MANAGEMENT OF ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION IN THE ED: STATE-OF-THE-ART ANTI-PLATELET AND ANTI-THROMBOTIC THERAPY

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OBJECTIVES:
1. Participants should understand the ACC/AHA guidelines for the treatment of ST-segment elevation myocardial infarction (STEMI).
2. Participants should understand the clinical trial evidence and rationale behind aspirin and clopidogrel use in the treatment of STEMI.
3. Participants should understand the clinical trial data supporting the use of enoxaparin in STEMI.
4. Participants should understand the clinical trial data supporting the early use of glycoprotein IIb/IIIa inhibitors upstream in the ED, prior to primary percutaneous intervention in STEMI.

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) remains one of the most important disease entities treated by emergency physicians. When minutes count, and time is muscle, emergency physicians can have a crucial impact on patient morbidity and mortality by providing appropriate therapy in a time-efficient manner. The recently published American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the treatment of STEMI outline the recommendations for the emergency department (ED) management of STEMI, including anti-ischemic, anti-thrombotic, and fibrinolytic versus catheter-based reperfusion therapy (Table 1). These guidelines were promulgated in an effort to standardize and optimize the evaluation, diagnosis, and management of patients with STEMI and to provide physicians with a framework for clinical decision-making. They have become the cornerstone of many ED protocols for the treatment of STEMI which are crucial to providing efficient care in the ED and seamless transition for our patients to the cardiac cardiac catheterization laboratory or coronary care unit (CCU). Within a few months after the ACC/AHA STEMI Guidelines publication, however, new clinical trials data were released and published which added significantly to our knowledge of the treatment of STEMI, confirmed some of the STEMI Guidelines recommendations, and provided valuable adjuncts to giving optimal care for STEMI in the emergency setting, beyond the Guidelines recommendations. Specifically, new clinical trials data support the use of clopidogrel, enoxaparin, and earlier administration of GP IIb/IIIa inhibitor therapy in the management of STEMI. Whether or not these new developments will be adopted into the next version of the Guidelines, or into routine clinical care, remains to be seen. The intent of this paper is to critically review some of these recent clinical trials involving anti-platelet agent and anti-thrombin use in STEMI.

Anti-platelet Therapy in STEMI
The pathophysiology of STEMI is
initiated by the endothelial rupture of an atherosclerotic coronary artery plaque. Plaque rupture leads to platelet aggregation, platelet activation, fibrin deposition, and downstream myocardial ischemia and necrosis after complete coronary artery occlusion. Anti-platelet agents, including aspirin and glycoprotein IIb/IIIa receptor blockers (GPI) have all been investigated in this group of patients in large multicenter clinical trials, and these therapies have been incorporated as Class I recommendations in the ACC/AHA Guidelines. Specifically, aspirin 325 mg p.o. is indicated at patient presentation regardless of the reperfusion strategy, while GPIs are indicated in the cardiac catheterization laboratory as an adjunct to primary percutaneous intervention (PCI) as a reperfusion strategy.

**Clopidogrel in STEMI: Results of the CLARITY and COMMIT Trials**

Clopidogrel is an oral anti-platelet agent that binds to platelets at the P2Y12 site, and inhibits platelet activation through the ADP-mediated pathway. The ACC/AHA Guidelines for Non-ST-segment elevation ACS recommend that clopidogrel 300 mg p.o. loading dose, and 75 mg per day, be given at patient presentation and continued for at least a month and then up to a year post discharge from the hospital. The 2004 ACC/AHA STEMI Guideline recommendations do not, however, include clopidogrel therapy. The recently completed CLARITY trial investigated the effectiveness of a 300 mg loading dose of clopidogrel, in conjunction with fibrinolytic therapy, in the treatment of STEMI. The CLARITY trial randomized 3491 STEMI patients to clopidogrel 300 mg load, and 75 mg per day versus placebo, initiated in the ED. The primary outcome of death, MI, and target vessel occlusion at angiography was reduced 36% (p=0.00000036) in the clopidogrel group ([Figure 1](#)), offset by only a 0.3% increase in bleeding. Death, MI and recurrent ischemia at 30 days were reduced 20% with clopidogrel (p=0.026). In the patients who went on to PCI after their initial fibrinolytic therapy, there was a 46% reduction in death, MI, and stroke in the patients treated with clopidogrel (p=0.008). These results were further supported by the COMMIT trial, which randomized almost 46,000 STEMI patients (recruited in Asia) who were treated with fibrinolytics or medical management, to 75 mg qd (no loading dose) of clopidogrel versus placebo. In the COMMIT trial, clopidogrel was associated with a 9% relative reduction in death, recurrent MI, and stroke (p=0.002) ([Figure 2](#)). The results of CLARITY and COMMIT are so strikingly supportive of the use of clopidogrel in the ED management of STEMI, with minimal side effects, that many practitioners have already added clopidogrel to their STEMI protocols.

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**AHA/ACC Guidelines Class I recommended ED pharmacologic and reperfusion therapy in STEMI.**

- Targeted ED Protocol and Collaboration
- O2, IV, monitor
- Aspirin immediately (162-325 mg)
- Nitrates, beta blockers (IV)
- Heparin weight based dosing (60 U IV bolus and 12 U/kg/hour infusion; maximum 4000 U total bolus/1000 U infusion)
- Fibrinolytics in less than 30 minutes (esp if chest pain <3 hours)
- PCI less than 90 minutes if available
- Treatment of Complications

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Plaque rupture leads to platelet aggregation, platelet activation, fibrin deposition, and downstream myocardial ischemia and necrosis after complete coronary artery occlusion.
Enoxaparin versus Unfractionated Heparin in STEMI

The ACC/AHA STEMI Guidelines recommend the administration of unfractionated heparin in the ED, either in conjunction with fibrinolytic therapy or in preparation for primary PCI. These same guidelines give enoxaparin a IIb recommendation as a substitute for heparin in conjunction with fibrinolytic therapy, in the absence of renal failure or age greater than 75 years. The recently presented EXTRACT TIMI-25 trial compared enoxaparin (30mg IVP, and 1 mg/kg given subcutaneously) to unfractionated heparin (weight based dosing) in 20,478 patients treated with a variety of fibrinolytics for STEMI.\(^5\) The trial was a double-blind, double-dummy design, carried out mostly in Europe. The primary outcome of death and MI at 30 days was reduced 17% (p<0.0001) in patients treated with enoxaparin versus heparin (Figure 3). Bleeding was increased 2% in the enoxaparin treated patients, but the intracranial hemorrhage rate was not significantly different. The new dosing strategy of enoxaparin 0.75 mg subcutaneously in patients greater than 75 years old eliminated an increased risk of intracranial hemorrhage compared to heparin in that population.

The results of the EXTRACT TIMI-25 PCI cohort were presented at the European Society of Cardiology in September, 2006.\(^6\) This subset analysis of EXTRACT analyzed PCI outcomes in 4676 EXTRACT patients who underwent PCI for a variety of indications in the 30 days post fibrinolytic therapy. In the enoxaparin treated patients, the primary outcome of death and MI at 30 days was reduced 23% (p<0.001), with no increase in bleeding. Ischemic strokes were seen three times more often in the heparin treated patients.
patients (p=0.006). The results were consistent in those patients treated early in their hospitalization, on blinded study drug through treatment with PCI. It appears from EXTRACT that enoxaparin is preferable to unfractionated heparin in STEMI patients treated with fibrinolytic therapy, even if it is followed by PCI.

Facilitated PCI
The ACC/AHA STEMI Guidelines give a Class I recommendation to primary PCI as a reperfusion strategy, as long as it can be accomplished expeditiously (<90 minutes door to balloon time) by experienced operators in high volume centers.1 Facilitated primary PCI, which involves the administration of pharmacologic reperfusion therapy prior to planned primary PCI, has been advocated as a method of enhancing the ease of primary PCI and/or preserving myocardial function while awaiting primary PCI. Half-dose fibrinolytics, full-dose fibrinolytics, or GPIs have all been used for facilitated PCI with variable results, mostly in small studies, subanalyses, or single-center reports.7-11 This approach of pre-PCI reperfusion therapy is of special interest to emergency physicians, who often find themselves feeling rather helpless, watching a patient infarct while awaiting activation of the cardiac catheterization laboratory for primary PCI or requiring transfer to a distant hospital offering PCI capability. The use of full-dose fibrinolytics for facilitated PCI has recently come under scrutiny with the results of the ASSENT 4 trial, which had to be prematurely terminated due to an increased in-hospital mortality (p=0.01) and an increased incidence of strokes in patients treated with full-dose TNK prior to primary PCI.10 Fibrinolytic therapy prior to PCI also resulted in the increased ischemic complications of reinfarction and revascularization. Routine use of fibrinolytics prior to immediate PCI is presently being discouraged.

Early GPI Use in STEMI: The ED versus the Cardiac Catheterization Laboratory
Glycoprotein IIb/IIIa receptor blockers have been given a Class I recommendation for use as an adjunct to primary PCI in STEMI, based on a number of clinical trials, and years of experience.1 Utilization of GPIs in the ED, prior to planned primary PCI, has been less well investigated, despite data demonstrating fairly potent “fibrinolytic” activity with GPI therapy.11 A recent meta-analysis of 931 STEMI patients randomized to ED versus cardiac catheterization laboratory administration of abciximab prior to primary PCI demonstrated improved TIMI-2 or TIMI-3 flow in the infarct related artery with ED administration (OR 1.69, 95% CI 1.28-1.22, p<0.001).12 Cutlip et al, in a single-center trial, showed that the early administration of eptifibatide was associated with a similar 43.4% increase in TIMI 2/3 flow at the time of primary PCI.13 Finally, this strategy was more rigorously evaluated in the TITAN TIMI 34 trial, in which 343 patients were randomized to eptifibatide in the ED versus cardiac catheterization laboratory.14 ED administration of eptifibatide was associated with higher TIMI-2/3 flow (p=0.08), greater levels of myocardial tissue perfusion (p=0.026), and higher full angiographic perfusion (p=0.059), with no significant increase in bleeding. [Figure 4]. Early administration of GPIs in the ED, while awaiting cardiac catheterization laboratory activation and primary PCI, appears to be a viable, effective, and safe alternative to providing no therapy for STEMI. Larger trials are needed to demonstrate more clinically significant benefits on mortality or morbidity with ED GPI administration in STEMI.
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SUMMARY

The CLARITY, COMMIT, EXTRACT, and TITAN TIMI-34 trials are only four examples of the many recent clinical trials involving the care of patients with STEMI. It is important for clinicians to understand the data from these studies, as well as the potential clinical implications, to optimize care for these patients presenting with STEMI.

REFERENCES


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