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REVIEW

Early Coronary Angioplasty After Thrombolysis

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KEY WORDS: *primary PCI; thrombolysis; door-to-balloon time; door-to-needle time; pharmacoinvasive strategy*

Abbreviations
PCI = percutaneous coronary intervention
STEMI = ST-elevation myocardial infarction
FMC=first medical contact

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ABSTRACT

Over the recent years it has been clearly demonstrated that reperfusion by primary coronary angioplasty in patients with ST-elevation myocardial infarction (STEMI) is the treatment of choice. For hospitals without the capacity of performing primary angioplasty, reperfusion with on-site thrombolysis or transportation of the patient to another institution for primary percutaneous coronary intervention (PCI) within a tight timeframe are the alternative options. For the latter strategy, an organized network of centers is needed to rapidly transfer STEMI patients for primary PCI. Although transferring STEMI patients for primary PCI is superior reperfusion therapy in comparison to on-site thrombolysis, there are concerns, regarding time delays of transfer in daily practice, which is a major drawback of this therapeutic strategy as delays of >120 minutes from first medical contact to primary PCI negate the advantage of primary PCI over thrombolysis.

The narrow time interval (<90-120 min) that is mandatory for the superiority of primary PCI, could be extended if a pharmacoinvasive strategy (fibrinolysis followed by routine "early" angioplasty of the culprit artery) was chosen. Convincing results from trials such as TRANSFER-AMI, FAST-MI, GRACIA-2, WEST-MI, CARESS-AMI, NORDISTEMI and STREAM indicated that combined use of thrombolysis followed by PCI after >3 hours to 6-12 hours in order to neutralize the thrombolysis associated complications of PCI and allow full action of antiplatelet and antithrombotic agents, had comparable efficacy in comparison to primary PCI regarding early and 1-year survival. This appears to be an effective alternative option for the treatment of STEMI patients, at least for those hospitals where immediate PCI is unavailable, an issue which is particularly relevant for patients suffering a STEMI on remote areas or islands.

INTRODUCTION

Over the last decade there were published the results from several trials (DANAMI-2,[1] PRAGUE-1,[2] and PRAGUE-2,[3] AIR–PAMI[4]), which compared on-site thrombolysis with primary PCI (defined as angioplasty and/or stenting without prior or concomitant fibrinolytic therapy), showed that primary percutaneous coronary intervention (PCI) is the cornerstone for effective treatment of ST-elevation myocar-

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dial infarction (STEMI) patients, when it can be performed by an experienced team. Combined data from those trials put emphasis on the superiority of primary PCI in significantly decreasing the composite endpoint of nonfatal myocardial infarction, stroke or death compared to fibrinolysis[5] along with superior effectiveness of the former in restoration of vessel patency, less re-occlusion, improved residual left ventricular function and better clinical outcome.[6]

The fact that many hospitals lack facilities for primary PCI, underlies the need for a well organized system of transport in order to safely and within acceptable time limits transfer such patients to PCI capable centers. However, optimal time limits of transfer cannot always be achieved and several trials tested the strategy of facilitated PCI. Several trials have indicated that pharmacoinvasive reperfusion before mechanical recanalization in combination with the appropriate time interval between the two therapies could be an alternative strategy for treating STEMI patients.

REPERFUSION STRATEGIES AND PRIMARY PCI DELAYS TIMES IN STEMI

Current European Society of Cardiology (ESC) guidelines[7] indicate primary PCI as the preferred pathway of treatment of STEMI patients. In PCI capable centers the aim is to achieve a delay of ≤60 min from presentation in the hospital to wire passage into the culprit artery (door to balloon delay). Patients referred to a non-PCI capable center should be transferred for primary PCI with a delay time (first medical contact -FMC to wire passage into the culprit artery) of ≤90 min while this delay should be reduced to ≤60 min in high risk patients with large anterior infarction and in early presenters (within 2 hours from symptom onset).[8] These target delays for implementation of primary PCI are quality indicators and they differ from the maximal PCI-related delay of 120 min, which is useful in selecting primary PCI over immediate thrombolysis as the preferred mode of reperfusion.[9]

In case that primary PCI cannot be performed within the aforementioned time limits, thrombolysis is the alternative reperfusion therapy within ≤30 min delay (time delay from FMC to needle).The patient can then be transferred to a PCI capable hospital in order to undergo rescue PCI in case of failed fibrinolysis, or angiography and delayed PCI if required, in case of successful fibrinolysis, in a time window of 3-24 hours. In the same wavelength, recently published guidelines of ACCF/AHA for the management of STEMI,[9] emphasize on primary PCI as the recommended method of treatment provided it can be performed within ≤90 min (from FMC-to-device time) in case that the patient is transferred directly to a PCI capable hospital, while FMC-to-device time should be ≤120 min if the patient is transferred from a non-PCI to a PCI capable hospital. In case that primary PCI cannot be performed within 120 minutes from the arrival to a non-PCI capable hospital, thrombolysis should be administered within ≤30 minutes of hospital arrival.

PCI-related time delay is the difference between the door-to-balloon minus the door-to-needle time. From randomized trials it was calculated that PCI-related time delay that can decrease the effectiveness of mechanical restoration of vessel patency over fibrinolysis varies between 60 and 110 minutes.[10,11] Pinto et al[12] calculated the mean PCI-related time delay where two reperfusion strategies appeared to have equal mortality rates and that time was found to be 114 minutes. According to Boersma and the Primary Coronary Angioplasty vs Thrombolysis (PCAT)-2 Trialists' Collaborative Group,[13] the advantage

TABLE 1. List of trials' acronyms used in the text.

1. AIR-PAMI: Air-Primary Angioplasty in Myocardial Infarction.
2. ASSENT-4 PCI: Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention.
3. CARESS-AMI: Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction
4. DANAMI: Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction.
5. FAST-AMI: French Registry on Acute ST-Elevation Myocardial Infarction.
6. FINESSE: Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention.
7. GRACIA: GRupo de Analisis de la Cardiopatia Isquemica Aguda.
8. LIMI: Limburg Interventional Myocardial Infarction.
9. NORDISTEMI: NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction.
10. NMRI: National Registry for Myocardial Infarction.
11. PRAGUE: PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis.
12. STREAM: Strategic Reperfusion Early after Myocardial infarction.
13. TRANSFER-AMI: Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction.
14. WEST: Which Early ST-elevation myocardial infarction Therapy.

of primary PCI over fibrinolytic therapy may remain with a PCI related delay of up to 120 minutes. However, this time delay varies according to age, time from symptom onset and infarct location.

TRANFERRING STEMI PATIENTS FOR PRIMARY PCI. ADVANTAGES AND DRAWBACKS

The concept of transferring patients with STEMI for primary PCI was supported by a number of trials. In the Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2),[1] 1.572 patients with STEMI were randomly assigned to on-site thrombolysis with accelerated tissue plasminogen activator or primary PCI at 24 hospitals in Denmark. Patients who were randomized to primary PCI at referral centers were transferred to one of 5 invasive centers, provided that the transfer would likely take up to 3 hours. The DANAMI-2 trial was stopped early because of an approximately 40% lower incidence of the primary end point of recurrent myocardial infarction, disabling stroke, or death at 30 days with primary PCI compared with fibrinolysis (8.5% vs 14.2%; p=0.002). This initial experience has shown that an organized network of centers could rapidly and safely transfer STEMI patients for primary PCI.

In the PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis, (PRAGUE) study,[2] the safety and feasibility of inter-hospital transfer of patients with STEMI in the Czech Republic was evaluated. A total of 300 patients were randomly assigned to three groups: group A (99 patients) received intravenous streptokinase; group B (100 patients) received streptokinase with immediate transfer to an invasive center for subsequent PCI; and group C (101 patients) was transported to an invasive center without receiving fibrinolytic therapy. Transfer was well tolerated,

TABLE 2. Occurrence of composite primary endpoint in different studies of transfer PCI, facilitated-PCI and thrombolysis followed by routine angioplasty.

	Transfer PCI			
STUDY (Number of patients)	**PCI included in initial treatment**	**PCI not included in initial treatment**	**P**	**Favours**
(DANAMI-2)[1]	8.5%	14.2%	p=0.002	PCI
(PRAGUE-1)[2]	8%	23%	p<0.02	PCI
(PRAGUE-2)[3]-All	6.8%	10.0%	p<0.12	PCI
(PRAGUE-2)[3] <3h	7.3%	7.4%	p=NS	NS
(PRAGUE-2)[3] >3h	6.0%	15.3%	p<0.02	PCI
AIR-PAMI[4]	8.4%	13.6%	p=0.33	PCI
	Facilitated PCI			
STUDY	**Primary PCI**	**Facilitated PCI**	**P**	**Favours**
ASSENT-4 PCI[18]	13%	19%	p=0.0045	Primary PCI
FINESSE[19]	10.7%	9.8%	p=0.55	NS
	Thrombolysis followed by routine angioplasty			
STUDY	**Routine PCI post thrombolysis**	**Rescue/delayed PCI**	**P**	**Favours**
TRANSFER-AMI[20]	11.0%	17.2%	p=004	Routine PCI
CARESS[24]	4.4%	10.7%	p=004	Routine PCI
NORDISTEMI[25]	6.0%	16.0%	p=0.01	Routine PCI
	Routine PCI post thrombolysis	**Primary PCI**	**P**	**Favours**
FAST-MI registry[21]	4.3%	5.0%	p=NS	NS
GRACIA-2[23]	10%	12%	p=0.57	NS
STREAM[26]	12.4%	14.3%	p=0.21	NS

with rare nonfatal complications and no deaths. The primary composite end point (re-infarction, stroke, or death at 30 days) was reduced across groups A, B, and C (23%, 15%, and 8%, respectively; p <0.02).

The following PRAGUE-2 trial[3] randomized 850 STEMI patients from community hospitals in Czech Republic to on-site fibrinolysis with streptokinase or transfer to invasive centers for primary PCI. There was a modest trend toward reduction in the primary end point of 30-day mortality with primary PCI versus streptokinase (6.8% vs 10.0%; p <0.12). Analysis of a pre-specified subgroup of patients who presented within 3 hours of symptom onset showed no mortality benefit with transfer for PCI (7.3% vs 7.4%), whereas patients who presented within 3 to 12 hours of symptom onset had a significant reduction in mortality (6.0% vs 15.3%; p <0.02). Therefore, the PRAGUE-2 results confirm the feasibility of transferring STEMI patients for primary PCI, but also suggest that transfer for primary PCI may primarily benefit patients who present late after symptom onset.

In the AIR-PAMI trial,[4] 138 STEMI patients were randomized to receive either on site thrombolysis (67 patients) or to be immediately transferred for primary PCI (71 patients). The time from arrival to treatment was delayed in the transfer group (155 vs 51 min, p <0.0001), mainly due to the initiation of transfer (43 min) and transport time (26 min). Primary PCI had a non-significant lower risk of re-infarction, disabling stroke, or death at 30 days (8.4% vs 13.6%; p=0.33).

Meta-analyses [5] of results from fibrinolysis versus primary PCI trials, included data from 5 trials (DANAMI-2, PRAGUE-1 and -2, AIR-PAMI, and the Limburg Intervention/MI trial) that compared on-site fibrinolysis with immediate transfer for primary PCI. Combined data from these trials indicate that transfer for primary PCI was associated with a significant decrease in the composite end point of nonfatal myocardial infarction, stroke, or death compared with fibrinolysis. These cumulative results underscore the concept that transferring STEMI patients for primary PCI appears to be a superior reperfusion strategy compared with on-site fibrinolysis at a non-PCI capable hospital.

However, the key point for successful reperfusion with primary PCI is short delay times in combination with a cardiac catheterization laboratory available 24 hours/7 days including experienced interventional cardiologists and supporting staff. For this purpose, not only a well organized medical system is mandatory, but also a well functioning network of centers for safe and rapid STEMI patient transportation. Short delay times for primary PCI is a task not always easy to achieve. Miedema et al[14] indicated that the greater delays from FMC at the referral hospital until arrival at the catheterization laboratory are observed when there is diagnostic dilemma, non-diagnostic ECG, hemodynamic compromise or bad weather conditions. In this particular study of 2034 patients transferred for primary PCI, only 30.4% were treated with primary PCI in ≤90 min and 65.7% in ≤120 min. Data from the National Registry for Myocardial Infarction (NRMI)[15] indicated that inter-hospital transfer from a non-PCI to a PCI-capable hospital is associated with low rates of door-to-balloon within time limits (4.2% for door-to-balloon <90 min, 16.2% for door-to-balloon <2 h).

In addition, Wang et al[16] indicated that STEMI patients requiring inter-hospital transfer for primary PCI had longer door-to-balloon times in comparison with direct arrival STEMI patients (median 149 min vs 79 min p<0.001) and few received PCI at ≤90 min (10% vs 63% p<0.001). Pinto et al[17] in an analysis from NRMI-2,-3,-4 and 5, reported that PCI-related delays are extensive among patients transferred for primary PCI and are associated with poorer outcomes. When transfer delays for primary PCI exceeded 120 min from FMC, there was no advantage of primary PCI over thrombolysis. As delays of >120 min and >90 min occurred in nearly half and in 68% of the patients respectively, there was no difference in mortality (5.7% vs 6.1%), in the composite end-point of death or myocardial infarction (6.7% vs 8.6%) and death, myocardial infarction or stroke (7.1% vs 9.3%).

THROMBOLYSIS FOLLOWED BY ROUTINE ANGIOPLASTY

From the aforementioned data, it is clear that time to treatment with primary PCI is an important determinant of the clinical outcome of STEMI patients. Thus, inter-hospital transfer to a PCI capable hospital is the strategy of choice under the premise that primary PCI can be performed within 120 min from FMC. Fibrinolytic therapy should be administered in the absence of contraindications, if the goal of less than 120 min delay cannot be achieved. The term *facilitated* PCI was used to describe a combined therapy of full- or half-dose fibrinolysis in order to maximize the initial reperfusion rate and immediate transfer for PCI within 90-120 min. However, the Assesment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT) -4 PCI[18] and Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE)[19] trials failed to show clinical benefit over primary PCI in STEMI patients, thus this strategy should be avoided. Failure of facilitated PCI may at least have been accounted for by thrombolysis-induced platelet activation, intra-plaque hemorrhage of the culprit lesion and increased bleeding risk with resulting propensity for acute complications during PCI. As discussed below, these shortcomings of facilitated PCI can be overcome by performing immediate PCI only in patients with failed thrombolysis, i.e., for rescue purposes, while delaying PCI in successfully thrombolysed patients.

The term *pharamacoinvasive* strategy is used to describe the administration of thrombolysis, either in a pre-hospital setting (ambulance) or at a non-PCI capable hospital, followed by the immediate transfer for early PCI. Ideal patients for receiving

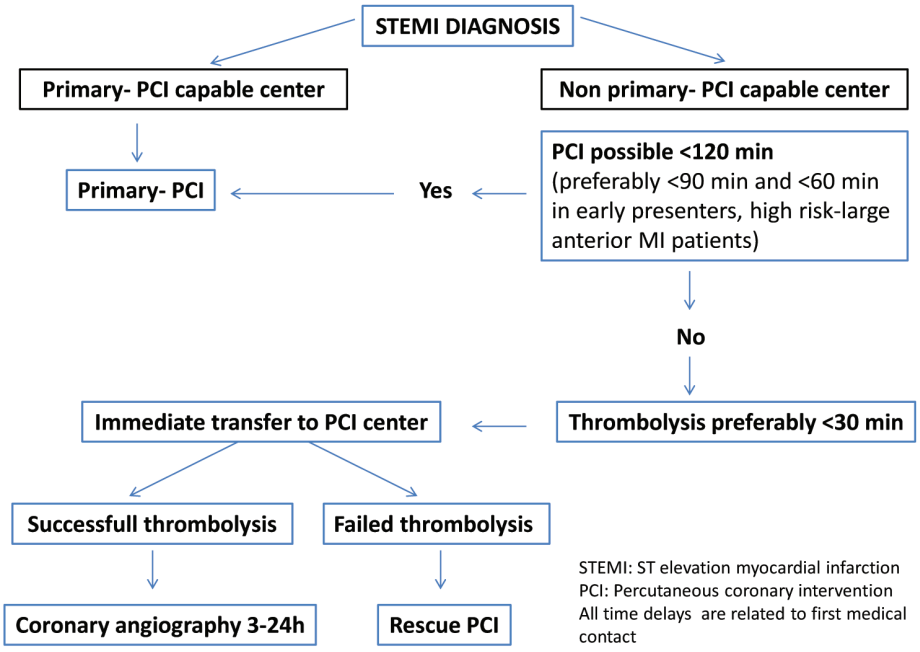

FIGURE 1. Flowchart of suggested reperfusion strategies in STEMI patients.

fibrinolysis as initial therapy, are early presenters (<2-3h from symptoms onset) with low bleeding risk and prolonged time delay to PCI. In order to achieve beneficial effect of primary-PCI over thrombolysis, PCI-related time might be extended if pharmaconvasive treatment with fibrinolysis, followed by routine angioplasty during the following hours, is selected. Results from several trials such as TRANSFER-AMI, FAST-MI, GRACIA-2, WEST-MI, CARESS-AMI, NORDSTEMI and STREAM are rather convincing because of overall consistency in their results.

In the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction trial (TRANSFER-AMI) trial,[20] 1.059 high-risk patients who had a STEMI and who were receiving fibrinolytic therapy at centers that did not have the capability of performing PCI, were randomized to either standard treatment (including rescue PCI, if required, or delayed angiography) or a strategy of immediate transfer to another hospital and PCI within 6 hours after fibrinolysis. All patients received aspirin, tenecteplase and heparin or enoxaparin; concomitant clopidogrel was recommended. The primary end-point was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days. PCI was performed in 67.4% of the patients assigned to standard treatment a median of 21.9 hours after randomization and in 84.9% of the patients assigned to routine early PCI a median of 3.9 hours after administration of tenecteplase. At 30 days, the primary end point occurred in 11.0% of the patients who were assigned to routine early PCI and in 17.2% of the patients assigned to standard treatment (relative risk with early PCI, 0.64; 95% confidence interval, 0.47 to 0.87; p = 0.004). There were no significant differences between the groups in the incidence of major bleeding.

The findings described in the TRANSFER-AMI confirmed the almost one year ago earlier published results of the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI)[21] registry, a report of daily practice of STEMI treatment in France. The purpose of the study was to assess contemporary outcomes in STEMI patients, with specific emphasis on comparing a pharmacoinvasive strategy (thrombolysis followed by routine angiography) with primary PCI. Of the thrombolysis group 96% underwent subsequent angiography, with 84% undergoing PCI (58% within 24 hours of receiving thrombolysis). In the thrombolysis cohort the mean time interval from lysis to PCI was 290 minutes and in the primary PCI group 300 min. In-hospital mortality was 5.0% in patients with primary PCI and 4.3% in those with thrombolysis. One-year survival was 94% for thrombolysis and 93% for primary PCI. Thus, when used early after the onset of symptoms, a pharmacoinvasive strategy that combined thrombolysis with a liberal use of PCI yielded early and 1-year survival rates that were comparable to those of primary PCI. Finally, when analyzed according to the timing of PCI after thrombolysis (according to quartiles of time delay from thrombolysis to PCI), 30-day mortality was 4.1% in the first and second quartiles (time from lysis to PCI=220 minutes) vs 3.6% in the third and fourth quartiles. Notably, mortality tended to be lower with increasing time from thrombolysis when PCI was performed on a systematic

basis, whereas it tended to increase with increasing time from thrombolysis when PCI was performed as a rescue procedure.

The Which Early ST-elevation myocardial infarction Therapy (WEST)[22] trial demonstrated that thrombolytic therapy followed by systematic PCI within 24 hours yielded results comparable to those of primary PCI. In the GRupo de Analisis de la Cardiopatia Isquemica Aguda (GRACIA)-2 trial[23] a total of 212 STEMI patients were randomized to full tenecteplase followed by stenting within 3–12 hours of randomization (early routine post-fibrinolysis angioplasty; 104 patients), or to undergo primary stenting with abciximab within 3 hours of randomization (primary angioplasty; 108 patients). The primary endpoints were epicardial and myocardial reperfusion (i.e., TIMI 3 epicardial flow and resolution of the initial sum of ST-segment elevation >70%) as well as the extent of left ventricular myocardial damage, as determined by means of the infarct size and the 6-week left ventricular function. Early routine post-fibrinolysis angioplasty resulted in higher frequency (21 vs. 6%, P=0.003) of complete epicardial and myocardial reperfusion following angioplasty. Both groups were similar regarding infarct size (area under the curve of CK-MB: 4613±3373 vs 4649±3632 mg/L/h, P=0.94); 6-week left ventricular function (ejection fraction: 59.0±11.6 vs. 56.2±13.2%, P=0.11; end-systolic volume index: 27.2±12.8 vs. 29.7±13.6, P=0.21); major bleeding (1.9 vs 2.8%, P=0.99) and 6-month cumulative incidence of the primary endpoint (10% vs 12%, P=0.57; relative risk: 0.80; 95% confidence interval: 0.37–1.74).

The results of the Combined Abciximab REteplase Stent Study (CARESS) trial[24] confirmed that a policy of systematic PCI after thrombolysis was superior to a policy of PCI restricted to cases needing rescue based on symptoms and lack of resolution of ST elevation. In this trial the primary outcome (a composite of death, re-infarction, or refractory ischemia) at 30 days, occurred in 13 patients (4.4%) in the immediate PCI group compared with 32 (10.7%) in the standard care/rescue PCI group (hazard ratio 0·40; 95% CI 0.21–0.76, log rank p=0.004) and the time interval between thrombolysis and PCI was 135 minutes.

In the NORDSTEMI[25] trial (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction), a total of 266 patients with acute STEMI with more than 90-min transfer delays to PCI were treated with tenecteplase, aspirin, enoxaparin and clopidogrel and randomized to immediate transfer for PCI or to standard management in the local hospitals with early transfer, only if indicated for rescue or ischemia-driven PCI. The median time from fibrinolysis to PCI was 163 min (2.7 hours) in the early invasive group. The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the conservative group (6% vs 16%, hazard ratio: 0.36, 95% confidence interval: 0.16 to 0.81, p=0.01).

Very recently, in the Strategic Reperfusion Early after Myocardial infarction (STREAM) trial,[26] 1892 patients with STEMI who presented within 3 hours from symptom onset and in whom primary PCI could not be performed within 60 minutes, were randomized to undergo either primary PCI or fibrinolytic therapy with tenecteplase, clopidogrel and enoxaparin before transportation to a PCI-capable hospital. Angiography was performed 6-24 hours after randomization unless fibrinolysis failed and emergency coronary angiography was performed as soon as possible. The primary endpoint was a composite of death, shock, congestive heart failure, or re-infarction up to 30 days. The primary endpoint occurred in 12.4% of fibrinolysis patients and in 14.3% in the primary PCI group (relative risk in the fibrinolysis group 0.86; 95% CI 0.68-1.09 p=0.21). Emergency coronary angiography was performed in 36.3% of patients after thrombolysis. The rest of the patients from the thrombolysis group underwent angiography within 17 hours after randomization. Rates of intracranial hemorrhage were higher in the thrombolysis group (1% vs 0.2% p=0.04), while rates of non-intracranial bleeding were similar in the two groups. The results of this trial indicated that pre-hospital or early thrombolysis followed by coronary angiography in patients with STEMI who could not undergo primary PCI within 1 hour from first medical contact, has similar efficacy in comparison with primary PCI. However, fibrinolysis was related with a slight increase in the risk of intracranial bleeding.

Finally it is now clearly established that in the pharmacoinvasive strategy of treating STEMI patients, the time window between fibrinolysis and PCI is crucial regarding the efficacy of such a strategy as longer delay is associated with reduced risk of bleeding and better outcome. The narrow time window between facilitated fibrinolysis and immediate PCI (90 min in ASSENT and 104 min in FINESSE) seems to have had a negative impact on hemorrhagic events, while results are better according to aforementioned trials if PCI is performed later after initial fibrinolysis, i.e., within a time-frame of a >3 and up to 24 hour timing at amelioration of the pro-hemorrhagic and pro-thrombotic effects of thrombolysis.

CONCLUSION

Primary PCI is the established method for treatment of STEMI patients, however there are some drawbacks regarding the achievement of strict time limits for this task. Combined pharmacoinvasive strategy in an appropriate time window could be an efficient therapeutic option especially for hospitals that lack facilities for primary PCI.

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