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Dear Colleagues:

Patients presenting to the Emergency Department (ED) with chest pain remain a major clinical challenge. In the United States alone there are over eight million annual visits for this problem, resulting in over four million admissions. Nontraumatic chest discomfort remains the primary catalyst for ED evaluation of possible acute coronary syndromes, including unstable angina, non-ST-segment elevation myocardial infarction and ST-segment myocardial infarction. The diagnosis and treatment of congestive heart failure is also critically important to emergency physicians and other healthcare providers. The diagnosis 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 stroke.

The Emergency Medicine Cardiac Research and Education Group-International (EMCREG) is pleased to present this educational monograph summarizing our 2003 EMCREG Symposium on cardiovascular and neurovascular emergency care held in Boston as a satellite to the ACEP Scientific Assembly. 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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The understanding of the pathophysiological mechanisms of atherosclerosis and of acute coronary syndromes (ACS) has progressed significantly in recent years. This has allowed for the opportunity for the more precise identification of ACS, development and implementation of more specific therapeutic interventions, in addition to the improved potential for primary prevention.

The purpose of this discussion is to highlight the key concepts in the current understanding of the pathophysiology of atherosclerosis and ACS and to illustrate the central role of inflammation and thrombosis in these processes. The reader is referred to the appended list of references and suggested readings that will provide greater detail regarding these complex processes and interactions.

ATHEROSCLEROSIS

Low-density lipoprotein (LDL) and other lipoproteins accumulate in the sub endothelial matrix of blood vessels. The LDL passively diffuses between endothelial cell junctions and is modified by a variety of processes, including oxidation. The accumulation of modified LDL stimulates endothelial cell production of a spectrum of pro-inflammatory mediators, including the manifestation of adhesive molecules on endothelial cell surfaces and expression of a variety of chemotactic factors. The endothelial cells express P-selectin, which mediates a “rolling” transitory contact between leukocytes and the endothelium, and Vascular Cell Adhesion Molecule-1 (VCAM-1), mediating a more sustained leukocyte adhesion to the endothelium. Chemokines attract monocytes and lymphocytes to the area allowing for their subsequent interaction with the endothelial adhesion molecules. Monocytes migrate between the endothelial cells and in response to a variety of chemical factors, mature into macrophages and express “scavenger receptors” on their surface. These macrophages ingest the modified LDL and become foam cells. The foam cells, and to a lesser extent T-lymphocytes, form the “fatty streak”, the earliest form of atherosclerotic plaque.

The cells, both macrophages and endothelial cells, in the inflamed intima generate a number of factors prompting media smooth muscle cells to migrate into the intima, to proliferate and generate components of the extracellular matrix. This ongoing process creates a fibrous cap serving to separate the underlying inflammatory process from the circulating blood elements. The fibrous cap undergoes continuous remodeling and demonstrates considerable metabolic activity. A lipid laden necrotic core accumulates beneath the fibrous cap as a result of breakdown of foam cells releasing lipids, and possibly a component of direct trapping of lipids. Thus a mature plaque demonstrates two main components, a hard collagen-rich fibrous tissue cap and

OBJECTIVES:

1. Discuss atherosclerosis and the role of inflammation in this process.
2. Discuss the pathophysiology of acute coronary syndromes.
a lipid atheromatous core. The plaque expands typically in an outward direction, initially maintaining the vascular lumen. With ongoing growth the plaque will ultimately begin to impinge on the lumen.

THE VULNERABLE PLAQUE

The stability of the atherosclerotic plaque and thus the risk of development of an acute coronary event are variable. The risk of development of ACS relates more to the composition and “vulnerability” of the plaque than to the degree of stenosis of the vessel. A number of characteristics of an individual plaque have been identified defining the vulnerability of the plaque to rupture and thus initiate a thrombotic event. These factors include:

- The size and consistency of the atheromatous core. Plaques with large lipid cores (greater than 50% plaque volume) are at higher risk.
- Thickness and collagen content of the fibrous cap covering the core. This represents a balance between the dynamic factors stimulating and inhibiting collagen production. A thin cap would characterize a plaque at higher risk.
- Degree of inflammation within the cap. Products of inflammatory cells, such as metalloproteinase’s, may result in degradation of the matrix and inhibition of fresh collagen production. Vulnerable plaques are characterized by a high density of macrophages and the resultant high levels of tissue factor and metalloproteinases produced by these cells.
- Cap “fatigue” or circumferential wall stress.

There is a very significant variation in the extent and nature of disruption of plaques and in the subsequent responses to that event. A variety of factors determine the thrombotic response to the disruption of a plaque including:

- The character and extent of exposed substrates including collagen and tissue factor.
- The degree of local blood flow disturbance including factors such as the degree of stenosis and vascular changes that may activate platelets.
- The balance in the thrombotic fibrinolytic equilibrium existing at the time of plaque disruption.
- The presence of local and systemic thrombogenic factors that may modify the extent and duration of the thrombus generated.

Local vasoconstriction may occur with the plaque disruption. This vasoconstriction process can occur as a result of interaction of a variety of factors including endothelial dysfunction, or the presence of factors generated by platelets or thrombin. The systemic aspects of the inflammatory response may alter the risk of a plaque disruption creating an occlusive thrombus. As the risk of development of ACS relates to characteristics of the plaque, circulating and systemic factors, the concept of the “vulnerable patient”, indicating a patient at risk of ACS, has been proposed.

The clinical manifestations of a plaque disruption will vary with the location of the plaque, the extent of the thrombotic response induced and the subsequent severity and duration of the ischemia created. A plaque disruption may be completely asymptomatic and may be a common factor in subsequent plaque progression and growth.

Disruption of the plaque and subsequent exposure of circulating blood to exposed tissue factor triggers the activation of the coagulation cascade leading to the generation of thrombin and the subsequent conversion of fibrinogen to fibrin.
the exposure of platelets to collagen or von Willebrand factor (VWF) on the subendothelial surface, platelet adhesion occurs involving multiple receptors. Primary platelet adhesion does not require platelet activation. Platelet activation occurs with platelet adhesion to collagen or in the presence of thrombin. A variety of other agents may also initiate platelet activation including thromboxane A2 and ADP. With the activation of platelets, the glycoprotein (GP IIb/IIIa) receptors are activated. This allows the binding of plasma glycoproteins, VWF and fibrinogen, which links the platelet to other platelets. This process is mediated by the GP IIb-IIIa receptor. Platelets have been identified as having multiple other roles in ACS. These may include expression of inflammatory mediators, interacting with leukocytes through induction of an inflammatory response in leukocytes, and in the activation of platelets in response to mediators from leukocytes. The interactions between the coagulation pathway and platelet activation and aggregation processes have a high degree of interdependence.

A variety of types of disruption of atherosclerotic plaque have been described with their clinical consequences. If the disruption and subsequent thrombus is contained within the plaque there may be no immediate clinically apparent results. This may increase the size of the atherosclerotic plaque and contribute to its progression. Another form of disruption of the plaque is described as a “plaque erosion”. Inflammatory mediators may cause apoptosis of endothelial cells and may activate proteases, with the consequence of endothelial cells separating from their underlying matrix. The resulting superficial endothelial erosion may initiate a thrombotic process. If the disruption of the plaque generates a thrombus that impinges on the vessel lumen the clinical consequences of partial or completed occlusion of this vessel may be manifest. The mechanism of plaque rupture and the resultant thrombosis account for the majority of ACS. A much less frequent etiology for thrombosis, the erosion of a calcific nodule within a plaque, has also been reported.

ISCHEMIC PRESENTATIONS

Stable angina is typically characterized as resulting from a fixed atherosclerotic stenosis of a coronary artery with symptoms being manifest when oxygen demand exceeds supply. Significant collateral vascular supply may be present with long-standing disease. ACS is a continuum of disease characterized by an abrupt imbalance in oxygen supply and demand typically resulting from a reduction in blood flow. In unstable angina (UA), a plaque disruption results in a reduction in blood flow. In this setting the thrombus is typically labile, transiently obstructing but not occluding the coronary vessel. Unstable angina may reflect both situations of reduced perfusion and/or increased oxygen demand. In a non-ST segment elevation myocardial infarction (NSTEMI), the plaque disruption results in a more persistent thrombotic coronary occlusion. There may be distal embolization of particles from the thrombotic process. The resultant ischemia may be limited by spontaneous thrombolysis, resolution of vasoconstriction, or by the presence of collateral circulation. A plaque disruption resulting in a fixed thrombus and complete occlusion of the coronary vessel creates transmural necrosis to the myocardium and the clinical presentation of NSTEMI.

ASSESSMENT OF CLINICAL RISK

The extent of obstruction of the vascular lumen from the atheromatous plaque is not the sole factor relating to the risk of thrombosis. Falk states “serial angiographic stud-
ies indicate that the more obstructive a plaque is, the more frequently it progresses to coronary occlusion and/or gives rise to myocardial infarction". However, myocardial infarction and ACS more frequently occur with mild to moderate stenotic lesions. Shah writes “retrospective analysis of serial angiograms, as well as prospective serial angiographic observations, have suggested that in nearly two-thirds of all patients presenting with acute ischemic syndromes, a coronary angiogram performed weeks or months before the acute event had shown the culprit lesion site to have <70% (often <50%) diameter narrowing”. The relatively greater frequency of mild coronary lesions when compared to much more stenotic lesions may account for their more commonly being the culprit in acute coronary syndromes.

A major clinical challenge is the identification of the mild coronary atherosclerotic plaque that is at risk of creating acute coronary syndrome with rupture. Coronary angiography has been clearly demonstrated to be useful to assess the severity of coronary artery disease and accordingly to predict the risk of morbidity and mortality related to occlusive coronary events. However, angiography cannot accurately predict the exact future sites of coronary occlusion, with the exception of an ulcerated plaque in angiography in the setting of an ACS. Theroux states, “the process of atherogenesis, lipid accumulation, cell proliferation and extracellular matrix synthesis is neither linear nor predictable.” This significant variation and rate of progress of atherosclerotic lesions adds further to the difficulty in identification of the patient at risk for an ACS.

Significant research effort has been directed at biomarkers of inflammation. C-reactive protein (CRP) is an acute phase reactant. Base line levels of CRP have been demonstrated to correlate with prospective cardiovascular risk. CRP may have a future role in the risk stratification of patients presenting with ACS. A number of other inflammatory bio-markers have been evaluated and demonstrated when present in increased basal levels, to be associated with increased vascular risk including cytokines, (IL-6 and tumor necrosis factor-alpha), cellular adhesion molecules (soluble ICAM-1 and P-selectin) and other acute phase markers, (fibrinogen and serum amyloid A).

The relationship between infectious diseases and atherosclerotic coronary artery disease has been the focus of considerable attention, however a causal relationship has yet to be proven. Libby has stated “prospective and well controlled seroepidemiological studies have failed to support a consistent link between infections and coronary events.”

As the complex pathophysiology of atherosclerosis and ACS has become more clearly defined, the key roles of inflammation and thrombosis and their complex interactions have become increasingly apparent. Knowledge of the pathophysiologic mechanisms of ACS is important for practicing emergency physicians in their assessment of patients with, or at risk for, ACS and for rational therapeutic decision-making. The development of future clinical assessment and therapeutic modalities for patients with ACS will be driven by this ongoing improvement of our understanding of these complex pathophysiological processes.
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UPDATES IN THE DIAGNOSIS OF ACS IN THE ED:
Symptoms, Markers, and ECGs
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Objectives:
1. Describe the difficulty in interpreting symptoms of acute coronary syndrome.
2. Review the literature for continuous ST-segment monitoring in the emergency department.
3. Describe the impact of utilizing the 99% cut-off for cardiac markers on clinical practice.

INTRODUCTION

The diagnosis of acute coronary syndrome (ACS), such as acute myocardial infarction (AMI) and unstable angina (UA), is extremely challenging for the emergency physician. The evaluation of patients who present with chest discomfort suggestive of ACS requires careful examination of patients’ symptoms and clinical presentation. Additionally, advances in treatment for ACS have led to increased pressure for rapid diagnosis in the emergency department (ED).

Accurate risk stratification of patients who present with chest pain to the ED is essential. Significant short-term mortality exists in all ACS groups. Advances in pharmaceutical treatments exist for risk stratifying patients to a high-risk group. A recent multicenter study demonstrated that approximately 2% of patients with myocardial infarction and 2% of patients with unstable angina are inadvertently discharged from the ED.¹

Synthesizing data from clinical tools such as the initial history, physical examination, electrocardiogram, and cardiac biomarkers enables clinicians to determine the risk that the patient’s symptoms are indicative of ACS. This process is a dynamic process as additional information is obtained for patients in the ED.

PRESENTATION

The patient’s history and physical examination are key components of the risk stratification process. From the patient interview and examination, the emergency physician develops a differential diagnosis and a treatment path. Inaccurate assessment of the etiology of the chest pain results in over/under utilization of resources and missed diagnoses. According to Pope et al. 2.0% of patients with myocardial infarction and 2.3% of patients with UA are sent home.¹ A patient’s description of chest pain can help assign the probability of disease, however no single symptom or sign is extremely sensitive for ACS. It has been shown that the duration and tempo of the anginal symptoms can be predictive of significant cardiac disease. In addition, high-risk clinical features have been reported in multi-center trials. These factors have been determined to be the nature of the anginal symptoms, prior history of CAD, sex, age, and the number of traditional risk factors present.²,³

The American Heart Association/American College of Cardiology have presented characteristics that are identified in the history and physical examination that are used to determine increased risks of adverse events in patients with unstable angina/Non-ST segment elevation MI.⁴ These factors include: an accelerated pattern of angina, ongoing rest pain >20 minutes, signs of CHF, hemodynamic instability, arrhythmias, and advanced age. Although these factors are important in determining risk in patients who are suspected to have unstable angina, they do not address the difficult clinical ques-
tion of does this patient have ACS when presenting to the ED.

Over the last year multiple articles have been published on the presentation of patients with ACS. Although chest pain is the most frequent and dramatic manifestation of symptoms in ACS, the difficult diagnostic dilemma is differentiating atypical symptoms of ACS with non-cardiac chest pain. Using data from the National Registry of Myocardial Infarction (NRMI), it has been reported that 1/3 of the patients with documented myocardial infarction did not have chest pain on initial presentation.

Symptomatology of ACS has been reported to differ among certain subgroups, such as women and diabetics, which has significant practical implication to the evaluation process in the ED. It has also been reported that race, age, and other risk factors may influence a patient’s presentation for ACS. In a study of 1996 patients with the diagnosis of acute myocardial infarction, 87% of the men and 80% of the women presented with chest pain. However women were more likely to present with a non-pain syndrome that included nausea, dyspnea or cough. In addition women were more likely to complain of pain in the arms, neck, back, or jaw. In this cohort of patients, the elderly and diabetics were less likely to complain of any pain and more likely to complain of dyspnea, nausea, weakness, and faintness. The results of this trial are similar to the study by Culie et al. who reported patients with acute myocardial infarction who were elderly, female gender, minority status, had a history of congestive heart failure, history of stroke, and diabetics were less likely to have chest pain at presentation.

Until recently, there have been little data regarding identification of subgroups of patients at risk for atypical presentations that are diagnosed with unstable angina. Clinically physicians have extrapolated data from the acute myocardial infarction patients to this group. In a descriptive study of 4,167 Medicare patients discharged with a diagnosis of unstable angina, only 48% had a typical presentation, defined as chest pain described as pressure or chest or arm discomfort worsened with exertion or relieved with rest or nitroglycerin. Patients with atypical features were more likely to be older, female gender, demented, and have no prior history of ACS. Also, 1 in 7 of the patients with atypical features had chest pain described as burning, sharp or pleuritic. In addition, the authors report that patients with atypical features were treated less aggressively, but had no difference in mortality. The lack of difference in mortality may be based on the result that in 66% of patients with typical presentation of UA, the physician documented a definite diagnosis of ACS compared to 56% with atypical symptoms.

To the treating emergency physician, studies such as those reported above serve as a reminder of the difficulty of evaluating the chest pain patient. Although these studies further support the concept that not all patients with ACS have chest pain that is typical in description, the studies confirm that the majority of patients present with some sort of chest pain or symptoms known to be suggestive of ACS such as dyspnea. Despite the high rate of atypical presentation in patients with unstable angina, a diagnosis based on history and physical examination is predictive of significant coronary artery disease.

**ELECTROCARDIOGRAMS**

The electrocardiogram (ECG) is the first objective evidence of myocardial injury available to the emergency physician. It provides immediate information that can dictate treatment and need for additional risk stratification. The initial 12-lead ECG obtained in the ED in patients with suspected ACS is diagnostic of acute injury in only 24% to 60% of patients with the final diagnosis of AMI.
reported that 15% of patients with AMI and 25% of patients with unstable angina had nondiagnostic ECGs. Recent guidelines for the management of UA and non-ST segment elevation myocardial infarction (NSTEMI) recommend that an ECG be obtained within 10 minutes of arrival to the ED in patients with ongoing chest pain and as soon as possible in all other patients. Early ECG acquisition is often a key component of the triage protocol for the chest pain patient. Initial ECG findings that have prognostic and diagnostic significance include ST-segment elevation, that may be prolonged or transient ST-segment depression, left bundle branch block, and T wave inversions. A recent study of undifferentiated chest pain patients reported that the findings of ST-segment elevation, ST-segment depression, pathologic Q waves, and T wave inversion on the presentation electrocardiogram were associated with increased odds of percutaneous coronary intervention, MI, or coronary artery bypass grafting. In addition, these findings on the initial electrocardiogram can also predict positive cardiac markers. The degree of ST-segment deviation is also predictive of poor prognosis. A recent study reported that the rate of death or myocardial infarction at 1 year was doubled among patients with major ST-depression, compared to patients with only minor or no ST-segment changes.

Unfortunately the ECG is not sensitive for the diagnosis of myocardial injury. The traditional findings of ST-segment instability are characteristic of myocardial ischemia. Approximately 50% of patients with chest pain and cardiac ischemia have a nondiagnostic ECG at ED presentation. Of these patients, 20% will have electrocardiographic evidence of a transmural infarction at the time of hospital discharge. The limitation of the sensitivity of the initial ECG is based on difficulty in diagnosing left circumflex and posterior lesions and the reliance of a single electrocardiogram that may have been obtained during a window of ST-segment normalcy. Serial ST-segment trend monitoring has the potential to aid in the diagnosis and disposition of patients who present to the ED with chest pain and initially nondiagnostic 12-lead ECG. Continuous monitoring allows early detection of subtle ECG changes that otherwise would have been missed. In addition, ST-segment ischemic changes identified by continuous monitoring have been shown to be an independent predictor of cardiac related death or myocardial infarction in patients with UA and nondiagnostic ECGs. The benefit of continuous monitoring appears to be in the patients with high risk for acute coronary syndrome. Decker et al. evaluated the use of this technique in an intermediate risk chest pain observation unit (OU) patient population and they reported that the addition of the continuous ST-segment monitoring increased the sensitivity of their traditional OU protocol from 58% to 65% while decreasing the specificity from 63% to 58%. He concluded that the use of ST-segment monitoring is of limited value in the diagnostic evaluation of the intermediate risk chest pain patients enrolled in a chest pain OU protocol. These results support the findings of early studies.

To improve the diagnostic accuracy of the ECG posterior and right-sided lead ECGs can be performed. The addition of a posterior V9 lead has been reported to improve the sensitivity of the ECG from 56% to 78% for the diagnosis of a posterior wall MI. A study by Zalenski et al reported that the sensitivity of a 15 lead ECG that incorporated VR4, V8, and V9 improved the sensitivity of detecting ST-segment elevation AMI from 48% to 59%. New technology that utilizes a body surface mapping ECG has been shown to have better sensitivity with no decline in specificity compared to the traditional 12-lead ECG. New technologies are being
investigated that improve current ECG computer interpretation and incorporate phonography into current ECG output.

The initial ECG provides valuable and diagnostic information. Emergency departments should incorporate a triage strategy that includes early ECG acquisition. Although the initial ECG provides the earliest objective evidence of myocardial injury in the chest pain patient, it only is one piece of the risk stratification process.

**CARDIAC MARKERS**

The use of cardiac serum markers for the evaluation of patients in the ED and chest pain centers has been well documented. The American Heart Association (AHA) / American College of Cardiology (ACC) guidelines recommend the use of an early rising cardiac marker such as myoglobin coupled with a more cardiac specific marker such as troponin. Repeat testing is recommended 9-12 hours after presentation. Over the last few years the myocardial contractile proteins troponin T (TnT) and troponin I (TnI) have gained acceptance as the new gold standard for the diagnosis of MI. These markers, along with creatine kinase and the MB isoenzyme, can be utilized to guide treatment algorithms and predict risk of adverse cardiac events in addition to their diagnostic ability. Current research now focuses on the identification markers of ischemia and plaque instability to identify patients earlier in the ACS pathway. These novel markers of ischemia, in addition to the redefinition of MI by the European Society of Cardiology (ESC) and ACC, account for significant opportunities to enhance the clinical practice of emergency physicians.

In September of 2000 a new definition of MI was proposed based particularly on the rising and falling levels of the cardio-specific biomarkers TnT and TnI in the appropriate clinical setting. In addition, the ESC and ACC recommended that the “normal” range for each assay be defined as the 99th percentile of the reference population, and this value be the cutoff value for the diagnosis of myocardial injury. This criterion was chosen to decrease the frequency of false-positive cardiac troponin elevations. The societies also recommended that the cutoff value be measurable with analytic imprecision (coefficient of variation) <10%. If this approach is adapted, the effect on the diagnosis of myocardial infarction is dependent on the assay used. At present, few assays are capable of meeting a standard that included the 99th percentile value and a level of 10% precision at the cutoff value. This approach will raise the cutoff value for the diagnosis of myocardial injury for assays with poor analytic performance, but decreases the value for those with good analytic precision compared with the use of the receiver operator curve (ROC)-determined cutoff value. Unfortunately this change will generate increased confusion and frustration to the practicing emergency physicians. The values between the >10% coefficient of variance and the value developed by the ROC analysis are a zone of cardiac injury where the etiology of the elevation is based on clinician impression. Myocardial injury associated with congestive heart failure, sepsis, or cardiac ischemia can occur in this range. Since these values are considered “positive” the disposition of this patient is challenging. Patients with presentations indicative of ischemia, biomarker elevation in this range are predictive of adverse cardiac events.

Another challenge to this new definition of MI is the interpretation of troponin values in patients with renal insufficiency. The prevalence of coronary artery disease in patients with chronic renal failure may be as high as 73%. Difficulties in electrocardiographic interpretation secondary to electrolyte disturbances and the high rate of silent ischemia in these patients underscore the importance of serum mark-
ers of myocardial necrosis for the identification of patients with myocardial infarction. Using the most current assays available, TnT is elevated more frequently than TnI in patients with renal failure when the suspicion for ACS is relatively low.27,28

The exact mechanism of this elevation is unknown however it may reflect subclinical myocardial damage that is independent of acute ischemic injury. Freda et al. report that whatever the mechanism involved in troponin elevation, sequential cardiac TnT or TnI elevation is indicative of acute myocardial damage and denotes increased risk of morbidity and mortality in patients with renal insufficiency regardless of the presence of symptoms.28

Over the last year there have been multiple studies evaluating markers of ischemia and plaque instability.24-26 Markers such as D-dimer and P-selectin have been found to be independent predictors of death and MI at 1 year in patients with normal TnI.25 Abnormal albumin cobalt binding has been shown to be indicative of recurrent ischemia and increased risk of progression to MI in patients with UA.26 Whole blood choline has been reported to be predictive of adverse cardiac events at 30 days in patients with normal troponins.24 Brain natriuretic peptide has been shown to be an early marker of myocardial injury and an independent predictor of adverse cardiac events.30 Combining markers of inflammation, ischemia and necrosis may provide clinically useful information about the spectrum of ACS.31 At this time further research needs to be done in the emergency setting to support the use of these markers.

SUMMARY

The evaluation and treatment of patients who present to the ED with chest pain is a difficult and challenging endeavor. The astute clinician utilizes the history and physical examination, ECG, and myocardial necrosis markers to risk stratify patients for the likelihood of ACS and the risk of adverse clinical events. Each tool utilized in risk stratification has its limitations and all results need to be evaluated in clinical context. As we improve our diagnostic ability for myocardial ischemia, the clinical diagnosis based on presentation and ECG needs to be further evaluated as we identify patients earlier in the course of ACS.


Acute coronary syndrome (ACS) has become one of the most common presentations to the emergency department (ED) in this decade. It is estimated that between 5-8 million visits to the ED are for evaluation of chest pain with suspected coronary artery disease. Emergency physicians have therefore become much better versed in the management of non-ST-elevation acute coronary syndrome and the appropriate therapies for this condition. This has been well recognized by the American College of Cardiology (ACC) and the American Heart Association (AHA), who have appointed several emergency physicians to their various committees, including the Acute Cardiac Care Committee of the AHA.

The non-ST-segment elevation infarction patients (NSTEMI) are a heterogeneous group, frequently elderly patients who tend to rule in with positive troponin levels. It is now well recognized that this group of patients with troponin elevations have a substantial 30-day as well as 1-year and 3-year increase in mortality compared to traditional patients with unstable angina. Furthermore, angioscopic investigation has documented that up to 75% of patients with unstable angina or NSTEMI have evidence of active thrombus in the coronary artery. Thus, the environment is rich with platelet activation where newer therapies, such as clopidogrel and IV glycoprotein IIb/IIIa receptor blockers, form an important part of the therapeutic armamentarium.

There is a well known cycle (Figure 1) of development of therapeutic agents that subsequently undergo clinical investigation and later become incorporated into the guidelines and clinical practice. However, physicians and administrators in general have paid little attention to the implementation of guidelines or improving the adherence to the guidelines. Recently, Jencks and colleagues have shown that adherence to simple measures of appropriateness of care, such as whether patients receive aspirin or beta blockers in the acute phase of ACS or whether they receive lipid-lowering therapy or referral
to cardiac rehabilitation on discharge, have found broad variation in these parameters throughout the United States. The CRUSADE Initiative was undertaken to further highlight the importance of NSTEMI ACS, and with the collaboration between emergency medicine and cardiology along with a broad array of pharmaceutical companies, to improve the adherence to the ACC/AHA guidelines. The CRUSADE Registry has now enrolled over 70,000 patients from 400 hospitals in 48 states around the country. Quality improvement initiatives are also undertaken at each hospital to further enlighten physicians and to facilitate systems to allow more patients to appropriately receive both acute and discharge therapies as well as diagnostic procedures such as cardiac catheterization. The CRUSADE CQI Initiative’s goal is to improve the adherence to the ACC/AHA guidelines for acute as well as discharge therapies (Table 1).

One of the more potent anti-platelet agents developed, intravenous glycoprotein IIb/IIIa receptor blockers, have impressive clinical trials data to support their use and guidelines recommendations. In a meta-analysis carried out by Boersma and colleagues, it has been shown that there is a significant reduction in death and non-fatal myocardial infarction when all the large-scale clinical trials are included (Figure 2).

### Table 1. Goal for CRUSADE CQI: Improve Adherence to ACC/AHA Guidelines

<table>
<thead>
<tr>
<th>Acute Therapies</th>
<th>Discharge Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aspirin</td>
<td>• Aspirin</td>
</tr>
<tr>
<td>• Clopidogrel</td>
<td>• Clopidogrel</td>
</tr>
<tr>
<td>• Beta blocker</td>
<td>• Beta Blocker</td>
</tr>
<tr>
<td>• Heparin (UFH or LMWH)</td>
<td>• ACE Inhibitor</td>
</tr>
<tr>
<td>• GP IIb/IIIa inhibitor - Early cath &lt;48h</td>
<td>• Statin/Lipid Lowering</td>
</tr>
<tr>
<td></td>
<td>• Smoking Cessation</td>
</tr>
<tr>
<td></td>
<td>• Cardiac Rehabilitation</td>
</tr>
</tbody>
</table>

### Figure 2. GP IIb/IIIa Inhibition for Non-ST-Elevation ACS. 30-Day Death or Nonfatal MI (Boersma. Lancet 2002).
This is also the case when accounting for the large GUSTO-IV ACS trial, which showed a trend to a worse clinical outcome. However, this trial was somewhat different from the other trials and enrolled a different patient population compared with the other NSTEMI trials. It has also been clearly documented that the troponin-positive patients have an improved 30-day mortality when all the trials have been combined (Figure 3). It has also been clearly documented that the troponin-positive patients have an improved 30-day mortality when all the trials have been combined (Figure 3). In general, there has been approximately 40% reduction in mortality when early use of IV glycoprotein IIb/IIIa receptor blockers have been administered.

There are three clinical trials (CAPTURE, PURSUIT, and PRISM-PLUS) that have examined the early administration of IV glycoprotein IIb/IIIa receptor blocker prior to cardiac catheterization. Consistently, there has been approximately 30% reduction in death and MI prior to any cardiac catheterization and an impressive 60% reduction in events when the same patients have gone on to angioplasty (Figure 4).

---

**FIGURE 3. Meta-analysis of GP IIb/IIIa and Troponin Status**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Troponin T Negative</th>
<th>Troponin T Positive</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAGON-B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRISM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPTURE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 4. GP IIb/IIIa blockade Before and After PCI: CAPTURE, PURSUIT, PRISM-PLUS.**

- Placebo
- GP IIb/IIIa inhibitors

Boersma, Circulation, 1999
This latter finding is consistent with the many randomized trials of IV glycoprotein IIb/IIIa receptor blocker during PCI where there is almost a 40% reduction in death and MI at 30 days, which is a consistent finding in all the trials (Figure 5). Recently, the ISAR-COOL study explored the role for abciximab at the time of PCI in low-risk patients after clopidogrel loading had been performed. They randomized 2059 patients who were troponin-negative, with no prior MI or diabetes mellitus, to all receive 600 mg loading clopidogrel more than 2 hours before the angioplasty and then randomized to placebo vs. abciximab at the time of PCI. Not surprisingly, there was no significant benefit observed with the addition of abciximab in this setting, presumably because this low-risk cohort (troponin-negative) was studied. However, the study raises the issue of how the low-risk patient population should be approached.

All of these trials that have been discussed have now been incorporated into the 2002 update of the ACC/AHA guidelines (Figure 6).7

Recommendations state that any glycoprotein IIb/IIIa receptor blocker should be added to aspirin and heparin for all NSTEMI patients who are to undergo car-

![FIGURE 5. GP IIb/IIIa Antagonist in PCI](image)

![FIGURE 6. 2002 ACC/AHA guidelines](image)

**2002 ACC/AHA guidelines**

**GP IIb/IIIa Inhibitors**

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Placebo</th>
<th>IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC</td>
<td>2,099</td>
<td>9.6%</td>
<td>6.6%</td>
</tr>
<tr>
<td>IMPACT - II</td>
<td>4,010</td>
<td>8.5%</td>
<td>7.0%</td>
</tr>
<tr>
<td>EPILOG</td>
<td>2,792</td>
<td>9.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1,285</td>
<td>9.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>RESTORE</td>
<td>2,141</td>
<td>6.3%</td>
<td>5.1%</td>
</tr>
<tr>
<td>EPISTENT</td>
<td>2,399</td>
<td>10.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td>ESPIRIT</td>
<td>2,064</td>
<td>10.2%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Pooled</td>
<td>16,770</td>
<td>8.8%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

0.62 [0.55, 0.71] \( p < 0.000000001 \)

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*High-risk: Age > 75; prolonged, ongoing CP; hemodynamic instability; rest CP w/ST; VT; positive cardiac markers

*The GP IIb/IIIa antagonist may also be administered just prior to PCI*
diac catheterization and/or PCI is planned (Recommendation IA). Furthermore, eptifibatide or tirofiban plus aspirin and heparin can be added to high-risk patients in whom early cath and PCI is not planned (Recommendation IIA). Finally, any intravenous glycoprotein IIb/IIIa receptor blocker should be added to aspirin and heparin plus clopidogrel if cath and PCI is planned. (Recommendation IIaB) These recommendations further strengthen the importance of the use of early administration of the intravenous glycoprotein IIb/IIIa receptor blockers in ACS.

The CRUSADE Registry is an academic collaborative project between Duke University Medical Center, the University of North Carolina at Chapel Hill, and the University of Cincinnati. This project is also establishing an excellent working relationship between emergency medicine and cardiology to improve adherence to the ACC/AHA guidelines as shown above. A very striking finding from CRUSADE is the dramatic higher in-hospital mortality in the registry compared to recent trials of ACS (Figure 7). Thus, the CRUSADE population represents more of what physicians see in practice and highlights the importance of collecting data in a registry format outside clinical trials to better understand the outcomes among NSTEMI patients.

Recently, Peterson and colleagues have documented an inverse relationship between hospitals that adhered to guidelines and in-hospital mortality (Figure 8). They found that the top quartile hospitals that had the highest adherence score also observed the lowest mortality among their patients. Conversely, hospitals where guidelines were poorly adhered to had the highest mortality (almost 40% higher). These data speak to the importance for hospitals and physicians to be aware of the guidelines and implement them into practice to translate into better outcomes for our patients.

The difference among the leading and the lagging centers are shown in Figure 9 for acute care in the first 24 hours. In general, the leading hospitals provided more aspirin, beta blockers, and anticoagulants for their patients compared to the lagging cen-
There has also been evidence of a difference in in-hospital mortality by the early use of glycoprotein IIb/IIIa receptor blockers within the first 24 hours. Data from CRUSADE suggests a 42% difference in mortality. However, when these mortality rates are adjusted for the difference in baseline characteristics, there is a strong trend in favor of mortality reduction as shown in Figure 10 and also recently shown in NRMI.15 Most importantly, however, is that this

There has also been evidence of a difference in in-hospital mortality by the early use of glycoprotein IIb/IIIa receptor blockers within the first 24 hours. Data from CRUSADE suggests a 42% difference in mortality. However, when these mortality rates are adjusted for the difference in baseline characteristics, there is a strong trend in favor of mortality reduction as shown in Figure 10 and also recently shown in NRMI.15 Most importantly, however, is that this
point estimate is almost identical to that seen in the meta-analysis of randomized trials as previously described in another adjusted analysis by Peterson and colleagues (Figure 11). This point estimate shows an approximate 10-20% reduction in mortality. This point estimate was also identified by Greenbaum and colleagues showing that patients who received glycoprotein IIb/IIIa receptor blockers prior to PCI had a trend towards better outcome.16

It is recommended that patients with NSTEMI who have no contraindication to cardiac catheterization should receive this therapy within the first 48 hours after hospitalization. In general, this has led physicians to withhold glycoprotein IIb/IIIa receptor blocker therapy and clopidogrel to the time when angiography is performed. The adherence to glycoprotein IIb/IIIa receptor blockers and clopidogrel post-PCI remains high, 84-88% of all patients being treated. How-
Leading and Lagging Hospitals Quartiles in CRUSADE: Discharge Care

![Graph showing leading and lagging hospitals in discharge care.]

However, less than 50% of patients undergo early cardiac catheterization in the first 48 hours, suggesting that the early use of glycoprotein IIb/IIIa receptor blocker therapy could benefit these patients, as they generally wait longer for this diagnostic procedure in U.S. practice.

The CRUSADE Registry is also focusing on discharge care. Similar to what is observed in the acute phase, leading centers are able to better discharge the patient on aspirin, beta blockers, ACE inhibitors, and lipid-lowering agents post-STEMI compared with the lagging centers (Figure 12). However, the most striking difference is the lack of use of clopidogrel among the patients being discharged post-STEMI. As already pointed out, a high proportion of patients receive these agents periprocedurally, but as only a minority of patients undergo PCI, there is a lack of discharge use of clopidogrel in the NSTEMI ACS patient.

It is important to recognize that the majority of events that occur 1-year post-STEMI actually occur more than 30 days after the initial hospitalization for NSTEMI. Thus, there is a large opportunity to improve outcomes for patients with STEMI if proactive use of clopidogrel was performed at the time of discharge. There are now several randomized clinical trials that have shown the benefit of clopidogrel in the NSTEMI population for the reduction of death, myocardial infarction, stroke, and recurrent ischemia. The largest trial to date was the CURE trial, which showed when patients were followed up to 1-year, there was a significant reduction in death, MI, and stroke among patients receiving clopidogrel compared with placebo.\textsuperscript{17,18}

There have now been two trials in the PCI population that have shown a 31 and 27% reduction in 1-year event, death and MI and stroke, in favor of patients receiving clopidogrel in this setting. Thus, systems need to be developed to ensure that the patients receive these therapies post-MI as well as post-PCI.

The CRUSADE project has identified several gaps in healthcare delivery for NSTEMI patients. This collaborative effort between emergency medicine, cardiology, academia, and the pharmaceutical industry promises to provide...
great help for healthcare systems to examine their own care and thereby improve the adherence to the ACC/AHA guidelines. As such, if this can be accomplished, CRUSADE will impart and improve outcomes for all patients in the United States with NSTEMI. This is a lofty goal but well within our reach.

REFERENCES:


INTRODUCTION

Patients presenting to the emergency department (ED) with chest pain and Non-ST-segment elevation acute coronary syndromes (NSTEACS) are at significant risk for short-term and long-term morbidity and mortality. Randomized clinical trials involving these patients have demonstrated 30-day combined incidences of death, myocardial infarction (MI), and urgent revascularization of over 15% in these patients.1-6 NSTEACS patients are relatively heterogeneous in their clinical symptoms, risk factors, ECG and serum cardiac biomarker results at presentation, and are therefore heterogeneous in their risk of adverse outcomes. Of patients who present with chest pain and presumed NSTEACS, those with ST depression and or a positive troponin assay are at highest risk for in-hospital death and myocardial infarction.7-10 Current ACC/AHA guidelines recommend early aggressive medical therapy followed by definition of coronary anatomy within 48 hours and subsequent revascularization in this group of patients.11-12 Upon patient identification in the ED, medical therapies including platelet and thrombin inhibitors should be initiated and continued through angiography. Following initial angiography, a minority of patients with left main and triple vessel disease will be referred for CABG; the vast majority will undergo percutaneous inter-
ST-segment 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\textsuperscript{1-2,4} 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\textsuperscript{1,2,13} (Figure 1).

Consequently, ACC/AHA guidelines advocate the early use 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\textsuperscript{14}.

**REGISTRY DATA AND RANDOMIZED CLINICAL TRIALS**

Evidence gathered from randomized clinical trials (RCTs) is only effective if it is implemented and translated into clinical practice. Patients in the general community are older and at higher risk than subjects enrolled in more stringent randomized clinical trials. Bias and consent issues are minimized in registry populations, allowing high risk patient enrollment. The benefit of many recent therapies appears to be highest in those at greatest risk. The higher event rates in the community may therefore give us unique insights into the potential magnitude of benefit for proven effective therapies that cannot be uncovered in a lower risk RCT population. Finally, registry data gives insight into real-world utilization patterns of specific therapies, with resultant real-world morbidity and mortality rates. Registry data can and should be utilized to verify the RCT results, especially in controversial areas like GPIIb/IIIa utilization in NSTE ACS.

The CRUSADE Quality Improvement Initiative is an ongoing voluntary observational and research initiative for hospitalized patients presenting with NSTE ACS. At the time of this publication, The CRUSADE registry population consisted of over 70,000 patients admitted with 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-segment deviation (ST-segment depression or transient (<30 minutes) ST-segment elevation) on the resting EKG, a positive troponin assay based on the local site cutoff, or both.

In a 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.\textsuperscript{15} 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. The association between early GP IIb/IIIa inhibition and mortality was assessed using logistic regression methodology, adjusting for 13
baseline clinical risk factors using a validated NSTE ACS mortality model. Patients receiving early GP IIb/IIIa inhibition 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 the CRUSADE analysis, early GP IIb/IIIa treatment registry was associated with a significant reduction in unadjusted mortality (Figure 2).

After 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 3). In the high-risk troponin positive patients, early GP IIb/IIIa inhibition was associated with a statistically significant reduction in risk of in-hospital mortality (OR 0.84, 95% CI, 0.71-0.99).

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 RCTs, Boersma et showed a trend toward decreased mortality with GP IIb/IIIa inhibitor utilization. A similar mortality benefit was reported by Peterson and colleagues using the NRMI-4 registry database. 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.

**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 a GP IIb/IIIa inhibitor in the ED versus later in the catheterization lab. Evidence from randomized clinical trials has supported early use of GP IIb/IIIa inhibitors in the time period prior to PCI, but GP IIb/IIIa inhibitors are still underutilized in this setting as evidenced by the CRUSADE and NRMI-4 registries. Yet there is a growing body of literature supporting early use of GP IIb/IIIa therapy, initiated in the ED.
It is intuitive, given the natural hospital course of NSTE ACS patients admitted from the ED, that if GP IIb/IIIa therapy is not started in the ED, it typically will not be started until the peri-PCI period. This is often greater than 24 hours after hospital admission. If GP IIb/IIIa therapy is started in the ED, it is associated with a higher utilization of oral antiplatelet agents, antithrombins, and early angiography/PCI. Early GP IIb/IIIa utilization is also associated with a shorter length of stay for patients hospitalized with NSTE ACS.15 Although it may not be possible to discern cause and effect from the present analyses, it appears that early GP IIb/IIIa initiation in the ED may “drive” downstream care patterns. At the very least, it appears that patients who are treated with comprehensive and aggressive ACC/AHA guideline-driven care, initiated in the ED, have improved outcomes, and shorter lengths of stay in the hospital.

CONCLUSIONS

Current literature suggests an overall underutilization of GP IIb/IIIa inhibitors in NSTE ACS. Lack of utilization of GP IIb/IIIa inhibitors appears associated with underutilization of vital adjunctive medications both acutely and on discharge as well as a decreased utilization of coronary angiography and overall revascularization. Consistent with both RCTs and registry data, the utilization of GP IIb/IIIa inhibitor therapy appears associated with a clinically significant mortality benefit after adjustment for all measurable variables. The findings also appear to support the ACC/AHA guidelines for utilization of a GP IIb/IIIa inhibitor early or at the time of PCI. Interventions to increase the utilization of these medications with proven clinical benefit in appropriate patients is clearly warranted.
REFERENCES:


INTRODUCTION

In the past 2-3 years, there have been many new advances in the treatment of patients with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI). These include numerous effective medical therapies such as antiplatelet therapies, cholesterol-lowering therapy, beta-blockade and others, as well as clearer definition of appropriate triage for cardiac procedures. The newest addition to the overall treatment is clopidogrel, and it is important to understand the recent clinical data on its role in ACS management.

The evaluation of patients with UA/NSTEMI begins with the clinical history, ECG and cardiac biomarkers to make an assessment of 1) the likelihood of coronary disease, and 2) the patient’s risk of death or recurrent cardiac events. For patients with a clinical history strongly consistent with UA/NSTEMI, antithrombotic therapy with aspirin, clopidogrel, heparin, or low-molecular weight heparin, beta-blockers and nitrates are recommended as initial management for all patients (Figure 1).

For higher-risk patients (ST-segment changes, positive troponin, TIMI Risk Score > 3), a benefit of the above-mentioned medications plus GP IIb/IIIa inhibition (thus, four antithrombotic agents) are recommended and an early invasive strategy is preferred (Figure 1).

OBJECTIVES:
1. To explain the mechanism of action of different antiplatelet agents
2. To explain the clinical benefits of clopidogrel in relation to other treatments for ACS
CLOPIDOGREL MECHANISM OF ACTION

Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation, increases bleeding time, and reduces blood viscosity. It achieves its antiaggregatory action by inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptors, specifically the P2Y12 receptor. (Figure 2) Blockade of this receptor will not only inhibit the ADP-induced platelet activation and subsequent aggregation, but it appears to decrease platelet activation by other outside stimuli (e.g. von Willebrand factor). Thus, because the P2Y12 receptor is part of the overall amplification of platelet activation within the platelet, inhibition of this receptor appears to have a broader effect in decreasing platelet activation than just inhibition of ADP-induced aggregation.

SECONDARY PREVENTION

Clopidogrel was first tested and approved by the Food and Drug Administration for long-term secondary prevention in a broad population of patients with atherosclerosis. In the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial, there was an 8.7% reduction relative to aspirin in the combined endpoint of ischemic stroke, MI, or vascular death during long-term follow-up. Clopidogrel also reduced recurrent MI by 19.2% over a 3 year period compared with aspirin.

STENTING

Clopidogrel or ticlopidine are commonly used for patients undergoing percutaneous coronary intervention (PCI) and stenting. Several trials using the ADP antagonist ticlopidine found that there was a dramatic 70 to 80% reduction in stent thrombosis and recurrent cardiac events post coronary stenting. However, ticlopidine is associated with neutropenia in approximately 1% of patients, and thrombotic thrombocytopenic purpura in a smaller percentage, but this latter event was fatal in 40% of those cases. On the other hand, clopidogrel is not associated with neutropenia and was twice as well tolerated as ticlopidine in the random-
ized Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). For efficacy, there have been two other randomized trials. The randomized trials demonstrate similar 30-day major adverse cardiac events, but when adding in the experience from clinical registries, a recent meta-analysis found a significantly lower rate of major adverse cardiac events with clopidogrel compared with ticlopidine (odds ratio 0.73, p = 0.003). Accordingly, clopidogrel has become the standard agent used for stenting.

**UNSTABLE ANGINA/ NON-ST ELEVATION MI**

Clopidogrel has a rapid onset of action, within 2 hours of oral treatment following a loading dose, and thus is attractive for use in patients with UA/NSTEMI. In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, 12,562 patients were randomized to receive aspirin alone (75-325 mg per day) or aspirin plus clopidogrel (300-mg loading dose, then 75 mg daily) for up to 1 year. The primary endpoint, cardiovascular death, MI or stroke through follow-up was reduced by 20%; 11.4% to 9.3%, p<0.0001. The reduction was seen in all subgroups, including patients with ST-segment depression and those without ST changes, those with positive or negative cardiac bio-markers, or when using the TIMI Risk Score. (Figure 3)

Relevant to early use, the Kaplan-Meier event rates began to show a reduction in events starting just 2 hours after randomization, and there was a significant 34% reduction in cardiovascular death/MI/stroke or severe recurrent ischemia. (Figure 4) This early clinical benefit is consistent with the early onset of action of clopidogrel. In addition, when analyzing the benefit in the first 30 days vs. after 30 days, there was a similar 20% relative risk reduction during both time periods. Thus, clopidogrel afforded both an early benefit and an ongoing benefit out to one year.

**Figure 3.** Benefit of clopidogrel plus aspirin vs. aspirin alone stratified by the TIMI Risk Score. Data from Budaj A, et al. Circulation. 2002;106:1622-1626.
In the 2002 Update of the ACC/AHA Unstable Angina/Non-ST elevation MI (UA/NSTEMI) Guidelines, it is recommended that clopidogrel be added to aspirin for both the acute and long-term management of UA/NSTEMI patients.\textsuperscript{18}

**PRE-TREATMENT - PCI-CURE**

There also appears to be a very important benefit of pre-treatment with clopidogrel, with lower rates of peri-procedural cardiac events. In the randomized PCI-CURE substudy of CURE, a total of 2,658 patients who had presented with unstable angina or non-ST elevation MI within the CURE trial subsequently underwent PCI.\textsuperscript{19} They had been randomly assigned to receive either clopidogrel or placebo. Treatment with clopidogrel prior to PCI was associated with a 30% reduction in the rate of cardiovascular death, MI or urgent target vessel revascularization 30 days post PCI, from 6.4% for placebo to 4.5% for clopidogrel ($p = 0.03$).\textsuperscript{19} The endpoint of cardiovascular death or MI was reduced from 4.4 to 2.9%, a 34% reduction ($p = 0.04$). As had been seen with IIb/IIIa inhibitors,\textsuperscript{20} clopidogrel was associated with a pre-PCI reduction in myocardial infarction from 5.1% down to 3.6% ($p = 0.04$). When looking out to one year follow-up post PCI, the rate of cardiovascular death or MI was reduced from 8% to 6%, a 25% reduction ($p = 0.047$).

The results from CURE have been strongly supported by the Clopidogrel for Recurrent Events During Observation (CREDO) trial. In this study, patients with planned or likely PCI (which included approximately two thirds of patients with ACS) were randomized to receive a loading dose of clopidogrel (300 mg) or placebo between 3 and 24 hours prior to PCI. Following stenting, all patients received open label clopidogrel for 28 days post stent. After 28 days, patients in the pretreatment group continued on clopidogrel for 1 year, whereas the non-pretreatment group was treated with matching placebo.

The efficacy results from CREDO also lend further support to the both early and long-term use of clopidogrel in UA/NSTEMI patients. Pretreatment with clopidogrel led to a non-significant 18.5% risk reduction in events, however, those given clopidogrel at least 6 hours before PCI had a significant 38.6% relat-
tive risk reduction in major events at 28 days (p=0.05) compared with no reduction with treatment less than 6 hours before PCI. This demonstrates the need to initiate clopidogrel as soon as possible on admission for UA/NSTEMI (i.e. in the Emergency Department), especially among patients with planned catheterization and possible PCI.

Overall, in CREDO, long-term treatment to 1 year with clopidogrel plus aspirin led to 26.9% relative reduction in death, MI, or stroke compared to post-PCI clopidogrel therapy for one month (8.5% vs 11.5% [placebo], p=0.02). This included an impressive further 37.4% relative reduction in major events from day 29 to 1 year with clopidogrel (p=0.04). In summary, the results of PCI-CURE and CREDO support pre-procedural loading and long-term therapy with clopidogrel in those scheduled or expected to undergo PCI.

SAFETY

The combination of clopidogrel plus aspirin was associated with a relative 35% increase in major bleeding (using the CURE trial definition), but the absolute increase was only 1%: from 2.7% to 3.7%. However, using the standard TIMI definition there was no significant increase, nor was there an increase in intracranial hemorrhage. In the CREDO study, there was a non-significantly increased higher rate of major bleeding, but interestingly no excess of bleeding among those who received a GP IIb/IIa inhibitor, aspirin, heparin and clopidogrel vs. placebo. Of note, when clopidogrel is used alone, it was associated with a significantly lower rate of gastrointestinal bleeding compared with aspirin.3

For patients who underwent CABG within the CURE trial, those who underwent CABG within 5 days of receiving study drug had a higher rate of major bleeding in the clopidogrel plus aspirin versus aspirin alone (9.6% vs. 6.3%, p=0.06). Those who could wait more than 5 days had no increase in bleeding. Of note, the CURE definition of major bleeding included receipt of 2 units of blood transfusion. Using the TIMI definition of bleeding, which is

related to actual blood loss and calculated from the fall in hemoglobin (and accounting for blood transfusions), there appears to not have been an increase in TIMI major bleeding. Based on available data, it appears that the apparent small increase in bleeding may be mild-moderate, but not major bleeding.

Interestingly, the other way that bleeding may be reduced is by lowering the dose of aspirin. In the CURE trial, patients could receive between 75 and 325 mg. To analyze the data, the investigators divided the dosing by <100 mg, 100 to 199 mg, >200 mg daily. There was a two-fold risk gradient for major bleeding over the one year during the trial. In patients treated with aspirin alone, and received less than 100 mg of aspirin, the major bleeding rate was 1.9%. It ranged up to 3.7% for patients getting 200-325 mg daily. Similarly, among those who received clopidogrel plus aspirin, the overall rates were slightly higher at 3.0% for low-dose aspirin, ranging up to 4.9% for those who received 200-325 mg of aspirin. Thus for long-term treatment, the optimal dose of aspirin appears to be 75-81 mg daily.

CONCLUSION

Thus, in addition to standard therapies, clopidogrel was seen to reduce major cardiac events by 20%. The benefit was similar in all subgroups of patients including low and high risk-patients. Importantly, there was a is 34% reduction in events during the first 24 hours. Early use in the ED will increase TIMI minor bleeding in patients going to early CABG, but this group constitutes only a small percentage of the total population, and it is balanced by a 20% reduction in major cardiac events in these CABG patients. For patients going on to PCI, use at least 6 hours pre-PCI reduces CV events by additional 30%. Thus, clopidogrel is a very effective new addition to our treatment regimen for UA/NSTEMI in the emergency setting.
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Identifying And Treating Heart Failure

Sean Collins, MD — Assistant Professor, Department of Emergency Medicine, University of Cincinnati; Cincinnati, Ohio

Objectives:
1. To explain the role of natriuretic peptides in the ED diagnosis of congestive heart failure.
2. To explain the results of the PROACTION trial and the role of nesiritide in the treatment of congestive heart failure

Congestive heart failure (CHF) is a worldwide problem of epidemic proportions and represents a tremendous burden to overall healthcare costs.

- More than 4.5 million Americans have heart failure and about 550,000 new cases are diagnosed each year.\(^1\)
- The incidence is expected to increase dramatically due to our aging population (9.8% prevalence of heart failure in individuals over age 74),\(^1\) improved survival from acute coronary syndromes, and management advances in cardiovascular diseases.\(^2-4\)
- In 1999 there were 54,913 deaths attributed primarily to heart failure, a mortality rate of 20.1 per 100,000 people. However, this is significantly increased in the elderly—35.8 to 138.1 to 821.9 for those ages 65-74, 75-84, and >85 years.\(^5\)
- In 1997, there were nearly one million CHF hospital discharges, a 150% increase from 1979. Ten million people are expected to have the disease by the year 2007.\(^6\)

This translates into staggering economic expenditures. Hospitalization for heart failure exacerbation accounts for the largest expenditure for care of these patients; it is estimated to be about $23 billion per year. The Centers for Medicare and Medicaid Services identified CHF as the disease most worthy of cost-effective management.\(^7\)

Emergency physicians have become the gatekeepers for this epidemic. One-third of all heart failure patients receive inpatient care each year and nearly 80% of emergency department (ED) presentations for heart failure are admitted.\(^1,8\) Emergency department patients seen, admitted, and treated in an inpatient bed for new onset heart failure or acute decompensation of CHF account for the majority of inpatient expenditures.\(^9\) Emergency physicians have an opportunity to have a significant impact on this epidemic if they can be armed with the proper diagnostic, therapeutic and risk-stratification tools.

Diagnostic Advancements

Until recently, a definitive diagnosis of CHF was often obtained after the patient was admitted to the hospital and had undergone echocardiography, right heart catheterization, or both. Rarely are these tests readily available in the ED, forcing the emergency physician to rely on history and physical examination, along with a few ancillary tests such as chest radiography and electrocardiography. The poor diagnostic accuracy of history and physical examination are well documented.\(^10\)

While an S3 heart sound has a specificity of 99%, its sensitivity of 24% makes it less than ideal as a screening tool in the...
Similarly, chest radiography misses 20% of echo-proven cardiomegaly, and many patients with chronic CHF will have elevated pulmonary capillary wedge pressures despite a lack of congestion on chest x-ray. While the signs and symptoms of CHF should raise the suspicion of CHF, a more objective test is needed to confirm the diagnosis.

**NATRIURETIC PEPTIDES**

The natriuretic peptides are promising markers of myocardial dysfunction and heart failure. It has been known for almost 50 years that the heart is not only a cardiorespiratory organ but an endocrine organ as well. In 1956, electron microscopy was used to demonstrate granules present in the atria that were absent in the ventricle, eventually shown to represent vesicles containing atrial natriuretic peptide (ANP). Henry and Pearce observed an increase in urine flow when a balloon was inflated in the atrium of a dog. Influenced by these initial investigations, subsequent studies have identified three natriuretic peptides: ANP (predominantly secreted from atrial myocardium), brain or b-type natriuretic peptide (BNP, predominantly secreted from ventricular myocardium) and c-type natriuretic peptide (CNP, predominantly secreted from vascular endothelium) (Figure 1).

Of these three peptides, BNP has been found to be the most useful. BNP is released under conditions of increased myocardial stretch and possesses vasodilatory and natriuretic properties. It is released as a prohormone and upon secretion from the myocyte it is cleaved into the biologically active BNP (32 amino acids in length) and the biologically inactive NT-proBNP (76 amino acids). BNP is primarily removed by natriuretic peptide receptors with a small amount of renal clearance, while NT-BNP is primarily cleared by the kidney (Table 1.).

**BNP**

In July of 2002, the Breathing Not Properly Multinational study confirmed findings from pilot studies that BNP was useful as a diagnostic marker in patients presenting to the ED with undifferentiated dyspnea. A BNP value <100 pg/ml virtually excludes CHF as a cause of dyspnea (sensitivity -90%, negative predictive value -89%). A patient with a BNP value over 400 pg/ml is highly likely to have CHF. However, there were a small percentage of patients with a history of CHF but “no acute exacerbation” that did have BNP values over 1000 pg/ml. Intermediate BNP levels (100-400 pg/ml) need

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**FIGURE 1.** Biochemical Structure of Natriuretic Peptides.
to be interpreted in the context of the patient’s clinical evaluation (Figure 2).

There will be a subset of patients where another disease process causes a rise in BNP and is responsible for the current episode of dypsnea. For instance, a young female with pleuritic chest pain may have right ventricular strain from a pulmonary embolus causing a 300-400 pg/ml rise in BNP. Knowledge of a patient’s compensated “dry weight” BNP would be useful during an acute decompensation, similar to baseline peak flows in an asthmatic with an acute asthma exacerbation (Figure 3).

The BNP study also demonstrated that those patients with diastolic dysfunction had significant elevations in BNP compared with those patients without CHF - median BNP 413 pg/ml in diastolic dysfunction and 821 pg/ml in systolic dysfunction.

While BNP has been helpful at levels < 100 pg/ml and > 400 pg/ml, there are some confounders when using the test. The cutoff levels mentioned above for patients with normal creatinine clearance do not apply to patients with renal insufficiency. In a separate analysis of the BNP study it was found that as creatinine clearance worsened the cut point for maximum diagnostic accuracy increased as well (Figure 4). For example, patients with non-cardiac dyspnea and moderately reduced renal function (eGFR 30-59 ml/min/1.73 m2) had a mean BNP level over 200 pg/ml (Figure 5). However, nearly 90% of subjects with a BNP value of > 500 pg/ml had CHF regardless of the severity of renal insufficiency.

Age and gender also appear to have an influence on BNP levels. Redfield and colleagues evaluated 2042 randomly selected residents of Olmstead County, Minnesota and found that in the subgroup of normal patients (n=767) that BNP values were significantly higher in women compared with men (p<0.001) (Table 2), and that BNP values increased with age within each gender. Interestingly, BNP was 21% higher in women taking hormone replacement therapy (HRT) than in women not on HRT.

**BNP SUMMARY**

Brain natriuretic peptide is most useful in excluding CHF as a diagnosis. With a high sensitivity and NPV at 100 pg/ml, it is highly unlikely that subjects with BNP’s < 100 pg/ml have CHF. Above 400 pg/ml, it is highly likely the patient suffers from decompensated CHF. However, a minority of patients will have “baseline” BNP values well above this level. In the area of 100–400 pg/ml, BNP requires clinical correlation because of the effect of age, sex, and other disease processes.

**NT-BNP**

While it has not been validated to the extent of BNP, recent studies of NT-BNP have confirmed earlier findings that NT-BNP is an accurate marker of left ventricular dysfunction. NT-BNP correlated well with each other (r2=0.94) and were predictive of New York Heart

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**TABLE 1. Characteristics of the BNP and NT-proBNP.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>32 AA</td>
<td>76 AA</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 minutes</td>
<td>60-90 minutes</td>
</tr>
<tr>
<td>Stability</td>
<td>Up to 4 hours at room temp</td>
<td>Up to 6 hours at room temp</td>
</tr>
<tr>
<td>Clearance</td>
<td>NPR-C, endopeptidase, kidney</td>
<td>Kidney</td>
</tr>
<tr>
<td>Use with Nesiritide</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Association (NYHA) classification (both markers \( p < 0.0001 \)) and ejection fraction in 92 ambulatory patients (BNP \( p = 0.0003 \) and NT-BNP \( p < 0.0001 \)). NT-BNP proved to be a strong marker of reduced systolic function (EF < 40%) in a cohort of 2193 patients admitted to a general hospital. Those patients with reduced systolic function were detected at a sensitivity of 78%, specificity of 76%, negative predictive value of 96% and positive predictive value of 30%. These findings were similar to earlier studies performed with the BNP assay.\(^6\) One would expect overall lower diagnostic test characteristics when an assay is compared solely to left ventricular ejection fraction (LVEF) because there is a large cohort of patients with diastolic dysfunction that would have elevated NT-BNP values but have “normal” LVEF. This study also found that both serum creatinine and age added significant information when predicting a reduced LVEF.

In 415 ambulatory patients with possible heart failure, NT-BNP increased as EF worsened (Table 3).\(^7\) It was less helpful in patients with diastolic dysfunction, especially those with only mild relaxation abnormalities. Interestingly, while NT-BNP was helpful in those subjects where the examining cardiologist felt there was a “strong” (NT-BNP = 227 pmol/L) or “no” (NT-BNP=66 pmol/L) suspicion of CHF, it was not helpful in the group with “moderate” clinical suspicion of CHF (mean NT-BNP = 85 pmol/L vs 73 pmol/L in normal subjects). This clinical scenario may be similar to the “intermediate” level seen with the BNP assay (100-400 pg/ml) where clinical suspicion combined with BNP levels may be most helpful.

While those with creatinine > 130 \( \mu \text{mol/L} \) had a significantly elevated NT-BNP compared to those with normal creatinine (NT-BNP = 173 pmol/L vs 81 pmol/L, \( p < 0.0001 \)), multiple logistic regression revealed no correlation between creatinine and NT-BNP. Similar to previous studies, after multiple logistic regression, age > 75 years predicted an increased NT-BNP. The age-dependence of the NT-BNP assay was also seen in a study of 243 consecutive healthy subjects with no history of cardiovascular illness or CHF risk factors. The authors suggested the normal NT-BNP cut-off for subjects < 50 years should be 100 pg/ml and the normal cut-off for subjects > 50 years should be 200 pg/ml.
NT-BNP AND BNP SUMMARY

Both BNP and NT-BNP have been validated against LVEF and have been found to have similar test characteristics. While, BNP increases with age and sex, NT-BNP seems to do so at a much greater degree. A number of studies have found age-appropriate cut-offs for NT-BNP, and one of the commercially available assays (Roche™) suggests 2 cutoffs based on age (age < 75 normal cutoff = 125 pg/ml, age > 75 normal cutoff = 450 pg/ml). Both BNP and NT-BNP are elevated in patients with renal insufficiency even though they may have no clinical or echocardiographic evidence of CHF. While BNP’s relationship to creatinine clearance has been well defined (> 90% chance of CHF when BNP > 500 pg/ml), the relationship with NT-BNP is less well delineated. Because only the kidney clears NT-BNP it would be expected that renal disease would have a much greater impact on interpretation of NT-BNP results than BNP results. Finally, while BNP has been confirmed in an ambulatory ED population, using hospital discharge diagnosis of CHF as the gold standard, which captures both systolic and diastolic dysfunction, NT-BNP has not been validated in a similar fashion.

HEART SOUNDS AND THE DIAGNOSIS OF CHF

Significance of S3 and S4 heart sound detection in CHF

While detection of an S3 can be “normal” in adolescents and young adults, its detection after the age of 40 is considered abnormal.28-30 Traditionally not very sensitive for left ventricular dysfunction, when detected, an S3 can be very predic-
tive of elevated left ventricular pressure. In a study of outpatients referred for cardiac catheterization, the detection of an S3 was the most specific finding of left ventricular end diastolic pressure (LVEDP) (95%). 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. Unfortunately, while having a high specificity for elevated filling pressures, an S3 has been reported to have a sensitivity of only 25%. Even 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.

Similarly, the presence of an audible S4 appears to be suggestive of cardiac disease, but there have been conflicting data in previous studies. Spodick and Quarry found the presence of an S4 to be no more common in patients with heart disease than those without. However, the temporal relationship of the S4 to the P wave may be more important than the mere presence of an S4. Those patients with increasing LVEDP have a decrease in the time interval between the onset of atrial contraction (P wave) and the development of an S4 (the P-S4 interval (PS4I)). Unfortunately, identification of an S3 or S4 is difficult in the ED setting and other clinical environments. In the aforementioned studies, which suggest a low incidence of S3 detection in heart failure, perhaps abnormal heart sounds may have been present but physicians were unable to detect them. Recent studies indicate that physicians are becoming less proficient at performing the physical examination, and physicians in residency programs have been shown to have poor cardiac auscultatory skills. 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 (recumbent) because of their dyspnea.

**PHONOCARDIOGRAPHY**

While detection of an S3 or S4 may be useful as a diagnostic and prognostic tool in ED patients with dyspnea, the traditional method of auscultation is less than ideal. However, technology has been developed to aid the clinician at bedside diagnosis of an S3/S4. The Audicor™ phonocardiogram (Inovise Medical, Inc) uses a dual sensor in conjunction with standard ECG electrodes. The dual sensor simultaneously acquires electrical and acoustical data from the V3 and V4 position on the standard 12-lead ECG. This allows simultaneous recording of both the 12-lead ECG and the acoustical information. The phonocardiogram attaches to the standard ECG machine. The sensors on

<table>
<thead>
<tr>
<th>Gender</th>
<th>BNP</th>
<th>Age 45-54</th>
<th>Age 55-64</th>
<th>Age 65-74</th>
<th>Age 75-83</th>
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<td>Women</td>
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<td></td>
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<td>10-93</td>
<td>13-120</td>
<td>16-155</td>
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<td>Shionogi</td>
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<td>9-192</td>
<td>11-233</td>
<td>13-284</td>
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<tr>
<td>Men</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Biosite</td>
<td>4-40</td>
<td>5-52</td>
<td>7-67</td>
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<tr>
<td>Shionogi</td>
<td>6-120</td>
<td>7-146</td>
<td>8-177</td>
<td>10-216</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2.** Age and Gender-Specific Ranges for Plasma BNP (pg/ml).
leads V3 and V4 are only slightly larger than standard ECG leads. Diagnostic algorithms then analyze both types of data and report on the presence of an S3, S4 and left ventricular hypertrophy (LVH). While limited, the initial data on the use of this technology appear promising. Using a gold standard of expert over-read of printed acoustical heart sounds, the Audicor™ had a sensitivity of 71% and a specificity of 94% for detection of an S3 in a study of 314 patients.\(^4\) This technology has not been validated in a cohort of dyspneic ED patients.

### THERAPEUTIC ADVANCEMENTS

While there have been numerous large scale trials over the last decade demonstrating the efficacy of beta-blockers and ACE inhibitors for the outpatient treatment of CHF, therapeutic trials involving ED patients with decompensated CHF have been lacking.\(^{45-48}\) In 2001 the FDA approved nesiritide (recombinant b-type natriuretic peptide) for use in acute decompensated heart failure. Nesiritide is a sterile, purified preparation of human B-type natriuretic peptide, manufactured from E. coli using recombinant DNA technology.\(^{49}\) Nesiritide leads to vasodilatation by binding to the guanylate cyclase receptor of vascular smooth muscle and endothelial cells. There have been 3 large inpatient trials establishing the efficacy and safety of nesiritide. The first study evaluated the effect of nesiritide on both pulmonary capillary wedge pressure (PCWP) and symptomatic improvement when compared with placebo and standard therapy in hospitalized patients with decompensated CHF.\(^{50}\) This study established nesiritide’s ability to improve hemodynamic parameters to a greater degree than placebo (efficacy trial). It also demonstrated the ability of nesiritide to improve most clinical parameters of decompensated heart failure (comparative trial) to the same degree as standard care agents. Nesiritide was then compared to nitroglycerin in hospitalized patients with

<table>
<thead>
<tr>
<th>Echocardiographic finding</th>
<th>N</th>
<th>Mean (SD) N-terminal proBNP, pmol/L</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>Normal SFN and DFN</td>
<td>214</td>
<td>73 (56)</td>
<td>26</td>
<td>56</td>
<td>16</td>
<td>2</td>
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<td>Systolic dysfunction</td>
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<td></td>
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<tr>
<td>EF 40-49%</td>
<td>55</td>
<td>89 (75)</td>
<td>18</td>
<td>55</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>EF 30-39%</td>
<td>45</td>
<td>152 (110)</td>
<td>9</td>
<td>33</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>EF &lt;30%</td>
<td>9</td>
<td>428 (352)</td>
<td>0</td>
<td>11</td>
<td>44</td>
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<tr>
<td>Isolated diastolic dysfunction</td>
<td>92</td>
<td>58 (39)</td>
<td>42</td>
<td>45</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Relaxation abnormalities</td>
<td>79</td>
<td>51 (31)</td>
<td>47</td>
<td>44</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Psuedonormal pattern</td>
<td>13</td>
<td>95 (58)</td>
<td>15</td>
<td>47</td>
<td>39</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 3.** Plasma N-terminal proBNP concentration in relation to cardiac function by Doppler echocardiography, and fractions of patients with different echocardiographic findings in the different quartiles of N-terminal proBNP concentration.
decompensated CHF.\textsuperscript{52} It was shown that nesiritide and nitroglycerin had similar effects on hemodynamic and clinical variables in these subjects. This study was criticized for the relatively small doses of nitroglycerin used (27-56 mcg/min), though both groups had similar changes in blood pressure. PRECEDENT was an open-label study that compared ventricular arrhythmias as well as clinical signs and symptoms in 255 patients with decompensated CHF receiving low-dose dobutamine (> 5 mcg/kg/min) or one of two nesiritide doses (0.015 or 0.030 mcg/kg/min infusion with no preceding bolus).\textsuperscript{53} Dobutamine significantly increased all endpoints of ventricular ectopy when compared to baseline Holter monitoring, while nesiritide produced less ventricular ectopy and no reflex tachycardia. The clinical significance of these outcomes is not clear. The authors argue that all premature ventricular beats are important because they not only increase the likelihood of ventricular failure and sudden death but also reduce stroke volume and worsen CHF. Though not powered for mortality, there were no differences in mortality at 14 days among the 3 treatment groups.

The PROACTION trial evaluated the efficacy of nesiritide use in ED patients with decompensated CHF.\textsuperscript{53} The results of this study were presented in abstract form at the American College of Cardiology conference in 2003. PROACTION was a multicenter, randomized, double blinded, pilot study of 250 patients that were felt to need prolonged treatment of decompensated heart failure evidenced by dyspnea at rest or walking less than 20 feet. Patients received nesiritide or placebo and standard therapy that included diuretics, O\textsubscript{2}, morphine and non-parenteral nitrates for at least 12 hours in an observation unit (OU). ACE inhibitors were withheld for 3 hours. Other vasodilators and inotropes were withheld for 3 hours and discouraged for the first 12 hours. Patients were either admitted or discharged after a maximum of 24 hours in the ED but could be continued on study drug. The overall admission rate was 55% for placebo and 49% for nesiritide, while the admission rate for CHF was 38% for placebo and 30% for nesiritide. In the patients admitted to the hospital, there was a 57% (23% placebo and 10% nesiritide) decrease in hospital readmissions in the nesiritide group, and those that were hospitalized spent 45% less time (8.3 vs 4.6 days) in the hospital when compared to placebo. Though there were more deaths in the nesiritide group compared with placebo (5 vs 1) the study was not powered to evaluate mortality. Of the 6 deaths, possibly 3 in the nesiritide (1 CHF, 1 unexplained, 1 apnea) and 1 in the placebo (sudden death) group may have been related to CHF. There was no comment made on the readmission rate in the patients discharged directly from the OU.

Results of PROACTION indicate that nesiritide is likely a safe alternative to nitroglycerin in decompensated CHF, may decrease admission rates from an OU as well as decrease overall hospital length of stay in a 30-day time period. Future clinical studies need to identify the subgroups of ED patients where nesiritide may be cost-effective as first-line therapy such as renal insufficiency, systolic dysfunction, etc. Until then, the expense of nesiritide at a cost of approximately $500 for a 24-hour infusion compared with about $30 for nitroglycerin prohibits it from being first-line therapy in the majority of ED patients with CHF.
SUMMARY

Heart failure is a disease of epidemic proportions whose prevalence will continue to increase over the next decade. As the majority of CHF admissions come from the ED, the emergency physician is ideally positioned to have an immediate impact on admission rates and healthcare expenditures. In the last couple of years we have seen the validation of natriuretic peptides as markers of CHF, as well as the development of a synthetic natriuretic peptide (nesiritide) that may prove to be a promising first-line treatment modality in certain subgroups of ED patients with decompensated CHF. With the continued development of new diagnostic and therapeutic strategies, not only will emergency physicians be able to improve their diagnostic certainty, they will also become better able to implement cost-effective therapy.

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Primary Results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT):
A Multi-center Trial Examining BNP Levels, Emergency Physician Decision Making and Outcomes in Patients presenting
with Shortness of Breath

Alan Maisel MD, Judd Hollander MD, David Guss MD, Peter McCullough MD, Richard Nowak MD, Gary Green
MD, Mitchell Saltzberg MD, Radmilia Kazanegra MD, Paul Clopton MS., Robert Jesse MD for the REDHOT
investigators.

BACKGROUND:

The vast majority of patients seen in the Emergency Department (ED) with congestive heart failure (CHF) are admitted
to the hospital, leading to exorbitant costs and resource utilization. There are few
tools that aid physicians in decision making with regard to ED treatment followed
by discharge versus immediate or delayed hospitalization. Hypothesis: BNP correlates
with the presence of CHF, disease severity, and prognosis. This is the first large
cohort that examines BNP in relation to physician decision making, patient dispo-
sition, and critical outcomes in emergency medicine. Methods: The REDHOT study
was a 10 center trial in which patients seen in the ED with shortness of breath were
consented to have BNP levels drawn on arrival, every 3 hours in the ED as well as
at time of admission or discharge. Physicians were only told whether the initial
BNP level was greater or less than 100 pg/ml, and blinded to subsequent BNP lev-
els. Patients were followed up for 90 days after discharge. Results: Of the 504 pa-
tients consented, 90% were hospitalized, even though only 68% were designated for
hospitalization upon initial evaluation. Sixty four percent of patients who were
admitted with a NYHA classification of III or IV had BNP levels < 200 pg/ml (13%
of total population). This group had a 90-day mortality of only 1.7%. Thirty-six pa-
tients were discharged from the ED with a BNP level > 400 pg/ml. The 90 days mor-
tality was 10% in this group, while patients discharged from the ED with a BNP level <
400 pg/ml had 0% mortality at 90 days. Patients who were discharged home from the
ED actually had higher BNP levels than those admitted (although the difference was
not statistically significant (976 versus 766, p=0.06). Using regression analysis, the
emergency physicians intention to admit or discharge a patient had no influence on
their 90 day mortality, while the BNP level was a strong predictor of 90 day mortal-
ity. Conclusion: In patients presenting to the ED with heart failure, there is a strong
disconnect between the perceived severity of CHF by emergency physicians and
severity as determined by BNP levels. The results of this study strongly suggest that
BNP levels will aid physicians in making appropriate triage decisions about whether
to admit or discharge patients. This should avoid prolonged stays in the ED, unnec-
essary hospitalizations, inappropriate discharges to home and overall lead to better
patient care.
PUTTING THE PIECES TOGETHER:

Can We Get Better with Hearts?

W. Brian Gibler, MD — Richard C. Levy Professor and Chairman, Department of Emergency Medicine, University of, Cincinnati College of Medicine, Cincinnati, Ohio, USA

Objectives:

1) Explain the interrelation of the early diagnosis and treatment of acute coronary syndrome.
2) Participants will explain how physicians can improve their hospital’s response to acute coronary syndrome and heart failure through improving relationships with Cardiology, Administration and the Laboratory.

The answer to the question posed by the title of this lecture is absolutely we can. Through a deliberate approach to building current thinking on acute coronary syndrome (ACS), including the impact of expert panel guideline implementation, the foundation has been developed for emergency physicians to become expert in this disease process. As noted in the two presentations on heart failure (HF), suboptimal understanding of the diagnosis and treatment of ACS, and failure to adhere to evidence-based approaches to care, can only increase the number of patients with HF. It is our hope that we are successful in providing a clear approach to the diagnosis and treatment of ACS and HF in the emergency department (ED).

An understanding of the pathophysiology of ACS has evolved substantially over the last decade. The role of inflammation and the acutely ruptured atheromatous coronary artery plaque has identified multiple new diagnostic and therapeutic approaches to the care of these patients. Markers of inflammation such as C-reactive protein can identify patients at greater risk for developing ACS and its complications. Efforts at reducing inflammation and the causes of atherosclerosis including elevated lipids (low density lipoproteins) with agents such as statins, now requires emergency physicians to be comfortable with this discussion. An acutely ruptured atheromatous plaque also requires rapid diagnosis and treatment to minimize complications including myocardial infarction and death.

Diagnostic evaluations for possible ACS have evolved dramatically. The development of the chest pain center concept now emphasizes the coherent approach to the diagnosis of ACS which includes an evaluation for myocardial necrosis, rest ischemia, and exercise-induced ischemia. The 12-lead ECG and troponins have been demonstrated as the best tools for risk stratification in patients with ACS. Through these two modalities, most patients with non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) at risk for MI and death can be identified. Radionuclide imaging has also proved to be enormously successful in evaluating patients with possible ACS in the ED, particularly for identifying the low risk patient that can be sent home. Provocative testing using exercise diagnostics such as graded exercise testing, dobutamine echocardiography, or exercise sestamibi testing can provide useful information as to patients with fixed, hemodynamically significant atheromatous lesions requiring treatment. Perhaps the most exciting new additions to the diagnostics for ACS are the various biomarkers of acute ischemia. In the coming years, ischemia modified albumin, brain natriuretic peptide, and fatty acid binding protein promise to provide further information on patients with rest ischemia in the emergency setting.
While diagnostic advances have been substantial during the last decade, the evolution of therapy for ACS has been truly amazing. The elucidation of the role of platelets in the very early pathophysiology of ACS has allowed enormous gains in therapy for this disease process. Glycoprotein IIb/IIIa receptor inhibitors such as eptifibatide and ADP receptor inhibitors such as clopidogrel have revolutionized therapy for patients with ACS through the inhibition of platelet aggregation. These agents improve both short term and long term outcome for these patients and in most cases can be appropriately administered in the ED. In addition, antithrombotic treatment with both unfractionated and fractionated low molecular weight heparin is better understood and has certainly improved care.

Chest pain centers provide a framework for EDs to develop a cohesive approach to the diagnosis and treatment of ACS. In collaboration with Cardiology, emergency physicians can develop a consistent approach to the early diagnosis and treatment of ACS. Involving the multiple constituents in this process of care, including Cardiology, Emergency Medicine, Internal Medicine, Family Medicine, Laboratory Medicine, and Administration, a coordinated diagnostic and therapeutic approach to ACS can be provided to every patient with chest discomfort presenting to the ED. Meeting with leaders from these various groups off-line and establishing diagnostic and treatment algorithms specific for a particular hospital, prevents a variable approach to each new patient which reflects individual emergency and cardiology clinician preference rather than an evidence-based approach.

The development of the CRUSADE Quality Improvement Initiative reflects this desire to incorporate evidence-based practice into the diagnosis and treatment of ACS. Based on the 2002 ACC/AHA guidelines for NSTEMI and UA, the CRUSADE initiative seeks to provide both the function of documenting care provided at over 500 hospitals across the United States and providing comparative data back to participating centers. A recent report from the RAND center estimates that physicians in a variety of disciplines across the United States follow expert specialty-based guidelines only 50% of the time. Data from the CRUSADE initiative demonstrate that centers which follow the 2002 ACC/AHA guidelines have fewer adverse outcomes, including death, from ACS than hospitals that do not have the same high level of adherence. Through providing specific tools to member hospitals such as algorithm cards, pre-printed nurse orders, and other aids, care for all patients with ACS at these institutions is expected to improve.

In a similar fashion to the diagnosis and treatment of ACS, HF has had a significant increase in new knowledge over the last decade. In the past, the diagnosis and treatment of HF was typically based on rather imprecise determination of a patient’s past medical history, symptoms, and presenting physical examination. The objective measurement of brain natriuretic peptide (BNP) has substantially improved the emergency physician’s diagnostic approach to these patients and also provides prognostic information as well. For HF, BNP serves as a diagnostic test as well as a therapy. In addition to the typical emergency treatment for HF which can include agents such as diuretics, ACE inhibitors, inotropic agents, morphine, and nitrates, BNP can provide an additional therapeutic modality for these severely ill patients. Emergency physicians must be adept at diagnosing HF on presentation and providing rapid treatment to prevent respiratory and cardiac complications. Better diagnostic and treatment regimens for ACS should presumably decrease the number of patients with HF presenting to emergency departments across the United States in the coming years.
In conclusion, an improved understanding of the pathophysiology of ACS has lead to significant advances in diagnostic testing and therapeutic agents. Diagnostic testing in the emergency setting must address not only myocardial necrosis, but also rest ischemia and exercise-induced ischemia. A thorough understanding of the 12-lead ECG, markers of necrosis such as troponin, and radionuclide testing can help provide better care for these ACS patients. Research into platelet biology has elucidated therapeutic mainstays such as glycoprotein (GP) IIb/IIa receptor inhibitors and ADP receptor antagonists which can prevent platelet activated aggregation. Chest pain centers, using ACC/AHA guidelines for NSTEMI and UA, can provide a consistent, cohesive approach to the care of these patients with ACS. The CRUSADE Quality Improvement Initiative not only tracks the care of these patients at the participating centers, but also provides feedback to these hospitals to improve their processes. Hopefully improving the care of ACS, up front in the emergency department, can decrease the number of patients having HF as a complication of their disease.
HOW DO WE EVALUATE AND TREAT THE TRANSIENT ISCHEMIC ATTACK?

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Objectives:
1. Explain the high rate of serious adverse events after a transient ischemic attack.
2. Outline the initial evaluation and management of the patient that presents to the emergency department after a transient ischemic attack.

INTRODUCTION

Transient ischemic attacks (TIAs) have long been defined as neurologic deficits attributable to a loss or decrease of cerebral perfusion that resolve within 24 hours. The duration of most TIAs, however, is much less than 24 hours with the majority clearing within 1 hour. In one study, the median duration of carotid distribution TIAs was 14 minutes, while vertebrobasilar TIAs had a median symptom duration of 8 minutes. Labeled by some clinicians as “unstable angina of the brain” the significance of this pathology is becoming better understood.

The importance of TIAs to the emergency physician is that they are a significant predictor for ischemic stroke in the near future, making rapid evaluation and management of TIAs critical. One study of 1707 emergency department (ED) patients diagnosed with a TIA by emergency physicians showed that 180 patients (10.5%) suffered a stroke within 90 days of the index TIA. Of those patients, 91 (5.3%) had a stroke within 2 days of the TIA. Patients also had a large incidence of cardiovascular events, with 44 (2.6%) patients hospitalized within 90 days. The combined risk of an adverse event (stroke, CHF, AMI, unstable angina, ventricular arrhythmia, death or recurrent TIA) was 25.1% within 90 days of a TIA. Transient ischemic attack is an ominous sign which merits early and aggressive evaluation and management.

The very high risk of patients presenting with a TIA was further confirmed in a population-based study in the Oxford Community Stroke Project. Similar to the 5.3% 2-day stroke risk in the previous study, these authors found a 5.1% 2-day risk of stroke after first-ever cerebral TIA. Further, in this study the 7- and 30-day stroke risks from onset of first-ever TIA were 8.6% and 12.0%, respectively.

In another study, a total of 790 patients presenting to the ED with a TIA were identified. The rate of stroke within 30-days was 9.2%, 13.3% by 90-days and 16.7% by 6-months. This study illustrates the significant likelihood of subsequent events. Despite the high rate of adverse events following a TIA, data from primary care literature suggests that TIAs are undertreated. As an example, data from one primary care practice for 95 patients with TIA found that only 2% of patients were admitted, 23% received imaging (CT or MRI), and 40% carotid ultrasonography. This apparent mismatch between potential disease severity and level of work-up and treatment suggests that there is much work to be done to improve patient outcome through more aggressive work-up and treatment of TIAs.

EPIDEMIOLOGY

TIAs are common, and represent a significant warning of ischemic stroke. Based on recent estimates of stroke incidence,
approximately 300,000 TIAs occur each year in the United States. In one study, one in fifteen individuals over the age of 65 years reported a history of TIA. The estimated direct medical cost in the US for stroke was $28 billion in 2001. The addition of indirect costs brings the total to a staggering $45.4 billion dollars per year.

PATHOPHYSIOLOGY

The underlying mechanism in TIA or ischemic stroke is a decrease in perfusion of a portion of the brain. Research has demonstrated a critical level of blood flow needed to maintain neuronal function and to prevent ischemic damage. Data suggest that normal cerebral blood flow lies between 40-60 ml/100g/min in the human. Below 20ml/100g/min normal neuronal function fails and neurologic symptoms begin. Below 8 ml/100g/min irreversible damage ensues. These data suggest a model of cerebral perfusion to explain the nature of a TIA. There is a reduction in cerebrovascular blood flow in an affected territory causing injury, but not an irreversible infarction. Most TIAs are the result of an occlusion or partial occlusion of an artery to the brain. This vascular occlusion is most commonly due either to a thromboembolic process secondary to atherosclerosis or a cardioembolic source. Less commonly, TIAs occur in association with hypercoagulable states, arterial dissection, arteritis, and use of drugs with vasoactive properties such as cocaine. While the occurrence of a TIA does not necessarily predict the underlying mechanism, some patterns are discernible. TIAs occur more frequently in patients with large-artery atherothrombotic disease. In a summary of recent studies, TIAs occurred before 25% to 50% of atherothrombotic infarcts but only 11% to 30% of cardioembolic strokes and 11% to 14% of lacunar infarcts.

In some patients, what appears to be a TIA clinically may actually represent a subclinical stroke. A study of 42 consecutive patients diagnosed with TIAs found that 48% demonstrated neuroanatomically relevant focal abnormalities on diffusion weighted magnetic resonance imaging (MRI). The authors noted a correlation between length of symptoms and presence of an identifiable lesion. In this study, the longer the patient had symptoms, the more likely they were to actually have had a subclinical stroke. Advanced MRI is very useful in making such a diagnosis.

By definition, symptoms of TIA can persist up to 24 hours. The issue of TIA symptom duration has been of interest since the initiation of thrombolytic therapy for acute ischemic stroke. Clinicians often ask how is it known that patients that appear well 24 hours after receiving rt-PA for an apparent acute ischemic stroke were not actually suffering a TIA. The answer lies in the placebo group from the National Institute of Neurological Disorders and Stroke, rt-PA Stroke Study. In that study, 312 patients were randomized to placebo with a median time to treatment of 90 minutes. Of those 312 patients only 2 percent were symptom free at 24 hours. Thus it is very unlikely that patients with a persistent neurological deficit of longer than 90 minutes will resolve spontaneously.

There has been a recent trend toward the redefinition of TIA based on symptoms and duration. An expert panel proposes the following new definition of a TIA: a TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction. The corollary is that persistent clinical signs or characteristic imaging abnormalities define infarction that is stroke.

EMERGENCY DEPARTMENT EVALUATION

In caring for a patient suspected of having TIA the emergency physician is faced with four concerns.
Identification of TIA in the ED is a complex and difficult task. Frequently the patients present to the ED after the symptoms have resolved. Neurologists, evaluating a patient scenario, often disagree on the diagnosis of TIA. TIA often present as vague complaints, which can be difficult to discern especially in patients who cannot provide classic histories. In addition, standard imaging such as non-contrast brain CT would not demonstrate any abnormality due to a TIA. A problem is the fact that in the majority of cases of true TIA, the symptoms have abated by the time patients are evaluated by an emergency physician. In addition, the differential diagnosis of TIA is extensive. It includes syncope, seizures, post-ictal (Todd’s) paralys, hypoglycemia, complicated migraines, multiple sclerosis, neuromuscular disorders, subarachnoid hemorrhage, Bell’s palsy, neoplasm, functional disorders, and vertigo. It is important to realize that a TIA is a final common pathway of a number of disease processes and not necessarily a distinct entity. The history, particularly the timing of the events, and physical examinations are of paramount importance in diagnosing the source of the TIA. As much information as possible is collected from paramedics, family, friends and other witnesses. Particular attention is given to the examination of cardiovascular and neurological systems.

TIA, like stroke, present with symptoms representing the distribution of neurons affected by the ischemic event. The blood flow to the brain is classified into two primary groups: the anterior and posterior circulations.

The presentation of TIA in the anterior circulation result from embolic or thrombotic occlusion or stenosis of arteries in the carotid distribution and therefore relate to the ipsilateral eye and brain served by carotid blood flow. The effects seen from ischemia in these areas include contralateral hemiparesis, contralateral hemisensory loss, disturbances in speech or language, monocular visual loss, and cognitive impairment.

TIA secondary to posterior circulation ischemia are caused by occlusions or stenosis in the vertebrobasilar system, and are more likely to be thrombotic in origin, but can also include rare conditions such as vertebral artery dissection. Compromise to the posterior circulation can lead to vertigo, diplopia, dysphagia, homonomous hemianopsia, dysarthria, ataxia, in addition to decreased level of consciousness, hemiparesis, and eye movement abnormalities. Finally, in patients with a proximal embolic source embolization to several areas of the brain can occur at different times, which can give a mixed clinical picture.

There are no concrete guidelines for ancillary testing in patients suspected of having TIA. Evaluation is based on the patient’s symptomology and the pre-test probability for each investigation. Current recommendations in the stroke literature call for a complete blood count, blood glucose level, chemistry profile, and prothrombin and activated partial thromboplastin time, ESR, and ECG. Imaging of the brain begins with an unenhanced CT of the brain. It is also useful to rule out nonvascular lesions such as a mass or subdural hematoma. The next step in the imaging of patients with TIA depends on the presentation and symptoms. Further
evaluation may begin in the ED depending on resources available. In many cases this evaluation continues after the patient has been dispositioned.

One very valuable test that can, depending on availability, may be initiated in the ED is carotid ultrasonography depending on local practice patterns and availability. It is important to exclude a flow-limiting lesion in the carotid arteries of patients with TIA. Patients with a symptomatic carotid stenosis may require surgical intervention in conjunction with medical management. Magnetic resonance imaging and magnetic resonance arteriography (MRA) are useful in evaluating infarct location and cerebral blood flow respectively. These advanced imaging evaluations are not necessarily indicated in all patients with TIAs, but their need is guided by the clinical presentation and the results of prior evaluations. MRI with MRA of the circle of Willis and the neck vasculature is particularly useful in cases of suspected posterior circulation TIAs. Further testing includes transthoracic or transesophageal echocardiography to look for thrombus or valvular disease.

Additional evaluation may include ambulatory ECG monitoring, investigations for the presence of a hypercoagulable state, CSF examination, to rule out stroke mimics such as multiple sclerosis, encephalitis, etc, and further investigation for myocardial ischemia. Extensive, time critical evaluations for certain patients with TIAs are a significant argument for admission of these patients to the hospital. Another argument in favor of hospitalization is the opportunity to observe for progression or recurrence of events, and to rule out other causes of the patient’s symptoms.

**ACUTE MANAGEMENT**

The primary goal of TIA management is the prevention of ischemic stroke. Necessary interventions include risk factor modification and directed medical or surgical therapies. Depending on the etiology for the TIA and the presence of comorbid conditions, three options for management include: anti-platelet therapy, anticoagulation and carotid intervention.

**Risk Factor Modification**

Treatment for patients with TIAs begins and ends with risk factor modification. Management of these can begin in the ED but needs to be carried through to the inpatient and outpatient settings. Appropriate management of risk factors have been shown to significantly reduce the risk of cardiovascular and cerebral ischemic disease although most of these studies have not included just patients with TIAs. Modifiable risk factors for stroke include hypertension, cardiac disease, including atrial fibrillation, diabetes, hypercholesterolemia, cigarette smoking, excessive alcohol use and physical inactivity, as well as stress. Recommendations from the American Heart Association include treatment of hypertension to maintain a blood pressure below 140/90, stopping cigarette smoking, appropriate treatment of heart disease, including coronary disease, congestive heart failure, arrhythmias and valvular heart disease, decreasing excessive alcohol use, treatment of hyperlipidemias, treatment of diabetes and increasing physical activity.

**Blood Pressure Management**

Acute elevation of blood pressure is quite common in cerebrovascular emergencies. Because a patient with a TIA may have a pressure-dependent flow problem, acute pharmacologic lowering of blood pressure is avoided. Unless blood pressure enters the range of hypertensive urgency often defined as 200/110 or above, acute blood pressure lowering is not warranted. The level of hypertension that is “tolerated” is based on the patient’s previous blood pressure history. The more significant the patient’s prior history of hypertension, the
higher the blood pressure that should just be observed without acute intervention.

**ATRIAL FIBRILLATION AND ANTICOAGULATION**

Anticoagulation is recommended in patients with a TIA and atrial fibrillation who do not have any contraindications to this therapy. The superior efficacy of anticoagulation over aspirin for prevention of ischemic stroke in patients with atrial fibrillation who have had a recent TIA or minor stroke was demonstrated in the European Atrial Fibrillation Trial. There is even greater evidence for the use of anticoagulation in patients considered to be at a higher risk of stroke. These include patients with a history of hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, a prior stroke or TIA, a history of systemic embolism, or age >75 years. Anticoagulation can be initiated in the ED with either intravenous unfractionated heparin or low-molecular weight heparin as a bridge to long-term therapy with warfarin sodium. A target of international normalized ratio [INR] of 2.5 (with a range of 2.0 to 3.0) is recommended. Patients with atrial fibrillation and contraindications to anticoagulation are prescribed anti-platelet therapy. The ED can be the point of first medical contact for many complaints referable to atrial fibrillation (AF). This places emergency physicians in a unique position to identify AF patients at risk for stroke. In one multi-center, retrospective study of 556 ED patients with AF on their ECG and a prior history of AF, 221 (40%) used warfarin alone, 155 (28%) were on antiplatelet therapy alone, 28 (5%) were on both these agents, and 152 (27%) were on no antithrombotic therapy. Sixty-nine patients (12%) were warfarin-eligible and were not prescribed antithrombotic therapy. An additional 63 (11%) of warfarin-eligible patients had antiplatelet therapy alone. In warfarin-eligible patients, no differences were identified between anticoagulated and non-anticoagulated groups on the basis of age, gender or race. Of patients on warfarin with a measured INR, 61% were outside the AHA recommended range. The authors concluded that AF is a common finding in an ED population and that many patients are warfarin-eligible and untreated or under-treated. Patients who do not have atrial fibrillation, and those without any significant carotid stenosis are best managed with anti-platelet medications. Options include (a) aspirin, (b) ticlopidine, (c) clopidogrel, and (d) extended-release dipyridamole plus aspirin.

**ASPIRIN**

Aspirin (acetylsalicylic acid) is the standard medical therapy used for prevention of ischemic stroke in patients who have had a TIA. Aspirin inhibits platelet function by blocking cyclooxygenase. Aspirin was approved by the US Federal Drug Administration for management of cerebrovascular disease primarily on the basis of two studies. Daily aspirin dosing remains controversial. Multiple studies have been performed in an attempt to determine the best dose for stroke prevention. The US Food and Drug Administration currently recommends the use of aspirin in doses of 50 mg/day to 325 mg/d for prevention of stroke. The expert panel that created the current American Heart Association Guidelines for the Management of TIAs similarly recommends a dosage range of 50 to 325 mg of aspirin per day for most TIA patients.

**TICLOPIDINE**

Ticlopidine hydrochloride prevents platelet aggregation induced by adenosine diphosphate (ADP). It is approved in the United States for prevention of stroke in patients with TIA or minor stroke. The use of Ticlopidine for the prevention of ischemic stroke is based largely on the Ticlopidine Aspirin Stroke Study (TASS). This blinded trial at 56 North American...
centers compared the effects of ticlopidine hydrochloride (500 mg daily) with those of aspirin (1300 mg daily) on the risk of stroke or death. The three-year event rate for nonfatal stroke or death from any cause was 17 percent for ticlopidine and 19 percent for aspirin. This represents a 12 percent risk relative reduction with ticlopidine. The rates of fatal and nonfatal stroke at three years were 10 percent for ticlopidine and 13 percent for aspirin. Thus there was a 21 percent risk relative reduction (95 percent confidence interval, 4 to 38 percent) with ticlopidine.26 The use of ticlopidine is limited, however, by the rates of adverse effects. In the TASS study the adverse effects of aspirin included diarrhea (10%), rash (5.5%), peptic ulceration (3%), gastritis (2%), and gastrointestinal bleeding (1%). In that same study, ticlopidine produced adverse effects at a higher rate: diarrhea (20%), skin rash (14%), and severe but reversible neutropenia (<1%).26 Unfortunately, since the publication of the TASS, reports have described another hematologic problem, thrombotic thrombocytopenic purpura (TTP). This rare but life-threatening disorder occurs in between 1 in 1600 and 1 in 5000 patients receiving ticlopidine.27 This has lead physicians to turn to alternative anti-platelet medications for stroke prevention.

**CLOPIDOGREL**

Clopidogrel is a new thienopyridine derivative whose mechanism of action and chemical structure are similar to those of ticlopidine. This drug also has been shown to be slightly better than aspirin alone in preventing ischemic events and appears to have a better side effect profile than ticlopidine.

In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial a 75 mg/d dose of clopidogrel was compared with a 325 mg/d dose of aspirin in patients with recent ischemic stroke or myocardial infarction or patients who had symptomatic atherosclerotic peripheral arterial disease. Notably, TIA patients were not eligible for this study. In this trial there was a small but significant relative risk reduction of 8.7% for the prevention of ischemic events, however the study was not designed to look at stroke in isolation. In addition, the adverse effect profile was at least as good for clopidogrel as for aspirin. While diarrhea and rash occurred more commonly in the clopidogrel group than in the aspirin group, gastrointestinal distress and hemorrhage were reported more often in the aspirin group. The dreaded occurrence of TTP as seen with ticlopidine is reported with clopidogrel but is far less common. When it is seen, it often occurs within the first two weeks of treatment.27

**EXTENDED RELEASE DIPYRIDAMOLE AND ASPIRIN**

The combination of aspirin and dipyridamole, a cyclic nucleotide phosphodiesterase inhibitor, is another alternative option for the prevention of stroke after a TIA. In the largest study of the combination of these agents to date, the European Stroke Prevention Study (ESPS-2), was designed to ascertain the efficacy of aspirin and an extended-release formulation of dipyridamole for prevention of stroke or death and to determine whether the combination of the two agents was superior to each agent given alone.28 ESPS-2 included 6602 patients with stroke (76.3%) or TIA (23.7%) within 3 months of enrollment. Compared with placebo, stroke risk was reduced by 18% with aspirin alone, 16% with dipyridamole alone, and 37% with combination therapy. Nearly twice as many events were avoided with combination therapy as with aspirin or dipyridamole alone. The most common side effects of extended-release dipyridamole-containing preparations were
headache and gastrointestinal events. The aspirin-containing regimens produced more frequent and severe bleeding episodes. In comparison with aspirin, reductions in stroke risk with the combination therapy of extended-release dipyridamole and aspirin were greater than those reported for clopidogrel, however, these agents have not been compared directly.

Patients who suffer a TIA while already taking aspirin may be a candidate for either one of the alternative antiplatelet agents or a combination of an alternative antiplatelet agent plus aspirin. If the patient had already failed such a change or combination then anticoagulation is considered. After a TIA, regardless of the preceding medical regimen, it should be augmented with one or more agents unless contraindicated.

**CAROTID ARTERY SURGERY**

Atherosclerotic narrowing of the internal carotid artery at the carotid bifurcation in the neck is a common cause of TIA and stroke. Three major prospective randomized trials - the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program 309 (VACSP 309) - evaluated the efficacy of carotid endarterectomy in symptomatic patients (patients with TIAs or small strokes) with high-grade carotid stenosis. The results of these studies demonstrate that symptomatic patients with >70% stenosis can expect a greater benefit from carotid endarterectomy than from medical therapy. Surgical benefits appear to be particularly robust for men, patients with hemispheric symptoms and without diabetes, and for persons with significant ulcerative atherosclerotic plaques as demonstrated by angiography. Benefit is less, but present in patients with stenosis of 50% to 69%. In addition, women and patients with retinal TIAs have not been shown to benefit. These findings remain unexplained. Angioplasty and Stenting Percutaneous transluminal angioplasty and intravascular placement of stents for treatment of carotid stenosis is currently being evaluated as an alternative to carotid endarterectomy. These may offer a less invasive method of restoration of flow but the true complication rate and long term outcome rates are unknown. Prospective randomized trials comparing angioplasty and stenting with carotid endarterectomy are ongoing. This procedure is currently considered investigational.

**HEPARIN**

Heparin is indicated for those with atrial fibrillation and others who need to be placed on anticoagulation until they are therapeutic on warfarin. This decision is best coordinated with a neurologist or the admitting physician. Heparin may be useful for those patients with TIAs that are rapidly increasing in frequency or severity (“crescendo TIAs”) or those who continue to have TIAs on conventional antiplatelet agents. Unless in specific conditions just mentioned, the routine use of heparin is not advocated for TIA patients in the ED.

**BARRIERS TO TREATMENT**

The primary barrier to optimal work-up and treatment does not lie in the fact that we do not have treatments and preventative therapies. The major barrier to treatment of cerebral ischemia, including TIAs, is that treatment has not been as aggressive as warranted based on the recent data. A retrospective study evaluated 95 TIA patients and 81 stroke patients who presented to a primary care provider. Only 2% of the TIA and 10% of the stroke patients were admitted to the hospital. Forty-five percent of the patients received specialist consultation and 30% received an imaging study. Twenty-eight percent of patients received carotid ultrasound studies, 19% electrocardiograms and 16% re-
ceived echocardiograms. Fewer than half of the 24 patients with a prior history of atrial fibrillation were anticoagulated. Although a small study, it underscores the need to treat TIAs more aggressively, whether in the outpatient setting or the ED.

**DISPOSITION**

Disposition of patients in the ED is often the most important decision that we make as emergency physicians. TIA may be regarded analogous to the patient with unstable angina with risk of catastrophic progression of disease. Yet practice patterns are such that patients are often not admitted to the hospital and do not receive the urgent investigations workup that recent data suggest to prevent evolution of their medical problems. The disposition of an emergency department patient with a suspected TIA requires great care since TIAs represent a significant warning of potentially impending stroke. When considering disposition, it is important to consider the short-term prognosis after a suspected TIA.

In an early incidence study from Rochester, Minnesota, investigators found a 10% incidence of ischemic stroke in the three months following a TIA. In a recent and landmark study of ED patients with suspected TIA, 1707 patients evaluated for TIA in emergency departments, 10.5% experienced a stroke within 90 days of diagnosis, 2.6% were hospitalized for cardiac events, and 1.4% died of causes other than stroke. This risk of stroke was over 50 times that expected in a cohort of similar age. Half of the strokes occurred within 2 days of the TIA.

The Johnston study also identified 5 independent risk factors for stroke within 90 days after TIA: age older than 60 years, diabetes mellitus, duration of episode greater than 10 minutes, and weakness and speech impairment with the episode. While this is a retrospective review and these criteria have not yet been prospectively validated, these risk factors may identify patients whose symptoms are more likely due to cerebral ischemia or may indicate pathophysiologic conditions associated with greater risk. The authors also noted that a reviewing neurologist thought the diagnosis of TIA improbable in 96 patients (5.6%). This means that 1 in 20 diagnoses of TIA may have been incorrect requiring further explanation of the patient’s symptoms.

One reason that TIA patients might not receive an aggressive work-up is the fact that symptoms frequently have resolved by the time the patient is in the ED or resolve during the patients stay. This fact coupled with the difficulty of diagnosis by ED physicians makes for a challenging patient. However, the disposition should not be so difficult. Recent data suggest that given the morbidity of stroke very few, if any, patients with TIA should be discharged from the ED. No data exist to identify patients who can safely be worked up on an outpatient basis. Intuitively, one would surmise that patients with transient symptoms of hemiparesis or aphasia might be at more risk of progression, but this is not known. An alternative to inpatient care, an observation unit with clinical protocols for diagnostic testing such as carotid duplex ultrasonography, echo, etc. and rapid discharge with risk factor modification and follow-up has been advocated.

Ideally, the emergency physician initiates the work-up beyond the baseline unenhanced brain CT when possible. In addition, the emergency physician initiates or advances the patient’s antiplatelet or antithrombotic therapy. The patient’s care is then transitioned to a primary care provider or neurologist for continuation of the observation and completion of the necessary work-up.
SUMMARY

Advances in the TIA research continues to give emergency physicians a new understanding of the disease process. Recent studies highlight significant potential morbidity due to TIA. It is now clear that initial therapeutic intervention and prompt and thorough evaluation must be undertaken to prevent devastating harm to this group of patients. This is truly a paradigm shift for many practitioners and consultants, and one area in which emergency physicians may lead in education and patient advocacy.

Acknowledgement

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REFERENCES


ADVANCES IN THE DIAGNOSIS OF ACUTE STROKE:
From Biomarkers To Neuroimaging

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Objectives:
1. Outline current methodology and some of the critical elements in the diagnosis of stroke as well as describe recent advances enabling the clinician to better manage stroke patients
2. Describe recent advances in neuroimaging and biomarkers in the diagnosis of cerebrovascular injury.

INTRODUCTION

No single element from the physical examination, laboratory testing, or neuroimaging is sufficient to accurately diagnose acute ischemic stroke (AIS) and exclude the numerous potential mimics. Only when this triad of stroke diagnoses is used together can patients be safely selected for thrombolytic therapy. This brief review will address some of the critical elements in the diagnosis of stroke and review recent advances enabling the clinician to better manage the acute stroke patient.

CLINICAL DIAGNOSIS

Despite the development of sophisticated neuroimaging techniques, the history and physical examination remain the single most essential element of the diagnostic triad. Information about risk factors and circumstances at the time of symptom onset helps the clinician develop a preliminary differential diagnosis. 

Past medical history

A review of symptoms, again focusing on neurologic elements of the past medical history, can begin to identify potential causes of the patient’s current symptoms, such as migraine or seizure. The neurologic review of symptoms includes associated headache, visual symptoms, hearing abnormalities, language difficulties, focal weakness, gait difficulty or numbness.

Physical examination

A focused directed neurologic examination is critical. Many emergency physicians feel uncomfortable with the neurologic examination, yet a focused exam is relatively easy to perform. A useful tool for quantifying the degree of neurologic impairment is the National Institute of Health Stroke Scale (NIHSS). Developed for use in clinical trials it remains a simple and effective way to quantify neurologic impairment, assist in localizing the vascular occlusion, and provide information regarding treatment selection and outcome. It is particularly well suited for evaluating patients with possible anterior circulation strokes. Patients with posterior circulation distribution stroke require additional neurologic evaluation of all cranial nerves and assessment for crossed neurologic findings.

LABORATORY EVALUATION

While not glamorous or technically sophisticated, prompt laboratory testing is critical in the timely evaluation of a stroke patient. Not only can metabolic abnormalities produce neurologic symptoms, but also many strokes occur in concert with other acute disease states, such as atrial fibrillation or acute myocardial ischemia.

Basic Laboratory Techniques

The most common stroke mimic encoun-
tered in the prehospital and emergency department setting is hypoglycemia. Rapid assessment of the serum glucose can identify this easily corrected cause of the patient’s neurologic impairment and spare the patient from additional testing and potential harm if not quickly identified and corrected. Additional testing for other electrolyte abnormalities and signs of cardiac ischemia are essential elements in the stroke patient evaluation.

Blood Markers of Neurologic Injury

Similar to the development of blood markers in the diagnosis of acute myocardial infarction and 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, transient ischemic attack, vasospasm associated with subarachnoid hemorrhage, 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 neurologic conditions and their severity, such as infarct volume, but also will assist in selecting the most appropriate therapies, measuring therapeutic efficacy, and providing some insight into patient prognosis.

It is important to understand the differences when comparing marker biokinetics 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 blood. Unless significant permeability changes occur, such as in injury, many markers cannot enter the blood freely.

Several recent publications have begun to demonstrate the potential of biomarkers in stroke. 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. More recently, investigators at Duke University and Biosite,
Inc. have published their results from 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-100B, 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 generation of research into biomarkers for brain injury, one with the promise of making an impact in the practice of emergency physicians.

NEUROIMAGING

Computed Tomography (CT)

Clearly the neuroimaging technique most familiar to emergency physicians is the CT scan. CT scanners are widely available and capable of generating images very quickly. CT scan images are transmittable to remote monitoring stations for interpretation and are excellent for ruling out acute intracerebral hemorrhage and are an adequate screening tool to look for stroke mimics such as tumors/metastases. Potential difficulty utilizing CT include 24 hour availability within a hospital, the significance of early ischemic findings specific to acute stroke and thrombolytics, and the skill and availability of personnel interpreting the CT images. Most importantly, it is the responsibility of hospital systems to provide timely (within 25 minutes of arrival) and skilled interpretation (within 45 minutes of arrival) of CT images in acute stroke patients, and emergency physicians should not be responsible for the interpretation of these images.

Advanced CT Imaging

The advent of next generation multidetector CT scanners has lead to exciting new possibilities in CT imaging of acute stroke. New techniques, including CT Angiography, Xenon CT perfusion studies, and CT perfusion studies may bring MRI quality imaging to the numerous hospitals settings without access to MRI technology.

CT ANGIOGRAPHY AND CT PERFUSION STUDIES

One newer CT modality is CT Angiography (CTA). This technique utilizes contrast administration and rapid data acquisition to create images of the larger vessels of the circle of Willis. Such a modality would offer information about the sites and degree of arterial occlusions and degree of collateral blood flow confirming the clinical diagnosis of acute stroke and potentially determining which patients may benefit from t-PA therapy.

Studies have tried to determine the feasibility of CTA among patients with acute hemispheric ischemia and to evaluate its relevance for thrombolytic therapy. In one study, investigators performed CTA in 40 consecutive patients with moderate or severe symptoms of acute hemispheric ischemia. CTA findings were compared with Doppler ultrasonography and digital subtraction angiography. The investigators stated that the CTA showed high agreement with Doppler ultrasonography and digital subtraction angiography, and concluded that CTA can provide important information for the initiation of thrombolytic therapy among patients with acute hemispheric ischemia. They point out that patients found to have open arteries, patients with complete carotid occlusions and patients with little or no collateral flow may have little potential for benefit from IV t-PA. They postulate that this modality may ultimately be useful in excluding patients that have little to gain and have a large potential risk with t-PA therapy. In another study, twenty-one patients with acute ischemic stroke were studied prospectively with conventional CT, CTA, and digital subtraction angiography. The
investigators found excellent agreement between the modalities and the readers, concluded that CT angiography quickly and reliably adds important information to conventional CT studies in cases of acute ischemic stroke. It shows the site of occlusion, the length of the occluded arterial segment, and the contrast-enhanced arteries beyond the occlusion as an estimate of collateral blood flow.

New CT perfusion studies with advanced multidetector CT scanners using intravenous contrast agents can accurately and quickly identify regional cerebral blood flow (rCBF) abnormalities. This technique offers several advantages over MRI: it can be performed during the standard noncontrast CT (method of choice for excluding hemorrhage), it is available with existing CT equipment (however, newer generation scanners and post-processing software required), and requires no specialized equipment. The CT perfusion results are similar to and correlated with rCBF measurements from Xenon CT. Rapid assessment with noncontrast CT, CT angiography, and CT perfusion can provide all the critical information required by the clinician responsible for selecting treatment options for patients with acute stroke.

**XENON CT**

Another extension of conventional CT scanning is Xenon enhanced CT. While still classified as investigational by the FDA, there is renewed interest in this technology. In this method, non-radioactive inert xenon gas is inhaled for 4 to 5 minutes and the temporal changes in radiographic enhancement produced by the inhalation are measured by sequential computed tomography. Time dependent xenon concentrations within various tissue segments in the brain are used to derive quantitative measures of cerebral blood flow (CBF). An assessment of this method reveals that it provides functional mapping of blood flow with excellent anatomic specificity. Recently XeCT scans and angiograms of 20 patients who presented within 6 hours of acute anterior circulation ischemic strokes were analyzed. The CT scans were abnormal in 11 (55%) of 20 patients. XeCT scans were abnormal in all 20 (100%) patients, showing regions of interest with CBF < 20 (mL/100 g per minute) in the symptomatic middle cerebral artery (MCA) territories. The authors conclude that XeCT is more sensitive than CT in detecting acute strokes and that CBF measurements correlate with early CT and angiographic findings. XeCT may allow for the hyperacute identification of subsets of patients with acute ischemic events who are less likely to benefit and more likely to experience complications from aggressive stroke therapy.

**Magnetic Resonance Imaging**

The clinical applicability of magnetic resonance imaging in acute stroke is still to be determined. Conventional MRI is quite sensitive in screening for intracranial pathology. MRI has significant clinical limitations including: 1) obtaining a MRI rapidly is impossible in many hospitals; even when available, the MRI takes longer to complete than CT, 2) monitoring a patient in an MRI scanner can be difficult, 3) standard MRI is not as sensitive as CT in identifying acute hemorrhage, and finally, 4) patient compliance can be a problem due to claustrophobia and/or the loss of image quality with even small amounts of motion. For these reasons and due to the wide availability of CT scanning, MRI is not routinely utilized for acute decision-making in ischemic stroke.

As clinicians and researchers continue to advance the science of acute stroke management, new methods of determining which patients may or may not benefit from early fibrinolytic therapy are being explored. Despite the stated limitations of conventional magnetic resonance im-
aging (MRI), investigators have placed considerable emphasis on MRI techniques that can differentiate between various forms or degrees of intracerebral pathology.

**DIFFUSION-WEIGHTED IMAGING (DWI) MRI**

DWI is a magnetic resonance imaging technique that detects the tiny random movements of water molecules (diffusion) in tissues. This technique allows a map of the average apparent diffusion coefficient (ADC), a measure of water mobility, to be calculated. Within minutes after the onset of an ischemic stroke, the ADC of affected brain tissue is significantly reduced because of cytotoxic edema, seen as areas of hyperintensity on the DWI image. Over several days, the rapid initial drop in ADC is followed by a return to pseudo-normal values at approximately 1 week. Subsequently, elevated ADC values are seen in chronic lesions. DWI is, therefore, remarkably sensitive in detecting and localizing acute ischemic brain lesions and allows differentiation of acute regions of ischemia from chronic infarcts. Recent studies have shown a high correlation between the volume of early DWI lesions and clinical neurologic outcome. In addition, the volume of the early DWI lesion correlates well with final infarct volume as measured by T2-weighted imaging.

**PERFUSION-WEIGHTED IMAGING (PWI) MRI**

This technique utilizes the passage of a contrast bolus through the microcirculation using high-speed MRI and can provide significant contrast enhancement between ischemic and normal tissues. In contrast to magnetic resonance angiography, which measures bulk vessel flow, PWI measures tissue-level blood flow. Computational analysis of acquired data provides images based on relative cerebral blood flow and highlights ischemic tissue. The images generated with this technique have been demonstrated to have excellent correlation to final infarct volume. Comparing regions of DWI and PWI can identify areas of ischemic tissue, which may be salvageable if tissue perfusion is restored. If the region of DWI abnormality closely corresponds (match) to the territory seen on PWI, recanalization is likely to have little chance for producing clinical improvement and only exposes the patient to the risk of hemorrhage. DWI and PWI might allow for better patient selection for recanalization strategies and may provide a highly sensitive technique for evaluating the efficacy of new treatments.

Magnetic resonance angiography (MRA) produces similar visualization of the major cerebral blood vessels as noted with CT angiography and is a noninvasive alternative to cerebral angiograms. Magnetic resonance spectroscopy (MRS) measures metabolic abnormalities within minutes of focal ischemia, similar to the more limited and expensive single photon emission computed tomography (SPECT) studies. Used together, MRA and MRS techniques may identify patients best suited for thrombolytic therapy.

These new MRI based techniques may ultimately drive the practice of acute stroke evaluation into the MRI suite as they will significantly improve diagnostic sensitivity and specificity for clinicians. What remains to be determined is whether these techniques can overcome the limitations of availability and time to image, and monitoring barriers inherent in MRI use, and whether MRI can achieve widespread, real-time use.

**Cerebral Angiography**

Cerebral angiography remains the gold standard for identifying cerebral vessel occlusion. Cerebral angiography is not only a useful tool in the identification of vascular obstructions and the degree of collateral blood flow, but also affords the invasive neuroradiologists access to the
clot. Once at or proximal to the occlusion, recanalization strategies, including thrombolytics or mechanical catheter devices, can be introduced in an attempt to restore vessel patency. As with MRI, angiography is limited in its availability but the potential to extend the 3-hour therapeutic window to possibly 6 hours or more using intra-arterial approaches holds promise for numerous stroke patients. Additionally, larger strokes refractory to intravenous thrombolytics are more effectively treated with intra-arterial strategies, with significantly better outcomes. Thus, angiography is likely to become a mainstay in the armamentarium of stroke treatment but access limited largely to tertiary care centers.

**Transcranial Doppler (TCD)**

Transcranial Doppler sonography has only recently become used in acute stroke. While a useful non-invasive diagnostic tool to assess vessel patency, champions of the technique describe other merits. Its uses extend beyond stroke: it can confirm the presence and location of occlusion, monitor embolization during cardiothoracic or carotid surgery, monitor therapy efficacy, serve as an adjunct to thrombolytic therapy, screen for vasospasm in subarachnoid hemorrhage, and identify children with sickle cell disease at high risk for stroke. As TCD use becomes more simplified it is likely to gain increased utilization in acute stroke.

**Other Imaging Techniques.**

While not discussed here, even more elaborate neuroimaging techniques are being investigated for application in the diagnosis of acute stroke. PET and SPECT scanning, once relegated to few centers, are becoming more commonplace and no longer are strictly research tools. Both will face the same challenges as MRI, very limited availability, difficulty with interpretation, and lengthy scan acquisition time to name a few.

**CONCLUSION**

The diagnostic techniques available to the emergency clinician will likely outpace the development of acute therapeutic interventions. These techniques will however provide for greater diagnostic accuracy and more patient-specific selection of therapeutic strategies. Like any new technology, the emergency physicians must keep abreast of these developments and understand how they may assist in their clinical practice.
REFERENCES


The Pathophysiology of Acute Coronary Syndrome

1) Which of the following is the predominant cell involved in the inflammatory process within an atherosclerotic plaque?
   a. Basophil
   b. Lymphocyte
   c. Macrophage
   d. Mast cell
   e. Polymorphonuclear leukocyte

2) Which of the following would be the most common pathophysiologic cause of an ST elevation myocardial infarction (STEMI)?
   a. Coronary artery dissection
   b. Plaque erosion with subsequent development of an occlusive thrombus
   c. Exposure of a calcific nodule in a plaque with subsequent thrombus development
   d. Plaque rupture with resultant thrombus occluding the vascular lumen
   e. Isolated vasospasm of the coronary artery.

Diagnosis of ACS in the ED: Symptoms, Markers and ECGs.

3) Continuous ST-segment monitoring provides the most benefit in:
   a. Low risk patients
   b. High risk patients
   c. All patients with chest pain
   d. None of the above

4) ESC and ACC recommended that the “normal “ range for each cardiac marker assay be defined as the 99th percentile of the reference population, and this value be the cutoff value for the diagnosis of myocardial injury. Choose the false statement.
   a. This was done to decrease number of false positives.
   b. Creates a uniform value across all manufactures and assays.
   c. The value is dependent of each individual assay.
   d. The recommendation has resulted in significant confusion.

CRUSADE Quality Improvement Initiative; Cardiologists and Emergency Physicians Working Together.

5) According to the 2002 Updated ACC/AHA guidelines, which the following therapies is NOT a Class IA recommendation for patients undergoing coronary catheterization and percutaneous coronary intervention (PCI):
   a. Aspirin
   b. Heparin
   c. Glycoprotein IIb/IIIa inhibitor
   d. Thrombolytics
   e. All of these are Class IA recommendations for such patients

6) Which of the following statements best describes the CRUSADE initiative?
   a. It is a prospective randomized trial of patients with ACS.
   b. This registry has a lesser short term mortality rate than similar ACS trials.
   c. It is an academic collaborative project between emergency physicians and cardiologists.
   d. CRUSADE study sites include roughly 10 hospitals across the United States and Europe.
   e. This initiative found no differences acute care between leading and lagging hospitals.

Treating UA/NSTEMI with antiplatelet agents

7) The CRUSADE Initiative ACS registry analysis presents advantages over NSTE ACS randomized controlled clinical trials. These include:
   a. The CRUSADE patient population has a higher mortality than published NSTE ACS randomized controlled trials.
   b. The CRUSADE population is larger than NSTE ACS trial populations.
   c. The CRUSADE registry population treatment is more representative of “real world” treatment patterns.
   d. Randomized controlled trials of NSTE ACS often exclude the “sickest” patients due to consent issues.
   e. All of the above
8) In the CRUSADE initiative, early GP IIb/IIIa inhibitor therapy is associated with which of the following?
   a. A lower unadjusted mortality
   b. Lower incidence of catheterization
   c. Poorer adherence to ACC/AHA guideline recommendations
   d. Longer lengths of stay in the hospital
   e. Higher bleeding rates

   The Use of Clopidogrel for ACS: Clinical Implications of the CURE Trial.

9) In the PCI-CURE substudy of the CURE trial, which of the following is true?
   a. Patients either received clopidogrel, abciximab, or placebo
   b. Treatment with clopidogrel prior to PCI resulted in a 30% reduction the cardiovascular endpoints when compared to placebo
   c. Clopidogrel was found to be most beneficial in those patients undergoing immediate CABG.
   d. A 10.7% incidence of major bleeding was noted in patients greater than 80 years of age.
   e. One year follow-up post PCI showed no significant difference in cardiovascular death or MI.

10) Clopidogrel performs its action only through inhibition of ADP-induced platelet activation.
    a. True
    b. False

   When the Heart fails: Identifying and Treating Heart Failure.

11) Which of the following may cause an elevation in BNP in the absence of heart failure?
    a. Pulmonary embolism
    b. Age
    c. Female sex
    d. Renal insufficiency
    e. All of the above

12) The following are true of nesiritide:
    a. Its primary action is as a vasodilator
    b. It has been shown to be superior to nitroglycerin
    c. It is recombinant b-type natriuretic peptide
    d. a and c
    e. all of the above

   How Do We Evaluate and Treat the Transient Ischemic Attack?

13) Approximately what percentage of patients will suffer a stroke within the first 90 days after experiencing a transient ischemic attack?
    a. 1-2%
    b. 2-8%
    c. 10-13%
    d. 18-22%
    e. 24-28%

14) Groups of patients with atrial fibrillation that have suffered a TIA and do not have a contraindication to anti-coagulation should be considered candidates for anti-coagulation. Patients with which of the following risk factors have even greater potential for benefit with anticoagulation?
    a. Patients with a history of hypertension
    b. Patients with a history of poor ventricular function
    c. Patients with prosthetic heart valves
    d. Patients over the age of 75
    e. all of the above

15) In the ESPS-2 trial patients with stroke or TIA received either aspirin, extended release dipyridamole or a combination. The stroke risk reduction for the combination therapy was?
    a. 1%
    b. 5%
    c. 10%
    d. 37%
    e. 88%

   Advances in the Diagnosis of Stroke: From Biomarkers to Neuroimaging.

16) Which CT change in acute ischemic stroke is an exclusion to thrombolytics:
    a. Loss of gray - white differentiation
    b. Sulcal effacement
    c. Loss of insular ribbon
    d. Compression of ventricular system
    e. Large area of hypodensity

17) The challenges in stroke diagnosis include:
    a. It is a diagnosis largely of exclusion
    b. There is no confirmatory test for stroke early in its evolution
    c. Mimics abound which clinically appear very similar to stroke
    d. Strokes may present with very atypical symptoms
    e. There is great urgency to making a diagnosis to be eligible for recannalization strategies
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