Coagulation Catastrophes: Taking Care of the Most Difficult Cases in Emergency Medicine

JANUARY 2015

EMCREG-INTERNATIONAL MONOGRAPH

Based on the October 26, 2014, Symposium

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Dear Colleagues,

In this EMCREG-International Monograph, you will find a variety of cardiovascular and neurovascular topics which will hopefully be helpful to you in your practice of Emergency Medicine and Hospital Medicine. These manuscripts are based on the 2014 EMCREG-International Symposium, a satellite symposium held on October 26, 2014, during the 2014 ACEP Scientific Assembly in Chicago. The symposium, COAGULATION CATASTROPHES: TAKING CARE OF THE MOST DIFFICULT CASES IN EMERGENCY MEDICINE, emphasizes the importance of understanding the role of coagulation in the care of critically ill and injured patients in the emergency setting and critical care setting.

The sections of this EMCREG-International Monograph discuss the diagnosis of acute coronary syndromes (ACS) using new diagnostic testing such as high-sensitivity troponin assays and CT coronary angiography and the treatment of ACS including heparin, low molecular weight heparin and the novel anticoagulant agents as well as antplatelet therapies including aspirin, clopidogrel, prasugrel, and ticagrelor. The incorporation of these diagnostic and treatment options into the latest ACCF/AHA guidelines is also presented. The role of collaboration between the interventional cardiologist and emergency physician in treating ACS is also discussed. In addition, novel diagnostic testing for determining a patient’s ability to clot blood using thromboelastography or TEG and the emerging role of telestroke in acute ischemia stroke care are described.

The primary emphasis of the first four manuscripts in this EMCREG-International Monograph is on ACS diagnosis and treatment. Appropriate risk stratification of the patient with chest pain in the emergency department (ED) can identify high risk patients who will benefit from antithrombotic treatment using agents such as heparin and low molecular weight heparin and antplatelet agents such as aspirin, glycoprotein IIb/IIIa receptor antagonists, and thienopyridine drugs such as clopidogrel and prasugrel, as well as the newest potent antplatelet agent ticagrelor. A discussion of the currently available antithrombotic and antplatelet agents, as well as controversies and research in these areas, will prepare the emergency physician and hospitalist to provide the highest level of care for ACS in the ED and during the very early period after hospitalization.

In addition to ACS, this monograph will feature two additional important areas of interest to the practicing emergency physician and hospitalist. The use of thromboelastography (TEG) as a diagnostic test for the patient’s ability to clot blood is expanding in use and indications. Routinely used now for trauma and monitoring intra-operative bleeding during hepatic and cardiac surgery, the potential exists for significant expansion of TEG’s use in the ED and intensive care units. For example, TEG has the ability to identify the patient with trauma or sepsis and hypocoagulability. In these patients, hypocoagulability is associated with increased risk of mortality. Finally, there is no other area of treatment for critically-ill patients which is more controversial than stroke management. The use of telestroke to help the practicing emergency physician treat acute ischemic stroke in the ED is growing. Having a stroke expert available using new image transfer technology promises to decrease the time to treatment for acute ischemic stroke and increase the number of appropriate patients treated.

It is our sincere hope that you will find these articles to be useful to you in your daily practice as an emergency physician or hospitalist. Written by EMCREG-International members who are expert clinicians and active researchers from across the United States, this 2014 EMCREG-International Monograph can hopefully serve as a useful source of information for you during the coming year. Each topic is also referenced should you wish to read more about a particular area of interest. In addition, instructions for obtaining CME from the University of Cincinnati College Of Medicine, Office of CME are available at the conclusion of this 2014 EMCREG-International Monograph. Thank you very much for your interest in EMCREG-International educational initiatives and we hope you visit our website for future educational interests in cardiovascular and neurovascular emergencies.

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W. Brian Gibler, MD
President, EMCREG-International
Professor of Emergency Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio USA
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Philadelphia, Pennsylvania

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Ann Arbor, Michigan

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Assistant Professor of Emergency Medicine; Fellow, Neurovascular Emergencies and Neurocritical Care, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH
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Opeolu M. Adeoye, MD
Associate Professor of Emergency Medicine and Neurosurgery, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH; Member, Greater Cincinnati/Northern KY Stroke Team
Objectives

1. Understand the pathophysiology of ACS – both ST-segment elevation and non-ST-segment elevation ACS presenting to the emergency department.

2. Differentiate between the various new technologies for ACS detection including high sensitivity troponin, CT coronary angiography, and novel diagnostic pathway.

3. Apply new diagnostic criteria to improve ACS therapy in the emergency department.

Introduction

The evaluation of patients presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS) has evolved significantly over the past five years. Much of this has been driven by improvements in diagnostic testing, particularly the widespread availability of increasingly sensitive troponin assays and the advent of validated, multimodal approaches to non-invasive assessment of potential coronary artery disease (CAD). The net result has been development of far more efficient and expeditious methods of assessment for patients with chest pain or other symptoms that may be attributable to ACS.

As these advances make their way into practice, physicians will need familiarity with both the utility and functional limitations of relevant diagnostic tests. However, in addition to knowledge of the testing modalities themselves, effective implementation of an early ACS diagnostic approach requires a solid understanding of clinical context and pretest probability. Thus, while contemporary cardiac specific troponins can detect increasingly low levels of cardiomyocyte injury, a positive test result should not be interpreted in isolation and caution should be exercised in assigning a diagnosis of “myocardial infarction” without an associated clinical suspicion of ACS. Likewise, in patients at moderate or high risk for ACS, negative serial troponins are insufficient to rule out the presence of underlying CAD and further testing may be needed.

Electrocardiography

Electrocardiography (ECG) remains the cornerstone of initial evaluation in patients with suspected ACS, serving as the most immediate means for detection of ST-segment elevation myocardial infarction (STEMI) and providing critical information to direct initiation of reperfusion therapy. While enhanced detection of occult STEMI may be possible using an 80-lead body surface mapping system, standard 12-lead ECGs remain the recommended modality for initial patient evaluation and serve as the criterion standard for establishment of a STEMI diagnosis.

Although little has changed from a technical perspective, much focus has been placed on time to ECG with guidelines calling for test performance within 10 minutes of arrival in patients who present with chest pain or other symptoms suggestive of ACS (class I, level of evidence C). Achieving such a broad mandate can be challenging in some clinical settings and attempts have been made to more precisely define the patient profile for whom a rapid ECG is truly warranted. While no approach will be perfect, prioritization schemes based on age and presenting symptoms (Figure 1) can help identify those at greatest risk for STEMI and streamline ECG performance at the point of initial assessment. For patients with a non-diagnostic ECG who remain symptomatic, serial ECGs at 15 to 30-min intervals during the first hour are also recommended (class I, level of evidence C).

Cardiac Biomarker Assessment

Perhaps the greatest advance in assessment of potential ACS exists in the area of cardiac biomarkers, where cardiac specific troponin has emerged as the preferred test to detect myocardial
injury. Unlike many other tests though, where there is uniformity in the meaning of a given result, interpretation of a cardiac specific troponin value requires a basic understanding of clinical chemistry and some insight on the precision profile of the particular assay used. Key operative terms to be familiar with (Table 1) include lower limit of detection, 99th percentile upper reference limit (URL), and coefficient of variation (CV).

### Table 1: Key Operative Terms that Define the Precision Profile of Troponin Assays

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limit of detection</td>
<td>The lowest concentration of troponin that can be detected by a given assay; serves as the cutpoint below which values for troponin will not be reportable.</td>
</tr>
<tr>
<td>99th percentile upper reference limit</td>
<td>The value of troponin which will be undetectable in 99% of the reference population for a given assay; serves as the decision level for diagnosis of acute myocardial infarction.</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>Defined as the ratio of standard deviation to the mean; serves as the primary measure of precision for a given assay and indicates the proportion of detected variability that is due to the assay itself; lower values = greater assay precision and increased reliability of test results.</td>
</tr>
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</table>

**Next Generation Troponin Assays**

According to the Third Universal Definition of Myocardial Infarction (MI), optimal precision is defined by a CV ≤ 10% at the 99th percentile URL. Any value above the 99th percentile URL at this precision level for a given assay is considered positive and serves as the standard for establishing a biomarker diagnosis of acute MI. Early troponin assays were unable to meet this requirement prompting development of more sensitive and precise assays that can reliably detect cardiac specific troponin T (cTnT) or I (cTnI) at increasingly lower concentrations. Referred to as 4th generation (cTnT only), contemporary sensitivity (cTnI only), high sensitivity, or ultrasensitive (Table 2), these newer troponin assays enable accurate identification of even minor degrees of myocardial injury.

While 4th generation and contemporary sensitivity assays have been widely implemented in the United States, high sensitivity and ultrasensitive troponin assays have yet to be approved by the Food and Drug Administration. Despite this, there is extensive experience with them in Europe (where they have been approved for several years) and an appreciation of their future role in the evolving landscape of cardiac care is essential.

### Timing of Measurement

Because newer assays can detect troponin at lower concentrations, they offer the ability to diagnose acute MI shortly after symptom onset and soon after ED presentation. In the vast majority of cases, troponin released from injured myocardium will be detectable with initial sampling on ED arrival or repeat testing three hours later. Thus, with increasingly sensitive troponin assays, most patients will either rule in or rule out for ACS within the first few hours of ED evaluation. When clinical suspicion of ACS is high, the timing of symptom onset is uncertain, or repeat testing at three hours is equivocal, a third test at six hours may be useful. There is little value in further testing beyond six hours and, absent stuttering angina symptoms or clinical deterioration, routine serial troponin measurement at subsequent time points is not needed. Likewise, for patients who present with persistent chest pain that has lasted unambiguously for more than six hours, measurement of a single troponin is reasonable.

### Is It Ischemia?

While the ability to detect the slightest cardiac insult has clear value, the information provided by newer assays represents a significant departure from what many clinicians are used to doing. Perhaps the most important thing to remember when using more sensitive assays is that an elevated troponin represents the likely occurrence of myocardial necrosis and does not, in and of itself, indicate a specific etiology. Experience with real world implementation has shown that increasingly sensitive assays result in many more positive troponin tests, a large proportion of which may not be attributable to ACS or underlying CAD. Though often described as falsely positive when ACS is absent, an elevated troponin, regardless of the cause and independent of the assay used, still represents underlying myocardial injury and portends an increased risk of adverse cardiovascular events. Even when the troponin rise is caused by something other than CAD, it is important not to minimize its significance.

When a non-ischemic etiology is present (Table 3), further management should be directed towards the underlying
problem rather than a presumed coronary based cause. For those with a suspected ischemic etiology, incorporation of ACS pretest probability into interpretation of the troponin result can help with therapeutic decision-making, particularly as it pertains to use of dual platelet and anticoagulant agents, and initiation of an invasive treatment strategy. To facilitate this, a classification scheme has been established with subtyping of patients into five different groups based on the suspected cause of myocardial necrosis (Table 4). From an ED perspective, the key is to distinguish ischemia due to a primary coronary event such as plaque rupture, fissure, or dissection (i.e., Type 1 or spontaneous MI) from an episode triggered by imbalance in myocardial oxygen supply or demand (i.e., Type 2 MI).²⁷

Differentiating between non-ischemic and ischemic causes, particularly in cases of acute heart failure, and among the subtypes of ischemia when present, can be challenging based on history or with measurement of only a single biomarker. Although some laboratories attempt to address this by reporting a troponin above the 99th percentile URL but below some other threshold (often set at 3-5 times the 99th percentile URL) as “indeterminate,” there is limited evidence to support this practice. Instead, demonstration of a rise or fall in cTnT or cTnI on serial testing over the first 3-6 hours is recommended to reduce such uncertainty and improve the specificity for diagnosis of both ACS and Type 1 MI. Determining the level of troponin change over time (i.e., the troponin “delta”) that best predicts ACS and Type 1 MI has remained elusive. Relative delta increases ≥ 20% when the initial troponin value is positive, and at least 50% greater than the 99th percentile URL when baseline levels are not elevated have been proposed.⁸ While such an approach does improve specificity compared to use of the 99th percentile alone, recent data suggest that absolute differences in troponin over time perform better diagnostically than relative ones.⁵ Though non-existent for most assays at present, as data emerge in this area it is likely that each manufacturer will eventually define a numerical delta that correlates with a greater likelihood of ACS and Type 1 MI. Until then, use of relative differences is reasonable to help determine the clinical significance of troponin values.

### Ruling Out Acute Myocardial Infarction

Although accurately detecting troponin elevations and defining the underlying cause is a critical part of emergency medicine, most patients who present to the ED with chest pain or other potential angina symptoms do not have cardiac disease. Identifying these low risk individuals early in the course of evaluation is important and helps to ensure that resources are utilized appropriately. Contemporary, and especially high sensitivity troponin assays allow for this, with undetectable levels carrying a negative predictive value (NPV) for acute MI above 99% when used in undifferentiated ED patients with suspected ACS.⁹,¹⁰ Consequently, the existence of myocardial necrosis can be safely excluded using newer troponin assays and, in the right clinical context, early discharge from the ED can be considered a viable option.

### Other Cardiac Biomarkers

The analytic performance of newer troponin assays obviates the need for measurement of more traditional cardiac biomarkers such as myoglobin and creatine phosphokinase myocardial isoenzyme (CK-MB). However, there is growing evidence to suggest that natriuretic peptides may be useful in patients with suspected ACS, providing additional information on myocardial strain and prognosis. Other markers including heart type-fatty acid binding protein, mid-regional pro-adrenomedullin,
and copeptin have been proposed as potential adjuncts for assessment of patients with suspected ACS. Only copeptin appears to add sufficient incremental diagnostic and prognostic value to be useful in clinical practice, particularly in low-risk patients who may be eligible for discharge from the ED.11

**SUBSEQUENT DECISION-MAKING**

Subsequent decision-making involves risk-stratification for potential major adverse cardiovascular events (MACE), including ACS. Objective determination of this using multivariable models (Table 5) such as the Thrombolysis in Myocardial Infarction (TIMI) risk score11, the Global Registry of Acute Coronary Events (GRACE) risk calculator12, the History, ECG, Age, Risk factors, and Troponin (HEART) score14, the North American Chest Pain Rule (NACPR)15, and the Vancouver Chest Pain Rule16 are preferred over approaches based strictly on clinical gestalt (Table 5). The TIMI risk score has time-honored significance as the first to be developed, but the other decision-support tools were derived from unifferentiated ED patients with suspected ACS and may be better suited for use in the ED setting. However, at present there is insufficient evidence to suggest that any one tool is clearly superior to another17 and all appear to be reasonable for application in clinical practice.

**Disposition Protocols**

By mixing the ability of newer troponin assays to accurately and rapidly detect the presence or absence of myocardial injury with models of objective risk assessment, it is now possible to implement reliable disposition protocols for patients with suspected ACS. An accelerated diagnostic protocol (ADP) that defined patients as low-risk if they had a normal ECG or one without new ischemic abnormalities, a TIMI risk score = 0, and negative contemporary cTnl at presentation and two hours later was recently tested in ED patients with suspected ACS (n=1,975) and found to have a NPV of 99.7% (95% confidence interval [CI]: 98.6-100.0%) for 30-day MACE.18 Changing the TIMI risk score to ≥ 1 and adding a high sensitivity cTnl assay as part of the ADP in a subsequent study involving a subset of the original cohort (n=1,635) and a secondary, validation cohort (n=909), the same NPV for 30 day MACE (99.7%) was demonstrated suggesting the potential to define a significant proportion of suspected ACS cases (approximately 40% in both cohorts) as low-risk with newer assays.19

Because patients deemed to be low-risk based on the combination of TIMI risk score (or one of the other stratification methods) and negative serial contemporary or high sensitivity troponin results appear to be truly low-risk, they may be potentially suitable for outpatient care without further ED testing. To improve uptake among more risk-averse ED practitioners, however, and to ensure that patients receive a consistent, comprehensive guideline based evaluation for potential ACS, any formalized approach to disposition that involves ED discharge should be collaborative in nature and include early cardiology follow-up (i.e., 48-72 hours). Ideally, this should be part of a larger, multidisciplinary pathway for management of suspected ACS with directed care plans for patients across the spectrum of risk. An example of such a pathway is provided in Figure 2.

**Non-Invasive Diagnostic Testing**

Although this discussion has centered largely on the evolving use of cardiac biomarkers, non-invasive diagnostic testing remains a cornerstone of subsequent evaluation. After initial assessment for patients with suspected ACS, emergency physicians are increasingly being called upon to order the most appropriate test, either from the ED or the observation unit. The current American College of Cardiology/American Heart Association (ACC/AHA) Guidelines support the use of provocative testing recommending treadmill ECG, stress myocardial perfusion imaging, or stress echocardiography either before or within 72 hours of discharge in patients with possible ACS who rule out.2 For patients in this group who lack known CAD, guidelines also propose the use of coronary computed tomography angiography (CCTA) to define coronary anatomy or rest myocardial perfusion imaging (MPI) with technetium-99m to identify existing areas of myocardial ischemia.2 While an
### Acute Coronary Syndrome Risk Stratification Scores and Rules

<table>
<thead>
<tr>
<th>NAME</th>
<th>VARIABLES</th>
<th>POINTS</th>
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<th>INTERMEDIATE RISK</th>
<th>HIGH RISK</th>
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<td>2 or more risk factors for CAD</td>
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<td>Prior coronary stenosis ≥ 50%</td>
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<td>ST deviation on ECG</td>
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<td>Use of aspirin in the prior 7 days</td>
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<td>History, ECG, Age, Risk factors, and Troponin (HEART)</td>
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<td>Risk factors</td>
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<td>≥ 3 risk factors or history of CAD</td>
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<td>Troponin</td>
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<td>≥2x normal limit</td>
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<td>1.2x normal limit</td>
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<td>&lt; normal limit</td>
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<td>North American Chest Pain Rule (NACPR)</td>
<td>No score derived. Decision making based on the following variables:</td>
<td>N/A</td>
<td>All 5 variables must be present</td>
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<td>- No history of CAD</td>
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<td></td>
<td>- No chest pain typical of ACS</td>
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<td></td>
<td>- Initial cardiac troponin is negative</td>
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<td>- Ages ≥ 40 years OR age 41-50 years with a negative repeat troponin at 6 hours</td>
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<td>Vancouver Chest Pain Rule</td>
<td>No score derived. Decision making based on the following variables:</td>
<td>N/A</td>
<td>All age-specific variable must be present</td>
<td>Not defined</td>
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<tr>
<td></td>
<td>- Normal initial ECG</td>
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<td></td>
<td>- No prior of ischemic chest pain</td>
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<td>- Age ≤ 40</td>
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<tr>
<td></td>
<td>- Age ≥ 40 with low-risk pain (non-radiating, non-pleuritic, and reproduced by palpation), and an initial negative Troponin</td>
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<td>- Age ≥ 40 with low-risk pain (non-radiating, non-pleuritic, and reproduced by palpation), an initial positive Troponin but no rise in troponin or new ECG changes on repeat at ≥ 3 hours</td>
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invasive strategy is generally recommended for those at greater risk, an ongoing National Institutes of Health funded study is investigating the potential utility of stress cardiac magnetic resonance (CMR) imaging in intermediate to high-risk patients with chest pain and a modestly elevated contemporary sensitivity troponin (NCT01931852).

The preferred test to perform and the appropriate timing of test performance are areas of lingering uncertainty. The ACC/AHA Guidelines are vague on this matter, leaving much of the decision-making to the clinician. From an ED perspective, CCTA has inherent advantages including a relatively rapid turn-around time and provision of results which require limited interpretation for next level decision-making (Table 6). As noted in a recent meta-analysis which included a total of 3,266 patients from four major trials conducted in ED patients with suspected ACS (1,869 undergoing CCTA and 1,397 evaluated by usual care), CCTA is associated with a significant reduction in ED length of stay (up to 77%) and per patient ED cost savings ranging from $286-$1321, compared to usual care.20

In addition, CCTA is safe, with no difference in the rate of death, MI, return ED visits, or recurrent hospitalization for cardiovascular causes versus usual care. Most importantly, the absence of coronary artery stenosis on CCTA precludes the need for further evaluation and essentially eliminates CAD as the underlying cause of chest pain or other suspected angina equivalents.

Despite these benefits, evaluation by CCTA is also associated with increased use of invasive coronary angiography (adjusted odds ratio [OR] = 1.36; 95% CI: 1.03-1.80) and treatment by revascularization (adjusted OR = 1.81; 95% CI: 1.20-2.72). This is a direct result of the information provided by CCTA which is anatomical rather than functional. At many centers, stenosis > 70% on CCTA is considered an indication for invasive coronary angiography, but not all such lesions require intervention. In fact, it has been suggested that a functional assessment should precede an invasive strategy when stenosis is seen on CCTA, but this would require use of a second, non-invasive test. Evaluation of potential hemodynamic compromise associated with coronary artery obstruction can be performed during CCTA without the need for additional contrast using fractional flow reserve (FFR), a ratio of existing versus expected coronary blood flow. Preliminary study of CCTA derived FFR suggests that it improves specificity for identification of lesions that would benefit from revascularization21, but the actual impact on clinical management has yet to be examined.

Whether the downstream costs of further evaluation prompted by the use of CCTA will be offset by potential reductions in the need for future cardiovascular testing and improved patient outcomes is not known. That said, analysis of the Premier database including 549,078 patients from 224 hospitals suggests there is no difference in subsequent readmission for acute MI in facilities with lower versus higher rates of non-invasive diagnostic testing including CCTA and it is unclear what specific value increased testing adds.22 While it may be tempting to perform non-invasive testing on the majority of ED patients with suspected ACS prior to discharge, particularly with modalities such as CCTA that are relatively easy to use, there are multiple considerations that should accompany this approach, including the potential to actually achieve further risk reduction in an already low-risk group. Indeed, of the two studies included in the CCTA meta-analysis that allowed clinician-driven decision-making in the usual care arms, 22% and 36% were safely managed with no additional diagnostic testing.20

**Conclusion**

There have been several important advances in the early diagnosis of ACS that will dramatically impact the future of patient care. The advent of increasingly sensitive troponins is perhaps the most significant of these, enabling earlier detection of myocardial injury and facilitate rule-out of ACS within 3-6 hours of ED arrival. When combined with a multidisciplinary care pathway that is based on objective risk stratification and incorporates a directed approach to non-invasive diagnostic testing, implementation of comprehensive treatment strategy which is clinically appropriate and cost effective may be achievable.

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**Table 6** Potential Reported Findings on Coronary Computed Tomographic Angiography

<table>
<thead>
<tr>
<th>Calcium Score</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lowest risk for coronary artery disease; no further evaluation indicated and assessment of stenosis not routinely needed.</td>
</tr>
<tr>
<td>1 - 80</td>
<td>Low risk for coronary artery disease; assessment of stenosis with risk factor modification and repeat testing in 2-5 years to monitor progression indicated.</td>
</tr>
<tr>
<td>81 - 400</td>
<td>Intermediate to high risk for coronary artery disease; assessment of stenosis with secondary disease prevention and repeat testing yearly to monitor progression indicated.</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>Highest risk for coronary artery disease; assessment for stenosis and admission for provocative testing indicated.</td>
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<table>
<thead>
<tr>
<th>Coronary Stenosis</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% - 25%</td>
<td>Acute coronary syndrome unlikely; routine follow-up not indicated.</td>
</tr>
<tr>
<td>26% - 48%</td>
<td>Acute coronary syndrome unlikely; routine follow-up for risk factor modification indicated.</td>
</tr>
<tr>
<td>50% - 69%</td>
<td>Acute coronary syndrome possible; admission for further evaluation indicated.</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>Acute coronary syndrome likely; admission for further evaluation with possible invasive coronary angiography indicated.</td>
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</tbody>
</table>
References


ANTIPLATELET AGENTS FOR ACUTE CORONARY SYNDROMES: OPTIMAL TREATMENT IN THE ED

James W. Hoekstra, MD
Professor and Chair, Department of Emergency Medicine, Wake Forest Baptist Medical Center, Winston Salem, NC

Objectives
1. Describe the appropriate application of oral antiplatelet agents in NSTE ACS and STEMI, according to the recommendations of the ACCF/AHA STEMI/NSTEMI Guidelines.
2. Describe the mechanism of action of prasugrel, and the trial design and results of TRITON TIMI 38.
3. Describe the mechanism of action of ticagrelor, and the trial design and results of the PLATO trial.
4. Describe the potential applications of prasugrel and ticagrelor in patients with STEMI and NSTEMI.
5. Describe the results of the EARLY trial, and its implications for upstream GPI inhibitor use in NSTEMI.

Antiplatelet therapy is crucially important in the treatment of acute coronary syndromes (ACS), especially at the time of emergency department (ED) identification and subsequently in patients who are transitioned to the cardiac catheterization laboratory for percutaneous coronary intervention (PCI). The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for ST-segment elevation myocardial infarction (STEMI) and Unstable Angina/non-ST-segment elevation myocardial infarction (NSTEMI) were revised, updated, and released to the public and online.1,2 These ACCF/AHA Guidelines incorporate recent clinical trials data and include updated recommendations on treatment strategies for STEMI and non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) treated with or without PCI. The guidelines are relatively specific with regard to ACS antiplatelet therapy options either upstream, prior to PCI, or in the cardiac catheterization laboratory, during PCI. In both STEMI and NSTEMI ACS, treated by an invasive pathway, dual antiplatelet therapy is recommended–aspirin plus another agent. The guideline recommendations for antiplatelet therapy for STEMI and NSTEMI ACS are illustrated in Figures 1 and 2.

Aspirin remains a mainstay in the early treatment of ACS. It carries a Level IA recommendation for the treatment of NSTEMI ACS, and a level IB recommendation for the treatment of STEMI.1,2 Patients with either STEMI or NSTEMI ACS should receive aspirin 162-325 mg prior to arrival or in the ED at the time of presentation. The guidelines also give an IB recommendation for the use of clopidogrel 600 mg orally in patients with either STEMI or NSTEMI. The 600 mg loading dose is recommended prior to PCI in STEMI patients, and as either upstream or pre-PCI therapy for NSTEMI patients. These therapies have been in place for many years, but the 600 mg dosage is relatively new, based on the CURRENT Trial.3 In this trial, the “double dose” of clopidogrel 600 mg loading dose and aspirin 150 mg per day resulted in significant reductions in death, myocardial infarction (MI), and stroke over standard 300 mg clopidogrel dosing.

Clopidogrel’s effectiveness is hampered by two factors. First, it is slow to achieve maximal platelet inhibition (3-6 hours) because it has to be metabolized through the liver to an active metabolite. Second, variability in clopidogrel absorption and liver metabolism has led to the identification of clopidogrel
“non-responders” who never achieve therapeutic platelet inhibition, even at higher doses. These issues are overcome by two new oral P2Y12 receptor inhibitors, prasugrel and ticagrelor. Both of these drugs are quickly absorbed, and thus achieve higher antiplatelet activity in a shorter time period after oral loading dose. Prasugrel is a prodrug which requires blood and intestinal esterases to be hydrolyzed to an active metabolite. Ticagrelor and its main metabolite are both pharmacologically active. Both are approved by the FDA, and available for treatment of STEMI or NSTEMI. These two drugs are not interchangeable, however. Prasugrel, for instance, has a longer half-life than clopidogrel, while ticagrelor has a shorter half-life in the blood. As such, their bleeding profiles are significantly different.

As an alternative to clopidogrel in NSTE ACS, the novel platelet P2Y12 inhibitor prasugrel was recently evaluated in the TIMI 38 trial. In this trial, 13,608 patients with either STEMI or moderate to high risk NSTE ACS and planned intervention for a known intracoronary lesion were randomized in a double blind fashion to receive either a 300 mg load of clopidogrel and 75 mg per day, or a 60 mg load of prasugrel and 10 mg a day, beginning at the time of catheterization and continuing for a year. It should be emphasized that this randomization occurred upstream in NSTE ACS, but only in the cardiac catheterization laboratory after the coronary anatomy was defined. The primary outcome of the trial was death, MI, or stroke at one year. Safety outcomes were also analyzed to determine net clinical benefit. At one year, prasugrel was associated with a 19% reduction in death, MI, and stroke (HR 0.81, 95% CI 0.73-0.90) compared to clopidogrel (Figure 3). Bleeding was increased in the prasugrel group, however, with an overall 0.6% increase in major bleeding (2.4% versus 1.8%, HR 1.32, 95% CI 1.03-1.68). Fatal bleeding, transfusions, and CABG bleeding were all significantly higher in the prasugrel group, and bleeding was especially higher in the elderly (>75 yo) patients with low body weight, and in patients with prior transient ischemic attack (TIA), or stroke (Figure 4). There was a definite trade-off noted between increased efficacy and increased bleeding, prompting the authors of the study to caution against the use of prasugrel in these three high risk groups. The lack of any pre-cath medical management in the TIMI 38 trial, and the high rate of coronary artery bypass grafting (CABG)-related bleeding, makes this drug less applicable in the ED setting for NSTE ACS. In the recent ACCOAST trial, the dangers of pre-treatment prior to catheterization with prasugrel were reiterated. Patients with NSTEMI who were pretreated with prasugrel in this trial had similar ischemic outcomes compared to those treated in the catheterization laboratory, but had an increased rate of bleeding. No benefits to upstream treatment with prasugrel were identified.

The TRITON-TIMI 38 trial also enrolled 3,534 patients with STEMI treated with either primary or secondary PCI. In these patients, prasugrel 60 mg resulted in a 19% relative risk reduction in death, MI, and stroke at 15 months (HR 0.81, 95% CI 0.66-0.99) compared to clopidogrel 300 mg. Bleeding still trended worse in the prasugrel arm, but there were no statistically significant differences in bleeding, including life threatening bleeding. Unlike the NSTE ACS population in
TRITON, the STEMI patients were often randomized to prasugrel upstream, prior to angiography. As such, these results support the use of prasugrel in the ED in STEMI patients.

The guidelines give a IB recommendation for the use of prasugrel 60 mg orally as a loading dose at the time of primary PCI for STEMI. They also give a IA recommendation for prasugrel 60 mg orally as a loading dose at the time of PCI for NSTE ACS, except in patients already on clopidogrel. There is no recommendation for upstream use of prasugrel in NSTE ACS patients. The guidelines also include a class III recommendation (harmful) for the use of prasugrel in patients with age >75 years or a prior history of TIA/Stroke.

The other potent antiplatelet which is FDA approved for ACS is ticagrelor. Like clopidogrel and prasugrel, ticagrelor is a P2Y12 platelet receptor inhibitor. Unlike clopidogrel and prasugrel, however, it is not a thienopyridine. Ticagrelor changes the conformation of the P2Y12 site, resulting in a reversible change in the receptor which is dependent on the drug’s concentration for inhibition. Oral intake of ticagrelor results in rapid onset of potent antiplatelet activity, higher than levels seen with clopidogrel. Ticagrelor has a shorter half-life than clopidogrel, necessitating twice daily dosing, and theoretically leading to earlier reversal of antiplatelet activity.

Ticagrelor was evaluated in the PLATO trial, which enrolled 18,624 patients with either STEMI or NSTE ACS destined for the cardiac catheterization laboratory. Unlike the TRITON trial, patients in PLATO were enrolled and randomized upstream, prior to their coronary angiograms. Also, unlike in TRITON, the loading dose of clopidogrel was not specified, allowing a significant percentage of patients in the clopidogrel arm to receive a 600 mg loading dose prior to PCI. Approximately 70% of the patients in PLATO underwent PCI, and 30% were treated with CABG, medical therapy, or no therapy. The primary outcome of the trial was death, MI, and stroke at one year.

Compared to clopidogrel, ticagrelor resulted in a 16% reduction in death, MI, and stroke in ACS patients at one year (HR 0.84, 95% CI 0.75-0.94). In addition, cardiac mortality was reduced in the ticagrelor group at one year from 5.1% to 4.0% (HR 0.79, 95% CI 0.69-0.91) (Figure 5). Total major bleeding, transfusions, and life-threatening bleeding were not significantly different between groups, but when non-CABG bleeding alone is analyzed, there was a significant increase in non-CABG bleeding with ticagrelor (4.5% versus 3.8%, p=0.026). This was offset by a non-significant decrease in CABG bleeding with ticagrelor (7.4% versus 7.9%, p=NS). Despite theoretical advantages of a short half-life antiplatelet agent in patients proceeding to CABG after angiogram, there were no significant reductions in bleeding in the CABG cohort in PLATO.

The PLATO trial enrolled 8,430 patients with STEMI, randomized to ticagrelor versus clopidogrel. Compared to clopidogrel, ticagrelor resulted in a 15% relative risk reduction in death, MI, and stroke at one year (HR 0.85, 95% CI 0.74-0.97). Bleeding rates in the STEMI patients were similar between ticagrelor and clopidogrel, making ticagrelor a viable option in ED treatment of STEMI prior to primary PCI. In the recent ATLANTIC trial, 1,862 patients with STEMI were randomized to receive ticagrelor upstream, in the ambulance prior to PCI, versus in the cardiac catheterization laboratory at the time of PCI. The primary endpoints of ST-resolution or TIMI-3 coronary artery flow prior to catheterization were not significantly affected by upstream ticagrelor treatment, but stent thrombosis was significantly reduced at seven days and 30 days. There were no differences in bleeding between groups.

The guidelines give a IB recommendation for the use of ticagrelor 180 mg orally as a loading dose at the time of primary PCI for STEMI. These guidelines also give a IA recommendation for ticagrelor 180 mg orally as a loading dose either upstream in the ED or at the time of PCI for NSTE ACS. Ticagrelor is also given a IIaB recommendation over the use of clopidogrel in NSTE ACS patients. This gives ticagrelor the unique advantage of being universally recommended for the invasive treatment of STEMI or NSTE ACS, regardless of the setting or the timing of therapy. It is also the only antiplatelet agent with an associated mortality reduction in clinical trials.

In addition to the oral P2Y12 agents, glycoprotein IIb/IIIa inhibitors (GPI) remain as antiplatelet alternative therapies in...
ANTIPLATELET AGENTS FOR ACUTE CORONARY SYNDROMES: OPTIMAL TREATMENT IN THE ED

STEMI and NSTE ACS. The GPI agents include abciximab, eptifibatide, and tirofiban. These are potent intravenous antiplatelet agents that provide instant antiplatelet activity at a higher level than oral agents. They have also, however, been associated with higher bleeding rates than the oral P2Y12 agents. All are approved for the treatment of high risk ACS in the cardiac catheterization laboratory, and the small molecule drugs (eptifibatide and tirofiban) are also approved for upstream use prior to the catheterization laboratory in NSTE ACS. The EARLY trial evaluated the use of eptifibatide upstream, prior to catheterization, in patients with NSTE ACS, versus routine use in the cardiac catheterization laboratory.13 Although there was a trend toward reduction of ischemic endpoints in patients treated with eptifibatide upstream, this was offset by a statistically significant increase in bleeding. This effect was also seen in the ACUITY Timing trial.14 As such, with these data and with the introduction of potent upstream oral antiplatelet alternatives, such as ticagrelor, the use of GPI upstream in NSTE ACS has decreased. The ACCF/AHA Guidelines for STEMI give GPI therapy a IIaB recommendation, only at the time of cardiac catheterization.1 The NSTE ACS Guidelines give GPI use a IIaB recommendation upstream, prior to catheterization, and a IIb recommendation at the time of cardiac catheterization.1

In high risk patients with chest pain and either STEMI or NSTE ACS, current ACCF/AHA Guidelines recommend early aggressive antiplatelet therapy followed by definition of the coronary artery anatomy and subsequent PCI. Upon patient identification in the ED, platelet inhibitors should be initiated early and continued through angiography. The currently available platelet inhibitors include aspirin, clopidogrel, prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors. The emergency physician must be knowledgeable regarding the use of these pharmacological agents in the treatment ACS in the ED.

References

ANTICOAGULATION FOR ACUTE CORONARY SYNDROMES: PROVIDING GUIDELINE-DRIVEN THERAPY IN THE ED

Charles V. Pollack, MD
Professor and Chair, Department of Emergency Medicine, Pennsylvania Hospital, University of Pennsylvania, Philadelphia, PA

Objectives

1. Describe the clotting system and its role in ACS.
2. Describe the use of heparin and low molecular weight heparin in the ED.
3. Describe the novel anticoagulants including their mechanism of action as well as their toxicity.

While the aggregation of activated platelets is thought to be at the pathologic root for occlusion of an epicardial artery that results in myocardial ischemia and infarction, activation of the coagulation cascade and the resulting conversion of fibrinogen to fibrin is the final step in stabilization of the platelet-rich thrombus. Antithrombotic therapy—both antiplatelet and anticoagulant—is therefore foundational in the management of acute coronary syndrome (ACS). A number of agents have been studied, validated, and approved for acute management of ACS and are therefore pertinent to emergency department (ED) care. Others have failed to demonstrate utility in acute management but may still have a role later in ACS care, such as in the cardiac catheterization laboratory. A group of novel oral agents may hold further promise of benefit in secondary prevention of ACS that, while not initiated in the ED, may impact ED management when the patient later presents for anginal symptoms, for abnormal bleeding, or for other issues unrelated to coronary artery disease.

Anticoagulation therapy is generally considered the first step in antithrombotic therapy in the ED management of suspected or confirmed ACS. Concomitant use of aspirin and a P2Y12 antiplatelet agent is supported by trial data, by label, and by guidelines, and is often initiated in the ED. Parenteral antiplatelet therapy with glycoprotein IIb/IIIa receptor antagonists may offer benefits in selected ED patients with ACS, however this group of drugs is primarily used in the cardiac catheterization laboratory. This paper, however, focuses only on anticoagulant agents.

Anticoagulation is appropriate for patients deemed to be at intermediate or higher ACS ischemic risk. There are many options for anticoagulation in the upstream or ED environment, and the choice is informed by many issues, including (1) emergency physician preference, (2) cardiologist preference, (3) perceived level of ischemic risk, (4) concern for hemorrhagic risk, (5) likely duration of therapy prior to angiography and possible revascularization, (6) logistical issues such as FDA labels and formulary inclusion, and (7) local standard of care.

Indirect and direct parenteral anticoagulants–unfractionated heparin, low-molecular-weight heparins, fondaparinux, and bivalirudin—all have evidence-supported roles in the early medical and interventional management of ACS. Other agents—notably and most recently, otamixaban—have been studied in ACS but have not been shown to have a beneficial role in ACS management. After the acute phase, a generally prothrombotic state, from persistent exposed prothrombotic material at the healing site of atherosclerotic plaque rupture and from the infarct-related artery and post-intravenous anticoagulant rebound hypercoagulability, may persist. Effective management of this ongoing risk from the coagulation cascade requires an understanding of the data available for each option among this broad class.

The ACCF/AHA Guidelines for the management of non-ST-segment-elevation (NSTE) ACS were updated in September 2014.1 The Class I recommendations for acute anticoagulation therapy listed are as follows:

1. In patients with NSTE ACS, anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:
   a. Enoxaparin: 1 mg/kg subcutaneous (SC) every 12 hours (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min), continued for the duration of hospitalization or until percutaneous coronary intervention (PCI) is performed. An initial intravenous loading dose is 30 mg. (Level of Evidence: A) Note that the use of intravenous enoxaparin in NSTE-ACS is NOT approved by the US FDA.
   b. Bivalirudin: 0.10 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients managed with an early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor, provided the patient is also treated with dual antiplatelet therapy. (Level of Evidence: B) Note that this recommendation is limited to the management of patients known to be destined for diagnostic angiography after ED care.
c. Fondaparinux: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed. (Level of Evidence: B) If PCI is performed while the patient is on fondaparinux, an additional anticoagulant with anti-IIa activity (either UFH or bivalirudin) should be administered because of the risk of catheter thrombosis. (Level of Evidence: B) Note that the use of fondaparinux in NSTE-ACS is NOT approved by the US FDA.

d. UFH IV: initial loading dose of 60 IU/kg (maximum 4,000 IU) with initial infusion of 12 IU/kg per hour (maximum 1,000 IU/h) adjusted per activated partial thromboplastin time to maintain therapeutic anticoagulation according to the specific hospital protocol, continued for 48 hours or until PCI is performed. (Level of Evidence: B)

Unfractionated Heparin

Unfractionated heparin (UFH) has been the standard for anticoagulation in the management of myocardial ischemia for many years, and generally remains despite its limitations the standard against which new anticoagulant options are measured. The UFH exerts its therapeutic effect by accelerating the action of circulating antithrombin III (AT-III, now often referred to as simply “antithrombin”), a proteolytic enzyme that inactivates Factor IIa (thrombin), Factor IXa, and Factor Xa. The UFH-AT-III complex prevents thrombus propagation but does not lyse or destabilize existing thrombi. Conventional teaching in ACS pharmacology is that UFH has both early, by blocking Factor Xa (when unimpeded has an important impact of amplification of the clotting cascade), and late (antithrombin [Factor IIa]) impact. Many cardiologists consider it an advantage that the effect of UFH can be readily and repeatedly measured—in the ED with the activated partial thromboplastin time (aPTT) assay and in the cardiac catheterization laboratory with the activated clotting time (ACT). Still, the disadvantages of UFH are widely recognized—namely, its relatively poor bioavailability which stems from its many nonproductive interactions with plasma proteins and endothelial cells and its activation of the PF4 receptor on platelets, which may result in heparin-induced thrombocytopenia (HIT) and paradoxical pathologic thrombosis. If necessary, UFH can also be rapidly and reliably reversed with protamine sulfate.

The initial, placebo-controlled support for UFH derives from six relatively small trials.\(^{5,7}\) In aggregate these studies suggest that the benefit of adding UFH to aspirin amounts to a statistically significant reduction in early (up to 30 days, depending on the study) death and myocardial infarction (MI) of up to 54%. For many years now the only “new” data on the use of UFH in ACS has been on its use as a control versus newer anticoagulants such as low-molecular weight heparins and bivalirudin. When used, UFH appears to be most effective when given via a weight-adjusted dosing regimen\(^{6}\) instead of a fixed initial dose (e.g., 5,000 IU loading dose, 1,000 IU/h initial infusion). The recommended weight-adjusted regimen is an initial loading dose of 60 IU/kg (maximum 4,000 IU) and an initial infusion of 12 IU/kg/h (maximum 1,000 IU/h), adjusted using a standardized nomogram.

The most recent ACCF/AHA Guidelines for the management of STEMI provide the following Class I recommendations for UFH.\(^\text{9}\)

1. In STEMI being managed with primary PCI: bolus of 40-60 U/kg (maximum 4,000 U) followed by an infusion of 12 U/kg/hr (maximum 1,000 U), or successive boluses in the cardiac catheterization laboratory based on ACT monitoring and whether or not glycoprotein IIb/IIIa inhibitors are used.

2. In STEMI being managed with fibrinolysis: bolus of 60 U/kg (maximum 4,000 U) followed by an infusion of 12 U/kg/hr (maximum 1,000 U) initially adjusted to maintain aPTT at 1.5 to 2.0 times normal.

Enoxaparin

The low-molecular-weight heparin (LMWH) enoxaparin is specifically supported by the most current ACCF/AHA Guidelines for both NSTE ACS and STEMI.\(^{1,9}\) LMWHs are readily absorbed after subcutaneous administration and exhibit less platelet activation and consequently a lower incidence of HIT.\(^{10}\) Also unlike UFH, the anticoagulant activity of enoxaparin does not require routine monitoring. The dose of enoxaparin is 1 mg/kg SC every 12 hours for NSTE ACS. In high-risk patients or those going expeditiously to the cardiac catheterization laboratory, an initial intravenous loading dose of 30 mg can be given but this dosing approach is NOT approved in the US FDA label. In patients with impaired renal function (creatinine clearance [CrCl] <30 mL/minute), which is a more common finding in older patients, the dose should be reduced to 1 mg/kg SC once daily, and strong consideration should be given to UFH as an alternative. Monitoring of its anticoagulant activity is not required, and enoxaparin does not affect the aPTT or ACT.

In the ESSENCE trial for patients with NSTE ACS, the rates of recurrent ischemic events and invasive diagnostic and
therapeutic procedures were significantly reduced by enoxaparin therapy in the short term compared to UFH and the benefit was sustained at one year.11 In the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial of high-risk patients with NSTE ACS managed with an early invasive strategy, there was no significant difference in death or MI at 30 days between those randomized to enoxaparin and those randomized to UFH. There was more TIMI major bleeding in those treated with enoxaparin, but similar rates of GUSTO severe bleeding and transfusion. It is thought that at least some of the increased bleeding may have been related to patients randomized to UFH and 9.9% of enoxaparin patients and in 13.8% of UFH patients within 30 days of STEMI, the primary endpoint occurred in 12% of patients randomized to UFH and 9.9% of those receiving enoxaparin (17% relative risk reduction [RRR], p < 0.001). There was a small excess of overall major bleeding in the enoxaparin arm, (2.1% vs 1.4%, p < 0.001), but not of fatal bleeding or intracranial hemorrhage.12 Furthermore, 2,178 patients went on to PCI after fibrinolytic therapy, which occurred on randomized therapy if it occurred within 8 days (n = 2,178). Among patients who underwent PCI within 30 days of STEMI, the primary endpoint occurred in 10.7% of enoxaparin patients and in 13.8% of UFH patients (23% RRR, p < 0.001), with no difference in major bleeding.13 Per FDA label and ACCF/AHA Guidelines, the recommended dose of enoxaparin in STEMI patients receiving fibrinolytic therapy is as follows:

1. When serum creatinine ≤ 2.5 mg/dL in men and ≤ 2.0 mg/dL in women—if ≤ 75 years of age, 30 mg IV bolus, then 1.0 mg/kg subcutaneously fifteen minutes later and every 12 hours thereafter;
2. If > 75 years of age, omit bolus and administer 0.75 mg/kg every 12 hours; if estimated creatinine clearance is < 30 cc/min, change 12-hour dosing intervals to 24 hours.9

The potential role of enoxaparin in STEMI managed invasively was evaluated in the ATOLL trial, which randomized about 900 patients undergoing PCI for acute STEMI to receive either IV enoxaparin or UFH with the procedure. The two groups' subsequent 30-day rates of a complex composite primary end point that included death and major bleeding were not significantly different, although the enoxaparin group showed a favorable trend. Also, the LMWH significantly outperformed UFH for most of the trial’s prospectively defined secondary end points, which generally were composites of serious clinical events.14 Intravenous enoxaparin is not labeled for support of primary PCI in STEMI, and is not mentioned in the most recent ACCF/AHA STEMI Guidelines.9

**Fondaparinux**

Fondaparinux is a synthetic pentasaccharide with the AT-III binding site of UFH. Because of its small and uniform chain size, the fondaparinux-AT-III complex can bind only Factor Xa, and not thrombin, so fondaparinux has no measurable antithrombin activity. It is also thought to be associated with a very, very low rate of PF4 activation and hence rare HIT risk. Fondaparinux is readily absorbed after SC dosing and has a long half-life, allowing once daily dosing. It is contraindicated in patients with a creatinine clearance less than 30 mL/min. Like enoxaparin, monitoring of its anticoagulant activity is neither required nor can it be measured by aPTT or ACT.

OASIS-5 considered the possible role of fondaparinux in NSTE ACS.13 The OASIS-5 investigators compared a control strategy of enoxaparin 1.0 mg/kg SC twice daily (once daily if creatinine clearance was < 30 cc/min), coupled with UFH at the time of PCI if performed more than 6 hours after the last enoxaparin dose, versus a strategy of fondaparinux 2.5 mg SC daily (one-third the venous thrombosis treatment dose), with more fondaparinux or UFH at the time of PCI. The OASIS-5 trial was designed and powered as a noninferiority trial, and was the first trial of anticoagulation in ACS that did not use UFH as a control arm. After enrollment of about 60% of the 20,078 NSTE ACS patients in the study, the protocol was amended to allow more UFH in the catheterization laboratory. This was in response to the finding that catheter-associated thrombus was reported three times more frequently (0.9% vs 0.3%) in the fondaparinux arm than in the enoxaparin arm,13 but given the findings of increased bleeding in the SYNERGY study among patients who received both enoxaparin and UFH,11 the change may have negatively impacted the safety profile of enoxaparin in this double-blind, double-dummy study.

In OASIS-5, only about two-thirds of the patients underwent diagnostic angiography; just over half of these had PCI, and
the CABG rate overall was under 10%. The primary ischemic outcome (death, MI, or refractory ischemia) at nine days showed no difference between the two groups (5.8% with fondaparinux, 5.7% with enoxaparin; hazard ratio for fondaparinux, 1.01; 95% CI, 0.90, 1.13), but met the noninferiority margin of 18.5%. At 30-day and at six-month follow-up, patients receiving fondaparinux showed a nonsignificant trend towards better composite ischemic outcomes, although the single endpoints of death at 30 days (p = 0.02) and 180 days (p = 0.05), and of stroke at 180 days (p = 0.04) significantly favored fondaparinux. In the safety analysis of OASIS-5, major bleeding was much less common in the fondaparinux arm at nine days (2.2% vs 4.1%; hazard ratio 0.52, p < 0.001), driving a net benefit (primary ischemic composite plus major bleeding) that favored fondaparinux (7.3% vs 9.0%; hazard ratio 0.81; 95% CI, 0.73, 0.89; p < 0.001).15

The OASIS-6 trial was an international, double-blind, double-dummy comparison of fondaparinux versus placebo or UFH in 12,092 patients with STEMI who presented within 12-24 hours of symptom onset.16 Patients with serum creatinine > 3.0mg/dL were excluded. Patients selected by their treating physician to receive STEMI management in which no UFH would ordinarily be given, such as fibrinolytic therapy with streptokinase or no reperfusion therapy were randomized to receive either fondaparinux or placebo (Stratum I, n = 5,658). Patients selected for fibrinolysis with a fibrin-specific agent, for primary PCI, or for no reperfusion therapy but with anticoagulation, were randomized to either fondaparinux or UFH (Stratum II, n = 6,434). The study dose of fondaparinux was 2.5mg IV at randomization, then 2.5mg SC daily thereafter. The median treatment duration was eight days for fondaparinux in Stratum I and, in Stratum II, seven days for fondaparinux and 45 hours for UFH. The primary endpoint for efficacy was death or nonfatal re-MI at 30 days.16

Nearly one-quarter of the patients in OASIS-6 received no reperfusion therapy. Overall, the primary endpoint was significantly reduced in the group receiving fondaparinux compared to control therapy (11.2% vs 9.7%, RRR 14%, p = 0.008), with a significant and persistent reduction in mortality at 9, 30, and 180 days. Fondaparinux was superior to the comparison treatment in both strata, but the subset of Stratum II patients undergoing primary PCI received no benefit compared to UFH (8.5% of fondaparinux patients with primary endpoint, vs 8.2% with UFH). At least some of this deficiency in primary PCI was due to guiding catheter thrombus in patients instrumented on fondaparinux monotherapy,18 a problem similar to that reported in patients with NSTE ACS in OASIS-5.15 There was a tendency towards fewer major bleeding complications with fondaparinux in OASIS-6.16

Fondaparinux is NOT labeled for use in ACS in the US. In the ACCF/AHA Guidelines for both STEMI (not managed with primary PCI) and NSTE ACS, it is a possible option, especially in patients with high bleeding risk.

**Bivalirudin**

Bivalirudin is an intravenous direct thrombin inhibitor—that is, it does not require the intercession of AT-III to impact the clotting cascade. It affects only Factor IIa (thrombin). Bivalirudin is approved as a procedural anticoagulant. There is evidence from both a large NSTE ACS trial (ACUITY) and a contemporary STEMI primary PCI trial that bivalirudin is an effective anticoagulant with a bleeding risk lower than that of indirect anticoagulants.17,18 However, from ACUITY (NSTE ACS) and from HORIZONS (STEMI), there is no clear evidence that initiation of bivalirudin in the ED is associated with, nor is it necessary for, improved ischemic outcomes. For example, in HORIZONS, 66% of the patients undergoing primary PCI who were randomized to receive bivalirudin actually received UFH in the ED, without apparent decrement in the overall benefit of bivalirudin.18 In the ACCF/AHA Guideline recommendations for NSTE ACS, bivalirudin receives a I-B recommendation, while in primary PCI for STEMI, it is graded at I-C.19 The anticoagulant effect of bivalirudin can be monitored in the catheterization laboratory by the activated clotting time (ACT).

**Omatixaban**

The rapidly acting, intravenous direct Xa inhibitor otamixaban has been viewed as a potential safe and effective anticoagulant for ACS being managed invasively. The TAO trial was a double-blind superiority trial that enrolled 13,229 patients with NSTE ACS and a planned early invasive strategy who were randomized to otamixaban (bolus and infusion, at one of two doses) or unfractionated heparin plus, at the time of PCI, eptifibatide. Results showed that the primary efficacy outcome—the composite of all-cause death or new MI through day seven—was not significantly different between groups. There were also no differences for the secondary end points, including procedural thrombotic complications, which were a problem with the previous factor Xa inhibitor, fondaparinux, in the OASIS-5 study. The primary safety outcome of TIMI major or minor bleeding through day seven was increased with otamixaban.19 There are no plans for further development of otamixaban in this therapeutic area.
Secondary Prevention and Newer Oral Anticoagulants

Warfarin has been effective in some studies of post-ACS patients, but other studies showed either no efficacy benefit over ASA alone or worrisome bleeding risks that outweigh ischemic benefit. The benefit-risk balance of warfarin is cited in the absence of support for routine use in secondary prevention in current ACS guidelines.

In the phase II ESTEEM trial, however, ximelagatran (an oral direct thrombin inhibitor) plus aspirin was significantly more effective than ASA monotherapy in reducing the composite endpoint of death, nonfatal reinfarction, and severe recurrent ischemia in a high-risk population randomized within 14 days after an acute event. The risk reduction was evident within the first month and the difference was maintained, or even increased, over six months of treatment. In contradistinction to warfarin trials, major bleeding was not significantly increased in the ximelagatran-treated groups relative to placebo, although the cumulative risk for total bleeding (major and minor) was higher in the ximelagatran groups. Nonetheless, the ESTEEM data have been widely interpreted as providing clear evidence that a non-warfarin oral anticoagulant might actually prevent new coronary events in a secondary prevention setting. Ximelagatran was subsequently found to be associated with hepatotoxicity that prevented its approval and widespread adoption and further study was stopped due to this side effect.

Even newer non-warfarin anticoagulants have potential utility in the longer term management of coronary artery disease, and they are the same agents being studied in stroke prevention in atrial fibrillation (AF): rivaroxaban, apixaban, and dabigatran. All three drugs have been studied as adjuncts to dual antiplatelet therapy (DAPT) in secondary prevention for patients after an episode of ACS.

The ATLAS ACS-TIMI 46 trial was a dose-ranging study designed to find the best dose of rivaroxaban in ACS. Patients were stratified by the choice of background antiplatelet therapy—dual antiplatelet therapy (DAPT) or aspirin monotherapy. Rivaroxaban caused significant and dose-dependent increases in bleeding, with the biggest increase in patients receiving DAPT. Although there were no overall significant differences in the primary endpoint of death, MI, stroke, or severe recurrent ischemia requiring revascularization, there was a significant benefit observed in the group of patients who received aspirin monotherapy.

ATLAS ACS 2-TIMI 51 was a Phase 3 trial that randomized 15,526 patients with recent ACS to receive twice-daily dosing of either placebo, rivaroxaban 2.5 mg, or rivaroxaban 5 mg. Ninety-three percent of patients received DAPT. Over a mean follow-up period of 13.1 months, rivaroxaban was found to reduce the triple endpoint of cardiovascular death, myocardial infarction, or stroke (HR = 0.84; 95% CI, 0.74-0.96; P = .008), with significant reductions versus placebo for both 2.5 mg BID and 5 mg BID. The 2.5 mg dose group had a significant reduction in all-cause mortality (HR = 0.68; 95% CI, 0.53-0.87; P = .002) compared with placebo. Rivaroxaban was also associated with an overall increase in major bleeding (HR = 3.96; 95% CI, 2.46-6.38; P = .001) without a significant increase in fatal bleeding, and there was a significantly decreased rate of fatal bleeding in the 2.5 mg dose group compared with the 5 mg dose group (P = .04). Rivaroxaban has been submitted to the FDA for approval in secondary prevention after ACS but has not yet been approved for this indication.

Apixaban has been studied in this regard in the Dose Ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients with Recent Acute Coronary Syndrome (APPRAISE) trials. APPRAISE-1 was a Phase 2, dose-ranging study that randomized 1,715 patients with recent ACS to receive either placebo or apixaban at one of four doses: 2.5 mg twice daily (BID), 10 mg QD, 10 mg BID, or 20 mg QD. Nearly all patients received aspirin and 76% received DAPT. The primary outcome was major or clinically relevant bleeding. The two higher-dose arms were discontinued early because of a relative excess in bleeding. The remaining results showed a dose-dependent increase in bleeding risk and a trend toward a reduction in ischemic events. Similar outcomes were found among patients taking ASA or DAPT. The follow-on APPRAISE-2 Phase 3 trial randomized 7,392 patients after ACS to receive either apixaban 5 mg BID or placebo with a primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke. Ninety-seven percent of patients received aspirin and 81% received DAPT. The study was terminated early due to an increase in major bleeding without a significant improvement in efficacy after a median follow-up of 241 days.

The RE-DEEM trial considered the potential role of the anti-IIa novel oral anticoagulant dabigatran in the secondary prevention of ACS. In this study, 1,861 patients with at least one cardiovascular risk factor aside from their acute event, which included prior MI in 29%, diabetes in 31%, and heart failure in 12%, were randomized to placebo or to dabigatran at one of four dosages starting within a few weeks (mean 7.4 days) of acute STEMI or non-STEMI and continuing for six months. Patients were already on aspirin and clopidogrel and about half had undergone PCI at the time of randomization. Dosages ranging from 50 mg twice daily to 150 mg twice daily were all associated with six-month rates of “major and clinically relevant
minor bleeds” that the investigators called “low and acceptable” - no higher than 2%—despite a significant dose-related rise in the risk of bleeding complications (p<0.001). Clinical event rates in the trial were also low, although RE-DEEM was not powered for clinical outcomes.33 No label for secondary prevention with dabigatran has been pursued to date.

Conclusion

Nowhere is it clearer than with anticoagulant therapy that “one size” does not fit all. Evaluation of anticoagulant strategies is an active, ongoing area of investigation. It is difficult to draw conclusions that one anticoagulant strategy is to be preferred over another based on studies in which dosing, treatment duration, timing, and concomitant medical and interventional therapy may vary. A number of acceptable anticoagulant strategies can be recommended, but preferences for one strategy over another may be elusive on a global basis. It is better to seek prospective agreement among all the stakeholders of ACS care (emergency physicians, hospitalists, noninterventional cardiologists, interventional cardiologists) within a specific institution and to develop evidence-based, guideline-consistent protocols that can be readily referenced and used to minimize the chance of medication errors and double anticoagulation when personal preferences are superimposed on an already-initiated treatment plan. It is often best, if sometimes politically challenging, for emergency physicians to take the lead in developing these approaches.

References


OBJECTIVES

1. Describe the collaborative relationship between emergency physicians and cardiologists in the care of patients with ACS.

2. Describe the development of a care pathway for ACS which involves input from both specialties and defines responsibilities for care.

3. Discuss the role of upstream care of ACS either from a referring hospital perspective or in the ED prior to the patient going for cardiac catheterization.

INTRODUCTION

Evaluation in the emergency department (ED) for patients with acute coronary syndrome (ACS) is one of the most important steps in the first part of the management of this disease process from ST-segment elevation myocardial infarction (STEMI) requiring reperfusion to other less emergent situations. The management of ACS to some extent mimics the setting of trauma where early diagnosis and intervention become key for survival and subsequent outcome. Much has been learned about the management of ACS in the last several decades. The field has been transformed with great collaboration among emergency physicians as well as cardiologists and invasive cardiologists. The importance of the ED in the early phase of ACS is highlighted by the involvement of emergency physicians in the development of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for STEMI and non-ST-elevation acute coronary syndromes (NSTEMI). This collaboration started some 15 years ago with a project to try to improve the adherence to the ACS guidelines. The time there was relatively little collaboration outside of clinical investigation between the two specialties which had been carried out for a number of years. With the development of guidelines and the evaluation for adherence to these pathways, the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACCF/AHA Guidelines (CRUSADE) Quality Improvement Initiative emerged as a project that addressed this important component. This project brought about a great level of collaboration that led to many improvements in the process of care for patients with NSTE ACS. This has evolved into a registry developed primarily for STEMI. In this review, some of the important features which led to this collaboration will be discussed, but also provide some in-depth information regarding how the field has evolved to a process of care that is now very much streamlined for improving outcomes in ACS.1

EARLY TRIAGE AND DIAGNOSIS

The ACS disease processes fall into two broad categories, namely STEMI and NSTE ACS. The former is based on the 12-lead electrocardiogram which identifies patients with STEMI in the need of reperfusion therapy; typically percutaneous coronary intervention (PCI) in today’s healthcare settings. The NSTE ACS patients are identified by non-specific electrocardiographic abnormalities and typically elevation in serum troponin markers (either T or I). The immediate triage of a patient with an electrocardiogram therefore becomes the key event in a patient that is being seen for acute chest pain or shortness of breath. ST-segment elevation indicates an acute emergency where reperfusion therapy should ideally be initiated immediately, within 10 minutes for fibrinolytic therapy or 60 minutes for primary PCI. This requires a very efficient system to make this happen. Unfortunately, not all hospitals offer primary PCI in the United States and even less hospitals do so internationally. Therefore, in smaller ED settings or hospitals where primary PCI is not available, the decision has to be made to use fibrinolytic therapy or send the patient for reperfusion therapy to another hospital with PCI capability. This latter approach takes time and such a delay increases cardiac muscle death, so having a process to deal with STEMI becomes important.

In addition to triage for a diagnosis of patients with possible ACS, it is also helpful to triage for risk. The Global Registry of Acute Coronary Event (GRACE) risk score has been used extensively worldwide to identify risk using very simple variables, as shown in Table 1.2 This score is of less value in patients with STEMI as the patient is triaged by 12-lead electrocardiogram immediately to acute cardiac catheterization with primary angioplasty, but it is much more helpful in the broader patient population of NSTE ACS, which includes NSTEMI as well as unstable angina. In this type of setting, a high GRACE risk score indicates a patient which should be managed more invasively and sooner compared with low risk patients.

In addition to the GRACE risk score, one also has to evaluate the risk for bleeding.3 By evaluating the risk for bleeding, concomitant antithrombotic therapies as the ones used in this
setting and the risk for bleeding complication can be assessed. Therapeutic strategies which are important during this triage phase include appropriate dosing of anticoagulant as well as antiplatelet agents. Particularly, intravenous glycoprotein IIb/IIIa receptor blockers need to be carefully adjusted not only for age but also for renal function. The CRUSADE bleeding score can also be easily calculated and will allow physicians also to consider different type of arterial access for the cardiac catheterization such as radial arterial access versus femoral access (Table 2).3

Importance of Adherence to Guidelines for Better Overall Outcomes

In the CRUSADE National Registry, the importance of adhering to the NSTE ACS guidelines can be linked with overall outcome.1 The hospitals with the best adherence also had the lowest 30-day mortality even when adjusted for differences in individual patient characteristics (Figure 1).1 This highlights the importance of adhering to the guidelines for improving care. What was most striking in this early evaluation was the importance of guideline adherence for the elderly (Figure 2).4

This further highlights that even among elderly patients where sometimes there is concern that multiple active treatment strategies may be harmful, following the guidelines improves outcomes. Furthermore, in the very elderly, such as the patients over the age of 90, there is also a step-wise relationship with better outcomes if the guidelines are followed. These seminal papers from the CRUSADE Registry were also highlighted by a similar observation from the GRACE Registry where a step-wise relationship to improved outcomes was identified.5,6 These findings and others suggest that adhering to guidelines is the optimal way for improving care in patients with ACS.

Another area that has not been studied much is how the early adherence to guidelines shapes further care. An important study from the CRUSADE Registry identified patients who had a high use of adherence-recommended therapies in the first 24 hours were also more likely to receive the appropriate discharge care medications.7 This builds on the concept if care is started early in the ED with appropriate identification and triage with use of the right therapies which are guideline based, discharge care will also be optimized.

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<th>GRACE Risk Model</th>
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http://gracescore.co.uk/

C-index = 0.84, validated in clinical trial and registry populations

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<th>TABLE 02</th>
<th>CRUSADE In-Hospital Major Bleeding Variables</th>
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COAGULATION CATASTROPHES: TAKING CARE OF THE MOST DIFFICULT CASES IN EMERGENCY MEDICINE
Observations on STEMI Care

In patients with STEMI, it is of paramount importance to achieve rapid reperfusion. An almost linear relationship between mortality and delays to reperfusion with primary PCI can be identified.8 Subsequent work has been undertaken to identify how this approach to early intervention in STEMI patients can be optimized as patients do not always present to the hospital where primary PCI can be performed. Furthermore, strategies to improve paramedic transportation to the hospital as well as early access to the cardiac catheterization laboratory have become critical. This issue in rural states such as North Carolina is important because there are many hospitals which do not have primary PCI facilities and geographically the state has many rural counties where transport delays are significant.

A program has been developed in North Carolina to improve access to primary PCI on a state-wide level. The program, called RACE (Reperfusion in Acute myocardial infarction in North Carolina EDs), was developed with a collaboration of smaller local hospitals and larger tertiary care hub centers.9 A strategy has been developed where patients are triaged by the emergency medical services (EMS) to have 12-lead electrocardiograms performed in the ambulance. If the electrocardiogram is positive for STEMI, smaller hospitals without PCI capability are bypassed in favor of a larger hospital where primary PCI can be performed. This approach improved the time to get to reperfusion compared to historical controls. This has now been developed on a national level to improve care further and has become a model program for the American Heart Association called Action LifeLine. The program highlights the importance of collaboration not only with the ED and cardiology, but also with the EMS such as local ambulance services which can use the pre-hospital 12-lead electrocardiograms to make the diagnosis of STEMI.

A number of studies have been carried out to try to identify how care can be improved in hospitals to achieve rapid reperfusion therapy. One study evaluated hospitals which consistently performed the most rapid reperfusion for STEMI.10 A number of key variables were identified as being essential for success. They are listed in Table 3. The unique aspect of this study is there was not one single variable but really the combination of all these variables which improved the time to reperfusion. On a national level, these important observations are now incorporated into better care for patients with STEMI.

Early Invasive Care in NSTEMI

While STEMI requires early and immediate cardiac catheterization with reperfusion therapy using primary PCI, the issues around high-risk patients with NSTEMI are less clear. A number of studies have evaluated whether an early invasive approach is beneficial in patients with NSTEMI. An individual patient meta-analysis of a number of small trials that had randomly allocated an early invasive strategy versus a delayed strategy has been performed.11 Uniformly, a significant reduction in death and MI was identified with the early invasive strategy. All the studies in the meta-analysis varied in the time to early invasive care but in general it was performed within the first 36 hours. This was followed by a randomized trial of very early invasive strategy for patients with high risk and NSTEMI (Figure 3).12 There was a reduction in death, MI, or stroke particularly among those patients with high GRACE risk score (>140). This emphasizes that for the highest risk patients, an early but not necessarily acute cardiac catheterization may be of value. This suggests there is a continuum of risk for patients from ST-elevation to high-risk NSTEMI where the early timing of angiography and PCI may be of particular value. Identifying patients where the invasive strategy is of benefit, even in a semi-acute fashion, is important. While there is a risk of vascular and bleeding complications with the early invasive strategy, the use of radial access has diminished this risk quite considerably. In a meta-analysis of radial versus femoral access it
was suggested that the radial approach may be beneficial in this setting. Ultimately the invasive cardiologist will need to use the method which he or she is most familiar with for access. There is a subset of patients where the radial access is less ideal, such as those who are very elderly with tortuous vessels, patients with thoracic aortic aneurysms, younger women who tend to have arterial spasm, and those patients who have known subclavian peripheral vascular disease. In addition, patients who have had prior coronary artery bypass grafting are hard to perform a full angiographic interpretation for multiple bypass grafts from the radial access. The radial access approach has changed the risk paradigm for procedural bleeding quite considerably over the last decade, and will continue to grow as the cardiologists become more familiar with this approach.

Some Clinical Challenges for the Future

While it seems that a lot of issues have been resolved in the management of patients with ACS, there are more things which will evolve and become important. With ACS now appearing in a predominantly elderly population, two large areas which may require further research needs to be considered. Firstly, patients are now arriving with STEMI or NSTE ACS and are already being treated with warfarin. Because of the potential risk of adding a number of antithrombotic therapies to a patient who is already anticoagulated, this can increase bleeding complications. An investigation of this particular issue has been undertaken and found, in general, patients who are anticoagulated tend to receive less evidence-based therapy because of the concern for bleeding. A number of treatment strategies will therefore need to be defined how to best approach patients who are on warfarin anticoagulation. The picture is even more confusing when the novel oral anticoagulants are considered. Dabigatran, a direct thrombin inhibitor, as well as rivaroxaban and apixaban, both oral Xa inhibitors, currently are considered. Dabigatran, a direct thrombin inhibitor, as well as rivaroxaban and apixaban, both oral Xa inhibitors, currently are being evaluated in large-scale trials for stroke prevention in atrial fibrillation and have shown clear benefit in this population. There is little knowledge on how to approach these patients when they present with STEMI and ACS. In general, the drug effect wears off comparatively quickly compared with warfarin. For patients not requiring immediate intervention, waiting 12-24 hours (on average) will remove any anticoagulation drug remaining. However for STEMI, physicians in general take these patients to the cardiac catheterization laboratory and try to minimize the bleeding by using direct thrombin inhibitors, such as bivalirudin, instead of heparin or radial access. Further research needs to be undertaken for this group of patients to improve our ability to provide care for them.

Secondly, one of the “side effects” of our very rapid care for patients with STEMI is that the patient’s wishes may not always be addressed. Many patients of older age (>85 years of age) have advanced directives including do not resuscitate orders. In the very rapid evaluation and assessment of such a patient, and the patient’s inability to communicate for themselves, it becomes unknown if these advance directives are being followed. While physicians in general are following the principle of trying to do the best standard therapy for STEMI, it should be recognized that some of the societal needs to address these directives are not necessarily at odds with a very rapid reperfusion strategy. Further research in this area should address the importance of these very elderly, sometimes vulnerable patients, to try to reflect their wishes for invasive care.

Conclusion

The tremendous collaboration that has occurred between emergency physicians and cardiologists over the last two decades has led to very rapid changes in the care of patients with ACS accompanied by substantial improvement in patient outcomes. While it is easy to appreciate these developments, there are many areas that still need to be addressed. Firstly, on a national level it is important to achieve the same high level of care which is delivered in urban/suburban areas for rural areas which don’t have immediate access to PCI. Newer antithrombotic therapies and their appropriate dosing will become increasingly important for the elderly population which are having ACS. Finally, how to best manage patients with multiple comorbid illnesses including atrial fibrillation and a history of stroke remains uncertain. As many of these elderly patients are on warfarin or novel oral anticoagulant agents, further study is needed to understand the ideal approach to these individuals.

References


EARLY INTERVENTION FOR ACS: COLLABORATION BETWEEN
THE INTERVENTIONAL CARDIOLOGIST AND THE
EMERGENCY PHYSICIAN


Thromboelastography (TEG): Diagnosis and Monitoring of Coagulation Abnormalities in Critical Illness and Injury

Natalie Kreitzer, MD
Assistant Professor of Emergency Medicine; Fellow, Neurovascular Emergencies and Neurocritical Care Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

Jordon B. Bonomo, MD
Assistant Professor of Emergency Medicine and Neurosurgery, Department of Emergency Medicine, University of Cincinnati College of Medicine, Cincinnati, OH

Objectives

1. Describe the importance of an intact coagulation process in patients.
2. Describe the role of thromboelastography in determining the coagulation status of patients in the ED and critical care unit.
3. Describe the importance of hypocoagulability and hypercoagulability in evaluating and treating patients with critical illness and injury.

Introduction

Thromboelastography (TEG), a point-of-care (POC) assay of the viscoelastic properties of blood, provides a comprehensive real-time analysis of hemostasis, from initial thrombin burst to fibrinolysis, permitting improved transfusion strategies resulting in the potential for goal-directed therapy of coagulation abnormalities following injury. TEG was first described in 1948 in Germany by Dr. Hellmut Hartert. Despite being used clinically and for research in Europe, until the process was automated and computerized in the late 20th century, it received little attention in the clinical literature, especially in North America.

There are two commercially available TEG systems, both of which are types of viscoelastic hemostatic assays (VHA): the rotational Thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany), and the modified traditional Thromboelastography (TEG®; Hemoscope Corporation, Niles, IL) which is the most prevalent system in use in North America. There is concurrent amplification when Factor VIII and V accelerate thrombin formation exponentially, which is known as the "thrombin burst." Thrombin subsequently activates Factor XIII which leads to cross-linking of the fibrin fibers. Thus, in order to describe the clot formation and simultaneous breakdown, the function and quantity of multiple proteins must be known. TEG is able to describe this balance both qualitatively (the tracing) and quantitatively (the measured values). A brief overview of the coagulation cascade is represented in Figure 1, and a demonstration of the qualitative tracings of VHAs [TEG and ROTEM] is shown in Figures 2 and 3.

VHA allows for product driven, goal-oriented resuscitation in the bleeding patient which is relatively unique. In particular, TEG allows for the global assessment of a patient’s coagulation status by evaluating factors that are difficult and time consuming to assess otherwise, such as platelet function and the state of fibrinolysis. The benefit of this is that a patient can receive timely workup and potential treatment of complex, multifocal coagulation disorders secondary to relatively common presentations in the emergency setting.

Clot Formation

In order to best understand TEG, a basic understanding of the process by which a clot forms is important. The most common way a clot forms is when damaged endothelium exposes underlying collagen and tissue factor to platelets. Platelets combine with von Willebrand factor (vWF) to link the platelets and collagen. Further platelet activation occurs and leads to strongly adhered platelets. The coagulation cascade, which consists of inactivated circulating zymogens, is thus activated, setting off an exquisite and intricate reaction in which downstream pro-coagulant factors are activated by one another. At the same time, tissue factor pathway inhibitor (TFPI) is activated. The resultant reaction leads to the final common pathway, in which thrombin cleaves fibrinogen into fibrin. Thrombin also activates multiple other proteins including protein C, which is inhibitory to clotting. The clot is then stabilized by Factor XIII which cross-links the fibrin fibers.

Compared to conventional studies of coagulation, TEG provides sophisticated and relevant information about the entire process of clot formation, not just initiation.
The TEG assay provides information that is different from conventional coagulation studies of PT/INR and aPTT. It is important to remember that primary coagulation is a complex interplay of both of the pathways of coagulation, extrinsic and intrinsic, and a final common pathway of platelet aggregation and the ultimate crosslinking of fibrin. TEG provides insight into each phase of the clotting cascade and theoretically allows for therapies targeting specific defects in the pathways.

The balance between hemostasis and fibrinolysis is intricate and TEG offers insightful information about that balance. One example is in the multisystem trauma patient who presents to the ED in shock. He or she likely has components of clotting and fibrinolysis simultaneously, and these components are difficult to capture with traditional assays of coagulation. The TEG assay is better suited to providing understanding of clot lysis than traditional markers of fibrin degradation such as d-dimer, fibrin degradation products, or fibrin split products, which are non-specifically elevated in many states of inflammation other than bleeding or clotting. Recently, Carroll and colleagues addressed the acute post-traumatic coagulopathy, reported by Brohi, et al., by VHA analyses of samples obtained at the scene of accident and upon arrival in the ED in 161 trauma patients. They found the clot forming parameters demonstrating hypocoagulability correlated with fatality, whereas none of the routine coagulation tests like PT and aPTT demonstrated such a correlation. This indicates that VHA is more sensitive in reflecting clinically relevant coagulopathies than routine coagulation tests.

One particularly useful measurement provided by modern TEG is the so-called LY30, which reports the percent of fibrinolysis that has taken place in 30 minutes, with a standardized reference range of 0 – 8%. In the acute setting, an elevated LY30 percentage likely signifies a hyperfibrinolytic state and some authors have advocated administering antifibrinolytic therapy, such as tranexamic acid to these patients. While no consensus exists currently on the effectiveness of this strategy, clinical trials are underway to explore the benefit of targeting acute antifibrinolytic therapies in these hyperfibrinolytic patients.

Understanding viscoelastic hemostatic assays and TEG

The TEG analysis is conducted on aliquots of citrated whole blood rather than separated blood and plasma components. In the most commonly employed TEG analyzer, a 0.36 mL sample...
of whole blood is placed into a cup which is then incubated to 37 degrees. Calcium is added to the sample to counteract the citrate, the cup is continuously rotated through 4° 25’ and a strain gauge pin is linked to a torsion wire which connects to a mechanical-electrical transducer. As changes in force are detected by the strain gauge during clot formation and degradation, the signal is translated into measurable data which is plotted in real time through automated signal translation (Figures 4 and 5).

An activating solution consisting of kaolin, phospholipids, and buffered stabilizers, is often used to help initiate the coagulation process in TEG, however this takes several minutes. This process can be further expedited in the setting of hemorrhagic shock by the addition of tissue factor, resulting in a “rapid-TEG” (rTEG). The rTEG assay allows a faster clotting profile to be created because the additional reagents activate both the intrinsic and extrinsic clotting systems simultaneously, and the earliest tracings of rTEG are viewed within ten minutes. Real time changes that are seen in the TEG profile represent the strength and speed of clot formation, and allow assessment of which clotting factors are contributing appropriately or inappropriately, thereby informing targeted blood product delivery in the bleeding or coagulopathic patient.

**What Information Does TEG Provide?**

**Clot strength.** A major advantage of TEG not present in other coagulation studies is information regarding the strength of a clot. Specifically, it provides information about both platelet aggregation and subsequent fibrinolysis. In order to obtain this information otherwise, multiple tests would need to be performed, including platelet count, platelet function, coagulation factors, fibrinogen, protein S, protein C and antithrombin. As mentioned previously, procoagulant and anticoagulant factors are activated during normal clot formation, and TEG is able to assess the balance between these reactions.

**Hyperfibrinolysis:** TEG can rapidly identify active hyperfibrinolysis in the immediate post trauma patient. While hyperfibrinolysis is rare, it is lethal. In 2012, Cotton and colleagues described the r-TEG evaluation of 1996 consecutive severe trauma patients, and 41 (2%) of patients at admission demonstrated hyperfibrinolysis. This subset had a 76% mortality rate, in contrast to 10% of the entire group. This study also demonstrated that prehospital crystalloid fluid administration resulted in a statistically significant higher hyperfibrinolysis score defined as more than 7.5% amplitude reduction at 30 minutes after maximal amplitude. Ultimately, if a higher percent of hyperfibrinolysis is noted in patients who have had crystalloid administration, and this TEG abnormality is associated with higher mortality, then blood products may ultimately prove to be preferential to crystalloids in the setting of acute traumatic hemorrhage.

The benefit of testing whole blood, rather than testing coagulation pathways piecemeal such as obtaining a CBC, PT, and aPTT is that dynamics of clot formation are visualized, such that thrombosis and fibrinolysis are both represented in sequence. Traditionally, prothrombin time (PT) and activated
partial thromboplastin time (aPTT) are utilized as markers to screen trauma patients for coagulation deficits during trauma. These lab values are, in reality, indirect markers of coagulopathy, in that they do not directly evaluate the quantity or function of coagulation factors despite classic training to the contrary. These traditional coagulation tests do not measure every coagulation factor, nor the process of clot formation as whole. Specifically, PT/INR and aPTT describe the time to the start of thrombus formation but all activity in the clotting cascade beyond that point remains unknown with these standard assays. It is of critical importance to remember that PT and aPTT do not account for fibrinolysis and may remain normal even in a hyperfibrinolytic state; additionally, PT and aPTT do not provide information regarding the interaction of platelets and other clotting factors, the final critical step in creating stable clots.1

Platelet Function: TEG is also able to provide direct information about platelet function. Traditional coagulation testing only tests for platelet counts, which may be normal even in the setting of severe platelet dysfunction. The TEG assay is helpful in the management of patients who are taking antiplatelet medications such as salicylates or clopidogrel, which inhibit platelet function but do not alter platelet counts.26 TEG is useful for evaluating patients on novel oral anticoagulants such as direct thrombin inhibitors (dabigatran) and factor Xa inhibitors such as rivaroxaban. Patients who are taking these medications will have prolonged R time or TEG Activated Clotting Times (ACT) in accordance with dose effect.

How to Interpret TEG

Broadly speaking, TEG variables which are reported include coagulation time (CT), clot formation time, the angle of clot formation, the maximum clot firmness, and lysis time.3 Typically, these are described in the automated TEG report as equation utilizing the other variables. TEG is modified by sex, age, and other factors, as demonstrated in Figure 6. See Tables 1 and 2 for interpretation and description of TEG variables.

<table>
<thead>
<tr>
<th>TABLE 01 Common Measurements in TEG</th>
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<tr>
<td>Period to 2-mm amplitude</td>
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<tr>
<td>Period from 2 to 20 mm amplitude</td>
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<tr>
<td>α Angle</td>
</tr>
<tr>
<td>Maximal strength</td>
</tr>
<tr>
<td>Amplitude (at set time in min)</td>
</tr>
<tr>
<td>Maximal lysis</td>
</tr>
<tr>
<td>CL after 30 and 60 min</td>
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<tr>
<td>TTL</td>
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<tr>
<td>Time to complete lysis</td>
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Abbreviations: CT, coagulation time; CFT, clot formation time; MA, maximal amplitude; ML, maximal lysis; CL, clot lysis; TTL, time to lysis; LOT, lysis onset time; LT, lysis time.

Adapted and reprinted with permission from MacDonald SG, Luddington RJ. Critical factors contributing to the thromboelastography trace. Transfus Med Rev 2012;26:1-13

<table>
<thead>
<tr>
<th>TABLE 02 Potential Therapy Based on TEG variables</th>
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<tbody>
<tr>
<td>Increased R time</td>
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<tr>
<td>Decreased angle</td>
</tr>
<tr>
<td>Decreased MA</td>
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<tr>
<td>Fibrinolysis noted</td>
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</table>

MA represents clot strength, R indicates the time until there is evidence of clot, K describes the time from R until the clot is 20 mm in size, α is a line from the start of the TEG tracing to the point of clot reaction time. This demonstrates the speed of clot formation, and is dependent on platelet number, platelet activity, and fibrinogen concentration and activation.17 CI describes the global coagulation state as derived from an

![FIGURE 06 Pretest modifiers of VHA](image-url)

Preanalytical variables affecting the viscoelastic hemostasis assay (VHA) trace. HCT, hematocrit; PLT, platelet; WBC, white blood cell count. Adapted and reprinted with permission from MacDonald SG, Luddington RJ. Critical factors contributing to the thromboelastography trace. Semin Thromb Hemost 2010;36:712-22.
TEG in the ED

There is increasing evidence that TEG is valuable in the emergency setting, particularly during resuscitations that involve massive transfusion. Massive transfusion is defined as the requirement of 10 units of packed red blood cells (pRBC) during the first 24 hours of admission and is consistently associated with increased morbidity and mortality in trauma patients.18 Damage control surgery is used in conjunction with damage control resuscitation, and using balanced blood products including fresh frozen plasma and platelets in fixed ratios is considered standard of care to correct the coagulopathy of trauma by many experts.19 This is consistent with numerous descriptions of the benefits of damage control resuscitation, born of retrospective military data, in which lower mortality rates were noted when transfusions are given in such a way as to mimic whole blood rather than simply transfusing pRBC’s.20 The TEG assay is most useful in guiding damage control resuscitation and blood product administration, allowing decisions regarding the necessity for repeat or continued damage control surgery. In a 2012 study, Petzold and colleagues found that for the endpoints of death and massive transfusion, clot strength (G) was found to independently predict massive transfusion and death in the early part of resuscitation. The G variable had the greatest adjusted area under the curve/receiver operator curve (AUC ROC) when compared to base deficit BD (0.87, P = .05), INR (0.88, P = .11), and PTT (0.89; P = .19) meaning that it is a better predictor of morbidity and mortality than more traditional markers of severity commonly employed in the ED.21 In 2011, Nystrup, et al. reviewed 89 subjects in the trauma registry who had a reduced clot strength defined as maximal amplitude < 50 mm on TEG and demonstrated a higher injury severity score (ISS), p = 0.006 compared with those who had a normal MA, as well as a greater need for transfusion of PRBC (p = .01), fresh frozen plasma (p = 0.04), and platelets (p = 0.03) during the first 24 hours of resuscitation, as well as a remarkably increased 30-day mortality (47% vs. 10%, p < 0.001).11 These authors hypothesized that TEG could be used to target patients to receive selected blood products preferentially in the setting of trauma induced coagulopathy.

Hyperfibrinolysis and post-traumatic coagulopathy are major risk factors for severe morbidity and mortality. In a prospective study of 161 trauma patients, decreased TEG MA values correlated with fibrinogen <100mg/dL, which also correlated with higher mortality (p = 0.013). In the 14 fatalities found in this study, both the TEG R time and MA times were significantly higher than in non-fatalities (R time was 3703 +/- 11,618 versus 270 +/- 393 s [P = 0.001], and MA was 46.4 +/- 22.4 versus 64.7 +/- 9.8 mm [p < 0.001]).22 TEG along with platelet count and hemoglobin count may be the most accurate method to assess the need for blood product requirement in trauma patients.

When viewed in the context of damage control resuscitation, it is appropriate to assume that the ratio of blood, plasma, and platelets likely differ from one patient to another. For instance, it may be harmful for some patients to receive the conventional 1:1:1 ratio of plasma, PRBC, and platelets, especially if they receive inappropriate and potentially harmful amounts of each product.23 By utilizing TEG appropriately, patients may receive only the products that they would likely require during damage control resuscitation.

Another benefit to having TEG in the ED is that results can be obtained typically within ten minutes, compared to 30-60 minutes for PT, aPTT, fibrinogen, and platelet counts.16 Although initiating transfusion therapy rapidly improves patient care when necessary, TEG may also be helpful in determining when it may not be useful since TEG provides a rapid, global assessment of a patient’s coagulation status. For example, a clinician may be able to avoid using blood products in a normotensive trauma patient with a normal TEG. This is important, given the risks associated with the administration of all blood component therapy including allergic reactions, infection transmission, transfusion associated acute lung injuries (TRALI), transfusion associated cardiac overload (TACO), and acute respiratory distress syndrome. These risks are low, but it is important to remember that platelets and FFP carry the highest risk of TRALI and platelets have been reported to carry a risk of bacterial contamination, usually from the donor’s skin.23

The TEG assay, like any laboratory test, is not without pitfalls. Values may be different when one machine is compared to another machine. When a patient has serial TEG studies, results

<table>
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<th>TABLE 03</th>
<th>Advantages of TEG</th>
<th>Disadvantages of TEG</th>
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<tr>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
<td></td>
</tr>
<tr>
<td>Can be used point of care (POC) to give rapid results</td>
<td>High variability²</td>
<td></td>
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<tr>
<td>Is an evaluation of global hemostatic function²</td>
<td>Stability of whole blood²</td>
<td></td>
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<tr>
<td>Allows the physician to assess for hyperfibrinolysis and monitor treatment in patients who are given recombinant activated factor VII or t-PA²</td>
<td>Normal ranges are different in newborns, infants, adults²</td>
<td></td>
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<tr>
<td>Detects low factor XIII activity²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small sample volume (attractive for pediatrics)²</td>
<td>requires only .33 mL of blood</td>
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Current Data and TEG Applications

The TEG assay is being studied increasingly in areas other than traumatic conditions and the surgical realms. One of these areas is in sepsis, where TEG is helpful in predicting mortality and helping to distinguish sepsis from disseminated intravascular coagulopathy (DIC). Adamzik, et al. in 2011 described 98 patients with sepsis who had a TEM obtained during illness. Within this cohort, the thirty day survival was 85.7% when all the TEM variables were normal, and 58.7% survival when one or greater variables were abnormal (p = 0.005). This highlights the importance of coagulation in sepsis. In this study, TEM was better able to predict 30-day survival than both the simplified acute physiology score (SAPS II) and sequential organ failure assessment score (SOFA) scores (p = 0.01; odds ratio of 4.1).24 Further research is necessary to determine the capabilities of TEG in sepsis in the diagnosis and treatment of sepsis induced coagulopathy.

Another avenue where the diagnosis and treatment of coagulopathy using TEG is being pursued is in traumatic brain injuries (TBIs). Davis, et al. studied 50 patients with TBIs and 10 controls in 2012. All patients had TEG performed, as well as platelet mapping.6 When the patients with TBIs were compared to normal controls, those with severe TBIs demonstrated an increased platelet ADP and arachidonic acid (AA) receptor inhibition. The ADP inhibition could distinguish survivors from non-survivors (p = 0.035), and correlate with severity of TBIs (p = 0.014).

TEG is being explored in a diverse number of modalities at this time. Current trials are describing the use of TEG to assist diagnosis and treatment in aspirin and clopidogrel resistance, cesarean deliveries, hemostasis after CABG, antiplatelet therapy guidance in acute coronary syndrome, fat emboli, and the use of antiplatelet inhibition in conjunction with percutaneous coronary intervention.

Cases

Q: A 34 year old previously healthy male presents to the ED after falling off his roof. His blood pressure is 85/40 and heart rate is 124 beats per minute. On initial assessment he has an obvious femur fracture. His chest x-ray demonstrates multiple rib fractures and he has a positive focused assessment with sonography in trauma (FAST). A TEG is performed and he has an LY30 of 12%. In addition to giving him blood products for his hemorrhagic shock, what other drug should you give him?

A: This patient should receive tranexamic acid (TXA) or aprotinin or aminocaproic acid. He demonstrates an elevated degree of fibrinolysis, which puts him at an increased risk of mortality following trauma.

Q: A 65 year old male presents to the ED three days after undergoing a left heart catheterization and left circumflex stent placement following a STEMI. He has a large groin hematoma secondary to the procedure. He feels lightheaded and his initial blood pressure is 82/40. A TEG is performed, and demonstrates a prolonged K time and decreased MA time. A CBC, PT, and PTT are all within normal limits. What are these values reflective of in this setting?

A: These values reflect platelet dysfunction, likely secondary to antiplatelet medications he is taking after having a stent placed. It is worth noting that although the more traditional labs that are used to assess coagulopathy (CBC, PT, PTT) are normal, the TEG is abnormal, offering insight into platelet function.

Further abnormal scenarios are represented below in Figure 7.
**Conclusion**

Thromboelastography is a promising technology that offers remarkable insight into the delicate balance between thrombosis and fibrinolysis, does so in real time, and is broadly applicable in the emergency and critical care environments. While further research is needed to clarify exact roles for utilization of TEG, clinical experience to date has demonstrated that TEG has remarkable potential in the care of the critically ill and injured and should become routine in the near future.

**Take Home Points**

1. TEG provides sophisticated information about a patient’s global capacity to form clot and offers insights into the function of platelets not seen with traditional coagulation testing (prothrombin time/international normalized ratio [PT/INR], activated partial thromboplastin time [aPTT]).

2. TEG tests whole blood rather than plasma. The benefit of this is that the complete dynamics of clot formation are visualized. Thrombosis, relative clot strength, and fibrinolysis are all represented in a TEG.

3. By utilizing TEG appropriately, patients may receive targeted blood component administration during active resuscitation.

4. TEG can typically be obtained within 10 minutes when used in the ED.

**References**


11. Nystrøg KB, Windelov NA, Thomsen AB, Johansson PI. Reduced clot strength upon admission, evaluated by thrombelastography (TEG), in trauma patients is independently associated with increased 30-day mortality. Scand J Trauma Resusc Emerg Med 2011;19:52.


US. While only 8% of AIS patients are in fact eligible for rt-PA, only about 4% of all AIS patients receive rt-PA annually in the US. To an acute care hospital capable of administering IV rt-PA, although 80% of the US population has access within an hour of symptom onset is the only United States (US) Food and Drug Administration (FDA) approved therapy for improving outcomes. The effectiveness of rt-PA is time dependent. In recent registry data of 58,353 patients treated with IV rt-PA, every 15-minute delay in time to rt-PA administration reduces the odds of discharge to home from the hospital and functional independence at hospital discharge, and increases the odds of symptomatic intracranial hemorrhage (sICH) and mortality. Further, it has been estimated that for every minute faster rt-PA is administered, the duration of disability after stroke is reduced by a day.

Although 80% of the US population has access within an hour to an acute care hospital capable of administering IV rt-PA, only about 4% of all AIS patients receive rt-PA annually in the US. While only 8% of AIS patients are in fact eligible for rt-PA, the low rates of treatment, even among eligible patients, are primarily due to late presentation of stroke patients to the emergency department (ED) and inefficient systems of care which prevent rapid evaluation and treatment of AIS patients who do present within the time window for treatment with rt-PA. Public service campaigns have been geared at improving the awareness of stroke with an emphasis on time and rapid presentation to an ED but these have not yielded great strides in public awareness. On the other hand, quality improvement efforts such as the American Stroke Association’s (ASA) Get With The Guidelines (GTWG) have markedly improved systems of stroke care in the past decade. Nonetheless, only 53% of AIS patients received rt-PA within the recommended 60 minutes from ED arrival at presumably motivated hospitals participating in GWTG. Patients who arrive at rural hospitals are ten times less likely to receive rt-PA than those who present to larger urban stroke-certified hospitals. Stroke is the fourth leading cause of death in the US, the leading cause of long-term disability worldwide and results in $36 billion in annual costs in the US alone, with the majority of this being post-acute care disability costs. Given the importance of time to treatment on AIS outcomes and the reduction in stroke disability with earlier treatment, there is great unmet clinical need for rapid access to stroke experts who may facilitate the evaluation of AIS patients at all hospitals and provide guidance on rt-PA administration.

Telesstroke As a Solution

The American Telemedicine Association defines telemedicine as “the use of medical information exchanged from one site to another via electronic communications to improve a patient’s clinical health status.” Listed telemedicine applications may include two-way video, email, smart phones, wireless tools and other means of electronic communication. With the advent of rt-PA for treatment of AIS in the late 1990s, the necessity of available acute stroke specialists for evaluation and treatment of possible stroke patients became apparent. Over 55 telesstroke programs involving >350 hospitals currently utilize two-way videoconferencing for telesstroke care in the US. Essential components of the ability to use telesstroke in the real-time care of AIS patients include: 1) reliable videoconferencing with sufficient fidelity to allow examination of the patient; 2) teleradiology with ability to rapidly transmit images in a fashion whereby the consulting expert is able to manipulate the images while reviewing them; 3) quality monitoring to ensure appropriate care is provided and patient outcomes are optimized; and, 4) minimized upfront and sustaining expenses of the telesstroke infrastructure in a cost-effective patient-centered manner.

Setting Up a Telesstroke Program

As with operationalizing many clinical programs, key stakeholders of developing a telesstroke videoconferencing program at both the “Hub” facility and its partner sites include: hospital administrators, information technology (IT) personnel, legal, credentialing, medical records, payor relations, and clinical champions (physicians and/or nurses). Hospital administrators...
Many major tertiary care centers in the US have an acute stroke team with a telestroke service. For smaller hospitals looking to bolster their acute stroke care, the first outreach should be to the closest tertiary center which may already have an existing referral partnership. For larger hospitals looking to either bolster existing services or establish a telestroke network, again, the first outreach should be to hospitals with existing referral partnerships. While individual champions will likely be needed to initiate discussions, all stakeholders mentioned above should be gathered together very early in the discussions to avoid inefficiencies in getting the program started.

Technological Options for Implementing Telestroke

Two considerations in audio-visual telestroke technology selection include the consulting stroke expert’s interface and the consulting ED/hospital interface. From the consulting expert’s perspective, a mobile portable device such as a computer tablet, laptop or smart phone with intrinsic or accessory wireless capabilities ensures maximum flexibility and allow the expert to “beam in” readily and conveniently. While many clinicians would be comfortable with this amount of flexibility in our current digital era, it is important to ensure PHI remains protected and that any chosen technology is approved/supported by the relevant local entities. From the ED/hospital perspective, options include a sturdy mobile cart or robot, or a tablet that’s readily available at the patient’s bedside in a location conducive for head-to-toe clinical examination.

Some institutions develop in-house telestroke technology, while a number of commercial vendors provide telestroke services which include software and hardware for the stroke expert and the consulting hospital (Figure 2). Robot devices may be maneuvered by the stroke expert remotely while cart-based devices may have some limited maneuverability with regard to camera angles, zooming, etc., and require clinical personnel to place the cart within viewing distance of the patient. Recent trends in telestroke seem to be going from the robots, which have generally required a joystick equivalent for maneuvering, to more tablet/smart phone based options.

The chosen technology modality should be integrated such that videoconferencing, Picture Archiving and Communication Systems (PACS) imaging and documentation/note taking in the medical record are feasible within the application. The PACS access is critical since it allows the stroke expert to review relevant imaging prior to clinical decision-making to administer rt-PA or not.

EXPERIENCE WITH TELESTROKE

Feasibility of Remote Neurological Clinical Exam

A major advantage of videoconferencing over telephone assessments is the ability to “lay eyes” on the patient. Nonetheless, challenges remain regarding the ability to perform a detailed
neurological exam that incorporates assessment of light touch, visual fields and other aspects of the NIH Stroke Scale (NIHSS) using videoconferencing. The NIHSS performed by neurologists and non-neurologists, however, using telemedicine has been found to have good reliability and consistency with exams performed by non-neurologists and neurologists at the bedside. Clinical decision-making should not be deterred by the inability of the remote stroke expert to directly perform sensory exams or visual field assessments. Further, a trial of 222 subjects with acute stroke randomized clinical decision-making to the usual telephone consultation versus telestroke videoconferencing. Correct decisions with regard to administration of rt-PA were greater in the telestroke videoconference group versus the telephone group (98% versus 82%; odds ratio, 10.9; 95% confidence interval, 2.7–44.6). The 2013 ASA guidelines for the management of AIS recommend implementation of telestroke consultation in addition to education and training.

US Telestroke Experience

The most recent available data on telestroke activity in the US dates back to 2009. In a survey of 97 potential programs identified via online search, 56 confirmed active telestroke programs in 27 states. Of these, 95% used videoconferencing and >80% of partner sites were small or rural hospitals. Telestroke allows rural hospitals to administer rt-PA with guidance provided in real time by a stroke expert. This mitigates the need to “ship and drip” which is suboptimal for the patient given the importance of time to treatment on outcomes. Telestroke also offers smaller or rural hospitals the option of “drip and keep” given the potential for the stroke expert to continue to provide treatment and management recommendations beyond the period of time in the ED. Inpatient teleconsultation was reported in 46% of programs in the 2009 survey. From the perspective of the patient and family, the inconvenience and anxiety resulting from traveling to larger cities/hospitals is decreased and there is reassurance that the relevant expert is in fact involved in the care of the patient.

Patient Outcomes

The main outcome of interest with regard to any novel approach to clinical care is the patient outcome. It is essential that quality metrics are tracked in an ongoing fashion for telestroke programs. Limited data are available regarding long term outcomes and sustainability of telestroke programs. However, a recent German study reported the experience of the use of telemedicine to facilitate rt-PA administration in the Bavaria region from 2002-2012. During the study period, median onset to treatment times steadily decreased from 150 to 120 minutes, while door-to-needle times decreased from 80 to 40 minutes. The proportion of AIS patients treated with rt-PA increased from 2.6% to 15%. In-hospital mortality for AIS was unchanged at a mean of 6% during the study period.

Costs of Telestroke

While telestroke services continue to expand and their clinical utility is apparent to practitioners, the evidence on cost-effectiveness of these services is mixed and available data are limited. No cost-effectiveness studies of telemedicine for stroke care were identified in a cost-effectiveness review of studies published from 1995-2008. A subsequent report used a decision-analytic model to compare telestroke networks with usual care. Telestroke resulted in an incremental cost-effectiveness ratio of $108,363/QALY gained in the 90-day horizon and $2,449/QALY in the lifetime horizon. The greater expense in the 90-day horizon is reflective of the upfront costs associated with telestroke implementation but the overall incremental cost-effectiveness ratio was <$50,000/QALY, a commonly accepted cost ratio in the US. Another report used two US telestroke systems to develop a decision-analytic model to compare costs and effectiveness with and without a telestroke network over five years. A model with one hub and seven partners predicted that 45 more patients are treated with rt-PA and an estimated 6.11 more discharges to home are possible compared with no telestroke network. Annual cost savings associated with a telestroke network was estimated to be $358,435.

Summary and Future Directions

Clinically, telestroke has demonstrated significant utility in making stroke experts readily available to patients and emergency physicians caring for them in facilities without in-house stroke expertise. Given the societal burden of disability due to stroke and the ability of telestroke to facilitate more rapid evaluation and treatment of AIS patients, efforts to make videoconferencing more ubiquitous in acute stroke care are warranted. Estimates with more cumbersome laptop/cart/robot systems suggest telestroke is cost-effective. Leveraging consistent advances in technology to make videoconferencing available in PHI sensitive smart phone/tablet options may allow less expensive development of future telestroke applications, thereby improving cost-effectiveness. As with all clinical programs, continuous quality monitoring of telestroke efforts should ensure appropriate care is provided and patient outcomes are optimized.
COAGULATION CATASTROPHES: TAKING CARE OF THE MOST DIFFICULT CASES IN EMERGENCY MEDICINE

References


Continuing Medical Education Post-Test

Based on the information presented in this monograph, please choose one correct response for each of the following questions or statements. **Record your answers on the answer sheet on page 49.** To receive Category I credit, complete the post-test and record your responses on the answer sheet. Mail in the return envelope no later than January 1, 2015. A passing grade of 80% is needed to receive credit. A certificate will be sent to you upon your successful completion of this post-test.

**Advances in the Early Diagnosis of Acute Coronary Syndromes** – Phillip D. Levy, MD

1) With widespread use of contemporary sensitivity troponin assays, clinicians can expect to see:
   a. More negative test results in patients with acute coronary syndromes
   b. More positive test results in patients without acute coronary syndromes
   c. Evidence of myocardial necrosis in only the highest-risk patients
   d. Detectable levels in more than 95% of the healthy population

2) According to current recommendations, evaluation of suspected myocardial infarction using contemporary or high-sensitivity assays should include which of the following?
   a. Serial measurement every 8 hours for a full 24 hour period
   b. Single point in time measurement upon arrival in the emergency department
   c. Initial measurement upon arrival in the emergency department and repeat measurement 3-6 hours later
   d. Initial measurement upon arrival in the emergency department in conjunction with other biomarkers including serum myoglobin and creatine phosphokinase

3) Success of rapid rule-out protocols for suspected acute coronary syndromes depends upon:
   a. Use of contemporary or high-sensitivity troponin assays and assurance of good outpatient follow-up
   b. Use of conventional troponin assays and a good lawyer
   c. Universal troponin testing on all patients who present to the emergency department with chest pain
   d. Implementation of a multidisciplinary pathway with early discharge of high-risk patients who have negative serial troponins

4) Which of the following are considered high-risk features on coronary computed tomographic angiography?
   a. A calcium score of 79 and 49% stenosis
   b. A calcium score of 0 and 50% stenosis
   c. A calcium score of 300 and 0% stenosis
   d. A calcium score > 400 and > 70% stenosis

**Antiplatelet Agents for Acute Coronary Syndromes: Optimal Treatment in the ED** – James W. Hoekstra, MD

5) Which of the following antiplatelet agents is metabolized to an active form by the liver after ingestion?
   a. Prasugrel
   b. Clopidogrel
   c. Ticagrelor
   d. All of the above

6) Which of the following antiplatelet agents is not recommended for upstream therapy in patients with NSTEMI?
   a. Prasugrel
   b. Clopidogrel
   c. Ticagrelor
   d. All of the above

7) Which of the following antiplatelet agents has the shortest half life?
   a. Prasugrel
   b. Clopidogrel
   c. Ticagrelor
   d. All of the above
8) Which of the following antiplatelet agents resulted in a reduction of cardiac death at one year in patients treated for STEMI and NSTEMI?
   a. Prasugrel
   b. Clopidogrel
   c. Ticagrelor
   d. All of the above

9) Which of the following IS NOT approved by the US FDA as anticoagulation therapy for ACS?
   a. Fondaparinux
   b. Enoxaparin
   c. Unfractionated heparin
   d. Bivalirudin

10) Which of the following is a recognized limitation of unfractionated heparin in ACS?
    a. Activity cannot be readily monitored
    b. Activates the PF4 receptor on platelets
    c. Cannot be used with platelet GP IIb/IIIa antagonists
    d. Has a long half-life

11) Which of the following is NOT true about enoxaparin?
    a. Can be dosed subcutaneously in the ED
    b. Has no antithrombin (IIa) activity
    c. Is the preferred anticoagulant for STEMI treated with fibrinolysis
    d. Dosing is weight-based

12) Which of the following is NOT true about the non-vitamin K oral anticoagulants (NOACs)?
    a. Not a consideration in the acute management of ACS
    b. No risk of inducing heparin-induced thrombocytopenia
    c. Rivaroxaban is approved for secondary prevention of ACS in the EU, but not in the US
    d. Could be a consideration in the acute management of ACS

13) Successful collaboration between interventional cardiology and emergency medicine includes:
    a. Pre-determined ED order sets for patients with ACS which are evidence-based
    b. Regular multi-disciplinary meetings which evaluate quality measures for ACS
    c. Defined time expectations for cardiac intervention in patients with STEMI
    d. All of the above

14) Development of a statewide RACE-ER STEMI strategy in North Carolina led to which of the following benefits?
    a. Patients with ECG identified STEMI were taken directly by ambulance to a PCI hospital
    b. There were shorter First Medical Contact to Device times at a PCI capable hospital
    c. Mortality was 6.3% vs. 9.3% in STEMI patients taken directly to PCI capable hospitals
    d. All of the above

15) The CRUSADE Quality Improvement Initiative demonstrated that every 10% increase in ACCF/AHA Guideline adherence for NSTE ACS care resulted in a 10% decrease in patient mortality
    a. True
    b. False

16) For patients with high risk NSTE ACS as determined by their GRACE score, early intervention with cardiac catheterization results in a reduction of all of the following outcomes EXCEPT:
    a. Myocardial Infarction
    b. Death
    c. Cardiac catheterization related bleeding
    d. Stroke
Thromboelastography (TEG): Diagnosis and Monitoring of Coagulation Abnormalities in Critical Illness and Injury – Natalie E. Kreitzer, MD and Jordon B. Bonomo, MD

17) The patient’s substrate used for TEG testing is:
   a. Citrated whole blood
   b. Plasma
   c. Platelet-reduced blood
   d. Non-citrated whole blood

18) The “R Time” reported during TEG testing most closely describes what portion of clot formation or degradation?
   a. The time until there is evidence of in vitro clot formation
   b. The time from clot formation to maximal amplitude
   c. The time required for a clot’s strength to be reduced 30% from maximum
   d. The time required for platelet activation

19) In a clinical scenario involving a blunt trauma patient with ongoing bleeding, which blood product would be most appropriate to administer in the setting of a decreased alpha angle on TEG?
   a. Fresh frozen plasma
   b. Cryoprecipitate
   c. Platelets
   d. DDAVP

20) In a clinical scenario involving a patient with severe traumatic brain injury, which blood product or therapy would be best suited to administer if the LY30 were elevated at 18%?
   a. Recombinant tissue plasminogen activator (r-tPA)
   b. Fresh frozen plasma
   c. Apheresed platelets
   d. Tranexamic acid (TXA)

Improving Stroke Care: Using TeleStroke to Treat Acute Ischemic Stroke for a Region – Opeolu M. Adeoye, MD

21) Which of the following contributes to low rates of treatment with rt-PA for acute ischemic stroke?
   a. Lack of adequate imaging
   b. Inability to diagnose stroke accurately
   c. Late presentation of stroke patients to the ED and inefficient systems of care
   d. Shortage of rt-PA

22) Which of the following patients is least likely to receive rt-PA for treatment of acute ischemic stroke?
   a. A patient presenting to a tertiary certified comprehensive stroke center
   b. A patient presenting to a rural hospital
   c. A patient presenting to a community hospital in an urban area
   d. A patient whose stroke is witnessed at the grocery store and is transported to a regional primary stroke center

23) Which of the following is required for a successful telestroke program?
   a. Reliable videoconferencing with sufficient fidelity to allow examination of the patient
   b. Teleradiology with ability to rapidly transmit images
   c. Quality monitoring to ensure appropriate care is provided and patient outcomes are optimized
   d. All of the above

24) Which of the following are advantages of a telestroke program?
   a. Telestroke allows rural hospitals to administer rt-PA with guidance provided in real time by a stroke expert
   b. Telestroke offers smaller or rural hospitals the option of “drip and keep”
   c. Telestroke mitigates the inconvenience and anxiety of patients and/or families traveling to larger cities/hospitals with reassurance that the relevant expert is involved in the care of the patient
   d. All of the above
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After you have read the monograph, carefully record your answers by circling the appropriate letter for each question and complete the evaluation questionnaire.

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