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PCI in Post Thrombolysis Stable STEMI Patients: A Timeline in Question

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Abstract

ST elevation myocardial infarction (STEMI) occupies a significant portion of the cardiovascular disease spectrum and poses a continuing challenge on the health care delivery system worldwide. A dilemma exists in the clinical triage system for appropriate strategic modalities of treatment, based on underlying triad of patient-hospital-cardiac pathological factors as well as cut off time-lines. Current European Society of Cardiology (ESC) guideline recommends percutaneous coronary intervention (PCI) within 3 to 24 hours in post thrombolysis stable patients. This review critically evaluated the evidences underlying the ESC recommendation. Trials included in this review are SIAM III, GRACIA 1, CAPITAL-AMI, CARESS-IN-AMI, NORDISTEMI, PRAGUE-1, WEST and LEIPZIG. Most of the evidences support the notion for immediate post thrombolysis PCI in stable patients within 1.9 to 2.7 hours, which contradicts the ESC timeline of up to 24 hours. Also, there is a reduced generalizability of the trial results due to differences in the design of the various trials, study population, composite endpoints, variations in drug dose & formulation, co-administration of pharmacotherapies and type of stents used. This warrants further research for standardization & optimization of the treatment protocol with respect to post thrombolysis PCI in stable STEMI patients.

Keywords

ST-Elevation Myocardial Infarction (STEMI), Percutaneous Coronary Intervention (PCI), Thrombolysis, European Society of Cardiology (ESC) Guideline

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1. Introduction

Acute coronary syndrome (ACS) is an umbrella term for a constellation of clinical symptoms and categoric manifestation of various stages of coronary atherosclerosis including unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) [1] [2]. ACS is a major contributor in cardiovascular disease (CVD) spectrum and is the leading cause of death worldwide for both developed and developing countries [3]. In the United States, every 43 seconds someone suffers from a myocardial infarction (MI) and in every minute someone dies from it [3]. It is postulated that by 2030, about 40.5% of the US population will suffer from some form of CVD (especially ACS) with about 61% increase in total health care cost [4]. On a global scale, ACS is responsible for 50% of all CVD related deaths [5]. According to a study done in the US in 2009, about 24% - 40% of all acute MI admissions were due to STEMI & rest due to NSTEMI [6].

STEMI is the deadliest among the three presentations of ACS. It is caused by sudden total occlusion of coronary arteries resulting in myocardial necrosis evidenced by raised cardiac biomarkers and ECG changes (ST elevation, Q wave) with substantial risk of death and disability. In the US only, every year there are about 250,000 cases of STEMI, of which about 30% fail to receive any therapy [7]. Among those who receive Percutaneous Coronary Intervention (PCI), only 40% are treated within first 90 minutes of symptom onset and those treated with thrombolysis/fibrinolysis, only less than 50% are done within timeframe (door to needle) of 30 minutes [7]. Further it has been found that mortality in patients with STEMI increases for each 30 minutes without proper intervention [7]. Some studies found that the incidence of STEMI is in a decreasing trend, but a significant portion (12%) of patients is still dying within 6 months of post diagnosis [8]. A study has projected that timely treatment of patients with STEMI reduced the in-hospital mortality from 11.2% to 9.4% [9]. Current treatment guideline emphasizes on early invasive therapy through optimized revascularization or thrombolytic therapy coupled with aggressive management based on evidence provided by randomized controlled trials. This justifies the continuous research and updates in treatment guidelines based on research findings. However, due to non uniform nature in the conduction of various trials, different outcome measures, and difference in the interpretation pose a challenge in the clinical significance and implication of various trial reports and hence the treatment. This paper focuses on the role and timing of post-thrombolytic stable patients based on the ESC guidelines [10].

2. Pathophysiology & Management of STEMI

Relentless and repeated progression of coronary artery plaque formation through phases of endothelial dysfunction, chemotactic inflammatory changes, foam cell and fatty streak formation results in the development of coronary atheroma and atherosclerosis [1] [11]. A fine balance exists between plaque stability and vulnerability factors. A slight shift in balance favors plaque rupture with resultant thrombus formation at site of rupture, propensity for complete occlusion and hence STEMI (as shown in **Figure 1**).

Diagnosis of STEMI is done mostly based on clinical history, changes in ECG and cardiac enzymes. It is a medical emergency and needs urgent in-hospital care consisting of standard medical care, thrombolysis and revascularization. Medical management and thrombolysis focuses on symptomatic treatment as well as plaque stabilization, prevention of progression of subsequent future events. But revascularization by either PCI or coronary artery bypass grafting (CABG) aims to re-establish coronary artery flow leading to improvement of ischemia and its manifestations [12]. The Urgency of the treatment is based on various pathologic changes in the myocardium following STEMI, which is illustrated in **Figure 2**.

Strategic modality of treatment and choice of therapy following STEMI is an intricate and fine balance between patient stability, contraindications, critical period of presentation, delay in the onset of management, presence of optimal network of PCI capable hospitals with efficient triage system and 24-hour cardiac catheterization lab with skilled staffs. Usually primary PCI is the gold standard and most preferred reperfusion intervention if performed within 90 to 120 minutes of symptom onset as shown by various trials and meta-analysis [8] [13]-[15]. But in cases where PCI cannot be performed within the critical time or there is lack of access to PCI capable hospital or contraindication to PCI, fibrinolysis is the modality of reperfusion [8] [15] [16] (**Figure 3**). However, irrespective of time, primary PCI is the dominant reperfusion strategy in Europe as opposed to fibrinolysis and fibrinolysis is done only in 6% to 8% of STEMI patients in European countries [17]-[19]. Both procedures have certain complications as depicted in **Figure 4** with significant excess risk of stroke, cerebral and non-cerebral hemorrhage with fibrinolytics [8]. Hence due to various contraindications, associated complications

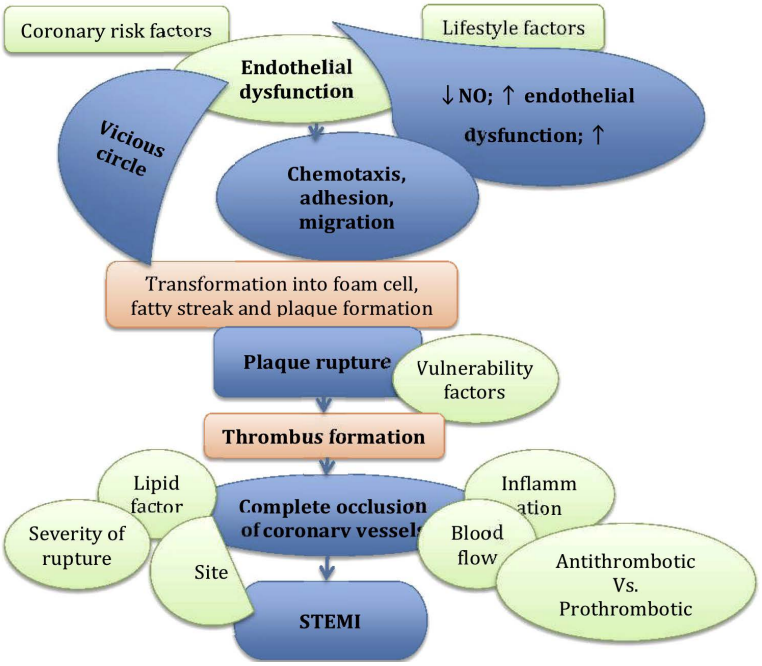

Figure 1. Pathophysiology of STEMI. NO, nitric oxide; ↑, increase; ↓, decrease. Various coronary risk factors and modifiable and non-modifiable life style factors results in endothelial dysfunction, which in turn through various sequential stages results in plaque formation. A continued vicious cycle between these two is translated into plaque rupture and thrombus formation with ultimate complete blockage of coronary vessels resulting in STEMI. The symptomatic manifestation of STEMI depends on various factors including site of obstruction, inflammation, patient factors, etc.

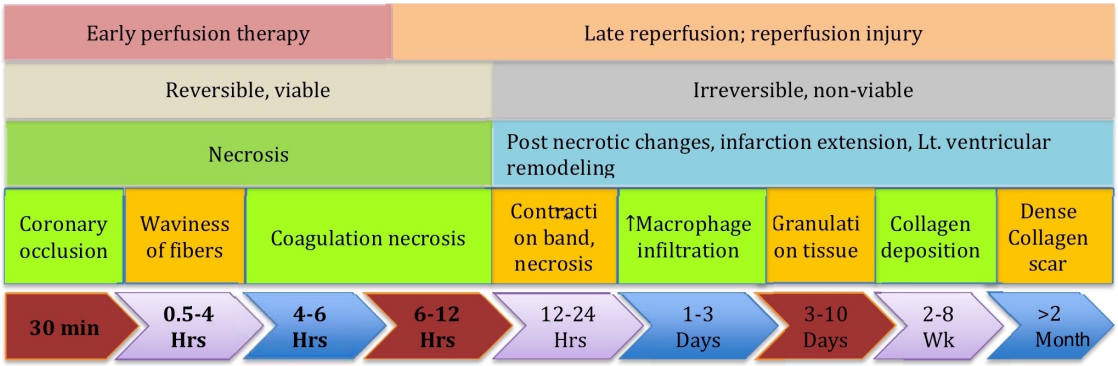

Figure 2. Timeline for myocardial changes in STEMI.

and limited effectiveness, various guidelines postulate the use of fibrinolysis as an adjuvant to PCI with PCI being performed either immediately or following watchful waiting in patients who develop LV dysfunction or severe ischemia.

3. The ESC Guidelines on Revascularization

The ESC guidelines for revascularization in 2014 recommend immediate post thrombolysis PCI within 3 to 24 hour of thrombolysis in stable patients rather than watchful waiting. However, question remains about the need of PCI in post thrombolysis stable patients and also the cut off timelines in doing so. This paper will critically review the evidences and actual objectives of different trial, which underlies the ESC recommendations in terms: 1) role of PCI in post thrombolysis stable patients and 2) timing of PCI in post thrombolysis stable patients.

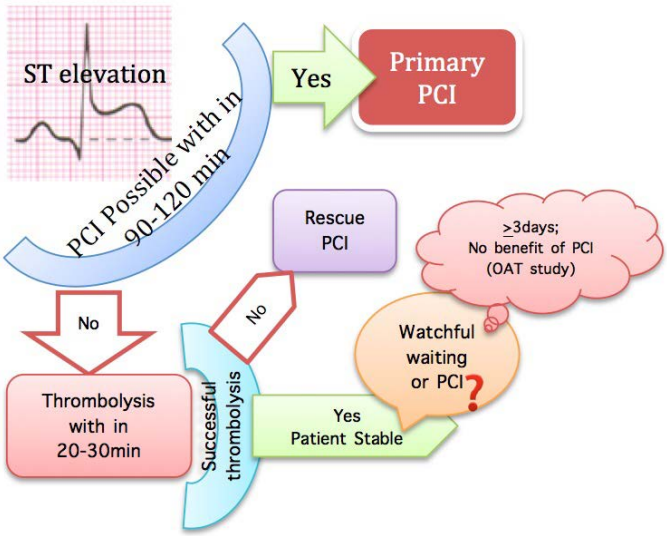

Figure 3. Management of STEMI.

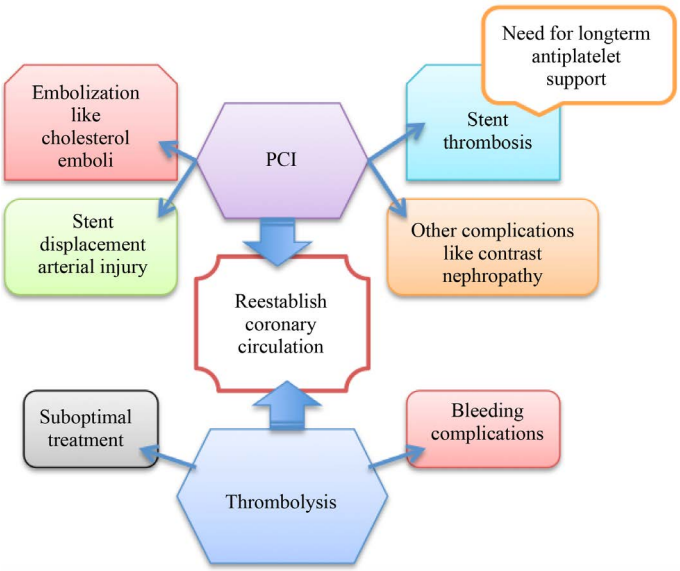

Figure 4. Complication following revascularization.

4. Review of Evidences

4.1. Role of PCI in Post Thrombolysis Stable Patients

ESC guideline regarding post thrombolytic PCI is based on several trials and meta-analyses done comparing immediate angioplasty with rescue angioplasty. One of the earliest trials looking at the association was SIAM III done on 197 patients with AMI where one group received angioplasty within six hours of thrombolysis with reteplase and the other after two weeks. It was found that the immediate stenting group had a significant decrease in primary endpoint of ischemic event, death, reinfarction and need for revascularization by 25% [20]. GRACIA 1 is another randomized intent to treat trial, which compared combined endpoints of death, reinfarction and revascularization at 12 months. 500 low to moderate risk STEMI patients were randomly assigned to immediate angioplasty within 6 to 24 hours post thrombolysis group and ischemia guided approach group [21]. PCI was done in 80% of the intervention group compared to 21% of conservative group. Though there was no difference in the incidence of cardiac events at 30 days but at one year there was significant decrease of primary endpoint

in 60% of intervention group [21].

The CAPITAL-AMI trial, which occurred immediately after GRACIA 1 trial looked at high-risk STEMI patients presenting ≤6 hours after onset of symptoms and thrombolysed with tenecteplase. Similar composite endpoints were compared between full dose of tenecteplase facilitated PCI group (within 3 hours) and tenecteplase alone group at 1 & 6 months respectively [22]. Unscheduled PCI was required for 53.7% of tenecteplase group at 6 months. There was a significant reduction of primary endpoints at 1 and 6 months in facilitated PCI group.

In keeping with preceding trials, another intent to treat trial called CARESS-IN-AMI was done in high risk patients treated with half-dose reteplase and abciximab [23]. The hazard of the primary outcome of composite death, reinfarction and ischemia at 30 days was lower (HR 0.40; 95% CI 021 - 070) in patients in immediate PCI group compared to rescue PCI group. Another trial looking at similar endpoints at 30 days as the above mentioned trials, found that in tenecteplase treated high risk group patients with STEMI, the risk of primary endpoints was significantly lower in immediate PCI group compared to rescue. PCI was performed in a median of 2.8 hours in intervention group compared to 32.5 hours in standard treatment [24]. In contrary to the above trials, the NORDISTEMI trial which looked at patients living at very far transfer distance to PCI, found no significant difference (P = 0.19) between immediate PCI and conservative treatment groups with respect to similar primary endpoints including stroke at 1 year [25].

The ESC guideline is also based on 4 meta-analyses. One of the first meta-analysis done by Collet *et al*. in 2006, looked at difference in composite endpoints of death or reinfarction between early PCI and ischemia guided PCI group [26]. Most of early PCI was done within 2 to 3 hours of fibrinolysis compared to an average of 26 to 30 days in rescue PCI group. Though there was no difference in mortality (P = 0.64) between the two groups, but there was significant of 2 folds (P = 0.0006) decrease in reinfarction in early PCI group in stent era.

Another systematic review of NORDSTEMI, TRANSFER-AMI, CARESS-IN-AMI, WEST, CAPITAL-AMI, LEIPZIG, GRACIA-1, SIAM III and PRAGUE-1 compared the primary endpoints of death, recurrent non-fatal MI, recurrent ischemia, stroke and major bleeding in period ranging from 1 to 12 months [27]. In most of the trials PCI was performed within 1 to 3.5 hours of fibrinolysis except two trials (13.2 & 16.7 hours). Among the 9 trials, 2 used half dose of fibrinolysis with most trials using tenecteplase. There was a significant reduction in risk of reinfarction, recurrent ischemia and mortality in the immediate PCI group compared to the conservative group. There was no difference in risk of stroke or major bleeding between the two groups. A meta-analysis done by F. Borgia *et al*. on 7 of the 9 above mentioned trials found that early PCI significantly reduce rates of reinfarction (P = 0.003) and combined endpoints of death, reinfarction & recurrent ischemia (P < 0.001) at 30 days follow up with persistent of result at 6 months (P = 0.01) and 1 year follow up [28]. Similar findings were replicated at 30 days for another meta-analysis done by S.P. D'souza *et al*. on 8 of the above-mentioned trials [29].

4.2. Timing of PCI in Post Thrombolysis Stable Patient

According to OAT study, which looked at 4 years cumulative risk of death, reinfarction or heart failure, there was no reduction in risk when PCI was done in stable patients 3 to 28 days post MI compared to medical management [30]. Following this trial and based on many subsequent trials, ESC guideline recommends immediate PCI within 3 - 24 hours of thrombolysis. However, there is a difference in timing at when various trials that underlie the ESC guideline, performed post thrombolysis PCI. For most of the trials including NORDSTEMI, CARESS-IN-AMI, TRANSFER-AMI, CAPITAL-AMI, LEIPZIG, SIAM III and PRAGUE-1, PCI was performed within a median of 1.9 to 2.7 hours post thrombolysis with the exception of WEST & GRACIA-1 trials where the median was 13.2 & 16.7 hours respectively. As such, in majority of the trials the minimum time period was less than 3 hours and for none of the trials it was more than 17 hours with only two trials between the time periods of 3 to 24 hours. Hence, based on only two trials done within the timeframe, it is very difficult to interpolate the results of the trials to a beneficial effect within 3 to 24 hours. Further well-designed studies with larger sample size are needed to be done based on this timeframe of 3 to 24 hours for better generalization of the results.

5. Discussion

Various evidences put forth by the different trials and meta-analyses; do support the notion that immediate post thrombolytic PCI has a better prognostic values related to reinfarction or recurrent ischemia compared to

watchful waiting. However, on careful analysis of the evidences provided it becomes evident that there are certain differences between how the trials are designed and conducted, which reduces the generalizability of the trials. All of the trials looked at primary endpoint as a composite of mortality, reinfarction and recurrent ischemia and hence might not have enough power to look at each individual outcome. Again the cutoff point for diagnosis of various outcome also varied between the trials, like reinfarction was diagnosed at serum CK >2 times (CAPITAL AMI) versus >3 times upper normal limit (SIAM III) which might create a misclassification of the primary outcome and bias the trial results. The outcomes were evaluated at different time points as 1 month versus 6 months versus 1 year, which reduces the comparability of effect. The timing, dosage and thrombolytic agent also varied among the trials. The timing of thrombolysis varied between 2 hours (NORDISTEMI) to 6 hours (CAPITAL AMI) to <12 hours (SIAM III, CARESS-IN-AMI, GRACIA-1) post symptoms. Two of the trials including CARESS-IN-AMI used half dose of thrombolytic. There was also a variation in type of thrombolytics used. Some of the earlier trials included both stenting era and balloon era which being of different efficacies might bias the result obtained. There is also variation in the use as well as type, dose, frequency and timing of co-administered pharmacotherapies including aspirin, clopidogrel, abciximab, ticlopidine, etc. For most of the trials the time between thrombolysis and PCI varied between 1.9 to 2.7 hours with only two trials at 13.2 and 16.7 hours respectively. Thus, on one hand there was very few trials supporting the 3 to 24 hour time duration as mentioned in the ESC guideline and on the other hand there was no cut off time for maximum benefit. On a different note, the median age of the study participants of all the trials ranged between 57 to 65 years with around 80% being males. As such the result from this trial cannot be generalized to younger age groups or females or people with comorbidities other than those looked at. Also, due to higher rates of rescue PCI in the watchful waiting group along with intent to treat analysis, there might have been a dilution of the overall effect with chance of lesser difference between the groups in case less rescue PCI. Last but not least some of the trials like CAPITAL AMI, CARESS-IN-AMI looked at high risk groups compared to others which looked at relatively stable patients. As such there is a need for careful weighting of evidences for and against immediate post thrombolytic PCI before generalizing them as treatment guideline.

Though in this paper we tried to evaluate all the trials and meta-analyses underlying the ESC recommendation, however there might be other related trials, which were beyond the scope of this paper. Thus, there is a need for more studies to correctly characterize the role and timeline of PCI in post thrombolysis stable patients.

6. Conclusion

Though current evidences show a potential for beneficial role of post thrombolytic PCI compared to watchful waiting in STEMI patients, there is a need for further research to be done in this field. Larger trial with broader inclusion criteria and follow-up is needed to correctly signify the benefits and determining the critical time interval for maximum effect.

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