin inhibitors

Direct thrombin inhibitors (DTIs) have undergone extensive evaluation in conjunction with fibrinolytic therapy. DIT should be utilized as an alternative to heparin in the setting of STEMI when Heparin Induced Thrombocytopenia (HIT) is an issue. Individual trials have not shown a dramatic improvement in clinical outcomes with DTIs as adjuncts to fibrinolytic therapy in AMI. The effects of desirudin (hirudin) with thrombolysis were tested in the TIMI-5, TIMI-6, and TIMI-9, GUSTO-II, Hirudin for the Improvement of Thrombolysis-3 and Hirudin for the Improvement of Thrombolysis-4 trials. Hirudin provided a more stable aPTT within the target range [161].

In TIMI-5, a lower rate of reinfarction observed with hirudin than heparin (4.3% vs. 11.9%, p=0.03) and a trend toward less reocclusion (1.6% vs. 6.7%, p=0.07). In the pilot trial TIMI-6, (193 patients), hirudin appeared to be as safe as heparin when administered with streptokinase and aspirin to patients with AMI. Death and nonfatal reinfarction after 6 weeks appear to be dose dependent, little difference in rates of unsatisfactory outcomes (34.3% vs. 37.3%) at hospital discharge (death, CHF, nonfatal reinfarction) with similar rates of major bleeding [161].

In HIT-III study; the Hirudin for the Improvement of Thrombolysis-3 trial, (1,208 patients) used a lower dose of lepirudin, achieved TIMI flow grade 3 in 40.7% in the lepirudin group vs. 33.5% in the heparin group (p=0.16). No differences were seen between

lepirudin and heparin in the rate of hemorrhagic stroke (0.2% vs. 0.3%), re-infarction (4.6% vs. 5.1%), or mortality (6.8% vs. 6.4%) at 30 days. Thus, lepirudin in conjunction with streptokinase did not significantly improve reperfusion or clinical outcomes in this study [162,165].

In the GUSTO-IIb trial, hirudin tested in >12,000 patients across the spectrum of acute coronary syndromes, hirudin result in significantly less re-infarction compared to heparin ( $p=0.04$ ), but only a trend toward reduction in death or MI at 30 days ( $p=0.06$ ). In patients with STEMI, the incidence of death or MI was slightly lower with hirudin ( $p=0.13$ ). There was an intriguing trend toward a greater benefit of hirudin in patients treated with streptokinase vs. t-PA in GUSTO-IIb, such finding was not observed in TIMI-9B. In the phase III, TIMI-9B trial, less re-infarction was noted during hospitalization ( $p=0.07$ ), but there was no difference in the primary end point of death, MI, severe CHF, or shock at 30 days (12.9% for hirudin vs. 11.9% for heparin,  $p=NS$ ). Similarly, the incidence of death or MI did not differ between the two anticoagulants (9.7% vs. 9.5% for heparin,  $p=NS$ ) [164,165].

A meta-analysis of 11 randomized trials, 35,970 patients treated 7 days with a DTI or heparin and followed up for 30 days. DTI associated with a lower risk of death or MI at the end of treatment ( $p=0.001$ ) and at 30 days ( $p=0.02$ ). This was due primarily to a reduction in MIs ( $p<0.001$ ) with no noticeable effect on deaths ( $p=0.69$ ). Subgroup analyses suggested a benefit of DTI on death or MI in trials of both acute coronary syndromes and percutaneous coronary interventions. A reduction in death or MI was seen with hirudin and bivalirudin but not with univalent agents. Compared with heparin, there was an increased risk of major bleeding with hirudin, but a reduction with bivalirudin. There was no excess in ICH with DTI [167].

In a pilot study; Hirulog Early Reperfusion/ Occlusion (HERO) trial, double-blind, randomized angiographic trials enrolled patients randomly to Hirulog 0.5 mg/kg/hour for 12 hours followed by 0.1 mg/kg per hour (low dose), Hirulog 1.0 mg/kg / hour for 12 hours followed by placebo (high dose), or to heparin 5000 U bolus followed by 1000 U/h titrated to a PTT; 2 to 2.5 times control after 12 hours. Hirulog yielded higher early patency rates in the IRA than heparin when used as adjunctive therapy to streptokinase and aspirin in the early phase of AMI. High doses are not superior to lower doses [166]. Testing with other agents found modest or no improvements compared with heparin [167]. The result HERO study had heartened to conduct of the HERO-2 trial, which randomized 17,073 patients with STEMI to adjunctive therapy with heparin vs. bivalirudin following initial streptokinase treatment. In this trial, bivalirudin did not reduce the primary 30-day mortality end point ( $p=0.85$ ) but reduce re-infarction at 96 h ( $p=0.001$ ). While the rates of severe bleeding and ICH tended to be higher with the use of bivalirudin [168].

**ACC/AHA practice guidelines summery:** In patients with known heparin-induced thrombocytopenia, it is reasonable to consider bivalirudin as a useful alternative to heparin to be used in conjunction with streptokinase [139]. Dosing according to the HERO (Hirulog and Early Reperfusion or Occlusion)-2 regimen (a bolus of 0.25 mg/kg followed by an intravenous infusion of 0.5 mg/kg per hour for the first 12 hours and 0.25 mg/kg per hour for the subsequent 36 hours) is recommended but with a reduction in the infusion rate if the PTT is above 75 seconds within the first 12 hours. (Class IIa, Level of Evidence: B).

## Fibrinolysis and Primary Percutaneous Coronary Revascularization, Which is Better?

Several trials compared primary coronary revascularization with thrombolysis and subsequently several investigators performed meta-analysis of these trials in an attempt to determine if one strategy is superior to the other (Table 10).

In an overview of seven trials comprising 1,145 patients with STEMI treated with either primary angioplasty or thrombolysis (streptokinase or t-PA). Those undergoing primary angioplasty had a considerable reduction in short term mortality up to 6 weeks with no long-term follow up data for mortality comparisons [169].

A review of 10 trials [170] adding together 2,606 patients included in PAMI study [171] and GUSTO IIB cohorts. [171] Primary angioplasty was compared to thrombolytic therapy in which 4 trials utilized streptokinase, 3 used accelerated t-PA and 3 used standard dose t-PA at 30 days angioplasty result in lower mortality (4.4% vs. 6.5%), lower death or re-infarction (7.2% vs. 11.9%) but similar hemorrhagic stroke (0.1% vs. 1.1%) such result is similar among thrombolytic agents used. Again, there was insufficient long-term data available for evocative comparisons but Gusto IIB 6-month follow-up showed significant decrease in the short-term benefits ascribed to primary angioplasty [172].

The Cochrane database reviewed 10 trials (2,573 patients), primary angioplasty associated with significant relative risk reduction in short-term mortality (RRR 32%, 95% CI 5% to 50%), death or re-infarction (RRR 46%, 95% CI 30% to 58%) and stroke (RRR 66%, 95% CI 28% to 84%) [173]. interestingly, in a subgroup analysis comparing results from the largest study, GUSTO IIB, to the pooled analysis. The results from GUSTO IIB were less imposing than the pooled data, suggesting that the mortality benefit of primary angioplasty is less impressive when performed in community hospitals, as in GUSTO IIB. Another possible explanation is the use of non-optimal thrombolytic therapy (streptokinase or standard dose t-PA) in the other pooled trials vs. accelerated t-PA that was used in GUSTO IIB. Every et al. analyzed at data from the Myocardial Infarction Triage and Intervention (MITI) registry comparing 1,050 patients underwent primary angioplasty with 2,095 patients had thrombolytic therapy (2/3 t-PA, 1/3 streptokinase) establish no difference in 4 years mortality [174]. Data from the second National Registry of Myocardial Infarction (NRMII-2) Comparing 4,939 patients undergoing primary angioplasty with 24,705 patients undergoing thrombolytic therapy (92% accelerated t-PA). For patients not in cardiogenic shock, in hospital mortality was similar for groups (5.2% vs. 5.4%) death/non-fatal stroke (5.6% vs. 6.2%). Cardiogenic shock patients had significantly lower in hospital mortality in the primary angioplasty group (32.4% vs. 52.3%,  $p<0.0001$ ) [175].

The Strategic Reperfusion Early After Myocardial Infarction study (STREAM) showed that Pre-hospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary PCI within 1 hour after the first medical contact. However, fibrinolysis was associated with a slightly increased risk of intracranial bleeding [176].

The TRANSFER-AMI study assessed the pharmaco-invasive strategy concept in high-risk STEMI patients. All patients received standard-dose TNKase, Aspirin, and either UFH or enoxaparin;

concomitant clopidogrel was recommended. Patients were randomized to either standard treatment (including rescue PCI, if required, or delayed angiography) or a strategy of immediate transfer to another hospital and PCI within 6 hours after fibrinolysis. The authors concluded that pharmaco-invasive therapy (early routine PCI) was associated with a lower rate of death/re-MI at 30 days in the low-intermediate risk stratum (8.1 vs. 2.9%,  $P < 0.001$ ), but a higher rate of death/re-MI in the high-risk group (13.8 vs. 27.8%,  $P = 0.025$ ). Similar heterogeneity in the treatment effects on 30-day mortality and death/re-MI at 1 year ( $P = 0.008$  &  $0.001$ , respectively), when the GRACE risk score was analyzed as a continuous variable ( $P < 0.001$ ) and when patients were stratified by the TIMI risk score ( $P = 0.001$ ) [177]. Many other studies [178-199] that compare primary angioplasty with thrombolysis are summarized in Table 10.

## Observational Studies from Different Parts of the World

Observational registries [200-232], although not true clinical trials, may afford significant evidence about the typical clinical practice and can be used to offset the potentially unworkable findings of the aforementioned clinical trials (Table 11). It reflects the local clinical practice from every part of this world, the developing and the developed world and the compliance with standard clinical guidelines of the treatment of acute coronary thrombosis. National registries for AMI are important, as they provide data that are unique for the specific country and could contribute to the optimal use of reperfusion therapies, with the ultimate goal of reducing mortality at a national level, mortality in STEMI patients could be reduced through three complementary actions. 1- Reducing the percentage of patients not receiving fibrinolytic therapy. 2- Fibrinolysis should be administered as early as possible and ideally in the pre-hospital phase. This is important for non-invasive hospitals that do not have the possibility to transfer patients for primary angioplasty within the recommended 90-120-minute time window and 3- Strict application of clinical guidelines of management of AMI.

## Role of Pre-Hospital Thrombolytic Therapy

AMI is the prototype of a real emergency, and both efficacy and speed are necessary for effective management. Reperfusion therapy should be initiated as early as possible. It is clear that in the early management of acute ischemic syndromes, saving time saves lives, and several large studies have demonstrated that pre-hospital initiation of thrombolysis is feasible and safe with respect to contraindications. Pre-hospital thrombolytic therapy has been shown to reduce both short-term relative in hospital mortality by 11% - 51% and long-term mortality at 10 years [24,233]. The mortality gain is dependent on the delay time of early reperfusion.

As shown above in large number of studies, the best way to describe the relationship as exponential: in the first 1 to 2 hours after the onset of chest pain, the benefit of thrombolysis is greater. Reducing the time to thrombolysis must therefore be the main objective of pre-hospital treatment of AMI. In the last 15 years, many strategies to reduce the time to reperfusion have been evaluated, including initiation of thrombolytic therapy prior to arrival to hospital. Like In France, pre-hospital emergency medicine is a fundamental part of the medical care system, a hospital department whose function is to centralize emergency medical calls and organize an appropriate response with the intention of ensuring the shortest delay between the initial call and the appropriate treatment. Pre-hospital thrombolysis is currently

the best treatment strategy. Such experience has proven that pre-hospital thrombolysis is both safe and effective.

During the last 10-15 years, the field of reperfusion during AMI was a real struggle zone between the proponents of thrombolysis and those of primary angioplasty. Many physicians considered that the best way is not to oppose these two effective methods but to find the most appropriate role for each or even better to combine them to accomplish reperfusion. In this concept, the idea of facilitated percutaneous intervention is a very attractive one with promising results. Numerous studies demonstrated its efficacy and to help us choosing the ideal combination of anti-thrombotic agents to be used. That is one of the main interests of the CAPTIM study. French trial studied whether pre-hospital thrombolysis could counterbalance the efficacy of primary angioplasty in AMI, found no significant differences between the treatment strategies in the combined primary endpoint of 30-day death, re-infarction or stroke (8.2% in the pre-hospital thrombolysis group, 6.2% in the angioplasty group). The mortality rate, however, was lower in the pre-hospital thrombolysis group, with 33% of patients requiring rescue angioplasty [234]. In an ideal situation, thrombolysis should be started within the 2 first hours of injury (Golden Hour). But, most of the time, the patient calls for an ambulance later than these 2 first hours after onset of symptoms. That could be the real life for AMI. We have to deem in this study the fact that 33% of the patients had a pre-hospital thrombolysis followed by a fast angioplasty. The results are impressive: the 30-day mortality in the pre-hospital thrombolysis arm is only 3.8%. But if the delay between pain to pre-hospital thrombolysis is under 2 hours this 30-day mortality falls down to 2.2%. Such outcome; superior in all the recent trials published comparing on site thrombolysis to primary angioplasty (DANAM II, PRAGUE II) [183,189] and other trials (Table 10).

The good strategy in a next future could be the association of pre-hospital thrombolysis and angioplasty. In a recent French registry (USIC 2000) [197] including all the patients arriving in coronary intensive care unit during a month and regarding the one-month mortality, this strategy seemed to be the best (3.6%). TNK-tPA is now changing the general management of pre-hospital AMI by reducing the time to treatment. This is clearly, the new standard of pre-hospital treatment. The reduction of UFH dose is recommended and the LMWH is considered as the next step as recently demonstrated in the ASSENT 3 and ASSENT 3 Plus trials. The other major problem is that late treatment mainly because of delayed call for the emergency system there are several ways to improve the time to treatment interval: patients and public education, shortening of the intra-hospital delays by better organization, finally and perhaps more importantly, pre-hospital triage and treatment. The efficacy and safety of the pre-hospital strategy is now recognized worldwide. The best strategy for AMI should involve emergency physicians and cardiologist in a real local task-force to join and coordinate their efforts.

### ACC/AHA Practice guidelines for pre-hospital fibrinolysis:

Establishment of a pre-hospital fibrinolysis protocol is reasonable in;

- 1) Settings in which physicians are present in the ambulance
- 2) well-organized EMS systems with full-time paramedics who have 12-lead ECGs in the field with transmission capability, paramedic initial and ongoing training in ECG interpretation and STEMI treatment, online medical command, a medical director

with training/experience in STEMI management, and an ongoing continuous quality-improvement program. (Class IIa. Level of Evidence: B).

## Conclusion, Expert Comments and Future Perspectives

The management of AMI has been matured in the last few decades and with advancement in both the pharmacological and interventional field of clinical cardiology. Research programs needed to: 1) Improve early pharmacological and mechanical reperfusion (new fibrinolytics, intravenous GP IIb/IIIa inhibitors, and stents). 2) Improve long-term antithrombotic therapy (e.g. oral GP IIb/IIIa inhibitors) and to increase plaque stability (e.g. statins). These new strategies, together with treatments aimed at improving tissue perfusion, may ultimately result in a further short and long-term mortality reduction. Fibrinolysis, the more accurate term, will continue to be the corner stone and effective treatment for acute coronary occlusion in spite of many drawbacks in its use including the time of administering fibrinolysis, underutilization and the competition with primary coronary revascularization.

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