ADVANCING THE STANDARD OF CARE:
Cardiovascular and Neurovascular Emergencies

EMCREG Monograph
From the ACEP 2005 Scientific Assembly
Satellite Symposium
September 26 & 27, 2005
Washington, DC

Produced by EMCREG International
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Produced by
EMCREG-International
[Emergency Medicine Cardiac Research and Education Group]
Dear Colleagues:

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International is pleased to present this monograph representing the proceedings of our satellite symposium at the ACEP Scientific Assembly in Washington, DC, in late September of 2005. This educational monograph presents state-of-the-art pieces on a variety of cardiovascular and neurovascular emergencies of interest to the clinician caring for patients in the emergency department. This material is also present at our www.emcreg.org website in both downloadable hardcopy and webcast formats.

In this monograph, you will find a variety of important topics covered including the CRUSADE Quality Improvement Initiative, clopidogrel's use in ST-segment elevation myocardial infarction, low molecular weight heparins in acute coronary syndromes, dyslipidemia, diagnosis and treatment on acute decompensated heart failure, evaluation of pulmonary embolism, cardiac biomarkers in point-of-care testing, the Stroke Center certification concept, evaluation of transient ischemic attacks, and the role of serum biomarkers in the diagnosis of stroke. We have also included CME questions which will provide Category I CME credit if you are interested. It is our sincere hope that you will find this monograph useful as you prepare to care for patients with cardiovascular or neurovascular emergencies. We appreciate your confidence in allowing EMCREG-International to help you provide outstanding care for patients.

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Sincerely,

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MAXIMIZING THE EFFECTIVENESS OF NSTE ACS CARE UTILIZING THE CRUSADE INITIATIVE: RIGHT PATIENT? RIGHT DOSE?

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OBJECTIVES:
1. Describe the CRUSADE initiative and how it is used to improve adherence to NSTE ACS guidelines in participating hospitals.
2. Describe patterns of care in acute guideline therapy for NSTE ACS, and its utilization in the ED.
3. Describe the relationship between adherence to the AHA/ACC guidelines and patient outcomes in patients with NSTE ACS.
4. Explain the correct dosing of heparin, enoxaparin, and eptifibatide in patients with mild to moderate chronic renal failure.

INTRODUCTION

Although non-ST-elevation acute coronary syndromes (NSTE ACS) represent a well-recognized source of morbidity and mortality for patients with cardiovascular disease, evidence-based therapies shown to improve outcomes for NSTE ACS are frequently underutilized in appropriate patients, especially in the emergency department (ED). The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Unstable Angina/Non-ST-Elevation Myocardial Infarction (NSTE ACS) were promulgated in an effort to standardize and optimize the evaluation, diagnosis, and management of patients with NSTE ACS and to provide physicians with a framework for clinical decision-making. Despite dissemination of these expert recommendations and ED-focused reviews of them in Annals of Emergency Medicine, significant barriers continue to limit the adoption of guidelines in clinical practice and appear to hinder the use of beneficial therapies and interventions in the ED. Unique and creative approaches are therefore needed to stimulate better adherence to practice guidelines and improve the quality of care for patients with NSTE ACS.

The CRUSADE Initiative

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) quality improvement and educational initiative provides an innovative and multi-faceted approach to the education of emergency physicians and cardiologists in the care of patients with NSTE ACS. The CRUSADE Initiative is a multidisciplinary cooperative effort involving over 400 EDs and medical centers across the U.S. It includes a large NSTE ACS registry designed to characterize demographic patterns and risk stratification results in patients who meet diagnostic criteria for high-risk NSTE ACS (chest pain >10 minutes and <24 hours in duration, and either ECG ST-segment depression/transient ST-segment elevation or elevated serum cardiac biomarkers of MI (CKMB or troponin)).

The CRUSADE quality improvement and educational initiative provides an innovative and multi-faceted approach to the education of emergency physicians and cardiologists in the care of patients with NSTE ACS.
The CRUSADE Initiative NSTE ACS registry measures the use of acute NSTE ACS treatment modalities including aspirin, heparin, beta-blockers, clopidogrel, glycoprotein (GP) IIb/IIIa platelet inhibitors, and early catheterization strategies as they are recommended in the ACC/AHA guidelines. The results of a given institution’s treatment patterns are reported back to the participating hospitals, with comparisons to best practice hospitals and national norms. Participating hospitals are then encouraged to provide feedback of their guideline performance to practitioners, either individually or in group settings, in order to improve the care of their NSTE ACS patients. Quarterly feedback reports allow trending of care patterns over time, to follow changes in care with implementation of patient care protocols, standardized orders, or CRUSADE toolbox documentation aids.

Beyond a static registry, these CRUSADE reports are coupled with educational efforts such as investigator meetings for CRUSADE advocates and coordinators, instruction in an assortment of quality assurance tools for utilization in patient care, local and regional educational programs and hospital consultations by the CRUSADE steering committee members, and scientific publications of NSTE ACS risk stratification patterns, treatment effectiveness, and quality assurance results. These educational efforts are targeted at key institutional leaders in cardiology and emergency medicine to maximize quality assurance efforts and improve the utilization of ACC/AHA guideline therapies in NSTE ACS patients. The CRUSADE initiative represents a truly innovative approach to improving care for NSTE ACS patients in the ED as well as in the hospital.

### Defining Patterns of Care

The CRUSADE Initiative was implemented nationally in 2001. By any measure, it has been a remarkable success. At the time of this publication, over 400 hospitals are involved in CRUSADE, with over 150,000 patients analyzed. The patients in CRUSADE remain at very high risk, with an average age of 67 years. Forty percent of the patients in CRUSADE are women, 33% diabetic, 31% have a prior MI, and 20% have prior coronary artery bypass grafting (CABG). Thirty-five percent of the CRUSADE patients have ST-segment depression on their presenting ECG, and 88% have an elevated troponin blood level. The in-hospital mortality for CRUSADE patients remains high at 4.3%, which is more than twice the 7-day mortality in published large randomized controlled NSTE ACS trials.5-7

Acute treatment patterns in the CRUSADE Initiative are summarized in Figure 1. As shown, early (<24 hours) utilization of aspirin, beta blockers, and heparin/LMWH remain fairly high in the US, whereas early utilization of GP IIb/IIIa inhibitors and clopidogrel represent targets for continued quality improvement efforts. Platelet inhibitor therapy remains underutilized in the ED despite the key role of platelets in the pathophysiology of NSTE ACS, and their Class IA recommendation in the ACC/AHA guidelines. Interestingly, an inordinately high 34% of CRUSADE patients receive only aspirin for platelet inhibition in the first 24 hours following hospital admission.

### Figure 1.

Utilization of acute class IA recommended medications within the first 24 hours in patients without contraindications from the CRUSADE Initiative.
The time to catheterization in the US remains suboptimal, however, with an average time of 26 hours, and only 58% of patients receiving catheterization within 48 hours of hospital admission. Longer delays to catheterization place NSTE ACS patients at risk for recurrent ischemia and recurrent MI in the pre-PCI time interval. These recurrent ischemia episodes have been shown to result in significant morbidity and mortality in randomized controlled trials, and underscore the need for aggressive up-front medical treatment of NSTE ACS in the ED and CCU.

**Influence of the CRUSADE Initiative on Guideline Adherence**

The efforts of the CRUSADE Initiative would be in vain if there were no correlation between ACC/AHA guideline adherence and clinical outcomes. In a recent analysis of the CRUSADE database, composite guideline adherence was correlated with in-hospital mortality. Hospitals whose ACC/AHA guideline adherence was in the lower quartile demonstrated a significantly higher mortality than hospitals with top quartile guideline adherence [Figure 2]. The CRUSADE initiative has been active for four-and-a-half years, allowing participating hospitals to receive up to twelve quarterly reports of their ACC/AHA guideline adherence. The results, in terms of improved guideline adherence, have been most gratifying. Utilization rates for all acute therapies have increased from quarter 1, 2002 to quarter 2, 2005 across CRUSADE participating hospitals. Catheterization rates have increased and the time to catheterization has decreased. The upward trends in acute therapy utilization have been gratifying, and participating sites that have increased their guideline adherence two quartiles over a two year period have noted coincident 40% decreases in their in-hospital NSTE ACS mortality. It is not entirely clear whether this improvement in guideline-driven care is due to the CRUSADE Initiative, or simply the result of improvement in national practice patterns, but the correlation of improvement with CRUSADE educational efforts is difficult to discount.

**Figure 2.** Relationship between overall guideline adherence and in-hospital mortality from the CRUSADE Initiative.
Correlation of Patient Risk with Aggressiveness of Care

We have learned many lessons from CRUSADE related to the effectiveness of pharmacologic therapies and catheter-based invasive strategies. One of these involves an analysis of the link between patient risk and the aggressiveness of therapy. Many studies have shown that patients at highest risk of adverse outcomes (such as elderly, congestive heart failure (CHF), chronic renal failure (CRF) and known coronary artery disease (CAD)) receive the most benefit from therapies such as platelet inhibitors and early PCI. Despite demonstrated higher mortality and morbidity in CRUSADE patients such as these, the utilization of aspirin, beta blockers, antiplatelet therapies, and catheterization strategies remains relatively low in high risk versus low risk patients [Figure 3].10 This paradoxical shift in care patterns allows the under-treated high risk patients to drive the 4.3% in-hospital mortality rate in CRUSADE. Quality assurance measures aimed at aggressive utilization of therapies in high risk patients has the potential to lower mortality significantly in the CRUSADE population, and across the nation. As a result, recent CRUSADE educational interventions have targeted the care of the elderly, women, and patients with CRF, CHF or other high risk clinical features.

Figure 3.
Paradoxical acute care patterns - Acute therapy guideline adherence versus patient risk from the CRUSADE Initiative

Appropriate Dosing of Antithrombin and Antiplatelet Therapies

Another lesson from CRUSADE which deserves mention involves the appropriate dosing of antiplatelet and antithrombin therapies in elderly patients with mild chronic renal failure. The overall transfusion rate in CRUSADE patients is approximately 10%, while in patients over 75 years old, it exceeds 18%.11,12 The reasons for this excessive bleeding in the elderly are probably multifactorial, but one possible explanation involves the inappropriate dosing of antithrombin or antiplatelet medications in elderly patients with undiagnosed chronic renal insufficiency. Analysis of the CRUSADE database illustrates that the majority of patients over 75 years old have creatinine clearances less than 50. Many of these patients have normal or near-normal creatinine levels, leading physicians to assume that they have normal renal function. These patients tend to receive overly high doses of heparin, enoxaparin, and GP IIb/IIIa inhibitors. They also tend to bleed at inordinately high rates when excessively dosed [Figure 4]. These extraordinary findings from CRUSADE led to an FDA label change for eptifibatide, and wide-spread education regarding the calculation of creatinine clearance in elderly patients prior to the initiation of GP IIb/IIIa inhibitors or an-

Figure 4.
Bleeding rates associated with excessive dosing of antiplatelet and antithrombin therapies from the CRUSADE Initiative
tithrombin therapy. Standardized protocols or standing orders for the utilization of these therapies should include the automatic calculation of creatinine clearance using the Cockcroft-Gault Equation (Table 1).

Table 1.

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<tr>
<td>Unfractionated heparin</td>
<td>Use weight-based dosing</td>
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<tr>
<td></td>
<td>Bolus: 60-70 U/kg → Infusion: 12-15 U/kg/hr</td>
</tr>
<tr>
<td>LMW heparin: enoxaparin</td>
<td>Use weight-based dosing</td>
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<tr>
<td></td>
<td>↓ to 1 mg/kg SC q24 hr, if CrCl &lt; 30 cc/min</td>
</tr>
<tr>
<td>GP IIb/IIIa: eptifibatide</td>
<td>↓ infusion to 1.0 µg/kg, if CrCl &lt; 50 cc/min</td>
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\[
CC = \frac{(140-\text{age})(\text{body weight in kg})}{72 \times (\text{serum creatinine})}
\]

* Dosing information collected in CRUSADE beginning first quarter of 2004
LMW=low molecular weight; GP=glycoprotein; CC=creatinine clearance

Reduction of dosing errors in the elderly should reduce bleeding complications, and may encourage practitioners to be more aggressive in elderly high risk NSTE ACS patients.

SUMMARY

The CRUSADE Initiative remains a powerful tool to increase adherence to published ACC/AHA guidelines for the care of patients with NSTE ACS. Improvement in adherence with the guidelines remains tightly correlated with improvement in outcomes in patients with NSTE ACS. Lessons from the CRUSADE Initiative, such as the linking of patient risk to aggressiveness of therapy, and appropriate dosing of antiplatelet and antithrombin therapies, should continue to improve outcomes, and ensure that the appropriate NSTE ACS patient receives the right therapy, at the right dose.

Recent CRUSADE educational interventions have targeted the care of the elderly, women, and patients with CRF, CHF or other high risk clinical features.
REFERENCES


OBJECTIVES:
1. Describe the mechanism of action for the thienopyridine derivative, clopidogrel, to inhibit platelet aggregation in patients with acute coronary syndrome.
2. Describe the indications for the use of clopidogrel in patients with unstable angina and non-ST-segment elevation myocardial infarction based on the CURE trial.
3. Describe the results from the administration of clopidogrel in patients with ST-segment elevation acute myocardial infarction based on the findings from the COMMIT and CLARITY trials.

INTRODUCTION
Clopidogrel is a thienopyridine derivative that selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and thus prevents numerous ADP-mediated platelet responses including dense and alpha-granule release, thromboxane A2 synthesis, P-selectin expression, and glycoprotein (GP) IIb/IIIa receptor activation.\(^1\) In addition, some data suggest that clopidogrel may have secondary anti-inflammatory activity as well.\(^2,3\) Clopidogrel is a prodrug that itself has no appreciable effects on platelet activity and must be transformed into an active compound by the hepatic cytochrome P450 system.\(^4\) In the absence of a loading dose, it takes approximately 3-5 days for the antiplatelet effects of 75 mg of clopidogrel daily to reach steady-state. The use of a 300-600 mg loading dose, even in the setting of chronic therapy, greatly accelerates that process and allows substantial platelet inhibition to be achieved after several hours.\(^5,6\)

Unstable Angina (UA) and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI)
The CURE trial randomized 12,562 patients presenting within 24 hours of symptom onset of UA/NSTEMI to either clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo.\(^7\) All patients got aspirin (75-325 mg) and most received heparin. At an average of nine months follow-up, clopidogrel therapy was associated with a significant reduction in the primary composite end-point of death from cardiovascular causes, nonfatal myocardial infarction, or stroke (9.3% vs. 11.4%, \(P<0.001\)). There was an increase in major bleeding (3.7% vs. 2.7%) but not in life-threatening bleeding or hemorrhagic stroke. Post-hoc analysis revealed that clopidogrel conferred long-term benefit to patients across the entire risk spectrum as defined by the TIMI risk score at the time of presentation\(^8\) and that a benefit emerges as early as 24 hours after initiation of therapy.\(^9\)
ST-Segment Elevation Myocardial Infarction and Thrombolysis

Fibrinolytic therapy remains the most commonly used treatment modality aimed at restoring blood flow in the acutely occluded coronary artery for patients presenting with STEMI worldwide. Despite its proven mortality benefits and wide spread acceptance, thrombolysis is limited by inadequate initial reperfusion and subsequent reocclusion of the infarct related vessel in a significant number of patients.

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) – Thrombolysis in Myocardial Infarction (TIMI) 28 trial evaluated the efficacy of adding clopidogrel to standard thrombolytic regimens including a fibrinolytic, aspirin, and heparin (unfractionated or low-molecular-weight heparin) in 3491 patients 18-75 years of age, presenting within 12 hours of symptom onset with a STEMI. Patients were randomized to clopidogrel (300 mg loading dose followed by 75 mg daily) or placebo at the time of enrollment. Per protocol, all patients were to undergo coronary angiography 48-192 hours after the start of the study medication to determine late patency. After angiography, study medication was discontinued and it was recommended physicians start open-label clopidogrel in patients undergoing PCI. The primary end point was a composite of an occluded infarct related artery (TIMI grade 0-1 flow) on angiography or death or recurrent MI before angiography. Patients were also followed for 30 days for clinical events including death from cardiovascular causes, recurrent myocardial infarction, and recurrent ischemia requiring urgent revascularization.

The addition of clopidogrel to standard thrombolytic regimens resulted in a 36% reduction in the odds of the primary endpoint (15.0% vs. 21.7% P<0.001) (Figure 1). The results were consistent across a broad range of prespecified subgroups based on age, sex, infarct location, type of fibrinolytic, and type of heparin. Clopidogrel also resulted in a 20% reduction in the odds of cardiovascular death, recurrent myocardial infarction, or recurrent ischemia requiring urgent revascularization through 30 days (P=0.026) (Figure 2). The analysis of several safety end-points including the incidence of major bleeding, intracranial hemorrhage, and minor bleeding showed no differences between the treatment groups.

Figure 1.
The findings from the CLARITY-TIMI 28 trial based on the primary endpoints of an occluded coronary artery on angiography or death/recurrent myocardial infarction before angiography.

Figure 2.
Thirty-day clinical endpoint for CLARITY-TIMI 28 [cardiovascular death, myocardial infarction, recurrent ischemia leading to urgent revascularization].
Complementing CLARITY-TIMI 28, the recently presented Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) / Chinese Cardiac Study (CCS) 2 also evaluated the role of clopidogrel in the management of STEMI.\textsuperscript{15} This very large randomized, double-blind, factorial (2x2) design trial enrolled nearly 46,000 patients in China within 24 hours of the onset of an acute MI. All patients received aspirin and roughly one half of the patients received a fibrinolytic. Treatment with clopidogrel was associated with a 9\% reduction in the rate of death, reinfarction, or stroke through index hospitalization (9.3\% vs. 10.1\%, \(P=0.002\)) and a 7\% relative risk reduction in the rate of death alone (7.5\% vs. 8.1\%, \(P=0.03\)), the two co-primary endpoints [Figure 3]. There was no excess in major bleeding or intracranial hemorrhage.

**Prehospital Therapy**  
In the CLARITY-TIMI 28 ambulance substudy, 216 patients in France, the United Kingdom, and Sweden were randomized in the ambulance to receive clopidogrel or placebo, along with a fibrinolytic, aspirin, and heparin.\textsuperscript{16} Compared to those treated in the hospital, treatment in the ambulance resulted in a significant shortening of the duration of ischemic symptoms (median 3.0 hours vs. 4.0 hours, \(P<0.001\)). Prehospital therapy also was associated with a higher proportion of patients achieving complete ST-segment resolution by 90 minutes after study medication (47\% vs. 37\%, \(P=0.02\)). Angiographic and clinical events were similar in the two groups. Prehospital therapy was safe with no excess in TIMI major bleeding or intracranial hemorrhage. Among the 216 patients treated in the ambulance, treatment with clopidogrel resulted in trend toward a 40\% reduction in the odds of having a closed infarct-related artery or death or myocardial infarction before angiography (OR 0.60, 95\% CI 0.30-1.17), consistent with the results seen in the overall trial. Again, there was no excess in TIMI major bleeding or intracranial hemorrhage.

**Percutaneous Coronary Intervention (PCI)**  
In the setting of PCI, the addition of a thienopyridine to treatment with aspirin has been shown to be superior to aspirin alone in both the ISAR and STARS trials.\textsuperscript{17,18} An unresolved question, however, is whether clopidogrel treatment should be started before the PCI. In the setting of PCI, platelet activation is immediate\textsuperscript{19} and therefore, given the pharmacokinetics of clopidogrel,
may be incompletely suppressed if treatment is initiated only at the time of PCI.

The PCI-CURE study presented data on 2,658 patients who had been enrolled in the main CURE trial and who subsequently underwent PCI.20 A significant 30% reduction in the composite endpoint of cardiovascular death, myocardial infarction, or urgent target vessel revascularization at 30 days after PCI was observed in patients pretreated with clopidogrel (4.5% vs. 6.4%, P=0.03). As the trial was conducted at sites that followed a generally conservative approach to patient management, however, the median time to PCI was 10 days, longer than typically is the case in the United States.

The CREDO trial examined the benefit of clopidogrel pretreatment before elective PCI in approximately 2100 patients.21 Pretreatment resulted in a trend towards an 18.5% reduction in the risk of odds of death, MI, or urgent target vessel revascularization through 28 days after PCI. Analysis by the duration of pretreatment found that patients in whom clopidogrel was initiated at least 6 hours prior to PCI had a 38.6% reduction in events with a strong trend towards statistical significance (P=.051). Of note, following PCI all patients received only 75 mg of open-label clopidogrel. Therefore, patients that did not receive clopidogrel pretreatment never received a loading dose of clopidogrel, which does not reflect current practice patterns in the United States.22

Analogous to PCI-CURE, the PCI-CLARITY study examined 1863 patients undergoing PCI after angiography in
CLARITY-TIMI 28. Importantly, angiography was mandated in CLARITY-TIMI 28 and was carried out in all but 4% of surviving patients. In PCI-CLARITY, the rates of both angiography and PCI were identical in the two treatment arms. Pretreatment with clopidogrel resulted in a significant 46% reduction in the odds of cardiovascular death, MI, or stroke following PCI (3.6% vs. 6.2%, P=0.008). Moreover, benefits were seen whether or not patients received a GP IIb/IIIa inhibitor at the time of PCI and whether or not patients received a loading dose of open-label clopidogrel at the time of PCI. Pretreatment with clopidogrel also resulted in a significant 38% reduction in the odds of MI or stroke prior to PCI (4.0% vs. 6.2%, P=0.028). Overall, looking at events from randomization to 30 days, pretreatment with clopidogrel resulted in a highly significant 41% reduction in cardiovascular death, MI, or stroke (7.5% vs. 12.0%, P=0.001). This benefit translates into a number needed to treat of 23 patients to prevent 1 major cardiovascular event. In terms of safety, there was no significant excess in the rates of TIMI major or minor bleeding.

**SUMMARY**

In conclusion, clopidogrel administration has been shown to benefit patients across the spectrum of acute coronary syndromes. In CURE, clopidogrel reduced the risk of death, MI, or stroke in patients with UA/NSTEMI, with a clear benefit emerging as early as 24 hours after initiation of therapy. With the recent results of CLARITY-TIMI 28 and COMMIT/CCS-2, compelling data exist that the addition of clopidogrel to thrombolytic therapy for STEMI improves infarct-related artery patency and reduces ischemic complications including mortality. The addition of clopidogrel to prehospital thrombolytic therapy has been demonstrated to be feasible, with prehospital thrombolytic therapy facilitating more rapid resolution of ischemic symptoms and ST-segment elevation. PCI-CURE, CREDO, and now PCI-CLARITY have demonstrated that pretreatment with clopidogrel before PCI reduces cardiovascular death or myocardial infarction both before and after PCI.

In PCI-CLARITY, the rates of both angiography and PCI were identical in the two treatment arms. Pretreatment with clopidogrel resulted in a significant 46% reduction in the odds of cardiovascular death, MI, or stroke following PCI (3.6% vs. 6.2%, P=0.008).
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LOW-MOLECULAR-WEIGHT HEPARIN FOR NON-ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

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OBJECTIVES:
1. Explain the role of antithrombotic therapy in the management of non-ST-segment-elevation acute coronary syndrome (NSTE ACS)
2. Explain the differences between low-molecular-weight heparins (LMWH) and unfractionated heparin (UFH)
3. Discuss the most recent clinical trial data comparing LMWH and UFH in NSTE ACS

INTRODUCTION

There is a strong evidence basis for the use of anticoagulant therapy in the management of ACS. Anticoagulants currently approved for use in ACS by the US Food and Drug Administration includes unfractionated heparin (UFH), low molecular weight heparin (LMWH), and hirudin. Hirudin is a direct thrombin inhibitor indicated only for anticoagulation in patients with a history of heparin-induced thrombocytopenia (HIT); serial platelet counts should be followed when UFH is used.

UFH exerts its anticoagulant effect by binding with circulating antithrombin III and then accelerating that enzyme’s inactivation of factor IIa (thrombin), factor IXa, and factor Xa. UFH is a heterogeneous mixture of glycoprotein strands that range in weight from 3 to 30 kDaltons. Because the length of the chain determines relative activity against various coagulation factors, UFH exerts an unpredictable anticoagulant effect. Its bioavailability is also limited by its dose-dependent clearance from the body and by indiscriminant binding to various plasma proteins, blood cells, and vascular endothelial cells. UFH must therefore be administered by continuous IV infusion and its activity must be measured by and titrated against frequent assays of the partial thromboplastin time (PTT). The utility of UFH is further compromised by a clinically significant incidence of heparin-induced thrombocytopenia (HIT); serial platelet counts should be followed when UFH is used.

There are currently two LMWHs (enoxaparin and dalteparin) approved for use in the US. These are enzymatic depolymerization products of UFH. They are shorter chains that have relatively lower activity against factor IIa than does UFH. Activity against factor Xa is retained, and consumption by extraneous activities is curtailed. The clearance of LMWHs is dose-independent, lengthening their half-life and making their anticoagulant activity both more reliable and sustained. LMWHs can therefore be administered by the subcutaneous route once or twice daily. The incidence of HIT is much lower with LMWH than with UFH.
Disruption of a coronary atherosclerotic plaque results in generation of thrombin (factor IIa) and activation of platelets. The efficacy of UFH in ACS is thought to be derived from its indirect inhibition of formed thrombin; it does not appreciably inhibit the generation of thrombin. Seven randomized, placebo-controlled trials have evaluated the efficacy of UFH in ACS; these trials together indicate that the early administration of UFH is associated with a reduction of borderline statistical significance in the incidence of AMI and other ischemic complications in patients presenting with NSTE ACS. This effect appears to be independent of, and additive to, the efficacy of aspirin (ASA). Further, continued ASA use may diminish the effect of reactivation thrombosis thought to occur following discontinuance of UFH therapy.

The LMWHs are more potent inhibitors of thrombin generation than is UFH, and are resistant to inhibition by activated platelets. The antithrombotic activity of LMWH stabilizes the disrupted plaque and decreases plaque propagation. Although the LMWHs are frequently discussed as a class, there are distinct differences between enoxaparin and dalteparin. They differ in terms of their relative anti-IIa and anti-Xa activities and their sensitivity to inhibition of platelet factor 4. In addition, enoxaparin is associated with lower release of the prothrombotic von Willebrand factor in unstable angina than dalteparin or UFH. Finally, the evidence from trials directly comparing the various LMWHs to UFH appears to be most supportive for enoxaparin.

In the FRISC study, SQ dalteparin was found to be superior to placebo in reducing the risk of death, MI, or revascularization in patients with UA/NSTEMI at six days after presentation. The two groups were, however, indistinguishable at 40 days. There have been four large randomized trials directly comparing LMWH with UFH. In both the FRIC study of dalteparin and the FRAXIS study of nadroparin, LMWH was found only to be equivalent to UFH in NSTE ACS patients, despite sometimes extended courses of therapy with the LMWH agent.

The ESSENCE study compared enoxaparin 1mg/kg SQ q 12h to standard UFH 5000U bolus + infusion titrated to keep aPTT between 55 and 86sec, over 2-8 days. The median duration in both groups was 2.6 days. Using the same clinical endpoints as were used in FRISC and FRIC, enoxaparin was associated with a statistically significant reduction in adverse cardiac events at 8, 30, and ultimately, 365 days when compared with UFH. The TIMI-11B trial also compared enoxaparin to UFH in UA/NSTEMI patients, but utilized an additional intravenous bolus of enoxaparin (30mg, independent of patient body weight) and an extended treatment arm (out to 6 weeks, 1mg/kg SQ q 12h). Enoxaparin use yielded statistically significant reductions in the triple cardiac endpoint compared to UFH early on, and at one and six weeks. The reductions in these endpoints persisted for at least one year, and it is notable that the benefit was independent of the extended outpatient treatment regimen.

A meta-analysis of the ESSENCE and TIMI-11B results showed that enoxaparin provided a statistically significant reduction in the double irreversible endpoint of death and MI at all time intervals considered, when compared to UFH. These advantages were realized without an increased risk of significant bleeding. There are no data that directly compare the different LMWH agents to each other, but in all major studies, LMWHs are at least as effective as UFH. Accordingly, LMWH—especially enoxaparin—should be considered for the medical management of all ACS patients who present without ST-segment elevation. This approach is entirely consistent with the comfort and convenience levels many emergency physicians and ED nurses associate with LMWH use.
Transitioning medically managed patients to the cardiac cath lab on enoxaparin has been the subject of several subsequent studies conducted in the context of a more aggressive approach to early revascularization and more frequent use of clopidogrel and glycoprotein (GP) IIb/IIIa antagonists.\textsuperscript{21-28} The two most recent trials, A to Z (Aggrastat to Zocor)\textsuperscript{28} and SYN-ERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors),\textsuperscript{25} found statistically insignificant trends toward reduction of the composite of death and MI with enoxaparin, coupled with trends toward excess bleeding. However, in both trials a larger treatment effect in reduction of ischemic events was found in patients who had not been treated with antithrombin therapy prior to randomization (approximately 25% of the enrolled patients), a strategy more consistent with contemporary evidence-based ED practice. Further, the SYNERGY study is problematic in its interpretation for the emergency physician because of the frequency of post-randomization protocol violations that dilute the purity of the comparison between enoxaparin and UFH. A systematic overview\textsuperscript{29} of the 6 randomized controlled trials comparing enoxaparin and UFH in NSTE ACS, considering 21,946 patients overall, found no difference in 30-day mortality (3.0% vs. 3.0%; OR, 1.00; 95% CI, 0.85-1.17). In patients treated with enoxaparin, there was a significant reduction in the composite end point of 30-day death or MI (10.1% vs. 11.0%; OR, 0.91; 95% CI, 0.83-0.99; number needed to treat, 107). Further analysis of the efficacy end-points for patients receiving no prerandomization antithrombin therapy demonstrated a decreasing trend in mortality in favor of enoxaparin. No significant difference was detected through 7 days after randomization in transfusion or major bleeding in the overall safety population or in the no-prerandomization therapy group. A modest but statistically significant increase in major bleeding was detected in the analysis of the no-prerandomization therapy population during hospitalization (OR, 1.34; 95% CI, 1.06-1.70), but there was no difference in blood transfusions (OR, 1.04; 95% CI, 0.85-1.27), which calls into question the clinical significance of the difference in bleeding rates.

**SUMMARY**

It is perhaps understandable that in contemporary ACS management, in which multiple modalities of medical management are used and may be supplemented by an intervention, the specific benefit of any single agent may be difficult to elicit. Nonetheless, the most recent studies and analyses indicate that even in the setting of rapid transition to intervention for NSTE ACS, enoxaparin is at least as effective as UFH and is appropriate for empiric use in the ED. An overarching, evidence-based, multidisciplinary approach to antithrombotic therapy is most likely to be associated with optimal outcomes for NSTE ACS patients.

The LMWHs are more potent inhibitors of thrombin generation than is UFH, and are resistant to inhibition by activated platelets.

\textsuperscript{29} A meta-analysis of the ESSENCE and TIMI-11B results showed that enoxaparin provided a statistically significant reduction in the double irreversible endpoint of death and MI at all time intervals considered, when compared to UFH.
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INTRODUCTION

The “Missing Link” of Cardiac Risk Factors

When evaluating a patient with potential acute coronary syndrome (ACS), every emergency physician immediately attempts to assess the patient’s level of risk. He or she rapidly uses all available information directly off the initial patient emergency department (ED) record to formulate an initial impression. Many times, further diagnostic and treatment measures are dictated by even those few pieces of information.

Following the steps of a history and physical examination, the initial assessment and the true ED workup and treatment begins.

The first few minutes of the evaluation reveal important factors such as age, sex, family history of coronary heart disease (CHD), blood pressure, diabetes mellitus, and tobacco use. Few charts have documented the seventh risk factor, “high cholesterol” or “dyslipidemia”. Many patients do not know their lipid status or are not adequately treated. Several of the cardiac risk factors such as age, sex, and family cannot be helped or changed. Only blood pressure, diabetes, tobacco use, and dyslipidemia can be considered to be “modifiable” risk factors. Modifiable risk factors also offer the opportunity for primary and secondary prevention. As further information about dyslipidemia unfolds, emergency physicians (EP) have to understand the associated risk stratification and treatment ramifications of this previously “missing link” in the ACS evaluation. The goal of this section is to familiarize the EP with common definitions, diagnoses, side effects, and treatment recommendations regarding patients with dyslipidemia while also predicting future implications for emergency medicine.

Dyslipidemia-Definitions and Statistics

Dyslipidemia most often refers to high levels of low density lipoprotein cholesterol (LDL-C). It is well known that an elevated LDL level is one of the major modifiable risk factors for the development of coronary heart disease and there is currently significant emphasis on its treatment.
We know from the recent guidelines and attention to dyslipidemia several remarkable facts.1,2

1) Less than 50% of patients who qualify for lipid modifying treatment for risk reduction receive it.

2) In patients with symptomatic CHD, less than 50% receive a lipid lowering agent.

3) Less than a third of treated patients are achieving their guideline recommended LDL goal.

4) Fewer than 6% of office-based visits include cholesterol screening.

**LDL As the Target of Therapy and Current Treatment Guidelines**

The National Cholesterol Education Program (NCEP) published their first guidelines on cholesterol screening and treatment in 1988.3 In the following years, with an increase in several safe and effective cholesterol lowering medications, the medical community realized strong evidence for LDL-C reduction in patients with CHD. With the publication of the second set of such guidelines (ATP II) aggressive identification and pharmacologic treatment in appropriate patients has now been in place for over ten years.4 More trials and further compelling evidence establishes the importance of an aggressive approach to identification and treatment of dyslipidemias.


Since the second report of the National Cholesterol Education Program in 19944, multiple prospective studies have clearly demonstrated that elevated levels of LDL-C are a major risk factor for the development of CHD and that treatment with statins reduces the risk for major coronary events. Since the 2001 ATP III publication, five major clinical trials evaluating statin therapy have been published. These studies confirmed the value of statins in high-risk patients including those with CHD, other occlusive arterial disease, diabetes, the elderly, and patients with hypertension. These trials included the Heart Protection Study, Pravastatin in elderly individuals at risk of vascular disease (PROSPER), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).6-9 Subsequently, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial demonstrated that intensive statin therapy could decrease LDL-C levels to <70 mg/dL, compared with standard dose statin therapy. The composite cardiovascular endpoint of death from any cause, myocardial infarction, documented unstable angina requir-
Despite the significant press given to myopathy as a side effect, it occurs in less than 1% of patients on statins.

**HMG CoA Reductase Inhibitors - The Statins**

The growing class of medications called “statins” has become the cornerstone of dyslipidemia therapy. Patients generally start on these medications once other causes of dyslipidemia have been eliminated such as hypothyroidism, nephrotic syndrome, and liver disease. Most patients with established CHD should be on statins as well as those who meet established guidelines for therapy. Pre-screening for statin initiation includes baseline determinations of liver enzymes and creatine kinase (CK).

With so many patients on statins, the EP should know about the most common associated complications and adverse reactions. While the most common side effects include headache and dyspepsia, myopathy is considered to be the most significant adverse effect of this class of medications. Despite the significant attention given to myopathy as a side effect, it occurs in less than 1% of patients on statins. Myopathy is more common in patients who are older, have multi-system disease, are on multiple medications, and present in the perioperative period. Patients may present with muscle pain, weakness, dark urine, and even rhabdomyolysis. Creatine kinase levels greater than three times

**Table 1.**

Summary of the proposed updated ATP III recommendations based on recent clinical trials.  

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC*</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk:</strong> CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL (100-129 mg/dL: consider drug options)</td>
</tr>
<tr>
<td><strong>Moderately high risk:</strong> 2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL (100-129 mg/dL: consider drug options)</td>
</tr>
<tr>
<td><strong>Moderate risk:</strong> 2+ risk factors (10-year risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td><strong>Lower risk:</strong> 0-1 risk factors</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

*TLC = therapeutic lifestyle changes  
*10-year risk = Framingham score
the upper limit of normal in symptomatic patients should prompt close follow-up. Rhabdomyolysis should be treated in the conventional fashion with fluid resuscitation with sodium bicarbonate added to normal saline. Levels greater than ten times the upper limit of normal levels for CK are very worrisome and strong consideration should be given to discontinuing treatment.\(^\text{12}\)

Mild liver transaminase elevations may occur and usually does not reach greater than three times the upper limit of normal. This is also a relatively rare occurrence (0.5-2.0\% of users) and is largely dose dependent.\(^\text{13}\) With such modest elevations, there is little significant symptomatic or clinical concern other than ensuring appropriate follow-up for these patients.

**Lipid Assessment in the Emergency Department – Evidence for Possible Future Approaches**

Whereas present day emergency medicine practice includes assessment of every traditional cardiac risk factor for acute coronary syndrome (ACS) with the exception of dyslipidemia, the future may be different. Three separate studies have demonstrated the feasibility of performing lipid screening in the ED and adjacent chest pain units.\(^\text{14-16}\) In the first study, 19\% of the screened patients had an elevated cholesterol level defined as 200-239 mg/dL. Only 41 (41\%) of the patients returned for follow-up to the hospital’s lipid research clinic and 12 (12\%) to their primary care physician. The authors concluded that the ED might serve as an effective site for mass population cholesterol screening.\(^\text{14}\) In the study conducted by Diercks et al., total cholesterol and high-density lipoprotein cholesterol levels were evaluated in an ED-based chest pain center population. Half of the patients tested were found to have abnormal lipid levels. The authors concluded that ED-based chest pain centers could be used to successfully screen patients presenting to the ED with elevated cholesterol levels\(^\text{16}\). In the third study, 25\% percent of the patients were found to have dyslipidemia further confirming that patients with chest pain presenting to the ED have a high likelihood of having this risk factor.\(^\text{15}\) All these studies show that dyslipidemias are common in the ED population being assessed for potential ACS. The clinical impact for EPs knowing about this risk factor is as of yet unknown. Furthermore, the patient impact of treating in the ED or referring for outpatient therapy has also yet to be determined.

**STAT Statin Use? – Demonstrating the Benefits of Early Therapy**

While statin administration is not routine in the ED, there are data to suggest that early administration of these agents may be beneficial for patient compliance and more importantly, outcome. It is well known that non-compliance to prescribed medication is an obstacle to all medical treatments. In-hospital initiation of statin therapy has been shown to improve achievement and maintenance of LDL-C target levels in patients with CHD. Furthermore, pre-discharge prescriptions have been shown to improve overall statin adherence. In a study of 600 patients with angiographically diagnosed coronary artery disease, prescription of statins at the time of discharge was associated with

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Myopathy occurs in less than 1\% of patients on statins.

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Early statin treatment in acute myocardial infarction may improve outcome.
improved long-term statin compliance. Additionally, those patients discharged with the statin prescription had a lower mortality rate (5.7% vs. 11.7%; p=0.05) when compared to those patients referred to an outpatient physician. Recommendations from a study of post-discharge lipid management in CHD patients recommended a pre-discharge statin prescription to prevent the patient from getting lost to follow-up or not receiving a statin prescription from the primary care provider. These studies indicate that the hospitalization and perhaps the ED visit present a “teachable moment” and an opportunity in which compliance with medical care can be improved. In a similar fashion, the ED may play a critical role in capturing patients at risk for CHD that are not admitted and may benefit from treatment of elevated LDL-C. There are also data to suggest that early statin treatment in acute myocardial infarction may improve outcome. In a recent publication of data from 300,823 patients in the National Registry of Myocardial Infarction (NRMI 4) registry, patients receiving early statin therapy within 24 hours of the index MI (n=21,978) or those already on a statin (17,118) were compared to those patients who did not receive early statin therapy (126,128) or in those where statin therapy was discontinued (9,411). Statin treatment in the first 24 hours, either new or continued, was associated with a mortality of 4.0% and 5.3%, respectively. In comparison, no statin treatment or discontinuation of statin treatment was associated with a 15.4% and 16.5% mortality, respectively. While this is a retrospective analysis of registry data, it provides strong clinical evidence that early statin treatment may have a cardioprotective effect.

The Metabolic Syndrome
While an EP may not diagnose or specifically treat metabolic syndrome, it is useful to know and understand the term in the context of recent cardiac literature on CHD risk factor modification. This syndrome encompasses several risk factors that are linked closely to insulin resistance. The specific components of this syndrome include abdominal obesity, high triglyceride level, low HDL cholesterol, physical inactivity, hypertension, and elevated blood glucose (Table 2). A patient with three or more of the factors in this table is considered to have metabolic syndrome. At any LDL level, CHD risk is greater in the presence of this condition. Treatment of metabolic syndrome depends on addressing each factor and can include specific treatment for the management of low HDL-C and high triglycerides. Patients with this syndrome are at high risk for CHD and cardiovascular events.

Table 2. Identifying Metabolic Syndrome – Three or more factors needed for consideration of this clinical condition.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference:</td>
</tr>
<tr>
<td></td>
<td>Men: &gt;102 cm</td>
</tr>
<tr>
<td></td>
<td>Women: &gt;88 cm</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Men: &lt; 50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&gt;130/85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>&gt;100 mg/dL</td>
</tr>
</tbody>
</table>

**SUMMARY**
Dyslipidemia is one of the seven major risk factors for CHD. We know that many patients being evaluated for possible ACS have dyslipidemia and more patients will present already being treated for this condition. LDL-C is principle target of therapy and statin agents are the major pharmacologic treatment. Side effects of statins are rare but include myopathy and elevated liver transaminases. There is some evidence to suggest that early identification and treatment of dyslipidemia in high risk patients may improve outcomes. Knowledge about dyslipidemia and its treatment will likely become more important for the EP in the future.
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OBJECTIVES:
1. Describe the optimal approaches to the diagnosis of acute decompensated heart failure (ADHF).
2. Describe the role of brain natriuretic peptide (BNP) in evaluating patients with ADHF.

INTRODUCTION
To determine optimal therapy for patients with acute decompensated heart failure (ADHF), the emergency physician must be able to confidently diagnose patients with heart failure. This requires knowledge of the diagnostic methods used to identify patients with heart failure as well as knowledge of the different etiologies of this disease.

Heart Failure Etiology
The potential etiologies of ADHF are multifactorial. They can be broadly divided into two major categories: (1) the underlying etiology of the heart failure (the baseline cause of dysfunction), and (2) the etiology of the acute precipitant that resulted in worsening from the chronic compensated state. For some patients, particularly those presenting for the first time, these two components may be identical. Coronary artery disease and chronic hypertension are the two most common causes of heart failure; however there are a myriad of other medical conditions that can also result in heart failure. They include dilated, hypertrophic, and restrictive cardiomyopathies; myocarditis; pericardial tamponade; valvular heart disease; and secondary effects of pulmonary diseases or metabolic disorders. Approximately 80% of patients presenting to the emergency department with ADHF have a prior diagnosis of heart failure so determining the etiology of the underlying (baseline) heart failure can usually be obtained by asking the patient or reviewing the medical records.

When the etiology of the underlying heart failure is not known, investigation of the underlying etiology is important to determine whether there is a reversible component of the disease; however, this is usually beyond the scope of the emergency physician. There causes are, however, several etiologies for heart failure that 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 hypertrophic obstructive cardiomyopathy, and pulmonary hypertension. Identification of patients with these conditions is important because aggressive preload and afterload reduction can lead to cardiovascular collapse since these patients cannot increase their forward blood flow through the fixed mechanical lesion (eg, 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, by medication or dietary noncompliance, or by development of new or complicating medical conditions such as ischemia, dysrhythmias, pulmonary embolus, or infection.

**Diagnosis of Acute Decompensated Heart Failure**

The diagnosis of ADHF 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 cannot be relied upon to always guide an accurate and appropriate diagnosis.

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

The Breathing Not Properly study was a multinational study of 1,586 patients who presented to emergency departments 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. In fact, BNP was more accurate than emergency physician estimates of the likelihood of heart failure. 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. 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. Thus, the Breathing Not Properly trial demonstrated that BNP levels have significant clinical utility for both the diagnosis and risk stratification of heart failure patients in the emergency department. Both diastolic and systolic dysfunction are associated with high BNP levels of more or less the same degree.

BNP must be used with caution in certain populations. Although BNP can help differentiate pulmonary from cardiac etiologies of dyspnea, some types of lung disease, such as cor pulmonale and pulmonary embolism, have elevated BNP levels; however BNP is not usually elevated to the same high level as it is in patients with ADHF. In a subgroup of patients with a history of reactive airway disease in the Breathing Not Proper trial, in 417 subjects with a history of asthma or chronic obstructive pulmonary disease without a history of heart failure, 21% were found to have newly discovered ADHF. Only 37% were identified in the ED, while a BNP >100 pg/mL identified 93%. Additionally, BNP levels >100 pg/mL provided diagnostic information beyond that obtained from individual chest radiographic indicators.
There is a significant inverse relationship between body weight (BMI) and BNP levels. 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. As a result, BNP levels should be used with caution in patients with obesity, unless of course baseline BNP values are known. 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 or not, thereby allowing the obese patient to be followed for a new acute decompensation.

The Breathing Not Proper Trial demonstrated that BNP is useful for the diagnosis of ADHF in the ED. The REDHOT Study suggests that BNP might also be useful to improve triage and disposition of patients who present to the ED with heart failure. 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 complaints 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 (976 pg/ml vs 766 pg/ml). With respect to the admitted patients, 11% had BNP levels < 200 pg/ml, which is indicative of less severe ADHF: most of these patients were perceived 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 been safe for discharge. With respect to patients that were actually discharged, 78% had BNP levels >400 pg/mL. At 90 days, mortality was 9%. There was no mortality for those discharged with BNP levels <400 pg/mL. This suggests that use of BNP in the ED might also help determine which well appearing patients are at high risk for a bad outcome over the short term (90 days).

It also suggests that when the clinician thinks the patients is safe for discharge but the BNP level is over 400 pg/ml, the clinician may wish to reconsider the disposition decision. Almost one in ten patients with these characteristics had died at 90 days. Thus, although the REDHOT trial did not demonstrate that admitting these patients to the hospital would 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. BNP levels are 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. Higher BNP levels were associated with a progressively worse prognosis. The relative risk of 6-month ADHF admission or death in patients with BNP levels >230 pg/mL was 24 times the risk of patients with levels less than 230 pg/mL. When combined with troponin I, both troponin I and BNP alone and in combination predict survival in ADHF. Both together have additive prognostic risk.
The utility of BNP to diagnose ADHF is well established however, it’s ability to drive treatment is still under study. REDHOT II is a randomized controlled trial comparing treatment and outcomes of patients where therapy is guided by serial BNP measurements in the experimental group. This study, which should complete enrollment soon, should shed some light on the utility of BNP to guide treatment.

Due to the large volume of data on the clinical utility of BNP, consensus panel guidelines were published last year. These recommendations state:

1. For patients presenting to emergency services with dyspnea, a history, physical examination, chest x-ray, and ECG should be performed together with laboratory measurements that include BNP.
2. As BNP levels rise with age and are affected by gender, comorbidity, and drug therapy, the plasma BNP measurement should not be used in isolation from the clinical context.
3. If the BNP level is <100 pg/mL, then heart failure is highly unlikely (negative predictive value, 90%).
4. If the BNP level is >500 pg/mL, then heart failure is highly likely (positive predictive value, 90%).
5. For BNP levels between 100–500 pg/mL, one should consider the following conditions in the differential diagnosis:
   a. Baseline BNP value due to stable underlying dysfunction
   b. Right ventricular failure from cor pulmonale
   c. Acute pulmonary embolism
   d. Renal failure
6. Patients may present with ADHF with normal BNP levels or with BNP levels below what would be expected can occur in the following situations:
   a. Flash pulmonary edema (<1–2 hours)
   b. Heart failure up-stream from the left ventricle (i.e., acute mitral regurgitation from papillary muscle rupture)
   c. Obese patients (body mass index [BMI] >30 kg/m²)

REFERENCES

OBJECTIVES:
1. Discuss the usual approach to the treatment of patient with acute decompensated heart failure (ADHF).
2. Describe the role of nesiritide in the treatment of ADHF, the physiologic properties of this agent, and current scientific trials data reflecting its use.

INTRODUCTION
The diagnosis of heart failure is becoming common with a prevalence of more than five million patients and over five hundred thousand new cases reported per year. A disease primarily of the elderly, its recent increase is likely due to the general aging of the population as well as improved survival of patients after myocardial infarction or other index events that lead to impaired ventricular function. A clinical syndrome not characterized by a single presentation, heart failure is frequently seen in the emergency department (ED) which is the most common portal of entry for hospital admission. Multiple challenges exist in management of acute decompensated heart failure (ADHF), including appropriate recognition and differentiation from other causes of dyspnea as well as choice of therapeutic regimen. The latter has recently become more of an issue as therapeutic decision-making had been somewhat stagnant over the past two decades due to a paucity of new, effective pharmacologic agents available to treat ADHF. This report will focus on three main objectives: 1) describe the role of nesiritide in the management of ADHF, with particular emphasis on concerns of increased morbidity and mortality recently raised in two meta-analyses; 2) Review additional mortality data not reported in the aforementioned papers in an attempt to further elucidate the potential risk of therapy; and 3) Describe recommendations for current “risk appropriate” use of nesiritide in ADHF, as well as future directions for investigation.

Therapeutic Management of ADHF
Although there are ample data and guidelines from various sources about the management of patients with heart failure, most pertain to chronic management. There is little consensus regarding the pharmacological management of patients with ADHF in the ED. In fact, no acute therapy for ADHF has demonstrated a mortality benefit in a prospective, randomized controlled trial (RCT). Despite their widespread acceptance as standard therapy, surprisingly little clinical outcome data exist for diuretics and the vasodilators nitroglycerin and nitroprusside to support their use in ADHF. Physician familiarity with nitroglycerin use in patients with chest pain makes the combination of nitroglycerin and diuretics frequent first line therapy for ADHF. The predictable effects of these agents on filling pressure and blood pressure have

Nesiritide produces significant reductions in pulmonary capillary wedge pressure, right atrial pressure, and systemic venous resistance within minutes and produces concomitant increases in stroke volume and cardiac output.
made them attractive choices. Nitroprusside can also be particularly useful in patients with acute pulmonary edema associated with hypertensive emergencies. However, there are several limitations to these therapies, including the need for titration, hemodynamic monitoring, and the deleterious effects of neurohormonal activation [Table 1]. This has led to the search for better therapeutic agents, ideally ones that improve acute symptoms and hemodynamics as well as decreasing mortality.

**Nesiritide**
Approved by the Food and Drug Administration (FDA) in 2001, nesiritide became the first commercially available natriuretic peptide used for the treatment of ADHF. It is structurally identical to human endogenous B-type natriuretic peptide (BNP). Although plasma levels of endogenous BNP are elevated in ADHF, the administration of additional exogenous BNP has beneficial effects. Several mechanisms have been suggested to explain this paradox, including BNP receptor down regulation, increased BNP degradation, and post receptor uncoupling at the tissue level. Probably the most important and significant mechanism is the general counter-balancing of vasoconstrictive neurohormones in patients with poor cardiac output. BNP serves as an antagonist to pathologic neurohormonal activation that occurs during heart failure. This feature is common among heart failure pharmacologic agents with proven mortality benefit such as angiotensin converting enzyme inhibitors and beta-blockers.

Nesiritide produces significant reductions in pulmonary capillary wedge pressure, right atrial pressure, and systemic venous resistance within minutes and produces concomitant increases in stroke volume and cardiac output. In addition, it does not possess many of the untoward properties associated with diuretics, inotropes, or other vasodilators [Table 1]. In the PRECEDENT trial, a comparison of nesiritide with dobutamine, the investigators found fewer arrhythmias and no increase in heart rate with nesiritide. Further, readmission rates at 3 weeks and mortality at 6 months were higher in the dobutamine arm. As shown in [Figure 1], data from the VMAC trial demonstrated nesiritide decreased pulmonary capillary wedge pressure more than either nitroglycerin or placebo at three hours and more than nitroglycerin at twenty-four hours. Dyspnea and global clinical status were improved compared to placebo and were similar to nitroglycerin. In addition, nesiritide’s he-

<table>
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<th>Diuretics</th>
<th>Vasodilators</th>
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<tr>
<td>• Decreased renal perfusion</td>
<td>• Tachycardia (NTG, NTP)</td>
<td>• Increased mortality</td>
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<tr>
<td>• Volume depletion</td>
<td>• Tachyphylaxis (NTG)</td>
<td>• Proarrhythmic</td>
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<tr>
<td>• Electrolyte abnormalities (K+, Ca+, Mg+)</td>
<td>• Neurohormonal activation (NTG, NTP)</td>
<td>• Tachycardia</td>
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<tr>
<td>• Neurohormonal activation: ↑ renin-angiotensin aldosterone ↑ sympathetic nervous system</td>
<td>• Thiocyanate toxicity (NTP)</td>
<td>• Neurohormonal activation</td>
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<tr>
<td></td>
<td>• Need for titration (NTG, NTP)</td>
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<td></td>
<td>• Need for invasive monitoring (NTP, ± NTG)</td>
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DHF = acute decompensated heart failure; NTG = nitroglycerin; NTP = nitroprusside

modynamic effects were longer lasting, without a need for up-titration. This was frequently necessary in the nitroglycerin group to maintain adequate reduction in wedge pressure.  

Nesiritide possesses several characteristics that provide convenience and ease of use: 1) no proarrhythmic effect; 2) no tachyphylaxis; and 3) no need for titration (hence not mandating ICU care), making it quite suitable for the ED or observation unit population. In 237 ED observation unit patients randomized to either standard care or at least 12 hours of nesiritide therapy in the PROACTION trial, the investigators report nesiritide use was associated with a 21% decrease in ADHF readmissions and a substantial decrease in the sum length of stay over the ensuing month after the index visit (2.5 vs. 6.5 days, p<0.032). Mortality and complications were uncommon and not statistically different between the two groups.

To date, nesiritide is the only therapy that has been shown in RCTs of ADHF to provide significant symptomatic and hemodynamic improvement compared to placebo plus standard care. Nesiritide has not been studied in a trial prospectively designed or adequately powered to evaluate its effect on mortality. However, data from the multicenter Acute Decompensated Heart Failure National Registry (ADHERE), suggest that patients treated with an intravenous vasodilator (nesiritide, nitroglycerin or nitroprusside) initiated in the ED versus later in the hospital or not at all had lower mortality (4.3% vs. 10.9%, unadjusted, p<0.0001) and shorter hospital lengths of stay (3 vs. 7 days, p < 0.001). These data generate some enthusiasm that early goal directed therapy initiated in the ED for ADHF may be effective and further study is indicated.

**Mortality risk with nesiritide?**

A recent meta-analysis of three trials reported that nesiritide may be associated with an increase in mortality. In this report, the authors conclude that “Compared with non-inotrope based control therapy, nesiritide may be associated with an increased risk of death after treatment for ADHF.” These conclusions were drawn from a compilation of data from three prospective, RCTs in which nesiritide was used in ADHF and 30 day follow-up data were available. Inclusion criteria consisted of the following: randomized, double-blind, parallel study group of patients with ADHF; nesiritide administered as a single infusion for at least 6 hours; control therapy that did not mandate use of positive inotropic agent; and reported 30 day mortality. In this review, 485 patients were randomized to nesiritide and 377 to control therapy. There was a statistically insignificant trend of...
increased 30 day mortality in the nesiritide group 35/485 (7.2%) vs. 15/377(4.0%) control patients; hazard ratio (HR) 1.80, 95% confidence interval (CI) 0.98-3.31; P = 0.057. The authors report that their findings were not conclusive, but only hypothesis generating. They recommend that the possibility of an increased risk of death should prompt an adequately powered, RCT comparing nesiritide to “standard” therapy with nitroglycerin and diuretics.

While this analysis is thought provoking, it is important to view the results in the proper context. None of the RCTs included in this analysis were powered to evaluate mortality. There were few deaths in each of these studies, so the CIs around the HR are wide. Each study was designed differently to achieve a specific endpoint and included dissimilar patient populations, control arms, and concomitant medications. Because of the small size and design of the trials included in the review, some potentially important baseline imbalances exist between the nesiritide group and the “control” group. These baseline characteristics are important as several are associated with an increased mortality in ADHF and were not accounted for in this meta-analysis. Deaths in the VMAC trial account for nearly 75% of the 30-day nesiritide deaths cited in the report, and patients randomized to nesiritide were more likely to have a baseline systolic blood pressure <100 mm Hg and a creatinine clearance <60 mL/min. A lesser known fact is that a number of trials have demonstrated that the use of intravenous inotropes in ADHF is associated with increased mortality. It is important to note that inotrope use was significantly greater in nesiritide patients compared to controls, 96/478 (20.1%) vs. 44/375 (11.7%), p <.001. Hence, all of these imbalances could have contributed to an increase in unadjusted mortality.

**Pooled analysis of all RCT data**

Rather than speculate about the effect of baseline imbalances, poor study design, omission of important data, and lack of adjustment, further analysis of existing additional data is more worthwhile. In April 2005, additional data was presented to the FDA as part of a revised package insert for nesiritide. Data from all seven trials of nesiritide versus standard therapy with at least 30 day reported mortality, including those from the current meta-analysis, were submitted. A critical review of this pooled data was recently reported by Abraham. The findings from this analysis appear to be different than the previously described meta-analysis of Sackner-Bernstein.

As previously noted, these seven trials are not homogeneous with respect to design, clinical endpoints, study population, standardized control therapy, or follow-up. Important trial characteristics are described in Table 2. Mortality data at 30 days are presented for all seven trials whereas six month mortality data are only available in four trials. Data from 1717 patients are available, including 1059 who received nesiritide and 658 in the “control” group. There were 84 (5.3%) deaths in the nesiritide group and 28 (4.3%) in the control group at 30 days, a nonsignificant difference, p= 0.299. Pooled analysis of data reveals a HR (95% CI) of 1.27 (0.81–2.01) for nesiritide relative to control. Because the FUSION trial was essentially an outpatient study of ambulatory patients receiving intermittent infusions of study drug, this study was excluded from the analysis. Figure 2 describes the 30-day mortality data for the seven individual trials and the two pooled analyses.

For 180-day mortality, pooled data from four of the seven RCTs (involving 1167 patients) are analyzed (Figure 3). Overall mortality was 21.7% (154/724) with nesiritide and 21.5% (94/443) with control therapy, HR (95% CI) 1.05 (0.81–1.36), p=0.725. As stated previously, results from FUSION were not included in the pooled analysis and data was only available for 16 weeks of follow-up as opposed to six months as in the other trials. However, during this interval there were 13/141 (9.4%) deaths in the nesiritide group vs. 9/69 (13.5%) in the control group, HR (95% CI) 0.68
The Sackner-Bernstein report is a selective analysis of only a portion of existing data. If all available mortality data are taken together, therapy with nesiritide does not appear to significantly increase the risk of mortality. However, these adverse trends warrant further investigation with a well-designed RCT.

Recent data from ADHERE provides further insight on this issue. Data from more than 65,000 patients who were admitted for management of ADHF were examined. Risk factor and propensity score-adjusted odds ratio (OR) for in-hospital mortality were calculated for a cohort of 15,230 patients who received nitroglycerin, nesiritide, milrinone, or dobutamine. The risk factor and propensity score-adjusted ORs for nitroglycerin were 0.69 (95% CI 0.53 to 0.89, p<0.005) and 0.46 (95% CI 0.37 to 0.57, p<0.005) compared with milrinone and dobutamine, respectively. Corresponding ORs for nesiritide were 0.59 (95% CI 0.48 to 0.73, 0.29–1.60). The Sackner-Bernstein report is a selective analysis of only a portion of existing data. If all available mortality data are taken together, therapy with nesiritide does not appear to significantly increase the risk of mortality. However, these adverse trends warrant further investigation with a well-designed RCT.

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Figure 3. Mortality hazard ratios, 95% confidence intervals (CI), and percent mortality (Kaplan-Meier estimate) for randomized and treated patients with nesiritide relative to control through 180 days for each of the 4 trials in which these data were collected and for a pooled analysis of these 4 trials as well as through week 16 for the FUSION trial. Adapted with permission from Abraham WT. Nesiritide and Mortality Risk: Individual and Pooled Analyses of Randomized Controlled Clinical Trials. Rev Cardiovasc Med. 2005;6(2).

Figure 4. Results of comparative mortality analysis of nesiritide treatment vs. nitroglycerin, milrinone or dobutamine, adjusted for covariates and propensity score. Adapted with permission from Abraham WT, Adams KF, Fonorow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the ADHERE registry. J Am Coll Cardiol. 2005; 46:57–64.

p<0.005) and 0.47 (95% CI 0.39 to 0.56, p<0.005), respectively. The adjusted OR of nesiritide compared to nitroglycerin was 0.94 (95% CI 0.77 to 1.16, p<0.58). In this report, the risk of in-hospital mortality was similar for nesiritide and nitroglycerin and both were associated with significantly lower in-hospital mortality than positive inotropic therapy in patients hospitalized with ADHF [Figure 4]. Although these results are not from a RCT but rather a retrospective review of registry data, the conclusions are still important. The findings are from “real world” patients and the numbers are quite large. The ORs are not only statistically significant, but also clinically relevant. The findings are similar to the pooled analysis[19]
and support the contention that there is no significant risk of increased mortality associated with nesiritide therapy. It should be noted, however, that results and conclusions from pooled analyses are not the same as those obtained from an adequately powered and properly designed RCT.

**Braunwald Panel Report**

An expert panel of cardiology and heart failure clinicians chaired by Eugene Braunwald, M.D. met in June 2005 to review and assess data associated with the use of nesiritide after questions about safety were raised. Scios Incorporated provided additional data from all available trials, including data submitted to the FDA for the original (August 2001) and the current (April 2005) package inserts. The panel convened with the following objectives: 1) review and discuss nesiritide efficacy and safety data; 2) provide guidance on proposed clinical development strategies for nesiritide; and 3) review the current package insert and provide recommendations on the use of nesiritide. After an in depth discussion of substantial additional analyses of existing data, the panel provided the following conclusions and recommendations:

1. **Renal function.** Nesiritide was associated with a dose-dependent increase in serum creatinine, even with the dose recommended for initiation of treatment (0.01 ug/kg/min). The mechanism of these creatinine changes, their duration, implications for survival, longer term renal function and other clinical consequences is not clear. Studies to clarify these issues, including the relationship of renal dysfunction and clinical outcomes, should be conducted.

2. **Mortality.** The panel noted that existing data suggest nesiritide was associated with a trend toward increased mortality at 30 days, with a HR of approximately 1.3. However, the 95% CIs are wide and the total number of deaths in all six of the RCTs (84) was insufficient to accurately determine an excess mortality risk. No increased hazard was identified at 180 days. They also recognized potentially important imbalances in baseline patient characteristics, concomitant treatments, and differences in control groups that may have affected outcomes. Because of the inconclusive nature of these findings, the panel recommended additional studies be conducted to assess the effect of nesiritide on survival.

3. **Clinical trials.** The panel strongly recommended continued enrollment in ongoing and planned trials that are soon to commence. The panel endorsed the manufacturer’s plan to conduct an RCT of several thousand patients to assess further the benefits and risks of nesiritide compared to standard therapy. The panel reiterated that this trial should include patients with ADHF and should be adequately powered to detect clinically important endpoints (mortality and cardio-renal morbidity) at 30-90 days and mortality at 180 days. Study design should incorporate appropriate risk stratification and subgroup analysis to further elucidate relationships between treatment groups and important clinical outcomes.

4. **Mandatory prescribing information.** Nesiritide should be strictly limited to patients presenting to the hospital with ADHF and dyspnea at rest. Clinicians should consider its efficacy, possible risks, and the availability of alternate therapies. Nesiritide should not be used for intermittent outpatient infusion, scheduled repetitive use to improve renal function, or to replace diuretics.

**Recommendations for Clinical Use of Nesiritide**

Appropriate management of ADHF is both challenging and controversial. Adverse trends in short term clinical outcomes from selective reports have caused concerns about the safety of nesiritide. However, the data, when examined in total, fail to firmly establish a deleterious effect. Conclusive evidence identify-
Because of the inconclusive nature of these findings, the panel recommended additional studies be conducted to assess the effect of nesiritide on survival.

Nesiritide should be strictly limited to patients presenting to the hospital with ADHF and dyspnea at rest.

Management of severe ADHF complicated by respiratory embarrassment and/or cardiogenic shock provides the greatest challenge to the ED physician. These patients frequently require complex combinations of vasoactive medications, typically guided by invasive hemodynamic monitoring and airway support in an intensive care unit. The role and beneficial mortality effects of all therapies, including nesiritide, are less clear in this scenario. Fortunately, this represents a minority of patients presenting to the ED.
SUMMARY

In summary, the relationship between cardio-renal interactions, neurohormonal adaptation and clinical events should be a major focus of clinical decision making for ADHF and future drug development. The best approach to these patients, including the role of nesiritide and more traditional therapies such as nitroglycerin and diuretics, remains to be determined. Systematic appraisal of all existing data, thoughtful design of prospective clinical investigations, and evidence based, protocol and guideline driven care are ultimately critical to the current successful management of ADHF in the ED.

Figure 5. Algorithm for the early stabilization of acute decompensated heart failure in the emergency department. ADHF = acute decompensated heart failure; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; CXR = chest radiograph; ECG = electrocardiogram; ETT = endotracheal tube; ICU = intensive care unit; LVH = left ventricular hypertrophy; NIV = non-invasive ventilation; O2SAT = oxygen saturation; prn = as needed; SBP = systolic blood pressure; SL = sublingual. Reproduced with permission of Peacock W et. al. Management of Acute Decompensated Heart Failure in the Emergency Department. Cong. Heart Fail. 2003; 9;5(1),3-18. Copyright 2003 by CHF, Inc.
REFERENCES


OBJECTIVES:
1. To describe the use of clinical decision rules, combined with D-dimer assays and helical chest computed tomography in the diagnosis and exclusion of pulmonary embolism.
2. To describe the pathophysiology of cardiac failure as a result of pulmonary embolism.
3. To highlight the potential for risk stratification of patients by using vital signs, detection of right ventricular failure with either echocardiography or CT findings, serum biomarkers such as troponin and BNP, and pulse oximetry.

INTRODUCTION
It is important to consider pulmonary embolism (PE) as a cardiovascular disease, rather than only a pulmonary condition, to properly diagnose and treat this disease process. Venous thromboembolic disease (VTE), the source of most PEs, can result in significant cardiac dysfunction that leads to cardiac death.

Mechanism of Death from Pulmonary Embolism
Death from PE typically results from acute heart failure leading to cardiogenic shock. The potential sequence of events from hemodynamically significant PE has been described by Luvaldi and Goldhaber. A large clot, or many smaller clots, lodges in the pulmonary arterial (PA) vasculature, causing an increase in pulmonary vascular resistance which leads to increased afterload on the right ventricle (RV). The RV typically pumps into a low resistance circuit and does not have great reserve to overcome an acute increase in afterload. When the pulmonary vasculature is approximately 40% obstructed, the increased pulmonary vascular resistance exceeds the capacity of the right heart and a number of consequences can occur.

The increase in PA pressure and RV afterload leads to increased RV wall tension as well as an increase in myocardial oxygen demand. At the same time, the RV dilates impairing its function. Coupled with the increase in RV wall tension, the subsequent impairment of coronary perfusion decreases the RV oxygen supply. When the supply-demand relationship deteriorates, RV ischemia and even infarction can occur. This RV ischemia leads to further RV dysfunction and dilation. The RV can enlarge to a size greater than the left ventricle (LV), both as a consequence of RV dilation and decreased size of the LV secondary to a shift in the motion of the septum toward the LV. This shift, along with decreased RV cardiac output, results in decreased LV preload. With LV preload impaired, systemic perfusion decreases and hypotension results. This further impairs coronary perfusion to the RV, and leads to a spiraling cycle of decreasing RV and LV function. The clearest example of this
ADVANCING THE STANDARD OF CARE: Cardiovascular and Neurovascular Emergencies

Table 1. Canadian Score for Pretest Probability

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td>Suspected deep venous thrombosis (DVT)</td>
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<tr>
<td>Alternative diagnosis less likely than pulmonary embolism (PE)</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart Rate &gt; 100 /min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.5</td>
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<tr>
<td>Malignancy (on treatment, treated in past 6 mo, or palliative)</td>
<td>1.0</td>
</tr>
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Figure 1. Charlotte Score: The Probability for PE with a “SAFE” score is 13% which allows for a rule-out with a Turbidometric or ELISA D-dimer.

Kasper et al. describe from a multicenter database nearly a doubling of mortality with each stage of RV failure. In patients with normal blood pressure and RV dilation on echocardiography, they observed a 7% mortality. With a systolic blood pressure of 90 mmHg or less, the mortality doubles to 14%. The presence of shock increases mortality to 23%. The need for cardiopulmonary resuscitation leads to a 60% mortality. Similar findings of graded mortality with RV failure have also been described in another study.

It is clear that embolism to the output track of the right heart can lead to right heart failure, and the extent to which that occurs determines the risk of mortality.

Algorithms for Diagnosis of Pulmonary Embolism

There are currently two validated clinical risk stratification tools to aid in sorting patients which have PE as a possible etiology for their symptoms. Both of these decision tools are intended to be used with a D-dimer screening test. Which decision tool is used partially depends on the D-dimer test available. The first tool is the Canadian Score which has 7 items with varying weights (Table 1). After scoring, the patient is placed into one of three risk categories (Table 2). The strength of this tool is that 40% of patients screened are in the low risk category and the probability for PE in this category is less than 4%. This allows use of a less sensitive D-dimer assay, the Simply Red assay (negative likelihood ratio (LR) = 0.2), to rule-out PE. The Charlotte Score uses a decision algorithm and places patients into a “SAFE” category which allows for use of an Enzyme-linked quantitative (ELISA) D-dimer to Rule out PE. (Figure 1) The risk for PE in the SAFE category is 13%, and 80% of patients fit into that category.
The ELISA D-dimers are very sensitive and have an excellent Negative LR of 0.08.4

Perhaps the greatest advance in the diagnostic approach to PE has been the multi-slice helical chest CT. The 8 and 16 row multi-slice units require less than a 10 second breath-hold and will delineate the pulmonary arteries to the 6th branch. The inter-reader reliability is superior to that of pulmonary angiography. In a meta-analysis of over 4657 patients in 23 publications, the 3 month VTE rate in patients with a negative Chest CT, regardless of generation of scanner, was 1.4%, similar to that of a negative pulmonary angiography.5 The added benefits include establishing alternative diagnoses in 30% of cases and only 5% of CT studies have equivocal interpretations. CT angiography is now considered optimal for evaluating PE.6

Echocardiography for Assessment of Risk for Mortality
Clinicians now commonly use echocardiography to assess RV size and function in the setting of an acute PE. Findings may include RV dilation, an increased end-diastolic RV to LV ratio, septal shift toward the LV or paradoxical septal motion, RV free wall hypokinesis, elevated RV systolic pressure, elevated PA pressure, and severe tricuspid regurgitation. There are no well accepted criteria for the definition of significant RV dysfunction or dilation using echocardiography. This has lead to different results between publications. An end-diastolic RV to LV ratio of > 1 seems to be the most reproducible, though it has not been adequately studied.7

How good is echocardiography in risk stratifying patients by evidence of RV dysfunction? Wolfe reported that of 90 normotensive patients with PE, 40% had RV hypokinesis.8 All recurrent PE’s and deaths occurred in those with identifiable RV hypokinesis. Kasper noted that RV failure carries a three-fold increased risk for all cause mortality and one-year mortality for normotensive patients with RV failure was 12.6% versus 1.3% for those without initial RV failure.9 Riberio reported that of 126 patients, 70 had moderate-to-severe RV dysfunction and all in-hospital deaths occurred in this group.10 Grifoni noted that in normotensive patients with RV dysfunction on echocardiography, 10% go onto shock while 5% expire in-hospital.11 In a systematic review of the current literature, ten Wolde et al. observed that in seven studies all suffered from severe methodological shortcomings. This included the fact that only 782 of 3395 patients with PE had echocardiography and the echocardiographic definition for RV failure was inconsistent.12 Overall the risk for mortality with RV failure was two-fold, however, only two of the studies delineated outcomes with normotensive patients. The authors concluded that a lack of evidence exists at the present time regarding the efficacy of echocardiography to identify normotensive patients at increased risk. The 30-day mortality in patients with normal or near-normal RV function is not clear. The most significant barrier to the use of echocardiography in PE risk assessment by emergency physicians is the lack of its availability 24 hours a day.

Table 2. Interpretation of Canadian Score

<table>
<thead>
<tr>
<th>Score Range</th>
<th>Mean Probability of PE</th>
<th>Patients with Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>3.6%</td>
<td>40%</td>
<td>Low</td>
</tr>
<tr>
<td>3-6</td>
<td>20.5%</td>
<td>53%</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;6</td>
<td>66.7%</td>
<td>7%</td>
<td>High</td>
</tr>
</tbody>
</table>

Markers for Assessment of Risk for RV Dysfunction and Mortality
In 1992, Adams et al. reported an intriguing observation that four of 53 patients with PE had a rise and fall of CK-MB typical for myocardial infarction. Three of these four had evidence of RV dysfunction on echocardiography. None had evidence of LV impairment typical for cardiac ischemia. Giannitsis et al. studied the sensitivity of cardiac troponin T measured within 12 hours of admission in identifying patients at risk for mortality with PE. Troponin T was elevated for 18 of the 56 patients in this study. They used a cutoff of 0.1 ng/mL and eight of the nine in-hospital deaths had an initial elevated troponin level, resulting an Odds Ratio of 29 (95% CI 3.3 - 265). In a regression analysis, troponin T was the only predictor of 30-day mortality, with an adjusted Odds Ratio of 15.2 (95% CI 1.22 - 190.4). The R Positive was 4 and LR Negative was 0.14 for in-hospital mortality, a moderately strong positive and negative predictor of in-hospital mortality. This study’s findings are limited because of the small sample size and few events. In a prospective study of 106 patients with PE, Konstantinides et al. performed serial measurements of both troponin T and I in relation to in-hospital mortality for patients with PE. An elevated troponin I had an OR of 16.9 (95% CI 1.61 – 177.7) whereas troponin T > 0.1 had an OR of 6.5 (95% CI 1.1 – 38.2) for in-hospital mortality. Pruszcyk et al. also prospectively studied 64 normotensive patients with PE using serial troponin T and CK-MB. All eight in-hospital deaths were from the cohort of 29 patients with a positive troponin T, though in one case, the troponin was not positive until the third determination at 12 hours. In addition, CK-MB was elevated in 26% of these patients, though the authors did not indicate the diagnostic performance of this marker. They used a cutoff of > 0.01 ng/ml for troponin T. The OR for elevated troponin T with serial determinations was 29 (95% CI 1.2 – 389). The LR negative was 0.1, a strong predictor of in-hospital survival. Finally Kucher noted that in 91 patients with serial troponin I’s < 0.06 ng/ml and a normal echocardiogram had a 98% three month survival. The LR negative in predicting adverse clinical outcomes for troponin I was 0.16, the echocardiogram was 0.43, and both were 0.1. These small studies individually are not convincing, however together they indicate a strong trend that a negative serial troponin is associated with a low risk for mortality in patients with PE. Troponins rise and fall quickly with PE, with peak levels in less than 20 hours and falls to undetectable levels within 72 hours.

Acute strain on the left ventricle increases serum Brain Natriuretic Peptide (BNP). Researchers have attempted to evaluate its use in patients with PE and presumed RV strain. In 2003, tenWolde noted an elevated risk of 30-day mortality from PE OR 14.6 (95% CI 1.7 – 126) and an all-cause mortality OR of 12.0 (95%
CI 2.4 – 59) in patients with PE and elevated BNP. The LR Negative for PE related mortality was 0.2. Kucher studied both BNP and troponin T in 73 patients with PE, including those presenting in shock. A BNP level < 50 pg/mL had a LR Negative of 0.08 for adverse clinical events, whereas a BNP > 90 pg/mL had a LR Positive of 3.4. In this cohort, BNP was a stronger predictor of adverse events than troponin T. Kruger observed that a BNP > 90 pg/mL was strongly associated with echocardiographic evidence of RV dysfunction - OR 28.4 (95% CI 3.2 – 251). It will be important to identify an optimal cutoff for BNP in patients with PE.

In another diagnostic evaluation, Kline reported from a large multicenter study that out of 27 factors, pulse oximetry < 95% on room air had a in-hospital mortality of 20% whereas those with a room air pulse oximetry results of 95% or greater had a significantly lower mortality of 2%. Emerging Treatment Options for Pulmonary Embolism

The advent of low molecular weight heparin for treatment of PE has opened the possibility of early outpatient treatment for patients with low-risk emboli. In a recent meta-analysis of 12 prospective randomized trials with a total 2110 patients, the OR at 3 months for LMWH was 0.68 (95% CI 0.42 – 1.09) compared to unfractionated heparin. Also, from a large randomized trial of 2213 patients, there was no statistical difference in outcomes of recurrent embolic events or mortality between fractionated versus unfractionated heparin. If patients that are at low risk for mortality can be safely identified, the possibility exists that these patients could be treated as outpatients.

For high risk patients, the mortality from PE is excessive once hypotension occurs. The use of fibrinolytic therapy for PE has not been clear. In a recent meta-analysis, there was a suggestion that significantly ill patients may have a mortality benefit. The current recommendation for patients with massive and sub-massive PE is to use fibrinolytic therapy for those patients in hypotensive shock and for those with a shock index (heart rate/systolic blood pressure) > 1.

SUMMARY

There are multiple techniques to diagnose PE in the ED. Complications from PE are primarily cardiac and tools typically used for assessment and treatment of acute coronary syndromes may prove effective in the management of PE.
REFERENCES


OBJECTIVES:
1. To describe recent point-of-care (POC) testing trials for cardiac markers in the ED
2. To describe the strengths and limitations of POC testing
3. To describe the stakeholders involved with implementation and regulation of a successful point-of-care testing program for cardiac markers in the ED

INTRODUCTION
Several factors in the medical care environment have influenced the growth of point-of-care (POC) testing. This is particularly true in the emergency department (ED) where there are now over 110 million visits each year and five million of these patients have potential acute coronary syndrome (ACS). EDs are now not only used for the treatment of the acute manifestations of illness, but have become in many ways diagnostic centers. What used to be routine inpatient evaluation for chest pain has become a standard evaluation in the ED or chest pain unit. Patient expectations of emergency evaluation include not only accurate and knowledgeable care, but also care that is efficient. Additionally, there has been a significant increase in time dependent therapies, particularly for patients with ACS. These accelerated demands and protocols have increased the need for rapid testing and reduction in laboratory result turn-around-time.

POC testing is a response to process challenges in the central laboratory. Central laboratory processing of blood samples includes the delivery of blood, clot extraction if serum is used, centrifugation, and up to 20 minutes of assay time for the large automated immunoassay analyzers. In the ED accelerated model with its combination of rapid diagnosis and treatment, demands for rapid laboratory information have clearly increased. These demands on the ED have translated to increased volume of testing and necessity of rapid turnaround. POC testing, often called “near patient testing,” occurs where patient care is rendered and has taken an increasingly larger role in most ED environments.

Recent consensus guidelines published by the American College of Cardiology and the American Heart Association for the diagnosis and treatment of ACS recommend that cardiac markers should be available within 30-60 minutes from the time of ED presentation. As many EDs and central laboratories are unable to meet this recommendation, POC testing has to be considered as an operational necessity in evaluating these patients.

Selected POC Cardiac Marker Assay Performance and Selected Trials
The most commonly used markers in cardiac risk stratification are CKMB, cardiac
troponin I or T (Tn), and variably myoglobin. Other markers such as brain natriuretic peptide (BNP), highsensitivity CRP (hsCRP), and D-dimer are also available but beyond the scope of routine ED evaluation.\textsuperscript{4-9}

There are many cardiac assays from which to choose \textbf{(Table 1)} hence initial trials evaluating POC testing assays generally focus on analytical performance and/or clinical utility.\textsuperscript{10,11} While there have been dozens of trials investigating POC assays in patients presenting with acute chest discomfort, the following paragraphs summarize some of the more noteworthy trials.

\textbf{Table 1.}

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
\textbf{Current Widely Available Cardiac Marker Assays} \\
\hline
1) Triage System (Biosite) \\
2) i-STAT®1 Analyzer (i-STAT) \\
3) Cardiac Reader (Roche) \\
4) RAMP System (Response Biomedical) \\
5) Stratus CS (Dade Behring) \\
\hline
\end{tabular}
\end{table}

It is clear that the accurate measurement of the cardiac troponins is a major focus for POC testing in patients presenting with potential ACS. As there is no value standardization between the many different assays, evaluation of analytical performance is complicated and requires laboratorian expertise. The analytical performance of the i-STAT whole blood TnI assay was evaluated in a recent trial of 248 total patients. Antibody specificity, detection limit, imprecision, linearity, assay specificity, sample type stability, interferences and reference limit determination were compared to the Stratus CS device. The detection limit was found to be 0.02 ng/L with a 99th percentile reference limit of 0.08 ng/L. This study showed that the i-STAT TnI assay was a sensitive and precise monitor of TnI and appropriate for use in the POC testing environment for the evaluation and risk assessment of patients with possible ACS.\textsuperscript{12}

In the Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (CHECKMATE) trial, “time to positivity” between POC testing and central laboratory were compared in the risk stratification of non-ST-segment elevation chest pain patients. The primary assessment of this trial was to relate marker status to 30-day death and myocardial infarction. Three markers strategies were compared: (1) POC myoglobin, CK MB, and TnI, (2) POC CKMB and TnI, and (3) local laboratory. The POC assay used in this trial was the Stratus CS instrument. This study found that time to positivity was decreased in both POC marker strategies (2.5 hours and 2.8 hours, respectively) when compared to the local laboratory (3.4 hours). Outcome data of 30-day death or infarction showed that the relation between the POC marker strategies was stronger than that of the local laboratory (positive 18.8% and 21.9% versus 13.6%). The authors concluded that POC multimarker determination provided faster and better risk stratification in this patient population.\textsuperscript{13}

The RAMP\textsuperscript{®} (Response Medical) CK-MB and TnI whole blood POC assays were evaluated in a multicenter trial in 185 patients suspected of acute coronary syndrome and 180 healthy subjects. The standard comparison assays were the Biosite Triage POC device and the Dade Behring Dimension RxL central laboratory system. Clinical sensitivity and specificity for AMI were determined using the redefined guidelines from the ESC/ACC.\textsuperscript{14} The authors concluded that for 39 AMI and 67 non-AMI patients, the clinical sensitivity, specificity, and diagnostic efficiency of the RAMP were similar to the predicate assays and this device was an acceptable alternative to automated central laboratory instruments. Total imprecision ranged from 7.2\% to 11.4\% for TnI over the range of 0.22 to 5 ng/mL and 4.8\% to 8.6\% for CKMB at 7, 14, and 25 ng/mL.\textsuperscript{15}
The ultimate goal is clearly high quality, cost-effective, and efficient health care.

In another trial conducted with 817 consecutive ED patients presenting with symptoms consistent with ACS, serial determinations of myoglobin, TnI, and CKMB at 0, 1.5, 3, and 9 hours were obtained using the Biosite Triage Cardiac Marker System. Sensitivity and negative predictive value were compared for both the multimarker POC approach and the central laboratory strategy. This study found that sensitivity and negative predictive value for myoglobin and TnI by 90 minutes was 96.9% and 99.6%, respectively. CKMB measurements did not add to this evaluation. Additionally, lab result reporting was on average 57 minutes faster with the POC assay.\textsuperscript{16}

Renal failure patients represent a particularly challenging population for cardiac marker assessment. False positive tests complicate the assessment and diagnosis in this high-risk group. POC testing has been successfully evaluated in these patients as well. Using the same patient population as the previously mentioned study by McCullough \textit{et al.}, patients were divided into five groups based on their renal function. Two independent cardiologists determined the diagnosis of AMI. TnI was found to be the most consistent across all patient groups without significant false positive results.\textsuperscript{16,17}

\textbf{Economic Assessment of Point of Care Testing}

As medicine is under constant scrutiny to provide quality medical care with reduced costs, implementation of additional laboratory services will be understandably called into question. Is POC testing cost effective? This question is central for all parties involved with implementation of such a program. Benefits of POC testing generally fall into the major categories of consumer demand, medical care, and time and resource management. The ultimate goal is clearly high quality, cost-effective, and efficient health care.

Both physicians and patients have a demand for POC testing. Physicians understandably want accessible and rapid results in the diagnosis and care of their patients. Patients and their insurers want rapid diagnosis and treatment for their conditions. In a world of internet, fast food, instant replay, e-mail, digital audio, cell phones, and pagers – does it not seem reasonable that lab results in acute care environments would return faster today than 10 years ago?

For time sensitive high morbidity medical conditions that are frequently encountered in the ED, rapid and improved turn-around time (TAT) for laboratory tests intuitively translates into improved medical care. If POC testing can improve the ability to diagnose efficiently, more effectively utilize medical treatment, improve pharmaceutical consumption, and decrease lengths of stay in the ED, the OR, the ICU, and the hospital, improve resource utilization, then certainly an economic benefit has to be realized. These inter-related parameters are extremely difficult to quantify. Just as in the implementation of any new intervention, the ultimate test for POC testing will be to determine its effect on these outcomes. Showing improvement of outcomes is difficult but will be imperative in the ultimate judgment of POC testing.
Most notably, the cost/benefit analysis is not as basic as simply comparing the cost of the lab result in the POC and central laboratory environments. This has traditionally been called, “cost-centered analysis.” Labor and reagent costs are not the only considerations. The focus of POC testing should be medical care and systems costs, not the very isolated cost of testing itself. The viewpoint of a global evaluation of the entire cost of a health care episode with an outcomes approach is imperative. Even with all the efforts of trying to find an answer to this question, we understand very little about what POC testing actually accomplishes in terms of benefits and outcomes.

The Time Issue
Decreased TAT is likely the central issue in POC testing. Lee-Lewandrowski et al. showed a 84.5% reduction in TAT using a qualitative POC TnI assay which translated to a length-of-stay reduction from 386 to 338 minutes. Likewise, Caragher et al. showed a TAT reduction of 55% compared to the central lab using the quantitative assay Stratus® CS Analyzer (Dade Behring) for TnI, CKMB, and myoglobin. POC assays can perform tests faster. While it is intuitive that a test performed at the bedside in 10 minutes would take less time than a test that has traditionally required 60 minutes, these studies illustrate that TAT can be decreased in the acute patient setting.

Does this decrease in laboratory TAT matter? The strength of POC testing is only as robust as the clinical assumption that fast diagnosis and treatment is better for patients. From numerous studies we know that early intervention and medical treatment is beneficial in patients with non-ST-segment elevation acute coronary syndrome. ED length of stay is also a critical factor for potential implementation of a POC system. Singer et al. demonstrated a reduced ED length of stay of 68 minutes for potential ACS patients after implementation of a POC cardiac marker system. The success and benefits of POC testing clearly require that action be taken on the results obtained (Figure 1).

Strengths and Limitations
It is important to note that POC testing supplements testing from the central laboratory. Some environments benefit more and are more conducive to POC testing. While the need for more rapid results is clear, the already burdened ED environment is challenging for non-laboratory personnel such as nurses or patient care assistants to perform rapid and high quality tests. Implementation of any POC system must start with clinical laboratory scientist’s direction. These individuals are specifically trained in quality control and assurance and can assist in the complex implementation of this kind of system (Table 2).

Figure 1. Model for Point-of-Care Testing

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Test</th>
<th>Result</th>
<th>Action</th>
<th>Patient Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td></td>
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</table>

“POC testing has value only if caregivers take action on the result.”
We know from previous studies that POC assays for cardiac markers are “good.” But, how “good” is “good enough?” The ACC and AHA recommend the cardiac specific troponins in the triage and treatment in patients with potential ACS. As even the most minor of elevations of troponin portend increased risk, how good does a POC test have to be? Trials such as TACTICS have shown that patients with troponin levels above the 99th cutoff percentile but below the 10% CV value are at increased risk.\textsuperscript{22-24} It is important for emergency medicine physicians to understand the limitations of POC testing and make informed decisions based on the qualities of the individual platforms.

**SUMMARY**

Studies demonstrating improvement in patient outcome and overall health care cost savings will determine the ultimate long-term success for POC testing. Additionally, success of ED POC cardiac marker testing will require standardization of the varied platforms. With nearly a dozen current manufacturers of TnI assays, correlation, particularly within the same clinical setting, is a significant concern. Physicians have to be able to communicate results to the patient and other physicians in a standardized format that can be interpreted from assay to assay. Evidence of improved outcomes, total cost savings, and assay standardization using POC testing will undoubtedly add to our ability as emergency physicians to provide the best care for our patients.

Singer et al. demonstrated a reduced ED length of stay of 68 minutes for potential ACS patients after implementation of a POC cardiac marker system.
REFERENCES


INTRODUCTION

Major advances have been made during the past several decades in stroke prevention, treatment, and rehabilitation. Despite successes in delivering effective new therapies, significant obstacles remain which prevent scientific advances from being translated into clinical practice. In many instances, these obstacles can be related to a fragmentation of stroke-related care. This is generally caused by inadequate integration of the various facilities, agencies, and professionals that should closely collaborate in providing stroke care. Multiple efforts are underway to improve the overall delivery of effective stroke care and three specific, published initiatives merit review. These are:

1. Recommendations for the Establishment of Primary Stroke Centers
2. Recommendations for Comprehensive Stroke Centers
3. Recommendations for the Establishment of Stroke Systems of Care

These three consensus documents collectively describe the individual components, and the architecture, for the creation of an improved system for stroke care delivery. Each paper has potential impact on the emergency physician and each will be reviewed with emphasis on the role of the emergency department team within this architecture.

The first two articles were published by the Brain Attack Coalition. This is a group of professional, voluntary and governmental entities dedicated to reducing the occurrence, disabilities and death associated with stroke. The goal of the Brain Attack Coalition is to strengthen and promote the relationships among its member organizations in order to help stroke patients or those who are at risk for a stroke. This group of 14 member organizations includes the American College of Emergency Physicians as the representative organization from emergency medicine. Individuals representing each of the member organizations participated in the drafting and ultimate approval of the consensus documents.

The Development of Primary Stroke Centers

The Brain Attack Coalition’s Recommendations for the Establishment of Primary Stroke Centers is an effort to respond to the marked variability and at times unavailability of coordinated stroke care.
that documents 66% of hospitals not having defined stroke protocols, and 82% lacking a rapid identification system for patients experiencing acute stroke. Citing the experience, and documented success, of trauma centers in organizing and providing care for a disease with significant time-dependence, the authors proposed that it is reasonable to explore the “center” concept for acute stroke. They also proposed that, like the trauma system, there should be more than one “level” of stroke center and therefore proposed a two tier system with the elements being the “primary stroke center” and the “comprehensive stroke center.”

In the primary stroke center paper, the authors outline and detail the essential elements of a “Primary Stroke Center.” The key elements of primary stroke centers include acute stroke teams, an integrated emergency response system, written care protocols, and a “stroke unit.” Important support services include availability and radiologic interpretation of computed tomography scans 24 hours per day as well as rapid laboratory testing. Administrative support, strong leadership, and continuing education are also important elements for stroke centers. The authors believe that the adoption of these recommendations may increase the use of appropriate diagnostic and therapeutic modalities and reduce post-stroke complications. Specific elements of this list that can affect the emergency physician merit further discussion and are described as follows:

The Acute Stroke Team of a primary stroke center requires a lead Physician and at least one other additional member. The stroke team physician can be a Neurologist/Neurosurgeon, Emergency Physician, Internist or other qualified physician. It must be noted that the document states that the core of the Acute Stroke Team can be wholly encompassed within the ED and consist of a stroke trained emergency physicians and an registered nurse/physician assistant staff. The team must have documented continuing medical education/nursing education in stroke specific areas, be trained in assessment of acute stroke patients and be proficient in the following areas: National Institute of Health Stroke Scale, blood pressure (BP) management in acute stroke, fibrinolytic agent administration and protocols. A member of the team must be available 24 hours per day for consultation, although they do not need to be in the hospital.

The rapid notification system of a primary stroke center requires a reliable method of communication whereby pre-hospital or emergency department staff can immediately notify on-call stroke team members of the arrival, or impending arrival, of a stroke patient. The notification system does not have to be activated for all strokes. It is preferable that the stroke team be contacted on all strokes that come to the ED who are possible candidates for intervention such as fibrinolytic therapy or who are at particular risk for complications with their stroke.

Written stroke protocols are required. Protocols, order sets and pathways should be available in the ED and acute care areas in either pre-printed documents or in electronic format. The protocols must include a recombinant tissue plasminogen activator (rt-PA) protocol for all institutions that deliver fibrinolytic therapy. The protocol can be developed by the institution or adapted from published guidelines. ED order sets should be incorporated into protocols or pathways. These may be different for patients that present <6 hours or >6 hours after onset of symptoms and should be monitored for adherence. Order sets should include laboratory and diagnostic imaging testing specific for stroke, BP management, no food or medication orally status until screened, and should require documentation of time of onset of symptoms.
Some hospitals that wish to be considered stroke centers will treat and then transfer most acute stroke patients. For these centers, a Letter of Agreement and/or Memorandum of Understanding with receiving institutions should be available in the EDs of both institutions. The document should include the process of communication and transport between the two institutions. The process should be clear so that at the time of crisis the patient’s care is not compromised.

The stroke center should have Emergency Medical Services (EMS) integrated into its very design and development. The EMS response to acute stroke will be a coordinated effort between the stroke center and the EMS system. All EMS systems that transport stroke patients to the stroke center should respond to suspected acute stroke patients at a high priority level. EMS Education is critical and should be done with the stroke center. Education for EMS will include stroke pathology, presentation, assessment and specific tools for pre-hospital evaluation and treatment. This education should specifically cover: Existing pre-hospital stroke scales and assessment tools, Documentation of stroke time of onset at the scene, Stroke-specific blood pressure management algorithms in the field, Typical stroke syndromes and stroke mimics, and Reasons for rapid transport and thrombolytic therapy.

All Primary Stroke Centers must have a defined “Stroke Unit.” While the inpatient stroke unit may not directly affect the ED team, bed availability is always within the emergency physician sphere of interest. The stroke unit does not have to be a specific enclosed area with beds designated only for acute stroke patients but it will be a specified unit to which most stroke patients are admitted. If a significant number of stroke patients are admitted to units other than the stroke unit they should be localized in an identified, secondary area and the staffing, training and monitoring capabilities should be comparable to the stroke unit. To provide effective care, the stroke unit (however defined geographically) needs to have personnel skilled in the assessment and treatment of acute stroke patients and the unit must have the monitoring capabilities to detect cardiovascular pathologies that may be indicative of the etiology or a complication of the acute stroke.

Emergency physicians that are asked to participate in their hospital’s bid to become a stroke center should have considerable expectation of the hospital’s administration. Any hospital that is to become a stroke center must have CT scan capability 24/7 with scan completion within 25 minutes of ordering and expert CT interpretation within 20 minutes of completion for acute stroke patients. The laboratory support must include rapid laboratory test turn-around to make rapid assessment possible. Specifically, the Laboratory service should complete initial stroke tests (complete blood count, PT/INR, blood chemistries) within 45 minutes of physician order. The hospital should provide a monitoring system to ensure that these capabilities are maintained.
Thus, the ED and emergency physicians will be affected by a hospital’s bid to become and maintain certification as a Primary Stroke Center. It is critical that emergency physicians are aware of the potential impact and roles that they may be asked to play in the era of stroke center certification.

Subsequent to the primary stroke center paper, the American Stroke Association (ASA) and Joint Commission for Accreditation of Hospitals Organization (JCAHO) formed a partnership to advance the process of “certification” of hospitals that sought designation as a stroke center. This came at the recommendation of an ASA advisory panel and has progressed such that there are now over 100 hospitals in the United States that are certified as stroke centers by the Joint Commission on Accreditation of Hospitals Organization (JCAHO).

The Development of Comprehensive Stroke Centers

After the publication of the Primary Stroke Center recommendations, the Brain Attack Coalition subsequently published its recommendations for the creation of Comprehensive Stroke Centers. The authors define a comprehensive stroke center as a facility or system with the necessary personnel, infrastructure, expertise, and programs to diagnose and treat stroke patients who require a high intensity of medical and surgical care, specialized tests, or interventional therapies. The types of patients who might use and benefit from a comprehensive stroke center include (but are not limited to) patients with large ischemic strokes or hemorrhagic strokes, those with strokes from unusual etiologies or requiring specialized testing or therapies, or those requiring multispecialty management.

While the general impact on the ED team of a hospital becoming a comprehensive stroke center may not be significantly different than that of a primary stroke center, the complexity of the neurological cases seen may be significantly higher and the overall number of cases greater. A parallel scenario is one of a hospital becoming a Level 1 Trauma Center in that the level of severity of the cases and the overall number of cases is likely to be higher than that of a Level 3 Center.

The recommendations paper specifically states that “It is vital that the comprehensive stroke center staff be fully integrated with EMS personnel and ED staff. EMS and ED personnel should be very familiar with the diagnosis and treatment of patients with cerebrovascular disease. Several studies have documented the importance of the EMS system and ED personnel for the rapid identification and transportation of stroke patients and the initiation of therapy. EMS and ED personnel should attend initial and ongoing educational programs (in-services, Continuing Medical Education (CME) programs, Grand Rounds) that focus on cerebrovascular disease. Ideally, the emergency physicians should be board certified. They should meet with the comprehensive stroke center director at least semiannually and review care issues. Other aspects of the integration of the ED/EMS personnel with a stroke center are reviewed in the primary stroke center recommendations.” Thus, it is clear that the ED staff will see an expanded...
role with a wider spectrum of neurovascular cases in a comprehensive stroke center. It is also clear that the ED will be a geographic coordinating center for stroke referral and triage. Fortunately and logically, along with the increase in complexity and volume of patients there must be a correlative increase in diagnostic test availability, consultant availability, and breadth of available therapeutic modalities.

The third paper in the series was published by the ASA. The ASA convened a multidisciplinary group, the Task Force on the Development of Stroke Systems, to describe the current fragmentation of stroke care, to define the key components of a “Stroke System”, and to recommend methods for encouraging the implementation of stroke systems. The authors state that a stroke system should coordinate and promote patient access to the full range of activities and services associated with stroke prevention, treatment, and rehabilitation, including the following key components:

- Primary prevention
- Community education
- Notification and response of emergency medical services
- Acute stroke treatment, including the hyperacute and ED phases
- Subacute stroke treatment and secondary prevention
- Rehabilitation
- Continuous quality improvement (CQI) activities

While this paper is designed to describe components and interactions of the entire spectrum of stroke care, there are recommendations that have specific implications for the emergency physician. The first is a specific recommendation for triage of stroke patients to the nearest primary stroke center or highest available level of stroke care. The recommendation is as follows:

“A stroke system should ensure that all patients having signs or symptoms of stroke be transported to the nearest primary stroke center or hospital with an equivalent designation, given the available acute therapeutic interventions. Air transport should be considered to shorten the time to treatment, if appropriate. Stroke patients who are not candidates for hyperacute interventions should be evaluated at the closest hospital and considered for transfer, if appropriate, to a primary stroke center or other facility through established referral processes. All available EMS transportation resources, including ground and air transport, should be considered to minimize transport time to the appropriate hospital. If no primary stroke center hospital is available within an appropriate time frame for available therapeutic interventions, then stroke patients should be transported to the closest hospital with a physician-staffed emergency department. Hospitals lacking the resources to provide primary stroke care, as defined in the Brain Attack Coalition’s recommendations for primary stroke centers, should enter into pre-event-negotiated transfer agreements with hospitals possessing such capabilities. If such a hospital is unavailable or beyond a reasonable transport time, then alternative plans should be in place for transport to the hospital that is best prepared for triaging and emergently treating stroke patients in that geographic area. Stroke transport protocols should be based on providing the highest possible quality of clinical care and reducing transport times. Hospital or corporate affiliations, as well as local and state boundaries, should not interfere with the safe and efficient care and transport of stroke patients.”

The most novel aspect of this recommendation is the specific directive to bypass non-stroke-center hospitals. It also states that boundaries that frequently affect EMS destinations such as state lines are not allowed to impede transport to the nearest stroke center. Finally, the directive to create transfer agreements between non-stroke-centers and stroke centers will alter the treatment of acute stroke patients at both ends of the transfer.
The paper also calls upon medical facilities to declare their level of stroke capability and publicly declare that ability so that EMS and the public can make informed decisions about their choices of care facility. The paper states that a stroke system should determine the acute stroke treatment capabilities and limitations of all hospitals and make this information available to primary care providers, EMS, and the public. Any hospital in the stroke system that provides emergency department services should be able to function as a primary stroke center or rapidly transfer appropriate patients through the use of pre-negotiated interhospital protocols, transfer agreements, and transport protocols. Suspected stroke patients should receive timely acute primary stroke care at any hospital in the stroke system, according to a prespecified care plan.

**SUMMARY**

It is clear that the era of stroke center designation and an emphasis on coordination of care will impact EDs and emergency physicians. The specific areas of impact are relatively predictable and will have effort required and resources garnered by the ED team. Ultimately it is important to realize that stroke is a multidisciplinary disease and we as ED teams will be seen as an important players in the process.

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INTRODUCTION

TIA represents a unique opportunity in medicine to avert the onset of a devastating disease process. The percentage of patients that proceed on to acute ischemic stroke (AIS) after a TIA is very high, but can be decreased with appropriate diagnosis and treatment. Evidence regarding new diagnostic and treatment modalities is published at a rapid rate, but keeping up with the latest science can help guide therapy to provide the best possible outcome for a patient seen in the Emergency Department (ED) with symptoms of a TIA.

The previous definition of TIA as a sudden, focal neurologic deficit that lasts less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery was originally established in the 1970’s and was based on the assumption of complete resolution of the ischemia. Newer imaging techniques have shown that in many TIA, while the symptoms resolve, small cerebral infarcts remain, implying more urgency to the evaluation and management. New definitions of TIA have been proposed that emphasize the fact that most TIA resolve within one hour and that TIA lasting longer than this frequently demonstrate an area of persistent ischemia within the affected vascular territory on MRI and are therefore an infarct and not a TIA. One proposed definition of TIA is “…a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms lasting less than one hour, and without evidence of acute infarction.” The authors of this definition compare TIA to unstable angina to emphasize both the usually short course of the symptoms and also the danger of progression to a much more severe disease process.1

TIA Evaluation and Diagnosis

The risk of stroke after TIA is around ten percent in the first 90 days in most population-based studies, although the estimates vary from 4-20% depending on the population selected.2-6 Importantly, studies agree that half of these strokes will occur within the first 48 hours after the initial TIA, highlighting the need for an expeditious evaluation and urgent treatment to avoid permanent neurologic deficit. The most recent update to the guidelines for the management of TIA published by the American Heart Association (AHA) Council on Stroke state that “A TIA should be promptly evaluated...
because delaying diagnosis risks preventable stroke.” They further state that “Hospitalization is often justified to expedite evaluation and lessen the possibility of stroke.”

There is no published or agreed-upon time limit under which the complete evaluation of a TIA should occur, but given the high short-term stroke risk, the ED is certainly a pivotal point in the patient’s care. Recommendations for initial work-up of a potential TIA include a complete history and physical examination, a non-contrast head computed tomography (CT) scan, blood tests as indicated, and an evaluation of the patient’s vascular anatomy, particularly the extracranial carotid arteries. An echocardiogram is recommended in some patients but is not mandated for all. While there are not yet any discrete blood tests that will document the presence of cerebral ischemia, the American Heart Association (AHA) recommends a complete blood count and chemistry profile, largely to exclude other possible etiologies for the patient’s presentation such as hypoglycemia. An electrocardiogram is also recommended to evaluate for dysrhythmias.

Although acute imaging, particularly a non-contrast head CT, has been recommended in the initial evaluation of a TIA, evidence for its utility is sparse. Most estimates place the findings of a non-vascular lesion accounting for neurologic symptoms at about one percent of all scans performed. Douglas performed a retrospective analysis of patients seen in the ED for TIA who underwent a head CT and had a new infarct seen despite complete resolution of symptoms. Patients were then followed for 90 days and the odds ratio for stroke within 90 days was determined. Of patients with a new infarct on CT, the odds ratio for a stroke at 90 days was 4 (95% CI 1.16 – 14.14) after adjustment for confounding variables. While the number of patients in the study with a new infarct was small, the study supports placing those patients with a new infarct on CT, despite being asymptomatic, in a higher-risk category and assuring timely evaluation and treatment.

There has been much work recently focusing on the evaluation of TIA using diffusion-weighted imaging (DWI) of MRI. This imaging modality is attractive for several reasons. The first is that a positive lesion on DWI confirms the diagnosis of TIA in a patient not currently symptomatic and eliminates many of the TIA mimics, similar to positive biomarkers in acute coronary syndrome. This possibility of confirmation of diagnosis does not exist with CT, as CT rarely demonstrates a lesion in real-time and is less sensitive for acute ischemia than DWI. In multiple series of patients evaluated for TIA, around forty percent of patients show DWI-positivity, with a range from 21 – 68%. Diffusion-weighted imaging becomes positive early in an ischemic insult, and when coupled with other MRI sequences, can identify which insults are acute and which are chronic in a much more accurate fashion than CT. Positive DWI tends to occur much more often in TIAs which last greater than one hour, with some studies demonstrating a correlation with duration of TIA and likelihood of positive DWI. DWI-positivity has been shown in TIAs lasting only ten minutes, however, and may still have a place in the diagnosis of TIA with short duration of symptoms. However, it is very unlikely that DWI will be positive in a patient with only seconds to a few minutes of ischemic symptomatology.

The second benefit of DWI would be further risk stratification of the TIA patient with a positive DWI scan. There are preliminary data which support that patients with positive DWI are more likely to have a stroke at 90-day follow-up. This makes sense intuitively, as at least half of DWI hyperintense lesions will progress to lesions on standard MRI or CT, thus defining them as infarctions. Coutts et al. described that patients with a lesion on DWI had a stroke risk of 10.8% - 32.6% at 90 days, but only 4.3% if there was no evidence of DWI abnormality. The study included minor stroke patients, but still provides support to the notion that patients with DWI lesions have a worse outcome if not intervened upon urgently.
The utility of DWI in the evaluation of TIA is still being defined. The patient with positive DWI most likely has a higher risk of subsequent stroke than all TIAs combined. In addition, the lack of a lesion on DWI does not refute the diagnosis of TIA, and these patients still have significant risk of future ischemia. At this point, DWI should most likely be regarded as a specific but insensitive test for transient focal cerebral ischemia, serving to confirm the diagnosis in some cases. Urgent evaluation is still required in all patients with a clinical diagnosis of TIA, regardless of cerebral imaging results.

One test that does help to risk stratify all patients with TIA and has proved to affect outcomes is evaluation of the extracranial vasculature. The gold standard of assessing the vasculature has long been catheter angiography, but there are many less invasive tests currently available that are reliable and reproducible. Duplex ultrasonography has largely replaced invasive angiography as a screening test of choice for critical carotid stenosis, although ultrasonography does tend to overestimate degree of stenosis and has difficulty determining the difference between very high-grade stenosis and occlusion. Further, in pooled analysis, duplex ultrasonography has a lower sensitivity than some other imaging modalities at 86%. Magnetic resonance imaging (MRA) is another test that has been used recently as a screening test for vessel stenosis and typically provides good images of the carotid and vertebral arteries as well as the intracranial arteries and Circle-of-Willis arteries not accessible by ultrasound. The sensitivity of MRA for high-grade stenosis is nearly 95% in pooled analysis, in comparison with digital subtraction angiography (DSA).

A newer imaging modality is CT angiography (CTA). CT angiography takes advantage of a technology already available in most EDs around-the-clock to image the cervical vessels with good sensitivity and specificity. Josephson et al. analyzed a retrospective case series of consecutive patients with TIA or stroke that had undergone both CTA and DSA to evaluate the cervical carotid arteries. Using a 70% cut-off for high-grade stenosis, CTA and DSA were in agreement in 96% of the vessels analyzed. CTA was 100% sensitive and 63% specific with a negative predictive value of 100% for determining cervical stenosis greater than 70%. This cut-off value is important as carotid endarterectomy is recommended for reasonable surgical candidates who are symptomatic and have greater than 70% stenosis of the extracranial carotid artery. The advantages of CTA are that it is usually available 24 hours per day, does not require an extra test or transport to be performed as many patients will undergo a head CT anyway, and has little risk beyond that of an IV contrast load. It does suffer from overestimating the degree of stenosis, but ultrasound and MRA have similar qualities. Further, it allows another crucial and urgent step in the work-up of TIA to be performed in real-time in the ED, theoretically resulting in improved risk-stratification and earlier treatment to prevent stroke.

Risk-stratification in a patient who presents with a focal neurologic deficit that is either present transiently during evaluation or resolved entirely by the time of evaluation is difficult. Johnston and colleagues described factors that made patients in their population higher risk for stroke after presenting to the ED and being diagnosed with a TIA. An episode that lasted greater than ten minutes, weakness during the episode, speech impairment, history of diabetes, and age greater than 60 years were all associated with an increased risk of stroke by 90 days using multivariate regression analysis. Rothwell et al. further attempted to define the stroke risk after TIA using a score derived from registries of TIA in a population-based study. While somewhat more complex, a score was derived that did correlate with 7-day stroke risk in their population. Neither of these rules has been prospectively validated outside their own populations to determine admission criteria at this point, however, and must be applied with caution. The emergency physician must still consider a general risk of stroke of 5% at 48 hours after TIA when determining disposition from the ED.
TIA Treatment

The treatment of TIA hinges on the presumed cause of the event. While TIA requires no treatment itself, the optimal method of preventing a future stroke is the clinical focus. Antiplatelet agents such as aspirin, clopidogrel, and dipyridamole are the cornerstone of treatment for many forms of TIA. Warfarin still plays a role in the treatment of TIA presumed to be of cardioembolic origin, while other antithrombotic agents remain controversial. Correction of critical stenosis within the extracranial carotid artery is of proven benefit in some patients, although there is debate whether surgery or stent placement is the best option in selected patients.

TIAs that are not thought to be cardioembolic in nature should initially be treated with an antiplatelet agent, unless immediate carotid surgery is planned. In patients not currently on an anti-platelet agent, aspirin in a dose from 50 – 325 mg/day is still the first line of therapy. Aspirin is thought to convey a 13-15% relative risk reduction versus placebo in secondary prevention of ischemic stroke or other vascular event. There has not been shown to be a definite difference in risk reduction across different doses of aspirin, with low doses appearing to be as effective as higher doses, but with fewer gastrointestinal and bleeding side effects.

In patients who have failed aspirin therapy from a recurrent event despite treatment, the second choice of an antiplatelet agent is less clear. Both clopidogrel and extended-release dipyridamole/aspirin combinations are available on the market and have been shown to have efficacy in secondary prevention, although they have not yet been compared head-to-head in published studies. Two ongoing clinical trials, ProFESS (Prevention Regimen for Effectively avoiding Second Strokes) and ESPRIT (European/Australian Stroke Prevention in Reversible Ischemia Trial) are testing extended-release dipyridamole/aspirin combinations against clopidogrel or aspirin alone, respectively. Current evidence from the CAPRIE trial suggests a marginal benefit for clopidogrel (75mg/day) over aspirin (325mg/day) in secondary prevention of stroke, myocardial infarction, or vascular death, with a relative risk reduction of 8.7% (95% CI 3.0 – 16.5). The MATCH trial found no benefit of the addition of aspirin (75mg/day) to clopidogrel (75mg/day) in secondary prevention, although the usual clinical question of the addition of clopidogrel to aspirin, instead of the reverse, was not answered. Clopidogrel is favored as a second-line antiplatelet agent in those patients who cannot tolerate aspirin secondary to gastrointestinal distress.

One major trial, the European Stroke Prevention Study 2, has evaluated aspirin versus an extended-release dipyridamole/aspirin combination in patients with TIA or stroke in the preceding three months. Four treatment groups were randomized, including placebo, aspirin alone (50 mg/day), extended-release dipyridamole alone (400 mg/day), and aspirin plus extended-release dipyridamole (50/400). The trial showed a benefit to both aspirin and dipyridamole over placebo in secondary prevention of stroke, but showed a significant benefit for the combination therapy over either agent alone. The relative risk reduction for the combination therapy was 37%, as compared to 18% for aspirin alone and 16% for dipyridamole alone. While these results have yet to be confirmed in other work, this preliminary result is encouraging.

The patient with atrial fibrillation and a TIA is usually presumed to have a cardioembolic source for the embolus. Guidelines currently recommend systemic anticoagulation with adjusted-dose warfarin in all patients who do not have a contraindication. Support for this recommendation is provided by the pooled analysis authored by Hart and colleagues. This analysis combined 2 randomized trials of patients with atrial fibrillation and TIA who were randomized to either aspirin or adjusted-dose anticoagulation with warfarin. In patients randomized to warfarin a relative risk reduction of 56% for ischemic stroke after TIA was observed versus aspirin. The absolute rate reduction in stroke was 4% per year for anticoagulation over aspirin. There is strong support for anticoagulation of the TIA patient with atrial fibrillation, unless a contraindication exists.
Oral direct thrombin inhibitors have also been studied for systemic anticoagulation in the setting of atrial fibrillation to reduce stroke risk. The benefit of such agents is that there is no need to monitor the International Normalized Ratio (INR) and that there are few drug-drug or drug-food interactions as seen with warfarin, thus making them easier and potentially more cost-effective. One study of ximelagatran (36 mg BID) versus adjusted-dose warfarin (INR 2.0-3.0) was undertaken in patients with atrial fibrillation at risk for stroke, although not all patients had a previous stroke or TIA. The data supported the efficacy of the agent in reducing stroke risk, showing no statistically significant difference in stroke or embolic events with a mean 20-month follow-up between the study drug and warfarin. Although this primary outcome is encouraging, six percent of patients developed an elevation of liver enzymes, with one documented fatal case of liver failure in the study group. Future study will focus on balancing an acceptable safety profile in addition to proven efficacy for such agents.

Carotid endarterectomy (CEA) has proved beneficial in patients with stenosis of 70 – 99% of the extracranial carotid artery who have had a TIA. While there is some immediate risk to surgery, the long-term risk favors surgical treatment over best medical management, with an absolute risk reduction of 17% over two years for subsequent ipsilateral stroke in the surgical treatment arm of the trial. The benefit in patients who have had a TIA and have stenosis of 50 - 69% is less robust at 6.5 percent absolute risk reduction over five years, but is still clinically relevant in patients who are reasonable surgical candidates and have good life expectancy. It appears that the benefit is realized more in early surgery after the initial TIA, and delay decreases the overall benefit. This is most likely due to the high incidence of stroke in the first 48 hours following TIA, which would not be prevented by delayed surgery. The benefit also appears to be attenuated somewhat in isolated amaurosis fugax and in women, although the latter may also be a timing effect. There is no proven benefit to CEA in patients with less than 50% stenosis, and these patients should be treated with an antiplatelet agent.

Stenting of the carotid artery in symptomatic stenosis is a procedure which has gained momentum in recent years, particularly in patients who are felt to be a poor surgical candidate due to concomitant health problems. While the technology of the devices advances rapidly, there are no randomized studies that currently demonstrate their efficacy versus CEA. Newer devices employ mechanisms to trap potential emboli released by deployment of the stent attempting to decrease intraoperative complications, but large clinical trials are currently ongoing and results have not yet been reported. As with all procedures, complication rates are lowest in experienced hands, and the long-term benefit of stent placement will depend on low rates of intraoperative complications. Current potential indications for stenting would include patients with symptomatic carotid stenosis of 70 – 99% not amenable to open CEA.

There are many groups and subtypes of TIA, including those caused by intracranial vessel stenosis, hypercoaguable states, and cryptogenic emboli from patent foramen ovale that are not covered in this review. Treatment of these patients is typically best managed in concert with a neurologist and consultation is warranted. New treatments develop constantly, but much controversy surrounds some of these less-common disease states.

The future of diagnosis and treatment of TIA will allow emergency physicians to further define the TIA population at highest risk for ischemic stroke. There is great potential for observational medicine to provide a complete work-up for TIA with neurologic consultation to begin appropriate treatment and avoid a hospital admission. Ongoing trials seek to further define the optimal antiplatelet agent for TIA and seek alternatives to warfarin for systemic anticoagulation when indicated.

**SUMMARY**

Both currently and in the future, TIAs should be treated as a medical emergency. The rates of subsequent stroke after TIA are substantial, many of which are
preventable with appropriate treatment. Only with a thorough evaluation can the appropriate treatment be instituted to attempt to avoid serious complications. If a complete work-up cannot be obtained in an urgent fashion as an outpatient, admission to the hospital is warranted. Optimal antiplatelet, antithrombotic, or surgical treatment can help avert death or severe disability caused by ischemic stroke.

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INTRODUCTION

Why should we care about stroke? We should care because stroke kills nearly 160,000 Americans each year. About 750,000 people suffer a new or recurrent stroke each year and there are approximately 4.5 million stroke survivors currently living in the United States. Stroke remains the nation’s third leading cause of death and the leading cause of adult disability. With current interventions for ischemic stroke being extremely time dependent, the burden of stroke diagnosis rests squarely on the shoulders of emergency physicians. Recent advances in biomarker discovery may provide an invaluable tool in the evaluation of patients with potential stroke.

To date, the diagnosis of many acute neurologic conditions remains largely one of exclusion. This is perhaps most true for acute ischemic stroke (AIS). In AIS, the history and clinical exam may suggest a patient’s physical findings are due to an ischemic stroke, and blood chemistry analyses and CT scans can exclude patients with hypoglycemia, intracranial hemorrhage, or neoplasm. Unless early ischemic changes are found on CT (less than a third of CT scans in AIS have ischemic changes within three hours from symptom onset) or advanced MRI imaging clearly defines decrease cerebral perfusion, the diagnosis of AIS remains based largely on clinical examination. With the development of acute interventions for stroke, especially fibrinolytic therapy with its narrow therapeutic time window, the certainty of diagnosis is paramount.

Similar to the development of serum markers in the diagnosis of acute coronary syndromes, several studies in the past decade have investigated direct and indirect biochemical markers of neuronal and glial cell damage in the human central nervous system. Biochemical markers of vascular injury, inflammation, and coagulation activation in stroke also show promise. Recent human studies have investigated potential markers in acute stroke, anoxic brain injury status post cardiac arrest, ischemia and embolic stroke during cardiopulmonary bypass, neonatal hypoxia, spinal cord injury, and traumatic brain injury. The hope is that either individually or as a panel these markers will aid in not only diagnosing

OBJECTIVES:

1. Review the current challenge in stroke diagnosis
2. Discuss the early diagnosis of acute ischemic stroke using biomarkers and review potential candidate proteins
3. Review other conditions which may benefit from the use of protein biomarkers in their diagnosis and management
neurologic conditions and their severity, such as infarct volume, but also will assist in tailoring therapies, measuring therapeutic efficacy, and providing some insight into patient prognosis. While not typically an issue in the Emergency Department (ED), similar markers may also assist in diagnosing early Alzheimer’s disease, multiple sclerosis exacerbations, vascular dementia, and Creutzfeldt-Jakob disease.

Before discussing individual markers and their applications, it is important to understand the differences when comparing the release kinetics of markers of myocardial damage to neurovascular injury. The brain is far more structurally heterogeneous than the heart, with multiple neuronal and glial cell types present and in varying distribution throughout the brain. Each cell line has varying degrees of sensitivity to ischemia and direct injury. Additionally, neurons in different regions of the brain show a wide range of susceptibility to injury. Thus the type of injury, the severity, and the duration will directly affect marker release.

Perhaps the most important difference from the cardiac analogy is the presence of the blood-brain barrier (BBB). When intact, it is very effective at limiting the egress of proteins from the CSF into the serum. Unless significant permeability changes occur, such as in injury, many markers cannot enter the serum freely. It is not uncommon to have over a thousand-fold difference when comparing the CSF to serum marker concentrations. Even when damaged, the BBB may still delay the presence of a marker in the serum, limiting its early diagnostic utility.

Markers can be classified based on the cell of origin or by their general activity. Table 1 is just a partial list of biomarkers that have been studied in acute stroke, traumatic brain injury, subarachnoid hemorrhage, and global ischemia. The markers vary greatly in their sensitivity for injury or activation, and their specificity.

It is unlikely that a single marker under current investigation will have the sensitivity and specificity necessary to be used alone in diagnosing cerebrovascular events. Rather, a combination of markers will be optimized for their sensitivity, specificity, accuracy, and time-to-positivity characteristics. Our long-term goal is to develop a sensitive and specific panel of serum protein markers for use in acute ischemic stroke that may help predict extent of focal brain injury and long-term outcome, identify patients at increased risk of hemorrhage following fibrinolytic therapy, and provide early diagnosis of acute cerebral ischemia to assist in treatment decisions.

**Table 1.** Biomarkers for neurovascular injury

<table>
<thead>
<tr>
<th>Direct neuronal and glial markers</th>
<th>Markers of coagulation / fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase isoenzyme (BB)</td>
<td>D-dimer</td>
</tr>
<tr>
<td>Glial fibrillary acid protein (GFAP)</td>
<td>Heat-shock proteins (HSP 70, HSP 130)</td>
</tr>
<tr>
<td>Myelin basic protein (MBP)</td>
<td>Monocyte chemoattractant protein-1</td>
</tr>
<tr>
<td>Neuron specific enolase</td>
<td>Plasmin-α2 antiplasmin complex</td>
</tr>
<tr>
<td>Phosphoglycerate Mutase-B</td>
<td>Protein C and S</td>
</tr>
<tr>
<td>S100β</td>
<td>Interleukins (IL-1, IL-6, IL-8)</td>
</tr>
<tr>
<td>Synapsin</td>
<td>Thrombin-antithrombin III complex.</td>
</tr>
<tr>
<td>Tau protein family (tau, MAP-2)</td>
<td></td>
</tr>
</tbody>
</table>

**Vascular markers**

- Endothelin 1 (ET 1)
- Selectin
- Thrombomodulin

**Apoptosis / Miscellaneous**

- Brain natriuretic peptide
- Caspase 3
- Calbindin-D
- Heat shock protein 60
- Cytochrome C

**Inflammatory mediators:**

- C reactive protein
- MMP-2,9
- Transforming growth factor β (TGF)
- Tumor necrosis factor (TNF)
- Ionized calcium and magnesium
- Neuronal cell adhesion molecule (NCAM)
- VCAM
- Vascular endothelial growth factor
- Excitatory amino-acids (glutamate, etc.)
Protein Markers of Neurovascular Injury in Stroke

Many biochemical markers have been studied in-vitro and in animal models, but relatively few have been evaluated in human in-vivo applications. The development and understanding of the biokinetics of neurovascular markers parallels that of the cardiac markers. Structural proteins, such as tau, require complete cell death and degradation before they are found in the CSF. Biochemical markers located in the cytoplasm are released not only in cell death, but also in reversible ischemic conditions. Cytoplasmic markers are typically released earlier in the development of injury, but are often less specific for neuronal tissue (i.e. neuron specific enolase (NSE)). Structural CNS proteins are detected later in the CSF and serum but tend to be more specific for neuronal and glial injury. From the cardiac marker experience and animal research it is clear that no one single marker will have the qualities of being the “perfect test”.

Markers under investigation indicate neuronal injury, glial cell injury, and vascular injury, as well as coagulation and platelet activation. In addition to stroke, several markers are also being studied in-vivo in neurovascular and traumatic brain injury. When a panel approach is developed and introduced to clinical practice it will undoubtedly contain at least one direct marker of neuronal or glial injury. The following is a brief introduction to several potential direct markers of cellular injury.

Myelin Basic Protein (MBP)

MBP has been extensively studied in demyelinating diseases. MBP is a membrane proteolipid produced by oligodendrocytes and has a molecular weight of 18.5 kD. Elevated levels of MBP have been found in the CSF and serum of patients with ischemic stroke, intracerebral hemorrhage, multiple sclerosis, and birth anoxia. It may be best suited for detecting deep strokes and intracerebral hemorrhage (ICH).

Neuron Specific Enolase (NSE)

NSE is the dimeric ($\gamma\gamma$) isomer of the glycolytic protein enolase, and is mainly located in the cytoplasm of neurons and cells of neuroendocrine origin. NSE is also found in smaller concentrations in erythrocytes and platelets. NSE has a molecular weight of 78kD. Its release into the CSF has been found in patients with acute head injury, stroke, seizures, encephalitis, and transient ischemic attacks. It is also being used as a surrogate marker for the effectiveness of neuroprotective agents in focal cerebral ischemia in animal models.

S100β

S100β is a 21 kD dimeric ($\alpha\beta$) calcium-binding protein found throughout astroglial and Schwann cells in a homodimer form ($\beta\beta$). Elevated CSF and serum levels of S-100 ($\beta\beta$) have been found in patients with stroke, head injury, anoxic brain injury, and ICH. Ongoing studies are also investigating the use of S-100 in detecting cerebral injury in patients undergoing cardiopulmonary bypass or cardiothoracic surgical procedures.

Fagnart et al. performed a survey of S100β concentrations in 50 healthy individuals, 325 patients with neurological disorders, and 20 patients with malignant melanoma. No healthy control, dementia, or meningitis patient had elevations, while less than 10% of patients with meningoradiculitis, peripheral neuropathy, encephalitis, Gillian-Barre syndrome, and AIDS had detectable levels. Nearly 90% of all patients with acute cerebrovascular disorders had detectable S100β concentrations. Of note, this study was conducted in 1988 and new forms of the S100β protein have since been identified. Current assays can measure S100 levels well below the 0.3 microgram/L sensitivity in this study. The S100 family of proteins is in the process of being reclassified but S100β will likely be one of the markers that will be useful.
**Tau Protein (TP)**

Tau protein is one of a class of proteins that are microtubule-associated proteins (MAP). Tau is a major intracellular structural cytoskeletal protein located solely in neurons, and as such has no detectable levels in healthy patients. It is synthesized in 1 of 6 isoforms in the proximal axon and then transported down the axon to stabilize microtubules. The isoforms have molecular weights between 48kD and 68kD. After neuronal injury, tau is proteolytically cleaved and released into the CSF. Initial studies showed that CSF tau had high sensitivity for Alzheimer’s disease, but a low specificity due to elevations also in vascular dementia. More recently it was found to be elevated in stroke patients and in TBI, but its sensitivity remains an issue. Because of its size (30-50kDa cleaved) it is assumed that the blood-brain barrier must be compromised for detectable levels of TP to be found in the serum.

**Other Recent Marker Advances:**

Several studies and surveys have identified the largest obstacle to widespread use of fibrinolytics for stroke is the risk of causing an intracerebral hemorrhage. To this end, several recent studies have reported efforts to identify patients at increased risk. In studies by Montaner, matrix metalloproteinases (MMP-9) levels at baseline predicted parenchymal hemorrhages following both cardioembolic strokes and following tPA therapy in acute ischemic stroke. Similarly, Trouillas, Derex and colleagues published data suggesting early fibrinogen degradation coagulopathy is predictive of parenchymal hematomas in cerebral rt-PA fibrinolytics. Further work will need to validate and refine these findings.

Some of the first investigators to approach the stroke biomarker problem from a panel approach have been teams at Duke University and Biosite, Inc. Reynolds, Lynch, and Laskowitz have published their results from several studies, including a large plasma protein screening project that resulted in marker panel comprised of 5 unique proteins associated with stroke (Figure 1). Utilizing plasma levels of S-100beta, B-type neurotropic growth factor, von Willebrand factor, matrix metalloproteinases-9, and monocyte chemoattractant factor-1, the derived panel algorithm provided a sensitivity of 92% at 93% specificity for ischemic stroke in patients within 6 hours from symptom onset. These studies represent the beginning of the second

**Figure 1.** Box and whisker plots of biomarker concentrations in patient samples (12 h from symptom onset) TIA patients with a discharge diagnosis of TIA; Isch., acute ischemic stroke; Hemor., intracerebral hemorrhage; Controls, samples from healthy controls.
generation of research into biomarkers for brain injury, one with the promise of making an impact for the practice of emergency physicians.

**Extension of Biomarkers for Stroke**

Since the brain responds to stress and injury in a fairly constant manner, irrespective of the precipitating event, researchers have expanded the search for biomarkers into other acute neurologic conditions. Serum markers are also being investigated in both subarachnoid (SAH) and intracerebral hemorrhages (ICH). In SAH, CSF concentrations of S100β have been shown to be reflective of the degree of immediate neurologic injury but also the later injury due to vasospasm. Persson's study of 43 patients with SAH found a threshold for CSF S100β concentrations that correlated with favorable outcomes.

**Status post cardiac arrest**

Several recent studies have used S100β and NSE as markers for the duration and extent of circulatory arrest. These markers have a high correlation between marker levels and duration of arrest, as well as being able to predict persistent coma.

**Traumatic Brain Injury**

Recently, traumatic brain injury (TBI) has become a focal point of public health. Similar to AIS and TIA, the diagnosis is largely by clinical exam and history, since common neuroimaging modalities are not able to detect subtle injuries. While several markers have been shown to be powerful predictors of outcome in severe TBI, it is hoped that serum markers will be able to identify minor TBI patients who are at increased risk for short and long term impaired neuropsychological performance.

**SUMMARY**

Based on the preliminary studies and several ongoing pilot studies, it is reasonable to expect commercially available products to become routinely used in the ED. Equally exciting is the use of these markers for traumatic brain injury and acute spinal cord injury. As they are refined, they will have the potential to assist in the diagnosis and management of an even broader scope of neurologic disorders.

**REFERENCES**


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 71. 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 January 1, 2007. 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.

Maximizing the Effectiveness of NSTE ACS Care Utilizing the CRUSADE Initiative: Right Patient? Right Dose?

1) Which of the following statements best describes the CRUSADE Initiative?
   a) The CRUSADE registry has a lower in-hospital mortality rate than randomized controlled ACS trials.
   b) CRUSADE is an academic collaborative quality improvement initiative for NSTE ACS.
   c) CRUSADE sites include roughly 100 hospitals across the United States and Europe.
   d) The CRUSADE initiative has not been able to change ACC/AHA guideline adherence over time in participating hospitals.

2) The CRUSADE Initiative includes which of the following educational interventions:
   a) A multicenter, interdisciplinary patient registry for NSTE ACS patients
   b) Educational programs by key CRUSADE faculty at participating hospitals
   c) A toolbox of CQI interventions to improve compliance with the ACC/AHA guidelines
   d) All of the above
   e) None of the above

3) In the CRUSADE initiative, which of the following patients is least likely to receive GP IIb/IIIa inhibitors and early percutaneous intervention?
   a) Younger patients
   b) Troponin positive patients
   c) Male Patients
   d) Patients cared for by cardiologists
   e) Elderly females

4) In the CRUSADE Initiative patients, which of the following clinical factors is associated with an increased risk of bleeding?
   a) Old Age
   b) Elevated creatinine clearance
   c) Excessive dosing of GP IIb/IIIa inhibitors
   d) Excessive dosing of heparin
   e) All of the above

Clopidogrel in ACS: New Trial Results

5) In the CURE Trial, the clopidogrel dose used and proven to be of benefit was:
   a) 75 mg loading dose, then 75 mg p.o. QD
   b) No loading dose, then 75 mg p.o. QD
   c) 300 mg loading dose, then 75 mg p.o. QD
   d) 600 mg loading dose, no follow-up dose
   e) 600 mg loading dose, then 75 mg p.o. QD

6) Which is NOT true of the CLARITY trial:
   a) The clopidogrel dose used was 300 mg loading dose, then 75 mg p.o. QD.
   b) Clopidogrel was added to standard fibrinolytic therapy including a fibrinolytic, heparin, and aspirin.
   c) The addition of clopidogrel to standard fibrinolytic therapy resulted in a 36% reduction in the odds of the composite endpoint of an occluded infarct-related artery, death, or recurrent MI.
   d) Bleeding was not significantly different in the clopidogrel and no clopidogrel groups.
   e) All are correct.
7) Low-molecular-weight heparins are more bioavailable than unfractionated heparin and therefore achieve and maintain more reliable levels of anticoagulation.
   a) True
   b) False

8) In noninterventional management of non-ST-segment elevation ACS, enoxaparin has been shown to be superior in efficacy to unfractionated heparin.
   a) True
   b) False

Dyslipidemia – What the Emergency Physician Should Know

9) According to the most recent NCEP guidelines, if a patient has known pre-existing coronary heart disease, what is the lowest LDL level where drug therapy should be considered?
   a) > 100mg/dL
   b) >130mg/dL
   c) >160mg/dL
   d) >190mg/dL
   e) None of these

10) The incidence of clinically significant myopathy in patients taking statin agents is closest to:
    a) 0.1%
    b) 2.5%
    c) 1%
    d) 10%
    e) 25%

Diagnosis of Acute Decompensated Heart Failure

11) A 57-year-old male tobacco smoker with a history of chronic obstructive pulmonary disease and congestive heart failure presents to the emergency department 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 congestive heart failure?
    a) Chest radiographic evidence of cardiomegaly
    b) A BNP level of 823 pg/dL in an obese patient
    c) Chest radiography with mild vascular redistribution and a normal heart size
    d) A BNP level of 335 pg/dL in a very thin patient

12) Which of the following patients with heart failure is the best candidate for initiation of vasoactive therapy with nesiritide?
    a) A 78-year-old woman with a blood pressure of 82/38 mm Hg with a right ventricular infarct
    b) A 3-year-old boy with tetralogy of Fallot and a pulse oximetry reading of 75%
    c) A 65-year-old man who was transferred from an outside hospital on intravenous nitroglycerin and a furosemide drip
    d) A 52-year-old woman with a blood pressure of 180/110 mm Hg and a pulse rate of 112 per minute with acute onset of severe heart failure 30 minutes prior to arrival
13) Nitroglycerin, nitroprusside, and diuretics all cause neurohormonal activation.
   a) True
   b) False

14) Nesiritide causes reduction of pulmonary capillary wedge pressure and systemic vascular resistance.
   a) True
   b) False

15) Nesiritide use should be restricted to patients presenting to the hospital with ADHF and dyspnea at rest.
   a) True
   b) False

17) The current diagnostic gold standard to “rule-out” a pulmonary embolism is:
   a) A Ventilation Perfusion Scan
   b) Multislice Computed Tomography
   c) Chest X-ray
   d) Pulmonary Angiogram

18) You diagnose a pulmonary embolism in a young woman. Her Vital Signs are BP 100/60, Pulse rate of 110, and a room air Pulse Oximetry of 92%. The hospital mortality for patients with this complement of vital signs are:
   a) 1%
   b) 5%
   c) 20%
   d) 50%

19) Which blood tests indicate an increased risk for mortality in patients with PE when elevated?
   a) Troponin
   b) CK-MB
   c) B-type Natruretic Peptide
   d) All of the Above

20) Standardization of troponin assays allows for ready comparison by platforms.
   a) True
   b) False

21) There are several successful models and hospital systems that have used POCT successfully.
   a) True
   b) False
The Stroke Center Concept

22) One measure used by JCAHO when evaluating a hospital for stroke center certification is documentation of stroke time on onset in the Emergency Department.
   a) True
   b) False

23) A Stroke Center Director does not have to be a neurologist and can be an emergency physician.
   a) True
   b) False

Advances in TIA Diagnosis and Treatment

24) At 48 hours after TIA, the rate of ischemic stroke is about:
   a) 0.6%
   b) 1%
   c) 5%
   d) 25%

25) In general, carotid endarterectomy results in improved stroke-free survival versus medical therapy in patients who have had a TIA and have carotid stenosis of 70-99% on the symptomatic side of the body.
   a) True
   b) False

Diagnosis of Stroke: The Potential of Serum Biomarkers

26) In future biomarker panels for acute stroke, proteins from the following classes will be likely included:
   a) Neuronal injury
   b) Inflammation
   c) Markers of coagulation/fibrinolysis
   d) Apoptosis
   e) All the above

27) To date, serum marker levels have been associated with all of the following in acute ischemic stroke except:
   a) Baseline neurologic deficit
   b) Size of infarct on CT scan
   c) Neurologic outcome
   d) Discriminating from intercerebral hemorrhage
ACEP 2005 Scientific Assembly EMCREG Symposia

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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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