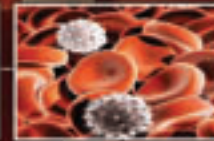


Emergency

CARDIOVASCULAR & NEUROVASCULAR EMERGENCIES

Advancing the Standard
of Care



JANUARY 2010

EMCREG-International Monograph
from the 2009 Satellite Symposium
in Boston, Massachusetts
on October 6, 2009

Produced by



ADVANCING THE STANDARD OF CARE: Cardiovascular and Neurovascular Emergencies

EMCREG-International Monograph
from the 2009 Satellite Symposium
in Boston, Massachusetts
on October 6, 2009

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Dear Colleagues:

The Emergency Medicine Cardiac Research and Education Group (EMCREG) – International is pleased to present this monograph serving as the proceedings from our satellite symposium held on October 6, 2009 at the EMCREG-International 2009 Satellite Symposium in Boston, Massachusetts. The faculty who presented at our symposium have prepared these pieces which cover topics of significant interest to clinicians caring for patients presenting emergently with cardiovascular and neurovascular diseases. This material can also be located at our www.emcreg.org web site in both downloadable hardcopy and web cast formats.

All content is solely the work of the contributing author. A number of important topics are covered in this monograph including ST-segment elevation myocardial infarction (STEMI), STEMI systems of care, novel anti-platelet agents, acute decompensated heart failure (ADHF), and the medical-legal aspects of the diagnosis and treatment of stroke.

Patients presenting with chest pain to the emergency department (ED) remain a major clinical challenge. In the United States alone, there are over 5 million annual visits to EDs for this problem, resulting in two million hospital admissions for acute coronary syndromes (ACS). The ACS literature continues to rapidly evolve and the understanding of the current guidelines for treatment and care of these patients is essential. The publication of the 2007 Guidelines for STEMI makes it extremely important for emergency physicians to be current with new recommendations for anti-thrombotic, anti-platelet, and fibrinolytic therapy for STEMI. The AHA Mission Lifeline initiative for developing a STEMI Regional System of Care will also be discussed.

The presence of heart failure is at epidemic proportions. Emergency physicians deliver acute therapy to the majority of patients hospitalized with acute heart failure. Improved survival from myocardial infarction, an aging population, and hospital overcrowding have also resulted in an increased ED burden of acute heart failure syndrome patients. Optimal diagnosis and treatment for this disease process will be discussed based on the 2009 Focused Update on Heart Failure.

The need to rapidly evaluate acute ischemic stroke patients will become critical as awareness of the role of acute therapy increases and the patient population ages, regardless of any ongoing controversy surrounding fibrinolysis. It is incumbent upon the emergency physician to be aware of all available tools which can help in their evaluation and treatment. A better understanding of the medical-legal aspects of caring for acute stroke will help emergency physicians decrease the likelihood of having adverse legal experiences in caring for these patients through improving care.

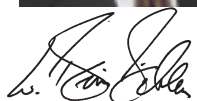
For those interested in obtaining Category 1 CME credit for reading this monograph, CME questions are available at the end of the document. We sincerely hope that you find this monograph interesting to read and its material helpful for your care of patients with cardiovascular or neurovascular emergencies. We greatly appreciate your interest in EMCREG-International and your confidence in both our symposia and enduring material pieces as a source of your continuing medical education.

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ST-segment Elevation Myocardial Infarction (STEMI): Optimal Anti-platelet and Anti-thrombotic Therapy in the Emergency Department

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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 Elevation MI (STEMI).
2. Participants should understand the clinical decision-making factors needed to determine the optimum reperfusion therapy for STEMI.
3. Participants should understand the recent clinical trial evidence and rationale behind the use of clopidogrel and enoxaparin in the treatment of STEMI with fibrinolysis.
4. Participants should understand the recent clinical trial evidence supporting the use of clopidogrel, prasugrel, and bivalirudin in the treatment of STEMI with primary PCI.

Introduction

When minutes count, and time is muscle, emergency physicians have the opportunity to make a crucial impact on morbidity and mortality by applying appropriate therapy in a very time-efficient manner in the treatment of ST-segment elevation myocardial infarction (STEMI). The 2004 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the treatment of STEMI and the 2007 ACC/AHA Focused Update (Focused Update) for STEMI outline the recommendations for the emergency department (ED) management of STEMI, including anti-ischemic, anti-thrombotic, and fibrinolytic versus catheter-based reperfusion therapy.^{1,2} 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 patients to the cardiac catheterization laboratory or CCU. Within a few months of the 2007 Focused Update publication, however, new clinical trials data were released and published which added significantly to the treatment of STEMI, and may change initial ED management of this disease process. Specifically, new clinical trials data support changes in the dosing and application of anti-platelet and anti-thrombin therapy in the treatment of STEMI.

The Choice of Reperfusion Therapy in STEMI: Fibrinolytics versus 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 wave front of necrosis developing from the subendocardium and extending transmurally to the epicardium over time. The longer the period of necrosis the higher the chance of heart failure and death. For every 30 minute duration of ischemia, there is an 8-10% increase in mortality.³ Reperfusion therapy, with dissolution or removal of the intracoronary thrombus, provides the best chance for mortality reduction. The Focused Update gives primary percutaneous coronary intervention (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.² 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 can't be accomplished within 90 minutes.

There is a distinct gray zone, however, in 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 inter-hospital transfer. The emergency physician must decide between fibrinolysis within 30 minutes followed by transfer, versus transfer for PCI, knowing that the chance of a door-to-balloon time of 90 minutes is remote. In the National Registry of Myocardial Infarction, the percentage of patients meeting the 90 minute window with a transfer from one hospital to another was less than 4%.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, for example > 120 minutes.

Whichever reperfusion strategy is chosen, it is important to maximize the effectiveness of that therapy by applying not only speed, but appropriate anti-platelet and anti-thrombin adjuncts. The recommendations for these therapies differ with the reperfusion method chosen. Appropriate protocol development demands maximization of the effectiveness of anti-platelet and anti-thrombin agents with each reperfusion choice.

Anti-platelet and Anti-thrombin Therapy with Fibrinolysis

If fibrinolysis is chosen as the reperfusion strategy, appropriate anti-platelet adjuncts include aspirin, clopidogrel, and glycoprotein IIb/IIIa (GPI) receptor blockers. All have been investigated in large multicenter clinical trials, but only aspirin and clopidogrel have been incorporated as Class I recommendations in the ACC/AHA Guidelines in patients treated with fibrinolysis.^{1,2} Specifically, aspirin 325 mg p.o. is indicated at patient presentation regardless of the reperfusion strategy, while clopidogrel 300 mg is indicated as the loading dose administered in the ED with fibrinolysis.

Clopidogrel is an oral anti-platelet agent which binds to platelets at the P₂Y₁₂ receptor 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 (Class IIaC). The CLARITY trial investigated the effectiveness of a 300 mg loading dose of clopidogrel, in conjunction with fibrinolytic therapy, in the treatment of STEMI.⁶ The CLARITY trial randomized 3491 STEMI patients to a 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. 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 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 45,852 STEMI patients (recruited in Asia) who were treated with fibrinolytics or medical management, to 75 mg q.d. (no loading dose) of clopidogrel versus placebo.⁷ 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 STEMI treatment algorithms in the ED, if not already in the care pathway, with a loading dose of 300 mg given in the ED.

The Focused Update for STEMI recommends the administration of an anti-thrombin 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 a Class IC recommendation, and enoxaparin a Class IA recommendation. The EXTRACT TIMI 25 trial compared enoxaparin (30 mg IVP, and 1 mg/kg subcutaneous) to unfractionated heparin (weight based dosing) in 20,478 patients treated with a variety of fibrinolytics for STEMI.⁸ The trial was a double-blind, double-dummy design, and 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. 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 subcutaneous in patients greater than 75 years of age eliminated any increased risk of intracranial hemorrhage compared to heparin in this population, and appears to be safe and effective in the elderly. EXTRACT demonstrated that enoxaparin is preferable to unfractionated heparin in STEMI patients treated with fibrinolytic therapy.

The combination of aspirin, clopidogrel, and enoxaparin, if appropriately dosed, comprises the best evidence-based protocol for STEMI treatment with fibrinolysis (Table 1).

Table 1. Summary recommendations for ED anti-platelet and anti-thrombin therapies for STEMI treated with fibrinolysis.

1. Targeted ED protocol and collaboration
2. ASA immediately (325 mg)
3. Morphine sulfate, nitrates, β -blockers by mouth (intravenous if tachycardia or hypertension present)
4. Clopidogrel 300 mg by mouth, 75 mg daily
5. Anti-thrombin:
Enoxaparin 30 mg IVP, 1 mg/kg subcutaneous (reduced in elderly) (PREFERRED)
OR
Heparin weight-based dosing (max 4,000 U/1000 U/hr)
OR
Fondaparinux 2.5 mg IVP, 2.5mg subcutaneously q.d.
6. Fibrinolytics in less than 30 minutes
7. Immediate transfer to PCI facility (for rescue PCI if needed)

Anti-platelet and Anti-thrombin Therapy with Primary PCI

Anti-platelet agents recommended by the Focused Update in the treatment of STEMI by primary PCI include aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors (GPI). Recent evidence supports a loading dose of 600 mg of clopidogrel with primary PCI, and other trials support the use of prasugrel as a new alternative to clopidogrel with primary PCI.

Clopidogrel, which is given as a 300 mg bolus with fibrinolytics, should be given as a 600 mg bolus prior to primary PCI. This dose is based on the ARMYDA 2 trial⁹ and is supported by the current ACC/AHA PCI guidelines.¹⁰ The ARMYDA 2 trial was a small 255 patient PCI trial investigating clopidogrel 300 mg versus clopidogrel 600 mg, given as a bolus before PCI. Although the patients in ARMYDA 2 were not high risk for adverse outcomes, there was a robust 67% reduction in death, MI, and urgent target vessel revascularization in the patients receiving the 600 mg clopidogrel loading dose (p=0.041). The recently presented multicenter CURRENT trial investigated clopidogrel 300 mg versus 600 mg head-to-head in 25,000 patients, 29% of which underwent primary PCI for STEMI. Clopidogrel was initiated upstream, in patients destined for PCI. The 600 mg load was associated with a lower rate of the combined endpoint of 30 day death, MI, and stroke (p=0.06), while stent thrombosis was reduced 42% (p=0.002)(Table 2).¹¹ These trials support the PCI guideline recommendation for administration of clopidogrel 600 mg upstream prior to PCI for STEMI.

Prasugrel is a new FDA approved oral P₂Y₁₂ platelet inhibitor which is more potent than clopidogrel. It was recently investigated in the TRITON-TIMI 38 trial where it was shown to be more effective than clopidogrel in reducing death and MI, but its effects were offset by bleeding, especially in

patients with prior stroke, advanced age, or low body weight.¹² The STEMI portion of TRITON TIMI 38 was recently published, demonstrating a similar reduction in death and MI in patients receiving prasugrel 60 mg load versus clopidogrel 300 mg load during primary PCI for STEMI.¹³ The ischemic benefits of prasugrel over clopidogrel were maintained in STEMI patients (Figure 1), while the bleeding effects were not statistically significantly different in the two groups. Prasugrel 60 mg remains a viable option as a substitute for clopidogrel 300 mg loading in STEMI patients undergoing PCI. It has not yet been tested head-to-head versus a clopidogrel 600 mg loading dose.

Since the Focused Update was published, another “anti-thrombin” has been investigated in the treatment of STEMI with primary PCI. The HORIZONS trial¹⁴ investigated the use of heparin plus a GPI versus bivalirudin with provisional GPI therapy in 3602 STEMI patients undergoing primary PCI. The primary outcome of the trial was the net clinical outcome of death, MI, stroke, or urgent intervention plus major bleeding at 30 days. Bivalirudin monotherapy resulted in no difference in ischemic endpoint, but a significant 40% reduction (8.3% versus 4.9%, p<0.0001) in major bleeding compared to standard therapy. The one year data from HORIZONS were recently presented which demonstrated a net death benefit in patients receiving bivalirudin therapy versus heparin plus a GPI (Figure 2).¹⁵ Of interest is that the majority of patients in the bivalirudin arm received unfractionated heparin, in the ED, prior to enrollment in the study. As such, the utilization of bivalirudin for primary PCI in the catheterization laboratory may not have significant effects on the ED treatment of STEMI patients prior to primary PCI.

Table 2. CURRENT trial 30 day ischemic endpoint results comparing clopidogrel 600 mg loading dose versus 300 mg loading dose prior to planned PCI.

			Clopidogrel		
	Standard N=8684 (%)	Double N=8548 (%)	Hazard Ratio	95% CI	P value
Stent Thrombosis	2.3	1.6	0.71	0.57-0.89	0.002
Definite	1.2	0.7	0.58	0.42-0.79	0.001
MI	2.6	2.0	0.78	0.64-0.95	0.012
MI or stent thrombosis	3.7	3.0	0.80	0.68-0.94	0.008
CV Death	1.9	1.9	0.96	0.77-1.19	0.68
Stroke	0.4	0.4	0.88	0.55-1.41	0.59
CV Death/MI/Stroke	4.5	3.9	0.85	0.74-0.99	0.036

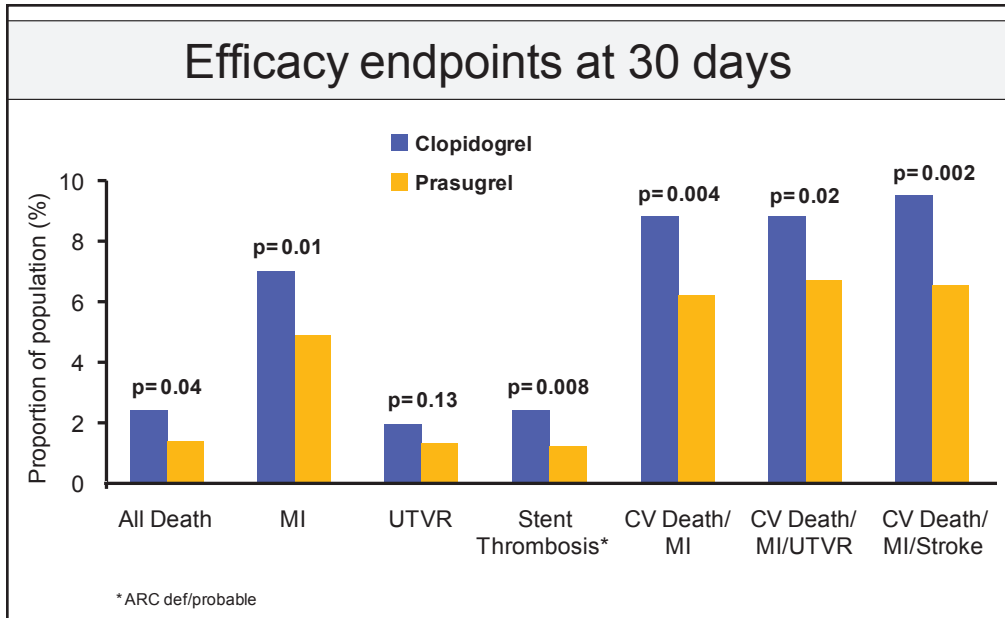


Figure 1: TRITON-TIMI 38 STEMI trial results: Reduction in ischemic endpoints with prasugrel 60 mg load versus clopidogrel 300 mg load upstream prior to PCI for STEMI. Adapted and reprinted with permission from Montalescot et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009; 373:723-731.

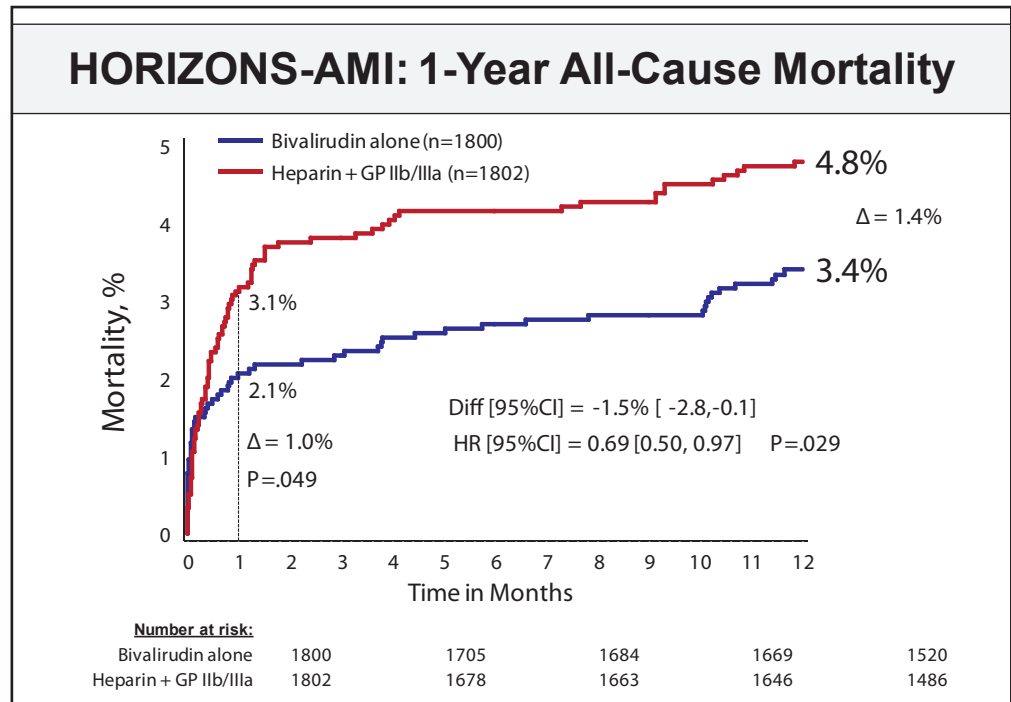


Figure 2: Results from the HORIZONS trial 1 year data: Reduction in mortality with bivalirudin versus heparin plus a GPI. Adapted and reprinted with permission from Stone et al. N Engl J Med 2008;358:2218-30. Bivalirudin during Primary PCI in Acute Myocardial Infarction. Presented at: Transcatheter Cardiovascular Therapeutics meeting (TCT 2008); 17, 2008; Washington, DC. October 12.

Synthesizing these data, it appears that the optimum ED management of STEMI for patients destined to undergo primary PCI includes clopidogrel 600 mg loading dose (or prasugrel 60 mg), heparin 4000 units IVP, and rapid transfer to the cardiac catheterization laboratory. The utilization of GPI or bivalirudin in the catheterization laboratory can be left to the cardiologist, and will not be hindered by emergency physician upstream management (Table 3).

Table 3. Summary recommendations for anti-platelet and anti-thrombin recommendations for STEMI treated by primary PCI.

1. Targeted ED protocol and collaboration
2. ASA immediately (325 mg)
3. Morphine sulfate, nitrates, β -blockers by mouth (intravenous if tachycardia or hypertension present)
4. P2Y₁₂ Platelet Inhibitor:
Clopidogrel 600 mg by mouth, 75 mg daily
OR
Prasugrel 60 mg by mouth, 10 mg daily
5. Anti-thrombin:
Heparin weight-based dosing (max 4,000U) for PCI (transition to bivalirudin?)
6. PCI in less than 90 minutes, prefer this from time of first medical contact
7. GPI inhibition in cardiac catheterization lab (provisional with bivalirudin)

Conclusions

The CLARITY, COMMIT, EXTRACT, HORIZONS, CURRENT, and TRITON-TIMI 38 trials are only a few 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. These trials must be interpreted in the light of current practice, with emphasis on applicability to the ED or in-patient hospitalist practice. Lessons from these trials may change practice, or strengthen the data behind current practice patterns. Emergency physicians and hospitalists must remain vigilant to the results of these and other trials to keep up-to-date and provide cutting edge care for STEMI patients.

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Novel Anti-platelet and Anti-thrombin Therapy for Acute Coronary Syndromes: STEMI and NSTEMI Optimal Anti-platelet and Anti-thrombotic Therapy in the Emergency Department

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Objectives:

1. Discuss the pathophysiology of acute coronary syndrome, STEMI and NSTEMI, to provide a basis for understanding therapies for these two disease processes.
2. Provide a basis for the thrombosis and platelet aggregation pathways which allow the clinician to understand agents which antagonize these processes.
3. Discuss specific anti-platelet treatments such as aspirin, thienopyridine ADP receptor inhibitors, and thrombin receptor antagonist.
4. Provide a fundamental knowledge base for emergency physicians to interact with other health care providers including cardiologists, hospitalists, pharmacists, and hospital administrators to provide optimal care for patients with STEMI and NSTEMI.

Introduction

Therapeutic advances in medicine are a significant challenge to the practicing clinician. Remaining current, particularly in a field as complex as acute coronary syndrome (ACS) therapy, requires almost continual effort. For emergency physicians and hospitalists alike, the last 15 years of research has provided clinicians with enormous information regarding ACS including insights

on pathophysiology, complications of the disease, and new anti-thrombin and anti-platelets therapies. In particular, the platelet in ACS has become a primary target for treatment advances. In this review of novel anti-platelet therapies for ACS, the evolution of these agents over the last 3 years will be described.

Pathophysiology and Platelet Biology in ACS

In patients with ACS, rupture of an atherosclerotic plaque in an epicardial coronary artery initiates a cascade of biochemical events ultimately causing myocardial ischemia and infarction. The ruptured plaque exposes circulating blood to von Willebrand factor and collagen which cause aggregation of platelets on the denuded endothelial surface. The stimulation of the coagulation pathway by the aggregating platelets releases thrombin, the most potent of platelet agonists. In addition, the extracellular release of thromboxane A₂ and ADP, secondary agonists which activate platelets, enhances platelet aggregation. The activated platelet also expresses glycoprotein IIb/IIIa surface receptors which bridge platelets together through fibrinogen. The aggregation of platelets, associated with insoluble fibrin generated through the thrombin-mediated change of fibrinogen, causes the development of the clot which occludes the coronary artery lumen adjacent to the ruptured plaque (Figures 1 and 2).¹

The ruptured plaque exposes circulating blood to von Willebrand factor and collagen which cause aggregation of platelets on the denuded endothelial surface.

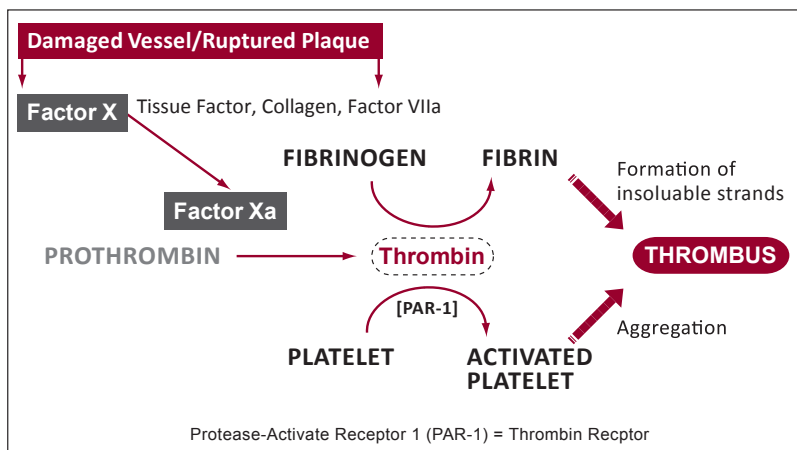


Figure 1: Formation of a thrombus in ACS.

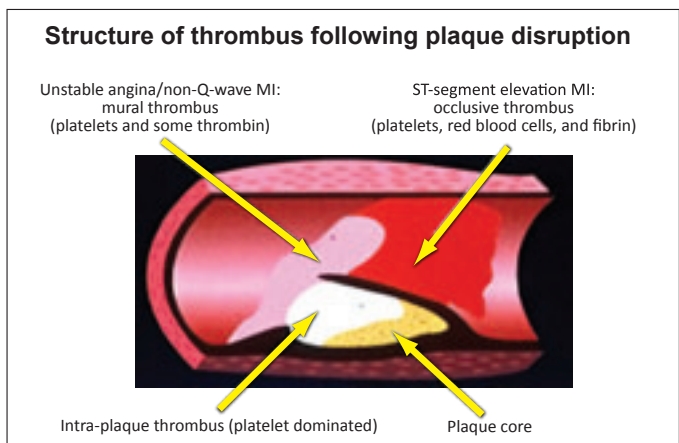


Figure 2: Structure of thrombus following plaque disruption. Adapted and reprinted with permission from Davies MJ. *Circulation* 1990; 82(supp II):II-38-II-46.

The multiple platelet receptors for these agonists which activate and aggregate platelets all serve as potential therapeutic targets. Thromboxane A₂, ADP through the P₂Y₁₂ receptor, and glycoprotein IIb/IIIa receptor all have been identified and successfully inhibited by agents which are currently available to the practicing acute care physician. It is important for the clinician to be aware of these pharmacologic therapies and ideally to understand the basis for their use in the patient with ACS (Figure 3).

Currently Available Therapy

Perhaps the best known treatment for ACS, aspirin, acts through inhibition of thromboxane A₂ production and cyclo-oxygenase. This mainstay of treatment should be given to all patients with ACS, unless there is a known allergy to aspirin. This is considered a Class I, level of evidence A, recommendation from the 2007 ACC/AHA Guidelines for the treatment of unstable angina/non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI).^{2,3}

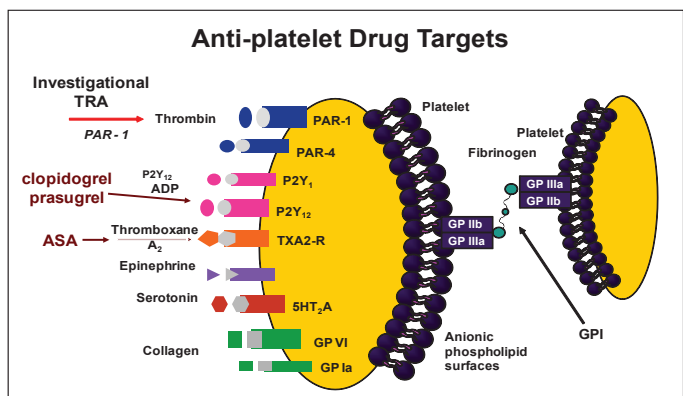


Figure 3: Anti-platelet drug target receptors in acute coronary syndrome.

Perhaps the best known treatment for ACS, aspirin, acts through inhibition of thromboxane A₂ production and cyclo-oxygenase. This mainstay of treatment should be given to all patients with ACS, unless there is a known allergy to aspirin.

Similarly, the thienopyridine clopidogrel, an irreversible antagonist of the P₂Y₁₂ receptor on the platelet, is a Class I A recommendation for NSTEMI and STEMI ACS as a 300 mg bolus followed by a 75 mg daily dose.⁴ Recently, presentation of the CURRENT trial at the European Society of Cardiology Meeting in Barcelona, identified an increased loading dose of 600 mg clopidogrel prior to percutaneous coronary intervention improved outcomes with minimal increase in TIMI major bleeding rates.⁵ Finally, multiple glycoprotein IIb/IIIa receptor antagonists including integrilin, abciximab, and tirofiban have support as major anti-platelet therapies for ACS by the guidelines.

Novel Anti-platelet Agents

Over the last 3 years, multiple new anti-platelet agents have been investigated. Prasugrel, ticagrelor, cangrelor, and thrombin receptor antagonist have now been studied in Phase III trials and will be discussed in this review. Only prasugrel has been approved by the FDA for use in the clinical setting.

Prasugrel

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38), prasugrel 60 mg loading dose followed by a 10 mg per day regimen was compared to the standard 300 mg loading dose plus a 75 mg daily dose of clopidogrel for up to 15 months in 13,608 moderate to high risk ACS patients undergoing PCI.⁶

For the primary endpoint of cardiovascular death, nonfatal MI, or stroke, there was a 19% relative risk reduction in the prasugrel treated group (642 patients, 9.9%) versus the clopidogrel treated group (781 patients, 12.1%) – (hazard ratio 0.81; 95% confidence interval 0.73 - 0.90; p = 0.0004). Reduction in MI drove the difference in primary outcome between the two groups (Figure 4).

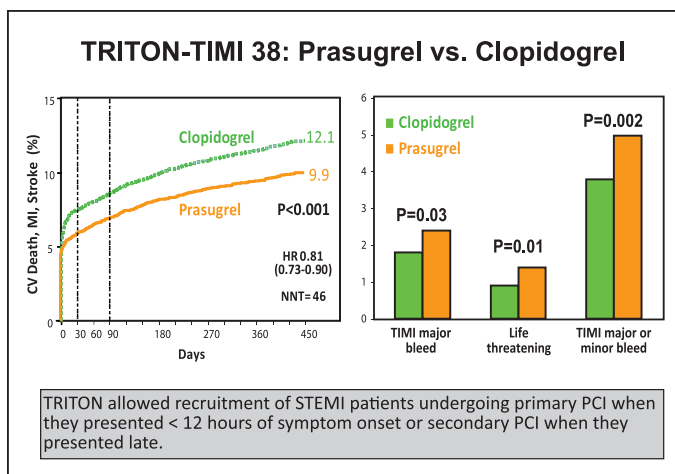


Figure 4: TRITON-TIMI 38 – prasugrel versus clopidogrel therapy. Adapted and reprinted with permission from Wiviott SD, et al. N Engl J Med 2007;357:2001-2015.

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In TRITON-TIMI 38, there was a significant difference in major bleeding, occurring in 2.4% of prasugrel patients versus 1.8% of clopidogrel treated patients (hazard ratio 1.32; 95% CI 1.03 – 1.68; p = 0.03). In particular, patients with a history of transient ischemic attack (TIA) or stroke, patients 75 years of age or older, and patients with a body weight <60 kg were at greater risk for bleeding. The drug should be avoided in patients with cerebrovascular disease as they are at increased risk for intracranial hemorrhage.

In a pre-designed substudy from TRITON-TIMI 38 of prasugrel versus clopidogrel in patients with STEMI undergoing PCI, a reduction in the primary endpoint was seen similar to the overall study without a significant difference in major bleeding between the two groups.⁷ This was likely due to the decreased age and increased weight of STEMI patients in the TRITON-TIMI 38 trial, and the lower incidence of cerebrovascular disease in this cohort. In receiving approval by the FDA in 2009, a boxed warning was given to avoid using prasugrel in

patients with active pathological bleeding or a history of TIA or stroke. Caution was advised in using prasugrel for patients aged 75 years of age or older, except in high risk patients with diabetes or prior myocardial infarction. Low weight patients, particularly individuals 60 kg or less, should be treated with caution.

The increase in efficacy of the thienopyridine prasugrel is thought to be due to more efficient metabolism by the cytochrome P450 system. This two step metabolism occurs in the gut and in the liver which synthesizes a pharmacologically active metabolite. Hence, prasugrel is absorbed by the gut and rapidly metabolized providing maximal inhibition of platelets in approximately one hour. In contrast, clopidogrel is metabolized in a 2 step process primarily by cytochrome P3A₄ in the liver. This cytochrome is variably present in patients or can be inhibited by commonly used drugs metabolized by this enzyme system. Approximately 85% of the dose of clopidogrel is metabolized to inactive metabolites (Figure 5). Typically, the maximum platelet inhibitory effect of clopidogrel is seen 4-6 hours after the oral loading dose is given. It is for these reasons the double bolus loading dose of 600 mg was chosen for evaluation in the CURRENT trial.⁵

The increase in efficacy of the thienopyridine prasugrel is thought to be due to more efficient metabolism by the cytochrome P450 system.

Cangrelor

Binding of both clopidogrel and prasugrel to the P₂Y₁₂ receptor of the platelet is covalent and therefore irreversible. In contrast, an intravenous agent cangrelor, which inhibits the same receptor in a rapid onset, rapid offset, and reversible fashion, has recently been evaluated. Despite several successful Phase II studies, the recent Phase III trials CHAMPION-PCI and CHAMPION-PLATFORM were prematurely stopped when cangrelor was not found to be superior to clopidogrel 600 mg as a bolus dose.

Ticagrelor

An oral, reversible inhibitor of the P₂Y₁₂ ADP receptor of platelets has been evaluated in a number of Phase II trials and the recently completed and published PLATO Phase III trial. In the PLATO study, high risk ACS patients presenting to the hospital within 24 hours of symptom onset were eligible for enrollment. In this multinational study of 18,624 patients

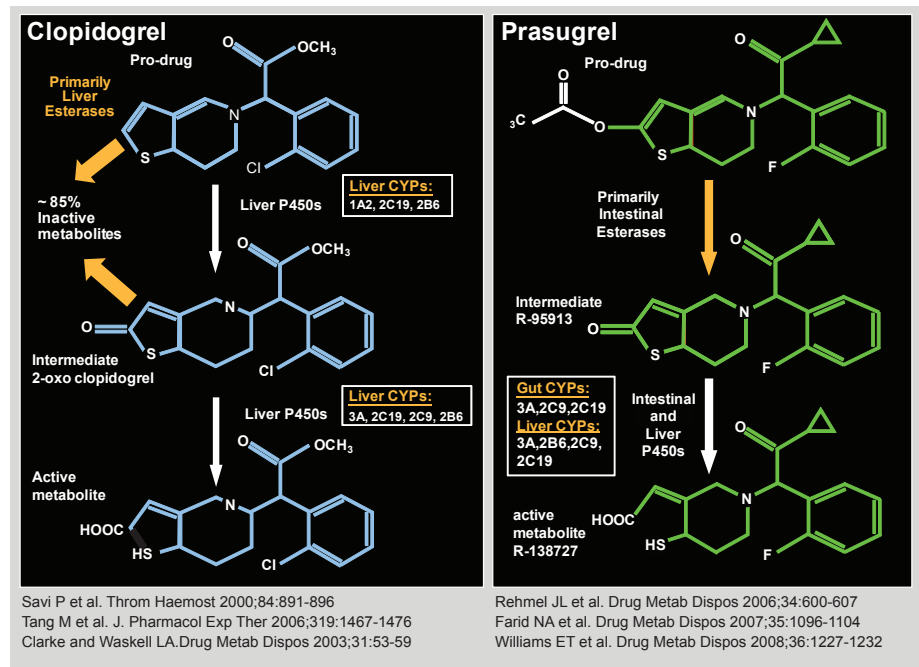


Figure 5: Generation of active metabolites of clopidogrel and prasugrel. Adapted and reprinted with permission Rehmel JL et al. Drug Metab Dispos 2006;34:600-607, Farid NA et al. Drug Metab Dispos 2007;35:1096-1104, Williams ET et al. Drug Metab Dispos 2008;36:1227-1232, Savi P et al. Throm Haemost 2000;84:891-896, Tang M et al. J. Pharmacol Exp Ther 2006;319:1467-1476, Clarke and Waskell LA. Drug Metab Dispos 2003;31:53-59.

with ACS, ticagrelor 180 mg loading dose and 90 mg twice daily maintenance dose was compared to clopidogrel (300-600 mg loading dose followed by a 75 mg daily maintenance dose) in a randomized double blind fashion.

For the primary endpoint, defined as a composite of death from any vascular cause, myocardial infarction, or stroke, ticagrelor was found to have a 9.8% occurrence of the primary endpoint versus 11.7% in those patients treated with clopidogrel (hazard ratio 0.84; 95% CI 0.77 – 0.92; p < 0.0001).

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versus 6.9% in the clopidogrel group, p = 0.005) and death from vascular causes (4.0% versus 5.1%, p = 0.001) was also observed in the experimental group. No difference in major bleeding was observed in the ticagrelor versus clopidogrel group (11.6% versus 11.2%, p = 0.43), however, bleeding not related to coronary artery bypass grafting (4.5% versus 3.8%, p = 0.03), including more instances of fatal intracranial bleeding, was greater in the ticagrelor treated group (Figure 6).⁹

Thrombin Receptor Antagonist

An inhibitor of the thrombin receptor on the platelet, the thrombin receptor antagonist SCH 530348, represents a new class of drug effective at decreasing platelet aggregation in ACS. This agent has minimal effect on bleeding time, suggesting it may have additive benefit to the other agents previously detailed in this review. Binding to the

protease-activated receptor (PAR)-1, the signaling of intra-platelet calcium ion elevation is decreased by TRA blunting of the response to thrombin and collagen stimulation.¹⁰

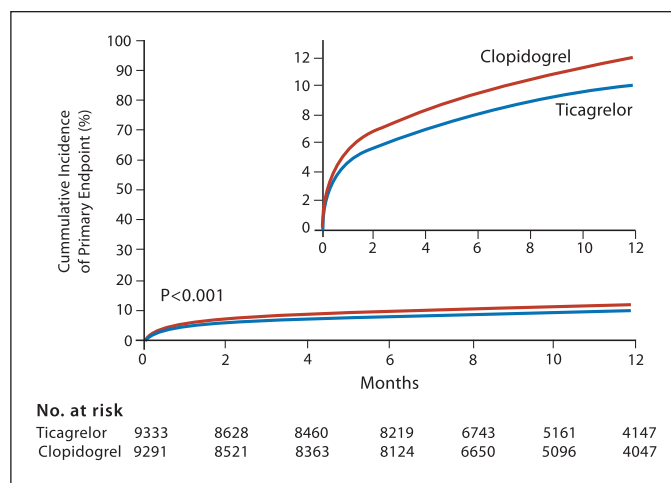


Figure 6: Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point. The primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; P<0.001). Reprinted with permission from Wallentin L, et al., N Engl J Med 2009;361:1045-57.

An inhibitor of the thrombin receptor on the platelet, the thrombin receptor antagonist SCH 530348, represents a new class of drug effective at decreasing platelet aggregation in ACS.

In the TRA-PCI study, SCH 530348 was used in addition to conventional treatment in addition to aspirin plus clopidogrel 300 or 600 mg as a loading dose with a maintenance dose of 75 mg for 1,030 patients scheduled for angiography and possible stenting. The SCH 430348 regimen was added in a 3:1 randomization scheme at 10, 20 or 40 mg loading doses, followed by a 0.5, 1.0, or 2.5 mg maintenance dose. The primary endpoint was TIMI major or minor bleeding in the PCI cohort at 60 days with a secondary endpoint of death or major cardiovascular events (Figures 7 and 8). On the basis of the success of the TRA-PCI study, the 40 mg loading dose and 2.5 mg maintenance were chosen for 2 large Phase III clinical trials which are now ongoing. In the TRA-CER trial, SCH 530348 will be evaluated in approximately 10,000 patients with ACS for at least 1 year. In the other trial, TRA 2P-TIMI 50 study, approximately 19,500 patients with a history of MI, ischemic stroke, or peripheral arterial disease will receive a 2.5 mg maintenance dose of the thrombin receptor antagonist versus placebo for secondary prevention.

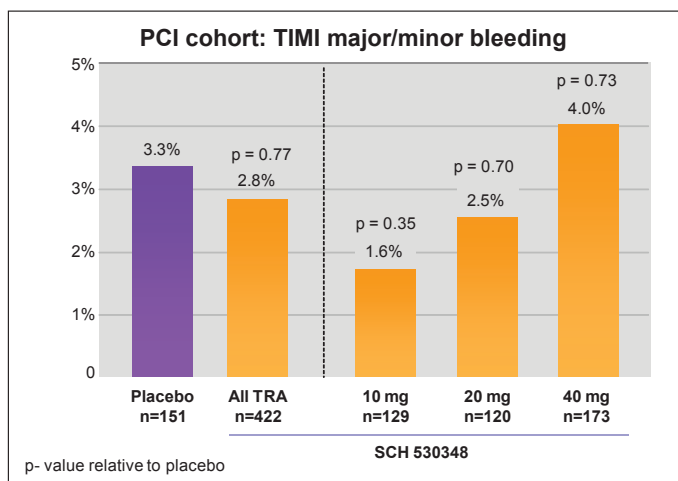


Figure 7: Bleeding in the PCI cohort in TRA-PCI. Adapted and reprinted with permission for Becker R. et al. Lancet 2009;373:919-928.

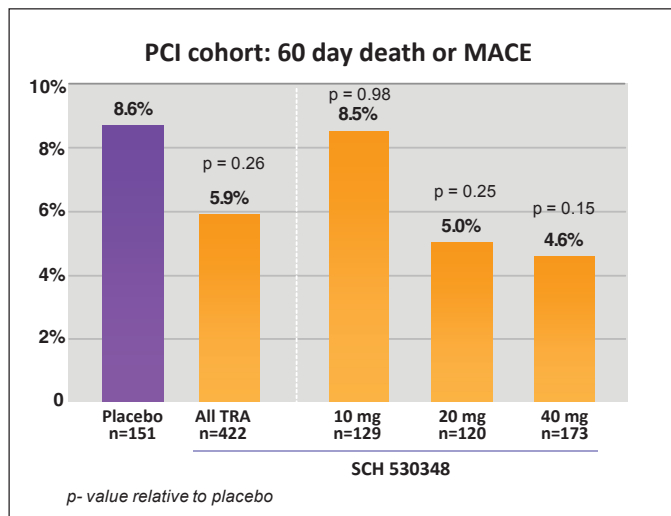


Figure 8: Sixty day death or major adverse clinical events (MACE) in TRA-PCI PCI cohort. Adapted and reprinted with permission for Becker R. et al. Lancet 2009;373:919-928.

Conclusion

Anti-platelet agents such as aspirin, clopidogrel, and the glycoprotein IIb/IIIa inhibitors have been the mainstay for treatment of NSTEMI and STEMI for the last decade. Novel anti-platelet drugs have been investigated which have the potential to improve care for patients with ACS. It is important for acute care physicians such as emergency physicians and hospitalists to understand the basic mechanism of action for these new drugs to optimally treat their future patients. In addition, having a working knowledge of the pharmacology of anti-platelet agents will improve communication and collaboration with cardiology colleagues caring for patients with ACS.

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American Heart Association Mission Lifeline: Developing a STEMI Regional Care System

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Objectives:

1. To describe the need for a change in current management of patients with STEMI.
2. Discuss the objectives of Mission Lifeline.
3. Review the Mission Lifeline plan for implementation of STEMI systems.

Optimizing STEMI care

ST-segment elevation myocardial infarction (STEMI) remains a major health care problem and serves as a target for quality improvement. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that reperfusion with fibrinolytic therapy should occur within 30 minutes of arrival in the emergency department (ED) or that primary percutaneous coronary intervention (PCI) be performed within 90 minutes of presentation.¹ Multiple studies support the use of primary PCI as the superior method of reperfusion strategy, with the caveat that the incremental delay of performing primary PCI be no more than 60 minutes.¹⁻⁴ Despite the existence of well established guidelines, care registry data show that the majority of sites in the United States are not achieving these desired target times to treatment.^{5,6} There are multiple practical issues which may impact timely reperfusion. Geophysical, financial, organizational, and operational issues within a healthcare system all can influence reperfusion strategies and time to treatment. Leaders within the cardiovascular field have presented the option of regionalization of STEMI care, a process similar to current strategies for the treatment of major trauma and stroke patients, as a means of improving time to reperfusion.

In May of 2004 an Advisory Working Group largely comprised of members from the AHA and ACC was recruited to explore methods for increasing the number of patients receiving

timely PCI. The compilation of work from this group resulted in a publication in *Circulation* which discussed the need for an improved method for the management of these patients.¹ With the continued support of the AHA and ACC, in April 2006 a stakeholder summit was convened which included 25 organizations to discuss and develop a system of care for STEMI patients. This resulted in multiple publications from writing groups comprised largely of cardiologists but including representation from emergency medicine, emergency medical services, and hospital administrators. As these working groups were finalizing their manuscripts, the AHA began to establish a cross-functional team to serve as the leadership of Mission: Lifeline. On May 30, 2007, the eleven manuscripts prepared as a result of these STEMI working groups were published in *Circulation*.⁷⁻¹⁷ At the same time the Mission: Lifeline program was launched. The initial Mission: Lifeline program had four key objectives:

1. EMS system assessment and improvement
2. Evaluate existing models
3. Establish local initiatives
4. Explore the possibility of national STEMI certification

Over the last two years this program has focused on these initial goals and has strived to establish registered systems of care across the United States with the aim of improving time to reperfusion in all patients with STEMI. Integral to this concept are three key venues of emergency care: Emergency medical services (EMS), hospitals that receive STEMI patients but can not perform PCI (STEMI referring hospital), and STEMI receiving hospitals that are PCI capable. This review will discuss each of these three key components as identified by Mission: Lifeline and the implications of new performance measures recently proposed by Cardiology.^{18,19}

Regionalization: key components

Mission: Lifeline suggests that a region is based on an integrated health care network, the “spoke and hub” concept, where outlying hospitals serve as the “spokes,” and a central hospital—a PCI capable center—serves as the “hub.” Proximity around such a hub center could define this integrated health care network. This is similar to the model used in the reperfusion of Acute Myocardial Infarction in North Carolina Emergency Department (RACE) project which organized treatment plans based on resources within a region, each individual hospital, and coordination among EMS systems to reallocate patients as needed.²⁰ The RACE project showed that the process of regionalization addressed existing barriers to timely reperfusion with PCI and fibrinolytics in regions where patient transfer could not readily occur.

Emergency Medical Services

Emergency medical services are an integral component of a coordinated system of care.²¹ Appropriately, Mission: Lifeline has established parameters for EMS systems. A key component of the EMS role in a STEMI system is the standardization of the evaluation and treatment of patients with symptoms suggestive of myocardial ischemia which includes the acquisition of a pre-hospital electrocardiogram (ECG). This allows coordinated transport to the appropriate locations.²²

Multiple studies have shown that pre-hospital ECG acquisition results in improved time to reperfusion in patients with STEMI. How the information from the ECG is incorporated into clinical care is also important. The Mission: Lifeline program acknowledges that ECG data acquisition and transmission occur by varying methods such as direct communication and interpretation by paramedics, computerized interpretation and transmittal, and wireless transmission with physician interpretation.

As Mission: Lifeline identifies PCI as the preferred reperfusion strategy, each EMS system should have a STEMI care pathway which designates transport to a PCI center by direct or inter-hospital transfer. The program acknowledges that fibrinolytic therapy should be given when PCI can't be performed within 90 minutes of first medical contact.¹⁹

Central to the development of any system is the ability to track and assess performance. In the realm of EMS, Mission: Lifeline recommends the evaluation of multiple facets of EMS care including:

1. Time from symptom onset to 911 call
2. Time the 911 call is first received by primary public safety answering point to vehicle arrival at hospital door
3. Time from first medical contact-to-balloon inflation (first device used).
4. Time from pre-hospital ECG-to-balloon inflation (first device used).
5. Proportion of patients with non-traumatic chest pain > 35 years treated by EMS for whom 12-lead ECGs were obtained
6. Proportion of patients with STEMI treated by EMS for whom 12-lead ECGs were obtained
7. Proportion of patients with field diagnosis of STEMI and activation of the cardiac catheterization laboratory for intended primary PCI that:
 - a. do not undergo acute catheterization because of misdiagnosis
 - b. undergo acute catheterization and found to have no elevation in cardiac biomarkers and no revascularization in the first 24 hours

8. Proportion of patients with EMS treated ventricular fibrillation (VF) who are taken to the cardiac catheterization laboratory
9. Survival to hospital discharge of all STEMI patients and of patients with VF (EMS and STEMI-Receiving Center to monitor jointly)

This depth of data collection and assessment has not traditionally been tracked by EMS providers and represents a change in philosophy as actions and interpretations by EMS significantly impact in-hospital outcomes for patients with STEMI.

STEMI Referral Center

In the development of a STEMI system, the establishment of patient transfer relationships between those hospitals that are PCI capable and those that are not is essential. Timely reperfusion strategies which require transfer of patients is difficult to obtain when established transfer pathways are not available. As shown by the RACE initiative, even in the best of systems it is difficult to obtain timely PCI in transferred patients.

As identification of patients with STEMI is the initial step to a system of care, Mission: Lifeline suggests appropriate protocols and standing orders should be in place for the identification of STEMI. In addition, each emergency department (ED) should have reperfusion pathways which designate primary PCI as the standard of care and a fibrinolysis pathway if PCI is not possible within a guideline recommended time frame. As already mentioned, transferring patients to another institution is often a timely process and each hospital should have a mechanism to initiate rapid transfer selecting the optimal transport method based on meeting existing door-to-balloon guidelines. It is important to realize that the door-to-balloon time in those patients transferred begins at the arrival of the patient at the STEMI referring hospital. Minimizing time to transfer requires the presence of an integrated system with seamless transition from the referring hospital to the receiving hospital, including the transport vehicle. On a practical note this may require the elimination of existing barriers to transferring patients as the Emergency Medicine physician cannot use valuable time contacting multiple different cardiologists to accept the patient in transfer.²³

Continuous quality improvement and assessment of practice requires communication between the STEMI referring hospitals. Mission: Lifeline recommends the following data points be routinely evaluated:

1. Door-to-first ECG time (goal <10 minutes)
2. Proportion of STEMI-eligible patients receiving any reperfusion (PCI or fibrinolysis) therapy.

3. STEMI Referral Center ED door-to-balloon (first device used) time for patients transferred to PCI center:
 - a. STEMI Referral Center ED door to ED discharge
 - b. STEMI Referral Center ED door-to-balloon (first device used) time within 90 minutes, including transport time to receiving PCI hospital

STEMI Receiving Center

The STEMI receiving center is the “hub” of a system of care. This center should play a major role in coordinating the system of care for STEMI patients, ensure communication with referring hospitals, and have a clear process to accept patients with STEMI within their coverage area. In addition, the receiving center must be able to perform timely PCI on a 7 day a week, 24 hour each day basis. It is also reasonable to assume that the interventional cardiologists at the receiving center are in compliance with AHA guidelines regarding procedural volume.

Despite these key principles there is limited literature regarding the success of such STEMI receiving centers when evaluated as part of a system. A recent study looked at a single regional system of care that included EMS diversion. In this study, a door-to-balloon time of 90 minutes or less was achieved for 651 (89%) patients, and 459 (62.5%) had EMS-patient contact-to-balloon times \leq 90 minutes. Transport to a STEMI receiving center resulted in ambulance diversion from a closer ED for 31% of patients and a median increase in transport time of 3.8 minutes.²¹ A recent trial evaluating time to reperfusion in elderly patients transferred for PCI reports a longer time to reperfusion, but no change in clinical outcomes.²² Other systems that have looked at time to reperfusion, however, have shown suboptimal compliance with the door-to-balloon recommendation of $<$ 90 minutes.

Since the goal of the STEMI receiving center is to meet the door-to-balloon time of $<$ 90 minutes from time of first medical contact, Mission: Lifeline recommends that care protocols should be established to ensure meeting this goal. This includes a plan for 24 hour capability for performing PCI, close proximity of the cardiac catheterization team to the hospital, and a comprehensive quality improvement team which is multidisciplinary and communicates with EMS and the referring hospitals. Several key data points are suggested as important parameters to be measured and including:

1. Door-to-balloon (first device used) time, non-transfer within 90 minutes
2. STEMI Referral Hospital ED door-to-balloon (first device used) time, transfer within 90 minutes
3. First Medical contact-to-balloon inflation (first device used) non-transfer within 90 minutes

4. First Medical contact-to-balloon inflation (first device used) transfer
5. Proportion of eligible patients receiving reperfusion therapy
6. Proportion of eligible patients administered guideline-based Class I therapies
7. Proportion of patients with field diagnosis of STEMI and activation of the cardiac catheterization laboratory for intended primary PCI that:
 - a. do not undergo acute catheterization because of misdiagnosis
 - b. undergo acute catheterization

STEMI System

Three components comprise the STEMI system advocated by Mission: Lifeline: the Emergency Medical System, the STEMI referring hospital and the STEMI receiving hospital. To have a successful system, coordination must be accomplished between all three components. It is important for the EMS providers to have a clear understanding of destination protocols. Mission: Lifeline advocates the identification of a physician champion for a system to maximize the likelihood of success. All participating hospitals should be able to meet the criteria discussed above and evaluate their operational practices. Through the process of registration in Mission: Lifeline, STEMI systems can receive feedback regarding their process of care.

A New Challenge

An essential component of understanding the implication of STEMI systems of care is the review of process of care measurements. The majority of current process of care measurements for STEMI patients involves treatment outside of the purview of emergency medicine. The recommendations for data collection from Mission: Lifeline require detailed data abstraction from EMS and ED processes of care. The need for the collection of performance measurements which span the care of STEMI patients from the STEMI referring hospital to the receiving hospital is emphasized.²³ The reporting of such performance measures may drive changes in how care for these patients organized. It is becoming clear that emergency medicine physicians will be held accountable on some level for the time a STEMI patient spends in the ED, even if the patient is transferred. This may require more involvement of the ED personnel in the collection of data which drives these processes and require additional resources be allocated to collect process of care measurements.

In conclusion, through Mission: Lifeline, the AHA has created recommendations for the management of patients with a

STEMI which spans a patient's entire medical encounter from EMS contact to time of reperfusion. This program provides multi-disciplinary guidance on mechanisms to improve time to reperfusion for STEMI patients. The framework established by Mission: Lifeline can serve as a tool to begin the integration of care for these patients and the creation of collaborative efforts between the emergency medical services and hospitals which care for patients with STEMI.

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Ideal Management of Acute Heart Failure Syndromes in the ED

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Objectives:

1. To understand the role of natriuretic peptide testing for diagnosis of heart failure.
2. To understand precipitants of acute heart failure syndrome.
3. To understand the approach to treatment of patients with acute heart failure syndrome.

The ideal management of heart failure requires timely diagnosis, identification of the etiology of the underlying pathology, identification of the etiology of the acute precipitant of the condition, and an assessment of the optimal approach to treatment of the individual patient. These management principles are necessary despite a paucity of evidence-based treatment recommendations. The approach to the patient with heart failure must therefore be accomplished based upon an individual assessment of each patient.

Diagnosis of Heart Failure

The diagnosis of heart failure has traditionally been challenging. Reliance upon clinical impression alone leads to diagnostic uncertainty because the signs and symptoms of heart failure are relatively nonspecific. Studies have shown that the inter-rater reliability of heart failure signs, such as an S3, or even the presence or absence of rales, is not very good. Key symptoms such as shortness of breath are nonspecific in patients with comorbidities such as reactive airway disease. Likewise, routine laboratory tests, electrocardiograms, and radiographs can't always be relied upon to guide an accurate and appropriate diagnosis.

Despite these challenges, diagnostic capabilities in heart failure have improved in recent years with recognition of the role which B-type natriuretic peptide (BNP) plays in the disease. In addition to being a pump, the heart is an endocrine organ which functions together with other physiological systems to control fluid volume. The myocardium produces

natriuretic peptides, one of which is BNP. This is a hormone with diuretic, natriuretic, and vascular smooth muscle relaxing properties. A natural antagonist for the sympathetic nervous system and the renin-angiotensin-aldosterone axis, BNP is secreted in response to wall stretch, ventricular dilation and/or increased filling pressures. Measurement of endogenous BNP is thus a clinically reasonable way to assess whether a particular patient has heart failure.

Reliance upon clinical impression alone leads to diagnostic uncertainty because the signs and symptoms of heart failure are relatively nonspecific.

The Breathing Not Properly study was a multinational trial of 1,586 patients who presented to emergency departments (EDs) with shortness of breath. It showed that BNP levels alone were more accurate predictors of the presence or absence of heart failure than any historical factors, physical findings, or laboratory values.^{1,2} In fact, BNP was more accurate than emergency physician estimates of the likelihood of heart failure. The BNP levels were much higher in patients who were subsequently diagnosed with heart failure than in those diagnosed with noncardiac dyspnea (675 pg/dL vs. 110 pg/dL). A BNP cutoff value of 100 pg/dL had a sensitivity of 90% and a specificity of 76% for differentiating heart failure from other causes of dyspnea, and a cutoff of 50 pg/mL had a negative predictive value of 96%. Without knowledge of BNP levels, emergency physicians had a 43% indecision rate in trying to make a diagnosis. The BNP levels added significantly to the clinical impression, as it was found that clinical decision-making in conjunction with BNP levels could have reduced the diagnostic indecision rate to 11%. In multivariate analyses, BNP levels always contributed to the diagnosis, even after taking into account findings from the history and physical examination. Both diastolic and systolic dysfunction are associated with high BNP levels of more or less the same degree.³

The BNP level must be used with caution in certain populations. Some types of lung disease, such as cor pulmonale and pulmonary embolism, have elevated BNP levels. However BNP is not usually elevated to as high a level in patients with pulmonary disease as it is in those with heart failure. In a subgroup of patients with a history of reactive airway disease in the Breathing Not Proper trial, only 37% of patients ultimately found to have heart failure were identified in the ED, while a BNP >100 pg/mL identified 93%.⁴ There is a

significant inverse relationship between body weight and BNP levels.⁵ Thin patients with heart failure are more likely to have elevated BNP values in the absence of heart failure. Conversely, obese patients are more likely to have lower levels of BNP for any given severity of heart failure. When baseline levels are known in obese patients, it would be reasonable to use the baseline level to determine if the current BNP is elevated. Following BNP levels for the obese patient can be followed for new acute decompensation. The performance of N-terminal pro-BNP is similar to BNP.^{6,7}

A BNP level might also be useful to improve triage and disposition of patients who present to the ED with heart failure.

The REDHOT study suggests that a BNP level might also be useful to improve triage and disposition of patients who present to the ED with heart failure.⁸ This trial demonstrated a “disconnect” between the physician perception of the severity of heart failure and the actual BNP value. In the first phase, 464 patients visiting EDs with a complaint of breathing difficulty had BNP measurements taken on arrival. Physicians were blinded to BNP results; however inclusion in the trial required a BNP > 100 pg/ml. Patients discharged from the ED had higher BNP levels than those admitted to the hospital. With respect to the admitted patients, 11% had BNP levels < 200 pg/ml, which is indicative of less severe heart failure. Most of these patients were perceived by the emergency physician to have class III or IV heart failure. Mortality for these patients was 0% at 30 days and only 2% at 90 days, suggesting that patients with heart failure and low levels of BNP might have actually been safe for discharge. With respect to patients who were actually discharged, 78% had BNP levels >400 pg/mL. At 90 days, mortality was 9%. There was no mortality in those discharged with BNP levels <400 pg/mL. These data suggest that use of BNP in the ED might also help determine which well appearing patient is high risk for a bad outcome over the short term (90 days). The trial also suggests that when the clinician thinks the patients is safe for discharge but the BNP is over 400 pg/ml, the clinician may wish to reconsider the disposition decision. Almost one in ten patients with these characteristics was dead by 90 days. Although the REDHOT trial did not demonstrate that admitting these patients to the hospital can alter the outcome, the clinician may wish to think carefully about the decision to discharge this cohort of patients (BNP > 400 pg/ml).

Elevations of BNP are useful for assessing risk stratification and prognosis in patients with heart failure.

Elevations of BNP are useful for assessing risk stratification and prognosis in patients with heart failure. The level of BNP is related to changes in limitations of physical activities and functional status. Harrison et al. followed 325 patients for 6 months after an index visit to the ED for dyspnea.⁹ Higher BNP levels were associated with a progressively worse prognosis. The relative risk of 6-month heart failure admission or death in patients with BNP levels >230 pg/mL was 24 times the risk of patients with levels less than 230. When combined with troponin I, both troponin I and BNP alone and in combination predict survival in heart failure.¹⁰ Both together have additive prognostic risk.

The 2009 Focused Update on Heart Failure recommends the use of BNP or NT-BNP to assist diagnosis as a Class I, Level of Evidence A recommendation.

The utility of BNP and NT-pro-BNP to diagnosis heart failure is well established, however, it's ability to drive treatment is still under study. IMPROVE-CHF¹¹ found the use of NT-pro BNP testing was useful for the management of patients with heart failure. The 2009 Focused Update on Heart Failure recommends the use of BNP or NT-BNP to assist diagnosis as a Class I, Level of Evidence A recommendation.¹²

Etiology of Heart Failure

The potential etiologies of acute heart failure are multifactorial and can be broadly divided into two categories: (1) the underlying etiology of the heart failure, and (2) the etiology of the acute precipitant that results in worsening from the chronic compensated state. For some patients, particularly those presenting for the first time, these two components may be identical. The most common etiologies of heart failure are coronary artery disease and long-standing hypertension.

Other potential etiologies include dilated, hypertrophic and restrictive cardiomyopathies, myocarditis, pericardial tamponade, valvular heart disease, and secondary effects of pulmonary diseases or metabolic disorders.

The potential etiologies of acute heart failure are multifactorial and can be broadly divided into two categories: (1) the underlying etiology of the heart failure, and (2) the etiology of the acute precipitant that results in worsening from the chronic compensated state.

Although investigation of the underlying etiology is important to help determine whether there is a reversible component of the disease, this can often be deferred to the in-patient team. There are several etiologies for heart failure which the emergency physician should be aware of, as they may require modification of initial therapy. These are severe aortic stenosis, idiopathic hypertrophic subaortic stenosis or asymmetric septal hypertrophy (an obstructive cardiomyopathy), and pulmonary hypertension. Identification of these conditions is important because aggressive afterload reduction or diuresis can lead to cardiovascular collapse since patients can't increase their forward blood flow through the fixed mechanical lesion such as a flow-restricted aortic valve.

Separate and distinct from the initial etiology is the cause of the acute precipitant. Heart failure can be exacerbated by worsening of the underlying condition, medication or dietary noncompliance, or by development of new or complicating medical conditions such as ischemia, dysrhythmias, pulmonary embolus, or infection. Approximately 80% of patients presenting to the ED with heart failure have a prior diagnosis of heart failure.

Treatment Options in the Emergency Department

Treatment of patients with heart failure in the ED also depends on the time course of the decompensation. Some medically noncompliant patients have a relatively slow decompensation and require minimal intervention in the ED. Others, such as those with acute decompensation, require more aggressive intervention. Selection of the appropriate treatment requires some knowledge of the pathophysiology of heart failure and

the mechanisms of action of the various therapeutic options. Most of the therapeutic options for acute decompensated heart failure have not been evaluated in well-designed clinical trials. The following overview of these therapies cites published studies when available. The 2009 Focused Update on Heart Failure does not contain any Class I, Level of Evidence A recommendations for treatment in the ED.¹²

The 2009 Focused Update on Heart Failure does not contain any Class I, Level of Evidence A recommendations for treatment in the ED.

Loop diuretics are traditionally used to reduce preload and improve the symptoms of heart failure. These agents do not have any direct myocardial benefit and activate the neuroendocrine system, which leads to elevations in serum aldosterone. Although diuretics have been used for decades, there is no evidence that they improve mortality in heart failure patients. In fact, they may worsen long-term outcomes, and mortality from heart failure did not improve during the period when they were considered the mainstay for acute heart failure treatment.¹⁴ Loop diuretics should be used with there is evidence of systemic volume overload. They are reasonable to use as a first line therapy in patients with normal systolic blood pressure and gradual onset of symptoms due to high likelihood of high filling pressures and volume overload.¹³ Diuretics may also be useful in patients with elevated systolic blood pressures in conjunction with vasodilators.¹³

Inotropic agents (dobutamine, milrinone) directly stimulate the myocardium, increasing cardiac contractility and cardiac output. However, data from clinical trials demonstrate that inotropic agents have significant adverse consequences on patient morbidity and mortality. They are proarrhythmic, increase cardiac workload, and have led to increased hospitalization rates and increased mortality when used chronically. They should be used only to maintain patients with symptomatic hypotension until further therapy such as an intra-aortic balloon pump can be implemented.

Vasodilators reduce preload and afterload to enhance ventricular function and cardiac output. Vasodilators, such as nitrates, are recommended as first line therapy in patients with elevated systolic blood pressures.¹³ *Morphine* reduces myocardial oxygen consumption, decreases heart rate, reduces preload and afterload, and decreases sympathetic outflow. Despite its long-standing use in patients with heart

failure, however, there are no well-designed clinical trials demonstrating efficacy on important outcomes. Moreover, the use of morphine is associated with an increased need for intensive care unit admission, primarily due to respiratory depression.¹⁵ As a result, the routine use of morphine is no longer recommended.¹³

Nitroglycerin improves symptoms, reduces preload and afterload, and decreases pulmonary capillary wedge pressure in patients with heart failure. The most significant clinical problem posed by nitroglycerin is tachyphylaxis. When nitroglycerin is used for more than a couple of hours, patients develop tolerance and its beneficial hemodynamic effects do not persist. Despite decades of nitroglycerin use, there are no clinical studies which show benefit on important outcomes such as mortality or readmission rates.¹³

Sublingual administration of captopril has been advocated by some for the treatment of patients with acute decompensated heart failure. The literature to support this practice consists of a single study which used unvalidated outcomes.¹⁶ However, there was a trend toward fewer intubations in the group that received captopril.

Nesiritide, a synthetic BNP, decreases preload and afterload without a direct inotropic effect and does not increase mixed venous oxygen consumption.¹⁷ Nesiritide also suppresses the renin-angiotensin-aldosterone system and reduces levels of norepinephrine, aldosterone, and endothelin. These effects are considered a desirable characteristic since many of the undesirable consequences of heart failure treatment are believed to result from activation of the neurohormonal pathways. It is not associated with tachyphylaxis. Questions have been raised about increased mortality and worsening renal function associated with its use.^{18,19}

Factors Influencing Treatment in the Emergency Department

The decision about which heart failure patients in the ED require treatment and which medications to use must include the time course of the decompensation, the patient's blood pressure and peripheral perfusion, and the degree of pulmonary congestion. Patients who become acutely ill will generally require more aggressive and urgent intervention. The degree of pulmonary congestion can be assessed through physical examination, oxygenation, BNP levels, and radiographic findings. In general, heart failure patients who develop sudden or acute worsening of symptoms will benefit from early initiation of vasodilator therapy. Some patients with chronic or subacute worsening of volume overload can be treated solely by adjusting their outpatient medical regimen and

administering intravenous diuretics in the ED. Many patients presenting to the ED though have some acute worsening of their condition and require vasodilator therapy.

Alternatively, there are some patients who should not receive vasodilator therapy. Vasodilators may be deleterious in patients who are preload-dependent because of severe pulmonary hypertension, critical aortic stenosis, or hypertrophic obstructive cardiomyopathy. Vasodilators should not be used in patients with heart failure who have a sustained systolic blood pressure of less than 90 mm Hg. Many of these patients, particularly those with cardiogenic shock, may require initial blood pressure support with dopamine and dobutamine.

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Advanced Stroke Care: Avoiding Medical-Legal Disasters in the Emergency Department

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Objectives:

1. Describe the danger of the young patient presenting with neurological focality.
2. Identify the pitfalls of posterior circulation ischemic strokes.
3. Describe the rare but critical diagnostic presentation of acute basilar artery occlusion.

Introduction

Emergency Department (ED) management of acute ischemic stroke has become a significant focus of medico-legal attention.^{1,2} With the advent of thrombolytic therapy for acute ischemic stroke came the potential for appropriately selected patients to benefit from such treatment. Correlative to that potential is an expectation that thrombolytic therapy would be offered to all eligible patients in all EDs. Occasionally a retrospective analysis of a patient's care leads to the conclusion that the patient may have been a candidate for thrombolysis yet was not treated. In such circumstances the presumed loss of opportunity to benefit from the therapy becomes the subject of litigation.

Far less common are claims that the use of thrombolytic therapy for an acute ischemic stroke was inappropriate or caused a hemorrhage.

What has become clear is that the preponderance of litigation surrounds a failure to treat ischemic stroke with

thrombolytic therapy. Far less common are claims that the use of thrombolytic therapy for an acute ischemic stroke was inappropriate or caused a hemorrhage. In cases of thrombolytic complications, litigation may also occur. Much to the surprise of the practicing community, these cases which were so feared in the early years of thrombolytic therapy for ischemic stroke have proven to be very rare.

It is evident that there are a series of themes woven into the majority of the claims filed against physicians and hospitals alleging malpractice in the setting of acute stroke care. These will be detailed in this monograph in an attempt to aid the practicing clinician in the care of these patients and to assist in avoiding future litigation.

Common themes which recur in suits filed against physicians when the management of acute stroke care is questioned include:

1. Failure to consider stroke in the differential diagnosis of young patients
2. Failure to recognize presentations of posterior circulation strokes
3. Failure to recognize the pitfalls associated with strokes of the cerebellum
4. Failure to thoroughly document the neurological examination
5. Failure to treat with thrombolytics

Failure to Consider Stroke in the Differential Diagnosis of Young Patients

While younger patients are statistically less likely to have an acute stroke than older patients, the potential remains quite real and when missed the consequences can be devastating. Beyond the obvious clinical implications of a missed diagnosis medico-legally, young patients have more potential quality of life years to lose than older patients and therefore represent a greater potential for monetary damages in legal action. It is important for emergency physicians to realize that young age is a leading "risk factor for missing the diagnosis of stroke."³ There are a number of potential causes of stroke in young patients and while a comprehensive list would be extremely long, some of the more common causes include:

1. Dissection of a carotid or vertebral artery
2. Patent Foramen Ovale / Structural Cardiac anomalies
3. Hypercoagulable states
4. Pregnancy

The majority of the acute presentations to an ED of a young patient, the presence of any of the above may well be unknown. In addition, it must be noted these cases are extremely rare

While younger patients are statistically less likely to have an acute stroke than older patients, the potential remains quite real and when missed the consequences can be devastating.

and any given emergency physician may never see such a case in their entire career. However, on rare occasion there may be historical or clinical clues that such underlying conditions exist. When a young patient presents with a focal neurological complaint and an underlying condition is known or suspected then the clinician must have an increased suspicion for stroke and act accordingly. The following clinical scenarios should alert the physician to consider the diagnosis of stroke.

The patient who presents with neck, occipital or retro-orbital pain in the setting of acute (possibly transient) neurological findings may be suffering from a carotid or vertebral artery dissection leading to neurological injury. This is even more likely if there is any history of recent head or neck trauma, a recent fall or motor vehicle accident even without apparent head trauma, sudden neck pain at the time of strenuous physical activity, or a family history of arterial dissection. While such clues may not be available, aggressive history taking is warranted in the setting of a focal neurological deficit. Further, unlike patients with dissecting aortic aneurysms and neurological findings, the patient with acute ischemic stroke due to extra cranial dissection is not excluded from thrombolysis, based on the underlying pathology.

The patient with a history of a structural cardiac anomaly, a significant murmur, a history of myocardial infarction or heart failure, or a history of valvular disease, presenting with focal neurological findings may well have suffered a cardiac embolism. It is most common that structural lesions such as patent foramen ovale are found only after an “idiopathic” stroke in a younger patient.

Hypercoagulable states are also more commonly diagnosed after the first thrombotic event but may be known prior to a stroke presentation. One cause of stroke in children is sickle cell disease, which can cause stroke at any point in life. Any history in the patient or family of clotting abnormalities should be considered in the patient with neurologic focality.

Finally, few entities are more frightening than complications associated with a pregnancy. The physiological changes associated with pregnancy are vast and one rare complication

is acute stroke. These patients would merit a very high level of care as the coordination of efforts between multiple disciplines is considerable.

Ultimately, focal neurological deficits in young patients may have many explanations. Stroke can present in very young patients and should remain in the differential diagnosis.

Failure to Recognize Presentations of Posterior Circulation Strokes

One of the most challenging aspects of diagnosing acute neurological complaints is deciphering the symptomatology of posterior circulation ischemia. All too often these patients present with confusing symptoms or a constellation of symptoms that are easily attributed to something other than stroke. Some examples of presentations which may be referable to posterior circulation strokes include:

Patients who present with dizziness, headache, nausea and vomiting may have a posterior circulation stroke. This constellation in isolation may represent any number of systemic illnesses and the diagnosis of stroke is rarely entertained in the acute setting. Such presentations when accompanied by any focal neurological complaint, however, should raise the alarm for possible stroke. The cases which rise to the level of medico-legal action commonly have some evidence in the record that neurological injury could have been considered but the complaint or finding was not incorporated into the medical decision making. The old adage “read the nursing notes” is excellent advice. For the patient presenting with:

Headache, nausea, vomiting, AND ...
arm weakness or dysarthria or ataxia or...

The latter complaint may be key and if ignored the diagnosis will surely be delayed or missed altogether.

Another consideration with posterior circulation ischemia is the confusing picture of crossed findings. Patients with vertebrobasilar ischemia may have cranial nerve findings on one side and motor findings of the arm/leg on the other. Here the error of “failure to understand the symptoms” leads to delay or missed diagnosis. These clinical presentations are rare but are the potential herald of a catastrophic brainstem stroke.

Finally, the patient with isolated hemianopsia is all too often missed. It is quite remarkable how often patients do not immediately recognize this loss of vision on one side. While the patient looks quite well to the casual observer they are actually suffering a rather disabling stroke. Patients with homonymous hemianopsia can't drive, must relearn how to walk down a hallway to avoid hitting objects in their now

blind visual fields, and must relearn the management of many otherwise simple tasks as they simply cannot see in one half of their visual field. Checking for visual field defects by direct confrontation as part of your neurological examination is very valuable and adds only seconds to the process.

Failure to Recognize The Pitfalls Associated with a Stroke of The Cerebellum

A stroke of the cerebellar hemispheres, both ischemic and hemorrhagic, are fraught with complications which are often under-appreciated. The problem with these strokes is their presence in an area of the posterior fossa. This anatomical compartment has very little room to spare and any addition to the space, whether it is the hematoma from a bleed or the edema of an infarct, will lead to complications. One of the most feared complications occurs when the swelling from the insult leads to compression of the fourth ventricle, and subsequent rapid development of hydrocephalus. This complication can lead to herniation and death within hours. For this reason cerebellar hemorrhage is the only type of intracerebral hemorrhage where surgery and clot evacuation and/or ventriculostomy is known to be beneficial. The same is often true with large ischemic cerebellar lesions when hydrocephalus becomes an issue.

Failure to Thoroughly Document a Complete Neurological Examination

In most medico-legal cases the chart is a major focus of the debate. What is abundantly clear is that a chart with incomplete documentation of the neurological examination is wide open to interpretation, often years later, by attorneys from both sides of the litigation. While limited charting does not imply poor care, the physician who documents “non focal” as the neurological examination in a possible stroke case has very little to use in their defense when the myriad allegations of missed findings are made. It is important to recognize that there are no real objective data points other than the neurological examination documentation during those critical first few hours of stroke. If the examinations are not well documented then the retrospective review of the case is performed through a very blurry lens.

One common problem with stroke cases is that patients may be considered “too mild to treat” during their acute window, with a medication as potentially dangerous as t-PA. For patients who present with minimal symptoms and later progress, however, the defense of a decision not to treat will have no traction without a well documented and thorough exam. The physician who takes the time to document a

complete neurological exam and details the findings will have a much easier time with any defense. This is especially true if the physician clearly describes the neurological exam at presentation and at ED disposition. While the realities of busy ED care often makes the repeat examination documentation a challenge it is well worth the time in the setting of the neurological patient.

It is important to recognize that there are no real objective data points other than the neurological examination documentation during those critical first few hours of stroke.

Other exam related problems are failure to check or document visual fields, lower extremity strength, gait, and ataxia. The patient reclining in a bed, who can speak intelligibly and raise both arms symmetrically, may appear “non focal” but may still be having an extremely debilitating stroke. The patient with a Posterior Cerebral Artery (PCA) stroke may only manifest with hemianopsia. As described above this is quite debilitating and may not be recognized by the patient early in their course. The patient with the Anterior Cerebral Artery (ACA) stroke may look quite well until leg strength or gait is tested. Only then is the weak leg recognized. Finally, as described above, the patient with the cerebellar stroke may look like a simple headache with nausea unless carefully examined. These findings may be missed but are sure to be found on a subsequent examination when the clinical picture becomes clearer.

Failure to Treat with Thrombolytics

Claims of medical negligence require all of the four following elements:

1. A **Duty** to treat the patient
2. A **Breach** of that duty
3. Injury **Caused** by the breach
4. **Damages** correlative to the injury

The duty to treat a patient in the ED is rarely questioned by either party in litigation, but in cases where a specialist was consulted and no t-PA was administered, the question of “whose duty was it?” can be asked. As we all know, roles and responsibilities blur and blend in the emergency scenario and occasionally become a contested element in a medico-legal case. Thus documentation of medical decision making is critical to a defense should a case come to litigation.

Breach and Causation are the most contentious elements for the physician. The Breach alleged in most emergency medicine stroke management cases is failure to treat a patient with t-PA. The first issue which will be examined is whether the patient was actually a candidate for t-PA therapy. The great challenge for the defense team is that there are a series of inclusion and exclusion criteria which are enumerated and indeed a patient may “meet the criteria” without truly being a good case based on clinical judgment.⁴ The patient’s actual eligibility will ultimately be judged based on the retrospective review of the record, deposition testimony and the opinions of experts. Thus it is critical for the physician caring for the acute stroke patient to document critical decision making in order to ensure that there is little room for misinterpretation later. Keep in mind that it is easy to allege that the patient “had no contraindications” retrospectively and to extrapolate that the patient was “therefore a good candidate” if there is no documentation to refute that claim.

The issue of Causation in these cases generally surrounds the concept that the patient would have received benefit if treated with t-PA and therefore would not have the same neurological insult they ultimately suffered from the stroke. This is an area where expert testimony is enormously important and where opinions about any given case may vary widely. Both the original NINDS t-PA data and the newer ECASS III data have been extensively discussed in the literature and multiple interpretations of the findings have been proposed.⁵ Because the interpretations of the actual data, superimposed on the merits of any given case, are so contentious, expert opinions in any case typically provide the primary basis for defense and prosecution of the stroke case.

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Continuing Medical Education Post-Test

Based on the information presented in this monograph, please choose one correct response for each of the following questions or statements. **Record your answers on the answer sheet on page 28.** To receive Category I credit, complete the post-test and record your responses on the answer sheet. Mail in the return envelope no later than February 1, 2011. A passing grade of 80% is needed to receive credit. A certificate will be sent to you upon your successful completion of this post-test.

ST-segment Elevation Myocardial Infarction (STEMI): Optimal Anti-platelet and Anti-thrombotic Therapy in the Emergency Department

- 1) Which of the following anti-platelet drugs is a Class I recommended treatment for STEMI in the 2007 ACC/AHA Focused Update?
 - a. Clopidogrel 75 mg a day with fibrinolytics
 - b. Glycoprotein IIb/IIIa inhibitors prior to PCI
 - c. Prasugrel 60 mg load prior to PCI
 - d. None of the above
- 2) Based on the EXTRACT trial, what are the effects of substituting enoxaparin for unfractionated heparin in addition to aspirin and fibrinolytic therapy in the ED treatment of STEMI?
 - a. Increase in intracranial hemorrhage
 - b. Reduction in death and MI with a minor increase in bleeding
 - c. Increase in PCI-related mortality
 - d. Reduction in bleeding complications.
- 3) According to the CURRENT trial results, the optimum loading dose of clopidogrel prior to primary PCI for STEMI is:
 - a. 300 mg po
 - b. 600 mg po
 - c. 60 mg po
 - d. No loading dose is needed
- 4) According to the HORIZONS trial, utilization of bivalirudin monotherapy versus heparin/GPI's for primary PCI results in:
 - a. Decreased death, MI, and target vessel reocclusion
 - b. Increased death, MI, and target vessel reocclusion
 - c. A significant reduction in bleeding
 - d. All of the above
- 5) According to TRITON-TIMI 38 trial results, prasugrel provides which of the following benefits over clopidogrel in conjunction with PCI?
 - a. Decreased death and myocardial infarction at one year
 - b. Increased bleeding
 - c. Decreased bleeding
 - d. None of the above

Novel Anti-platelet and Anti-thrombin Therapy for Acute Coronary Syndromes: STEMI and NSTEMI Optimal Anti-platelet and Anti-thrombotic Therapy in the Emergency Department

- 6) Of the following drugs, which does not directly inhibit platelet aggregation:
 - a. Aspirin
 - b. Glycoprotein IIb/IIIa inhibitors
 - c. Clopidogrel
 - d. Prasugrel
 - e. Enoxaparin
- 7) The thienopyridines, clopidogrel and prasugrel, work by inhibiting the P₂Y₁₂ receptor on the platelet.
 - a. True
 - b. False

- 8) The primary biological difference between clopidogrel and cangrelor is that clopidogrel forms a covalent, irreversible bond with its platelet receptor while cangrelor is rapidly reversible and has a short half-life.
- True
 - False
- 9) Prasugrel should not be used in which of the following patients:
- 40 year old female with no illness except NSTEMI
 - 50 year old diabetic male with STEMI
 - 52 year old male STEMI patient with previous TIA now on aspirin
 - 70 year old diabetic female weighing 70kg with STEMI
- 10) Understanding platelet biology and the role of novel agents for treating ACS will help acute care physicians do the following:
- Communicate with cardiology colleagues regarding new therapeutic approaches
 - Provide better care for their patients
 - Provide information input to hospital-wide care pathways for ACS patients
 - All of the above.
- 11) The following is a false statement regarding current STEMI care:
- Median door to balloon benchmark is 90 minutes
 - In the ACTION registry the patients presenting to a PCI capable center have a median door to balloon time within guideline recommendations
 - In the ACTION registry the patients transferred to a PCI capable center have a median door to balloon time within guideline recommendations
 - Current AHA/ACC guidelines recommend that the time of first medical contact be used when determining time to PCI
- 12) New performance measures established by the AHA have determined the following time period as the bench mark for the time a patient presents to a STEMI referral hospital and is diagnosed with a STEMI and the time the patient leaves that hospital for transfer to a PCI center:
- 60 minutes
 - 45 minutes
 - 30 minutes
 - No time frame has been provided as no data exists to determine the optimal time span.
- 13) The Mission Lifeline program was developed by the following organization/organizations:
- American Heart Association
 - American College of Cardiology
 - American Heart Association and the American College of Cardiology
 - The major Cardiology and Emergency Medicine Organizations
- 14) According to Mission Lifeline, which of the following components is part of a STEMI system of care:
- Emergency Medical Services
 - Non-PCI capable Hospitals
 - PCI capable Hospitals
 - All of the above

American Heart Association Mission Lifeline: Developing a STEMI Regional Care System

- 11) The following is a false statement regarding current STEMI care:
- Median door to balloon benchmark is 90 minutes
 - In the ACTION registry the patients presenting to a PCI capable center have a median door to balloon time within guideline recommendations
 - In the ACTION registry the patients transferred to a PCI capable center have a median door to balloon time within guideline recommendations
 - Current AHA/ACC guidelines recommend that the time of first medical contact be used when determining time to PCI

Ideal Management of Acute Heart Failure Syndromes in the ED

- 15) A 57-year-old male tobacco smoker with a history of chronic obstructive pulmonary disease and congestive heart failure presents to the ED with shortness of breath of 2 days' duration. He has 10-step exertional dyspnea and orthopnea. Physical examination reveals scant wheezing and crackles at the bases with 7 cm of jugular venous distention, an S4 heart sound, and no murmur. His baseline BNP level when he feels well in the cardiology clinic is 300 pg/dL. Which of the following best supports a diagnosis of worsening heart failure?
- Chest radiographic evidence of cardiomegaly

- b. A BNP level of 1023 pg/dL
 - c. Chest radiography with cardiomegaly and mild vascular redistribution
 - d. A BNP level of 335 pg/dL
- 16) Which of the following patients with heart failure is the best candidate for initiation of vasoactive therapy?
- a. A 56-year-old woman with a blood pressure of 82/38 mm Hg
 - b. A 7-year-old boy with tetralogy of Fallot and a pulse oximetry reading of 72%
 - c. A 65-year-old man who was transferred from an outside hospital on intravenous sodium nitroprusside and a furosemide drip
 - d. A 52-year-old woman with a blood pressure of 110/70 mm Hg and a pulse rate of 112 per minute in moderate to severe heart failure secondary to an ischemic dilated cardiomyopathy
- 17) Which of the following etiologies of heart failure should not receive aggressive treatment with afterload reduction immediately after ED arrival?
- a. Severe pulmonary hypertension
 - b. Critical aortic stenosis
 - c. Idiopathic hypertrophic subaortic stenosis (IHSS/ASH)
 - d. All of the above
- 18) Which of the following recommendation of the AHA/ACC focused update in heart failure are recommended for upfront management based upon level of evidence A (the highest level of evidence)?
- a. Use BNP or NT pro-BNP in patients with dyspnea if the contribution of heart failure is not known.
 - b. Use beta blockers in the acute setting of heart failure
 - c. Use diuretics for most patients with heart failure as the initial management strategy.
 - d. Use vasoactive medications (such as nitroglycerin) in patients with heart failure and a normal blood pressure.

Advanced Stroke Care: Avoiding Medical-Legal Disasters in the Emergency Department

- 19) High Risk Clinical Scenarios in which Emergency Physicians must have a heightened suspicion for acute stroke include:
- a. Young patients with stroke like symptoms
 - b. Patients with Dizziness and any other focal neurological sign
 - c. Patients with unexplained extensor posturing
 - d. All of the Above
- 20) Which of the following is true regarding acute stroke legal cases:
- a. Symptomatic intracranial hemorrhages after tPA are the most common cause of litigation
 - b. Failure to offer tPA to a potential candidate is a common complaint in legal actions
 - c. Careful documentation of the neurological examination is not helpful in legal defense
 - d. Discordance between the physician note and the nursing notes is a low risk for legal action
- 21) Which of the following is not a required component in a legal action:
- a. Duty to Treat the Patient
 - b. Breach of the standard of Care
 - c. Damages as a result of the Breach
 - d. A disagreement between the physician and the patient

Continuing Medical Education Post-Test Answer Form and Evaluation

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question and complete the evaluation questionnaire.

Mail the answer sheet to:

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