ADVANCING THE STANDARD OF CARE: Cardiovascular and Neurovascular Emergencies

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[Emergency Medicine Cardiac Research and Education Group]
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Dear Colleagues:

Patients presenting to the Emergency Department (ED) with cardiovascular and neurovascular emergencies remain a major clinical challenge. In the United States alone, there are over ten million annual visits for these conditions, resulting in over three million hospital admissions. Nontraumatic chest discomfort remains the primary catalyst for ED evaluation of possible acute coronary syndromes (ACS), including unstable angina, non-Q wave myocardial infarction and ST-segment elevation myocardial infarction. The diagnosis and treatment of congestive heart failure (CHF) are also important to emergency physicians and other healthcare providers. The diagnosis and treatment of cerebrovascular disease is equally difficult, with up to one million patients presenting to the emergency department with stroke each year. Therefore, it is essential that emergency physicians remain on the forefront of state of the art diagnostic and treatment options involving the newest regimens for ACS, CHF, and neurovascular emergencies.

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International is pleased to present this educational monograph summarizing our 2004 EMCREG Symposium on cardiovascular and neurovascular emergency care held in San Francisco. It is our hope that this material will provide emergency physicians with information necessary to help care for these seriously ill patients.

Sincerely,

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Atherothrombosis is defined as atherosclerotic plaque disruption with superimposed thrombus, is the leading cause of mortality in the Western world.

Atherosclerosis is not a disease unique to modern civilization. Mummies from 1500 BC showed evidence of atherosclerotic lesions, yet understanding of this complex process is still evolving. Advances in our understanding of atherogenesis and processes that lead to plaque rupture – the pathophysiologic hallmark of acute coronary syndromes (ACS), allow for more precise identification, risk stratification and treatment in the future.\(^1,2\)

This section will focus on evolving concepts of atherosclerosis and the pathophysiology of ACS. Pivotal to this discussion is the understanding that the atherosclerotic plaque occurs as a “response to injury” and that factors effecting the vessel wall, blood flow and thrombogenicity are critically interrelated. Response to plaque rupture is determined by local and systemic factors, with inflammation and thrombosis playing central roles.

**Atherosclerosis**

Atherosclerosis as a “response to injury” was first suggested by Russell Ross in 1973. There are four steps in his model; 1) endothelial damage, 2) migration of LDL particles across the endothelial layer into the intima where they are modified, 3) inflammatory response, 4) formation of a fibrous cap. The endothelium can be damaged by a variety of factors such as hypertension, diabetes, tobacco, infections, or oxidative and shear stress.\(^4\) These insults lead to the expression of surface adhesion molecules [P-selectin, Vascular Cell Adhesion Molecule -1 (VCAM-1)] and chemokines encouraging more sustained leukocyte adhesion and interaction within the endothelium. This results in increased endothelial permeability with transmigration of low-density lipoprotein (LDL) and...
monocytes into the intima and decrease in vascular response to nitric oxide. The monocytes mature into macrophages and express scavenger receptors. The LDL particles are then modified by oxidative stress or enzymatic degradation and subsequently taken up by macrophages producing foam cells which accumulate into intimal “fatty streaks”. Macrophage activity is a potent stimulus for the production and release of various cytokines [granulocyte-macrophage colony stimulating factor (GCSF), IL-1, IL-6, tumor necrosis factor (TNF), CD40 and C-reactive protein] as well as cytotoxic substances. Locally acting cytokines within the inflamed intima recruit more macrophages, T-cells and smooth muscle cells, and in addition, further up-regulate endothelial adhesion molecules and increase endothelial permeability. Trapped foam cells aggregate into lipid pools forming the core of the atherosclerotic lesion. Smooth muscle cells migrate from the media into the intima, where they lay down collagen, forming a fibrous cap which stabilizes the plaque by walling off the lipid core from the blood stream. This is a self-perpetuating process as endothelial permeability to LDL is influenced by local and systemic inflammation. Modified LDL leads to amplification of the inflammatory response by macrophages. The local inflammation feeds back, promoting further transmigration of LDL into the intima and subsequent modification. Stimulated macrophages produce matrix metalloproteinases (MMPs) which degrade collagen. Intimal smooth muscle cells appear to be subject to apoptosis (programmed cell death). The fibrous cap thins, it is more likely to rupture, exposing the thrombogenic contents of the plaque to the bloodstream, resulting in clots formation. These proinflammatory forces drive plaque growth and instability, but there are also anti-inflammatory forces striving to limit growth and promote stability. Cytokines such as IL-4 and TGF-β as well as the actions of smooth muscle cells, act to decrease the amount of inflammation present in the plaques. A balance of forces, similar to that seen in wound healing develops. The balance can be tipped in either direction. If it leans towards progression, ongoing growth begins to impinge on the vessel lumen and the plaque becomes vulnerable to erosion and rupture.

Vulnerable Plaques
The stability of the atherosclerotic plaque and the risk for development of an ACS are variable. It is now appreciated that the risk of developing ACS relates more to the composition and “vulnerability” of the plaque than to the degree of vessel stenosis. Risk factors can be categorized as abnormalities of the vessel wall, blood flow or thrombogenicity, or as local versus systemic effects.

The process of initiation, progression and complications of acute coronary arterial thrombosis can be related to Virchow’s triad for thrombogenesis, first described in 1856. Complex lesion morphology (vessel wall) is the angiographic hallmark of ACS. Two percent of patients with acute myocardial infarction are found to have “normal” coronary angiograms. Perhaps these patients have significant atherosclerotic lesions that may not be apparent in the catheterization lab. Angiography however, doesn’t provide information about the remodeling process the atheroma is undergoing. Vulnerability to disruption appears to be determined by the presence of a large lipid-rich core and thin fibrous cap with eccentric morphology, heavily infiltrated by inflammatory cells and acted upon by numerous cytokines, rather than the size of the plaque or severity of the stenosis before disruption. The thinner fibrous cap is less likely to withstand the mechanical stresses of hemodynamic changes, particularly at the shoulders of the cap where there is diminished collagen and smooth muscle. The external physical forces that expose the vessel wall to blood flow at different shear rates also influence the occurrence and progression of plaque disruption, thrombosis and atherosclerosis. A tight stenosis of the vessel
THE PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

does not precipitate ACS, rather it is the physical disruption of the plaque that causes occlusive thrombi. Endothelial dysfunction initiates plaque formation at arterial bifurcations and sites of disturbed flow. Blood flow and vessel wall stress (mechanical and hydrostatic) are key external factors that trigger disruption of plaques. “Cap fatigue” is due to stresses from fluctuations in pressure or motion of the vessel such as bending, compression (vasoconstriction) stretching, and shear – resulting from blood flow within the vessel (laminar and oscillatory). Although plaque rupture is thought to be the main cause of ACS, frank rupture with thrombus-lipid core communication is seen in only 60% of cases. Thrombus associated with superficial plaque erosion devoid of endothelial cells is seen in the rest. These lesions are more common in women, smokers and those with systemic risk factors for a hypercoagulable state. A fracture of the fibrous cap would not likely have significant consequence was it not for the ensuing thrombus. Factors such as lipid and hormonal metabolism, hyperglycemia, fibrinolysis, platelet and leukocyte function are associated with increased blood thrombogenicity. Many plasma hemostatic indices such as fibrinogen, factor VII, von Willebrand factor (VWF), D-dimer have been identified as independent predictors of subsequent cardiovascular events.13

Plaque rupture is thought to occur because of changes in the plaque itself (local) and systemic changes in the patient. Interestingly, contributing factors seem to overlap to a great extent and might even be interrelated.14 From a local perspective, plaque rupture is attributed to changes that occur in the atherosclerotic plaque. The most well understood mechanisms are inflammation and matrix turnover in plaque progression. The degree of plaque disruption (ulceration, fissure or erosion) or substrate exposure is the key factor for determining thrombogenicity at the local site. From a systemic perspective, plaque rupture doesn’t occur as an isolated phenomenon but rather as a systemic disease. In this view, it is the “vulnerable patient” instead of a patient with a localized, vulnerable atherosclerotic plaque. Vulnerable patients often present with multiple ruptured plaques. In one angiographic study of patients with ACS, 39% had multiple complex plaques that were associated with an increased incidence of recurrent ischemia. Rioufol et al., using intravascular ultrasound found 79% of patients presenting with ACS had multiple ruptured plaques at sites other than the culprit lesion that caused the clinical symptoms.15 The occluding thrombus determines the clinical presentation but it is only a focal manifestation of an underlying systemic disease process that includes many rupture-prone or vulnerable lesions. Systemic factors that correlate with plaque rupture are altered increased coagulability, increased systemic inflammation and recurrent infections. These unfavorable systemic changes often interact synergistically with the risk factors of atherosclerosis and plaque rupture, such as hyperlipidemia, smoking and diabetes.16 Systemic contributing factors may explain discrepancies in terms of atherogenesis, lipid accumulation, cell proliferation and extracellular matrix synthesis between patients. As Theroux noted, the progression of atherosclerotic disease is neither linear nor predictable.17

In a minority of cases fatal coronary thrombosis results from superficial erosion of the intima without frank rupture through the plaque fibrous cap. Erosion occurs when inflammatory mediators cause apoptosis of endothelial cells and activate proteases, with the consequence of endothelial cells separating from their underlying substrate, portions of which are thrombogenic. Endothelial cells can also express proteinases regulated by inflammatory cytokines and oxidized lipoproteins. Activation of the proteases in response to inflammatory stimuli can sever the tethers that hold the endothelial cell to its underlying matrix promoting desquamative injury to the intima thus initiating a thrombotic process. If the disruption of the plaque leads to a significant thrombus it may impinge the vessel lumen and manifest itself clinically.18
When the plaque is disrupted all three components of Virchow’s triad come into play simultaneously. Highly thrombogenic material (especially tissue factor) is released from the lipid core and acts the extrinsic clotting cascade. Tissue factor forms high affinity complexes with factors VII/VIIa which activate factor IX and factor X, leading to formation of the prothrombinase complex and ultimately to the generation of thrombin and fibrinogen conversion to fibrin. The exposure of platelets to collagen or von Wildenbrand’s Factor (VWF) on the subendothelial surface leads to platelet adhesion with multiple receptors. Platelet adhesion is followed by activation and aggregation with concomitant release of thrombogenic constituents. With the activation of platelets, the glycoprotein (GP) receptors are activated. Glycoproteins, VWF and fibrinogen bind together linking platelets. Many local and systemic factors coexist to increase the thrombogenicity around the injured plaque, including increased turbulence and stasis around disrupted region, leading to propagation of the thrombus in the coronary artery.

**Ischemic Presentations**

Plaque disruption with a subsequent change in plaque geometry and thrombosis results in complicated lesions. A rapid change may result in acute occlusion or subocclusion with clinical manifestations of unstable angina or other ACS. More frequently however, the rapid changes seem to result in mural thrombus without evident clinical symptoms. Such thrombus may be the main contributor to the progression of atherosclerosis. Local and systemic circulating factors influence the degree and duration of thrombus deposition. Acute coronary syndromes are a continuum. Symptoms occur when there is an abrupt imbalance between oxygen supply and demand influenced by extrinsic (exercise) and intrinsic (flow) factors.

Stable angina is characterized by atherosclerotic plaques with fixed stenosis. Clinical symptoms occur when oxygen demand exceed supply (exercise, stress). There is often significant vascular collaterals if the problem is long standing. Unstable angina usually results from decreased perfusions (plaque disruption resulting in thrombus and reduced flow) or increased oxygen demand (oxygen mismatch). The thrombus is often labile with obstruction or transient occlusion. Here the myocardium is stressed by ischemia but recovers. Non ST–segment elevation myocardial infarction (NSTEMI) occurs when myocardial perfusion is disrupted due to persistent thrombotic occlusion or vasospasm. Spontaneous thrombolysis, resolution of vasoconstriction or flow from collateral sources limit the resulting ischemic injury. Plaque disruption and thrombosis that result in complete coronary artery occlusion leads to transmural ischemia and necrosis, the hallmark of ST-segment elevation myocardial infarction (STEMI).

While NSTEMI and STEMI are felt to share a common underlying pathophysiology it is unclear why they behave differently in terms of therapeutic response. It has been postulated that the thrombus differ in cellular composition. Variations in clinical manifestations in “vulnerable patients” are likely impacted by multiple systemic factors.

**Therapeutic Implications**

Recognizing the role of inflammation in atherothrombosis opens the window for new diagnostic strategies and therapies. Inflammatory markers are making their way into real-time clinical practice. Patients with ACS who have high levels of inflammatory markers (CRP), are at higher risk for developing ACS and require evaluation for anti-inflammatory therapy. Elevated markers at the time of percutaneous coronary intervention (PCI) predict adverse outcomes. We are entering a period when many new biomarkers for inflammation and cellular ischemia – not just necrosis, are becoming available. It is too early to tell which ones will be added to our armamentarium, but it is likely that in the future we will approach risk stratification of ACS patients differently. We may...
also someday follow inflammatory marker levels to assess the effectiveness of interventions such as diet, statins, and ASA. Our understanding of “vulnerable patients”, not just vulnerable atherosclerotic plaques, highlights the importance of systemic factors on cardiovascular outcomes. The role of proteomics in assessing population-based therapeutic efforts is also on the horizon for EP's.

In most situations therapy is based on pathophysiology. In atherosclerosis, treatment has evolved from epidemiologic outcome correlations, including statins for hyperlipidemia, diabetic glucose control, diet and weight control, and exercise. Investigations suggest that many of the approaches embraced over the last few decades addressing cardiovascular health modify atherothrombosis in part by reducing inflammation.8,25 The level of physical activity was independently associated with a lower odds ratio for an elevated CRP, WBC or fibrinogen levels. Healthy subjects undergoing a 6-month exercise program saw reductions in atherogenic cytokines (IL-1, TNF) by as much as 58% and atheroprotective cytokines (IL-4, TGF-beta) increased by 35%. Some have suggested that obesity is proinflammatory. Weight loss, on average 14 kg/14 months, reduced CRP levels by 32%. Low fat diets appear to improve endothelial function and lower adhesion molecules such as P-selectin. Aspirin remains of the most effective therapies for primary and secondary prevention of coronary disease. Given its modest antiplatelet effect, aspirin’s anti-inflammatory properties are probably just as important. Thienopyridines bind to platelets through an adenosine diphosphate (ADP) receptor. The beneficial effects were thought to be related to their ability to decrease clot formation but recent evidence suggest they could also have anti-inflammatory effects. Clopidogrel inhibits platelet expression of CD40 ligand. Platelet activation leads to expression of CD40 ligand, and these agents may block the pathway. Angiotensin-converting enzyme (ACE) inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) have been shown to significantly reduce cardiovascular events. The degree of benefit is greater than would be expected from blood pressure reduction or lipid lowering alone. The renin-angiotensin system plays a direct role in inflammation. In animal studies statins have been found to significantly reduce leukocyte adherence to endothelial cells and transmigration, hence decreasing inflammation. Ross noted that atherosclerosis resulted from a “response to injury” three decades ago. It has become very clear that inflammation plays a central role in this process. Future therapeutic modalities are likely to target the inflammatory system. Therapies that interfere or block the actions of adhesion molecules, cytokines, T cells and macrophages and other inflammatory mediators may one day become important adjuncts in preventing and managing ACS.26

**SUMMARY**

Assessment, risk stratification and treatment of patients with ACS demand that emergency physicians have a working understanding of the pathophysiology of atherothrombosis. The risk of plaque disruption and thrombus formation is related to aberrations in the coronary vessel wall, blood flow and underlying degree of thrombogenicity. Inflammation plays a key role in determining coronary vessel response to injury. Atherothrombosis results from both local and systemic effects; the importance of recognizing the vulnerable patient is gaining acceptance. The complexity of the pathways involved offer a wide array of future diagnostic and therapeutic approaches.
REFERENCES


OBJECTIVES:
1. Discuss the available point-of-care tests for ACS in the ED setting
2. Discuss clinical implementation of ACS point-of-care testing in the ED setting

BACKGROUND

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 (TAT).

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. [Table 1]

Table 1. Current Widely Available Cardiac Marker Assays.

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<tr>
<td>1) Triage System (Biosite)</td>
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<td>2) i-STAT®1 Analyzer (i-STAT)</td>
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<td>3) Cardiac Reader (Roche)</td>
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<td>4) RAMP System (Response Biomedical)</td>
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<td>5) Stratus CS (Dade Behring)</td>
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Selected POC Cardiac Marker 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), high-sensitivity CRP (hsCRP), and D-dimer are also available but beyond the scope of this manuscript1-6. Trials evaluating POC testing assay generally focus on analytical performance and/or clinical utility7-8. 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.

It is clear that the accurate measurement of the cardiac troponins is a major focus for POC testing in patients presenting with potential ACS. Evaluation of analytical performance is complicated and often 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 µg/L with a 99th percentile reference limit of 0.08 µg/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 of diagnosis and risk assessment of patients with possible acute coronary syndrome9.

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 infarction. Three markers strategies were compared: (1) POC myoglobin, CKMB, 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 for 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%). This study concluded that POC multimarker determination provided faster and better risk stratification in this patient population10.

The RAMP® (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/ACC11. The authors concluded that on 39 AMI and 67 non-AMI patients, the clinical sensitivity, specificity, and diagnostic efficiency of the RAMP were similar to the comparison 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/mL12.

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 value to this evaluation. Additionally, lab result reporting was on average 57 minutes faster with the POC assay\textsuperscript{13}.

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 populations as well. Using the same patient population as the previously mentioned study by McCullough 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{13,14}.

**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 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 challenge 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 cannot be 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\textsuperscript{15}. 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\textsuperscript{16}. 
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 occurred 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 syndrome17-19.

So the success of POC clearly requires that action be taken on the result obtained. This is the only way to benefit from POC testing and improve patient care and outcomes (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 frequently non-laboratory personnel to perform rapid and high quality tests. Implementation of any POC system must start with clinician 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.

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 risk20-22. It is important for emergency physicians to understand the limitations of POC testing and make informed decisions based on the qualities of the individual platforms.

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**Figure 1.**

Model for Point-of-care Testing

- **Clinical Question**
- **Test**
- **Result**
- **Action**
- **Patient Outcome**

**Time**

“POC testing has value only if caregivers take action on the result.”
**Future Directions**
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. *(Table 2)*

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**Table 2.**
Anatomy of Successful POC Testing

<table>
<thead>
<tr>
<th>Equipment management (purchase, maintenance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing procedures</td>
</tr>
<tr>
<td>Notification of results and integration in medical record</td>
</tr>
<tr>
<td>Monitoring of quality</td>
</tr>
<tr>
<td>Training and proficiency testing of personnel</td>
</tr>
<tr>
<td>Accreditation and regulatory requirements</td>
</tr>
<tr>
<td>Integration of results into a central medical record system</td>
</tr>
</tbody>
</table>
REFERENCES


THE ROLE OF HEART SOUNDS RECORDING AND ANALYSIS IN THE DYSPNEIC ED PATIENT

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OBJECTIVES:
1. Describe the etiology and importance of S3 and S4 heart sound recording and analysis in the ED
2. Describe the role S3 and S4 heart sound recording and analysis can play in the diagnosis of decompensated heart failure

INTRODUCTION

Extra diastolic heart sounds are produced as a result of increased stiffness and decreased compliance of the left ventricle. The third heart sound (S3) occurs 0.12 to 0.16 seconds after the second heart sound in early diastole (Figure 1). Of the many proposed theories, the most likely explanation is that excessive rapid filling of a stiff ventricle is suddenly halted, causing vibrations that are audible as the third heart sound. The fourth heart sound (S4) occurs after P wave onset and before the first heart sound in the cardiac cycle. It is produced in late diastole as a result of atrial contraction causing vibrations of the left ventricular muscle, mitral valve apparatus, and left ventricular blood mass. Atrial and ventricular “gallows” have been described in the literature dating back to the late 1800’s. The ventricular gallop is recognized as a third heart sound. The atrial gallop is synonymous with a fourth heart sound.

Auscultation of the S3 and S4
Both an S3 and S4 are auscultated in similar fashion. Harvey has suggested the “inching” technique as a way to distinguish the often times pathologic S3 and S4 from the physiologic S1 and S2. In both situations it is best to examine the patient in the left lateral position using the bell of the stethoscope. Starting at the aortic area (where the S2 is the loudest) the examiner “inches” down to the cardiac apex, using the S2 as a reference point. If one encounters an extra sound in diastole, just after the S2, this is an S3 or diastolic gallop. The S3 is generally absent at the base, so that as the examiner moves toward the apex the S3 is encountered. The opposite maneuver results in detection of an S4. In this instance the examiner inches from the apex upward.

Figure 1. Location of Heart Sounds in the Cardiac Cycle.
to the base. The first heart sound (loudest at the apex) is used as a reference, because the S4 occurs in early systole, just before S1. If the stethoscope is moved away from the apex the S4 disappears. A further method to distinguish a split S1 from an S3 is to place pressure on the bell of the stethoscope - an S3 will disappear, while a fixed S1 will remain.

**Significance of an S3 and S4**

** Decompensated Heart Failure**

While detection of an S3 can be “normal” in adolescents and young adults, its detection after the age of 40 is considered abnormal.\(^6\) [Table 1] Traditionally not very sensitive for left ventricular dysfunction, when detected, an S3 can be very predictive of elevated left ventricular pressure. In a study of outpatients referred for cardiac catheterization, the detection of an S3 was the most specific finding elevated left ventricular end diastolic pressure (LVEDP) (95%).\(^9\) A more recent study has also found that the detection of an S3 has a high specificity and positive predictive value in detection of patients with low ejection fractions.\(^10\)

More importantly, it has been suggested that patients with a detectable S3 have an increased risk of hospitalization and death compared to those patients without a detectable S3.\(^11-13\) [Table 1]

Furthermore, in patients with decreased ventricular compliance (i.e. heart failure) a greater proportion of filling occurs in late diastole. As a result, the atrial component of ventricular filling is increased resulting in a large amount of blood being forced into a stiff, noncompliant ventricle. The net result is an S4.\(^14\)

**Acute Coronary Syndromes**

Patients with coronary artery disease without acute ischemia do not have an S4. However, an S4 may be present in the early phases of acute ischemia and acute myocardial infarction, with an incidence approaching 100%.\(^15\) The prevalence of the S4 in healthy individuals has previously been a subject of great debate. Previous heart sound studies have found a prevalence of S4’s from as low as 11%\(^16\) to as high as 75%\(^17\) as well as many values in between.\(^18-23\) The vast majority of these studies enrolled fewer than 300 patients, and suffered from enrollment bias because many of the subjects had been referred for cardiac workup, including left and right heart catheterization.

**Table 1.**

Clinical relevance of heart sounds.

<table>
<thead>
<tr>
<th>Physical exam finding</th>
<th>Healthy subjects less than 40</th>
<th>With symptoms of ACS</th>
<th>With symptoms of heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S3</strong></td>
<td>May be present</td>
<td>High-risk feature, but not as sensitive as S4</td>
<td>Highly specific for LV dysfunction</td>
</tr>
<tr>
<td><strong>S4</strong></td>
<td>Usually not present</td>
<td>High likelihood of CAD</td>
<td>Indicative of high LV pressure</td>
</tr>
</tbody>
</table>
Coronary heart disease (CHD) without LV dysfunction does not produce an S3. However, if CHD results in LV dysfunction (either acute or chronic) leading to a poor ejection fraction, an S3 may develop. An S3 during acute myocardial infarction suggests a large infarction and does not necessarily mean LV dysfunction that requires treatment. The intensity of an S3 tends to decrease as the myocardium recovers from acute infarction. \(^{24}\)

The ACC/AHA guidelines recommend that patients with unstable angina and a concurrent auscultated S3 be classified in the group at highest risk for adverse outcomes and considered candidates for an early invasive strategy. \(^{25}\)

**Detection of S3 and S4 on Physical Exam**

Recent studies indicate that physicians are becoming less proficient at performing the physical examination, and physicians in training programs have been shown to have poor cardiac auscultatory skills. \(^{26-29}\)

Furthermore, interobserver agreement of S3 detection is poor, with board-certified cardiologists having no better agreement than house staff. \(^{30-32}\)

Compounding the difficulty of S3 or S4 detection is the loud ED environment, confounding illnesses such as COPD and obesity that make detection difficult, and the inability of the patient to tolerate being placed in the ideal examining position (left lateral decubitus) because of their dyspnea.

**Heart Sound Recording and Analysis Advances**

The introduction of new heart sound recording and analysis technology has allowed this topic to be revisited. The Audicor\(^{\circ}\) System is an example of a cardiac diagnostic tool that may aid physicians in the diagnosis of cardiac conditions such as acute myocardial infarction and decompensated heart failure at the point of care. The Audicor\(^{\circ}\) System uses correlated audioelectric cardiography (COR) to combine an analysis of electrical signals from the ECG with heart sound detection in a correlated report format, without altering current ECG testing procedures. The Audicor\(^{\circ}\) device uses a dual sensor in conjunction with standard ECG electrodes (Figure 2). The dual sensor

**Figure 2.**

Placement of acoustic heart recording chest leads in the V3 and V4 position.
Perform CHF workup
Suspected Decompensated Heart Failure

Perform acoustic heart sound recording or cardiac auscultation for detection of S3 and/or S4
S3 detected
S3 not detected

If decompensated, heart failure likely
Initiate simultaneous CHF workup and treatment

If decompensated, heart failure likely
Initiate simultaneous CHF workup and treatment

S4 Detected: consider LV dysfunction or ACS
S3 not detected
S3 not detected

Perform ACS Workup
Suggestions CHF and high risk

Consider early invasive strategy
Repeat acoustic heart sound recording or cardiac auscultation for detection of S3 and/or S4
Patient disposition to appropriate level of care

Simultaneously acquires electrical and acoustical data from the V3 and V4 position on the standard 12-lead ECG. The phonocardiogram device attaches to the standard ECG machine. The sensors on leads V3 and V4 are only slightly larger than standard ECG leads and impose minimal to no additional inconvenience to the patient. Diagnostic algorithms then analyze both types of data, generating a report detailing the presence of an S3, S4, acute MI, prior MI, ischemia and left ventricular hypertrophy (Figure 3).

Figure 3.
Example of an electrocardiograph printout with accompanying acoustical information.

Figure 4.
Early Diagnostic and Treatment Pathway for CHF and ACS

* An early invasive strategy is recommended in patients with MI/STEMI and any of the following high-risk indicators: Class I Level of Evidence A: recurrent angina/pain at rest or with low-level activities despite intensive antiischemic therapy; elevated TnT or TnI at rest or in response to new IT-regional depression; new left bundle branch block (LBBB); new or progressive cardiogenic shock; or recurrent mismatched perfusion defects on nuclear imaging studies. A IIa level of evidence approach may be reasonable for patients with elevated TnT or TnI at rest or in response to new IT-regional depression, new left bundle branch block (LBBB), or new or progressive cardiogenic shock. Class IIa level of evidence approach may be reasonable for patients with recurrent angina/pain at rest or with low-level activities despite intensive antiischemic therapy, or new left bundle branch block (LBBB).

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SUMMARY

An S3 and S4 are often produced as a result of pathologic processes that produce elevated ventricular pressures. The presence of an S3 or S4 in a symptomatic ED patient should alert the treating physician to the presence of underlying cardiovascular abnormalities (Figure 4). The difficulty in identifying an S3 or S4, even for the trained practitioner, is well documented. Fortunately, with recent technological advancements, the treating physician is now able to electronically detect these abnormal heart sounds readily with no inconvenience to the patient.

REFERENCES


Chest Pain Centers (CPCs) are focused on addressing the number one cause of death in this country - acute coronary syndromes (ACS), including myocardial infarction (MI) and other ischemic heart disease. This discussion will focus on the components of a successful CPC, and new developments related to their function.

Let’s begin by stating what a chest pain center is NOT. It is not a hospital’s marketing campaign. It is no longer just a specific area of the emergency department, or an algorithm for the safe and efficient evaluation of low-risk patients. A Chest Pain Center in the year 2004 is an institution wide program, integrated with its community and its EMS system, which is aimed at optimizing the care of ACS patients. A CPC is a multidisciplinary program that incorporates elements from the emergency department, cardiology, nursing, laboratory, administration and other areas. Think of a Trauma Center. A Trauma Center is, similarly, an integrated, facility-wide, multidisciplinary program. It is not an operating room, an ED, or a neurosurgeon. These are all necessary components of a successful Trauma Center, and all of these (and other components) build from the synergy necessary to optimally respond to the epidemic of trauma. Establishment of such an interdisciplinary team, in this instance focused on the epidemic of coronary artery disease, is a model for the delivery of healthcare now and in the coming decades.¹ The key elements of a successful Chest Pain Center are outlined in Table 1.

### OBJECTIVES:
1. Describe the key elements of a successful Chest Pain Center in the year 2004
2. Understand the concept of a ‘Code’ response to the prehospital diagnosis of ST-segment elevation myocardial infarction
3. Learn how the recently revised ACC/AHA guidelines for the management of myocardial infarction impact the processes of a Chest Pain Center

### Table 1. Key Elements of a Successful Chest Pain Center

1. Emergency Department integration with EMS
2. Emergency care of patients with ACS (Attack program)
3. Evaluation of patients with ‘low likelihood’ for ACS
4. Functional facility design
5. Personnel, competencies and training
6. Organizational structure and commitment
7. Process improvement orientation
8. Community outreach
CPC begin their mission in their communities, where patients experience symptoms. It includes an EMS system with providers trained and equipped to identify and treat ACS patients. EMS providers are called on to initiate diagnostic testing and treatments as soon as possible. Prehospital electrocardiography is key to the earliest diagnosis of ST segment elevation myocardial infarction (STEMI). Because of the advantage in rapid diagnosis of ACS and STEMI, the American College of Cardiology/ American Heart Association find it reasonable that “all advanced cardiac life support providers perform and evaluate 12 lead ECGs routinely on chest pain patients suspected of STEMI”. Some leaders are calling for the establishment of regional cardiac centers capable of immediate intervention in STEMI around the clock. Prehospital electrocardiography is a prerequisite to establishing such specialized cardiac destination centers. The debate regarding the benefits of an early invasive strategy vs. medical management in STEMI persists. Regardless of the reperfusion strategy employed by a particular facility, time is of the essence. The recently revised ACC/AHA guidelines state that fibrinolytic drugs should be started within 30 minutes and balloon inflation in PCI is accomplished within 90 minutes of the patient’s first contact with the medical system. This includes the contact made by EMS providers and the time they spend with the patient. Strategies to optimize the time the patient is being treated by paramedics include prehospital lytic drug administration or activation of the cardiac cath lab based on prehospital information.

The ED based ‘attack program’ for the response to patients with readily identified MI or unstable angina is a cornerstone of the CPC. Many institutions that have interventional cardiology facilities have adopted PCI as the standard mode of treating STEMI. The multidisciplinary response required to mobilize the resources of the institution for PCI has prompted some hospitals to institute a “Code” team for STEMI patients. This system has been associated with reduction in time to intervention during both daytime hours, as well as during nights and weekends, when cath teams may not be assembled within the hospital. A “Code STEMI” response consists of coordinated communication (between prehospital, ED, and cardiology), pre-arrival assignment of registration numbers, a standard order set, rapid delivery of nursing interventions, and notification to cath lab staff of an impending emergent patient. All of these components are designed to eliminate unnecessary delay in the provision of definitive care of the STEMI patient – reestablishment of blood flow in the culprit artery.

The CPC includes careful and complete evaluation of patients whose symptoms may suggest ACS, but are not definitive. A standardized strategy for evaluation and treatment of such ‘low-likelihood’ patients reduces variability in their care, and reduces inappropriate or incomplete care. The algorithms that constitute this strategy vary by institution, but all are comprised of similar elements: serial clinical evaluations, ECG monitoring, measurement of markers of myocardial necrosis, stress testing, and patient disposition decisions. By instituting such a strategy, hospitals can reduce the chance of inadvertent discharge of patients with MI. This benefit is achieved with a shorter length of stay and at a lower cost. New modifications of such rapid-evaluation protocols have been designed to further speed these evaluations. For example, the Erlanger Protocol uses continuous ST segment trend monitoring and blood sampling at presentation and two hours later. By evaluating the change (delta) in the concentration of troponin and CK-MB over this two-hour interval, dispositions are made more rapidly than the typical protocols that use serial testing over 6 to 12 hours. Amsterdam and his colleagues at UC Davis waste little time in getting their patients to a stress test. For low-risk patients (normal or minimal
non-diagnostic changes on the initial ECG, able to exercise, hemodynamically stable, no arrhythmias, and a single normal serum marker of necrosis), their protocol calls for immediate stress testing. They have assessed nearly 3000 patients using this strategy with no adverse events. Perhaps the time has come for a more widespread adoption of these accelerated diagnostic protocols.

New technology is being applied in the diagnostic testing for evaluation of patients with chest pain and may find application in CPCs. Electrocardiography has been the most useful diagnostic tool for detecting and risk stratifying the patient with ACS. Unfortunately it is a relatively insensitive instrument. The standard ECG incorporates 12 leads and reflects about 10 seconds of information. Serial ECGs may be automatically obtained as frequently as once or twice a minute, and ST segment amplitudes evaluated by software algorithms for signs of ischemia.12 The spatial limitations of viewing only 12 leads of information have been addressed, as well. Using a vest-like application of 80 leads, a more complete evaluation of the cardiac electrical information available at the body surface is now possible.13 Isopotential mapping and color enhancements augment the visual display and assist with the interpretation of these body-surface ECGs. These techniques offer a more complete picture of the cardiac electrical information regarding ischemia, and bring the appropriate time domain (minute to minute surveillance) to the ECG.

Non-invasive detection of significant coronary artery disease is a major goal of CPCs. To date, this has been accomplished by using exercise ECG testing, nuclear perfusion studies, or stress echocardiography. Recently the techniques of computed tomography (CT) and magnetic resonance imaging (MRI) have been applied to the detection and risk-stratification of ACS. Early studies of coronary artery calcium scoring using electron beam CT have been somewhat difficult to interpret since the presence of a small amount of coronary artery calcium may be associated with adverse events, and other lesions responsible for an ACS may show little or no calcification in the plaque. Current generation multidetector CT scanners can image the intravascular anatomy of the coronary tree.14 Gating the image acquisition to the ECG, and using beta blockade to slow the heart rate can eliminate much of the artifact caused by cardiac motion. The resolution of the images is quite favorable, but still not quite as sharp as angiography via cardiac catheterization. Imaging strategies using MRI have been developed to detect reversible wall motion abnormalities and perfusion defects.15 Magnetic resonance imaging may hold promise in assisting with the evaluation of emergency department patients for cardiac ischemia.16

Quality improvement initiatives continually evaluate the practice that is used to deliver care. They study the current status of the process, identify areas for improvement, implement changes in the process, and re-measures in order to evaluate its impact. Several such initiatives are specifically targeted at the care of acute MI and ACS patients. The CRUSADE initiative is a registry of non-ST segment elevation MI and unstable angina patients.17 Individual hospitals submit data regarding acute care and long term care of their patients. National, like-hospital and best-practice results are presented for comparison to the individual hospital. The intent is to enhance the ability of the institutions to evaluate their performance, and make improvements in the process that is used to deliver care for the ACS patients. All CPCs should participate in an ongoing process of quality improvement. If for no other reason, hospital reimbursement may soon be linked to ‘quality’ indices.
The CPC model has evolved in concept and practice over the past 15 years. What was once a single ‘low likelihood’ algorithm or even a marketing instrument of the hospital is now a facility-wide program. To ensure that CPCs meet the criteria that have been established as constituting a complete and successful program, the Society of Chest Pain Centers developed a means of accrediting CPCs (http://www.scpccp.org/accreditation/process.html). Approximately 75 US hospitals have become accredited by this Society in the 18 months since the program’s inception. To gain accreditation, hospitals submit documentation describing their compliance with each of the eight key elements [Table 1]. The processes and institutional strategies used for the evaluation and treatment of patients with symptoms of ACS are reviewed at the time of a site visit by representatives of the Society.

The CPC comprises an open, interdependent system that begins in the community, incorporates EMS, the emergency department, cardiology services, other hospital services and providers, and returns to the community in outreach efforts and education. The CPC continues to evolve as a rapid, safe, and cost-effective means for the diagnosis and treatment of patients with emergency cardiac disease.

REFERENCES

Patients presenting to the emergency department (ED) with chest pain and non-ST-segment elevation acute coronary syndromes (NSTE ACS) are at significant risk for short-term and long-term morbidity and mortality. Randomized clinical trials have demonstrated 30-day combined incidences of death, MI, and urgent revascularization of over 15% in these patients, and current ACC/AHA guidelines recommend early aggressive medical therapy followed by definition of coronary anatomy and subsequent revascularization in high risk NSTE ACS patients. Upon patient identification in the ED, medical therapies including platelet and thrombin inhibitors should be initiated early and continued through angiography. The emergency physician must be knowledgeable in the utilization of pharmacological agents used to treat NSTE ACS. Platelet inhibitors are an important piece of this pharmacological armamentarium.

**Platelet Inhibitors in NSTE ACS:**
The pathophysiology of NSTE ACS is initiated by the endothelial rupture of an atherosclerotic coronary artery plaque. Plaque rupture leads to platelet aggregation, platelet activation, fibrin deposition, and downstream myocardial ischemia and necrosis. Therapies aimed at reversing platelet activation, platelet aggregation, and coagulation cascade activation are especially effective in NSTE ACS. Platelet inhibitors, including aspirin, clopidogrel, and glycoprotein IIb/IIIa (GP) receptor blockers have all been investigated in this group of patients with remarkable results.

**Oral Antiplatelet Agents:**
The two oral antiplatelet agents indicated for the treatment of NSTE ACS are aspirin and clopidogrel. The Class IA recommendation for aspirin in the acute treatment of NSTE ACS is based mostly on substantial evidence from STEMI trials, where aspirin was shown to significantly reduce the incidence of death, MI, and stroke compared to placebo. The evidence for its effectiveness in NSTE ACS is less compelling, but still substantial. The Antiplatelet Trialists Collaboration, in a compilation of NSTE ACS trials, demonstrated significant benefit to early aspirin, in addition to antithrombin therapy, in NSTE ACS. The initial dose of aspirin remains controversial, although most authors recommend 325 mg. chewed, either initiated on arrival in the ED or in the pre-hospital arena. The maintenance dose is recommended at 75-150 mg daily, with most patients choosing the 81 mg baby aspirin for daily prophylaxis, especially when combined with clopidogrel.
Clopidogrel is recommended by the ACC/AHA Guidelines as a Class IA therapy for NSTE ACS based mostly on the results of the CURE trial. The CURE trial randomized over 12,500 patients with NSTE ACS to aspirin plus placebo versus aspirin plus clopidogrel, administered during initial hospitalization and continued for one year after discharge. Clopidogrel utilization was associated with a statistically significant reduction in death, MI, and stroke at one year. An even more substantial beneficial effect was noted in patients who underwent PCI during their hospitalization, with an absolute reduction in death and MI of 4% at one year (Figure 1). The clinical benefits of clopidogrel in NSTE ACS have been substantiated in PCI trials like EPISTENT and ESPRIT, as well as the recently completed CREDO trial. In the CREDO trial, the administration of clopidogrel between 6-24 hours prior to PCI was associated with improved outcomes versus placebo in patients treated with PCI. Clopidogrel’s benefits were noted to be additive to GP IIb/IIIa inhibitors in PCI as well.

The ACC/AHA guidelines recommend early administration of clopidogrel 300mg orally at the time of patient identification as high risk. The early utilization of clopidogrel in the ED remains somewhat controversial, however, due to downstream bleeding concerns. In the CURE trial, patients who underwent CABG while taking clopidogrel had a higher incidence of surgical bleeding complications. As such, the guidelines recommend holding clopidogrel for 5 days prior to CABG. This often leads to the withholding of clopidogrel in the ED and prior to catheterization, until the coronary anatomy is defined, and the determination is made that patient is not destined for CABG.

A second controversial issue with clopidogrel revolves around the appropriate loading dose. Pharmacokinetic studies have shown that a 600mg. loading dose confers earlier, more therapeutic antiplatelet function than the recommended 300 mg dose. In the ISAR REACT trial, clopidogrel 600 mg. loading was found to be equivalent to IV IIB/IIIa agents in elective PCI, albeit in extremely low risk patients. These studies have led many practitioners to alter their loading dose of clopidogrel to 600 mg at the time of patient identification.
Intravenous Antiplatelet Agents

A large body of evidence now supports the substantial clinical benefit of adjunctive platelet GP IIb/IIIa utilization with percutaneous intervention in the setting of unstable angina and non ST elevation myocardial infarction. ACC/AHA guidelines recommend GP IIb/IIIa therapy in NSTE ACS patients in whom PCI is anticipated, and those patients deemed at high risk of short term adverse outcome. Patients with elevated troponin levels, ST deviation (ST depression or transient elevation) on their ECG, or other high risk features (ongoing pain, rest pain, CHF, atrial fibrillation, hypotension, or advanced age) should be considered for both GP IIb/IIIa therapy followed by PCI within 48 hours. All three GP IIb/IIIa inhibitors have been shown to be effective in association with PCI in this patient population and are utilized to a widespread extent in the catheterization laboratory.

A smaller but significant benefit with GP IIb/IIIa inhibitors is also discerned in the time period following initiation of treatment but prior to percutaneous intervention (Figure 2).

Consequently, ACC/AHA guidelines advocate the utilization of GP IIb/IIIa inhibitors in NSTE ACS patients destined for early angiography and subsequent intervention before the time of percutaneous intervention. Despite these recommendations, utilization of GP IIb/IIIa inhibitors in the ED and in the pre-intervention period remains relatively low.

Antiplatelet Utilization in the CRUSADE Initiative

The CRUSADE registry is an ongoing voluntary observational quality improvement and research initiative for hospitalized patients presenting with NSTE ACS. At the time of this publication, The CRUSADE registry population consisted of well over 100,000 patients admitted with a NSTE ACS to participating hospitals. CRUSADE patients are included in the registry if they present with chest pain of less than 24 hours and suspected NSTE ACS with either ST deviation (ST depression or transient (<30 minutes) on the resting EKG, a positive troponin assay based on the local site cut-off or both.

Data from the CRUSADE initiative illustrate the relatively low utilization of appropriate antiplatelet therapy in the ED and in the first 24 hours after hospital admission. Utilization of early aspirin in the CRUSADE initiative averages over 97%, while the utilization of other antiplatelet agents remains suboptimal (Figure 3). In patients with high risk NSTE ACS, such as those with elevated troponin

Figure 2. Benefit of GP IIb/IIIa Therapy Before and after PCI: Meta Analysis of Randomized Controlled Trials of GpIIb/IIIa Therapy in NSTE ACS (CAPTURE, PURSUIT, PRISM-PLUS)
levels or ST deviation, it is imperative to provide optimum antiplatelet protection in the time period after patient identification in the ED and prior to subsequent PCI. Yet, according to CRUSADE data, 34% of these patients receive aspirin as their sole antiplatelet therapy. This represents a prime target for quality assurance programs and NSTE ACS program initiatives.

In another recent analysis of the CRUSADE database, patients who received early treatment with a GP IIb/IIIa inhibitor were compared with those who were untreated or treated > 24 hours after index hospital presentation.22 Patient baseline demographics, clinical characteristics, care patterns, and in-hospital outcomes, as well as the features of hospitals to which they were admitted were compared between groups. Patients receiving early GP IIb/IIIa therapy were significantly different from their counterparts who did not receive early GP IIb/IIIa therapy, and medical treatment varied significantly between the two groups. Patients who received early GP IIb/IIIa therapy were more likely to be treated with antithrombin or oral antiplatelet agents, and were more likely to receive early angiography and PCI. They also had a significantly lower length of stay in the hospital.

In this analysis, early GP IIb/IIIa treatment was associated with a significant reduction in unadjusted mortality. After using logistic regression analysis adjusting for patient risk, treatment propensity, and hospital characteristics, early GP IIb/IIIa inhibition was associated with a strong statistical trend towards reduction in in-hospital mortality (OR 0.90, 95% CI, 0.81-1.03) [Figure 4]. These CRUSADE results are consistent with other analyses of GP IIb/IIIa effectiveness in NSTE ACS [Figure 4]. In a meta-analysis of GP IIb/IIIa randomized clinical trials, Boersma, et showed a trend toward decreased mortality with GP IIb/IIIa inhibition utilization.20 A similar mortality benefit was reported by Peterson and colleagues using the NRMI-4 registry database.23 Results from the CRUSADE registry now appear to further corroborate these observations. In the highest risk patients with troponin positivity, early GP IIb/IIIa use is associated with a statistically significant reduction in mortality.

These observational registry data will be investigated further in the EARLY-ACS trial. In this ongoing 10,500 patient prospective randomized clinical trial, patients with NSTE ACS will be randomized to

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**Figure 3.**

Acute Utilization (<24 hours after admission) of Oral and Intravenous Antiplatelet Therapy in the CRUSADE Initiative.
either ED-initiated versus cath-lab initiated GP IIb/IIIa therapy. Primary outcomes include death, MI, and urgent revascularization in the first 96 hours after admission. This trial should clarify the role of ED initiated GP IIb/IIIa inhibitors in NSTE ACS.

**Implications for ED Clinical Practice**

Emergency physicians are often faced with critical decisions in the care of NSTE ACS patients. One of the more controversial of these decisions revolves around the question of initiation of either clopidogrel or a GP IIb/IIIa inhibitor in the ED versus the later in the catheterization lab. Evidence from randomized clinical trials has supported early use of clopidogrel and GP IIb/IIIa inhibitors in the time period prior to PCI, but both antiplatelet agents are still underutilized in this setting as evidenced by the CRUSADE registry. Patients with chest pain and presumed NSTE ACS are at highest risk for recurrent ischemia, recurrent MI, and death in the 24-48 hours after admission and prior to cardiac catheterization. It is imperative that emergency physicians treat these patients aggressively and expectantly during this vulnerable period. Platelet inhibitors play a crucial role in that aggressive treatment.
REFERENCES:


ANTICOAGULATION IN ACUTE CORONARY SYNDROMES IN THE EMERGENCY DEPARTMENT - UNFRACTIONATED VS LOW-MOLECULAR-WEIGHT HEPARIN: DOES IT MATTER?

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OBJECTIVES:

1. Discuss trial performance of low molecular weight heparin compared with unfractionated heparin in acute coronary syndrome
2. Discuss the evidence-based recommendations for antithrombotic therapy in acute coronary syndrome

Recent guidelines published by American College of Cardiology/American Heart Association Task Forces on the care of patients with acute coronary syndromes (ACS) include Level I recommendations for the use of antithrombin therapy.\textsuperscript{1,2} The antithrombin therapies used most often in ACS are unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs); the most commonly used LMWH is enoxaparin.\textsuperscript{3}

For the physician caring for a patient with suspected or confirmed ACS in the Emergency Department (ED), initiation of antithrombotic therapy has traditionally been viewed as a very basic intervention. The choice between UFH and LWMH for the patient needing anticoagulation, however, often seems increasingly complicated. Despite the publication of many studies addressing this choice--more in the non-ST-segment-elevation (NSTEMI) ACS patient population than in those with ST-segment elevation (STEMI)--there remains much debate over the optimal agent for each management (interventional and medical) strategy.

STE ACS Patients  The 2004 Guidelines recommend the use of UFH in STEMI patients, regardless of revascularization strategy, with a I-C rating.\textsuperscript{1} A small mortality benefit attributable to UFH use in patients managed with lytic agents has been demonstrated.\textsuperscript{4} Specifically, a bolus of 60U/kg (maximum 4000U) UFH followed by an infusion of 12U/kg/hr (maximum 1000U/hr) is recommended in STEMI patients receiving alteplase, reteplase, or tenecteplase (I-C).\textsuperscript{1} The activated partial thromboplastin time (aPTT) in these patients should be maintained at 1.5-2 times control (50-70 sec).

Further, UFH should be given to patients receiving nonselective fibrinolytic agents (streptokinase, anistreplase, urokinase) if they are at high risk for systemic emboli (I-B), or to patients receiving streptokinase regardless (IIb-B).\textsuperscript{1} The different levels of support for UFH derive from the recognition that the nonspecific lytic agents produce a systemic coagulopathy and are themselves anticoagulants, while streptokinase and the more fibrin-specific agents are either procoagulants or induce little systemic anticoagulation.\textsuperscript{5,7}
In patients managed with primary PCI, weight-adjusted boluses of UFH 70-100U/kg are recommended by the Task Force, with the goal of maintaining an activated clotting time (ACT) in the catheterization lab of 250-350 seconds. The initial bolus-infusion regimen described above is appropriate for ED anticoagulation of the STEMI patient prior to PCI.

Cardiologists may choose to reduce heparin doses if platelet glycoprotein IIb/IIIa receptor (GP-IIb/IIIa) antagonists are being used. A baseline platelet count should be obtained in the ED before UFH is administered, to assist in subsequent monitoring for heparin-induced thrombocytopenia.

LMWHs receive less specific support in the 2004 STEMI Guidelines. There is a IIb-B recommendation in favor of a LMWH in patients younger than 75, with normal renal function (serum creatinine less than 2.5mg/dL in men or 2.0mg/dL in women), who are receiving lytic therapy. Enoxaparin (30mg IV bolus, then 1mg/kg subcutaneously every 12 hours), used with full dose tenecteplase, is the best-studied regimen in this regard; in ASSENT-3, patients under 75 years of age who received this combination had lower rates of 30-day mortality, inhospital reinfarction, and inhospital recurrent ischemia than did patients who received UFH and tenecteplase. This difference was not maintained at one-year follow-up. There are two Class III recommendations regarding LMWHs in STEMI: they should not be administered to patients over the age of 75 if receiving lytics (weight of evidence, B), and they should not be given to patients with significant renal dysfunction regardless of age (B).

The direct antithrombin agent bivalirudin is recommended in the 2004 STEMI Guidelines only as an alternative to UFH in patients receiving streptokinase who are known to have a history of heparin-induced thrombocytopenia.

NSTE ACS Patients A number of important studies have addressed the choice between LMWH (namely, enoxaparin) and UFH in managing patients with unstable angina and NSTE myocardial infarction. There is a clear advantage (superior efficacy and equivalent safety) to enoxaparin in conservatively treated NSTE ACS patients; this is reflected by a I-A recommendation for enoxaparin as first-line therapy in the European Society of Cardiology guidelines. The preferred management of high-risk patients with NSTE ACS in the United States, however, is interventional. The most aggressive studies of interventional care of NSTE ACS—A to Z and SYNERGY—failed to conclusively demonstrate a clinically significant difference between the two anticoagulation options. Unlike earlier studies, however, these two studies may have confounded the impact of antithrombin therapy with early invasive management, improved stent technology, and adjunctive potent antiplatelet therapy.

The issue of performing PCI in patients anticoagulated with LMWH and therefore whose aPTT or activated clotting time (ACT) do not accurately reflect the extent of anticoagulation, was addressed by Collet et al, who showed in a study of 293 UA/NSTEMI patients that PCI can be performed safely with the usual dose of enoxaparin. Because the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 hours, although the need for CABG cannot reliably be predicted in the ED.

The advantages of LMWH preparations vis-à-vis the ease of subcutaneous administration and the absence of a need for monitoring are particularly appealing in the ED. Furthermore, the LMWHs stimulate platelets less than UFH and are less frequently associated with heparin-induced thrombocytopenia. Finally, the response to enoxaparin may be magnified in patients who present at higher risk and it appears from
multiple studies\textsuperscript{12-15} that LMWH therapy can be safely combined with advanced antiplatelet therapy in patients with NSTE ACS. The usual dose of enoxaparin in NSTE ACS is 1 mg/kg subcutaneously every 12 hours, but various IV doses have also been explored.\textsuperscript{11,15}

A systematic overview of 21,946 patients involved in the six major studies comparing enoxaparin and UFH in NSTE ACS, shows a composite superiority of enoxaparin in the prevention of the composite endpoint of death + MI at 30 days, with no significant differences in major bleeding or need for transfusion.\textsuperscript{19} There was no difference in mortality. This meta-analysis was complicated by frequent off-protocol crossover of patients’ antithrombin therapy, usually from enoxaparin to UFH at the time of intervention. Patients from these trials who received solely enoxaparin, when compared to those who received solely UFH, gained a statistically significant 14.6% relative risk reduction for 30-day death + MI, a nonsignificant trend towards mortality reduction, and no difference in rates of transfusion (Figures 1 and 2).\textsuperscript{19}

**SUMMARY**

In a majority of ACS patients encountered in EDs in the United States in 2004—conservatively managed NSTE ACS patients plus those STEMI patients who receive lytic therapy—there appears to be a consistent efficacy advantage to the use of enoxaparin over UFH, with equivalent bleeding risk between the two options. In patients with ACS managed...
interventionally, the data are not as clear, and it is appropriate for emergency physicians and interventional cardiologists to work together to develop institution-specific protocols, starting in the ED, that reflect the latest data and minimize the likelihood of antithrombin cross-over after ED management. The ease of use, convenience, and medical error reduction accompanying LMWH use in the ED are arguments in favor of that approach, regardless of subsequent strategy.

REFERENCES


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 were promulgated in an effort to standardize and optimize the evaluation, diagnosis, and management of patients with NSTE ACS and to provide physicians with an evidence-based framework for clinical decision-making. Despite dissemination of these expert recommendations and ED-focused recapitulations of them in Annals of Emergency Medicine, significant barriers continue to limit the adoption of guidelines in clinical practice and appears to hinder the use of beneficial therapies and interventions in the ED. Unique quality improvement approaches are therefore needed to stimulate better adherence to practice guidelines and improve the quality of care for patients with NSTE ACS, starting in the ED.

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) national quality improvement and educational initiative provides an innovative, multi-faceted and multidisciplinary approach to the education of emergency physicians and cardiologists in the care of patients with NSTE ACS. The CRUSADE Initiative is a cooperative effort involving more than 400 medical centers across the United States. It includes a large web-based registry designed to characterize demographic patterns and risk stratification results in patients who meet diagnostic criteria for high-risk NSTE ACS (chest pain syndrome >10 minutes and within 24 hours of presentation, plus either ECG ST-segment depression/transient ST-segment elevation or elevated cardiac biomarkers of myocardial necrosis). CRUSADE also measures the use of acute NSTE ACS treatment modalities including aspirin, heparin, beta-blockers, clopidogrel, platelet inhibitors, and early catheterization strategies as recommended in the ACC/AHA guidelines. Finally, demographic and practice patterns are correlated to in-hospital morbidity and mortality outcomes. The results of a
given institution’s treatment patterns and outcomes in their NSTE ACS patients are reported back to the institution quarterly, along with comparisons to national norms and goals for improved compliance with guidelines.

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 improvement tools for utilization in patient care (pocket cards, risk assessment tools, placards, standardized orders, treatment algorithms, etc.), local and regional educational programs and in-person or remote telephonic hospital consultations by the CRUSADE steering committee members. The CRUSADE Initiative has also yielded multiple scientific publications that demonstrate NSTE ACS risk stratification patterns, treatment effectiveness, and quality improvement results. Individual sites are also able to tailor the CRUSADE quality improvement feedback reports to address specific institutional treatment questions, right down to details like service-specific or physician-specific outcome data. CRUSADE educational efforts are targeted at key institutional leaders to maximize quality improvement 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 throughout their hospital stay and beyond discharge.

**Analysis of the First 100,000 CRUSADE Initiative Patients**

In early June, 2004, the CRUSADE Initiative reached a significant milestone when it included its 100,000th high-risk NSTE ACS patient. This achievement culminated a two-and-a-half year effort, which began in January, 2002 and continues today. Patient inclusion in CRUSADE has surpassed investigators expectations and analysis of CRUSADE results continues to provide invaluable insights into the treatment of NSTE ACS patients in the United States. The CRUSADE Initiative represents the largest NSTE ACS registry ever assembled, and offers for the first time a true representation of United States treatment patterns for NSTE ACS.

The patients in CRUSADE, chosen after qualification for basic objective high-risk features, remain 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 previously undergone CABG. Thirty-nine percent of the CRUSADE patients have ST-segment depression on their presenting ECG, and 87% have an elevated troponin level. The in-hospital mortality for CRUSADE patients remains high at 4.9%, which is more than twice the 7-day mortality in published large randomized controlled NSTE ACS trials of “high-risk patients with NSTE ACS.”

The CRUSADE population has offered the unique opportunity to validate the predictive

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**Figure 1. Acute Medication Use within first 24 hours in patients with contraindications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>95%</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>87%</td>
</tr>
<tr>
<td>Heparin (LMW + UFH)</td>
<td>88%</td>
</tr>
<tr>
<td>GP IIb-IIIa Inhibitors</td>
<td>43%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>52%</td>
</tr>
</tbody>
</table>

Q4 2003 CRUSADE data
capabilities of Troponin levels, CKMB levels, and clinical risk scores such as the one developed from the PURSUIT Trial. However, patients considered being at the highest risk for mortality, including those with advanced age, diabetes, heart failure, or high troponin levels are paradoxically treated less aggressively than their lower risk counterparts.

Acute treatment patterns in the CRUSADE Initiative are summarized in Figure 1. As shown, early (<24 hours) utilization of aspirin, beta blockers, and anticoagulation with heparin or low-molecular-weight heparin (LMWH) remains fairly high in participating hospitals, whereas early utilization of glycoprotein (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 the Class IA recommendations for GP IIb/IIIa inhibitor use in high risk patients with NSTE ACS who are destined for the catheterization laboratory for PCI (Figure 2). Their relative underutilization underscores the need for more coordination between the ED and cardiology in the preparation of these patients for an invasive PCI strategy.

Interestingly, an inordinately high 34% of CRUSADE patients receive no advanced antiplatelet therapy (i.e., beyond aspirin) in the first 24 hours following presentation. Invasive diagnostic and management strategies are utilized in the majority of CRUSADE patients, with 70% of patients undergoing catheterization, 41% undergoing PCI, and 10% undergoing CABG. The time to catheterization in the United States remains suboptimal, however, with an average time to catheterization of 26 hours, and only 52% of patients receiving catheterization within 48 hours of hospital admission, averages deemed optimal by the guidelines. Longer delays to catheterization put 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.

Randomized controlled trials have repeatedly demonstrated that specific individual therapies for NSTE ACS are of most benefit in the highest risk patients. As such, the CRUSADE Initiative provides an invaluable research platform to investigate, in a retrospective fashion, the effectiveness of any given therapy. To date, abstracts have been presented examining the clinical utility of heparin/LMWH, GP IIb/IIIa inhibitors, and early catheterization strategies in the CRUSADE population. Whereas these retrospective analyses are not as powerful as prospective randomized trials, they offer invaluable insights into real-world treatment patterns and outcomes.
Targets for Quality Improvement Efforts

The efforts of the CRUSADE Initiative would all 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 significantly correlated with in-hospital morality. Hospitals whose ACC/AHA guideline adherence was in the lower quartile demonstrated a significantly higher mortality than hospitals with top quartile guideline adherence (5.8% versus 4.0%) [Figure 3].

Yet, as noted above, large gaps still exist between CRUSADE patterns of care and the recommended guideline treatment outlined in the ACC/AHA guidelines. Thirteen percent of NSTE ACS patients in CRUSADE still don’t receive an antithrombin in their first 24 hours of treatment, and 48% don’t receive a GP IIb/IIIa inhibitor. Time intervals to cardiac catheterization remain relatively high, and utilization of invasive procedures remains relatively low despite demonstrated mortality reductions in patients who undergo an invasive strategy as part of their care.

In addition to under-utilization of specific therapies, it appears that the patients who are highest risk for adverse outcomes are not being treated as aggressively as they should. Despite demonstrated higher mortality and morbidity in CRUSADE patients with high PURSUIT risk scores, the utilization of aspirin, beta blockers, antiplatelet therapies, and catheterization strategies remains relatively low in high risk versus low risk patients. This paradoxical shift in care patterns allows the under-treated high risk patients to drive disproportionately the 4.9% in-hospital mortality rate in CRUSADE. Quality improvement 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.

Finally, it appears that the educational efforts of the CRUSADE Initiative may not be aimed at all the key participants in NSTE ACS care. Significant gaps exist between acute NSTE ACS treatments administered by cardiologists versus other primary care providers such as internists, hospitalists, and family practitioners. Utilization of all acute therapies,
especially anti-platelet and catheterization therapies, are reduced significantly when internal medicine or family medicine physicians are the primary responsible physician providing care.\textsuperscript{18} It appears the CRUSADE initiative educational efforts should be targeted at these physicians as well.

**Effectiveness of CRUSADE Educational Interventions**

The CRUSADE Initiative has been active for two-and-a-half years, allowing participating hospitals to receive up to eight quarterly reports of their ACC/AHA guideline adherence. The results, in terms of improved guideline adherence, have been most gratifying. There has been a consistent increase in guideline adherence during this time. Utilization rates for all acute therapies have increased from quarter 1, 2002 to quarter 4, 2003 across CRUSADE participating hospitals. Catheterization rates have increased and the time to catheterization has decreased. The upward trends in acute therapy utilization demonstrate that the active monitoring and targeted educational interventions CRUSADE provides can impact clinical practice and help improve outcomes.

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. Still, some hospitals have been more successful than others in promoting change, particularly in the ED management of these patients. In a recent survey of ED directors and advocates at CRUSADE hospitals, factors which were correlated with improved guideline adherence included a strong hospital administration commitment to quality improvement, strong collaboration between the ED and hospital administration, ongoing collaboration between the ED and cardiology, and an identified algorithm for NSTE ACS care in the ED.\textsuperscript{19} These are the educational principles which CRUSADE supports, both educationally as well as logistically. CRUSADE provides the educational tools and expertise, and the participating hospitals and their patients benefit.

**SUMMARY**

In its first two-and-a-half years, the CRUSADE Initiative has been a remarkable success. The CRUSADE NSTE ACS registry now includes over 100,000 patients, providing invaluable insights into NSTE ACS treatment patterns in the United States. More importantly, CRUSADE provides insights into areas where NSTE ACS care can improve, and it provides the tools to facilitate those improvements. Judging from the first 100,000 patients, continued education and quality improvement efforts are needed to improve risk stratification and identification of high risk NSTE ACS patients who may benefit most from NSTE ACS treatments. In addition, improvement is needed in the utilization of guideline-driven ED treatments in high risk NSTE patients. Finally, coordination of care between the ED, cardiology, and other care givers is needed to truly optimize the care of NSTE ACS patients. The CRUSADE initiative has proven to be an excellent tool to change clinical practice, and improve patient outcomes for NSTE ACS.
REFERENCES


INTRODUCTION

In August 2004 the American College of Cardiology and the American Heart Association Task Force on Guidelines for the Management of Patients with ST-Segment Elevation Myocardial Infarction (STEMI) published their recommendations. This is the first time that guidelines have focused specifically on STEMI. Many of the recommendations confirm those from the 1999 recommendations within the guidelines for management of myocardial infarction but certain changes are significant and clarify appropriate current management.

This paper outlines the Class I recommendations (should be performed) for prehospital and emergency department (ED) phases of care for STEMI. Level of evidence will be cited as A (effective based on evidence from multiple randomized trials or meta-analyses), B (effective based on limited evidence from a single randomized trial or nonrandomized studies) or C (effective based on expert opinion, case studies or standard of care).

The most important change in the guidelines relates to identification of the best first reperfusion therapy, fibrinolysis or primary percutaneous coronary intervention (PCI). Primary PCI is not always the therapy of choice and may often be inferior to rapid delivery of fibrinolysis. The reasons for a variable approach based on the degree of incremental benefit in certain patient situations are advanced below.

2004 AHA/ACC STEMI GUIDELINES: CLASS I RECOMMENDATIONS

Prehospital Recommendations

1. All EMS first responders who respond to patients with chest pain and/or suspected cardiac arrest should be trained and equipped to provide early defibrillation. (Level A)
2. All public safety first responders who respond to patients with chest pain and/or suspected cardiac arrest patients should be trained and equipped to provide early defibrillation with AEDs. (Level B)
3. Dispatch staffing 9-1-1 center emergency medical calls should have medical training, should use nationally developed and maintained protocols, and should have a quality improvement system in place to ensure compliance with protocols. (Level C)

4. Prehospital EMS providers should administer 162 to 325 mg of aspirin (chewed) to chest pain patients suspected of having STEMI unless contraindications exist or aspirin has already been taken by patient at home prior to EMS arrival. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. (Level C)

5. Patients with STEMI who have cardiogenic shock and are less than 75 years of age should be brought immediately or secondarily transferred to facilities capable of cardiac catheterization and rapid vascularization (PCI) or CABG if it can be performed within 18 hours of the onset of shock. (Level A)

6. Patients with STEMI who have contraindications to fibrinolytic therapy should be brought immediately or secondarily transferred promptly (ie, primary-receiving hospital door-to-departure time less than 30 minutes) to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). (Level C)

7. Every community should have a written protocol that guides EMS system personnel in determining where to take patients with suspected or confirmed STEMI. (Level C)

Note: The use of 12-Lead ECGs, fibrinolytic check-lists and prehospital fibrinolysis all remain Class IIa recommendations with Level B or C levels of evidence.

ED Initial Assessment
1. A targeted history of STEMI patients taken in the ED should ascertain whether the patient has had prior episodes of myocardial ischemia such as stable or unstable angina, MI, CABG, or PCI. Evaluation of the patient’s complaints should focus on chest discomfort, associated symptoms, sex- and age related differences in presentation, hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding, and clinical cerebrovascular disease (amaurosis fugax, face/limb weakness or clumsiness, face/limb numbness or sensory loss, ataxia or vertigo. (Level C)

2. A physical examination should be performed to aid in the diagnosis and assessment of the extent,
location and presence of complications of STEMI. (Level C)

3. A brief, focused and limited neurologic examination to look for the evidence of prior stroke or cognitive deficits should be performed on STEMI patients before administration of fibrinolytic therapy. (Level C)

4. A 12-lead ECG should be performed and shown to an experienced emergency physician within 10 minutes of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of STEMI. (Level C)

5. If the initial ECG is not diagnostic of STEMI but the patient remains symptomatic, and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous 12-lead ST-segment monitoring should be performed to detect the potential development of ST-segment elevation. (Level C)

6. In patients with inferior STEMI, right-sided ECG leads should be obtained to screen for right ventricular (RV) infarction. (Level B)

ED Laboratory and Imaging

1. Laboratory examinations should be performed as part of the management of STEMI patients but should not delay the implementation of therapy. (Level C)

2. Cardiac-specific troponins should be used as the optimum biomarkers for the evaluation of patients with STEMI who have coexistent skeletal muscle injury. (Level C)

3. For patients with ST-segment elevation on the 12-lead ECG and symptoms of STEMI, reperfusion therapy should be initiated as soon as possible and is not contingent on biomarker assay. (Level C)

4. Although handheld bedside (point-of-care) assays may be used for a qualitative assessment of the presence of an elevated level of a serum cardiac biomarker, subsequent measurements of cardiac biomarker levels should be performed with a quantitative test. (Level B)

5. Patients with STEMI should have a portable chest X-ray, but this should not delay implementation of reperfusion therapy (unless a potential contraindication, such as aortic dissection, is suspected). (Level C)

6. Imaging studies such as high-quality portable chest X-ray, transthoracic and/or transesophageal echocardiography and a contrast chest computed tomography scan or an MRI scan should be used to differentiate STEMI from aortic dissection in patients for whom this distinction is unclear. (Level B)

ED Ancillary Treatment

1. Supplemental oxygen should be administered to patients with arterial oxygen desaturation (SaO2 less than 90%). (Level B)

2. Patients with ongoing ischemic discomfort should receive sublingual nitroglycerine (0.4 mg) every 5 minutes for a total of 3 doses, after which an assessment should be made about the need for intravenous nitroglycerine. (Level C)

3. Intravenous nitroglycerine is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. (Level C)

4. Morphine sulfate (2-4 mg IV with increments of 2-8 mg IV repeated at 5- to 15-minute intervals) is the analgesic of choice for management of pain associated with STEMI. (Level C)

5. Aspirin should be chewed by patients who have not taken aspirin before presentation with STEMI. The initial dose should be 162 mg (Level A) to 325 mg (Level C). Although some trials have used enteric-coated aspirin for initial dosing, more rapid absorption occurs with non-enteric-coated aspirin formulations.

6. Oral beta-blocker therapy should be administered promptly to those patients without a contraindication irrespective of concomitant fibrinolytic therapy or performance of primary PCI. (Level A)
7. Patients undergoing percutaneous or surgical revascularization should be given UFH. (Level C)

8. UFH should be given intravenously to patients undergoing reperfusion therapy with alteplase, reteplase, or tenecteplase with heparin dosing as follows: bolus of 60 U/kg (maximum 4000U) followed by an initial infusion of 12 U/kg per hour (maximum 1000U/hour) adjusted to maintain a partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds). (Level C)

Note: LMWH may be considered acceptable in patients less than 75 years of age and without significant renal dysfunction. (Class IIb)

9. UFH should be given intravenously to patients treated with nonselective fibrinolytic agents (streptokinase, anistreplase, or urokinase) who are at high risk of systemic emboli (large or anterior MI, atrial fibrillation, previous embolus, or known LV thrombus). (Level B)

ED First Reperfusion Therapy

1. All STEMI patients should undergo rapid evaluation for reperfusion therapy and have a reperfusion strategy implemented promptly after contact with the medical system. (Level A)

2. STEMI patients presenting to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should undergo fibrinolysis unless contraindicated. (Level A)

3. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and the ST-segment elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads. (Level A)

4. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB. (Level A)

5. Healthcare workers should ascertain whether the patient has neurologic contraindications to fibrinolytic therapy, including any history of intracranial hemorrhage (ICH), significant closed head or facial trauma, uncontrolled hypertension or ischemic stroke within the past 3 months. (Level A)

6. STEMI patients at substantial (greater than or equal to 4%) risk of ICH should be treated with PCI rather than fibrinolytic therapy. (Level A)

7. The occurrence of a change on neurologic status during or after fibrinolytic therapy, particularly within the first 24 hours after initiation of treatment, is considered to be due to ICH until proven otherwise. Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until brain imaging scan shows no evidence of ICH. (Level A)

8. Neurologic and/or neurosurgery or hematology consultation should be obtained for STEMI patients who have ICH as dictated by clinical circumstances. (Level C)

9. In patients with ICH, infusions of cryoprecipitate, fresh frozen plasma, protamine, and platelets should be given, as dictated by clinical circumstances. (Level C)

10. Diagnostic angiography should be performed in candidates for primary or rescue PCI (Level A); in patients with cardiogenic shock who are candidates for revascularization (Level A); in candidates for surgical repair of ventricular septal rupture or severe mitral regurgitation (Level B); and in patients with persistent hemodynamic and/or electrical instability. (Level C)

11. If immediately available, primary PCI should be performed in patients with STEMI (including true posterior MI) or MI with new or presumably new LBBB who can undergo PCI of the infarct artery within 12 hours of symptom onset, if performed in a timely fashion (balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (individuals who perform more
The procedure should be supported by experienced personnel in a appropriate laboratory environment (performs more than 200 PCI procedures per year), of which at least 36 are for primary PCI for STEMI, and has cardiac surgery capability. (Level A)

12. Primary PCI should be performed as quickly as possible, with a goal of a medical contact-to-balloon time of within 90 minutes. (Level B)

13. If the symptom duration is within 3 hours and the expected door-to-balloon time minus the expected door-to-needle time is within 1 hour, primary PCI is generally preferred; if greater than 1 hour, fibrinolysis is generally preferred. (Level B)

14. If the symptom duration is greater than 3 hours primary PCI is generally preferred and should be performed with a medical contact-to-balloon time as brief as possible with a goal of within 90 minutes. (Level B)

15. Primary PCI should be performed for patients younger than 75 years old with ST-segment elevation or LBBB who develop shock within 36 hours of AMI and are suitable to revascularization that can be performed within 18 hours of shock, unless further support is futile because of patient’s wishes or contraindications/unsuitability for further invasive care. (Level A)

16. Primary PCI should be performed in patients with severe CHF and/or pulmonary edema and onset of symptoms within 12 hours. The door-to-balloon time should be as short as possible (goal within 90 minutes). (Level B)

17. Primary PCI should be performed in fibrinolytic-ineligible patients who present with STEMI within 12 hours of onset of symptoms. (Level C)

**PCI vs Fibrinolytic: Rapid Reperfusion is Still the Goal**

**Importance of Time to Treatment**

One of the mantras of emergency physicians is “time is muscle”. The understanding that viable myocardium, now ischemic due to occlusion of the nutrient coronary artery, and will necrose within 4-6 hours mandates rapid diagnosis and rapid reperfusion therapy coordinated by the physician of first contact. [Figure 1]

Time to treatment with Fibrinolytics GISSI-1 demonstrated the relationship of time to treatment and the observation has been repeated many times since. The Fibrinolytic Therapy Trials group combined data sets from fibrinolytic vs placebo trials and demonstrated a 5-6% absolute reduction in mortality for patients seen in the first hour and ever-diminishing return for each subsequent hour. [Figure 1]
Time to Treatment with Primary Angioplasty
Although some studies have demonstrated that primary angioplasty is not dependent on time, recent evidence demonstrates and the new STEMI guidelines articulate that time matters with PCI much as it does with fibrinolysis. De Luca and others have recently demonstrated that patients treated in the first 2 hours after symptom onset have better outcomes than those treated later.\textsuperscript{5,6} As time marches on, PCI and the opening of the infarct-related artery provide benefit for the healing of the infarct zone, however the ability of fibrinolysis to dissolve the clot and maintain an open artery becomes more difficult. The benefit provided by PCI is not as time sensitive only because benefit is more notable in late presenters. In early presenters (< 3 hours), the reperfusion time delays are as important as with fibrinolysis. Antoniucci demonstrated that in low-risk infarctions there is little advantage of early PCI vs later PCI but in high risk infarctions, the reduced mortality associated with early treatment was clear.\textsuperscript{7} Patients with a substantial myocardium at risk also demonstrate a greater benefit with rapid PCI compared to delayed PCI. (Figure 2)

Three Important Time Intervals
We traditionally have tried to reduce time to treatment by attempting to reduce 2 consecutive time intervals:

1. **Time from onset of symptoms** to arrival at hospital
2. **Time from arrival to delivery of the treatment** (pharmacologic or mechanical intervention).

However, a third very important time interval must be evaluated in order to choose the best first reperfusion therapy:

3. The interval from potential delivery of the fibrinolytic therapy to the time when the balloon is inflated in the artery (*door to balloon time – door to fibrinolytic time*).

At the point when the diagnosis is made, and the patient is eligible for fibrinolytic therapy, PCI may be the best choice but only if it can be delivered in an appropriate time frame. That appropriate time frame is now considered to be less than 60 minutes.

Figure 2.
Absolute risk reduction in 4- to 6-week mortality rates with primary PCI as a function of PCI-related time delay. Circle sizes reflect the sample size of the individual study. Values >0 represent benefit and values <0 represent harm. Solid line represents weighted meta-regression. Reprinted with permission from Nallalmothu et al. Am J Cardiol 2003.\textsuperscript{9}
The initial primary angioplasty vs fibrinolytic therapy trials had an average added time for angioplasty of 47 minutes. A meta-analysis by Nallamothu evaluated the incremental benefit of primary angioplasty compared with fibrinolysis and related the benefit to this time difference. He concluded that the benefit was greatest the shorter the delay, and at 60 minutes after potential fibrinolysis, the incremental benefit of PCI disappeared.

**Duration of Symptoms Modifies PCI Benefit**

It is also true that the duration of symptoms modifies this differential benefit. In the MITI trial evaluating prehospital fibrinolysis, the 30 day mortality rate for patients treated within 70 minutes of symptom onset was 1.2%. It is unlikely that primary angioplasty can improve on this excellent result. The CAPTIM trial in France, comparing ambulance fibrinolysis to urgent transfer for primary angioplasty, found an overall benefit for primary angioplasty. However, in those presenting in < 2 hours, the mortality was the lowest in the fibrinolysis group (p=0.58).

**Practical Choice of Optimum Reperfusion Therapy for Stable Patients**

The new ACC/AHA STEMI guidelines help to define the best choice of first reperfusion therapy based on the time difference between potential fibrinolytic therapy and guaranteed balloon inflation. These recommendations exclude patients in shock or those ineligible for fibrinolytic therapy.

In patients presenting in less than 3 hours, fibrinolysis will be the treatment of choice unless angioplasty can be accomplished in less than 60 minutes from that decision point. This will virtually never be possible if a transfer to an interventional center is needed. In fact, it is not possible at some interventional centers and certainly not unless cardiac catheterization staff are in-house. Although not specifically mentioned in the guidelines, the earlier the patient presents even within the first 3 hours, the less acceptable any delay to angioplasty. The target of 60 minutes from potential fibrinolysis to balloon inflation may be too long in patients presenting within one hour of symptoms.

For patients presenting after more than 3 hours of pain, PCI will generally be the preferred reperfusion method and the sooner the better but only if the balloon can be inflated less than 90 minutes after first medical contact. Once again, this time goal will be difficult to achieve in...
many situations and if it cannot, fibrinolysis is the preferred first treatment of choice.

The result of this fresh look at time and its importance in the prevention of myocardial necrosis will correct a misconception PCI is preferred regardless of the potential delay. PCI should be the preferred therapy only if the health care system measures time to balloon inflation and there is strong assurance that the delay will be less than 60 minutes from the time of potential fibrinolysis administration. In all other cases, fibrinolysis is preferable and it should be delivered within 30 minutes of arrival. Use of fibrinolysis as the first reperfusion therapy of choice does not preclude appropriate subsequent mechanical intervention for failure to reperfuse, development of CHF or shock, and for subsequent spontaneous or provokable ischemia.

SUMMARY

The new ACC/AHA guidelines for STEMI are a must read for emergency physicians. The most profound impact is the re-instatement of fibrinolysis as the preferred treatment for STEMI unless PCI can be guaranteed in a very timely manner.
A BNP expert consensus panel¹, consisting of individuals with basic, methodologic, and clinical expertise, was convened in 2004 to create a summary document to help guide the clinician on the recent explosion of natriuretic peptide (NP) data. This document contains the data from their recommendations most applicable to the emergency physician.

NP Physiology
More than a pump, the heart is a critical endocrine organ functioning with other physiological systems to control fluid volume. Myocytes manufacture a family of peptide hormones, termed the NPs, represented by atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Release of the NPs is stimulated by volume overload², and physiologically, they have powerful diuretic, natriuretic, and vascular smooth muscle relaxing actions. Importantly, they also serve as antagonists to the sympathetic nervous system and the renin-angiotensin-aldosterone axis (RAAS)³⁴. Release of NP's results from cardiac wall stretch, ventricular dilation, or increased pressures from circulatory volume overload. The effects of NP’s result in lowering blood volume and pressure.

BNP is derived from a precursor, pre proBNP, which undergoes several cleavages. The assay relevant products are the inert N-terminal pro-BNP fragment, and physiologically active BNP. BNP's are preferentially produced and secreted by the cardiac ventricles⁵, although fluid overload may cause rapid BNP manufacture in both heart chambers⁶. The primary function of NPs is to defend against volume overload. After release into circulation, BNP actions are modulated at target sites by specific cell membrane receptors, termed A, B, and C, which mediate physiological actions by cyclic GMP⁷. Cyclic GMP has potent vasodilatory actions. BNP also causes an intravascular

**OBJECTIVES:**
1. Discuss the application and limitations of BNP testing in the emergency setting
2. Describe the appropriate candidate for BNP therapy

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**Figure 1. BNP EFFECTS**

- **Hemodynamic** (Balanced vasodilation)
  - Veins¹
  - Arteries¹
  - Coronary arteries²

- **Neurohumoral**
  - Aldosterone³
  - Endothelin¹
  - Norepinephrine³

- **Renal¹**
  - Diuresis
  - Natriuresis

---

fluid shift, from the capillary bed into the interstitium, which contracts intravascular volume and decreases BP. In addition, BNP is a RAAS antagonist, where it counteracts sodium conservation, vasoconstriction, and volume retention. BNP also inhibits the release of renin from kidney cells and aldosterone from adrenal cells. BNP is primarily metabolized by the NPR-C receptor, although some additional degradation may occur by neutral endopeptidase. Neutral endopeptidase has a wide tissue distribution, including adipose, kidneys, lung, and brain. (Figure 1)

Biologic Determinants on BNP Measurements. Blood levels of NPs are affected by a variety of factors, including circadian rhythm, age, exercise, and body posture. Many drugs including diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists, sex and thyroid hormones, glucocorticoids, sodium intake, and other conditions impact levels. BNP increases with age and gender. Baseline and pathologic levels are higher in women. The age induced BNP increase may be due to the decline in myocardial function or to decreased clearance.

BNP Assay
It should be made clear that the BNP assay is not a stand-alone test. Its greatest value is when it is used with the physician’s clinical judgment, and with other appropriate testing. The Triage BNP assay system is the only FDA approved point-of-care assay. It requires 15-minutes to perform, and reports BNP levels from 5 to 5000 pg/mL. This assay is rated as moderately complex assay per Clinical Laboratory Improvement Amendments (CLIA) regulations.

BNP for Diagnosis of Heart Failure
Despite advances in our understanding of heart failure (HF) pathophysiology, diagnosis is still difficult. While emergency department (ED) diagnosis needs to be rapid and accurate, the signs and symptoms of HF are nonspecific. Respiratory distress can preclude obtaining the history, and dyspnea is nonspecific in the elderly or obese. Routine labs, ECG, and x-rays are also not accurate enough to always make the correct diagnosis.

The Breathing Not Properly study was a large, multinational, prospective study using BNP to evaluate dyspnea in 1586 dyspneic ED patients. BNP levels were measured on arrival, and physicians assessed the probability of the patient having HF. Two cardiologists, blinded to the BNP level, reviewed all data after hospitalization to produce a “gold standard” clinical diagnosis. BNP levels alone more accurately predicted the presence or absence of HF than any other find-
BNP levels may also help in disposition decisions. The Rapid Emergency Department Heart Failure Outpatient (REDHOT) Trial demonstrated a “strong dis-connect” between the perceived severity of HF, and illness severity as determined by BNP. On average, patients discharged from the ED had a higher BNP than those admitted, 976 pg/mL, versus 766 pg/mL, respectively. BNP also predicted outcomes of patients discharged, 78% had a BNP > 400 pg/mL, however, there was no mortality at 30 days if the BNP was less than 400 pg/mL.

The Swiss BASEL Study examined cost-effectiveness of using BNP through the diagnosis and hospitalization in acute decompensated heart failure (ADHF). In 452 patients, ED measurement of BNP was associated with a 10% decrease in hospital admissions, a 3-day decline in length of stay, and an $1800 savings, with no effects on mortality or re-hospitalization rates.

### CONSENSUS STATEMENT: USING BNP TO HELP TRIAGE ED PATIENTS WITH DYSPNEA.

BNP is of diagnostic utility in the evaluation of patients with acute dyspnea. Thus, in new patients presenting with dyspnea to an emergency setting, a history, physical examination, chest x-ray and ECG should be undertaken together with laboratory measurements that include BNP. Current data suggest the following guidelines:

- As BNP rises with age and is affected by gender, comorbidity, and drug use, it should not be used in isolation from the clinical context.
- If the BNP is <100 pg/mL, then HF is highly unlikely (NPV = 90%).
- If the BNP is >500 pg/mL, then HF is highly likely (PPV = 90%).
- If the BNP is 100–500 pg/mL, consider: a baseline BNP elevated due to stable underlying dysfunction, right ventricular failure from cor pulmonale, acute pulmonary embolism, or renal failure.
- Patients may present with HF and a normal BNP, or with levels below what is expected in the following situations: flash pulmonary edema (<1–2 hours), HF up-stream from the left ventricle (such as with acute mitral regurgitation from papillary muscle rupture and obese patients (body mass index [BMI] >35).
BNP and Renal Failure
Chronic kidney disease (CKD) influences the cut-point for BNP. In general, as CKD advances, a higher BNP cut-point is implied. A cut-point of approximately 200 pg/mL is reasonable for those with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m². Using this approach, BNP maintains a high level of diagnostic utility, with an area under the ROC curve of >0.80 across all CKD groups.

Cardiopulmonary Disease
Some non-HF cardiopulmonary disease may cause BNP elevations. These include cor pulmonale, lung cancer, pulmonary embolism (PE) and primary pulmonary hypertension. In these, BNP may be elevated, but not to the extent found in ADHF. In PE, BNP may be prognostic since patients with a BNP in the upper normal range or > 100 pg/mL have a higher mortality rate. Although BNP is not an adequate screening test for PE, in the setting of a suspected or confirmed embolic event, a BNP elevation implies RV pressure overload and increased mortality risk. Finally, in primary pulmonary hypertension, BNP elevations parallel the extent of pulmonary hemodynamic changes and right HF.

CONSENSUS STATEMENTS: COMORBIDITIES AND SPECIAL ISSUES THAT INFLUENCE THE INTERPRETATION OF BNP LEVELS.

- BNP is altered with chronic renal insufficiency (estimated GFR < 60 mL/min), with a recalibration of the cut off value to 200 pg/mL.

- BNP is helpful in the evaluation of dyspnea when it is very low or high. NT pro BNP has greater correlation with eGFR than BNP, hence levels can be elevated even with the normal age related decline of renal function in the eGFR 60-90 mL/min range.

- When the eGFR is below 60 mL/min, N terminal proBNP can be considerably elevated and in this setting its utility in the evaluation of HF is unknown.

- Baseline BNP levels might therefore be important in dialysis patients, as changes most likely reflect volume status. Thus a pre-dialysis BNP may help determine the amount of volume which should be removed.

CONSENSUS STATEMENT: BNP IN PULMONARY AND ASSOCIATED CARDIAC DISEASE.

- In approximately 20% of patients with pulmonary disease, BNP is elevated implying combined HF and lung disease, cor pulmonale, or a misdiagnosis when the true etiology of dyspnea is HF.

- In the setting of PE, BNP is elevated in 1/3 of cases and is associated with RV pressure overload and a higher mortality. BNP is not diagnostic for acute PE.

- Pulmonary disease which results in pulmonary hypertension and RV pressure or volume overload can lead to elevated BNP levels, usually in the range of 100-500 pg/mL.
Preserved Systolic Function (PSF) Heart Failure
Diastolic myocardial dysfunction, also known as PSF, is the cause of HF in as many of 50% of cases and is also associated with high BNP\cite{29,30}. BNP has been found to be approximately half as high in PSF as in cases of systolic dysfunction\cite{31}.

BNP and Acute Coronary Syndromes (ACS)
Large studies report NP elevations in unstable angina without myocardial necrosis\cite{39,40}. As ischemia may result in only small NP elevations, their sensitivity and specificity are inadequate as a “rule out” tool. However if present, an elevation of NP in ACS is a powerful predictor of adverse events. In 2,525 patients\cite{41} grouped into BNP quartiles 40 hours after ACS onset, an increasing BNP was associated with higher 10-month mortality, and this relationship persisted even without evidence of HF or myocardial necrosis.

Obesity
Obesity is an important risk factor for coronary artery disease and HF\cite{32,33,34,35}. Physiologically, adipose tissue is related to the natriuretic clearance receptor\cite{36,37} and obesity can interfere with the usual diagnostic approach to HF. Mehra\cite{38} documented an inverse relationship between Basal Metabolic Index (BMI) and BNP. Lower levels of BNP in the obese (BMI>30Kg/M2) were noted, despite similar severity of HF compared to a lean cohort, and nearly 40% of obese patients had BNP <100 pg/mL.

BNP and Prognosis
BNP elevation is a powerful marker of HF prognosis. In 325 patients, followed for 6 months after an ED visit for dyspnea, the relative risk of 6-month HF admission or death, was 24 times higher if the BNP was >230 pg/mL (Figure 2)\cite{42}. This was confirmed by the Val-HeFT trial, where the lowest quartile of BNP (<50 pg/mL) had the lowest all-cause mortality and the highest quartile (>238 pg/mL) had the highest mortality, 32% at 30 months. (Figure 2)
ADVANCING THE STANDARD OF CARE: Cardiovascular and Neurovascular Emergencies

Figure 2.

BNP as Therapy
When ADHF occurs, the balance between vasoconstrictors and endogenous vasodilators is disturbed. This forms the basis as to why exogenous BNP is given as therapy despite high endogenous levels, is analogous to giving insulin for insulin resistance. In ADHF, high levels of BNP occur as a “distress hormone”, where supra-normal levels are no longer effective at maintaining the balance of vasoconstriction and vasodilation. Hence giving BNP, in the form of nesiritide, can restore neurohormonal homeostasis.

NP are much closer to ideal drugs for ADHF than other agents. The use of nesiritide is associated with reduced filling pressures, decreased pulmonary vascular resistance, lowered central venous pressures, and reduction in systemic BP. There is also increased cardiac output due to the unloading effect of vasodilatation, but without reflex tachycardia. Moreover, reducing preload and afterload without increasing heart rate is consistent with decreased myocardial oxygen consumption and a decrease in ventricular stress - a stimulus presumed to drive the neurohormonal activation of ADHF. Lastly, tolerance to these effects does not occur, and these changes in hemodynamics are present and persistent throughout the administration of nesiritide.

To date, nesiritide is the only natriuretic peptide available in the US for IV therapy. Colucci et al. in the Efficacy Trial, showed that nesiritide causes a dose-related decrease in PCWP, systemic vascular resistance, mean right arterial pressure, dyspnea, fatigue, a significant increase in cardiac index, and an improvement in global status. The most common side effect was dose-related hypotension. The Comparative Trial evaluated nesiritide versus many other cardiovascular agents, including dobutamine, milrinone, nitroglycerin, dopamine, and amrinone. Global clinical status, fatigue, and dyspnea improved in all groups, with no significant differences between nesiritide and standard therapy. The most common side-effects were bradycardia and dose-related hypotension.
In 1998, Burger et al.\textsuperscript{45} conducted the PRECEDENT study. Its primary objective was to compare heart rate and arrhythmias with two doses of nesiritide (0.015 or 0.03 µg/kg/min) to dobutamine. They concluded that although inotropic HF therapies, including dobutamine and milrinone, are associated with favorable hemodynamic and symptomatic effects, they cause arrhythmias and tachycardia which may increase myocardial oxygen demand, ischemia, and mortality. They demonstrated fewer arrhythmias and no heart rate increase with nesiritide. Furthermore, the rates of 21-day readmission and 6-month mortality were higher with dobutamine. The authors concluded that nesiritide is safer than dobutamine for short-term ADHF management.

The VMAC trial\textsuperscript{46} was a safety and efficacy study of intravenous nesiritide versus intravenous nitroglycerin or placebo in 489 ADHF patients with dyspnea at rest. Swan Ganz catheterization was performed in roughly half, at the physician’s choice. Patients were randomized into four blinded groups, each receiving standard therapy and: fixed dose nesiritide, titratable nesiritide, titratable nitroglycerin, or placebo. Nesiritide had a faster onset and greater reduction in PCWP than nitroglycerin. The improvement in clinical status and dyspnea was similar in both groups [Figure 3]. They concluded that when added to standard care, nesiritide improves hemodynamic function more effectively than IV nitroglycerin or placebo.

In another evaluation, a risk adjusted comparison of outcomes from the ADHERE registry of more than 100,000 ADHF patients found improved survival with vasodilators compared to inotropes. When comparing vasodilators, there are similar outcomes between nesiritide and nitroglycerin.

The current approved use of nesiritide is for ADHF. Although guideline statements are lacking, the totality of diagnostic and therapeutic data regarding nesiritide yield an intuitive rationale and a reasonable evidence-based approach for ADHF assessment and management. One of the most valuable findings is that beginning vasoactive therapy in the ED is associated with a 3.1-day reduction in hospital length of stay compared to therapies not initiated until after admission. This suggests that the choice of therapy in the ED may critically impact the course of the patient.\textsuperscript{47}

**INTEGRATING BNP LEVELS INTO A RATIONAL USE OF NESIRITIDE**

While BNP is approved by the FDA for HF diagnosis, its usefulness to monitor treatment is still under study. However, some suggestions can be made. We believe

\begin{figure}[h]
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\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Vasodilation in the Management of Acute CHF (VMAC) trial: Primary end point is pulmonary capillary wedge pressure changes over 3 hours.\textsuperscript{46}}
\end{figure}
that one can stratify patients to the high-risk category in part by using BNP levels. Fonarow recently analyzed the ADHERE database and found that high BUN levels provide a poor prognosis for patients in ADHF. Thus, the combination of high BNP and poor renal function identifies high-risk patients (Figure 4).

If patients are admitted with BNP levels <500 pg/mL and BUN levels are <40 (i.e., lower risk), one can often start treatment with parenteral diuretics. Subsequently, they can be reclassified into low- or high-risk groups based on their response over the next 6–12 hours. Those with an adequate diuresis, a fall in BNP, and no deterioration in renal function may be candidates for continued diuretics/vasodilators until euvoolemia is reached. Hopefully this will lead to a BNP level <400 pg/mL in these patients. In one study, patients whose discharge BNP levels were < 430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days. If the BNP level was > 400 pg/mL, the volume status required re-evaluation. If the patient is not yet euvolemic, nesiritide might be considered for 24 hours.

If patients after receiving 6–12 hours of intravenous diuretics have an inadequate diuresis, no change or an increase in BNP, and worsening renal function, they should be considered at high risk. If their systolic BP is at least 90 mm Hg, they can be given 1–2 days of nesiritide with iv diuretics. BNP can then be checked 6 hours after cessation of nesiritide and oral vasodilators and diuretics can be used until euvoolemia is achieved.

Patients with systolic BPs <90 mm Hg often need vasopressors and/or inotropes, sometimes under Swan-Ganz guidance. In our experience at the Cleveland Clinic, if these individuals show improvement in BP and symptoms, we will then transition their therapy to nesiritide. If there is no improvement on inotropes or pressors, further invasive strategies should be considered. Finally, it is conceivable that in patients who are admitted with very high BNP levels, or have impaired renal function, nesiritide might be started immediately.

In conclusion, the BNP Consensus Panel of 2004 has provided consensus approaches for the use of BNP for the diagnosis and treatment of HF. Ideally, the use of these recommendations will improve the care of your patients.
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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 Medicine 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 thrombolytic 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

Stroke remains the nation’s third leading cause of death and the leading cause of adult disability.

The diagnosis of many acute neurologic conditions remains largely one of exclusion.
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, 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 thrombolytic 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>Vascular markers</th>
<th>Apoptosis / Miscellaneous</th>
<th>Markers of coagulation / fibrinolysis</th>
</tr>
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<tr>
<td>Creatine kinase isoenzyme (BB)</td>
<td>Endothelin 1 (ET 1)</td>
<td>Brain natriuretic peptide</td>
<td>C reactive protein</td>
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<td>Caspase 3</td>
<td>D-dimer</td>
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<td>Tau protein family (tau, MAP-2)</td>
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<td>Thrombin-antithrombin III complex.</td>
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**Inflammatory mediators:**

- 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. 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 (γγ) isomer of the glycolytic protein enolase, and is mainly located in the cytoplasm of neurons and cells of neuroendocrine origin. NSE (γγ) is also found in smaller concentrations in erythrocytes and platelets. NSE has a molecular weight of 78kD. Its release into the CSF has been founds 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 (αβ) calcium-binding protein found throughout astroglial and Schwann cells in a homodimer form (ββ). Elevated CSF and serum levels of S-100 (ββ) 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 S100β 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 thrombolytics 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 thrombolysis. 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 investigators 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 chemotactic 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

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**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 in 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.

**The Future is Now**

Based on the preliminary studies and several ongoing pilot studies, it is reasonable to expect commercially available products to enter use within the coming years. Equally exciting is the use of these markers in 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**


OBJECTIVES:
1) To describe the role of CT imaging in ischemic stroke
2) To explain the role of MRI in ischemic stroke
3) To elaborate on the expanding role of MRI for acute ICH

INTRODUCTION

The treatment of acute ischemic stroke and intracerebral hemorrhage has seen significant advances in the past decade with the FDA approval of recombinant tissue plasminogen activator (rt-PA) for ischemic stroke and aggressive intensive care strategies for both ischemia and hemorrhage. Likewise, the field of diagnosis and particularly neuroimaging associated with stroke has advanced rapidly over this same time period. While the standard for acute imaging in suspected stroke remains non-contrasted computed tomography (CT) of the brain, the advent of spiral CT scanners as well as faster magnetic resonance imaging (MRI) protocols stand ready to add volumes to the evaluation and treatment of stroke in real-time in the Emergency Department (ED).

The basis of imaging in acute stroke is both to rule out hemorrhage as well as select patients for treatment with rt-PA or other revascularization protocols. This review will summarize the most current applications of neuroimaging related to both ischemic and hemorrhagic stroke, as well as their use in selection of patients for thrombolysis and other treatment measures. The availability and practicality of any imaging study, particularly in a time-critical area such as thrombolysis of acute ischemic stroke (AIS), is important to the emergency physician (EP) and this will likewise be addressed in this review.

Computed Tomography (CT) in Ischemic Stroke

Non-Contrast Computed Tomography

The non-contrasted CT of the brain has become the standard of care in imaging of the patient who presents with an acute neurologic deficit. It is generated in minutes and is the most readily available imaging modality in most hospitals and EDs. Non-contrasted CT is the gold standard for detection of acute hemorrhage and can provide a good method of screening for mass lesions that may mimic acute stroke. Non-contrasted CT does lack sensitivity for ischemic changes in hyperacute stroke, but CT interpretation can be improved through the use of standardized measures and experience.

While the sensitivity of non-contrasted head CT for ischemic changes in the hyperacute period is variable and ranges from 31-75%, there are certain hallmarks...
ADVANCING THE STANDARD OF CARE: Cardiovascular and Neurovascular Emergencies

Figure 1: ASPECTS study form.

A=anterior circulation; P=posterior circulation; C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; MCA=middle cerebral artery; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterio MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6).

Barber et al. developed a scoring system that split the MCA territory on non-contrast CT into ten defined zones including basal ganglia and regions of cortex, each of which is worth one point. (Figure 1). If ischemia is present in a particular zone, that zone is scored a zero, whereas if ischemia is absent it is scored a one. All patients enrolled in the study had symptoms of ischemia in the anterior circulation and all were treated within three hours with intravenous (IV) rt-PA. The score, referred to as the Alberta Stroke Programme Early CT Score (ASPECTS) is reasonably simple and at a cutoff of 7 or less was shown to sharply correlate with dependence and death at 3 months (OR 82, 95% CI 23-290). Further, an ASPECTS score of 7 or less produced an odds ratio of 14 (95% CI 1.8-117) for symptomatic intracerebral hemorrhage (ICH) in patients treated with rt-PA. While this score does allow some prognostic indication as to outcome, it has not been validated in a randomized trial and should not be used to exclude patients from treatment, as all patients in the study were treated and it is possible that the patients with lower ASPECTS scores would have fared even worse without thrombolysis.

In an effort to identify variables associated with intracerebral hemorrhage in patients with acute ischemic stroke who receive tissue plasminogen activator, the investigators from the NINDS rt-PA study group performed subgroup analyses of data from a randomized, double-blind, placebo-controlled trial of intravenous rt-PA administered to stroke patients within 3 hours of onset. Using multivariable regression modeling, they assessed the relationship of baseline and after-treatment variables with symptomatic intracerebral hemorrhage. The only variables independently associated with an increased risk of symptomatic intracerebral hemorrhage were the severity of neurological deficit and brain edema (defined as acute
hypodensity) or mass effect on CT before treatment (OR, 7.8; 95% CI, 2.2 to 27.1). Notably, however, in the subgroup of patients with edema or mass effect by CT, rt-PA-treated patients were more likely than placebo-treated patients to have a favorable 3-month outcome (adjusted OR, 3.4; 95% CI, 0.6 to 20.7). The likelihood of severe disability or death was similar for rt-PA and placebo patients in this group with CT changes. These authors concluded that despite the higher rate of intracerebral hemorrhage, patients with edema or mass effect on the baseline CT are reasonable candidates for rt-PA if it is administered within 3 hours of onset.3

Recent analyses indicate that patients with early infarct signs and ischemia on CT may be at higher risk for intracerebral hemorrhage. At this point, clinicians should be wary of significant early infarct signs, although they are not an exclusion to treatment within three hours of onset of symptoms. If rt-PA therapy is to be considered in such patients it must be done with the understanding that the hemorrhage risk is considerably higher than the baseline hemorrhage rate of 6.4% symptomatic hemorrhages found for all patients treated. Further discussion of the risks and benefits should be undertaken with the patient and family.

Computed Tomographic Angiography
Computed tomographic angiography (CTA) takes advantage of the widespread availability of CT scanners in EDs to allow a non-invasive look at the cerebral vasculature to assess for stenosis or occlusion. The technique uses spiral CT scanners with a 50 cc contrast bolus. The axial cuts, or source images, are then reformatted into a three-dimensional projection that allows visualization of the circle of Willis as well as proximal portions of the MCA, anterior cerebral artery (ACA) and vertebrobasilar system. The entire process typically adds 10-15 minutes to the standard non-contrasted CT imaging.

The advantages of CTA include its speed and availability as compared to magnetic resonance angiography (MRA) or standard digital subtraction angiography (DSA) as well as its ability to demonstrate occlusion of the cerebral vessels that could affect treatment algorithms. Lev et al.4 used CTA in 44 consecutive patients who presented within six hours of onset of symptoms to assess for occlusion of a cerebral vessel prior to angiographic correlation with DSA. The study was designed to assess the feasibility that CTA could be used as a screening tool to decide when to proceed on to intraarterial (IA) thrombolysis. Of 224 vessels studied with diagnostic angiography after CTA, the sensitivity of CTA for large-vessel occlusion was 98.4% with a specificity of 98.1% and overall accuracy of 98.2%. The CTA added an average of only 11.7 ± 4.2 minutes to the study time, with an estimated 3 minutes required for reconstruction and review. They concluded that CTA is highly accurate in the detection of large vessel occlusion and may be valuable for the triage of patients for intraarterial thrombolysis.

Another study performed by Verro et al.5 evaluated 54 consecutive patients with non-contrasted CT followed by CTA of the circle of Willis. All patients presented with symptoms of acute ischemia. The study was used to select patients who
did not meet standard National Institute of Neurological Disorders and Stroke (NINDS) criteria for IV thrombolysis for DSA and potential IA thrombolysis. In total, 30 of the 54 patients had an occlusion documented on CTA, of which 9 underwent DSA. CTA diagnosis of arterial occlusion was confirmed by DSA in all 9 patients. In total, CTA determination of occlusion was found to be consistent with at least one other study in 43 of 51 patients, demonstrating a sensitivity of 87% and a specificity of 84%. Mean discharge NIHSS scores were worse in patients with a CTA-documented occlusion, regardless of whether thrombolysis was given. The authors concluded that CTA provides an accurate assessment of occlusion in the acute setting and may be used to screen candidates for aggressive treatment who might otherwise not receive standard IV therapy due to exclusion.

The importance of CTA in the setting of acute stroke is two-fold. First, in a setting where IA thrombolysis is available, CTA can rapidly identify candidates with large vessel occlusion that may derive more benefit from IA therapy or combination IV/IA therapy than IV therapy alone. Intraarterial therapy has classically been extended out to six hours, allowing more patients to be treated in this setting given the expanded time window. Secondly, CTA has the potential to reliably exclude patients without large vessel occlusion from the risks and cost of undergoing acute interventional angiography, although further prospective study will be required to prove this. Additionally, in centers where IV thrombolysis is the only therapy available, CTA documentation of a large-vessel occlusion provides additional information and assurance of the diagnosis of AIS. It is important to remember, however, that even in the absence of documented occlusion on CTA, a candidate for IV thrombolysis should still be treated, as reversal of the neurologic deficit can still be achieved in a small-vessel occlusion not visualized on CTA.

Cerebral Perfusion CT
The goal in the use of rt-PA for thrombolysis of an acute ischemic stroke is to salvage the maximum amount of neuronal tissue that has not yet infarcted. It has been shown that in acute arterial occlusion there is a central core of brain that infarcts within minutes due to complete loss of blood flow and a larger area of ischemic brain which remains viable but functions abnormally due to loss of normal oxygen supply, previously termed the ischemic penumbra. Magnetic resonance imaging (MRI) has the ability to differentiate the ischemic but not yet infarcted tissue from that which is irreversibly lost, but an emergent MRI is difficult to obtain in most EDs.

A newer technology, cerebral perfusion CT (PCT), seems to possess similar abilities to MRI to differentiate ischemic from infarcted tissue. In PCT, a bolus of contrast is given IV and the attenuation of various parts of the brain parenchyma is then measured relative to both a cerebral artery and vein, with the thought that as the contrast passes through the parenchyma, the attenuation of the brain tissue will increase. Further, in the case of arterial occlusion, the increase in attenuation will be delayed or lost altogether in tissue that has decreased blood supply, allowing CT to identify tissue at risk of infarct or already infarcted. Tracking the contrast bolus in the parenchyma gives measures of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) of the contrast. Reduced perfusion with preserved or increased CBV is thought to represent areas of ischemia, while reduced perfusion coupled with reduced CBV is thought to represent already infarcted tissue. Subtraction of areas of decreased CBV from decreased CBF allows the ultimate goal of determination of the penumbra.

Studies of this technology have generally included small numbers of patients, but appear promising in comparison with MRI. Wintermark et al.6 evaluated 22 patients upon presentation to the ED with perfusion CT and then compared these images to delayed
MRI diffusion-weighted images (DWI) and found that the area of perfusion deficit on initial CT strongly correlated with the final DWI abnormality in patients without vessel recanalization (n= 8, correlation coefficient 0.958). The study further found that in those patients with arterial recanalization, the final infarct on the DWI was smaller than the area of total ischemia on initial CT, but larger than the area of initial infarct on CT, which they interpreted to show accurate CT depiction of the penumbra with some recovery after clot lysis (n=13). Ultimately, the authors concluded that PCT gives an accurate estimate of the area of ischemia and infarct when compared with MRI.

Another study by Schramm et al. compared perfusion CT with perfusion-weighted MRI (PWI) and DWI to determine correlation between the two studies of area of perfusion and diffusion defect. In this study, 22 patients underwent both CT and MRI within six hours of onset of acute neurologic deficit. This study found no significant difference between perfusion CT lesion volume and PWI. Further, PCT evidence of infarction correlated well with DWI. This suggests good reproducibility between PCT and MRI for evaluation of the ischemic penumbra, although this will need to be confirmed with larger studies. The perfusion CT averaged approximately 10 minutes to complete and can be performed on most spiral CT scanners with the addition of imaging software, making it more accessible to most EDs in real-time.

**Magnetic Resonance Imaging in Ischemic Stroke**

**Diffusion and Perfusion Magnetic Resonance Imaging**

The presence or absence of an ischemic penumbra seems to correlate with the prognosis for recovery after thrombolysis. The lack of ischemic but not yet infarcted tissue reflects poorly on the chance of recovery after treatment. The gold standard for evaluation of the ischemic penumbra is investigation by MRI. Diffusion-weighted MRI involves a technique that detects decreased diffusion of water within the brain. As tissue becomes damaged from ischemia and unable to support its membrane permeability, intracellular water is released into the extracellular space, resulting in an overall decrease in the diffusion of water on the cellular level. The decrease in diffusion is reflected as a hyperintense signal on diffusion MRI and shows tissue which may be unsalvageable and irreversibly damaged. While conventional MRI or non-contrast CT takes up to six hours to demonstrate changes of ischemia, DWI will document these changes within minutes from onset of ischemia.

Perfusion-weighted MRI tracks a bolus of gadolinium through the brain. Both CBV and the time it takes for the contrast signal to reach maximal intensity in the brain, which is related to the mean transit time of the contrast, can be assessed, allowing CBF to be indirectly imaged. A decrease in CBF reflects the area of tissue which is hypoperfused, encompassing both the infarct core and the penumbra. Comparison of the DWI to the PWI allows the clinician to subtract the DWI hyperintense signal from the abnormal signal on PWI to ascertain whether there is still tissue which is viable but hypoperfused. This area, commonly called diffusion/perfusion mismatch, is the target area of tissue for reperfusion. A matched area of DWI and PWI signal abnormality suggests little benefit to thrombolysis, as the infarct is completed.

Studies involving MRI in the hyperacute time period are small but encouraging. Parsons et al. performed a study utilizing DWI/PWI in acute stroke of less than 6 hours duration. The study involved 19 patients treated within 6 hours with IV rt-PA matched with 21 historical controls. All patients underwent DWI/PWI, but they were given thrombolysis based on standardized protocols and not by selection with MRI. The study showed that when patients treated out to six hours from onset were analyzed by group as either treated or not treated, there was a trend towards benefit with treatment, but no significant difference between the groups. However, when only patients with a DWI/PWI mismatch were analyzed, there was a significant
improvement in both outcome National Institute of Health Stroke Scale (Mean 5.3 points, 95% CI 1.0 – 11.7 points, p < 0.01) and functional independence by modified Rankin Scale ($\chi^2 = 4.6$, p = 0.03) in the treated patients. Despite the small numbers in this study, it suggests that more benefit may be gained by treating patients with a DWI/PWI mismatch on MRI.

Further support that MRI could be used to evaluate patients in the acute time period comes from Röther et al.\(^{10}\) in a non-randomized study used to evaluate 139 patients for open-label use of rt-PA within six hours of onset of ischemic injury. This study documented large numbers of patients with DWI/PWI mismatch (120/139) but were unable to show a treatment effect based on volume or presence of mismatch, although patients treated with rt-PA did significantly better, whether using a 0-3 hour time interval or 3-6 hour time interval (OR 0.20, 95% CI 0.05-0.83 and OR 0.17, 95% CI 0.04-0.76, respectively). Typical MRI protocols in the hyperacute time period added only 20 minutes to overall treatment time.

**Magnetic Resonance Angiography**

Magnetic resonance angiography (MRA) is the final piece in the puzzle of hyperacute MRI for ischemic stroke. MRA performed of the circle of Willis can document occlusion or stenosis in the proximal vessels with three-dimensional imaging. It is non-invasive, requires no contrast, and further adds information about the possible risks and benefits of thrombolysis.

The obvious downside to the use of MRI in the acute evaluation of ischemic stroke is the lack of availability of the hardware and technologists. Many EDs do not have 24-hour MRI availability or require significant time to complete the imaging protocol, despite reasonably quick scan times. Further, as CT improves its ability to provide imaging of perfusion defects and angiography, perceived need for MRI in the acute phase may decrease. At this point, most centers still require a non-contrast CT as the gold standard to rule out hemorrhage, and moving a patient requiring time-sensitive treatment to multiple scanners becomes impractical.

**Currently, the ideal patient for acute multimodal MRI is the patient who arrives in the 3-6 hour time period from onset of symptoms in which advanced imaging with the capability to reliably demonstrate a DWI/PWI mismatch and vessel patency may help to guide therapy.**

**DWI in Transient Ischemic Attack (TIA)**

DWI has also been shown to have sensitivity of 14-67% in the detection of an acute ischemic lesion in TIA.\(^{11-14}\) Kidwell et al.\(^{14}\) studied 42 patients with DWI who presented with symptoms of TIA. Twenty of the 48 patients (48%) demonstrated a DWI hyperintense lesion, despite the fact that only 2 of the twenty DWI-positive patients remained symptomatic. Most studies have shown that the rate of DWI-
positivity increases as duration of TIA symptoms increases, but the time from symptom onset to MRI does not seem to be crucial, as long as it is performed in the acute or subacute period.\textsuperscript{15,16} This DWI-positivity reflects that TIA is not a benign process and frequently does neuronal damage, although whether these patients with DWI lesions are more prone to develop symptomatic stroke is not yet known.

\textbf{Intracerebral Hemorrhage}

\textit{Non-Contrast Computed Tomography}

The gold standard of imaging for acute hemorrhage continues to be non-contrasted CT. CT is capable of documenting hemorrhage within minutes of onset and gives some idea of the age and chronicity of the blood. Hemorrhagic stroke can present in a very similar fashion to an ischemic insult, and because of CT’s sensitivity in detecting hemorrhage coupled with its ability to evaluate for ischemia and stroke mimics such as tumor in the acute setting, CT will continue to be the screening test-of-choice for acute neurologic deterioration in the ED for the foreseeable future. However, two forms of MRI, Fluid-Attenuated Inversion Recovery (FLAIR) and susceptibility-weighted imaging (SWI), show significant sensitivity for hemorrhage in the acute setting.

\textit{Magnetic Resonance Imaging}

One of the classic limitations of the use of MRI as the screening study for stroke upon arrival to the ED has been concerns over its utility in the detection of acute hemorrhage. Even in centers where MRI is available for ED imaging in real-time to evaluate for the possibility of thrombolysis, patients have been subjected to non-contrast CT to rule out hemorrhage prior to treatment in addition to MRI, thus forcing the use of two separate imaging modalities and requiring even more time to treatment.

Magnetic susceptibility is a property that causes distortion of a magnetic field at an interface between two different types of tissue. MRI has taken advantage of this with the use of susceptibility-weighted imaging (SWI), which shows areas of hemorrhage as a hypointense ring of deoxyhemoglobin around a hyperintense, heterogenous core. Two large multicenter trials have undertaken to evaluate the sensitivity of MRI in the detection of hyperacute hemorrhage. In all cases the standard for comparison is non-contrast CT. Fiebach et al.\textsuperscript{17} described 62 patients with hyperacute hemorrhage taken from an ongoing Stroke MRI registry. The images were matched with images from 62 controls with ischemic strokes and then randomized and given to blinded readers. The readers were 100\% sensitive and specific in the detection of hemorrhage as compared to CT. While the patients were not necessarily consecutive and bias is therefore possible, the accuracy of MRI in this study is impressive. MRI further identified 4 cases of old hemorrhage not seen on CT.

Another multicenter trial by Kidwell et al.\textsuperscript{18} reports preliminary data on 169 patients prospectively enrolled in a stroke MRI protocol with symptoms of less than 6 hours duration who also underwent CT. CT visualized acute hemorrhage in 23 patients, 22 of which were seen on MRI. One hemorrhage was misdiagnosed as a meningioma on MRI. MRI further identified 3 patients with acute blood (2 hemorrhagic transformations and 1 subarachnoid hemorrhage) not seen on CT.

Subarachnoid hemorrhage (SAH) is another type of bleed for which noncontrast CT is very sensitive. There have been few studies on the use of MRI in the detection of SAH, however Wiesmann et al.\textsuperscript{19} described one series of 13 consecutive patients within 2 – 12 hours of onset of SAH imaged with MRI. FLAIR imaging was 100\% sensitive in this series for detection of SAH, as confirmed by CT. Certainly it is possible that CT missed some cases of SAH that would also have been missed by MRI, but the study did demonstrate that SAH can be visualized on MRI. At this point in time it is encouraging that MRI may be capable of being the first and only screening tool in acute stroke, but more prospective evidence will be
required to confirm its ability to detect SAH and ICH in the acute setting before it is safe to forgo CT.

Other imaging modalities that continue to be largely relegated to the investigational and research roles include Single-photon emission CT (SPECT), Positron-emission tomography (PET), and Xenon-enhanced CT imaging. These modalities give more detailed and quantitative imaging related to cerebral perfusion, but are rarely available from the ED.

The imaging of acute stroke is complex and continues to advance quickly as more powerful hardware and software becomes available. Much of the diagnostic imaging performed is based on speed and availability at the institution where the patient presents. Both CT and MRI have a place in the acute evaluation of a stroke patient, although in the ED, CT continues to be the more readily available diagnostic tool. The information obtained from both CT and MRI increases continually while the time necessary to obtain the images decreases. Now more than ever, advanced imaging techniques allow the proper mating of ischemic or hemorrhagic stroke patients with the best treatment to optimize outcomes and reduce disability.

REFERENCES

OBJECTIVES:

1. Recognize that initiating aspirin therapy within 24 hours of ischemic stroke provides an 11% relative risk reduction (1% actual risk reduction) in death or non-fatal stroke
2. Recognize that Heparin and the heparinoids have never been demonstrated in a large randomized trial to produce any net neurological or survival benefit in any subset of the stroke population
3. Be familiar with the latest evidence of the clinical benefit of rt-PA for patients treated within 3 hours of acute ischemic stroke symptom onset

INTRODUCTION

Literature on the management of acute ischemic stroke has been considerable over the past 10 years. Many large clinical trials using a number of agents have been published. The primary emphasis within this segment will be on the current evidence regarding the use of the following agents in acute ischemic stroke:

- Aspirin
- Heparin/Heparinoids
- Tissue Plasminogen Activator (IV or IV/IA)
- New Catheters
- GP IIb/IIIa Receptor Antagonists
- Neuro-protectives

Aspirin

Two trials have shown that starting aspirin early in acute ischemic stroke (AIS) can reduce the risk of death or recurrent stroke in hospital and improve functional recovery. These studies are the Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST). At the 1999 American Heart Association conference on stroke and cerebral circulation, an analysis of these two studies on the use of aspirin in acute ischemic stroke was presented. The presentation reviewed the indications for early aspirin use in acute ischemic stroke using the combined analysis of over 40,000 randomized patients.\(^1\)\(^-\)\(^3\)

This analysis utilized individual patient data from 40,090 randomized patients. The results were as follows: there were 3464 (8.6%) deaths or non-fatal strokes and 310 (0.8%) transfused extracranial hemorrhages. The early use of aspirin reduced the relative risk of death or non-fatal stroke by 11% (SD 3). There was no good evidence that the proportional risk reduction differed from 11% in any particular subgroup (age, delay from symptom onset, AF status, stroke subtypes and whether the patient had a CT scan prior to randomization). Consequently, the absolute benefit with aspirin in a specific category depends on the magnitude of the absolute risk observed, and is thus greater in high risk patients than in the low risk. Among the patients who did not die in hospital, however, aspirin was associated with an excess of 3 (SD 1) per 1000 extracranial hemorrhages. This excess appeared to be greater in the presence of heparin (8 per 1000) than in its absence (2 per 1000). Among 800 patients randomized with a cerebral hemorrhage, aspirin showed no evidence of any adverse effects. The conclusion from this analysis is that aspirin is beneficial for a wide range of patients, and it should be considered for almost all patients with suspected acute ischemic stroke.
Heparin/Heparinoids

Anticoagulation with heparin is used commonly for treatment of acute ischemic stroke, but its use remains controversial because it has not been shown to be effective or safe. More recently, the low molecular weight heparins have become widely utilized in ACS and physicians have questioned whether they might be useful in AIS.

The largest single trial of unfractionated heparin in AIS is the International Stroke Trial (IST). This study was a large, randomized, open trial of up to 14 days of antithrombotic therapy started as soon as possible after stroke onset. The aim was to provide reliable evidence on the safety and efficacy of aspirin and of subcutaneous heparin. Half of the patients were allocated to receive unfractionated heparin (5000 or 12,500 IU bid [twice daily]). One quarter was given aspirin 300 mg daily and one quarter received no antithrombotic therapy. Among patients receiving heparin, there were non-significantly fewer deaths within 14 days (876 [9.0%] vs. 905 [9.3%]), corresponding to 3 (SD 4) fewer deaths per 1000 patients. At 6 months the percentage dead or dependent was identical in both groups (62.9%). Patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9% vs. 3.8%), but this benefit was offset by a similar-sized increase in hemorrhagic strokes (1.2% vs. 0.4%), thus the difference in death or non-fatal recurrent stroke (11.7% vs 12.0%) was not significant. Heparin was associated with a significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1000. The authors concluded that neither heparin regimen offered any clinical advantage at 6 months.

The issue of heparinoids was decided by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST). This was a randomized, double-blind, placebo-controlled, multicenter trial. A total of 1281 persons with acute stroke were enrolled at 36 centers across the United States. A 7-day course of ORG 10172 or placebo was given initially as a bolus within 24 hours of stroke, followed by continuous infusion in addition to the best medical care. Doses were adjusted in response to anti-factor Xa activity. The results are based on clinical assessment tools with endpoints of “favorable outcome” and “very favorable outcome” as well as assessment of hemorrhage rates. At 7 days, 376 (59.2%) of 635 persons given ORG 10172 and 344 (54.3%) of 633 receiving placebo had favorable outcomes (p=0.07). For the same interval, 215 (33.9%) of 635 persons given ORG 10172 and 176 (27.8%) of 633 persons administered placebo had very favorable outcomes (P=.01; odds ratio, 1.36; 95% confidence interval, 1.06-1.73). Within 10 days of onset of treatment, serious intracranial bleeding events occurred in 14 patients given ORG 10172 (15 events) and in 4 placebo-treated patients (5 events) (P=0.05). At 3 months, however, this benefit was not found. At 3 months, 482 (75.2%) of 641 persons assigned to treatment with ORG 10172 and 467 (73.7%) of 634 patients treated with placebo had favorable outcomes (P=.49); 49.5% and 47%, respectively, of patients in each group had very favorable outcomes at 3 months. Patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9% vs. 3.8%), but this benefit was offset by a similar-sized increase in hemorrhagic strokes (1.2% vs. 0.4%), thus the difference in death or non-fatal recurrent stroke (11.7% vs 12.0%) was not significant. Heparin was associated with a significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1000. The authors concluded that neither heparin regimen offered any clinical advantage at 6 months.

One area of acute stroke where the use of heparin is quite common is in the setting of atrial fibrillation. It seems intuitive that patients with acute ischemic stroke and atrial fibrillation have an increased risk of early stroke recurrence. In this setting anticoagulant treatment with heparins has been widely advocated, despite missing data on the balance of risk and benefit. To address this issue investigators performed the Heparin in Acute Embolic Stroke Trial (HAEST) trial. This was a multicenter, randomized, double-blind, and double-dummy trial on the effect of low-molecular-weight heparin (LMWH, dalteparin 100 IU/kg subcutaneously twice a day) or aspirin (160 mg every day) for the treatment of 449 patients with acute ischemic stroke and atrial fibrillation. The
primary aim was to test whether treatment with LMWH, started within 30 h of stroke onset, is superior to aspirin for the prevention of recurrent stroke during the first 14 days.

The study’s results demonstrated that the frequency of recurrent ischemic stroke during the first 14 days was 19/244 (8.5%) in dalteparin-allocated patients versus 17/225 (7.5%) in aspirin-allocated patients (odds ratio=1.13, 95% CI 0.57–2.24). The secondary events during the first 14 days also revealed no benefit of dalteparin compared with aspirin: symptomatic cerebral hemorrhage 6/224 versus 4/225; symptomatic and asymptomatic cerebral hemorrhage 26/224 versus 32/225; progression of symptoms within the first 48 hours 24/224 versus 17/225; and death 21/224 versus 16/225. There were no significant differences in functional outcome or death at 14 days or 3 months. The authors concluded that present data do not provide any evidence that LMWH is superior to aspirin for the treatment of acute ischemic stroke in patients with atrial fibrillation. However, the study could not exclude the possibility of smaller, but still worthwhile, effects of either of the trial drugs.5

**Tissue Plasminogen Activator (t-PA)**

The 1995 publication of the National Institute of Neurological Disorders and Stroke (NINDS) Tissue Plasminogen Activator for Acute Ischemic Stroke trial has led to considerable change in the management of acute ischemic stroke. There are areas of considerable concern to clinicians who must decide which patients to offer thrombolytic therapy for AIS. Questions which will be addressed here include: who should be treated, what is the effect of time to treatment, was the data analysis correct, can we gain information from the other rt-PA stroke trials, and what other interventions are being utilized?

**Who Should Be Treated?**

In a post hoc analysis of the NINDS trial, the NINDS investigators sought to identify subgroups of stroke patients in whom thrombolytic therapy is particularly hazardous or efficacious. Variables were identified that might predict outcome and/or differential response to t-PA therapy. Multivariable procedures were used to find information that could guide selection of patients for t-PA therapy. In the final analysis, no pretreatment information significantly affected patients’ response to t-PA. The power of the model to detect a treatment interaction was greater than 90%. Apart from t-PA therapy, outcome was related to age-by-deficit severity interaction, diabetes, age-by-blood pressure interaction, and early CT findings. These variables and interactions altered long-term patient outcome irrespective of t-PA treatment but did not alter the likelihood of responding favorably to t-PA therapy. The NINDS investigators concluded that patients should be selected for t-PA thrombolysis according to the guidelines published in the report of the NINDS t-PA Stroke Trial.
What is the effect of time to t-PA treatment?
The initial report of the NINDS t-PA Stroke Study showed no difference in 3-month outcome or the rate of intracranial hemorrhage within 36 hours for patients randomized at 0-90 minutes after stroke onset compared to those randomized at 91-180 minutes. The NINDS investigators have subsequently performed a more detailed analysis of the effect of time to treatment. A univariate analysis identified potentially confounding variables associated with onset to treatment time. In this analysis it was noted that the patients treated earlier had more severe strokes and thus for the 3-month outcome, the patient’s stroke severity met criteria for a masking confounder. Taking onset to treatment and baseline covariates into consideration, the adjusted odds ratio for a favorable three-month outcome associated with t-PA was 2.11 in the 0-90 minute time window and 1.69 in the 91-180 minute time window. The investigators conclude that patients given t-PA within 90 minutes from stroke onset were more likely to show improvement at 24 hours and to have an increased odds of favorable 3-month outcome over patients treated later. Based on this analysis, the NINDS investigators urge continued efforts to treat patients as quickly as possible within the established 3-hour time window.

The NINDS rt-PA trial re-analyzed
In May 2002, in response to concerns about the results of the NINDS rt-PA Stroke Study, an independent Committee was established at the request of NINDS. The main charge given to the committee was: “to address the concern that eligible stroke patients may not benefit from rt-PA given according to the protocol used in the trials and, whether the subgroup imbalance invalidates the entire trial as claimed by some of the critics.” This independent review group then received the original patient case-report-form level data from the NINDS rt-PA stroke trial to perform their re-analysis.

The review committee found that despite subgroup imbalances in baseline stroke severity, when the drug was administered according to the study protocol, there was a statistically significant, and clinically important, benefit of t-PA treatment measured by an adjusted t-PA to placebo odds ratio of 2.1 (95% CI: 1.5-2.9) for a favorable outcome at three months. The analysis was adjusted for center, time to treatment (0-90 minutes and 91-180 minutes), study part, age, baseline NIHSS, diabetes, and pre-existing disability. The committee examined all of the adjusting variables to determine if they modified the treatment effect of t-PA as measured by the adjusted t-PA to placebo OR. The analyses found no evidence that any variable modified the t-PA treatment effect. In particular, neither baseline NIHSS, nor time from symptom onset to treatment, modified the t-PA treatment effect.

The Pooled Analysis
Recognizing that the sample size in the NINDS rt-PA stroke trial has lead to concern, investigators from all of the placebo controlled randomized trials of rt-PA in the setting of acute stroke performed an analysis on the data pooled from all of their trials. Unlike a meta-analysis this effort pooled the individual patient-level data on all of the patients from all of the randomized trials of rt-PA in the setting of acute ischemic stroke.

The investigators pooled common data elements from six randomized placebo-controlled trials of intravenous rt-PA. Using multivariable logistic regression they then assessed the relation of the interval from stroke onset to start of treatment (OTT) on favorable 3-month outcome and on the occurrence of clinically relevant parenchymal hemorrhage. Treatment was started within 360 min of onset of stroke in 2775 patients randomly allocated to rt-PA or placebo. Median age of the patients was 68 years, the median baseline National Institute of Health Stroke Scale (NIHSS) 11, and median OTT 243 min.

The results demonstrated that the odds of a favorable 3-month outcome increased as OTT decreased (p=0.005). Odds were 2.8 (95% CI 1.8–4.5) for 0–90 min, 1.6 (1.1–2.2) for 91–180 min, 1.4 (1.1–1.9)
for 181–270 min, and 1.2 (0.9–1.5) for 271–360 min in favor of the rt-PA group.

Figure 1 documents the decrease in odds ratio of a favorable outcome over time. The hazard ratio for death adjusted for baseline NIHSS was not different from 1.0 for the 0–90, 91–180, and 181–270 min intervals; for 271–360 min it was 1.45 (1.02–2.07). Hemorrhage was seen in 82 (5.9%) rt-PA patients and 15 (1.1%) controls (p<0.0001). Hemorrhage was not associated with OTT but was with rt-PA treatment (p=0.0001) and age (p=0.0002). The investigators concluded that the sooner that rt-PA is given to stroke patients, the greater the benefit. The authors state that the results suggest a potential benefit beyond 3 h, but that this potential might come with some risks.9

Combined: Intra-arterial/Intravenous t-PA
To investigate the feasibility and safety of a combined intravenous (IV) and intra-arterial (IA) approach to recanalization in patients with ischemic stroke investigators performed the Interventional Management of Stroke (IMS) pilot trial. In this trial, subjects ages 18 to 80 with an NIH Stroke Scale (NIHSS) greater than 10 at baseline had IV recombinant tissue plasminogen activator (rt-PA) started (0.6 mg/kg, 60 mg maximum over 30 minutes) within 3 hours of onset. The patients were then taken to angiography. If a clot was identified, additional rt-PA was then administered via microcatheter at the site of the thrombus up to a total dose of 22 mg over 2 hours of infusion or until thrombolysis. Primary comparisons were with similar subsets of placebo and rt-PA–treated subjects from the NINDS rt-PA Stroke Trial.

In this trial a total of 80 subjects were enrolled. They had a median baseline NIHSS score of 18. The median time to initiation of IV rt-PA was 140 minutes as compared with 108 minutes for placebo and 90 minutes for rt-PA–treated subjects in the NINDS rt-PA Stroke Trial. The 3-month mortality in Interventional Management Study (IMS) subjects (16%) was numerically lower but not statistically different than the mortality of placebo (24%) and rt-PA–treated subjects (21%) in the NINDS rt-PA Stroke Trial. The rate of symptomatic intracerebral hemorrhage (6.3%) in IMS subjects was similar to that of rt-PA–treated subjects (6.6%) but higher than the rate in placebo-treated subjects (1.0%, P=0.018) in the NINDS rt-PA Stroke Trial. IMS subjects had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures (odds ratios greater than 2). The authors concluded that a randomized trial of standard IV rt-PA as compared with a combined IV and IA approach is needed.10

Mechanical Thrombolysis
Another very active arena of clinical research in acute ischemic stroke is the ongoing search for devices that can be used to mechanically open an occluded artery. Many such devices designed to perform “mechanical thrombolysis” are currently under investigation. Methods currently undergoing research include the use of micro-catheters with tips that emit ultrasound waves to either mechanically disrupt clot or potentiate pharmacologic thrombolysis. Other micro-catheters have a laser tips designed to ablate the offending clot. Others use classically mechanical means such as wire loops passed beyond the clot and pulled through the clot, suction devices or a jet of water combined with suction to remove the clot.
Recently (8/15/04) the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) device (Concentric Medical Inc.) was approved by the FDA. The key feature of the MERCI retrieval system is a wire with a tapered nitinol helical tip which looks something like a corkscrew. This corkscrew shaped device resides within a micro-catheter and is angiographically placed into and distal to the offending clot. A balloon on a guide catheter is used to occlude the artery proximally and after the MERCI retrieval device is deployed the retrieval device and clot are simultaneously pulled back into the guide catheter and the entire system is removed.

**GP IIb/IIIa Inhibitors**

Understanding that acute ischemic stroke is usually due to a thromboembolism and accepting that the aggregation of platelets and the associated cross-linking with fibrin are central to thrombus formation one can envision a number of potential therapeutic uses for an antagonist to activated platelet GP IIb/IIIa receptors. If platelet aggregation and fibrinogen cross-linking can be adequately disrupted by a GPIIb/IIIa antagonist then acute vascular occlusion, via a platelet rich thromboembolism, may be relieved by disaggregation of the platelets and subsequent dissolution of the offending thromboembolism. Just as fibrinolysis is effective via arterial recanalization of the primary infarct artery in acute myocardial infarction and acute ischemic stroke so might recanalization be achieved via platelet disaggregation.

In fact, the potential utility in the setting of acute clot is considerable. Currently utilizing only a fibrinolytic has significant disadvantages. While the fibrin component of a thromboembolism an acute ischemic stroke may be sensitive to lysis by plasminogen activators, the aggregated platelets resist dissociation.\(^1\)\(^2\) In addition, in the setting of coronary fibrinolysis, platelets accumulate at the clot surface thereby slowing clot dissolution.\(^3\) Moreover, rt-PA has been shown to stimulate platelet aggregation and may potentially promote microthrombosis extension.\(^1\)\(^4\) The potential to augment thrombolysis and/or prevent vascular occlusion via platelet aggregation inhibition has undergone considerable study.

Finally, increasing emphasis is being placed on importance of patency of the microvasculature in the region of acute ischemia. Both primary microvascular occlusion with aggregated platelets and embolic consequences of recanalization strategies leave an opportunity for improvement in tissue salvage via the prevention of platelet aggregation. In order to explore the literature to date on the use of GP IIb/IIIa antagonists in acute ischemic stroke we will divide the discussion between efforts to restore and maintain larger (macroscopic) artery patency, prevent reocclusion after recanalization, and efforts to preserve microvasculature patency.

**Large Artery thrombosis**

The use of GP IIb/IIIa receptor antagonists for larger artery patency can be divided into two areas of application: first, used alone as a primary recanalization strategy, second, in combination with a fibrinolytic as a primary recanalization strategy.

There has been one published human randomized, double-blind, placebo-controlled trial of a GPIIb/IIIa blocker (abciximab) alone in ischemic stroke.\(^1\)\(^5\) In this dose-escalation safety study, no treated patients were identified as having a fatal or nonfatal major ICH within 5 days (primary endpoint) or 3 months after randomization.\(^1\)\(^5\) Subsequently, the Abciximab in Emergent Stroke Treatment Trial (AbESTT) has been completed. This randomized double-blind, placebo-controlled trial of intravenous abciximab enrolled 400 patients with acute ischemic stroke within 6 hours of onset. Final results are not yet published but were encouraging enough that the phase 3 trial is in the early phases.\(^1\)\(^6\)
One very recent study has been done to evaluate the combination of intravenous eptifibatide (Integrilin®) and intra-arterial rt-PA in the setting of acute ischemic stroke. IV eptifibatide combined with intra-arterial rt-PA was given to 24 patients. There was a trend toward better revascularization (TIMI 2 or 3 flow) in patients treated with rt-PA plus eptifibatide (58%) compared to patients who received intra-arterial rt-PA alone (31%). There was one symptomatic hemorrhage in the combination therapy group. These investigators conclude that the combined use of IV eptifibatide and IA rt-PA appears safe in the setting of acute ischemic stroke.

One published series retrospectively reviewed 37 consecutive patients with ischemic stroke who were treated with systemic application of low-dose rt-PA and body weight-adjusted tirofiban (a non-peptide GP IIb/IIIa receptor antagonist). Patients in the rtPA+tirofiban group were compared with a group of patients treated with a dose of rt-PA 0.9 mg/kg in a different center (rt-PA group; n=119). The patients treated with rtPA+tirofiban or rt-PA groups reached a Rankin Scale score of 0 to 2 in 63% and 55%, respectively. Death rates (8% in rtPA+tirofiban group and 5% in rt-PA group) were similar among the 2 treatment groups. They included one fatal hemorrhage in the rtPA+tirofiban group and four fatal hemorrhages in the rt-PA group. The authors concluded that systemic combined thrombolysis with rt-PA+tirofiban “seems to be a feasible treatment in acute stroke.”

Similar pilot work on the combination of a fibrinolytic (rt-PA) and a GP IIb/IIIa inhibitor (abciximab) has been reported. In this pilot series the authors report feasibility of the co-administration of a fibrinolytic and a GP IIb/IIIa inhibitor.

Currently underway the Combined approach to Lysis utilizing Eptifibatide And rt-PA (CLEAR) Stroke Trial is a multi-center, sequential, dose-escalation, double-blind, randomized safety study designed to provide data concerning the risks and benefits of combining a glycoprotein IIb/IIIa antagonist, eptifibatide, with low-dose intravenous rt-PA in 100 acute ischemic stroke patients in whom treatment is begun within 3 hours of onset. Patients will be randomized to a combined intravenous eptifibatide and low-dose rt-PA regimen, or a standard dose (0.9 mg/kg) rt-PA regimen in a 3 to 1 ratio. The primary outcome measure is rate of symptomatic ICH. The study is funded by NIH/NINDS and is coordinated at the University of Cincinnati.

**Microvascular compromise**

A recent trend in both the cardiac literature and the cerebrovascular literature places emphasis on the microvasculature as a target for therapy. It is becoming evident that the accumulation of microemboli in the microvascular beds reduces tissue level perfusion, even in the setting of widely patent primary arteries. With the availability of advanced imaging technology that including magnetic resonance, myocardial contrast echocardiography, and transcranial Doppler (TCD), microvascular obstruction has been documented in a far greater proportion of patients than ever conceived. The potential of GP IIb/IIIa receptor antagonists to either block platelet aggregation and therefore prevent or minimize microvascular occlusion makes them an attractive candidate therapy. Supportive animal research demonstrates that in both mice and rats significant microvascular platelet accumulation occurs in the setting of MCA occlusion. Microvascular occlusion by platelet aggregates has been shown to be preventable with the use of an experimental GPIIb/IIIa inhibitor given just prior to MCA occlusion. In another study, infusion of an experimental GPIIb/IIIa inhibitor immediately after cessation of an MCA occlusion has been associated with a significant reduction in platelet accumulation and was associated with a reduction in cerebral infarct size by 70%. The data suggest an important role for post-occlusive distal platelet deposition in the evolution of an acute ischemic stroke.
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 59. 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 March 1, 2005. A passing grade of 80% is needed. A certificate will be sent to you upon your successful completion of the post-test.

The Pathophysiology of Acute Coronary Syndromes

1) All of the following are key components of Virchow’s triad of thrombogenesis except
   a. Blood thrombogenicity
   b. Disturbed blood flow
   c. Abnormal blood vessel walls
   d. Ruptured Fibrous cap

2) Which of the following are not part of the “response to injury” model for atherosclerosis described by Ross?
   a. Endothelial repair by activated macrophages
   b. Migration of LDL across the endothelial layer into the intima
   c. Inflammatory response often initiated by monocytes
   d. Formation of a fibrous cap

3) A significant minority of fatal cases of coronary thrombosis result from
   a. Anaphylactoid-like reactions induced by circulating antibodies
   b. Superficial erosion of the intima without frank rupture through the plaque fibrous cap
   c. Activation of T cells by triglycerides leading to a neurohormonal blockade
   d. Direct trauma to the arterial wall

4) Which of the following are required for a successful point-of-care program?
   a. Quality control
   b. Education of physicians
   c. Laboratory accreditation and regulation
   d. Defined and regulated testing procedures
   e. All of the above

5) Factors that should be considered in the cost analysis of a point-of-care testing program include all of the following EXCEPT:
   a. Laboratory result turn-around-time (TAT)
   b. Time to disposition
   c. Patient and physician (consumer) demand
   d. Cost of testing platform and reagents
   e. All of the above are correct.

The Role of Heart Sounds Recording and Analysis in the Dyspneic ED Patient

6) The following physical exam finding is highly specific (>90%) for acute decompensated heart failure:
   a. pulmonary rales
   b. lower extremity edema
   c. the S3 gallop

7) All of the following are true about the S3 except:
   a. it is caused by early diatolic filling of an incompletely relaxed or stiff ventricle
   b. it is caused by the atrial component of diastolic filling
   c. it can be a normal finding in those less than age 40

Update: Chest Pain Centers in 2004

8) Which of the following is a component of a successful Chest Pain Center:
   a. Community outreach
   b. Integration with EMS
   c. Process improvement orientation
   d. All of the above

9) The algorithms that constitute a strategy for “low likelihood” chest pain patient evaluation vary by institution, but all include which of the following elements:
   a. Immediate diagnostic cardiac cath
   b. Serial clinical examinations, cardiac markers and electrocardiography
   c. Admission to an ICU
   d. Lipid lowering therapy
10) Recent technological advances that may further assist in the diagnostic evaluation of chest pain patients include:
   a. Changes (delta) in serum markers of myocardial necrosis measured over relatively short time intervals
   b. Computed tomography and magnetic resonance imaging of cardiac structure and function
   c. ECG body surface mapping with up to 80 leads of information
   d. All the above

Understanding the Role of Anti-Platelet Agents in Non-ST-Elevation Acute Coronary Syndromes

11) Which of the following properties of Clopidogrel limits it’s usefulness as an early anti-platelet agent in the ED?
   a. Long half life of platelet inhibition
   b. Early achievement of therapeutic antiplatelet activity
   c. High cost of therapy
   d. Intravenous loading dosage
   e. Lack of early benefit prior to PCI

12) Which of the following antiplatelet agents has the highest antiplatelet activity in therapeutic doses?
   a. aspirin
   b. clopidogrel
   c. enoxaparin
   d. eptifibatide
   e. bivalrudin

13) According to the 2002 Updated ACC/AHA guidelines, which the following therapies is a Class IA recommendation for patients destined to undergo coronary catheterization and percutaneous coronary intervention (PCI):
   a. Aspirin
   b. Heparin
   c. GP IIb/IIIa inhibitor
   d. Clopidogrel
   e. All of these are Class IA recommendations for such patients

Anticoagulation in Acute Coronary Syndromes in the Emergency Department - Unfractionated vs Low-Molecular-Weight Heparin: Does It Matter?

14) According to the CRUSADE Initiative analysis, which of the following statements is true regarding early GP IIb/IIIa inhibitor utilization?
   a. Early GP IIb/IIIa utilization is effective only in low risk NSTEMI patients
   b. Early GP IIb/IIIa utilization is correlated with a trend in reduction of in-hospital mortality
   c. Early GP IIb/IIIa utilization is less effective in troponin positive patients.
   d. Early GP IIb/IIIa utilization is correlated with higher mortality in NSTEMI patients

15) Which of the following statements is NOT true regarding the use of heparins in patients with ACS?
   a. Clinical trial data suggest that the low-molecular-weight heparin enoxaparin is superior to unfractionated heparin in patients with NSTE ACS managed medically.
   b. Clinical trial data suggest that the low-molecular-weight heparin enoxaparin is superior to unfractionated heparin in patients with STEMI.
   c. It is often difficult to establish and maintain stable therapeutic aPTT levels in patients with ACS.
   d. The risk of bleeding with the use of low-molecular-weight heparins is increased in ACS patients with renal insufficiency and those who are older than 75 years.

16) Which of the following statements is NOT true regarding the use of heparins in patients with STEMI?
   a. Consideration should be given to reducing the dose of unfractionated heparin in STEMI patients who also receive GP IIb/IIIa inhibitors.
   b. Low-molecular-weight heparins are less often associated with the development of antiplatelet antibodies and subsequent heparin-induced thrombocytopenia than is unfractionated heparin.
c. There are no differences in the recommendations for heparin use based on choice of fibrinolytic agent (streptokinase, anistreplase, alteplase, reteplase, tenecteplase).

d. Bivalirudin is an appropriate substitute for heparin in patients with a history of heparin-induced thrombocytopenia.

CRUSADE - A Roadmap for Change. Interim Analysis of First 100,000 Patients Enrolled in the CRUSADE Initiative

17) Criteria for patient inclusion into the CRUSADE Quality Improvement Initiative does not include:
   a. Chest pain syndrome >10 minutes within 24 hours of presentation
   b. ST-segment changes including ST-segment depression or transient ST-segment elevation
   c. ST-segment elevation of 1 mm or greater in 2 electronically contiguous leads
   d. Elevated cardiac biomarkers of necrosis CK-MB or Troponin

18) Which of the following acute therapies for NSTE ACS is relatively underutilized in the first 24 hours:
   a. Aspirin
   b. Beta-blockers
   c. Heparin or low molecular weight heparin
   d. Glycoprotein IIb/IIIa receptor antagonists

19) Adherence to the 2002 ACC/AHA guidelines for unstable angina/NSTEMI improves clinical outcomes in patients with NSTE ACS.
   a. TRUE
   b. FALSE

ST-Segment Elevation Myocardial Infarction: New Guidelines with a Refocus on Time to Treatment

20) What time interval is the most important to determine the choice between primary angioplasty or fibrinolytic therapy for STEMI?
   a. time from onset of symptoms
   b. time from door to intervention
   c. additional delay to angioplasty compared to fibrinolytic therapy administration
   d. All of the above

21) For patients with STEMI and less than 6 hours from symptom onset and planned PCI, what is the maximum acceptable time delay for balloon inflation in the artery over the projected time of fibrinolytic drug delivery?
   a. none
   b. 60 min 3. 90 min
   c. 120 minutes

The Evolving Role of BNP in the Diagnosis and Treatment of CHF: A Summary of the BNP Consensus Panel Report

22) BNP levels may be elevated in the following conditions:
   a. Acute Myocardial Infarction
   b. Pulmonary Embolus
   c. Primary Pulmonary Hypertension
   d. Acute Decompensated Heart Failure
   e. All of the above

23) In the patient presenting with a clinical picture of acute decompensated heart failure, BNP levels may be lower than predicted in the following conditions:
   a. Acute Myocardial Infarction
   b. Pulmonary Embolus
   c. Primary Pulmonary Hypertension
   d. Morbid Obesity
   e. Vegetarians

24) A patient presents to the emergency department with acute decompensated heart failure. Nesiritide is begun, and shortly thereafter the patient develops symptomatic hypotension. What are the appropriate treatment steps?
   a. Stop nesiritide
   b. Administer a fluid bolus
   c. Reassess the differential diagnosis
   d. all of the above
Biomarker Advances in Acute Ischemic Stroke

25) 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

26) 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

Latest Imaging for Acute Ischemic Stroke and Intracerebral Hemorrhage

27) The ASPECT score is used to quantify:
   a. Quantity of hemorrhage in acute ICH
   b. Likelihood of reperfusion after treatment with t-PA
   c. Extent of early ischemic changes on non-contrast CT
   d. Initial neurologic deficit in ischemic stroke

28) The area of the Diffusion/Perfusion mismatch on multimodal MRI is thought to represent:
   a. Area of brain that has decreased blood flow and is at risk, but not yet infarcted
   b. Area of vasogenic edema surrounding an acute hemorrhage
   c. Area of reperfusion injury caused by treatment with t-PA
   d. Area of acute hemorrhage not well visualized on non-contrast CT

Latest Advances in Stroke Treatment

29) In the setting of acute ischemic stroke, which of the following clinical variables should be used to exclude patients from the use of rt-PA
   a. Elderly patients.
   b. Patients with a history of diabetes.
   c. Patients with an NIH Stroke Scale above 20
   d. None of the above

30) Which of the following is true regarding Heparin of the Heparinoids used in the treatment of acute ischemic stroke?
   a. Patients with new onset atrial fibrillation and newly diagnosed ischemic stroke should be immediately anticoagulated.
   b. Patients with acute ischemic stroke in the first 24 hours that are not rt-PA candidates have a survival benefit if anticoagulated.
   c. Patients with acute ischemic stroke in the first 24 hours that are not rt-PA candidates have a better neurological outcome if anticoagulated.
   d. Heparin and the heparinoids have not been proven to benefit patients with acute ischemic stroke in the first 24 hours after symptom onset.

31) With regard to the use of aspirin after ischemic stroke which of the following are true?
   a. Patients’ ability to swallow should be checked before any oral medication is provided.
   b. Aspirin therapy has been demonstrated to be beneficial after acute stroke by reducing death or disabling stroke by 11% relative, 1% actual risk reduction.
   c. If swallowing is compromised initiation of rectal aspirin is an option.
   d. All of the above
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On a scale of 1 to 5, with 1 being highly satisfied and 5 being highly dissatisfied, please rate this program with respect to:

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