Dear Colleagues,

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International was established in 1989 as an emergency medicine cardiovascular and neurovascular organization led by experts from the United States, Canada, and across the globe. We now have Steering Committee members from the US, Canada, Australia, Belgium, Brazil, France, Netherlands, Japan, Singapore, and the United Kingdom. Now in our 27th year, we remain committed to providing you with the best educational programs and enduring material pieces possible. In addition to our usual Emergency Physician audience, we now reach out to our colleagues in Hospital Medicine with our EMCREG-International University of Cincinnati Office of CME accredited enduring materials.

In this EMCREG-International Monograph, you will find a variety of cardiovascular articles which will hopefully be helpful to you in your practice of Emergency Medicine and Acute Care Medicine. These manuscripts are based on the 2015 EMCREG-International Satellite Symposium which was held on October 25, 2015, during the 2015 ACEP Scientific Assembly in Boston, Massachusetts. The symposium and this Monograph entitled Optimal Therapy for Acute Coronary Syndromes: Using Guideline-Based Treatments in the Emergency Setting explore multiple Acute Coronary Syndrome (ACS) topics which are extremely important to emergency physicians, hospitalists, and other acute care providers such as physician assistants and nurse practitioners as they care for these often critically-ill patients.

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, CT coronary angiography, and cardiac magnetic resonance imaging. Appropriate risk stratification of the patient with chest pain in the emergency department (ED) can identify high risk patients including those with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) who will benefit from anticoagulant treatment using agents such as heparin and low molecular weight heparin, novel anticoagulants such as Factor Xa inhibitors such as rivaroxaban, and antiplatelet agents including aspirin, clopidogrel, prasugrel, and ticagrelor. The challenges of optimizing antiplatelet therapy for patients with acute coronary syndromes are presented from the perspective of a cardiologist who is dual trained as a hematologist. The incorporation of these diagnostic and treatment options into the latest 2014 American College of Cardiology Foundation/American Heart Association guideline for NSTE-ACS and 2013 American College of Cardiology Foundation/American Heart Association guideline for treatment of STEMI are emphasized, including extension of care into the pre-hospital setting. The role of collaboration between the interventional cardiologist and emergency physician in treating ACS is also articulated. In addition, novel diagnostic testing for determining a patient’s ability to clot blood using thromboelastography or TEG is described. The use of thromboelastography (TEG) as a diagnostic test for the patient’s ability to clot blood is expanding in use and indications.

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 January 2016 EMCREG-International Monograph can hopefully serve as a useful source of information for you during 2016. 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 2016 EMCREG-International Monograph. Thank you very much for your interest in EMCREG-International educational initiatives and we hope you visit our website (www.emcreg.org) for future educational events and publications.

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Objectives

1. Describe the correct use of the 12-lead ECG to improve time to treatment for ACS.
2. Describe the optimal cardiac biomarker strategy to detect necrosis.
3. Describe the role of rest ischemia testing.
4. Describe the current role of stress echocardiography, graded exercise testing, and other provocative testing for ACS.

Introduction

The approach to patients with suspected acute coronary syndrome (ACS) has undergone rapid advances in the past decade. Improvements in biomarker assays, electrocardiogram (ECG) analysis, and non-invasive imaging modalities have greatly improved the risk stratification of patients with suspected ACS. However, changes in technology pose challenges to clinicians who must be familiar with a diverse array of diagnostic strategies and few consensus guidelines. The adaptation to this changing landscape is complicated by pressures to limit cost and maintain safety. This means greater use of accelerated diagnostic pathways in select low risk patients, and the judicious use of advanced imaging in those deemed higher risk. A summary of the latest diagnostic strategies and a brief examination of emerging technologies for ACS risk stratification are presented here.

Electrocardiogram

The Emergency Department (ED) evaluation of patients with suspected ACS begins with an immediate 12-lead ECG. Current guidelines recommend that the initial ECG be performed within 10 minutes of arrival. Patients with concerning symptoms and an initial non-diagnostic ECG should have the ECG repeated every 15-30 minutes for the first hour (Class IC recommendation) [Figure 1].1 This can be challenging for busy EDs, and is best achieved using protocols that prioritize patients based on age and symptoms. Whenever possible, patients arriving by ambulance with symptoms suggestive of ACS should have had a field ECG performed as well, since recent studies demonstrate improved outcomes in those having prehospital ECGs.2

Unfortunately, 12-lead ECG analysis has poor sensitivity for identifying patients with ACS. Additional lead technology has been shown to improve performance;3,4 thus, patients with concerning symptoms and a non-diagnostic 12-lead ECG may benefit from use of additional leads, such as right-sided, posterior, or 80-lead body mapping (Class IIaB).1,3,4

Optimal Cardiac Biomarker Strategy

Cardiac troponin (cTn) is the preferred serologic test to diagnose myocardial infarction (MI), and all patients with suspected ACS should have an initial cTn drawn at presentation (Class IA).1 The optimal timing of additional cTn values for serial analysis is a topic of considerable debate due to increasing availability of contemporary sensitivity assays having optimal precision (coefficient of variation < 10%) at the 99th percentile upper reference limit. In addition, the variable nature of cTn release after the onset of symptoms prevents a uniform approach to the timing of subsequent measurements. Thus, optimal timing for additional measurements is determined by an accurate assessment of symptom onset and the risk for major adverse cardiac events (MACE) using established risk stratification tools such as Thrombolysis in Myocardial Infarction (TIMI) Score or Global Registry of Acute Coronary Events (GRACE) calculator.

Low Risk Patients

There is growing evidence that certain patients deemed low risk for MACE are candidates for accelerated diagnostic testing using contemporary sensitivity cTn assays. A second negative measurement taken three hours after the first effectively rules out MI in these low risk populations when there is no significant change in the value between measurements.5 These patients are candidates for early discharge with prompt outpatient follow-up according to established institutional practices. Although there are no national guidelines advocating the use of single cTn values to rule out MI, emerging data from Europe using high-sensitivity assays (hs-cTn) suggest that certain low risk populations may be eligible for discharge after a single negative value once these assays have FDA approval in the United States.6

When using accelerated diagnostic pathways, physicians should have a clear understanding of what constitutes a significant rise in troponin after serial analysis in cases where the values remain below the threshold of positive. Using conventional troponin assays, the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation task force for the universal definition of MI and the National Academy of Clinical Biochemistry consider a 20% elevation as a significant change in cTn.1,7 On the other hand, an absolute rise in cTn has been shown to have greater diagnostic accuracy compared to relative
increases using newer hs-cTn assays, and the actual values for a significant rise (0.01 vs 0.02 ng/dL) differ depending on the sampling interval and assay characteristics.8, 9 Given the diversity of troponin assays available, physicians must be familiar with the method of troponin measurement at their institution. Patients showing a significant absolute or relative rise in cTn that does not cross the threshold of positive at three hours should have an additional measurement at six hours to insure that they are not ruling-in for MI.

Moderate and High Risk Patients

Contemporary cTn assays have shortened the symptom duration needed to detect a MI and most patients who rule-in are diagnosed on the initial or subsequent three-hour measurement. However, a few moderate to high risk patients rule-in for MI on troponin measurements up to six hours after the initial sample (Class IA).1 Additional troponin values beyond six hours are rarely diagnostic, but are recommended for patients with concerning clinical or ECG changes that develop during their evaluation (Class IA).1 Once ruled-out for MI, moderate to high risk patients require further risk stratification with functional or anatomic testing either before or within 72 hours of discharge (Class IIaB).1

Resting Myocardial Perfusion Imaging

A number of studies have been performed to evaluate the utility of resting perfusion imaging with Tc-99m sestamibi as a means to rapidly identify high risk patients, or to reduce the need for hospitalization in those deemed low risk. One early study demonstrated that positive rest perfusion imaging predicted a high incidence of MI or need for revascularization, while negative imaging predicted a low incidence of MACE.10 This study was conducted prior to the use of contemporary cTn assays, and has limited usefulness in the modern era of MI diagnosis. A more recent study found that supplementing the standard evaluation of low to moderate risk chest pain patients with resting sestamibi added no benefit to those with ACS, but may reduce the need for admission in patients with non-cardiac chest pain.11 The addition of gated analysis for functional cardiac measurement improves the diagnostic accuracy of resting perfusion studies, but there is no evidence that this technology is superior to three-hour accelerated diagnostic protocols using contemporary cTn assays in low risk populations. In fact, accelerated diagnostic protocols likely accomplish the same task as resting perfusion studies with less cost and radiation exposure.12

Functional Cardiac Assessment

Stress testing is the traditional non-invasive method of assessing cardiac function in patients suspected of ACS who have negative cTn. This involves the use of exercise or pharmacologic agents to raise myocardial oxygen demand and provoke detectable myocardial ischemia in the presence of coronary artery stenosis. In some instances, vasodilators are used to expose relative differences in myocardial perfusion caused by the inability of diseased vessels to match the flow of normal vessels. The vast majority of functional assessments take advantage of imaging technologies, using either echocardiogram or nuclear perfusion imaging with single-photon-emission-computed-tomography (perfusion SPECT).

Stress Test Effectiveness

Numerous studies have compared the diagnostic accuracy of various stress tests for detecting obstructive coronary artery disease (CAD) that is defined as 50% or more stenosis by coronary angiography. The standard exercise ECG has a pooled sensitivity of only 68% and specificity of 77%.13 Because of this poor performance, an imaging modality (either echocardiogram or perfusion SPECT) is often added, increasing the sensitivity to 80-90% but with little improvement in specificity as seen in Table 1.14, 15 These estimations may be overly optimistic since the use of cardiac catheterization as a reference standard introduces an element of referral bias.16 Thus, clinicians must take into account the pre-test probability of disease when interpreting these tests, since at least 20% of stress tests will yield a false positive or false negative result.

Predicting outcomes after a stress test is challenging due to the wide array of endpoints across studies. However, the general trend in the literature is that patients having a normal stress test with either perfusion SPECT, echocardiogram, or cardiovascular magnetic resonance (CMR) imaging have a low annualized rate of MI or cardiac death as seen in Figure 2.17 Unfortunately, pharmacologic stress testing does not perform quite as well, likely due to a higher incidence of co-morbid conditions and greater CAD burden in patients receiving these tests.

Cardiovascular Magnetic Resonance Imaging

CMR is an emerging technology for the evaluation of patients with suspected ACS that allows both functional and anatomic measurements. Recent trials have proven CMR to be more accurate than SPECT for detecting clinically
relevant coronary heart disease. A series of trials demonstrated the efficacy of this modality in managing intermediate to high risk patients with acute chest pain in an observation unit setting. Cine imaging allows accurate assessment of global as well as left and right ventricular function. Myocardial perfusion imaging tracks the passage of a gadolinium contrast agent during rest and in conjunction with vasodilator stress, and thereby allows for the detection of coronary stenosis and perfusion defects (Figure 3). T2-weighted imaging can be used to detect myocardial edema as a sign of transient ischemia or necrosis (Figure 4). Finally, delayed gadolinium enhancement detects myocardial scarring and, when considered with the other CMR components, aids in distinguishing old versus recent infarcts (Figure 5). This comprehensive assessment acquired with CMR is most advantageous in more complex patients. Studies are ongoing to determine the role of CMR in patients at moderate to high risk of ACS and with detectable to mildly elevated cTn levels using contemporary assays (NCT01931852).

Non-Invasive Anatomic Coronary Imaging

Coronary Computed Tomography Angiography

Coronary computed tomography angiography (CCTA) has been proposed as an alternative to traditional stress testing in patients without known CAD. Initial studies with CCTA suggested that it possessed superior diagnostic accuracy and the unique ability to detect prognostically significant non-obstructive CAD when compared to stress testing. Recent large clinical trials have compared CCTA to usual care in ED patients with chest pain. In the ACRIN-PA 4005 trial, no patients with negative CCTA exams experienced adverse cardiac events at 30 days (0/640, 0%, 95% CI 0-0.57%). Furthermore, in this trial, patients randomized to CCTA had a shorter length of stay and were more commonly diagnosed with coronary disease. In the ROMI-CAT II Trial, the safety and length of stay benefits of CCTA were replicated, and the CCTA arm was also associated with an increase in downstream testing and radiation exposure. The recent PROMISE Trial was a prospective, randomized study of over 10,000 participants that compared the effectiveness of two initial diagnostic strategies in non-ED patients suspected of having symptomatic CAD: 1) functional testing with exercise ECG, stress nuclear imaging, or stress echocardiogram, or 2) anatomic testing with CCTA. In this study, there was no difference in the composite primary endpoint of death, MI, need for hospitalization, or major procedural complications; the CCTA group had fewer cardiac catheterizations showing no obstructive disease (3.4 vs. 4.3%) and higher cumulative radiation exposure. In aggregate, clinical trials demonstrate CCTA to be safe and effective. At some institutions, CCTA is first line. At others, it is reserved for patients who are poor candidates for stress testing, frequently present with chest pain, or have an indeterminate stress test.

Selecting an Imaging Strategy

The choice of stress test is largely determined by the patient’s exercise capacity, baseline ECG, and institutional availability. Patients with a normal
ECG who are able to complete the exercise protocol are candidates for exercise ECG stress testing. Most institutions have incorporated either perfusion SPECT or echocardiogram imaging into their stress testing to improve diagnostic performance, especially in patients with baseline ECG abnormalities. Ultimately, the choice of imaging modality is often determined by institution practices and availability. Although the exercise perfusion SPECT has marginally better diagnostic accuracy than stress echocardiogram, the latter offers the advantages of less radiation and the ability to evaluate valve function. On the other hand, the diagnostic accuracy of stress echocardiogram is limited in obese patients, those with chest wall deformities, and patients with emphysema or prior MI. The comprehensive assessment provided by CMR is most beneficial in intermediate and high risk patients. Primary reasons to avoid CMR relate to claustrophobia, implanted metal objects, renal insufficiency, and patient body habitus.

Patients who are unable to complete the exercise protocol require some form of pharmacologically enhanced imaging evaluation either with dobutamine or a vasodilator such as adenosine or persantine. Dobutamine is the preferred agent in patients with asthma, since vasodilators may stimulate reactive airway disease. On the other hand, dobutamine should be avoided in patients with a history of tachyarrhythmia. The use of CCTA is also a reasonable imaging modality in those who cannot exercise or who have indeterminate functional testing and a low pretest probability of CAD.

**Conclusion**

The evaluation of patients with suspected ACS continues to evolve with advances in technology. New generations of cTn assays have shortened the ED disposition time in many low risk populations. Emergency physicians now have a wide array of functional and anatomic imaging choices for the evaluation of suspected ACS with more advanced technology around the corner in the form of CMR. This will allow more individualized and cost-effective care plans as the advances are incorporated into contemporary practice.

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2013 AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION GUIDELINE FOR STEMI PATIENTS

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Objectives

1. Describe the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of ST-Elevation Myocardial Infarction (STEMI).
2. Describe the clinical trial evidence and rationale behind Emergency Department (ED) use of antplatelet and antithrombin therapy as an adjunct to reperfusion in the treatment of STEMI.
3. Discuss the value of Emergency Medical Systems (EMS)/ED/ Cardiology collaboration and its effects on reperfusion time.
4. Discuss the value of regionalization of STEMI care and the choice between percutaneous coronary intervention and fibrinolytics.

Introduction

There are very few diagnostic or therapeutic challenges that require speed and efficiency more than the care of a patient with ST-elevation myocardial infarction (STEMI). When minutes count, and time is muscle, emergency physicians have the opportunity to make a crucial impact on morbidity and mortality in patients with STEMI. Applying appropriate therapy in a very time-efficient manner in the treatment of STEMI requires a systematic approach across the care continuum, from the patient’s home to the cardiac catheterization laboratory. It also requires an in-depth knowledge of the treatment protocols for STEMI, especially as they relate to antplatelet, antithrombin, and catheter-based therapy.

The 2013 Update of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of STEMI outlines the recommendations for the prehospital and Emergency Department (ED) management of STEMI, including antplatelet, antithrombotic, and fibrinolytic versus catheter-based reperfusion therapy. These guidelines were promulgated in an effort to standardize and optimize the evaluation, diagnosis, and management of patients with STEMI and to provide physicians with a framework for clinical decision-making. They have become the cornerstone of many ED protocols for the treatment of STEMI, and these protocols are crucial to providing efficient care in the ED and seamless patient transitions to the cardiac catheterization laboratory or cardiac care unit. More than ever, the 2013 ACCF/AHA Guideline emphasizes the creation of systems of care that speed the diagnosis, recognition, and timely transfer of a patient with STEMI to the cardiac catheterization laboratory, even after fibrinolytic therapy. In addition, new clinical trial data support changes in the dosing and application of antplatelet and antithrombin therapy in the treatment of STEMI, and emergency physicians should be familiar with these changes.

Systems of Care for STEMI

Time is of the essence in the care of patients with STEMI. Care occurs across the continuum, not only at the patient’s bedside in the ED but includes the emergency medical system (EMS) transport to the ED and ultimately to the cardiac catheterization laboratory. The care of a patient with STEMI is influenced by patient education (recognition of symptoms), EMS dispatch (availability of 911 capability), EMS access and capability (availability of field electrocardiogram [ECG] and rapid response/transport), EMS communication (ED or cardiac catheterization laboratory activation), ED nursing (throughput and patient stabilization), emergency physician care (stabilization, activation of cardiac catheterization laboratory, appropriate therapy), cardiac catheterization laboratory staff (patient preparation and equipment) and interventional cardiology (rapid and skilled percutaneous intervention) (Figure 1). Coordination across all these groups with the goal of achieving a first-medical-contact (FMC) to balloon time of 90 minutes or less can be a formidable task. The ACCF/AHA Guideline for the Management of STEMI recommends that “all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and hospital-based activities. Performance can be facilitated by participating in programs such as Mission: Lifeline and the D2B Alliance” (Class IIB recommendation) (Figure 2).

The development of systems of care begins with optimizing the capability of EMS to recognize, treat, and appropriately transport patients with STEMI to the closest facility capable of STEMI care. The ACCF/AHA Guideline recommends performance of a 12-lead ECG by EMS personnel at the site of...
OPTIMAL THERAPY FOR ACS: USING GUIDELINE-BASED TREATMENTS IN THE EMERGENCY SETTING

The EMS, ED and cardiology communications and patient transfer protocols need to be studied, analyzed, and refined to optimize speed and reduce the time from FMC to reperfusion. Many process improvement methodologies, including Lean, Six Sigma, and others, have been successfully utilized to reduce time to reperfusion in the prehospital, ED, and cardiac catheterization laboratory settings. Data capture, data analysis, and continuous performance feedback to providers is needed to reduce unnecessary steps along the reperfusion pathway. Participation in state-wide or national registries such as the D2B Alliance or Mission Lifeline can provide the tools necessary for an individual health system to put a “system of care” into place.

The Choice of Reperfusion Therapy in STEMI: Fibrinolysis versus Percutaneous Coronary Intervention

The pathophysiology of STEMI is initiated by the endothelial rupture of an atherosclerotic coronary artery plaque. Plaque rupture leads to platelet aggregation, platelet activation, fibrin deposition, and downstream myocardial ischemia and necrosis. Downstream necrosis is time dependent, with a wavefront of necrosis developing in the subendocardium and extending transmurally outward with time. As the duration of ischemia increases, so does the risk of heart failure, patient morbidity, and death. For every 30 minutes of ischemia, mortality increases 8-10%. Reperfusion therapy, with dissolution or removal of the intracoronary thrombus, provides the best chance for mortality reduction. The 2013 ACCF/AHA Guideline gives primary PCI a Class IA recommendation for reperfusion for all STEMI patients with symptoms less than 12 hours duration, as long as it can be accomplished with a FMC to balloon inflation time of 90 minutes or less. If the EMS has a choice between PCI-capable and non-PCI-capable hospitals, they should transport the patient to a PCI-capable hospital, as long as a FMC to balloon time of less than 90 minutes can be achieved (Class IB recommendation). Fibrinolysis, which is less effective than PCI in head-to-head trials, is given a Class IB rating as an alternative to primary PCI, as long as it can be accomplished within 30 minutes of FMC (Figure 3).

PCI versus Fibrinolytics: Inter-Hospital Transfer Decisions

Emergency physicians who work in PCI-capable hospitals should choose PCI as their reperfusion methodology of choice. Those who work in rural hospitals, where patient transfer to a PCI-capable hospital would prolong time to treatment, should choose timely fibrinolysis as their reperfusion strategy of choice. There is a distinct gray zone, however, in patients for whom the choice must be made between timely fibrinolysis versus patient transfer for “minimally or moderately delayed” primary PCI. The emergency physician must decide between fibrinolysis within 30 minutes of FMC versus transfer for PCI, knowing that the chance of a FMC to balloon time of less than 90 minutes in the setting of an inter-hospital transfer is remote. In the National Registry of Myocardial Infarction (NRMI), the percentage of patients meeting the 90 minute reperfusion window after a transfer from one hospital to another was less than 4%.

The 2013 ACCF/AHA Guideline provides much more specific guidance for these inter-hospital transfer scenarios. If a patient with STEMI presents to a non-PCI capable facility, the ACCF/AHA Guideline gives a Class IB recommendation for transfer of the patient to a PCI capable facility, as long as a FMC to balloon time of 120 minutes is achievable as a system goal (Figure 4). Despite this recommendation, these “gray zone” patients often require difficult decisions around fibrinolytic therapy versus PCI. Factors that mitigate against “prolonged PCI times” and support fibrinolytic therapy use include young age, anterior MI, and early (<3 hrs of pain) presentation. Fibrinolytics are very effective within three hours of symptoms, but less effective in late presenters, and they are ineffective in patients with 12-24 hours of symptoms. Factors which make delayed PCI the preferred strategy include contraindications to fibrinolysis, cardiogenic shock, cardiac arrest, advanced age, inferior MI, and delayed presentation.

The recent STREAM clinical trial investigated the question of fibrinolysis versus minimally delayed PCI. In this trial, patients with less than three hours of symptoms who were anticipated to have a moderate delay (>1 hour) to PCI for STEMI were randomized to receive either moderately delayed PCI versus immediate fibrinolysis followed by PCI within 6-24 hours. The time from FMC to reperfusion in the PCI group was 117 minutes, versus 38 minutes in the fibrinolytic group. In the fibrinolytic group, 36% of patients underwent rapid fibrinolysis.


*The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.
PCI within 2.2 hours of randomization (termed “facilitated PCI”) and 64% underwent less urgent PCI at an average of 17 hours. In the 1,892 patients studied, there were slightly fewer ischemic endpoints in the fibrinolytic group, but the difference was not statistically significant (p=0.24). Bleeding outcomes were marginally more frequent in the fibrinolytic group, but again without statistical significance (p=0.11). The exception was the frequency of hemorrhagic stroke, which was significantly higher in the fibrinolytic group (p=0.03), even though the absolute number of hemorrhagic strokes was small. The STREAM Trial was controversial in its results, but reinforced the concept that clinical outcomes, including ischemic and bleeding endpoints, were similar when a strategy of either early fibrinolysis or moderately delayed (<120 min FMC to PCI) PCI are employed, even in patients with symptom durations of less than three hours. The results of the STREAM Trial are consistent with the ACCF/AHA Guideline recommendation to transfer STEMI patients from a non-PCI-capable hospital to a PCI-capable hospital when a FMC to balloon time of <120 minutes is achievable.2

Another question that emergency physicians face in non-PCI-capable EDs is whether transfer for potential PCI is required immediately after fibrinolytic therapy. This question was investigated in the TRANSFER AMI Trial.13 In this trial, patients presenting to rural non-PCI-capable hospitals were randomized to receive fibrinolytics followed by immediate transfer for PCI (termed “pharmaco-invasive strategy”) versus fibrinolytics and standard care, often with delayed PCI. The patients who received pharmaco-invasive therapy and early PCI after fibrinolysis had a 6.2% absolute reduction in adverse cardiac events (p=0.004) compared to the standard fibrinolytic group, with no significant increase in bleeding events. It is clear from this trial that early transfer to a PCI capable center after fibrinolytic administration is appropriate, and early PCI after fibrinolytic therapy is a preferred strategy.

**Antiplatelet and Antithrombin Therapy with Fibrinolysis**

If fibrinolysis is chosen as a reperfusion strategy, appropriate antiplatelet adjuncts include aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors (GPI). All have been investigated in large multicenter clinical trials, but only aspirin and clopidogrel have been incorporated as Class I recommendations in the ACCF/AHA Guideline in patients treated with fibrinolysis.2 1-2 Specifically, aspirin 325 mg orally is indicated at patient presentation regardless of the reperfusion strategy (Class IB recommendation), while an oral loading dose of clopidogrel 300 mg is indicated for administration in the ED with fibrinolysis (Class IB recommendation). Clopidogrel is an oral antiplatelet agent that binds to platelets at the P2Y12 site, and inhibits platelet activation through the ADP-mediated pathway. The Guideline gives clopidogrel 75 mg daily a Class IB recommendation for STEMI. The 300 mg load is recommended with fibrinolysis (Class IIaC) based on the results of the CLARITY and COMMIT Trials.14 15

The 2013 ACCF/AHA Guideline also recommends the administration of an antithrombin agent as an adjunct to reperfusion therapy; this should be initiated in the ED, either in conjunction with fibrinolytic therapy or in preparation for primary PCI.2 The Guideline gives unfractionated heparin a Class IC recommendation and enoxaparin a Class IA recommendation.16 The combination of aspirin, clopidogrel, and enoxaparin, if appropriately dosed, comprises the best evidence-based protocol for STEMI treatment with fibrinolytic therapy.

**Antiplatelet and Antithrombin Therapy with Primary PCI**

Antiplatelet therapy recommended by the 2013 ACCF/AHA Guideline for the Management of STEMI by primary PCI includes aspirin (Class IB), clopidogrel, prasugrel, ticagrelor (all Class IB), and glycoprotein IIb/IIIa inhibitors (GPIs) (Class IIaB). Recent evidence supports an oral loading dose of 600 mg of clopidogrel with primary PCI;17 other recent evidence supports the use of prasugrel 60 mg or ticagrelor 180 mg as new alternatives to clopidogrel with primary PCI.18 19 Prasugrel and ticagrelor are now FDA approved oral P2Y12 platelet inhibitors that are more potent than clopidogrel. Both provide higher antiplatelet activity than clopidogrel. Prasugrel is contraindicated in patients >75 years of age, weight less than 60 kgs, and in those with previous stroke.

Class I antithrombins recommended for PCI in STEMI include unfractionated heparin (IB) and bivalirudin (IB).2 The HORIZONS Trial20 investigated the use of heparin plus a GPI versus bivalirudin with provisional GPI therapy in 3,602 STEMI patients undergoing primary PCI. The primary outcome of the trial was net clinical adverse events, including cardiac events – death, MI, stroke, or urgent intervention, or major bleeding at 30 days. Bivalirudin monotherapy resulted in no difference in ischemic endpoints, but a significant 40% reduction (8.3% versus 4.9%, p<0.0001) in major bleeding compared to standard therapy. The recently presented one-year data from HORIZONS demonstrated a net death benefit in patients receiving bivalirudin therapy versus heparin plus a GPI.21 Of interest is that the majority of patients in the bivalirudin arm received unfractionated heparin in the ED prior to enrollment in the study. As such, the utilization of bivalirudin for primary PCI in the cardiac catheterization laboratory may not have a significant effect on the ED treatment of STEMI patients prior to primary PCI.

Synthesizing these data, it appears that the optimum ED management of STEMI destined for primary PCI includes aspirin, a P2Y12 oral antiplatelet agent (clopidogrel, ticagrelor, or prasugrel), heparin 4,000 units intravenous push, and rapid transfer to the cardiac catheterization laboratory. The utilization of GPI or bivalirudin in the cardiac catheterization laboratory can be left to the discretion of the cardiologist, and will not be hindered by upstream management in the ED (Figure 5).
Conclusion

Care of the patient with STEMI requires speed, efficiency, and precision. Understanding the ACCF/AHA Guideline for the Management of STEMI and incorporating the recommendations into EMS, ED, and cardiac catheterization laboratory protocols are essential to providing STEMI patients with the best quality care. Given the complexity of decisions in non-PCI-capable hospitals, well-developed, prospective STEMI protocols and systems of care are also essential. Emergency physicians are in the perfect position to lead the development of these STEMI protocols and systems of care.

References


1. Explain and substantiate the platelet hypothesis for the pathophysiology of non-ST-segment elevation acute coronary syndrome (NSTE-ACS).
2. Demonstrate a working knowledge of the role of antiplatelet therapy in ACS management.
3. Formulate a care pathway for the management of NSTE-ACS that aligns with the 2014 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline and maximizes the potential role of the emergency care provider in that care.
4. Describe the distinctions among anticoagulants, anti-activation anti-platelet agents, and anti-aggregation anti-platelet agents, and explain how those differences inform appropriate, risk-stratified use of each in the management of NSTE-ACS.

Introduction

The latest edition of evidence-based guidance from the American Heart Association (AHA) and American College of Cardiology (ACC) on how to manage non-ST-segment elevation (NSTE) acute coronary syndrome (ACS) was released in the fall of 2014. This is a full guideline update rather than a “focused” update that only addresses limited changes from the most recent prior guideline, which in this case was published in 2012. The supporting data remain fresh, as the evidence review was conducted through October 2012, and other selected references published through April 2014 were reviewed by the guidelines writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to the guideline. Similar to previous editions, much of what is discussed and recommended in this guideline is of limited applicability to “upstream” providers, especially non-cardiologist emergency care providers. “Upstream” refers to the interval of care of an ACS patient that occurs prior to diagnostic angiography—that is, prior to knowledge of the coronary anatomy. The upstream interval is the domain of emergency medical services (EMS), emergency physicians, hospitalists, and non-interventional cardiologists. It is sometimes referred to as the “empiric” treatment interval, as, again, the coronary anatomy is unknown. Still, even with that limitation, emergency care providers strive to diagnose, risk-stratify, and safely treat patients with suspected or confirmed ACS as they transition patient care to (often interventional) cardiologists. The goal is to “hand off” a thoroughly evaluated and clinically stable patient. The Emergency Department (ED) evaluation of the NSTE-ACS patient, those with unstable angina or NSTE myocardial infarction (NSTEMI), is more problematic than that of the ST-segment elevation myocardial infarction (STEMI) patient. The former tend to be older, have more atypical presentations, carry more comorbidities, and have more obscure findings in laboratory and electrocardiography (ECG) evaluation.

Sites of Service

The Guideline refers to preferred sites of service:

**CLASS I**

1. Patients with **suspected ACS and high-risk features** such as continuing chest pain, severe dyspnea, syncope/presyncope, or palpitations should be referred immediately to the ED and transported by EMS when available. (Level of Evidence: C)

**CLASS IIb**

1. Patients with less severe symptoms may be considered for referral to the ED, a Chest Pain Unit, or a facility capable of performing adequate evaluation depending on clinical circumstances. (Level of Evidence: C)

**Electrocardiography and Serum Cardiac Biomarkers**

In most EDs, the path to the “Chest Pain Unit” is through the ED, after an initial evaluation. The Guideline further suggests an early, basic risk stratification strategy using ECG and continuous/serial monitoring, as well as laboratory analysis for cardiac biomarkers of necrosis:

**CLASS I**

1. In patients with chest pain or other symptoms suggestive of ACS, a **12-lead ECG** should be performed and evaluated for ischemic changes within 10 minutes of the patient’s arrival at an emergency facility. (Level of Evidence: C)

2. If the initial ECG is not diagnostic but the patient remains symptomatic and there is a high clinical suspicion for ACS, **serial ECGs** (e.g., 15- to 30-minute intervals during the first hour) should be performed to detect ischemic changes. (Level of Evidence: C)

3. **Risk scores** should be used to assess prognosis in patients with NSTE-ACS. (Level of Evidence: A)

Appropriate and accurate risk stratification of patients with possible or confirmed NSTE-ACS is dependent on accurate interpretation of ECG data. While many emergency physicians have good cardiology support, it is important both to recognize the presence of findings suggestive of ischemia including dynamic ST-segment changes; ST depression, especially downsloping at the J-point; Wellens’ T waves; new T wave flattening or inversion in the patient with angina symptoms, and inverted U waves and to realize that the most common ECG abnormalities in patients who go on to have NSTEMI are the very non-diagnostic findings of sinus tachycardia and nonspecific ST-T wave changes.

Risk scores are popular in the ED evaluation of possible ACS, as they can lend quantification to a complex clinical scenario. The most commonly accepted scores for NSTE-ACS are from the TIMI Group (Figure 1) and the GRACE Group (Figure 2). Both can be downloaded onto mobile platforms for bedside use, but emergency care providers should always keep in mind that these scores are best used as supplements to, and not replacements for clinical judgment. Although the scores were derived from cohorts of patients already enrolled in ACS trials, and therefore with very high pre-test probability, at least one ED-based study has qualitatively validated the TIMI Score in an unselected cohort of ED patients with chest pain syndrome.
Emergency care providers will note that there is no suggested specific sampling interval for serial assessments of cardiac biomarkers. There are broadly applicable data from the pre-high-sensitivity troponin assay literature that attribute value to “two-hour-delta” measures of troponin levels to exclude myocardial necrosis, but with more sensitive assays such approaches may require recalibration. Reichlin et al. have initiated this discussion in a post-Guideline publication that showed "a simple algorithm incorporating hs-cTnT baseline values and absolute changes over two hours allowed a triage toward safe rule-out, or accurate rule-in, of acute MI in the vast majority of patients, with only 20% requiring more prolonged monitoring and serial blood sampling.”

Often, an accurate time of symptom onset is obscure or the emergency care providers tend to be skeptical about history that is provided. The 2014 Guideline provides actionable guidance to start the six-hour clock ticking at ED presentation in such cases.

**Chest Pain Observation**

The Guideline does not provide much help in the discharge of patients with chest pain from the ED dialogue that often leaves emergency care providers feeling insecure and at medicolegal risk. Interestingly, there are no Class I recommendations in this regard. The following general recommendations, however, receive Class IIa support:

**CLASS IIa**

1. It is reasonable to observe patients with symptoms consistent with ACS without objective evidence of myocardial ischemia (nonischemic initial ECG and normal cardiac troponin) in a **Chest Pain Unit or Telemetry Unit with serial ECGs and cardiac troponin at 3- to 6-hour intervals.** (Level of Evidence: B)

2. It is reasonable for patients with possible ACS who have normal serial ECGs and cardiac troponins to have a treadmill ECG (Level of Evidence: A), stress myocardial perfusion imaging, or stress echocardiography **before discharge or within 72 hours after discharge**. (Level of Evidence: B)

3. In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of coronary artery disease (CAD), it is reasonable to initially perform **(without serial ECGs and troponins)** coronary computed tomography **angiography** to assess coronary anatomy (Level of Evidence: A) or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia. (Level of Evidence: B)

4. It is reasonable to give low-risk patients who are referred for outpatient testing daily aspirin, short-acting nitroglycerin, and other medication if appropriate (e.g., beta blockers), with instructions about activity level and clinician follow-up. (Level of Evidence: C)

The emergency medicine literature is replete with supporting evidence for chest pain observation. The “holy grail” of chest pain syndrome evaluation, however, is the abbreviated rule-out, preferably coupled with either provocative functional testing or anatomic characterization. Imaging protocols are gaining in popularity and in accessibility to the typical emergency physician, and the data on the evaluation of patients already stratified to a low or low-to-moderate level of risk are convincing. The remaining challenges are being certain about the initial risk level assignment, scheduling on-demand
testing, and arranging good follow-up for patients after ED/observation care is complete. The interested reader is referred to a number of contemporary references cited in the Guideline regarding provocative and imaging studies of patients with symptoms consistent with ACS, but otherwise non-diagnostic evaluations.7-13

Early Hospital Care and Anti-Anginal Treatment

The 2014 Guideline (and, in fact, prior editions) are not at all specific about therapy for NSTE-ACS that is specifically to be given or not to be given while the patient is physically in the ED. There is occasional guidance about performing an intervention or giving a medication “as soon as possible” or “after the coronary anatomy is defined.” Here we will review only the recommendations that are pertinent to pre-angiography care. This is not meant to suggest that there is a standard of care holding that these recommendations should be followed in every ED. The goal of enumerating these recommendations here is to make sure that the key stakeholders in ACS care—the emergency care providers—are aware of the Guideline. Listed first are the Class I and III recommendations, then selected Class II recommendations, for general management (Figure 3). More extensive commentary will be provided on recommendations for antithrombotic therapies.

### FIGURE 03 Early Hospital Care and Anti-Anginal Treatment Recommendations For Non-ST-Segment Elevation Acute Coronary Syndrome Per Guideline

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxygen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer supplemental oxygen only with oxygen saturation &lt;90%, respiratory distress, or other high-risk features for hypoxemia</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer sublingual NTG every 5 min for continuing ischemic pain and then assess need for IV NTG</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Administer IV NTG for persistent ischemia, HF, or hypertension</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>Analgesic Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV morphine sulfate may be reasonable for continuing ischemic chest pain despite maximally tolerated anti-ischemic medications</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>Beta-adrenergic Blockers</strong></td>
<td></td>
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</tr>
<tr>
<td>Initiate oral beta blockers within the first 24 h in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade directed with their use</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTE-ACS, stabilized HF, and reduced systolic function</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Re-evaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>IV beta blockers are potentially harmful when risk factors for shock are present</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>CCBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval &gt;0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects*ns</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Long-acting CCBs and nitrates are recommended for patients with coronary artery spasms</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Immediate-release nifedipine is contraindicated in the absence of a beta blocker</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>Cholesterol Management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate or continue high-intensity statin therapy in patients with no contraindications</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Obtain a fasting lipid profile, preferably within 24 h</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

*Short-acting dihydropyridine calcium channel antagonists should be avoided.
CCB indicates calcium channel blocker; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; MACE, major adverse cardiac event; N/A, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non-ST-elevation acute coronary syndromes; and NTG, nitroglycerin.

CLASS I

1. **Supplemental oxygen** should be administered to patients with NSTE-ACS with arterial oxygen saturation less than 90%, respiratory distress, or other high-risk features of hypoxemia. (Level of Evidence: C)

2. Patients with NSTE-ACS with continuing ischemic pain should receive **sublingual nitroglycerin** (0.3 mg–0.4 mg every 5 minutes for up to 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin if not contraindicated. (Level of Evidence: C)

3. **Intravenous nitroglycerin** is indicated for patients withNSTE-ACS for the treatment of persistent ischemia, heart failure (HF), or hypertension. (Level of Evidence: B)

4. **Oral beta-blocker therapy** should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade such as PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease. (Level of Evidence: A)

5. In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta blockers, a **nondihydropyridine calcium channel blocker** (CCB) (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant left ventricular dysfunction, increased risk for cardiogenic shock, PR interval greater than 0.24 second, or second- or third-degree atrioventricular block without a cardiac pacemaker. (Level of Evidence: B)

6. **Oral nondihydropyridine** calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta blockers and nitrates. (Level of Evidence: C)

CLASS III: HARM

1. **Nitrites should not be administered** to patients with NSTE-ACS who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafl. (Level of Evidence: B)

2. **Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin)** should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of major adverse cardiac events (MACE) associated with their use. (Level of Evidence: B)

3. **Administration of intravenous beta blockers is potentially harmful** in patients with NSTE-ACS who have risk factors for shock. (Level of Evidence: B)

CLASS IIIb

1. In the absence of contraindications, it may be reasonable to **administer morphine sulfate** intravenously to patients with NSTE-ACS if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. (Level of Evidence: B)

These basic recommendations should already be part of the standard ED approach to patients with chest pain syndrome that may be anginal in origin. Supplemental oxygen, 2-3 liters by nasal biprongs, is always appropriate, even in patients with chronic obstructive pulmonary disease (COPD). The problem in angina is diminished oxygen supply to the myocardium, so any efforts to improve that have the potential for incremental benefit. Nitroglycerin (NTG) is indicated for symptom relief in possible or confirmed ACS. Sublingual or topical application is usually sufficient, though in patients with signs and symptoms of heart failure, an intravenous (IV) infusion may be helpful both for treating angina and for inducing some pulmonary venodilation. Concomitant patient use of drugs for erectile dysfunction may cause profound hypotension with NTG, so patients, including females, should always be queried in this regard. The use of NTG should be avoided in patients who have signs of volume depletion and ECGs which suggest inferior ischemia; should hypotension occur after NTG administration, a fluid bolus with or without Trendelenberg positioning is usually effective to restore blood pressure. It should be kept in mind that there has never been a randomized, controlled trial that suggests that NTG has a mortality effect; the drug is given only for symptom relief. Likewise, it is important to remember that the response of symptoms to NTG does not “rule-in” ACS as an etiology of the symptoms of interest. The pain of esophageal spasm, which can be described in very similar terms as angina, often responds readily to NTG.

As an anti-anginal measure, there may also be a role for beta blockers, calcium channel blockers, and morphine, but not for NSAIDs such as ketorolac. NSAIDs interfere with the antiplatelet efficacy of aspirin and should be avoided acutely and longer term. Beta-blockers reduce myocardial oxygen demand, primarily by reducing heart rate, and may therefore help with angina. They should be given orally if needed in the ED, because IV administration increases the risk of cardiogenic shock. In the past, beta-blockers were given to all ACS patients in the ED; the past several updates of the Guideline, however, simply suggest that the drugs be started in the absence of contraindications within 24 hours of arrival, taking them off the emergency care provider’s to-do list in most cases. Also, persistent tachycardia in a patient with chest pain syndrome may indicate volume depletion, sepsis, or pulmonary embolism, and therefore warrants further clinical investigation at the time beta-blockers are being considered. As mentioned above, there is a limited potential role for non-dihydropyridine calcium blockers, such as verapamil and diltiazem, in anginal relief when beta-blockers are contraindicated or when beta-blockers plus nitrates are ineffective. The immediate-release forms of these drugs should not be used in the absence of beta blockade; immediate-release nifedipine causes a dose-related increase in mortality in patients with CAD.

Most patients with a clinical picture consistent with NSTE-ACS are treated with NTG and then, if pain persists, morphine sulfate. Data from the CRUSADE Registry showed that, even after adjustment for risk and concomitant medications, IV morphine given to patients with NSTEMI or unstable angina with ST-segment depression is associated with an increase in mortality. Morphine is the only opioid with which there is extensive experience in anginal pain, though none is randomized and controlled, and it is an effective analgesic, anxiolytic, and venodilator. The Guideline recommends that in patients with symptoms despite antianginal treatment, morphine (1 mg to 5 mg IV) may be administered with blood pressure monitoring. The morphine dose may be repeated every 5 to 30 minutes to relieve symptoms and maintain the patient’s comfort. The CRUSADE analysis, while observational and uncontrolled, raises important safety concerns around the known adverse effects of nausea, vomiting, hypotension, and respiratory depression. There
really is no vetted alternative to morphine in managing angina in the ED, so it should be used sparingly such as using 2 mg aliquots up to a 10 mg total dose. Naloxone (0.4 mg to 2.0 mg IV) should be used if needed for respiratory or circulatory depression.

**Antithrombotic Therapy**

With respect to the administration of antithrombotic therapy (anticoagulants and antiplatelets) in the ED, these are the latest ACCF/AHA recommendations (Figure 4):

**CLASS I**

1. **Non-enteric-coated, chewable aspirin** (162 mg to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 mg/day to 325 mg/day) should be continued indefinitely. (Level of Evidence: A)

2. In patients with NSTE-ACS who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. (Level of Evidence: B)

3. In patients with NSTE-ACS, **anticoagulation**, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:
   - **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 IV loading dose of 30 mg has been used in selected patients. (Level of Evidence: A)
   - **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 (DAPT). (Level of Evidence: B)
   - **Fondaparinux**: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed. (Level of Evidence: B)
   - **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/hour) 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)

4. **A P2Y12 inhibitor (either clopidogrel or ticagrelor) in addition to aspirin** should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with either an early invasive or ischemia-guided strategy. Options include:

---

### Summary of Antithrombotic Therapy For Non-ST Segment Elevation Acute Coronary Syndrome Per Guideline

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Dosing and special considerations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-enteric-coated aspirin to all patients promptly after presentation</td>
<td>165 mg-325 mg</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• Aspirin maintenance dose continued indefinitely</td>
<td>81 mg/d - 325 mg/</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>P2Y12 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin</td>
<td>75 mg</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
| • P2Y12 inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy:  
  – Clopidogrel  
  – Ticagrelor | 300-mg or 600-mg loading dose, then 75 mg/d  
  180-mg loading dose, then 90 mg BID | I | B |
| • P2Y12 inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents | N/A | I | B |
| • Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy | N/A | IIa | B |
| **GP IIb/IIIa inhibitors** |                                         |     |     |
| • GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin) | Preferred options are eptifibatide or tirofiban | IIb | B |

Patients with confirmed NSTE-ACS, especially with high-risk features such as dynamic ST-segment changes or elevated cardiac biomarkers, should receive advanced oral antiplatelet therapy in addition to ASA and anticoagulation. This can be done with anti-activation oral antiplatelet therapy (OAP), active at the P2Y12 (ADP) platelet receptor, with either ticagrelor or clopidogrel (prasugrel is not indicated as upstream OAP in NSTE-ACS), or with IV anti-aggregation antiplatelet therapy (GP IIb/IIIa receptor antagonists), using eptifibatide or tirofiban (abciximab is not indicated upstream in NSTE-ACS), or both. In contemporary practice, there is very little upstream use of GP IIb/IIIa agents. The Guideline does not specify an optimal timeframe for administration of one of the OAP agents, but preference is given to ticagrelor for patients with NSTE-ACS treated with an early invasive strategy.

The preference for ticagrelor over clopidogrel is based on the head-to-head PLATO study, and on prior evidence that ticagrelor has a more rapid and consistent onset of action compared to clopidogrel. In addition, because ticagrelor is reversible, it has a faster recovery of platelet function, perhaps making cardiovascular surgeons more comfortable if urgent coronary artery bypass grafting (CABG) is required in NSTE-ACS patients after OAP loading. In patients with NSTE-ACS treated with ticagrelor as opposed to clopidogrel, there was a reduction in the composite outcome of death from vascular causes, MI, or stroke (reduction: 11.7% to 9.8%; HR: 0.84; p<0.001). The mortality rate was also lower in those patients treated with ticagrelor. Although overall major bleeding was not increased with ticagrelor, a modest increase in major bleeding and non–procedure-related bleeding occurred in the subgroup of patients who did not undergo CABG (major bleeding: 4.5% vs. 3.8%, p=0.02; nonprocedure major bleeding: 3.1% vs. 2.3%, p=0.05); however, there was no difference in blood transfusion or fatal bleeding. The loading dose of ticagrelor for patients treated either invasively or with an ischemia-guided strategy is 180 mg followed by a maintenance dose of 90 mg twice daily. It is the only OAP that requires twice-daily dosing. Side effects unique to ticagrelor, though not likely to be seen in the ED, include dyspnea, which occurs in up to 15% of patients within the first week of treatment but is rarely severe enough to cause discontinuation of treatment and bradycardia. The benefit of ticagrelor over clopidogrel was limited to patients taking 75 mg to 100 mg of aspirin, but that does not impact the standard loading dose of ASA for suspected ACS listed above (162-325 mg). Finally, although the Guideline points out that while ticagrelor has not been studied in the absence of aspirin, its use in aspirin-intolerant or aspirin-allergic patients is “a reasonable alternative.”

Special Populations

Diabetic patients comprise a “special population” within the NSTE-ACS cohort, with diabetes having both higher ischemic risk and higher bleeding risk. Several studies evaluated the benefit of OAP in this cohort. In TRITON-TIMI 38, using prasugrel versus clopidogrel was not studied for upstream therapy in NSTE-ACS. Patients with diabetes mellitus had a greater reduction in ischemic events without an observed increase in TIMI major bleeding with prasugrel compared with clopidogrel. In PLATO, ticagrelor compared with clopidogrel reduced ischemic events irrespective of diabetic status and glycemic control, without an increase in major bleeding. The Guideline, however, does not recommend one over the other specifically in diabetics, instead referring back to the general OAP recommendations in the treatment of diabetic patients.

Likewise, patients with renal insufficiency (CKD) represent a NSTE-ACS cohort with poor outcomes. Patients with advanced CKD exhibit high residual platelet reactivity despite treatment with clopidogrel. Hyporesponsiveness

- Clopidogrel: 300 mg or 600 mg loading dose, then 75 mg daily (Level of Evidence: B)
- Ticagrelor: 180 mg loading dose, then 90 mg twice daily (Level of Evidence: B)

CLASS IIa

1. It is reasonable to use ticagrelor in preference to clopidogrel for P2Y12 treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. (Level of Evidence: B)

CLASS IIb

1. In patients with NSTE-ACS treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin), a glycoprotein (GP) IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. (Level of Evidence: B)
Post-Emergency Department Management

Although post-ED management of NSTE-ACS is often determined primarily by the consulting cardiologist, it is worthwhile to review the very succinct guidance from the ACCF/AHA Task Force (Figure 5). The Class I recommendations emphasize the appropriateness of an urgent or early invasive strategy, that is, early diagnostic angiography and anatomic-guided downstream therapy (medical vs. stent vs. CABG):

### Immediate invasive (within 2 hours)
- Refractory angina
- Signs or symptoms of HF or new or worsening mitral regurgitation
- Hemodynamic instability
- Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
- Sustained VT or VF

### Ischemia-guided strategy
- Low-risk score (e.g., TIMI [0 or 1], GRACE [<10])
- Low-risk TN-negative female patients
- Patient or clinician preference in the absence of high-risk features

### Early invasive (within 24 h)
- None of the above, but GRACE risk score >140
- Temporal change in Tn (Section 3.4 of guidelines)
- New or presumably new ST depression

### Early invasive (within 24 h)
- None of the above but diabetes mellitus
- Renal insufficiency (GFR <60 mL/min/1.73 m²)
- Reduced LV systolic function (EF <0.40)
- Early postinfarction angina
- PCI within 6 mo
- Prior CABG
- GRACE risk score 109–140; TIMI score ≥2

CABG indicates coronary artery bypass graft; EF, ejection fraction; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; Tn, troponin; VF, ventricular fibrillation; and VT, ventricular tachycardia.

### CLASS I

1. An urgent/immediate invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in patients (men and women) with NSTE-ACS who have refractory angina or hemodynamic or electrical instability without serious comorbidities or contraindications to such procedures. (Level of Evidence: A)

2. An early invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in initially stabilized patients with NSTE-ACS without serious comorbidities or contraindications to such procedures who have an elevated risk for clinical events. (Level of Evidence: B)

### Conclusion

The 2014 ACCF/AHA Guideline makes a number of strong recommendations for the upstream assessment and management of NSTE-ACS, including:

1. **Early evaluation in the ED**
   - Key objective components: ECG, cardiac biomarkers, risk score

2. **Anti-anginal therapy with NTG**
   - Supplementation with beta-blockers as needed, which should be given orally, not parenterally
   - Occasional use of calcium blockers
   - Judicious use of morphine as needed to treat persistent anginal symptoms
   - Avoidance of NSAIDs such as ketorolac

3. **Initial antithrombotic therapy with ASA and parenteral anticoagulation**

4. **Use of advanced oral antiplatelet therapy for patients with high-risk features such as dynamic ST-segment changes and elevated biomarkers, and especially if the patient has diabetes or CKD**
   - Ticagrelor preferred over clopidogrel

An overall summary on the following page, including downstream recommendations, is shown in Figure 6.
In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. ASA indicates aspirin; CABG, coronary artery bypass graft; cath, catheter; COR, Class of Recommendation; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; LOE, Level of Evidence; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; pts, patients; and UFH, unfractionated heparin. Reprinted with permission from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Dec 23; 64(24):2713-4.
References


CHALLENGES IN OPTIMIZING ANTIPLATELET THERAPY FOR STEMI AND NSTE-ACS

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Objectives
1. Define the pathobiology of ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation (NSTE) acute coronary syndrome (ACS).
2. Summarize pharmacologic options for optimal management of patients with suspected ACS in the Emergency Department (ED).
3. Highlight the strengths and potential limitations of current national guidelines for the management of patients with suspected ACS.
4. Discuss rational options for reversing the pharmacodynamic effects of Food and Drug Administration (FDA) approved platelet directed therapies used in the management of patients with suspected ACS.

Introduction
Atherosclerotic coronary artery disease is highly prevalent in the United States, Europe and an increasing number of countries in Asia. Many authorities anticipate a pandemic of the disease as western culture behaviors, characterized by inactivity and high caloric intake, spread around the globe. The clinical phenotypes of atherosclerotic coronary disease include stable angina pectoris, non-ST-segment elevation acute coronary syndrome (NSTE-ACS), ST-segment elevation ACS and arrhythmic sudden cardiac death.

The clinical presentations of atherosclerotic coronary artery disease that initiate a diagnostic and therapeutic cascade of evidence-based responses among physicians and healthcare providers are currently grouped into two general categories based on a 12-lead surface electrocardiogram (ECG):

1. ST-segment elevation myocardial infarction (STEMI), which generally reflects complete (100%) occlusion of an epicardial, infarct-related coronary artery
2. Non-ST-segment elevation MI (NSTEMI), which generally reflects partial or transient occlusion of an epicardial coronary artery

The initial challenge faced by clinicians who are trying to optimize care is securing a diagnosis of ACS (Figure 1). The differential diagnosis is broad, crosses many organ systems and includes several other life-threatening conditions that, like ACS, require immediate therapeutic intervention (Table 1). For non-ACS related life-threatening causes of chest pain, traditional treatment options, such as antithrombotic therapy, are either not beneficial or can be harmful. Non-ACS related causes of chest pain may also be associated with elevated serum levels of troponin, which adds an additional challenge to clinicians in their quest to optimize therapy (Table 2).

Out-of-Hospital Cardiac Arrest Survivors
Cardiac arrest is a major health concern in the United States, although there have been recent improvements in survival and neurological recovery resulting from local, regional and nation-wide initiatives for cardiopulmonary resuscitation and maintaining a strong “chain of survival.”

Early post-cardiac arrest resuscitation care falls under the purview of Emergency Departments (EDs) at tertiary care hospitals and includes targeted

TABLE 01
Initial Assessment of Patients with Suspected Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Low Likelihood</th>
<th>High Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presentation</td>
<td></td>
</tr>
<tr>
<td>2. ECG</td>
<td></td>
</tr>
<tr>
<td>3. Troponin</td>
<td></td>
</tr>
<tr>
<td>4. Diagnosis</td>
<td>Non-cardiac</td>
</tr>
</tbody>
</table>

TABLE 02
Initial Assessment of Patients with Suspected Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>Pulmonary embolism</td>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>Tension Pneumothorax</td>
<td>Symptomatic aortic aneurysm</td>
</tr>
<tr>
<td>Tachyarrhythmias</td>
<td>Bronchitis, pneumonitis</td>
<td>Stroke</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>Pleuritis</td>
<td></td>
</tr>
<tr>
<td>Hypertensive emergencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takotsubo cardiomyopathy</td>
<td></td>
<td></td>
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<tr>
<td>Coronary spasm</td>
<td></td>
<td></td>
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<tr>
<td>Cardiac trauma</td>
<td></td>
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</tr>
</tbody>
</table>

TABLE 03
Differential Diagnosis of Chest Pain

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Orthopedic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis, reflux, or spasm</td>
<td>Musculoskeletal disorders</td>
<td>Anxiety disorders</td>
</tr>
<tr>
<td>Peptic ulcer, gastritis</td>
<td>Chest trauma</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Muscle injury/inflammation</td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Costochondritis</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

TABLE 04
Causes of Elevated Troponin

<table>
<thead>
<tr>
<th>Tachyarrhythmias</th>
<th>Heart failure</th>
<th>Hypertensive emergencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical illness (e.g., shock/sepsis/burns)</td>
<td>Myocarditis</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Takotsubo cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Structural heart disease (e.g., aortic stenosis)</td>
<td>Aortic dissection</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism, pulmonary hypertension</td>
<td>Renal dysfunction and associated cardiac disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary spasm</td>
<td></td>
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<tr>
<td></td>
<td>Acute neurological event (e.g., stroke or subarachnoid hemorrhage)</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac contusion or cardiac procedures (e.g., coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), ablation, pacing, cardioversion, or endomyocardial biopsy)</td>
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</tr>
<tr>
<td></td>
<td>Hypo- and hyperthyroidism</td>
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<tr>
<td></td>
<td>Infiltrative diseases, such as amyloidosis, hemochromatosis, sarcoidosis, scleroderma</td>
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</tr>
<tr>
<td></td>
<td>Myocardial drug toxicity or poisoning (e.g., doxorubicin, 5-fluorouracil, Herceptin, snake venoms)</td>
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<tr>
<td></td>
<td>Extreme endurance efforts</td>
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</tr>
<tr>
<td></td>
<td>Rhabdomyolysis</td>
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temperature management and early decision-making that directly impacts survival. Currently, one of the more challenging decisions is whether to perform early coronary angiography. Management guidelines for patients with ST-segment elevation on a presenting ECG recommend coronary angiography with the goal of identifying a culprit infarction-related vessel and restoring myocardial perfusion by primary percutaneous coronary intervention (PCI) (Table 3). This recommendation is based on a totality of evidence derived from 28 studies, primarily single center retrospective analyses and registries, published between 2007 and 2014. Whether patients who arrive in the ED in a comatose state or who do not exhibit ST-segment elevation should follow a similar pathway is a question open for discussion.

A recent single center retrospective study of 746 comatose post-cardiac arrest patients, including 198 with ST-segment elevation and 548 without ST-segment elevation on a presenting ECG, revealed the following:2

- Overall survival was greater among patients with ST-segment elevation (55.1% vs. 41.3%; p=0.001).
- Overall survival was similar among all patients who underwent early angiography regardless of findings on presenting ECG (54.7% and 57.9% for those with and those without ST-segment elevation, respectively).
- Culprit coronary arteries were identified more often in patients with, compared to those without, ST-segment elevation (80.2% vs. 33.2%, p=0.001).
- A majority of culprit coronary arteries were occluded – 92.7% in patients with ST-segment elevation and 69.2% in patients with no ST-segment elevation.

The approach to patients with out-of-hospital cardiac arrest (OHCA) who have achieved a return of spontaneous circulation (ROSC) but who remain comatose must be individualized according to the best available evidence and standards of care (Figure 2).3 Unfavorable resuscitation features that especially if multiple unfavorable resuscitation features are present should not be included in public reporting. A national platform for tracking outcomes of cardiac arrest patients undergoing PCI is needed and should distinguish patients with and without ST-segment elevation.

The key for optimal outcomes among patients with OHCA is for each health system and hospital to take a coordinated approach to management. Several vital components of this process are summarized in Table 4.

### TABLE 03 Management of Patients with Myocardial Infarction Experiencing Cardiac Arrest

<table>
<thead>
<tr>
<th>Management of Patients with Myocardial Infarction Experiencing Cardiac Arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate coronary angiography and percutaneous coronary intervention (PCI) when indicated in patients whose initial electrocardiogram (ECG) reveals ST-segment elevation (Class I)</strong></td>
</tr>
<tr>
<td><strong>Targeted temperature management (Class I)</strong></td>
</tr>
<tr>
<td><strong>Immediate coronary angiography with a view toward primary PCI should be considered in survivors of cardiac arrest without ECG ST-segment elevation, but with a high suspicion of ongoing infarction (Class IIa)</strong></td>
</tr>
</tbody>
</table>

### TABLE 04 A Proposed Strategy for the Management of Out-Of-Hospital Cardiac Arrest Survivors

- Easily implementable algorithm to identify resuscitated comatose patients after cardiac arrest who are appropriate candidates for emergency coronary angiography
- Urgent consultation and evaluation by a multi-disciplinary team, including the interventional cardiologist, should occur before the patient is transferred to the cardiac catheterization laboratory
- Early initiation of targeted temperature management is strongly recommended
- Percutaneous coronary intervention (PCI) outcomes in cardiac arrest patients should not be included in public reporting. A national platform for tracking outcomes of cardiac arrest patients undergoing PCI is needed and should distinguish patients with and without ST-segment elevation
- Randomized controlled trials of early PCI in post-cardiac arrest patients without ST-segment elevation are needed

### Pre-Hospital Best Practices

Emergency Medical Services (EMS) agencies play a critical role in the initial diagnosis and management of STEMI. Several core measures have been developed by the American Heart Association (AHA) Mission Lifeline Program to facilitate best practices on local, regional, and national levels; these include 1) ECG capability at the scene; 2) destination protocols; 3) cardiac catheterization laboratory activation before hospital arrival; and 4) 12 lead ECG quality review. Recent data suggest that fewer than 15% of all EMS systems have adopted all four core elements; however, nearly 50% use protocols to determine hospital destination, cardiac catheterization laboratory activation, and communication with the receiving hospital.

Destination protocols must take the patient’s overall clinical status and available resources into consideration. For example, a patient with ACS complicated by cardiogenic shock must be transported to a tertiary or preferably quaternary hospital with advanced medical therapies, such as a mechanical...
circulatory assist program and surgical expertise including coronary artery bypass grafting and heart transplantation capability available 24 hours per day, 7 days per week.

Following the Guidelines for Patients with Non-ST-Segment Elevation Myocardial Infarction

According to the most recent guidelines, patients with NSTEMI should receive a full complement of pharmacological therapies designed to attenuate myocardial ischemia, lessen the need for emergent intervention, and prevent reinfarction. Accordingly, antithrombotic therapy directed specifically at thrombin and platelets is the standard of care (Figure 3). The likelihood of benefit is greatest when therapy is initiated soon after the diagnosis of NSTEMI has been made for patients selected for an invasive (i.e., coronary angiography, PCI) or conservative strategy of management (Figure 4).

Pre-Treatment with Antiplatelet Therapy

Pre-hospital administration of platelet-directed therapy has been evaluated in patients with STEMI. In the Atlantic (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST-segment elevation MI to open the Coronary artery) Trial, 1,862 patients with STEMI of less than six hours duration received ticagrelor either pre-hospital (in the ambulance) or in-hospital (in the cardiac catheterization laboratory). The median time from randomization to angiography was 48 minutes, and the median time difference between the two treatment strategies was 31 minutes. The absence of ST-segment resolution (> 70%) before PCI was 86.8% and 87% in the pre-hospital and in-hospital administration groups, respectively (OR 0.93; 95% CI 0.69 to 1.25). The absence of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related coronary artery was 82.6% and 83.1% in the pre-hospital and in-hospital administration groups, respectively (OR 0.97, 95% CI 0.75 to 1.25). There was a significant reduction in definite stent thrombosis among patients receiving pre-hospital ticagrelor. There were no differences in major bleeding between the treatment strategy groups.

In the ACCOAST (A Comparison of prasugrel at the time of percutaneous Coronary intervention or as pre-treatment At the time of diagnosis in patients with non-ST-Segment elevation myocardial infarction) Trial, 4,033 patients were diagnosed with NSTEMI and 68.7% underwent PCI. A total of 1,394 patients received pre-treatment with prasugrel (30 mg loading dose) and 1,376 patients received placebo. At the time of PCI the pre-treatment group received an additional 30 mg of prasugrel and the placebo group received 60 mg of prasugrel. The composite primary efficacy end point of cardiovascular death, MI, stroke, urgent coronary revascularization or glycoprotein IIb/IIIa inhibitor use at seven days occurred in 13.1% and 13.1% of patients, respectively. Stent thrombosis rates did not differ between the groups. Pre-treatment was associated with a 3-fold increase in TIMI major bleeding and a 6-fold increase in life-threatening bleeding compared to treatment at the time of PCI.

Considering the totality of evidence, pre-treatment with dual antiplatelet therapy should be considered for patients in whom the benefit outweighs the risk (Figure 5).

Possible Need for Coronary Artery Bypass Grafting

Surgical revascularization remains an option for patients with ACS; however, advances in percutaneous options, operator experience and medical therapy have significantly lessened the need for emergent surgery. Exceptions include patients with mechanical complications of myocardial infarction for whom percutaneous options are either not available or not adequately developed. Urgent coronary artery bypass grafting (CABG) for failed PCI, coronary artery dissection or coronary artery perforation is also relatively uncommon in expe-
CHALLENGES IN OPTIMIZING ANTIPLATELET THERAPY FOR STEMI AND NSTE-ACS

Experienced medical centers. Early, within seven days of hospitalization, CABG is undertaken in 5-10% of patients and presents a risk for bleeding, particularly if there are lingering effects of antithrombotic and antiplatelet therapies at the time of sternal closure. The potential risks and benefits must be weighed carefully on a patient-by-patient basis.5

Emergency Department Bypass in Patients with Acute Coronary Syndrome

The American College of Cardiology Foundation/AHA STEMI guidelines recommend a time frame of 90 minutes from the time of first medical contact to reperfusion therapy with primary PCI in most instances. Several strategies have been proposed to optimize and shorten reperfusion times, including routine employment of the pre-hospital ECG and availability of a fully-staffed cardiac catheterization laboratory within 20 to 30 minutes of activation. While the European Society of Cardiology STEMI guidelines have endorsed direct transport to the cardiac catheterization laboratory as a means to reduce reperfusion delays, hospital-EMS systems in the United States have embraced this strategy with varying degrees of rigor. In the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network Registry - Get With The Guidelines (ACTION Registry - GWTG), including those participating in the AHA Mission: Lifeline Program, ED bypass significantly shortened reperfusion times (Figure 6), improved the achievement of reperfusion quality benchmarks, and had no adverse impact on in-hospital mortality. In fact, the in-hospital adjusted risk of mortality was 0.69 (95% CI 0.45-1.03).4

Conclusion

There are challenges for optimizing the management of patients with ST-segment elevation and non-ST-segment elevation ACS that clinicians and hospitals face on a day-to-day basis. Securing a diagnosis and expediting evidence-based treatment are the hallmarks of a well-versed, systematic approach that has its foundation in quality, safety and value. Best practice processes must also consider patient populations and regional systems of care that are inherent to a particular hospital. Employing an electronic medical record that facilitates data gathering, timely assessment, and actionable metrics as a foundation for change is required for success in the current healthcare environment.

References


THROMBOELASTOGRAPHY (TEG) – UNDERSTANDING THE PATIENT’S ABILITY TO CLOT BLOOD

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Objectives

1. Describe the emerging role of thermoelastography (TEG) in resuscitation in the Emergency Department and Critical Care environment.
2. Discuss how TEG informs a practitioner about correctible causes of bleeding during critical illness and injury, allowing differentiation between diminished hemostatic capacity and active fibrinolysis.
3. Describe the value of TEG as a marker of global hemostasis and inflammation in critical illness and emergency medicine.

Introduction

Thromboelastography (TEG), an 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 that result in the potential for goal-directed therapy of coagulation abnormalities following injury.1 TEG was first described in 1948 in Germany by Dr. Hellmut Hartert, and the process was automated and computerized in the late 20th century. There are two commercially available TEG systems, both of which are types of viscoelastic hemostatic assays (VHA): the rotational thrombelastometry (ROTEM®; Tem International GmbH, Munich, Germany) and the modified traditional thrombelastography (TEG®, Hemoscope Corporation, Niles, IL), which is the most prevalent system in use in North America. VHA technology is currently used and well validated in trauma, liver transplant surgery, cardiac surgery, obstetrics, bedside extracorporeal membrane oxygenation (ECMO) management, diagnosis of hypercoagulable states, major surgeries, hemophilia, and monitoring of antithrombotic therapy.2-4 In order to monitor antithrombotic therapy, TEG platelet mapping (TEM/PM) is also used. TEG/PM compares the patient’s platelet inhibition percentage against maximum platelet function measured by the assay, allowing relative changes in platelet contribution to clot formation to be clearly detected.1 Within the specialty of Emergency Medicine, TEG has seen its most prolific and validated use in trauma patients, but recent expansion of use has included traumatic brain injury, severe sepsis and septic shock. More recently, TEG has been described in the realm of acute coronary syndrome and hypothermia.

The VHA allow for unique product driven, goal-oriented resuscitation in the bleeding patient. In particular, TEG facilitates a 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 capability 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 yet modern understanding of the process by which a clot forms is important. The most common scenario in which a clot forms occurs 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 resulting coagulation cascade, which consists of the activation of previously inactivated circulating zymogens, sets 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 resulting 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 concurrently amplified when Factors 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 of multiple interacting proteins must be known. TEG is able to describe this balance both qualitatively (via the tracing) and quantitatively (via the measured values). A brief overview of the coagulation cascade is represented in Figure 1, and demonstrations of the qualitative tracings of VHAs (TEG and ROTEM) are shown in Figure 2 and Figure 3.
THROMBOELASTOGRAPHY (TEG) – UNDERSTANDING THE PATIENT’S ABILITY TO CLOT BLOOD

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 Emergency Department (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. TEG is more 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 TEG analyses of samples obtained at the scene of accident and upon arrival in the ED in 161 trauma patients.\(^3\) Interestingly, they found that 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 TEG is more sensitive in reflecting clinically relevant coagulopathies than routine coagulation tests.\(^3\)

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 transaminic 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

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 then added to the sample to counteract the citrate, and the cup is continuously rotated through 45° while a strain gauge pin, linked to a torsion wire, 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 that is plotted in real time through automated signal translation (Figure 4 and Figure 5).\(^3,11\)

As the blood clots in the cup, the degree of torque is increased. The amount of torque is measured electronically, and is representative of the degree to which clot formation has taken place. An activating solution consisting of kaolin, phospholipids, and buffered stabilizers is often used to help initiate the coagulation process in TEG, although this still 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). rTEG allows a faster clotting profile to be created because the additional reagents activate both the intrinsic and extrinsic clotting pathways simultaneously, and the earliest tracings of rTEG can be viewed within ten minutes.\(^1,3,12\)

TEG provides insight into each phase of the clotting cascade and theoretically allows for therapies targeting specific defects in the pathways. Because TEG tests whole blood rather than plasma, the complete dynamics of clot formation are visualized. Thrombosis, relative clot strength, and fibrinolysis are all represented in a TEG.

**FIGURE 02**

**VHA Terminology and Parameters**

![Diagram](https://via.placeholder.com/150)

**FIGURE 03**

**Variables That Affect a TEG Tracing**

![Diagram](https://via.placeholder.com/150)

**TEG vs. Conventional Measures of Coagulation**

Compared to conventional studies of coagulation, which include prothrombin time (PT)/ international normalized ratio (INR) and activated partial thromboplastin time (aPTT), TEG provides sophisticated and relevant information about the entire process of clot formation, not just initiation, and offers insights into the function of platelets not seen with traditional coagulation testing. It is important to remember that primary coagulation is a complex interplay of the intrinsic and extrinsic pathways of coagulation, 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. Because TEG tests whole blood rather than plasma, the complete dynamics of clot formation are visualized. Thrombosis, relative clot strength, and fibrinolysis are all represented in a TEG.
and colleagues described the rTEG evaluation of 1,996 consecutive severe trauma patients, and 41 (2%) of those patients demonstrated hyperfibrinolysis at admission. This subset had a 76% mortality rate, in contrast to 10% in the entire group. This study also demonstrated that prehospital crystalloid fluid administration resulted in a statistically significantly higher hyperfibrinolysis score, defined as more than 7.5% amplitude reduction at 30 minutes after maximal amplitude. Ultimately, if a higher percentage 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 be proven to be preferential to crystalloids in the setting of acute traumatic hemorrhage.

The benefit of testing whole blood, rather than testing coagulation pathways piecemeal with separate complete blood count (CBC), PT, and aPTT tests, is that dynamics of clot formation are visualized, such that thrombosis and fibrinolysis are both represented in sequence. Traditionally, PT and 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 a 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.

**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. This is helpful in the management of patients who are taking anti-platelet medications such as salicylates or clopidogrel, which inhibit platelet function but do not alter platelet counts. TEG platelet mapping can be utilized to determine if patients are therapeutically on or are currently taking aspirin or clopidogrel if that information is unknown.

**How to Interpret TEG**

Broadly speaking, reported TEG variables include coagulation time (CT), clot formation time (CFT), the angle of clot formation, the maximum clot firmness, and lysis time. Typically, these are described in the automated TEG report as reaction time (R, in seconds), clot kinetics (K, in seconds), the angle of the curve (α), maximum amplitude (MA, measured in mm), coagulation index (CI, measured in dynes/sec), lysis at 30 minutes (percent of clot lysis), and clot firmness (G, measured in dynes/sec). Individual results may be compared to normative TEG values, allowing for an assessment of the derangements in clotting that are present. Please see Table 1 for more information.

The MA value represents clot strength, R indicates the time until there is evidence of clot, and K describes the time from R until the clot is 20 mm in size. The α angle is the angle formed by the horizon and 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. The CI describes the global coagulation state as derived from an equation utilizing the other variables. TEG is modified by sex, age, and other factors, as demonstrated in Figure 6. Please see Table 1 and Table 2 for interpretation and description of TEG variables.

**TABLE 1** Common Measurements in TEG

<table>
<thead>
<tr>
<th>Description</th>
<th>TEG term</th>
<th>ROTEM term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clot initiation</td>
<td>R time</td>
<td>CT (coagulation time)</td>
</tr>
<tr>
<td>Rate of clot formation</td>
<td>K time</td>
<td>CFT (coagulation formation time)</td>
</tr>
<tr>
<td>Angle of clot formation</td>
<td>α (slope between K and R)</td>
<td>α (Angle of tangent at 2mm amplitude)</td>
</tr>
<tr>
<td>Maximum strength of clot</td>
<td>MA (Maximum amplitude)</td>
<td>MCF (Maximum clot formation)</td>
</tr>
<tr>
<td>Amplitude (at set time in min)</td>
<td>A30, A60</td>
<td>AS, A10, A15, A20, A30</td>
</tr>
<tr>
<td>Maximal lysis</td>
<td>-</td>
<td>ML</td>
</tr>
<tr>
<td>Clot lysis (at set time in min)</td>
<td>CL30, CL60</td>
<td>LV30, LV60</td>
</tr>
<tr>
<td>Time to lysis</td>
<td>TTL (2 mm drop from MA)</td>
<td>LOT (lysis onset time, 85% of MCF)</td>
</tr>
</tbody>
</table>


**FIGURE 06** Preanalytical Variables Affecting the Viscoelastic Hemostatic Assay (VHA) Trace

- Anticoagulants
- Increased time to clot
- Neonates vs. > 2 yrs and adults
- Raised PLT Count
- Increased WBC
- Fibrinolytic drugs
- Increased age
- Female vs. male

KEY: Preanalytical variable Effect on VHA trace

HCT, hematocrit; PLT, platelet; WBC, white blood cell count.


**TABLE 02** Utilizing Thromboelastography (TEG) Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased reaction time (R)</td>
<td>Slow initiation of clot</td>
<td>Give fresh frozen plasma (FFP)</td>
</tr>
<tr>
<td>Decreased angle (α)</td>
<td>Slow rate of clot formation</td>
<td>Give cryoprecipitate, consider platelets</td>
</tr>
<tr>
<td>Decreased maximum amplitude (MA)</td>
<td>Decreased strength of clot</td>
<td>Give platelets</td>
</tr>
<tr>
<td>Percentage of decrease in amplitude at 30 minutes (A30 or LV30) is elevated</td>
<td>Fibrinolysis</td>
<td>Give tranexamic acid, aprotinin or aminocaproic acid</td>
</tr>
</tbody>
</table>

TEG in the Emergency Department (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. 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. 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 were given in such a way as to mimic whole blood rather than simply transfusing pRBCs. TEG is most useful in guiding damage control resuscitation and blood product administration and allowing decisions regarding the necessity for repeat or continued damage control surgery. In a 2012 study, Pezold 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 clot strength G had the greatest adjusted area under the receiver operating characteristic curve (AUC ROC) when compared to base deficit (BD) (0.87, P = 0.05), INR (0.88, P = 0.11), and PTT (0.89; P = 0.19), meaning that it is a better predictor of morbidity and mortality than more traditional markers of severity commonly employed in the ED. 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. They demonstrated a higher injury severity score (ISS, p = 0.006) compared with those who had a normal MA, a higher need for transfusion of packed red blood cells (p = 0.01), fresh frozen plasma (p = 0.04), and platelets (p = 0.03) during the first 24 hours of resuscitation, and a remarkably increased 30-day mortality (47% vs. 10%, p < 0.001). 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-fatals (R time was 3,703 +/- 11,618 vs. 270 +/- 393 seconds [P = < 0.001], and MA was 46.4 +/- 22.4 vs. 64.7 +/- 9.8 mm [p < 0.001]).

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 a 1:1:1 ratio of plasma, pRBCs, and platelets, especially if they receive inappropriate and potentially harmful amounts of each product. 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 the fact that results typically can be obtained within ten minutes, compared to 30-60 minutes for PT, aPTT, fibrinogen, and platelet counts. Although initiating transfusion therapy rapidly improves patient care when necessary, TEG may also be helpful in deter-
mining when transfusion may not be useful, since it 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 (ARDS). 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.

TEG, 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, they should be run on the same machine with the same kind of activator. The machine requires calibration 2-3 times per day, and personnel using TEG require additional training. The advantages of TEG are presented in Table 3.

### Current Data and TEG Applications

TEG is being studied increasingly in areas other than traumatic conditions and the surgical realms. One of these areas is in acute coronary syndrome, where TEG may be used to identify patients with impaired endogenous fibrinolysis, aspirin or clopidogrel resistance, or at risk for thrombosis following percutaneous coronary intervention (PCI).

Gurbel et al. demonstrated that increased thrombogenesis after PCI, as measured by TEG, was an independent risk factor for thrombosis within three years following PCI in one of the largest series of patients on this topic. Fu et al. described similar results later in a series of 861 consecutive patients who had routine TEG platelet mapping following PCI. Of these, 249 patients developed in stent restenosis (ISR). The frequency of clopidogrel hyporesponsiveness in the ISR group was significantly higher than that in non-ISR group (p < 0.01), and the authors concluded that clopidogrel hyporesponsiveness, as measured by TEG, was an independent risk factor for ISR.

Despite these findings and the ability of TEG platelet mapping to identify aspirin and clopidogrel non-responders, the clinical benefit of routine platelet mapping after PCI has not yet been demonstrated. Xu, et al. randomized patients following high risk PCI to a control group or to a group in which clopidogrel dosing was adjusted based on TEG results. There was no difference between the two groups at six months for the endpoints of myocardial infarction, emergency target vessel revascularization, stent thrombosis, or death. Another avenue where the diagnosis and treatment of coagulopathy using TEG is being pursued is in hypothermia, where initial studies have surprisingly not demonstrated hypothermia induced coagulopathy. The interim analysis of the Cooling And Surviving Septic shock (CASS) study, which prospectively enrolled 100 patients with severe sepsis or septic shock to mild induced hypothermia (32º to 34ºC) vs. control (no temperature regulation), demonstrated that coagulopathy based on TEG MA and R parameters actually improved in the mild hypothermia group, but was not corrected in the control group. The Targeted Temperature Management (TTM) Trial compared normothermia (36ºC) to mild induced hypothermia (33º) following cardiac arrest. A predefined sub study of this trial compared TEG parameters of both groups, given that there is concern related to induced hypothermia and coagulopathy. They demonstrated no significant difference in TEG parameters between the two groups or with respect to adverse bleeding or clotting.

TEG is being explored in a diverse number of disease states at this time. Current trials are describing the use of TEG to assist in cesarean deliveries, hemostasis after coronary artery bypass grafting (CABG), fat emboli, traumatic brain injury, and acute ischemic stroke.

### Cases

**Case 1:**

A 34 year old previously healthy male presents to the emergency department after falling off his roof. His blood pressure is 85/40 and his heart rate is 124 beats per minute (bpm). 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 for 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?

**Case 2:**

A 65 year old male presents to the ED three days after undergoing a left heart catheterization and left circumflex stent placement following an ST-segment elevation myocardial infarction (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?

These values reflect platelet dysfunction, likely secondary to anti-platelet medications he is taking after having a stent placed. It is worth noting that although the more traditional laboratory tests that are used to assess coagulopathy (CBC, PT, PTT) are normal, the TEG is abnormal, offering insight into platelet function.
Case 3:
A 72 year old male with a history of a STEMI and stent placement three weeks ago presents to the ED with chest pain. He reports that he has been compliant in taking the clopidogrel and aspirin prescribed to him. Although data are still preliminary, how might TEG platelet mapping help in management of this patient?

TEG platelet mapping can be used to identify patients who are aspirin or clopidogrel nonresponders and hyporesponders. At this time, clinical benefit has not been established by performing routine platelet mapping once anti-platelet therapy is started to identify these patients. However, in the setting of in stent restenosis, TEG platelet mapping should be considered to help determine the cause of the event.

Further abnormal scenarios are represented in Figure 7.

**Conclusion**

In summary, TEG 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 environment. 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 more routine in the near future.

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Optimizing Collaboration Between Emergency Physicians, Hospitalists, And Cardiologists For Treatment of ACS

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Objectives

1. Clearly define the roles of the various specialists essential for quality acute coronary syndrome (ACS) care.
2. Be able to develop institutional-specific protocols for ACS care.
3. Identify ways to improve transition of care for ACS patients leaving the Emergency Department.
4. Describe the role Emergency Medical Service providers play in the continuum of ACS care.

Introduction

The optimal care of patients suffering from ST-segment elevation myocardial infarction (STEMI) is a major focus in health care delivery. Outcomes can be affected by care delays measured in minutes, as the rapid diagnosis and treatment of STEMI preserves not only myocardium, but productive years, livelihood, quality of life, and ultimately mortality. High-quality STEMI care is complex and resource intensive, requiring collaborative efforts within and across numerous disciplines. The American Heart Association (AHA) has called for organization and standardization of care across regional networks of hospitals. In order to accomplish this, all participants must be familiar with the components involved, from the roles of emergency medical services (EMS) providers and the various physician specialties directly involved in STEMI care to the various institutional practices, protocols and guidelines. In this review, the best practices of the various components of STEMI care at the level of EMS providers, physicians, and entire medical institutions will be outlined.

Emergency Medicine

The Emergency Department (ED) is the point of entry for almost all patients with STEMI and the emergency physician plays a central part in the quality of care for these patients. The role of the emergency physician can be divided into three critical components: identification, stabilization, and disposition. There is no question that early identification of STEMI is critical for high quality management. While the diagnosis of STEMI can be as easy as obtaining a 12-lead electrocardiogram (ECG), not all STEMI patients present with obvious signs or symptoms, or with classic ECG changes. It is important to remember that atypical non-pain symptoms such as dyspnea, diaphoresis, neurological complaints, vague gastrointestinal symptoms and weakness can be present in almost 10% of patients. These atypical complaints are more typical in the elderly, diabetics and women. Additionally, the interpretation of the ECG is not always straightforward; there are numerous STEMI equivalents that warrant emergent percutaneous coronary intervention (PCI), as well as several non-acute coronary syndrome conditions that may present with STEMI changes on ECG. It is, therefore, essential that the emergency provider be an expert in the ECG diagnosis of ischemia and infarction.

Quality management of STEMI patients in the ED goes beyond recognition and disposition. It is well documented that patients with STEMI have the potential for rapid decompensation and therefore are at high risk of suffering a fatal event. It is mandatory that all STEMI patients receive the highest priority of care on presentation to the ED. Aggressive medical management, including support of heart rate and blood pressure, swift administration of aspirin, judicious use of oxygen, and adequate pain control, is paramount.

With STEMI patients, as with all patients in the ED, the emergency provider must always be moving rapidly towards definitive management. In STEMI, there are two potential therapeutic endpoints: PCI in the cardiac catheterization laboratory (CCL) or fibrinolytics rapidly administered in the ED. In the past, the decision to activate the CCL and even to administer fibrinolytic therapy fell under the discretion of the cardiologist in their primary role of caring for STEMI patients. However, CCL activation by the emergency physician, rather than waiting on a cardiologist to do so, has been shown to significantly reduce door to balloon (D2B) times, and has become a widespread practice. Furthermore, it has been shown that CCL activation by emergency physicians is very accurate, resulting in very few unnecessary CCL activations.

For those providers caring for patients at non-PCI centers, the treatment and disposition for STEMI patients is often more challenging. Transfer to a PCI center is often not enough, as less than 10% of transfer patients ultimately meet a total D2B time of less than 90 minutes. Transfer via helicopter is not usually the answer either, as studies suggest that STEMI patients transferred via helicopter EMS (HEMS) rarely meet total D2B times of less than 90 minutes. Early fibrinolytics, within 30 minutes of arrival, should be strongly considered by those emergency physicians providing care at non-PCI centers where D2B of less than 120 minutes cannot be achieved in transfer. Recently, it has been shown that the practice of fibrinolytics followed by transfer to a PCI center can produce clinical outcomes similar to those reached in patients treated with primary PCI.

Cardiology

The interventional cardiologist is essential for almost all STEMI patients, providing the PCI necessary for optimal results. These physicians must serve as one of the leaders in helping to develop protocols both in the prehospital and hospital setting. It is essential that a hospital’s cardiologists feel well represented in any protocol affecting STEMI patients’ care and disposition. All team members should know and follow the same pre-agreed upon care protocols. Similarly, in those medical centers where hospitalists care for acute coronary syndrome (ACS) patients, they too, should be represented in the design and implementation of care protocols that include discharge planning, cardiac rehabilitation and lifestyle counseling. All team members must share and promote similar views on smoking cessation, healthy eating, weight control, and the need for regular exercise along with blood pressure and lipid lowering strategies.
Institution-Specific Protocols

The development and implementation of institution-specific protocols for the care of STEMI patients has significantly improved patient care. In the landmark 2006 article, a number of key strategies were outlined that when implemented, significantly reduced door to balloon times.1 These strategies included ED physicians activating the CCL via a single-call system, utilization of pre-hospital ECGs, establishing institutionally mandated time goals for CCL activation and interventional team response, and maintaining active lines of communication for feedback between EMS, the ED, the CCL and hospital administration. Although the majority of these strategies have now become common place in most EDs, many opportunities for improvement still remain.

The rapid diagnosis of a STEMI depends on the rapid acquisition of an ECG within 10 minutes of ED arrival for the patient. In most institutions there is a protocol-based process to obtain an ECG, predetermined by an algorithm. Most patients complaining of chest pain are likely to receive an ECG during the ED triage process, regardless of the algorithm in place. However, many patients suffering from a STEMI will not complain of “classic” substernal chest pain, which unfortunately can lead to significant delays in the acquisition of the ECG. A simple protocol rule in which ECGs are obtained immediately in all patients over 50 years old who present with dyspnea, altered mental status, upper extremity pain, syncope or generalized weakness, and all patients over 80 years old with abdominal pain or nausea/vomiting, has been shown to identify 92% of STEMI patients.6 Some health care systems may also choose to add this latter group of symptoms to those over age 50 to minimize missing an ACS event. While such an expansion of triage ECGs may not be feasible at all institutions, it is clear that extending the triage ECG beyond those patients presenting with chest pain will likely reduce STEMI detection times.

The resources needed for efficient and high-quality STEMI care are significant, but when health care outcomes are measured in minutes, the rapid accessibility of these resources is essential. There is considerable variability in resource availability, not only between institutions, but also within institutions when standard business hours are compared to nights, weekends and holidays. This can negatively impact STEMI care, as myocardial infarctions occur at all hours of the day and night, and all days of the year. In a recent meta-analysis involving over 1.8 million STEMI patients, those patients presenting in “off-hours” (nights and weekends) were shown to be more likely to have longer D2B times, be less likely to receive PCI within 90 minutes, and have higher short-term mortality.7 More can be done at some institutions to ensure that the same high-quality care can be provided to all patients, regardless of their time of presentation.

The above strategies focus on the care of patients presenting directly to PCI centers. However, the majority of hospitals are not-PCI capable. As already noted, the vast majority of transfer patients do not meet the recommended reperfusion goals set forth by the AHA. In one area of rural Pennsylvania, it has been shown that when PCI centers allow their resources to be accessed and activated by referral hospital staff, STEMI patients presenting after transfer can routinely meet first contact-to-PCI times of less than 90 minutes.8 This protocol is as simple as opening direct communication lines between rural ED physicians and receiving center interventionalists. This is an easy intervention that should be strongly considered by all PCI facilities that do not as of yet have a similar system in place.

Identifying Ways to Improve Transitions

All providers involved in the care of STEMI patients share the common goal of rapid reperfusion. During the transition of care from the ED to the CCL, the team members from the ED and CCL can have what can seem like somewhat different priorities. The ED teams’ focus centers on accurate diagnosis, resuscitation, ruling out alternative diagnoses, and rapid transport to the CCL. Although rapid transport for catheterization is also of paramount focus for the CCL team members, other major concerns are devoted to what medications have been given and what still needs to be administered, contraindications to catheterization and available sites for vascular access. At their core, these seemingly disparate objectives are aligned for the common goal of rapid reperfusion. At this critical juncture it is essential that the transition of care between the ED and CCL teams be smooth, seamless, and efficient.

Preparation is vital, and is the essential tool to accomplish a smooth and effective transition from the ED to the CCL. Open communication between the ED staff, the CCL team, and hospital administration is essential. In order to optimize care, representatives from the ED, including physician and nurse leaders, must meet with key members of the CCL, cardiology, the coronary care unit (CCU) and hospital administration. Every single step in care, from patient arrival in the ED to transport to the CCL and then into an inpatient area, must be mapped out and thoroughly discussed and agreed upon by all team members. Once this process has been analyzed and documented, appropriate time goals must also be established for each step in the transition, including such metrics as time from door to ECG, ECG interpretation to CCL notification, CCL notification to team arrival in ED, ED arrival until CCL transport and patient CCL arrival to balloon inflation. It is only via careful monitoring of each critical time interval that improvements can be made and variations can be noted, analyzed and improved upon. Similarly, each therapy, medication and patient care maneuver must also be pre-agreed upon, including dosages and which medication will be administered by which team member. A treatment “worksheet” can then be created that clearly outlines the critical actions that should be taken with every STEMI patient. These actions will fulfill the objectives of both the ED and CCL teams.

Through the STEMI worksheet, a standardized physician order set can be created, often through a computerized physician order entry system. The advantages here are substantial, allowing numerous complex orders to be executed with a few of clicks of the mouse. This allows care to be optimally standardized, so that confusing orders are eliminated, delays in order entry and completion are avoided, and medication errors are minimized. It also becomes much easier, with a computer-based data system, to analyze all aspects of the process. Along similar lines, an ED STEMI “Box” or “Kit” containing all of the medications and equipment needed to execute the critical steps needed for efficient STEMI care can expedite and standardize treatment. This provides the nursing and ancillary staff all of the requisite supplies needed for care without having to waste time acquiring them, allowing the focus to remain on a rapid, standardized and efficient transition of care. Standardization of STEMI care within the ED helps to assure high quality care of every STEMI patient with a smooth and efficient transition of care from the ED to the CCL. It can only occur via planning and input from all ED staff members, the CCL team, and hospital administration. The creation of worksheets, along with standardized order sets and medication/equipment kits, allows for both high-quality care and effective transitions of care for all STEMI patients.
The Role EMS Providers Play in the Continuum of Acute Coronary Syndrome Care

The above discussion primarily focused on systems-based practices in the care of STEMI patients within the hospital. However, a large proportion of STEMI patients are initially evaluated and treated by EMS providers in the pre-hospital setting. Every second is critical in the care of a patient with STEMI, and it is imperative that EMS providers also provide the highest level of care to all ACS patients. Below we will discuss a number of key pre-hospital practices that can significantly impact the care of STEMI patients.

Prehospital ECG

The prehospital ECG has become a key component of STEMI diagnosis and represents a critical EMS intervention in quality STEMI care. The term D2B is changing to E2B where “E” represents the first 12-lead ECG performed by EMS. In a recent study of national registry data from Britain involving over 200,000 prehospital ECGs, ACS patients who had pre-hospital ECGs were more likely to have reperfusion via primary PCI, had shorter overall door-to-balloon time with increased percentages of PCI within 90 minutes, had increased frequency of fibrinolytic therapy within 30 minutes, and had a 9% (relative) risk reduction in 30-day mortality. This study also demonstrated that pre-hospital ECGs were less likely to be obtained in women, those of advanced age, and those with increased comorbidities, highlighting the importance of obtaining ECGs in the populations at increased risk for missed STEMI. Additionally, a recent meta-analysis on the benefits of advance ED notification by EMS providers of the presence of STEMI based on pre-hospital ECGs showed significant reductions in 30-day mortality in those patients receiving either PCI or fibrinolysis. Clearly, there is a tremendous benefit of pre-hospital ECG with little perceivable downside. It is essential that EMS providers be routinely complimented on their performance of ECGs, but also reminded of those populations and presentations where STEMI may go unrecognized.

Another reason ECGs performed by EMS are so essential relates to the dynamic changes that ECGs in patients with STEMI undergo. Approximately 1 in 10 STEMI may have an initial ECG that is non-diagnostic. Also, important changes seen on the initial EMS ECG, including ST elevation, may be gone by the time the patient arrives in the ED. Some centers may choose to have direct paramedic activation of the CCL. However, multiple studies have shown that when computerized ECG interpretations of STEMI and paramedic overreads are combined with an ED physician’s interpretation of an electronically transmitted ECG from the field, STEMI recognition can be maximized and CCL activation for non-STEMI patients minimized.

Bypassing Non-Percutaneous Coronary Intervention Centers

Decreasing the time between first medical contact (FMC) and PCI is an essential component to quality STEMI care. For EMS providers, this goes beyond early recognition, as appropriate disposition is also essential for optimal results. The closest destination is not always the best destination for a STEMI patient. The EMS bypass of non-PCI capable institutions in favor of direct transport to those centers that are PCI-capable is a commonly proposed systems-based approach to reducing time to reperfusion. In North Carolina, such practices have been shown to reduce the median FMC to primary PCI time by 68 minutes, with a median FMC to PCI time of 93 minutes in the direct transport group. While this study demonstrates improvements on a state-wide level, it is certainly reasonable to believe that implementation of similar protocols could improve care in regional, county or city-based EMS systems. It is therefore essential that STEMI care be regionalized and destination guidelines are very clear before 911 is ever activated.

Helicopter EMS

While the bypass of non-PCI capable centers is a reasonable option in the urban and suburban settings, this practice is often impractical, if not impossible, in the rural setting. Helicopter EMS has been proven to be a key factor in improving outcomes in rural communities, most notably in trauma. Expanding HEMS to STEMI care is a logical step, especially in those rural settings where a HEMS infrastructure is already established. In a recent study of STEMI care in rural Belguim, primary transport of STEMI patients by HEMS resulted in a significant decrease in FMC to PCI time, including a 99.4% rate of FMC to PCI in < 90 minutes in those transported by HEMS, vs 17.3% in those transported by ground. Emergency medicine physicians, cardiologists and EMS leaders in rural communities should work together to create optimal transportation guidelines to maximize the likelihood of D2B times of less than 120 minutes.

Conclusion

Optimal STEMI systems of care are dependent upon collaboration between providers at all levels, from EMS providers to interventionalists, with the ultimate goal of early reperfusion. At first contact, EMS providers must obtain early ECGs and transport patients rapidly to PCI-capable institutions, allowing ED providers to rapidly make an accurate diagnosis and initiate treatment. Institutions should establish guidelines and protocols that ensure STEMI patients will receive efficient and comprehensive treatment, as well as facilitate smooth transitions to CCLs that can be activated and staffed by skilled professionals at all hours of the day and night. With continued collaboration of all team members, STEMI care can be optimized to reduce D2B and E2B times, preserve myocardium, improve outcomes and save lives.

References


IDENTIFICATION OF PATIENTS WITH ACS IN THE EMERGENCY DEPARTMENT AT HIGH RISK OF ADVERSE OUTCOMES – Chad Miller, MD, and Lane Smith, MD

1. The current American Heart Association guidelines recommend that patients arriving to the hospital with suspected acute coronary syndrome (ACS) should have an electrocardiogram (ECG) performed:
   A. Within the first hour
   B. At the time of the first troponin measurement and at every subsequent measurement
   C. Immediately on arrival
   D. Within 10 minutes of arrival and every 15-30 minutes for the first hour in patients with concerning symptoms

2. Which patient population is eligible for early discharge from the hospital using accelerated diagnostic pathways and contemporary troponin assays?
   A. Low risk patients with a single negative troponin
   B. Select low risk patients with two undetectable troponins drawn 3 hours apart and with good out-patient follow-up
   C. High risk patients with a negative resting myocardial perfusion scan
   D. Any patient with negative coronary computed tomography angiography (CCTA)

3. The stress test that has the highest sensitivity for obstructive coronary artery disease while also having the lowest annualized major event rate (myocardial infarction or death) after a normal test is:
   A. Exercise Electrocardiogram
   B. Dobutamine Stress Echocardiogram
   C. Exercise Perfusion SPECT
   D. Vasodilator Perfusion SPECT

4. Which of the following statements about CCTA is true?
   A. It has superior outcomes when compared to stress testing in low-risk patients
   B. It generally reduces cumulative radiation exposure
   C. It can be safely used in patients known to have pre-existing coronary artery disease (CAD)
   D. It can be used to risk stratify patients who cannot exercise or who have an indeterminate stress test and no known CAD

5. Which of the following best describes the current role of cardiovascular magnetic resonance imaging (CMR) in patients with acute chest pain?
   A. It is an emerging technology for the evaluation of moderate to high-risk patients and has the capability of allowing both functional and anatomic measurements
   B. Recent trials have shown routine stress testing to be superior to CMR
   C. It is best suited for low-risk patients
   D. It is safe for patients with renal impairment or implanted metal devices

2013 AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION GUIDELINE FOR STEMI PATIENTS – James W. Hoekstra, MD

6. According to the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for ST-Elevation Myocardial Infarction (STEMI), establishing a “system of care” is associated with which of the following benefits?
   A. Increased EMS transport directly to percutaneous coronary intervention (PCI) capable centers
   B. Increased use of fibrinolytics
   C. Decreased use of prehospital electrocardiograms
   D. Increased PCI-related mortality

7. If a STEMI patient is transferred directly from a non-PCI-capable Emergency Department to a PCI-capable hospital, the first medical contact to balloon time should be:
   A. <90 minutes
   B. <120 minutes
   C. <60 minutes
   D. There is no limit

8. Following administration of fibrinolytics for STEMI, appropriate patient disposition is:
   A. Immediate transfer to a PCI-capable hospital for PCI within 24 hours
   B. Immediate transfer to a PCI-capable hospital for immediate (<2 hours) PCI
   C. Admission to the Cardiac Care Unit at the non-PCI-capable hospital
   D. All of the above

9. Which of the following antiplatelet drugs is a Class I recommended treatment for STEMI in the 2013 ACCF/AHA Guideline?
   A. Clopidogrel 600 mg oral load prior to PCI
   B. Ticagrelor 180 mg oral load prior to PCI
   C. Prasugrel 600 mg oral load prior to PCI
   D. All of the above

10. Which of the following antithrombin medications has been shown to reduce mortality in patients undergoing PCI for STEMI?
    A. Unfractionated heparin
    B. Enoxaparin
    C. Bivalirudin
    D. Fondaparinux

(Continued Next page)
11. Which of the following statements regarding treatment for patients with STEMI is NOT true?
   A. The optimal timing of PCI is within 90 minutes of first-medical-contact.
   B. Factors that favor delayed PCI over fibrinolytics include young patient age, anterior myocardial infarction, and early presentation (<3 hours of pain).
   C. The combination of aspirin, clopidogrel, and enoxaparin should be administered with fibrinolysis.
   D. Following administration of fibrinolytics for STEMI, the patient should be immediately transferred to a PCI-capable hospital for urgent PCI.

2014 AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/AMERICAN HEART ASSOCIATION GUIDELINE FOR TREATING NON-ST-SEGMENT ELEVATION ACS PATIENTS – Charles V. Pollack, MD

12. The 2014 ACC/AHA Guideline gives recommendations pertinent to the Emergency Department (ED) for which of the following risk stratification strategies:
   A. Timing of serial ECGs
   B. Timing of serial troponin assays
   C. Criteria for discharge from a chest pain unit
   D. Use of coronary computed tomography angiography

13. Which of the following is NOT a component of the TIMI Risk Score for non-ST segment elevation acute coronary syndrome NSTE-ACS?
   A. Age
   B. Presenting blood pressure
   C. Use of aspirin
   D. Prior significant coronary artery disease

14. Which of the following is NOT a concern in administering nitroglycerin in the ED to a patient with possible ACS?
   A. Blood pressure
   B. History of esophageal spasm
   C. Recent use of tadalafil
   D. ST-segment depression in inferior electrocardiogram (ECG) leads

15. Which of the following oral antiplatelet agents is specifically NOT recommended for upstream use in NSTE-ACS?
   A. Prasugrel
   B. Ticagrelor
   C. Aspirin
   D. Clopidogrel

16. The 2014 ACC/AHA Guideline specifically recommends ticagrelor over clopidogrel in patients with NSTE-ACS undergoing an early invasive or ischemia-guided strategy. Which of the following is NOT a supporting factor for this strategy?
   A. Ticagrelor has faster onset
   B. Ticagrelor is associated with lower overall mortality
   C. Ticagrelor is more effective in patients with chronic kidney disease
   D. Ticagrelor has a longer half-life

CHALLENGES IN OPTIMIZING ANTIPLATELET THERAPY FOR STEMI AND NSTE-ACS – Richard C. Becker, MD

17. Life-threatening causes of chest pain that should always be included in the differential diagnosis of suspected acute coronary syndrome (ACS) include:
   A. Acute pulmonary embolism
   B. Myopericarditis
   C. Hypertensive emergency
   D. All of the above

18. The American Heart Association/American College of Cardiology Foundation recommends (class I) immediate coronary angiography for patients who have survived an out-of-hospital cardiac arrest with ST segment elevation on the presenting electrocardiogram:
   A. True
   B. False

19. Which of the following is an unfavorable post-cardiac arrest resuscitation feature?
   A. >30 minutes to return of spontaneous circulation (ROSC)
   B. pH <7.2
   C. Lactate >7 mmol/L
   D. All of the above

20. Pre-hospital administration of dual antiplatelet therapy to patients with suspected ACS is an American Heart Association/American College of Cardiology Foundation Class I recommendation:
   A. True
   B. False

THROMBOELASTOGRAPHY (TEG) – UNDERSTANDING THE PATIENT’S ABILITY TO CLOT BLOOD – Jordan Bonomo, MD, Natalie Krietzer, MD, and Christopher Zammit, MD

21. Thromboelastography (TEG) provides the clinician with insight into all of the following components and settings of hemostasis, except:
   A. Sluggish venous flow
   B. Platelet activity
   C. High shear stress
   D. Fibrinolysis

22. A decreased maximum amplitude (MA) on TEG (or maximum clot firmness on ROTEM) may be the result of all of the following except:
   A. Qualitative platelet defect
   B. Tissue factor dysfunction
   C. Fibrinogen deficiency
   D. Factor XIII deficiency

23. In trauma patients, abnormal values recorded on the TEG are associated with increased mortality, even if other measures of coagulation are normal (e.g., prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR], platelet count):
   A. True
   B. False
24. Randomized control trials have definitively proven that TEG-guided blood product administration in trauma patients reduces mortality.
   A. True  
   B. False  

25. TEG has been shown to objectively identify abnormal coagulation in patients undergoing mild therapeutic hypothermia.
   A. True  
   B. False  

26. A patient with an ST segment elevation myocardial infarction (STEMI) is transferred from an outlying hospital to a PCI center. What door to balloon (D2B) time is considered the standard to be met or exceeded?
   A. ≤ 60 minutes  
   B. ≤ 90 minutes  
   C. ≤ 120 minutes  
   D. ≤ 150 minutes  

27. Which key strategy reduces D2B time the most?
   A. Emergency Department (ED) physician activation of cardiac catheterization lab  
   B. A single STEMI alert page  
   C. Emergency medical services facilitating pre-arrival alerts  
   D. Cardiologist on site  

28. How long after a patient arrives in the ED should an electrocardiogram (ECG) be performed?
   A. As quickly as possible  
   B. ≤ 10 minutes  
   C. ≤ 15 minutes  
   D. ≤ 20 minutes  

29. Prehospital ECGs decrease D2B time in patients with acute coronary syndrome. How do they affect mortality?
   A. No overall effects in large population studies  
   B. May decrease mortality in anterior acute myocardial infarctions  
   C. May decrease mortality up to 10-20%  
   D. May decrease mortality by nearly 40%  

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