OBJECTIVES:
1. Participants should be familiar with the 2007 Focused Update on STEMI and its relationship to the 2004 ACC/AHA guidelines for the treatment of ST-segment elevation MI (STEMI).
2. Participants should understand the clinical decision making factors needed to determine the optimum reperfusion therapy in STEMI.
3. Participants should understand the recent clinical trial evidence and rationale behind the use of clopidogrel, enoxaparin, and bivalirudin in the treatment of STEMI.
4. Participants should understand the concept of facilitated PCI, and the clinical trial data supporting its recommendations in the treatment of STEMI.

INTRODUCTION
ST-segment elevation myocardial infarction (STEMI) remains one of the most important disease states for emergency physicians. When minutes count, and time is muscle, we have the opportunity to make a crucial impact on morbidity and mortality by applying appropriate therapy in a very time-efficient manner. The 2004 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, antithrombotic, and fibrinolytic versus catheter-based reperfusion therapy.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 transitions for our patients to the catheterization lab or CCU. However, within a few months of the ACC/AHA STEMI Guidelines publication, new clinical trials data were released and published which added significantly to our knowledge of the treatment of STEMI, confirmed some of the STEMI Guideline recommendations, and provided valuable adjuncts to “cutting edge care” of STEMI, beyond the Guidelines. These clinical trial results were incorporated in the recommendations included in the Focused Update for STEMI, which was published in December, 20072 [Table 1]. This focused update is meant to be a supplement or addendum to the 2004 Guidelines. It lists specific changes in the recommendations of 2004 that are changed based on new clinical trial data. Specifically, new clinical trials data support the use of clopidogrel, enoxaparin, and bivalirudin in STEMI, while downgrading the use of facilitated percutaneous coronary intervention (PCI).
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. Downstream necrosis is time dependent, with a wavefront of necrosis developing from the subendocardium and extending to the epicardium (transmural) with time. The longer the period of necrosis, the higher the chance of CHF and death. For every 30 minutes of duration of ischemia, mortality increases 8-10%. Reperfusion therapy, with dissolution or removal of the intracoronary thrombosis, provides the best chance for mortality reduction. The focused update gives primary PCI a Class IA recommendation for reperfusion, as long as it can be accomplished with a first medical contact to balloon inflation time of 90 minutes or less. Fibrinolysis, which is less effective than PCI in head-to-head trials, is given a Class IB rating as an alternative to primary PCI, as long as PCI cannot be accomplished within 90 minutes.

There is a distinct gray zone, however, for patients in whom the choice must be made between timely fibrinolysis versus “minimally delayed” primary PCI. This decision is often made in the context of an interhospital transfer. The emergency physician must decide between fibrinolysis within 30 minutes followed by transfer, versus transfer for PCI, knowing that the chances of a door to balloon time of 90 minutes are remote. In NRMI, the percentage of patients meeting the 90 minute window with a transfer from one hospital to another was less than 4%. Factors which preclude “waiting for PCI” include young age, anterior MI, and early (<3 hrs of pain) presentation. Factors which make delayed
PCI the preferred strategy include contraindications to fibrinolysis, cardiogenic shock, advanced age, inferior MI, and delayed presentation.\(^5\) It is clear, from the data, that a “one size fits all” approach may not be adequate, especially if delays to primary PCI are substantial (>120 minutes).

**Antiplatelet Therapy in STEMI**

Antiplatelet agents, including aspirin and glycoprotein IIb/IIIa receptor blockers (GPIs) 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.\(^1,2\) Specifically, aspirin 325 mg po is indicated at patient presentation regardless of the reperfusion strategy, while GPIs are indicated in the catheterization laboratory as an adjunct to primary PCI as a reperfusion strategy.

**Clopidogrel in STEMI**

Clopidogrel is an oral antiplatelet agent that binds to platelets at the P2Y\(_{12}\) site, and inhibits platelet activation through the ADP-mediated pathway. The focused update gives clopidogrel 75 mg daily a Class IA recommendation for STEMI. The 300 mg load is recommended with fibrinolysis (IIaC) and the 600 mg load is recommended for primary PCI.\(^6\) 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.\(^7\) 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, offset by only a 0.3\% increase in bleeding [Figure 1]. 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 40,000 STEMI patients (recruited in Asia) who were treated with fibrinolytics or medical management, to 75 mg per day (no loading dose) of clopidogrel versus placebo.\(^8\) In the COMMIT trial, clopidogrel was associated with a 9\% relative reduction in death, recurrent MI, and stroke (\(p=0.002\)). Clopidogrel should be added to the STEMI treatment algorithms in your ED if it has not been already.

---

**Figure 1. Primary Results of the CLARITY Trial: Reduction in Death, MI, and Occluded Infarct Related Artery with Clopidogrel and Fibrinolytic Therapy Initiated in the ED**

Antithrombins in STEMI

The focused update for STEMI recommends the administration of an antithrombin as an adjunct to reperfusion therapy, initiated in the ED, either in conjunction with fibrinolytic therapy or in preparation for primary PCI. The focused update gives unfractionated heparin an IC recommendation, and enoxaparin an IA recommendation. The recently presented EXTRACT TIMI 25 trial compared enoxaparin (30mg IVP, and 1 mg/kg) to unfractionated heparin (weight based dosing) in 20,478 patients treated with a variety of fibrinolytics for STEMI. 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 2). 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/kg subcutaneous in patients greater than 75 years old eliminated any increased risk of intracranial hemorrhage.

The utilization of bivalirudin for primary PCI in the cath lab may not have significant effects on the ED treatment of STEMI patients prior to primary PCI.

Facilitated PCI

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, sub-analyses, or single-center reports. 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 cath lab for primary PCI. The focused update significantly downgrades the concept of facilitated PCI.
Figure 2. Results of the EXTRACT TIMI 25 Trial: Comparison of Enoxaparin to UFH, In Conjunction With Fibrinolytic Therapy, In STEMI

Figure 3. Results From the HORIZONS Trial: No Difference in Ischemic Endpoints But a 40% Reduction in Bleeding in Patients Treated With Bivalirudin During Primary PCI

Primary Outcome Measures (ITT)

- Heparin + GPIIb/IIIa inhibitor (N=1802)
- Bivalirudin monotherapy (N=1800)

- **Net adverse clinical events**
  - Diff = -2.9% [-4.9, -0.8]
  - RR = 0.76 [0.63, 0.920]
  - P_NI ≤ 0.0001
  - P_SUP = 0.006

- **Major bleeding**
  - Diff = -3.3% [-5.0, -1.6]
  - RR = 0.60 [0.46, 0.77]
  - P_NI ≤ 0.0001
  - P_SUP = 0.0001

- **MACE**
  - Diff = 0.0% [-1.6, 1.5]
  - RR = 0.99 [0.76, 1.30]
  - P_SUP = 1.00

7.2% of Bivalirudin group received a GPIIb/IIIa inhibitor in cath lab

*Not related to CABG

**MACE = All cause death, reinfarction, ischemic target-vessel revascularization or stroke
PCI in the treatment of STEMI. 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-t-PA prior to primary PCI. Fibrinolytic therapy prior to PCI also resulted in an increase in ischemic complications of reinfarction and revascularization. Routine use of full dose fibrinolytics prior to immediate PCI is presently being discouraged. The use of half-dose fibrinolytics or GPIs in facilitated PCI is still given a IIbC recommendation, however, in patients with low bleeding risk, or when the time to primary PCI may be delayed (as with an interhospital transfer). Larger trials are needed, however, to demonstrate more clinically significant benefits on mortality or morbidity with ED GPI administration in STEMI.

A recent investigation brings into question this Class III rating for facilitated PCI between full dose fibrinolytics and PCI in patients undergoing interhospital transfer. In the recently presented TRANSFER AMI trial, patients with STEMI were treated with fibrinolysis at smaller, referral hospitals, and then transferred to a tertiary care hospital with PCI capabilities. Half of the patients were taken to PCI immediately after transfer (average 2 hours post fibrinolysis) and half were admitted and underwent PCI within 48 hours. The patients who were treated immediately with PCI (so-called facilitated PCI) had a 46% reduction in the combined outcome of death, reinfarction, refractory ischemia, and stroke compared to the standard of care arm (Figure 4). Bleeding rates were not significantly higher in the facilitated PCI group either. It appears that waiting as little as 2 hours after fibrinolysis may reduce the risk of facilitated PCI, and make interhospital transfers for PCI after fibrinolysis a viable strategy.

**Figure 4. Results From the TRANSFER AMI Trial: Reduction In Combined Outcome In Patients Treated With Fibrinolysis, Followed by Interhospital Transfer to Immediate PCI**

<table>
<thead>
<tr>
<th>TRANSFER-AMI: Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary End Point: 30-Day Composite</strong> (death, reinfarction, recurrent ischemia, CHF, shock)</td>
</tr>
<tr>
<td>Standard treatment</td>
</tr>
<tr>
<td>% of Patients</td>
</tr>
<tr>
<td>16.6</td>
</tr>
</tbody>
</table>

Cantor WJ. Presented at: American College of Cardiology 2008 Scientific Sessions/i2 Summit-SCAI Annual Meeting; March 30, 2008; Chicago, IL.
SUMMARY

The CLARITY, COMMIT, EXTRACT, HORIZONS, and TRANSFER MI trials are only five examples of the many recent clinical trials involving the care of patients with STEMI. Like many past clinical trials, these recent trials answer some clinical questions, but raise others. They must be interpreted in the light of our practice, with emphasis on their applicability to ED practice. Lessons from these trials may change our practice, or strengthen the data behind our practice patterns. Emergency physicians must remain vigilant to the results of these and other trials, to keep up-to-date and provide cutting edge care for STEMI patients.

REFERENCES


