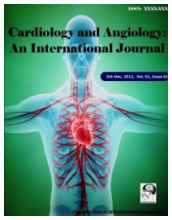

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Treatment of ST Elevation Myocardial Infarction from Fibrinolysis to Primary PCI: In Terms of Risks and Benefits

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Authors' contributions

This work was carried out in collaboration between all authors. Author HARK managed the literature searches designed the study, wrote the manuscript, and wrote the first draft of the manuscript. Author JAIS assisted in literature searches and in writing the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The treatment of ST elevation myocardial infarction (STEMI) has undergone significant advances over the past three decades. Current practice guidelines raise the importance of promptly restoring normal coronary blood flow and myocardial perfusion in the infarct zone after the onset of chest pain, through either pharmacologic or mechanical reperfusion strategies.
Fibrinolytic therapy remains the most widely used reperfusion strategy worldwide. With the development of newer fibrinolytic agents and adjuvant potent anti-platelets therapies, this approach carries an increased risk of bleeding complications. The current research present up-date review of

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the use of reperfusion strategies for the treatment of STEMI, using data through the search of MEDLINE, PubMed, EMBASE, as well as related extracts from the annual report of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. We summarized data from the available studies conducted over the past last 30 years in relation to pharmacologic reperfusion therapy in regards to risks and benefits.

Conclusion: Fibrinolytic therapy remains the main reperfusion strategy used for the treatment of STMI worldwide. In the current era, there is a lack of fibrinolytic therapy trials, mainly because of increased focus in mechanical reperfusion therapies' studies in the developed world. Clinical trials on the use of the fibrinolytics with newer platelet agents are urgently needed.

Keywords: Fibrinolytic agents; streptokinase; retaplase; alteplase; tenecteplase; acute myocardial infarction; patency rate; bleeding; intracranial hemorrhage.

ABBREVIATIONS

SK; streptokinase, t-PA; Alteplase, r-PA; Reteplase, AMI: Acute Myocardial infarction, iv.Intravenous, sc.; subcutaneous, CHF: Congestive heart failure, STEMI; ST elevation Myocardial infarction, (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, INJECTtrial: 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 Anti-thrombin 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: Groupo 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, COMMIT study: ClOpidogrel and Metoprolol in Myocardial Infarction Trial, PLATO study; The Study of Platelet Inhibition and Patient Outcomes, 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 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.

1. INTRODUCTION

Thrombolytic (fibrinolytic) therapy is a major advance in the management of AMI; it acts by lysing thrombi and attaining reperfusion therapy, reducing infarct size, upholding left ventricular function, and improving survival. Several techniques and regimens are used in which reperfusion rates increase and accordingly result in improvement of clinical outcome. These techniques include the followings; different dosing regimens of established agents; combinations of different agents; use with adjunctive agents such as direct anti-thrombin (AT) agents, low-molecular-weight heparin (LMWH), or glycoprotein IIb/IIIa receptor antagonists and the development of novel thrombolytic agents with enhanced fibrin specificity, resistance to native inhibitors, or prolonged half-lives permitting bolus administration. The term thrombolytic agent is ambiguous when applied to plasminogen activators (convert plasminogen to plasmin) that degrades fibrin, a major structural component of the thrombus and hence; the more correct term is *fibrinolytic therapy*. The field of thrombo-cardiology deals with the frail equilibrium between thrombotic complications and bleeding risk which is an important part of clinical cardiology [1-4].

We identified studies via MEDLINE, PubMed, EMBASE, and Current Contents searches and by reviewing reference lists. Pertinent abstracts from the annual meetings of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology were reviewed. We selected for review studies that evaluated the pharmacokinetics and pharmacodynamics of the various fibrinolytic agents including streptokinase, alteplase, reteplase and tenecteplase, and assessed the effects of these fibrinolytic drugs in clinical and angiographic perspective in terms of benefits, risks and long-term clinical outcomes. We also reviewed publications of observational studies of fibrinolytic therapy use among AMI patients in registries from around the world. The current review summarizes the findings from studies published over the last 30 years in this field. Studies are categorized into two subgroups; clinical or angiographic studies.

2. HISTORICAL BACKGROUND OF FIBRINOLYSIS

Fletcher and colleagues in 1958 were the first to report the use of fibrinolytic therapy in patients with AMI [5]. Early in the 1960s and 70s up to 24 trials evaluated the efficacy of intravenous streptokinase [6], but without established theoretical basis for the administration of thrombolytic therapy, together with the lack of evidence of efficacy in a single trial, led to the desertion of further investigation into this mode of treatment. In 1969, Chazov was the first who administered intracoronary streptokinase in Russia and it is now nearly 35 years since Rentrop et al. [7,8] reported its use, thereby invigorating interest in reperfusion as a treatment modality for the management of AMI. Since then, several newer fibrinolytic agents were developed, including tissue plasminogen activators, TPA (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.

3. CLINICAL TRIALS

3.1Streptokinase (SK) (Table1)

In 1958, SK was first used in AMI patients, which has revolted the treatment of AMI. SK had not been exposed to a true form of dose ranging angiographic trial only until 1980s [9]. Nevertheless, the placebo-controlled trials of this agent were very influential in terms of significant mortality reduction with intravenous SK for AMI. Several trials [10-27] have reported patency of the infarct related artery (IRA) at different time points among patients not receiving fibrinolytic therapy. Most patients did receive aspirin and heparin, although aspirin was not standard therapy for AMI until the International Study of Infarct Survival *(ISIS)-2* trial [28] results in 1988. Several angiographic trials also were done to discover the patency and recanalization rates with intravenous SK.

The efficacy of SK with regard to mortality reduction was evaluated in 4 large, placebo-controlled trials (Table 1) [28-31]. The first true mortality trial for SK [the *Gruppo Italiano per lo Studio Streptokinasi nell'Infarto Miocardico (GISSI-1)* trial]; an open label, randomized trial of 11,806 patients. In this trial 14% of patients received aspirin and only 62% received any heparin (adjunctive therapies were at the investigator's discretion). SK use resulted in 18% reduction in-hospital mortality compared with standard therapy. This benefit was time

dependent, mortality 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. The reduction in mortality was maintained at 12 months (17.2% with SK vs. 19.0% for control subjects; p=0.008). SK treatment was comparable to placebo in regards to the rate of intra-cranial hemorrhage (ICH) and other major bleeding complications (Table1) [29].

The Intravenous Streptokinase in Acute Myocardial infarction study (ISAM) [30]: a double blind randomized trial of SK vs. placebo in 1,741 patients with ST elevation AMI (STEMI), there was 11% reduction in 21-day mortality, although not of statistical significance, but in harmony with the GISSI-1 conclusions. Significantly more bleeding is seen in SK group vs. placebo group (p=0.0001) (Table1); cerebral hemorrhage occurred in 4 patients in the SK group resulting in 2 deaths. Brady and tachy-arrhythmias occurred more frequently in patient treated with SK.

The *2nd ISIS trial*; a large double blind placebo-controlled study of IV SK in patients with suspected MI, (17,187 patients enrolled up to 24 h of symptoms' onset, but the majority were enrolled within 12 h of symptoms' onset) in 417 hospitals worldwide. The study's aim was testing aspirin alone (162.5 mg/d for 1 month), SK alone (1.5 MU. 1 h), both, or neither; SK resulted in a 25% reduction in 35-day vascular mortality vs. placebo. Aspirin alone resulted in relative mortality reduction by 23%. Combination of SK and aspirin significantly reduced re-infarctions, strokes and deaths. The differences in vascular and in all-cause mortality produced by SK and by aspirin remained highly significant after 15 months of follow-up. Aspirin also reduced re-infarction rates, cardiac arrest, rupture and stroke. Again, as in GISSI-1 trail, the benefit was is time dependent; treatment within 6 h of symptoms resulted in improved survival and this benefit persisted for treatment within up to 12 h after symptom's onset. SK resulted in excess bleeding requiring transfusion and of confirmed ICH, but with fewer other strokes. Aspirin did not result in increased risk of ICH or in bleeding requiring transfusion. An excess of non-fatal re-infarction was observed in the SK only group [28].

A smaller, *South American trial (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur*); a double-blind, placebo-controlled trial of SK strictly which included patients presenting at least 6 h after but within 24 h of symptom's onset. The 35 days mortality did not differ significantly in the 3,568 studied patients, a conclusion was contradictory with the other 3 major trials (Table 1) [31].

A clear conclusion can be drawn from all the above trials in *terms of the benefits*; treatment value witnessed in the first 21 - 42 days was maintained up to 1 year. The overall benefit was perceived among patients with ST-segment elevation or bundle-branch block regardless of age, sex, blood pressure, heart rate, prior MI, or diabetic status. Into the bargain; the earlier treatment commenced the greater benefit. *In the term of risks*: SK therapy was associated with about 4/1000 extra strokes occurred within 2 days. Approximately 50% were associated with an early death, accounted for in the overall mortality reduction, 25% are moderately to severely disabled and the other 25% were not [32].

3.2 Alteplase (t-PA) Table (2)

Alteplase (t-PA), historically was the second fibrinolytic agent studied after SK in many trials. The accelerated infusion of t-PA for AMI (most common used protocol in AMI) is 15 mg IV bolus, followed by 0.75 mg/kg (up to 50 mg) IV/30 minutes, then 0.5 mg/kg (up to 35 mg) IV/60 minutes. The maximum total dose is 100 mg for patients weighing >67 kg.

The hypothesis of early reperfusion improves survival was strongly supported by the results of *GUSTO-1 trial* (41,021 AMI patients) with 30-day mortality as primary end point [33,34]. It involved 4 groups; the reference two groups both used SK, one with subcutaneous heparin and one with IV heparin. Third arm used front-loaded t-PA and IV heparin. The fourth arm: used combination fibrinolytic therapy, which involved about 2/3 of the typical doses of t-PA and SK with IV heparin. All patients received aspirin, 325 mg/d. There was significant reduction in 30 days mortality rate in the accelerated t-PA arm when compared with each of the 3 other groups. The mortality improvement was evident as early as 24 h after treatment was initiated; with t-PA treated patients having a significantly lower mortality rate, cardiogenic shock, CHF and ventricular arrhythmias [33]. Overall thrombolysis resulted in 25% relative (2% absolute) improvement in mortality rates compared with placebo. Accelerated t-PA benefit was seen in almost every subgroup: patients with anterior or inferior

MI, in all age groups. The absolute benefit was greater in higher-risk patients ICH occurred only rarely in GUSTO-1 despite the aggressive regimens of thrombolysis, aspirin, and heparin. For each of the SK arms, ICH occurred in 0.5% compared with 0.7% of patients treated with accelerated t-PA and 0.9% of patients treated with combination fibrinolytics [33].

The *TIMI-4 trial*; a double-blind trial comparing accelerated t-PA, anistreplase and their combinations, in addition to aspirin and IV heparin.60 minutes patency rate was seen in 78% with accelerated t-PA vs. 60% for anistreplase or combination fibrinolytics [35]. At 90 min, patency and TIMI grade 3 flow rates significantly better in the accelerated t-PA arm. Superior overall clinical outcomes and 1-year survival was observed with t-PA. This result was consistent with that of the GUSTO-1 trial. The *GISSI-2* and *ISIS-3* trials used the slower infusion of t-PA or duteplase and delayed sc. heparin, which did not elevate the APTT level until approximately 24 h after the start of treatment during which re-occlusion of IRA frequently occurred resulting in 3 folds higher mortality. The benefits of accelerated t-PA seen in the GUSTO-1 and TIMI-4 trials compared to the lack of benefit seen in GISSI-2 and ISIS-3 in a pooled analysis of coronary arterial patency and LV function after IV thrombolysis for AMI can be explained by the t-PA regimen used and heparin dosing. GUSTO-1 and TIMI-4 used the accelerated t-PA regimen, which begets higher rates of IRA patency and early IV heparin use enhanced late IRA patency. This link between early reperfusion i.e. TIMI grade 3 flow and improved survival was established in the GUSTO-1 angiographic sub study [27,36-39].

The attentiveness of a double bolus regimen of t-PA was derived from a series of patients to whom two 50-mg boluses of t-PA were given 30 min apart which achieved TIMI grade 3 flow in 88% of patients. [40]. *COBALT trial* (7169 patients) compared double-bolus vs. accelerated t-PA. This study was terminated early with the concern about the safety of the double-bolus regimen. 30-day mortality rates tended to be higher in the double-bolus group than in the accelerated-infusion group. The rates of hemorrhagic stroke = 1.12% after double-bolus t-PA vs. 0.81% after accelerated infusion of t-PA [41] in a later randomized trial, 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 [42]. Other studies in the term of the risks and benefits are summarized in Table 2.

3.3 Reteplase (r-PA)

The r-PA was one of the first mutant t-PA molecules which had undergone extensive clinical testing with best therapeutic efficacy resulted when r-PA was divided into two boluses (10 U/10 U) given 30 min apart (Table 3) [43].

The *INJECT* study compared the use of double-bolus r-PA to SK (Table 3). 35-day mortality rate with r-PA = 9% vs. 9.5% with SK. In-hospital stroke rates were 1.23% for r-PA vs. 1% for SK, with similar bleeding rates in the both groups (0.7% 1.0% respectively) and similar incidence of recurrent MI, but significantly fewer cases of atrial fibrillation, asystole, cardiac shock, heart failure and hypotension in the r-PA group. The study suggested that r-PA was at least equivalent to SK [44].

The *GUSTO-3 study*: a superiority trial, (15,059AMI patients within 6 h of symptom's onset), compared double-bolus r-PA with accelerated t-PA and tested whether the reported 16% increase in TIMI grade 3 flow with r-PA compared with t-PA would result into improved 30-day mortality, primary end point of 30-day mortality rates reached in 7.47% of r-PA vs. 7.24% of t-PA. The 95% CI for the absolute mortality difference of 0.23% ranged from 1.11% in favor of t-PA to 0.66% in favor of r-PA. The mortality rates were comparable when patients were sorted into subgroups by; age, infarct location, and enrolling region. There was an interaction between symptom duration and outcomes with r-PA vs. t-PA with borderline significance (p= 0.05). No significant difference in the rates of stroke, bleeding, and ICH [45].

3.4 Clinical (Mortality) Trials with Tenecteplase (TNKase) (Table 4)

TNKase: A highly fibrin specific. The TNKase conformational change reduces its elimination and prolongs its plasma half-life. Nitrates do not appear to affect TNKase levels, additionally, it is less to inhibit PAI-1 by 80 times, with more intense antiplatelet properties both in vitro and in vivo compared with those of t-PA. In experimental models the thrombolytic potency of TNKase is 3-fold higher than that of t-PA [46-49].

Several trails have evaluated TNKase for the treatment of STEMI (Table 4). *TIMI-10A trial*: 113 patients presenting within 12 hours treated with a single bolus of TNK-TPA over 5 to 10 seconds with doses ranging from 5 to 50 mg. TIMI grade 3 flow at 90 minutes in the IRA appeared to be higher with the 30- to 50-mg doses compared to lower doses with a 30 days mortality of 3.5%. Patency (TIMI grade II-III flow) of the IRA was seen 85%in overall with no differ across the full range of doses tested. Serious bleeding occurred in 6.2% at the vascular access sites. No strokes or ICH reported. Re-infarction spotted in 4.4% of patients, pulmonary edema in 2.7%. No immune reaction to TNK-TPA detected t at 30 days (Table 4) [50].

The *TIMI 10B*, 886 patients presented within 12 hours of symptoms' onset were randomized to receive either a single bolus of 30 or 50 mg TNK-t-PA or front-loaded t-PA and underwent immediate coronary angiograph, both agents result in similar TIMI grade 3 flow rates at 90 minutes (62.8% vs. 62.7%, respectively, P=NS); with lower rate for the 30-mg dose (54.3% vs. 65.8%) for the 50-mg dose. A pre-specified analysis of weight-based TNK-t-PA dosing using median TIMI frame count demonstrated a dose response (P=0.001). *In terms of risk*; dose responses for serious bleeding and ICH has been reported, but significantly lower rates were observed for both TNK-t-PA and t-PA after the heparin doses were lowered and titration of the heparin was started at 6 hours in this trial. The 50-mg dose discontinued early because of ICH and replaced by a 40-mg dose, with lower heparin doses (Table 4) [51].

In the *ASSENT-1 trial*:safety assessment was made of 3235 patients receiving either 30 or 40 or 50 mg TNKase as a bolus injection or front-loaded t-PA. At 30 days: total stroke rate =1.5% and ICH rate = 0.8% reported without significant differences between groups. Serious bleeding, requiring transfusion, occurred in 1.4% in the TNKase group vs. 7% with front-loaded t-PA [52]. Importantly, TIMI-10B and ASSENT-1 displayed the magnitude of reducing the heparin dose in conjunction with TNKase to lessen ICH risk [53].

In *ASSENT-2 trial*, an equivalence trial (16,949 patients presented within 6 hours of symptoms' onset) received either weight-adjusted TNKase over 5 to 10 seconds or front-loaded t-PA, in addition to aspirin and reduced-dose UFH with the primary end points of all-cause mortality at 30 days. No difference in mortality (6.18% vs. 6.15%) and stroke rates, including ICH was observed. Moreover, the TNKase group had fewer rates of non-cerebral bleeding major bleeding (4.68% vs. 5.94%, p = 0.0002) and blood transfusion. Female above 75 years who weighed <67 kg had less ICH. ASSENT-2 trial's results confirmed the benefits in all major subgroups regardless of age, gender, infarct location, Killip class or diabetes status. TNKase reduced the rate of CHF. In summary, ASSENT-2 trial indicated that single-bolus TNKase is equivalent to the more complex accelerated t-PA infusion, in terms of mortality and mortality/stroke combination, with decreased major bleeding rate. Such results persist after 1 year [54-56].

In the *ASSENT-3 trial*, anefficacy plus safety trial (6095 STEMI patients) treated with full-dose TNKase + UFH, full-dose TNKase + enoxaparin, or half-dose TNKase + UFH and the GPIIb-IIIa inhibitor abciximab. The study also compared enoxaparin with UFH; the primary end-point (30-day mortality plus in-hospital re-infarction and in-hospital refractory ischemia) was reduced by enoxaparin and by the combination of UFH + abciximab. Significant reduction (14.2%, p = 0.01416) was observed in the enoxaparin group and in the UFH + abciximab group; on adding the in-hospital ICH or major bleeds to the primary end-point (efficacy plus safety end-point). Higher rate of thrombocytopenia with Abciximab vs. enoxaparin and UFH (3.2% vs. 1.2% and 1.3% respectively, p = 0.0001) with higher treatment cost [57,58].

The *ENTIRE-TIMI- 23trial* [59], the design was similar to that of ASSENT-3, with the additional group receiving enoxaparin in combination with abciximab and half-dose TNKase. Enoxaparin with TNKase, compared to UFH resulted in reduction in the combined incidence of death/MI at 30 days. Abciximab did not decrease events and was associated with increased risk of major bleeding. Major bleeding increased when half-dose TNKase was combined with eptifibatide, a small-molecule GP IIB-IIIA inhibitor in the *INTEGRITI* study [60]. In conjunction with the GUSTO-V data [61], ASSENT-3, ENTIRE-TIMI-23 and INTEGRITI (see below) indicate that GP IIB-IIIA agents should not be coupled with thrombolytic drugs.

The *ASSENT-3-PLUS* study evaluated the pre-hospital phase of STEMI treatment. With electrocardiographic confirmation obtained in the field in 1639 patients treated with TNKase and randomly allocated to enoxaparin or UFH

adjunctive treatment. Enoxaparin reduced the composite of 30-day mortality or in-hospital re-infarction, or in-hospital refractory ischemia to 14.2% vs. 17.4% for UFH (P=0.080), no difference for composite end point plus in-hospital ICH or major bleeding was observed. There were reductions in in-hospital re-infarction and refractory ischemia but increases in total stroke and ICH (> 75 years) were observed in this study (Table 4) [62].

Data analysis of ASSENT-3 and ASSENT-3-PLUS trials essentially confirmed the usefulness of using enoxaparin as an alternative to UFH in combination with TNKase in reducing the primary efficacy end-point from and the primary efficacy plus safety (ICH or major bleeding) end-point. This advantage was greater in the urgent revascularization setting (15.4% vs. 10.1%, p = 0.013). The high stroke rates observed with enoxaparin (1.3% vs. 0.9%, P=NS), was mainly due to excess in ICH among women of more than 75 years old in *ASSENT-3-PLUS*[63]. In the *EXTRACT-TIMI 25 trial*, treatment with enoxaparin as additive to fibrinolysis for STEMI throughout the index hospitalization was superior to the treatment with UFH for 48 hours but on the expense of increased major bleeding episodes [64].

4. TRIALS ON OTHER FIBRINOLYTICS

4.1 Staphylokinase

Undergone limited testing in humans. In a randomized angiographic trial, 48 patients received staphylokinase (double bolus of either 10 mg or 20 mg), dose dependent TIMI grade 3 flow rate of 62% vs. 58% for 52 patients given t-PAwere observed. No excess mortality, hemorrhagic, mechanical or allergic complications were reported, however, anti-staphylokise antibodies were observed after the second week of treatment [65,66]. In conflicting study of 82 patients, a bolus and infusion dose tested (15 mg, 30 mg, or 45 mg). 90-min TIMI grade 3 flow rates showed no evidence of a dose response [67].

4.2 Urokinase

Studied in sparse clinical trials. A number of smaller angiographic trials were carried out in the 1980s [68-71]. These collectively showed angiographic patency and TIMI grade 3 flow rates that were superior to SK and similar to those observed with t-PA, particularly with higher dose (3 million units). Urokinase was tested in a trial of 2,201 patients with a dose of 2 million units of urokinase plus heparin vs. heparin alone achieved 16 days mortality rate 8% vs. 8.3% respectively [72]. An angiographic trial with saruplase (scu-PA), achieve higher 60 min patency rate vs. SK alone. Such effect was modest at 90-min. Saruplase had less bleeding complications (p<0.01) [73]. *SESAM* Study; an angiographic trial compared saruplase against 3 h of t-PA (473 patients). 60 min patency rates were similar with similar safety data [74]. Consequently *COMPASS trial*; a randomized equivalence trial compared saruplase to SK (3,089 patients randomized to 80 mg of scu-PA or 1.5 million units of SK with IV heparin in both groups) [75]. 30-day mortality rates were 5.7% for saruplase and 6.7% for SK. Significantly higher rate of ICH with scu-PA (0.9%) vs. with SK (0.3%; p=0.038), mistrust the validity of the SESAM Study [76,77].

4.3 Lanoteplase (n-PA)

Modified single-bolus agent t-PA molecule with longer half-life tested in an angiographic trial (602 patients with AMI, doses of 15-120 KU/kg), at the highest dose, the patency rate was higher with n-PA vs. accelerated t-PA. There was a trend toward higher TIMI grade 3 flow rates (57% vs. 46%, respectively). Lanoteplase was well tolerated at all doses with safety comparable to that of t- PA [77]. In a large phase-III randomized equivalence trial; The *In TIME-II*. A (15,078 patients treated with n-PA (120- KU/kg) vs. accelerated t-PA.30-day mortality was similar between the two agents (n-PA, 6.7% vs. t-PA, 6.6%; p<0.05 for equivalence). Though, n-PA resulted in higher ICH (1.13% vs. 0.62%; p<0.003) [78].

4.4 Anistreplase

The *GREAT Trial*; a randomized double-blind parallel-group clinical trial; 311 patients received anistreplase (30 UIV) either at home or in hospital. The median time saved by domiciliary thrombolysis about 130 min. after 1-year lower mortality rates were seen in patients who received anistreplase at home (10.4% vs. 21.6%, p = 0.007) [79].

Table1. Clinical trials with streptokinase (SK)

Author/year	Study	Patient included	Benefits	Risk
GISSI-1investigator [29] 1986	GISSI -1	11,806 STEMI patients/1.5 IU SK	Overall hospital mortality = 10.7% in SK recipients vs. 13% in controls, 18% RRR (p = 0.0002, 0.81).	▼Incidence major bleeds (>2 U of blood) &anaphylactic shock. Cerebrovascular events (ischemic+ Hemorrhagic episodes) in the SK & control groups:<1%)
ISAM investigator 1986 [30]	ISAM	1741 STEMI patients/1.5 IU SK	21 days mortality = 6.3 % in the SK group &7.1% in the placebo group. SK group had↑global EF (56.8 vs. 53.9 %, P<0.005)	Bleeding occurred in 5.6% in SK group vs. 1.5% in the Placebo group (p=0.0001) ICH occurs in 4 patients in SK group result in 2 deaths.
ISIS-2 investigator 1988 [28]	ISIS-2	17,187 STEMI patients	Significant▼ in 5-week vascularmortality 9.2% in SK treated pt. vs. 12.0% placebo treated patient (OR: 25% SD 4; 2p<0.00001); 9.4% vascular deaths in aspirin treated patients vs. 11.8%in placebo group (OR: 23% p<0.00001).	▲bleeds requiring transfusion (0.5% vs. 0.2%), ICH= (0.1% vs. 0.0%) in SK treated pt., but with fewer other strokes (0.6% vs. 0.8%). No ▲ in total strokes (0.7% SK vs. 0.8% placebo infusion)
EMERAS investigator 1993 [31]	EMERAS	4534 patients admitted up to 24 h after the onset of suspected AMI	No significant difference in in- hospital mortality (11.9% in SK group vs. 12.4% in controls). Patients presented 7-12 h have▼ deaths with SK (11.7% SK vs. 13.2% control). Slight difference among the 1791 patients presenting after 13-24 h (11.4% vs.10.7%)	- Significant trend for ▲ bleeding with heparin addition -No significant difference in the incidence if stoke between treatment groups

▼ =Decrease; ▲ = Increase; STEMI = ST elevation myocardial infarction, SK =streptokinase, EF= Ejection fraction, RRR=relative risk reduction, ICH =intracranial hemorrhage

Table 2. Clinical trials with alteplase (t-PA)

Author/year	Study	Patient included	Benefits	Risks
No Author listed 1993 [33]	GUSTO-1	41,021 patients with evolving MI	The mortality rates in the 4 treatment groups: SK &subcutaneous heparin, 7.2% ; SK& IV heparin, 7.4 %; accelerated t-PA & IV heparin, 6.3 %, & The combination SK &tPA with IV heparin, 7.0 %. With 14 % ▼ (95 % CI, 5.9 to 21.3 %) in mortality for accelerated t-PA vs. 2 SK - only strategies (P=0.001).	Hemorrhagic stroke=0.49 %, 0.54 %, 0.72 %, & 0.94%in the 4 grps, respectively, with significant ↑of hemorrhagic strokes for accelerated t-PA (P = 0.03)& for the combination strategy (P< 0.001 vs.SK only. ▲combined end point of death or disabling stroke in the accelerated-tPA grp. vs. SK-only grp. (6.9 % vs. 7.8 %, P = 0.006).
Cannon CP et al. 1994 [35]/USA	TIMI 4	382 patients with STEMI	IRAP atency [TIMI] grade 2-3 flow) at 60 min after the start of thrombolysis significantly ▲ inrt-PA (77.8% vs. 59.5% for APSAC-treated pts. & 59.3% for combination-treated [r-PA vs. APSAC, p = 0.02; rt-PA vs. combination, p = 0.03). At 90 min, the incidence IRA patency &TIMI grade 3 flow significantly ▲ in rt-PA (60.2% had TIMI grade 3 flow vs. 42.9% & 44.8% of APSAC- & combination; respectively [rt-PA vs. APSAC, p < 0.01; rt-PA vs. combination, p = 0.02]).	The incidence of unsatisfactory outcome = 41.3% for rt-PA vs. 49% for APSAC &53.6% for the combination (rt-PA vs. APSAC, p = 0.19; rt-PA vs. combination, p = 0.06).
No authors listed 1990 [36]	GISSI-2:	12,490 AMI pts. randomized to 4treatment gps (SK, SK +heparin, tPA alone, tPA+ heparin).	No specific differences between 2 thrombolytic agents in regards the combined end-point (tPA 23.1%; SK 22.5%; relative risk 1.04, 95% CI 0.95-1.13), nor after the addition of heparin to the aspirin treatment (heparin 22.7%, no heparin 22.9%; RR 0.99, 95% CI 0.91-1.08).	→major in-hospital cardiac complications (reinfarction, post-infarction angina). The incidence of major bleeds significantly ▲ in SK + heparin treated patients (respectively, tPA 0.5%, SK 1.0%, RR 0.57, 95% CI 0.38-0.85; hep 1.0%, no hep 0.6%, RR 1.64, 95% CI 1.09-2.45), -similar overall incidence of stroke in all groups.
No authors listed 1992 [37]	ISIS-3	41 299 AMI patients up to 24 h (median 4 h) after the onset	Randomized: SK: 1.5 MU tPA, duteplase: 0.60 MU/kg (APSAC), anistreplase: 30 U over about 3 min). No significant difference in the pre-specified endpoint of 35-day mortality (10.3%] aspirin+ heparin vs. 2189 [10.6%] aspirin alone). , slightly fewer deaths in the aspirin + heparin group (days 0-7 in hospital: 7.4% vs.7.9%; 2 p = 0.06), with a slight convergence by day 35 (598 further deaths [3.1% of survivors] vs. 556 [2.9%]).	Heparin+ aspirin was associated with ▲transfused or major non-cerebral bleeds (1.0% aspirin + heparin vs. 0.8% aspirin alone; 2p<0.01) & of definite or probable ICH (0.56% vs. 0.40%; 2p<0.05), no significant differences in total stroke (1.28% vs. 1.18%). Re-infarctions were slightly less common among those allocated aspirin plus heparin (3.16% vs. 3.47%; 2p = 0.09).
Purvis JA et al. 1994 [40] UK	Prospectiv e study	84 patients with AMI	IRA patency of TIMI flow grade 3 in 86%pts (95% [CI] 75%-93%) TIMI flow grade 2 or 3 in 91%pts (95% CI 81% to 97%). At 90 min IRA patency of TIMI flow grade 3 achieved in 88%pts(95% CI 79% to 94%)& TIMI flow grade 2 or 3 in 93%) pts (95% CI 85% - 97%).	Minor bleeding episodes reported. No cerebrovascular bleeding. - One month mortality=6 %. - Early angiographic re-occlusion=2.4% -Late reinfection=11.9%
No Author listed 1993 [41]	COBALTst udy	7169 patients with AMI	30-days mortality▲ in the double-bolus group than in the accelerated-infusion group: 7.98 % vs. 7.53%.	The respective rates of any stroke &of hemorrhagic stroke = 1.92 & 1.12 % after double-bolus t-PA vs. 1.53 & 0.81% after an accelerated infusion of t-PA (P=0.24 & P=0.23, respectively).
Bleich SD et al. 1998 [42]	multicente r, randomize d, open-label trial,	461 patients with AMI	The 90-minute angiographic patency rates = 74.5% in the double-bolus group & 81.4% in the infusion group (p = 0.08). Patency rates were comparable for the 2 groups at 60 minutes (76.8% vs. 77.5%) & 24 hrs (95.5% vs. 93.5%) after initiation of treatment.	In-hospital mortality rates = 4.5% in the bolus group & 1.3% in the infusion group (p = 0.04); 30-day mortality rates = 4.5% & 1.7%, respectively (p = NS)with comparable frequency of all other adverse events in both group.

▼ = Decrease; ▲= Increase,→ = no diference/ similar, AMI = acute myocardial infarction, IRA = infarct related artery. SK =streptokinase, t-PA = alteplase, grp = group. IV = intravenous

Table 3. Clinical trials with reteplase (r-PA)

Study	Patients, no.	Fibrinolytic agent	Benefits:Mortality at 30–35 d, %	Risks comment
INJECT trial 1995 [44]	3,004 3,006	r-PA 10 U +10 U SK. 1.5 MU	Mortality at 30–35 d, = 9.02 % Mortality at 30–35 d, = 9.53%	In-hospital stroke rates = 1.23% for rPA & 1.00% for SK. Bleeding events = 0.7% in rPA, 1.0% SK. ICH= 0.77% for r-PA&0.37% SK.
GUSTO-III 1997 [45]	10,138 4,921	r-PA 10 U + 10 U Accelerated t-PA	Mortality at 30–35 d, = 7.47% Mortality at 30–35 d, = 7.24%	Stroke rate: 1.64% of patients treated with r-PA & in 1.79 % of those treated with t-PA (P= 0.50).ICH=0.91% in r-PA group vs.0.87% in t-PA group The respective rates of the combined end point of death ornon-fatal, disabling stroke =7.89 %& 7.91 % (P=0.97; OR, 1.0; 95 %CI, 0.88 to 1.13).

Table 4. Clinical trials with tenecteplase (TNKase)

Trial (year)	Patients no.	Comparison	Benefits	Risks
Cannon CP 1997 [50] TIMI 10A	113patients STEMI presenting within 12 hrs	a single bolus of TNK-t-PA /5 - 10 seconds / 5 to 50 mg. doses	TIMI grade 3 flow at 90 minutes = 57% - 64% of pts. at the 30- 50-mg doses. Mortality at 30 days =3.5%	Serious bleeding =6.2% at a vascular access site in 6 patients & after CABG in 1 patient. There were no strokes or ICH.
TIMI 10B 1998 [51]	886patients with AMI	a single bolus 30 or 50 mg TNK-t-PAvs. 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	The 50-mg dose discontinued early because of ▲I CH &replaced by a 40-mg dose, heparin doses decreased. A prespecified analysis of weight-based TNK-t-PA dosing using median TIMI frame count showed a dose response (P=0.001). Similar dose responses observed for serious bleeding &ICH but significantly ▼rates observed for both TNK-t-PA & t-PA after the heparin doses ▼& titration of the heparin started at 6 hours.
ASSENT-1 1999 [52]	3235patients with AMI	TNKase as a bolus vs. front loaded t-PA	This is safety trail	Total stroke rate at 30 days = 1.5%. ICH rates=0.77%): (0.94%)in the 30-mg group &0.62%). the 40-mg group No strokes occurred in the 73 patients treated with 50 mg TNK-t-PA. In patients treated within 6hrsafter symptom onset the rates of ICH= 0.56% (30 mg TNK-t-PA) & 0.58 (40 mg TNK-t-PA). Death, death or nonfatal stroke, or severe bleeding complications: 6.4%, 7.4%, and 2.8%, respectively, without significant differences among treatment groups.
ASSENT-2 1999 [54]	16,949patients with AMI	TNKase vs. r-PA	-Identical covariate-adjusted 30-day mortality rates for the two groups--6.18% for TNKase= 6.15% & for t-PA. -The 95% one-sided upper boundaries of the absolute & relative differences in 30-day mortality = 0.61% &10.00%, respectively,	Similar rates of ICH= (0.93% forTNKase&0.94% for t-PA), but ▼ non-cerebral bleeding complications (26.43 vs. 28.95%, p=0.0003) &▼blood transfusion (4.25 vs. 5.49%, p=0.0002) with TNKase. Death or non-fatal stroke rate at 30 days = 7.11% withTNKase&7.04% with t-PARR; 1.01 [95% CI 0.91-1.13]).

ASSENT-3 (2001) [57,58]	6,095 AMI In Efficacy & safety trail	TNKase + Enoxvs. abciximabvs. UFHa	Significantly fewer efficacy endpoints in the Enox. & abciximab groups than in the UFH group	Significantly ▼ efficacy & safety endpoint: 280/2037 (13.7%) vs. 347/2036 (17.0%; 0.81 [0.70-0.93], p=0.0037) for Enox.&287/2016 (14.2%) vs. 347/2036 (17.0%; 0.84 [0.72-0.96], p=0.01416) for abciximab.
ENTIRE-TIMI 23 (2002) [59]	483STEMI patient	TNKase + Enoxvs. abciximabvs. UFHa	-TIMI 3 flow at 60 minutes: *52% & 48% to 51% with Enox. *48% with UFH & 47% to 58% with Enox. The rate of TIMI 3 flow among all UFH patients * 50% &51% in Enox. pts. ---30 days, death/recurrent MI in the full-dose TNK grp= 15.9% of patients with UFH &4.4% with Enox. (P=0.005). In the combination therapy grp., the rates = 6.5% with UFH &5.5% with Enox.	The rate of major hemorrhage with full-dose TNK = 2.4% with UFH &1.9% with Enox. With combination therapy= 5.2% using UFH & 8.5% with Enox.
ASSENT-3-PLUS 2003 [62]	1,639 STEMI patient	TNKase + Enoxvs. UFHa, pre-hospital delivery	▼ the composite of 30-day mortality or in-hospital re-infarction, or in-hospital refractory ischemia to 14.2% vs. 17.4% for UFH(P=0.080)	No difference for composite end point of death, in-hospital ICH or major bleeding (18.3% vs. 20.3%, P=0.30). ▼ in-hospital re-infarction (3.5% vs. 5.8%, P=0.028) & refractory ischemia (4.4% vs. 6.5%, P=0.067) ▲in total stroke (2.9% vs. 1.3%, P=0.026) &ICH (2.20% vs. 0.97%, P=0.047). The ▲ in ICH seen in patients >75 years

▼ = Decrease/less, ▲= Increase/higher, ► = Equal, PPCI = primary percutaneous coronary intervention, UFH = unfractionated heparin, F = facilitated. ICH = intracranial hemorrhage, Enox = enoxaparin

5. ANGIOGRAPHIC TRIALS

5.1 Streptokinase

Many trials were conducted to evaluate the angiographic findings after treatment with SK in STEMI patients (Table 5), these trials accomplished as soon as possible after SK administration looking for coronary artery patency (defined as TIMI grade 2 or 3 flow) [9,11,15,18,19,22,24,26,27,73,80-94]. Overall, the angiographic data suggested patency rates with SK of ≈ 44%, 48% at 60 and 90 min respectively and 72% at 2 to 3 h after beginning therapy, and a rate of 75-85% at 24 h to 21 days after therapy from a pooled meta-analysis. These rates are substantially higher than those of control patients [27] while the bleeding and other complications rates in these studies are summarized in Table 5.

5.2 Alteplase (t-PA) (Table 6)

The first comparative trial between t-PA and SK was the *TIMI-1 trial*; 290 patients had angiography after receiving either SK or t-PA, in addition to IV heparin. The primary end point; 90 min reperfusion of an initially IRA was achieved in 62% of t-PA group vs. 31% of SK group ($p < 0.001$). The patency rate at 90 min was 70% for the t-PA vs. 43% for the SK group ($p<0.001$) achieved (Table 5). There was comparable bleeding events, transfusions requirements and re-occlusion rates of the IRA between the two groups [11]. Subsequently t-PA was tested in numerous other angiographic trials [17,20,21,23,25,83,92-110] (table 6), reporting that the 3-h dosing regimen of t-PA resulted in higher patency and TIMI grade 3 flow at 60 min and 90 min. Neuhaus and colleagues [102] developed an "accelerated" 90-min dosing regimen for t-PA, which achieved higher rates of early reperfusion compared to the 3-h regimen of t-PA, anistreplase treatment or SK treatment [34,35,98,102,107-110]. The *GUSTO-1 angiographic sub study* (2,400 patients) randomized patients to angiography at 90 min, 180 min, 24 h, or 5 days. At the important, 90-min time point, t-PA-treated patients had a significantly higher patency rate and a much higher rate of TIMI grade 3 flow [33,34] and this was associated with improved survival at 24 h and at 30 days, thus stressing the benefits of rapid reperfusion [39].

5.3 Reteplase (r-PA) (Table 7)

Two angiographic trials compared t-PA with r-PA. The first, the Reteplase Angiographic Phase II International Dose-finding, *RAPID trial*, compared 3 dosing strategies for r-PAwith an infusion of alteplase (Table 7). The TIMI grade 3 flow rates at 90 min were 63% vs. 49% ($p < 0.05$) respectively. The 30-day mortality rate in the 10+10-MU group was 1.9% vs. 3.9% in the t-PA group. Similar re-infarction rates and congestive heart failure rates, 1 stroke in the r-PA groups (1/452) compared with 6 in the t-PA group (6/154). The incidence of stroke in the 10+10-MU r-PA group was less than that observed in the t-PA group ($P=0.03$) (Table 7) [111].

A second, larger trial (*RAPID-2*) compared the best regimen from RAPID with accelerated t-PA. The r-PA was superior to accelerated t-PA. When these two trials were combined, TIMI grade 3 flow rates at 90 min were 61% vs. 45% ($p<0.01$) respectively. The 16% absolute increase in TIMI grade 3 rates with r-PA over accelerated t-PA was less than the 24% increase seen with t-PA over SK in the GUSTO-1 angiographic sub-study, but this smaller difference translated into a much larger difference in mortality in the RAPID trials (3.1% for r-PA vs. 8.4% for t-PA). 35-day mortality was 4.1% for r-PA and 8.4% for t-PA (P = NS). No significant differences in bleedings requiring transfusion or hemorrhagic stroke (between the 2 groups (Table 7) [112].

5.4 Tenecteplase (TNKase) (Table 8)

Many angiographic trails evaluated TNKase [113-116]. In *CAPITAL AMI*; (170 high-risk STEMI patients) which compared TNKase alone vs. facilitated PCI. The primary end-points were: composite of death, re-infarction, recurrent unstable ischemia or stroke at 6 months. The median symptoms to needle time: 120 minutes and symptoms to balloon inflation: 204 minutes. The primary end-point was reduced by immediate PCI from 24.4% to 11.6% ($p = 0.04$). No significant differences in the rates of death or stroke between the 2 groups. Major bleeding risk was comparable; 7.1% vs. 8.1% of the TNK-alone vs. TNK-facilitated angioplasty group respectively ($p = 1.00$) (Table 8) [113].

The *WEST study*, an open-label, randomized feasibility study (304 STEMI patients) randomized to either TNKase, or to TNKase followed by PCI within 24 hours and primary

angioplasty, all patient received aspirin and enoxaparin, symptoms to randomization time: 113, 130 and 176 minutes respectively. No differences between the 3 groups in the primary composite of death or re-infarction, refractory ischemia, CHF, cardiogenic shock or major ventricular arrhythmia. Higher rate of the death/re-infarction combination in TNKase group, but not of death (Table 8). The WEST trial confirms the data from CAPTIM 9 in regards to pre-hospital thrombolysis, TNKase is very competitive with primary PCI [114].

The larger *ASSENT-4 PCI trial*; an open-label trial (1667 patients); investigated TNKase facilitation on the prognosis of patients expected to have time-delay of 1 to 3 hours before primary PCI. The primary end-point was the composite of death or CHF or shock within 90 days. The trial was interrupted by the data and safety monitoring board for an excess of in-hospital mortality in the group where primary PCI was facilitated by TNKase. A TIMI-3 flow of 43% in primary PCI/TNKase-treated patients vs. 15% in the control group (p = 0.0001). The primary end-point at 90 days was increased in the facilitated group (19% vs. 13%, p = 0.0045), along with the stroke rates (1.8% vs. 0%, p = 0.0001) (Table 8) [115].

The *GRACIA-2* study (212 patients) a non-inferiority trial compared pharmaco-invasive" approach (TNKase followed by early routine PCI within 3–12 hours) with primary PCI with primary end-points of epicardial and myocardial reperfusion and the extent of left ventricular damage evaluated by infarct size and LVEF. Electrocardiographic ST-segment resolution spotted more frequently in the TNKase group (61% vs. 43%, p = 0.01). ICH occurred in 1.0%, 0.6%, and 1.7% of patients treated with any combination, eptifibatide 180/2/180 and half-dose TNK, and TNK monotherapy, respectively. Infarct size and LVEF were similar in the two groups [116]. ASSENT-4 PCI found that TIMI grade 3 flow in the IRA before PCI, occurring either spontaneously or obtained by fibrinolysis, is associated with a higher TIMI patency after PCI, better ST resolution and a trend towards a favorable 90 days clinical outcome [117]. GRACIA-2 confirmed the WEST study results, suggesting the analogous efficacy of TNKase (with rescue/routine PCI) and primary PCI. Utmost pertinent to pathophysiology and clinical practice, is the finding of GRACIA-2 (in combination with ASSENT-4 PCI) that routine PCI after TNKase should be deferred at least 3 to 12 hours to achieve the benefit [118].

6. FIBRINOLYSIS AND ADJUNCTIVE THERAPIES

6.1 Fibrinolytics and Antiplatelet Agents

Persuasive evidence of the effectiveness of aspirin was demonstrated by the ISIS-2 trial, [29] in which the benefits of aspirin and SK were additive. The benefit of initial aspirin therapy was sustained long-term in the ISIS-2 trial. Treatment with aspirin (75-162 mg) should be continued indefinitely. The *Antiplatelet Trialists Collaboration* reported 40 further deaths, re-infarctions, or strokes prevented/1,000 patients in the first few years of sustained treatment [119,120].

Clopidogrel, a potent platelet inhibitor of thienopyridine derivative. In the *CLARITY* trial, patient's ≤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 and including the day of angiography with a maximum of 8 days (mean=3 days). By 30 days, clopidogrel reduced the odds of the composite end-point of death from cardiovascular causes, recurrent MI/ischemia, with 20% reduction for urgent revascularization. No differences inmajor bleeding and ICH in the two groups [121] (Table 9).

In the *COMMIT study,* 45 852 Chinese patients (<1000 patients aged >75 years) with MI (93% with STEMI) randomized to clopidogrel 75 mg (without loading dose) or placebo in addition to aspirin. Significant 9% (95% CI 3-14) reduction in death, re-infarction, or stroke (9.2% vs. 10.1%; p = 0.002) in favor of clopidogrel, with significant 7% proportional reduction in any death (7.5% vs. 8.1%; p = 0.03). Such benefits appeared consistent across a wide range of patients and independent of other treatments. *In terms of risk;* no significant excess risk noted with clopidogrel, either overall (0.58% vs. 0.55%; p=0.59), or in patients aged older than 70 years or in those given fibrinolytic therapy [122].

Table 5. Angiographic studies with streptokinase

Author	Time to patency	Patient no.	Strep dose MU	Door needle time	Benefits:Patency rate %	risk
Cribier et al. [15]		21	1.5	115 min	52%	----------
PRIMI study group [73]	60 min	203	1.5	140 min	48%	Less bleeding complications with rscu-PA vs.SK
Spann et al. [80]		43	1.5	60 min	49% recanalization rate	No serious bleeding
Rogers et al. [81]		16	1.0	45 min	44% recanalization rate	Bleeding requiring transfusion1/51
de Marneffe et al. [82]		10	1.5	30min	80% recanalization rate	Few bleeding events1/10
ECSG-2 ; Verstraete et al. [83]	90 min	65	1.0	156 min	55%	Bleeding & other complications; less common in the rt-PA vs. SK
Chesebro et al. [11]		159	1.5	286 min	43%	No ICH, minor bleeding only
Stack et al. [84]		216	1.5	180 min	44%	GI bleeding in 14% of patients. All over bleeding : 72%
Lopez-Sendon et al. [85]		25	1.5	<6 h	60%	----------
PRIMI study group [73]		203	1.5	140 min	64%	See above
Charbonnier et al. [86]		58	1.5	168 min	51%	Hemorrhages ; 9/58pts with APSAC (15.5 p. 100) & 13/58 treated with SK (22.4 p. 100);
Hogg et al. [87]		63	1.5	209 min	53%	----------
Hillis et al. [88]		34	1.5	60 min	32% recanalization rate	----------
Chesebro et al. (TIMI-1) [11]		119	1.5	60min	31% recanalization rate	See above
Monnier et al. [89]	2 - 3 h	11	1.5	135 min	64%	No life threating complication
Golf et al. [90]		135	1.5	138 min	70	----------
Six et al. [9]		56	1.5	150 min	60%	Blood transfusion 2%, Major bleeding; 1 patient
PRIMI study grp [73]	24hr	203	1.5	140	88%	Less bleeding in urokise compared to steptokinase
Durand et al. [19]		35	1.5	149 min	82%	----------
Lopez-Sendon et al. [85]		25	1.5	<6h	75%	----------
Hogg et al. [87]		63	1.5	209	88%	----------
Ribeiro et al. [91]		50	1.2	180 min	80%	no major bleeding events,
White et al. [24]		107	1.5	180 min	75%	Deaths with SK vs. placebo; 2.5 % vs. 12.9 %, P = 0.012).
Bassand et al. [26]		52	1.5	210 min	68%	7/55 deaths in heparin grp&4/52 deaths in SKgp.
Kennedy et al. [22]		191	1.5	210 min	69%	Bleeding, in SK group (13.1% vs. 0.6%), allergic reactions (2.1% vs.0%).
Lopez-Sendon et al. [85]		25	1.5	<6h	90%	----------
Magnani (PAIMS) [92]		85	1.5	127min	77%	ICH occurred 1/85 patient
White et al. [93]		135	1.5	150 min	75%	No ICH in the SK group
Cherng et al. 1992 [94]		63	1.5	294 min	57%	In hospital bleeding 11.1% in SK vs. t-PA 13.6%

MU=million unit. APSAC= anisoylated plasminogen streptokinase activator complex, ICH = intracranial hemorrhage, SK =streptokinase

Table 6. Alteplase (t-PA) angiographic trials

Author/year	Time-patency	Patient no.	Alteplase dose	Symptoms-needle time	Benefits; patency rate %	Risk
Topol et al. [95]	60 min	75	1.25 mg/kg/3 h	216 min	57 %	Moderate or severe bleeding: 39% of t-PAvs. 32% of placebo/intracoronary SK (p = NS).
Smalling et al. [96]		91	1.25 mg/kg/3 h	228 min	45 %	Bleeding rate were comparable in both dose protocol
de Bono [97]		183	100 mg/3 h	156 min	60 %	Non-significant ▲ in bleeding in heparin group(include (ICH)
Carney et al. [98]		138	00 mg/3 h	168 min	63 %	Similar rates of recurrent ischemia, re-infarction, angiographic re-occlusion, stroke& death) & bleeding complications
Verstraete et al. [83]	90 min	64	0.75 mg/kg/1.5h	180 min	70 %	Less common in the bleeding episodes and other complications t-PA patients than in the SK group. Hospital mortality was identical in the 2 treatment groups.
Chesebro et al. [11]		157	80 mg/3 h	287 min	70 %	No ICH, minor bleeding only
Topol et al. [95]		75	1.25 mg/kg/3 h	216 min	69 %	See above
Topol et al. [95]		142	1 mg/kg/h	190 min	72 %	See above
Johns et al. [100]		68	1 mg/kg/1.5 h	180 min	76 %	Bleeding complication occur more frequently in T PA (P =NS)
TIMI-IIA [101]		133	100 mg/6 h	168 min	75 %	
Neuhaus et al. [102]		124	70 mg/1.5 h	,<4 h	69 %	Five cardiac deaths in each group, 1 fatal ICH in the t-PA group. In-hospital re-infarction rate =8.9% vs. 13.2% for patients treated with t-PA & urokinase, respectively.
Topol et al. [103]		134	1.5 mg/kg/4 h	168 min	79 %	Bleeding complications=13% in t-PA & heparin group vs. 18% in patients treated with t-PA only (p = 0.53). The only ICH occurred in a patient initially treated without heparin.
Topol et al. [104]		50	100 mg/3 h	243 min	52 %	----------
Smalling et al. [96]		91	1.25 mg/kg/3 h	228 min	70 %	See above
Califf et al. [105]		95	100 mg/3 h	200 min	71 %	No difference in bleeding complication rates was observed with any thrombolytic regimen.
Whitlow & Bashore [106]		206	100 mg/3 h	<6 h	63 %	----------
Grines et al. [99]		107	100 mg/3 h	180 min	64 %	In-hospital mortality (6% vs. 4%) &serious bleeding similar between the two groups(12% vs. 11%)
Carney et al. [98]		138	100 mg/3 h	168 min	77 %	See above
Topol et al. [95]	2 to 3 h	75	1.25 mg/kg/3 h	216 min	79 %	See above
Guerci et al. [17]		72	80–100 mg/3 h	192 min	66 %	No fatal or ICH occurred, and episodes of bleeding requiring transfusion were observed in 7.6 %t of the placebo group and 9.8%of the t-PA group
Neuhaus et al. [102]	24hr	124	70 mg/1.5 h	<4 h	78 %	See above
TIMI-IIA [101]		128	100–150 mg/6 h	174 min	82 %	
TIMI-II [107]		1,366	100 mg	156 min	85 %	ICH%=1.9 %with 150 mg of rt-PA &0.5 %with 100 mg of t-PA
Anderson et al. [108]		164	100 mg	168 min	86 %	Mortality (APSAC 6.2%, rt-PA 7.9%) stroke, ventricular

TEAM III						tachycardia, ventricular fibrillation, heart failure within 1 month, recurrent ischemia &re-infarction were comparable in the 2 groups
de Bono [23]	3 to 21 d	367	100 mg/3 h	156 min	87 %	increased mortality in the intervention group
O'Rourke et al. [25]	-----	74	100 mg/3 h	120 min	81 %	More bleeding in the rt-PAgrp Most minor in nature
NHFA [21]		73	100 mg/3 h	195 min	70 %	
TIMI-IIA [101]		389	100–150 mg/6h	174 min	79 %	
Neuhaus et al. [102]		124	70 mg/3 h	<4 h	73 %	See above
Bassand et al. [20]		93	100 mg/3 h	172 min	76 %	
Magnani [92]		86	100 mg/3 h	124 min	81 %	ICH occurred 1/85 patient
White et al. [93]		135	100 mg/3 h	150 min	76 %	No ICH in the SK group
Rapold et al. [109]		34	100 mg/3 h	186 min	81 %	----------
Thompson et al. [110]		241	100 mg/3 h	155 min	80 %	No difference in bleeding complications
de Bono et al. [97]		652	100 mg/3 h	170 min	79 %	See above
Cherng et al. [94]		59	100 mg/3 h	312 min	77 %	In hospital bleeding 11.1% in SK vs. r-TPA 13.6%

ICH = intracranial hemorrhage, SK =streptokinase

Table 7. Retaplase (r-PA) angiographic trials

Study	Patients, no.	Fibrinolytic agent	Benefits: patency % vs. TIMI grade 3 flow at 90 min, %	Risk
RAPID [111]	146	r-PA 15 U	63 % vs. 41%	-Bleeding complications were similar between the gps -The incidence of re-occlusion was not different between the groups
	152	r-PA 10 U plus 5 U	67% vs. 46%	
	154	r-PA 10 U plus 10 U	85% vs. 63%	
RAPID II [112]	154	Alteplase 100 mg/3 h	77% vs. 49%	-35-day mortality = 4.1% for-PA & 8.4% for t-PA (P = NS. -No significant differences between r-PA & t-PA in bleedings requiring a transfusion (12.4% vs. 9.7%) or hemorrhagic stroke (1.2% vs. 1.9%).
	169	r-PA 10 U plus 10 U	83% vs. 60%	
	155	Alteplase (accelerated)	73% vs. 45%	

Table 8. Angiographic tenecteplase (TNKase) trials in AMI

Trial (year)	Patients no.	Comparison	Benefits	risk
INTEGRITI trial [60]	438	eptifibatide + ½ dosage TNK asevs. TNK asemonotherapy	TIMI-3 flow, overall patency& ST-segment resolution is similar	-More major hemorrhage (7.6% vs. 2.5%, p=0.14) &transfusions (13.4% vs. 4.2%, p=0.02). ICH=1.0%, 0.6%, & 1.7% of patients treated with any combination, eptifibatide 180/2/180 &1/2dose TNK, and TNK monotherapy, respectively.
CAPITAL-AMI [113]	170	F-PCIvs. TNKase	▼ residual ischemia with F-PCI	-No significant differences in the rates of death or stroke. -Major bleeding; 7.1% of the TNK-alone group vs. 8.1% of the TNK-facilitated angioplasty group (p = 1.00).
WEST [114]	304	TNKasevs. F-PCIcvs. PPCI	TNKase & F-PCI comparable to P-PCI	-No differences in 3 groups in the primary composite of death or reinfarction, refractory ischemia, CHF, cardiogenic shock or major ventricular arrhythmia (25% vs. 24% vs. 23%, p=NS). -In the plain TNKasegp. ▲rate of the death/re-infarction combination (13.0% vs. 6.7% vs. 4.0%, p=0.021), but not of death (4.0% vs. 1.0% vs. 1.0%, p=NS).
ASSENT-4 [115]	1,667	F-PCIvs.PPCI	----------	-Trial prematurely interrupted by the data &safety monitoring board for an excess of in-hospital mortality in the group where primary PCI facilitated by TNKase (6% vs. 3%, p=0.0105).
GRACIA-2 [116]	212	TNKase vs. PPCI	Similar infarct size (area under the curve of CK-MB: 4613 +/- 3373 vs. 4649 +/- 3632 microg/L/h, P=0.94); 6-week LVF(EF: 59.0 +/- 11.6 vs. 56.2 +/- 13.2%, P=0.11; ESVI: 27.2 +/- 12.8 vs. 29.7 +/- 13.6, P=0.21);in both groups	-Major bleeding (1.9 vs. 2.8%, P=0.99) & 6-month cumulative incidence of the clinical endpoint (10 vs. 12%, P=0.57; relative risk: 0.80; 95% confidence interval: 0.37-1.74).

▼ ---- Decrease; ▼ = Increase; ► = Equal, PPCI = primary percutaneous coronary intervention, UFH = unfractionated heparin, F = facilitated. LVF = left ventricular function, EF = ejection fraction. ESVI = endsystolic volume index

Ticagrelor an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 with more rapid onset and pronounced platelet inhibition has not adequately studied in STEMI treated with fibrinolytics. The *PLATO trail* a multicenter, double-blind, randomized trial, compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) to clopidogrel (300-to-600-mg loading dose, 75 mg daily subsequently) for the prevention of cardiovascular events in 18,624 ACS patients with or without STEMI. Ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, MI, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding [123].

Fibrinolytics and gp IIb/IIIa inhibitors were studied in many trials. Initial trials were performed with full doses of both agents (Table 9) [124,125]. *In terms of risk and benefits;* these trials consistently showed improvement in the angiographic and ECG measures of reperfusion, but with concerns of bleeding risks with this combination therapy that guided the evaluation of partial-dose fibrinolytic therapy with GP IIb/IIIa inhibition combination [126,127].

The dose-finding phase of the *TIMI-14* (677 patients). Subjects studied received partial-dose t-PA (20 mg, 35mg, 50 mg, or 65 mg) with abciximab (ABX) (0.25 mg/kg bolus/0.125 microg/kg/min infusion) or ABX with SK, 0.5, 0.75, 1.25, or 1.5 million units. Heparin 60 U/kg bolus/7 U/kg infusions. *In terms of risk and benefits:* ABX accelerates thrombolysis, with marked increases in TIMI 3 flow when combined with half dose alteplase without an increase in the risk of major bleeding. Substantial reductions in heparin dosing may reduce the risk of bleeding. Modest improvements in TIMI 3 flow can be achieved when combination of ABX and SK is used, but with increased risk of bleeding [127].

Similarly, the Strategies for Patency Enhancement in the Emergency Department study (*SPEED study*) (Table 9) randomized 304 patients to full-dose Abciximab (ABX) alone or ABX + r-PA. The preferred combination of r-PA (5 U + 5 U) with ABX compared to standard dosage (10 U + 10 U) of r-PA in 224 additional patients. In this angiographic trial, TIMI-3 flow rates at 60 to 90 min with half-dose r-PA and ABX, standard r-PA, and ABX alone were 62%, 47%, and 27%, respectively. Major bleeding rates in phase A were 3.3% for ABX alone, 5.3% for abciximab + r-PA; rates in phase B were 9.8% for ABX + r-PA 5+5 U and 3.7% for r-PA alone. The increased patency rates observed with combination therapy may further decrease mortality [126].

GUSTO-V enrolled 16,588 patients within 6 h of STEMI. Patients were randomized in a 1:1 ratio to receive standard-dose r-PA (10U + 10U,30-min apart) andheparin (5,000-U bolus followed by 1,000 U/h) or a combination of ABX (0.25 mg/kg bolus, 0.125 microg/kg/min infusion—maximum 10 microg/min) for 12 h with half-dose r-PA (5 U + 5 U, 30 min apart) with 60 U/kg (5,000 U maximum) followed by 7 U/kg/h. The primary end point of 30-day mortality is similar in both r-PA - and combination treated patients (5.9% vs. 5.6%; OR, 0.95; 95% CI, 0.83 to 1.08; p = 0.43). *In term of risks:* Similar incidence of nonfatal disabling stroke or any stroke between the two groups with double risk of ICH in patient >75 years (1.1% vs. 2.1%; p =0.069).*In terms of benefits;* Re-infarction rates (3.5% vs. 2.3%, p<0.0001) and recurrent ischemia (12.8% vs. 11.3%, p<0.0001) were significantly reduced with combination therapy. Similar 1-year all-cause mortality in the r-PA -alone and combination therapy was found (Table 9) [61,128].

The ASSENT-3 described above; showed similar rates of all stroke (1.49% vs. 1.52%) and ICH (0.94% vs. 0.93%) for combination therapy as compared to standard treatment. Total, major, and minor bleeding rates were all significantly higher with combination treatment. Major bleeding with combination therapy in the elderly was noticeably higher than with TNKase therapy alone (13.3% vs. 4.1%) [118]. Consequently GUSTO-V and ASSENT-3 findings call attention to abciximab combination with half-dose fibrinolytic has a beneficial effect on the end point of re-infarction, with no impact on short or long-term mortality.

INTRO AMI trial randomized patients to receive double-bolus eptifibatide, with 50-mg t-PA; eptifibatide, with standard, full-dose, weight-adjusted t-PA. TIMI-3 flow rates at 60 min 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 [129].

The *INTEGRITI* trial, the Integrilin and TNKase in Acute Myocardial Infarction phase II angiographic trial [60] (Table 8) enrolled 438

patients within 6 h of STEMI. The combination of eptifibatide with half-dosage TNKase and UFH selected after the dose-finding phase. TIMI-3 flow was similar (59% vs. 49%, P = 0.15), as well as overall patency (85% vs.77%, p = 0.17), and ST-segment resolution (71% vs. 61%, p = 0.08) as standard TNKase monotherapy (0.53 mg/kg). ICH risk was 0.6% with combination therapy vs. 1.7% with standard therapy. Other trial (130) on other potent antiplatelet is summarized in Table 9.

6.2 Fibrinolytics with Unfractionated (UFH) vs. Low Molecular Weight Heparin (LMWH)

Fibrinolytic in combination with anticoagulants had been tested in many trials (Table 10) [57,59,62, 131-139]. Patient receiving SK, anistreplase, or t-PA in the ISIS-3 and GISSI-2 trials [36,37] received adjunctive SC heparin or no heparin. Treatment with SC heparin 12,500 IU initiated 12 hrs. in GISSI-2 and 4 hrs. in ISIS-3. In ISIS-3, an initial mortality reduction was observed but not at one month. There was an increase in hemorrhagic stroke (0.1- 0.2%) and excess bleeding (0.3-0.5%) with heparin. A combined analysis of the two trials showed *in terms of benefits*: early mortality reduction (0.5%) with heparin during the treatment period (6% vs. 7.3%) but not at 35 days or 6 months. *In term of risk;* heparin increases the absolute major bleeding of 3.2±0.7%. Heparin (IV and SC with SK) in the GUSTO-I trial bore similar clinical outcomes of death and re-infarction (with a propensity to increased rates of bleeding and hemorrhagic stroke with IV UFH).

The evidence for use of heparin with t-PA is sounder with higher patency rate. The superiority of front-loaded t-PA with UFH over SK in the GUSTO-I trial led to widespread clinical use of the t-PA/UFH. In large trials with t-PA GUSTO-I, GUSTO-IIb, TIMI 9B, COBALT, and GUSTO-III—all utilized heparin (5,000-U bolus + 1,000 U/h). Newer t-PA derivatives have all been tested in combination with UFH; therefore, information regarding its contributory beneficial effects is not available [29,131,132].The rate if ICH in GUSTO-I trial was 0.72% [133]. Higher heparin infusion rate (higher PTT) in the GUSTO-IIA and TIMI 9-A studies resulted in a prohibitive increase in ICH that was more evident with SK (3%). Heparin dosages decreased afterwards in the TIMI-9B and GUSTO-II B trials. It is preferable to use weight-adjusted bolus heparin (aPTT: 50 –70 s) irrespective of the reaction of the thromboplastin [57]. The use of an early 3-h aPTT in TIME-II trial resulted in an observed ICH rate of 0.62%. These Data suggest 60 U/kg bolus with maintenance of 12U/kg/h is adequate with fibrin-specific agents [61], though no differences in patency rate in the combination of heparin (IV or SC) with SK vs. t-PA [127]. Patency appeared to be better with IV heparin with t- PA [128,97]. Close dose weight adjustment of IV heparin may decrease the risk of non-cerebral bleeding [57,110].

The largest trial comparing LMWH to UFH after fibrinolytic therapy completed to date was the ASSE*NT-3 trial* (standard dose of enoxaparin + TNKase for 7 days), enoxaparin reduced in-hospital re-infarction/refractory ischemia in contrast to heparin (Tables 10 and 4) [57]. Though, in the *ASSENT-3 PLUS* (n=1639) trial, pre-hospital administration of the same dose of enoxaparin showed significant increase in ICH rate in elderly patients [62]. In the large *ExTRACT trial* (Table 10) (n = 20,506), a lower dose of enoxaparin was given to patients >75 years and impaired renal function patients (estimated GFR: 30 mL/min).Significant reduction in the risk of death and re-infarction at 30 days vs. weight adjusted heparin dose on the cost of a significant increase in non-cerebral bleeding complications was observed (Tables 10 and 4) [134,135].

S*econd Trial of Heparin and Aspirin Reperfusion Therapy (HART II)* (400 patients); non-inferiority of enoxaparin versus UFH for 3 days with an accelerated t-PA and aspirin in regard to IRA patency (Table 10). The 90 minutes patency rates (TIMI flow grade II/III) of 80.1% and 75.1% respectively. Re-occlusion at 5-7 days from TIMI grade 2/3 - TIMI 0 or 1 flow and TIMI grade 3 - TIMI 0/1 flow, respectively, occurred in 5.9% and 3.1% of the enoxaparin group vs. 9.8% and 9.1% in the UFH group with similar adverse events [136].It is worthy to mention that GP IIb/IIIa antagonists were not used in this trial. Guidelines issued by the ACC and AHA for the treatment AMI at the time of this trial recommend the adjunctive use of intravenous UFH in patients undergoing reperfusion therapy with thrombolytic agents. The guidelines advocate starting UFH at the initiation of thrombolytic therapy and continuing for 48 hours, or longer for patients at high risk of systemic or venous thromboembolism [136].

In the large *OASIS-6 trial*, a low dose of fondaparinux (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 the subgroup of 1021 patients in whom concomitant heparin was felt to be indicated fondaparinux was not superior to heparin in preventing death, re-infarction, or major bleeding complications (Table 10). However, this trial has limitation; it is not proposed to have sufficient power to independently examine the impact of fondaparinux in various subgroups, it is planned to have adequate power to detect clinically outcomes founded on the overall study population. The separate analysis of the main types of reperfusion therapy (primary PCI, thrombolytic and no reperfusion) was pre-specified in statistical analysis plan [137].

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 anterior AMI of subcutaneous dalteparin. Thrombolytic therapy and aspirin were administered in 91.5% and 97.6% of patients, respectively; dalteparin significantly reduced LV thrombus formation in anterior AMI but on the expense of increased hemorrhagic risk. (Table 10) [138], one more trial (139) described in Table 10.

6.3 Fibrinolytics and Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) have endured broad evaluation in conjunction with fibrinolytic therapy. DTI 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 hirudin with thrombolysis were tested in the TIMI-5, TIMI-6, and TIMI-9, *GUSTO-IIb*, Hirudin for the Improvement of Thrombolysis-3 *(HIT-III)* and Hirudin for the Improvement of Thrombolysis-4 trials*(HIT-III).*

In *TIMI-5*, a randomized, dose-ranging of hirudin vs. heparin as adjunctive with rt-PA administered to patients with AMI. Lower rate of re-infarction was observed with hirudin vs. heparin (4.3% vs. 11.9%, p = 0.03) and less re-occlusion (1.6% vs. 6.7%, p = 0.07) [140]. In the pilot trial *TIMI-6,* (193patients)*:* high dose hirudin achieved lower death and nonfatal re-infarction after 6 weeks vs. lowest dose (5.7% vs. 17.6%) with similar incidence of major hemorrhage in heparin and hirudin dose groups At hospital discharge the occurrence of death, nonfatal re-infarction, CHF, or cardiogenic shock was greater with lowest dose of hirudin (21.6%) than in those receiving the higher doses of hirudin (dose 2 = 9.7%, dose 3 = 11.4%) [141].

In *HIT-III study*; 7000 AMI patients within 6 hours of chest pain were randomized to IV heparin or hirudin. Thetrial was stopped after increased rate of ICH observed in the hirudin group than heparin group (3.4% vs. 0 %) with stroke rate of 3.4% vs. 1.3% respectively. The safety findings from HIT-III were not strictly conclusive; the high rates of life-threatening bleeding in 3 independent trials (TIMI-9 and GUSTO-II and HIT III) with two hirudins and two different fibrinolytics gave important concern. In addition to patient selection (age, comorbidity), the combination of hirudin with fibrinolytics per se might increase the risk of bleeding by potentiating effects on lytic agent and/or hemostasis mechanisms. It may be simply an unrecognized dosing issue in phase II studies. The similar observed bleeding rates with significantly lower doses of hirudin in the HIT-III trial than in the GUSTO II and TIMI 9 trials point to a finer therapeutic range when combined with thrombolytics [142]. In HIT-4 trial: Lepirudin as adjunct to thrombolysis with SK did not significantly improve restoration of blood flow in the IRA as assessed by angiography with no increase in the risk of major bleedings with lepirudin [143].

GUSTO-IIb trial, hirudin tested in >12,000 ACS patients. Re-infarction rates were less with hirudin (5.4% vs. 6.3% for heparin, p = 0.04), with a trend toward reduction in death or MI at 30 days. In patients with STEMI, the incidence of death or MI was slightly lower with hirudin (9.9% vs. 11.3%, p = 0.13). A captivating trend toward a greater advantage of hirudin in patients treated with SK vs. t-PA, which is not observed in TIMI-9B. In the phase III, *TIMI-9B trial*, less re-infarction was noted during hospitalization (2.3% vs. 3.4%, p = 0.07), however there was no differences in the primary end point of death, MI, CHF, or shock at 30 days for hirudin vs. heparin (12.9% vs. 11.9% p = NS) [144,145].

A meta-analysis of 9,947 subjects (from 5 trails) reported a significant reduction in the end point of recurrent MI with DTI, compared to heparin therapy (2.5% vs. 3.4%), with overall mortality 4.1% vs. 3.9% respectively. No significant

reduction in the combined end point of death and recurrent MI (6.3% vs. 6.9%) [145].

In a pilot study; *Hirulog Early Reperfusion/Occlusion (HERO) trial*, double-blind, randomized angiographic trial randomized patients 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 per hour for 12 hours followed by placebo (high dose), or to heparin 5000 U bolus followed by 1000 U/h titrated to aPTT of 2-2.5 times control after 12 hours**.** Hirulog achieved higher patency rates in the culprit artery with Hirulog combined with SK and aspirin in the early phase of AMI. Serious bleeding complications were observed in 22% of patients treated with the low dose of Hirulog, 18% with the high dose of Hirulog, and 31% with heparin. Blood transfusion needed in 5% of the Hirulog-treated patients and 31% of the heparin (P<0.02). No ICH or stroke was reported [146]. The superior TIMI grade 3 flow achieved with the combination of SK and bivalirudin in the *HERO-1* study had hearten to conduct of the *HERO-2 trial*, (17,073 patients with STEMI) randomized to adjunctive therapy with heparin vs. bivalirudin following initial SK treatment. In this trial; *in terms of benefits:* No reduction in the primary 30-day mortality end point with bivalirudin (10.8% vs. 10.9%; p = 0.85). *In terms of risk:*Severe bleeding occurred in 0.7% of bivalirudin group vs. 0.5% of the heparin group (p = 0.07), and ICH occurred in 0.6% vs. 0.4%, respectively (p=0.09). Moderate and mild bleeding was significantly higher in the bivalirudin group. Transfusions needed in 1.4% in the bivalirudin group vs. 1.1% in the heparin group (p = 0.11) [147].

7. FIBRINOLYSIS AND PRIMARY PERCUTANEOUS CORONARY REVASCULARIZATION, WHICH IS BETTER? (TABLE 11)

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 11)

In an overview of 7 trials comprising 1,145 patients with STEMI treated with either primary angioplasty or thrombolysis (streptokinase or t-PA). Those undergoing PPCI had a considerable reduction in short term mortality up to 6 weeks with no long-term follow up data for mortality comparisons [148].

A review of 10 trials [149] totaling 2,606 patients included the in PAMI study [150] and GUSTO IIB cohorts was done [151]. PPCI was compared to thrombolytic therapy in which 4 trials utilized strepokinase, 3 used accelerated t-PA and 3 used standard dose t-PA. At 30-days, PPCI resulted 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 results were similar among the various 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 [151].

The Cochrane database reviewed 10 trials (2,573 patients), PPCI was associated with significant relative risk reduction in short-term mortality (RRR 32%, 95% CI 5-50%), death or re-infarction (RRR 46%, 95% CI 30-58%) and stroke (RRR 66%, 95% CI 28-84%) [152]. A subgroup analysis comparing results from the largest study, GUSTO IIB, to the pooled analysis was done. 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), established no difference in 4 years mortality [153]. Data from the second National Registry of Myocardial Infarction (NRMI-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%) and 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) [154].

Many other studies [155-176] that compare primary angioplasty with thrombolysis are summarized in (Table 11).

Table 9. Clinical trials of full-dose fibrinolytic therapy with anti-platelet; agents clopedogril, GP IIb/IIIa inhibition

Trial/year	Patients no.	Primary treatment	Benefits:TIMI 3 Flow at 90 Min, %	Risk
CLARITY-TIMI 28 [120]	3491	Clopidogrel (300-mg loading dose, followed by 75 mg once daily) or placebo+ fibrinolytic + Wt. adjusted heparin	improves the patency rate of the infarct-related artery, ▼ ischemic complications	-Similar rates of major bleeding and ICH in the two groups
COMMIT [121]	45,852	Clopedogril 75 mg+aspirin 162 mg + slandered fibrinolysis	▼ mortality and major vascular events in hospital	-No significant excess risk was noted with clopidogrel, in regards fatal, transfused, or cerebral bleeds together,
PLATO trail [122]	18,624 ACSpts. with /without ST elevation.	Ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) vs. clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter)	Ticagrelorvs. clopidogrel significantly ▼ the rate of death from vascular causes, MI, or stroke 9.8% vs. 11.7%	No ▲ in the rate of overall major bleeding but with ▲ in the rate of non-procedure-related bleeding.
INTEGRITI [60]	438	-Eptifibatide + TNK +heparin 60 U/kg bolus; 7 U/kg/h infusion -TNK alone 60 U/kg bolus; 12 U/kg/h infusion	TIMI 3 Flow/ 90 Min =62%, TIMI 3 Flow/ 90 Min =49%	-▲ Major hemorrhage (7.6% vs. 2.5%, p = 0.14) and transfusions (13.4% vs. 4.2%, p = 0.02). ICH = 1.0%, 0.6%, & 1.7% of patients treated with any combination, eptifibatide 180/2/180 & 1/2dose TNK, &TNK monotherapy, respectively.
TAMI-8 [123]	68	m7E3 +t-PA	▲angiographic patency. Less recurrent ischemia m7E3 Fab-treated patients vs. control subjects (13%vs 20%)	- 25% m7E3 Fab-treated patients vs. 50%)control patients had major bleeding
IMPACT-AMI [124]	132	Eptifibatide +t-PA	▲acute TIMI grade 3 flow &faster ECG resolution vs. t-PA	-Similar rates of the composite end point (43% versus 42% for placebo-treated patients) & severe bleeding (4% vs. 5%, respectively).
GUSTO-V [61,127]	16,588	-r-PA +heparin vs. r-PA 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	-No difference in the incidence of nonfatal disabling stroke or any stroke between 2 groups. Patient aged > 75 years receiving combination therapy, had a double ICH risk (1.1% vs. 2.1%; p =0.069
SPEED [125]	528	-Abciximab + r-PA + heparin 60 U/kg boluses -Abciximab + r-PA + heparin 40 U/kg boluses -r-PA + heparin 70 U/kg boluses	TIMI 3 Flow/ 90 Min 61% TIMI 3 Flow/ 90 Min =51% TIMI 3 Flow/ 90 Min =47%	-Major bleeding rates in phase A were 3.3% for abciximab alone & 5.3% for abciximab + r-PA 5+5 U; rates in phase B were 9.8% for abciximab + r-PA 5+5 U and 3.7% for r-PA alone. - Major bleeding was similar with standard- or low-dose heparin (6.3% vs. 10.5%, P=0.30).
TIMI-14 [126]	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%	-The SK study arm was abandoned due to unacceptable bleeding risk. -With standard t-PA treatment with no difference in the overall major bleeding rate (7%)
INTRO AMI [128]	649	-Eptifibatide + t-PA + heparin 60 U/kg bolus; 7 U/kg/h infusion -t-PA alone + heparin60 U/kg bolus; 7 U/kg/h infusion	TIMI 3 Flow/ 90 Min= 56% TIMI 3 Flow/ 90 Min= 40%	-Similar rates of major bleeding & ICH.in both groups
PARADIGM [129]	345	Lamifiban + t-PA or SK	▲ST-segment resolution vs. fibrinolytic alone	-More bleeding associated with lamifiban (transfusions in 16.1% lamifiban-treated vs. 10.3% placebo-treated patients)

▼= Decrease, ▲= Increase, ►= Equal,r-PA= reteplase, t-PA = Alteplase, SK = streptokinase

Table 10. 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	Benefits & risks
OASIS-6 trial [135]	5436	Predominantly SK	Fundapurinoxvs UFH	30-d death, in-hospital re-infarction,	-Significant ▼the risk of death, re-MI &severe bleeds
ExTRACT trial [133,134]	20506	SK or fibrin specific fibrinolysis	Enox. throughout hospitalization or UFH for at least 48 h	30-d death, in-hospital re MI, in-hospital refractory ischemia	-Significant ▼in the risk of death &re-infarction at 30 vs. weight adjusted heparin dose, but with a significant ▲ in non-cerebral bleeding complications.
ASSENT-3 PLUS [62]	1,639	Tenecteplase	Enox 30 mg IV bolus pre-hospital + 1 mg/kg sc. bid (up to 7 days) vs. UFH	30-d death, in-hospital re-infarction, in-hospital refractory ischemia	-53% of pts.to receive pre-hospital fibrinolysis within 2 hrs. of symptom onset. combination of tenecteplase + Enox ▼early ischemic events,
ENTIRE-TIMI 23 [59]	483	full or half-dose tenecteplase + abciximab	Enox30 mg IV bolus+ 1 mg/kg SC bid (up to 8 d) vs. UFH	TIMI 3 flow (60 min)	-Enox associated with similar TIMI 3 flow rates as UFH at an early time point
Baird et al. [138]	300	SK , anistreplase,or t-PA	Enox40 mg IV bolus+ 40 mg SC tid (96 h) vs. UFH	Death, reinfarction, or unstable angina readmission (30 d)	-Fewer recurrent cardiac events at 90 days. -Independent of other important clinical and therapeutic factors.
AMI-SK [131]	496	SK	Enox 30 mg IV bolus+1 mg/kg bid (3–8 d) vs. placebo	TIMI 3 flow (5–10 d)	-Triple clinical end-point of death, re-infarction & recurrent angina at 30 days ▼ with Enox 13% vs. placebo21%,P=0.03
ASSENT-3 [57]	4,075	Tenecteplase	Enox 30 mg IV bolus+ 1 mg/kg SC bid (upto 7 d) vs. UFH	30-d death, in hospital re infarction, refractory ischemia	-▼ The risk of in-hospital re-infarction or in-hospital refractory ischemia compared to heparin.
HART II [135]	400‡	t-PA	Enox 30 mg IV bolus + 1 mg/kg SC bid (3 d) vs. UFH	IRA patency (90 min)	-▲ recanalization rates & ▼ re-occlusion at 5 to 7 days -Similar frequency of adverse events in both treatment groups
BIOMACS II [130]	101	SK	Dalteparin 100 IU/kg pre SK + 120 IU/kg at 12 h vs. placebo	TIMI 3 flow (20–28 h)	-▲ rate of TIMI grade 3 flow in infarct-related artery compared to placebo, 68% vs.51% (p = 0.10). -Dalteparin had no effects on noninvasive signs of early reperfusion
FRAMI [137]	776	SK	Dalteparin 150 IU/kg bid (in hospital) vs. Placebo	LV thrombus + Arterial thromboembolism (9 d)	-Significantly ▼ LV thrombus formation in anterior AMI , ▲ hemorrhagic risk

IRA = infarct related artery, Enox = Enoxaparin, UFH; unfractionated heparin, LV ; left ventricular , ▼ = Decrease, ▲ = Increase , SK = streptokinase

Table 11. Studies comparing fibrinolysis and primary angioplasty

Author	Registry	Patient no	Mean age	Result
Yan AT et al. Canada [155]	TRANSFER-AMI trial	1200 pts. high-risk STEMI presenting to non-PCI centers.	---------	-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 an ▲ rate of death/re-MI in the high-risk group (13.8 vs. 27.8%, P=0.025)
Pipilis et al. (156) Greece	HELIOS Registry(a cohort)	PCI n=84, 9.7% & FL n=497,57.1%	61 ± 12 vs62 ± 13	In hospital mortality 3.6% In PCI group & 4.6% in FL group. MR 30 days& at 6 months = 7.2% &11.3% in PCI group &5.8% & 7.1% in FL group , respectively.
Gao RL et al. China [157]	multicenter randomized clinical trial	PCI group n=101; (r-Sk) group (n=104); & (rt-PA) group (n=106)	57.33±9.18	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 group of STEMI pts with late presentation & delayed treatments. life-threatening hemorrhage =2.9%
Itoh T et al. Japan [158]	IMPORTANT study multicenter, prospective, randomized study	101 pts. have prior-t-PA group (n=50) & PPCI group (n=51).	55.8±10.6	Patency rate & LVEF in the prior-t-PA group▲than in the P-PCI group (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 group ▼ than PPCI group (58.7% vs. 80.9%; P=0.03). The MACE-free rate in the F-PCI group = to PPCI group (73.7% vs. 80.9%; P=0.39), MACE-free rate in the prior-t-PA-alone group ▼in the PPCI group (48.1% vs. 80.9%; P=0.01)
StoltSteiger V et al. Switzerland [159]	Swiss prospective national registry data ACS in (AMIS Plus).	12 026 STEMI pts In 68 hospitals.	64 ± 13 years ,73% male	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.
Soares et al. Brazil [160]	cohort, observational, prospective	158 pts. with STEMI	60.8 years (22-89)	TT used in only 33% of cases. Death rate 21.2% vs. 2.1 in angioplasty treated pt. major bleeding =2.2%
Busk M et al. Denmark [161]	DANAMI-2 trial	1572 pts. with STEMI	63 (54–73) years	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), l re-infarction in 8.9 vs. 12.3% (P = 0.05), stroke in 3.2 vs. 4.7% (P = 0.23)
Prieto et al. Chile [162]	GEMI network, from 2001 to 2005	3,255 pts.	FL= 60 ± 11 in PCI =60 ± 13	MR in TT group= 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),
Di Mario et al. [163] France, Italy,& Poland	CARESS-in-AMI trial	600 pts. ► PPCI vs. rescue PCI 1/2-dose after FL	75 years or younger	Death, re-infarction, refractory ischemia at 30 days occurred in 4.4%,in the immediate PCI group compared 10.7% in the standard care/rescue PCI group (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).
Grajek et al. Poland [164]	WIelkopolska regional 2002 Registry (WIRE Registry)	3780 pts. with STEMI	59.1±11.6 yr. - PCI. 56.1±10,4 yr. in r-TPA gp. 65.6±11.8 l yr. SK gp.	t-PA in pts.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.
Greig et al. Chile [165]	Chilean National Registry of Acute MI	1,634 STEMI pts. 72%► FL	967 pts ,60±12 yrs, 77% Males.	Hospital MR among pts. treated with FL =10.9% & PCI= 5.6% (p =0.01),
Nallamothu B et al. [166]	GRACE a prospective, observational cohort study 106 hospitals	1786 (45.1%) pts. have FL	63 (53 to 73)	Treatment delays associated with▲6-month mortality in both FL & PPCI pts (p<0.001) with FL, 6-month MR ▲ by 0.30% per 10-min delay in door-to-needle time= 30 & 60 min compared with 0.18% per 10-min delay in door-to-balloon time between 90 & 150 min for PPCI pts.

	in 14 countries			
Widimsky et al. Czech Rep [167]	The PRAGUE-2 trial	850 STEMI pts. in non cath lab hospitals in 12 h	64 (31–86)years	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%
Kalla et al. Austria.[168]	Vienna STEMI Registry	1053 pts with acute STEMI	60.8±13.0	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.
Boersma E et al. [169]	25 randomized trials analysis testing the efficacy of PPCI vs. FL	7743 pt. / 3383 receive FL	62 (53–71)	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 (0.420.84)].
McNamara RL et al. USA [170]	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. [171]	a randomized controlled trial	47882 AMI pts.	76 (70-82)yr	30-day MR ▲ in pts.with ▲TIMI scores (TIMI score 2: 4.4% vs. TIMI score >8:35.6%, P <0.0001 for trend).
Magid DJ et al. USA [172]	Cohort study 1999 _2002.	68 439 pts. with STEMI,FL & 33 647 treated with PCI)	Age, mean (SD), y 63 ±(13)	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).
Fassa AA et al. Switzerland [173]	AMIS Plus project : prospective ACS registry	PPCI, n = 1419 FL ;n = 2833	60.2 (12.5) vs. 62.7 (12.4)	In-hospital MR▼over the study period (p , 0.001). in-hospital mortality predictors by multivariate analysis ;PPCI (OR) 0.52, 95% (CI) 0.33 to 0.81), TT (OR 0.63, 95% CI 0.47 to 0.83), and Killip class III (OR 3.61, 95% CI 2.49 to 5.24) & class IV (OR 5.97, 95% CI 3.51 to 10.17) at admission
Danchin et al. [174]	French Nationwide USIC 2000 Registry /FAST MI	1922 AMI pts.	median age, 67 yrs.; 73% men)	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
Dalby et al. [175]	meta-analysis 6 clinical trials	3750 pts.	-----	Re-infarction ▼by 68% (95% CI, 34% to 84%; P=0.001) & stroke by 56% (95% CI, _15% to 77%; P_0.015). ▼ In all-cause mortality of 19% (95% CI,=3% to 36%; P=0.08) with transfer PCI.
Sakurai k et al. [176] Japan	Registry of Miyagi Study Group for AMI (MsAMI)	3,258 AMI pts.	66.5 years	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.
Keeley et al. [179] 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	-PPCI was better than TT at:1)- ▼ 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 on long-term follow-up independent of both the type of thrombolytic agent used, and whether or not the patient was transferred for primary PTCA.

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, RT = reperfusion therapy, TT = thrombolytic therapy, IC- T = intracoronary thrombolysis, F-PCI = facilitated percutaneous coronary intervention, MR = mortality rate, ▼= Decrease, ▲= Increase , ► = Equal, pts.= patients, hrs.= hours, yr.= year, yrs.= years

8. ROLE OF PRE-HOSPITAL THROMBOLYTIC THERAPY

Acute myocardial infarction (AMI) is the prototype of a real emergency that requires efficacy and speed 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 hoards 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% to 51% and long-term mortality at 10 years [32,177]. The mortality gain is dependent on the delay time of early reperfusion, such relationship is best described as exponential: in the first 1 to 2 hours after the onset of chest pain, the benefit of thrombolysis is greater. In the last 15 years, a large number of strategies to reduce the time to reperfusion have been evaluated, including initiation of thrombolytic therapy prior to arrival to hospital. For example, 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 PPCI. 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. A large number of 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 [178]. 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 determinant in the real life for AMI. We have to deem in this study the fact than 33% of the patients had a pre hospital thrombolysis followed by a fast angioplasty. The results are impressing: 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 fall down to 2.2%. Such outcome: superior in allrecent trials published comparing on site thrombolysis to primary angioplasty (DANAM II, PRAGUE II) [161,167] and other trials [179] (Table 10). These good results in the CAPTIM study when the delay pain to treatment is less than 2 hours include also the occurrence of cardiogenic shock in favor of pre hospital thrombolysis (1.3%).

The good strategy in a next future could be the association of pre hospital thrombolysis and angioplasty. In a recent French registry (USIC 2000) [174] including all the patients arriving in coronary intensive care unit during a month and regardingone-month mortality (3.6%), this strategy seemed to be the best. TNK-t-PA is now changing the general management of pre-hospital AMI by reducing the time to treatment. This is clearly now 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. Several recent registries have shown than reperfusion offered to only half of the patients and may not offered which is unjustified in nearly half of the cases resulting in a very poor prognosis. The other major problem is that patients are treated too late mainly because the call for the emergency system too late. There are several ways to improve the time to treatment: information of the patients, shortening of the intra-hospital delays by better organization and 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.

9. FUTURE PERSPECTIVES

Thrombolytic therapy has been a foremost encroachment in the treatment of AMI, that is easy to administer compared to angioplasty. The therapeutic goal is early restoration of complete flow of IRA after the acute coronary occlusion that had great impact on the immediate and long-term morbidity and mortality. Several ways in which reperfusion rates and clinical outcomes can be improved: 1) Different dosing regimens of established agents. 2) Combinations of different agents. 3) Improved adjunctive therapy such as direct anti-thrombin agents, LMWH, or GP IIb/IIIa receptor antagonists. 4) Development of novel thrombolytic agents with enhanced fibrin specificity, resistance to native inhibitors, or prolonged half-lives allowing bolus administration. 5) Pre-hospital administration of fibrinolysis. Till the date of writing this article, the extensive developed researches include both clinical and angiographic trials with considerable patients population from different parts of the world. Most of these major trials included the early generations of non-fibrin selective fibrinolytic agent. To best of our knowledge, this is the first article, which summarizes all the clinical and angiographic trial in term of risks and benefits in detailed description.

In spite of the extensive researches, still there is missing information about the stratification of risk vs. benefit of fibrinolytics, regarding the time of administration (pre hospital administration). This target has been poorly studied. The combination of fibrinolytic therapy with newer antiplatelet agents with or without the use of newer antithrombotics may have great impact; it may increase the risk or improve the outcome of such mode of therapy.

As mentioned above the principal goal of benefits of thrombolytic (fibrinolytic) therapy is to achieve earliest reperfusion after the proper clinical diagnosis of STEMI, such aim may be compromised by many factors including: 1) when and where to administer the fibrinolytic agent. 2) The proper antiplatelet agent. 3) The target aim that the patency of the culprit vessel may be condensed by ensuing re-occlusion of the IRA which can result in loss of ventricular function that doubles the mortality rate. In addition to the risk of ICH and major bleed requiring emergency transfusion, such risk augmented with new advent of anti-platelets, anti-thrombin, patient age and associated morbidities. Physician using thrombolytic in AMI should be very meticulous in judging the risk benefit ratio and more careful patient's selection for thrombolysis, keeping in mind the absolute and relative contraindication for acute fibrinolysis. It is very sensitive decision making, giving the fact the ceiling of the time interval with aim to reduce the door - needle time as per guidelines recommendations.

Fibrinolytics are the most broadly studied drug in the history of medicine (200 000 patients) in both clinical (mortality and safety trials) and angiographic trials. It is still safe medicine in spite of the low risk of bleeding with relatively good re-canalization (up to 80%) rate specifically with the new adjuvant of platelets inhibitors. Further clinical trial needed in particular with the newer antiplatelet like third generation thienopyridine, Prasugrel and Ticagrelor which had not been tested adequately in combination with the fibrinolytics. To achieve this aim, researches are needed to administer these treatment as soon as the patient presented which is measured now as door to needle time, in fact we need to achieve shorter symptoms to needle time, to reach this aim, we need to establish proper system for diagnosis of STEMI; this can be accomplished starting from patients, family and public education. Pre-hospital administration of thrombolytics requires highly skilled staff, trained in ECG diagnosis of STMI with proper communication with cardiologist which may be possible with new electronics, keeping in mind the contraindication to use of thrombolytics. This in our opinion is the biggest challenge to optimize the potential and undiscovered benefits of thrombolytic.

Unfortunately the clinical trials are shifting to the angioplasty side probably due to the influence of industry. In spite of the emergence of the newer antiplatelet, no trial tested these with the newer fibrinolytics, though the fibrinolytics continue to be the most suitable and the mostly used way of recanalization of STEMI. It looks that fibrinolytics became part of the past from the research point of view though it is the most expanded in this field of thrombo-cardiology.

Again we think that research should directed to pre-hospital administration of thrombolytic that carries potential for higher recanalization rate in the setting of acute occlusion of coronary arteries though this carried a lot of legal and ethical challenges.

10. CONCLUSION

The management of AMI has been revolted in the last few decades with innovations in both the pharmacological and interventional field of clinical cardiology. Fibrinolytic agent considered the best easily accessible and administered pharmacologic agent keeping in mind the good patency and relative safety profile when used accurately and meticulously. Many improvements in pharmacological reperfusion appear possible. Not only a higher initial patency rates can be achieved and maintained, but the net clinical benefit resulting from successful reperfusion can probably also be increased. The "ideal" thrombolytic agent has not yet been developed. Judiciously accomplished dose-ranging studies to select the best dose for attainment of TIMI grade 3 flow with satisfactory safety profile are needed to improve the results with t-PA, together with large clinical trials to assess clinical end points and safety.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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