The Evolving Landscape of ACS in the Emergency Setting:
Focus on Antiplatelet and Anticoagulation Therapy

2013 SAEM EMCREG-International Symposium, Seattle, WA

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Course Objectives

Understand and incorporate the recently released 2013 ACCF/AHA guideline recommendations and latest evidence when assessing and making treatment decisions for ACS patients with STEMI.

Understand and incorporate the recently released 2012 ACCF/AHA Focused Update guideline recommendations and latest evidence when assessing and making treatment decisions for ACS patients with UA/NSTEMI.

Identify and utilize effective strategies for meeting ACCF/AHA guideline recommendations in the emergency setting.

Apply evidence-based literature and guideline updates for decisions regarding appropriate antiplatelet and anticoagulant selection and dosing for various patient populations.

The following are highlights from the 2013 EMCREG-International Symposium held in Seattle, Washington on October 13, 2013. This is presented as an interactive piece which features discussion of the new 2012 ACCF/AHA Guideline for the Treatment of Non-ST-segment Elevation Myocardial Infarction and Unstable Angina and the 2013 ACCF/AHA Guideline for the treatment of ST-segment Elevation Myocardial Infarction. Emphasis will be placed on the antiplatelet and anticoagulant portion of the guidelines. We hope this monograph is helpful to you as you care for patients with acute coronary syndromes.

W. BRIAN GIBLER, MD: The guidelines we are discussing represent a collaboration between the American Heart Association and the American College of Cardiology Foundation and provide a literature-based structure for treatment of patients with non-ST elevation MI (NSTEMI) and unstable angina as well as ST-segment elevation (STEMI) acute coronary syndrome (ACS).

JAMES W. HOEKSTRA, MD: It is necessary to achieve a working diagnosis to appropriately treat a patient with ACS. The first electrocardiogram (ECG) the patient receives on entering the emergency system, either by EMS or private vehicle, determines the treatment pathway. If a patient has ST-segment elevation on an initial ECG, a diagnosis of STEMI is indicated and the individual is treated according to the STEMI guidelines. If the patient has ST-segment depression or flipped T waves on an initial ECG, or maybe a normal ECG and a positive serum troponin level, or perhaps just an excellent history for unstable angina but negative cardiac biomarkers and non-ischemic ECGs, the patient likely has unstable angina or NSTEMI and would be treated according to this guideline.

The first group of patients we’re going to address, as is indicated by the large red circle, is the unstable angina/NSTEMI group of patients (Figure 1). This is the largest ACS patient population, most complicated, and often these patients spend five to six hours in the emergency department (ED) during treatment and disposition.

Let’s begin with anticoagulant therapy. This important therapy is used to treat patients with certain unstable angina or NSTEMI. These patients have ECG changes or a positive troponin which identifies them as having clear ACS. These patients should be treated with anticoagulant therapy. The anticoagulant therapy you use is typically a heparin or low molecular weight heparin.
or bivalirudin, a direct thrombin inhibitor. Which one you choose will depend on whether the patient will undergo an invasive strategy, meaning going to the cardiac catheterization laboratory (cath lab), or whether the patient is going to be treated by a conservative strategy, meaning medical treatment without a cardiac catheterization. The patient receives serial markers, serial observations, and maybe a stress test later on. Medical therapy is for patients who are at lower risk and is for patients who have contraindications to cardiac catheterization. The invasive therapy is for patients who are high risk, with a positive troponin, ECG changes, and are going to the cath lab.

If you look at the anticoagulant therapy in the invasive strategy it’s typically enoxaparin or unfractionated heparin. Both of these have a 1A recommendation in the guidelines—1A is as high as you can get—or bivalirudin, which for the most part is a cath lab drug and it’s a 1B. On the other side of the coin, the conservative therapy, is a little different. If you look at the guidelines it still states enoxaparin or unfractionated heparin, but in general for medical therapy heparin is not a very good drug. It’s difficult to monitor and it’s not quite as good in terms of outcomes either. In these patients who are treated medically you are better off with a low molecular weight heparin such as enoxaparin as opposed to unfractionated heparin. With the invasive ACS group, typically unfractionated heparin is our drug of choice that we use while we’re getting the patient ready to go to the cath lab.

That’s briefly unstable angina, non-STEMI, and the anticoagulant therapies. I want to spend a little more time discussing the antiplatelet agents. There’s really not anything new with anticoagulant therapy in ACS, but there is a lot of new information regarding antiplatelet therapy in ACS.

Everybody understands aspirin. Aspirin inhibits cyclo-oxygenase and provides about 25% platelet inhibition. All the trials that look at antiplatelets in unstable angina and non-STEMI have aspirin as a baseline. Remember, it is a relatively impotent inhibitor of platelets. The heparins actually have some inhibition of platelets as well, especially the low molecular weight heparins. Direct thrombin inhibitors like bivalirudin will inhibit platelets also, but really those are anticoagulants and not really antiplatelet agents.

I want to briefly mention glycoprotein IIb/IIIa inhibitors, the intravenous antiplatelet agents. The glycoprotein IIb/IIIa inhibitors inhibit the IIb/IIIa receptor site on the platelet which is a site that allows the platelets to crosslink. Think of the IIb/IIIa inhibitors as IV antiplatelets on steroids. These have the highest potency and highest level of antiplatelet activity. They are given intravenously, they are expensive, and for the most part nowadays they are limited to cath lab utilization. There is some upstream utilization of IIb/IIIa inhibitors, but mostly these agents are used in the cath lab.

Realistically when we’re talking about emergency physicians’ utilization of antiplatelets now, we’re talking about these three: clopidogrel, prasugrel, and ticagrelor (Figure 2). Clopidogrel we all know well. It’s been around for a long time. The CURE trial came out in early 2000 and we’ve had approximately 13 years of utilization of clopidogrel. The other two agents we don’t know as well because they are relatively new, but they are important and they’re growing in their utilization. They are more potent in terms of their mechanism. All three of these drugs act at the P2Y12 site on the platelet. We call them P2Y12 inhibitors. All three of them are oral agents. All three of them are relatively inexpensive, especially if you compare them to the glycoprotein IIb/IIIa cath lab drugs.
If you look at them side by side in terms of pharmacokinetics, there are a couple of things to remember (Table 1). When you take clopidogrel, in order for it to work it has to be ingested, dissolved, pass through your liver, and ultimately has to be metabolized to an active metabolite to work. The onset is slow because it has to pass through your liver, so it requires one to two hours after ingestion. The time required for clopidogrel to reach peak inhibition of the platelets is 12 hours with mean platelet inhibition of about 50%. It has a long half-life.

Prasugrel is a newer antiplatelet agent. It is a higher potency antiplatelet agent than clopidogrel. Prasugrel is a prodrug and has to undergo metabolism to become an active form. There is 70% platelet inhibition for prasugrel as opposed to 50% for clopidogrel. Like clopidogrel, it hangs around for a long time. It latches on to the platelet and it will not let go. It is what we call an irreversible blocker of the platelet.

The newest antiplatelet agent is ticagrelor. It’s different than prasugrel in that it binds to the platelet P2Y12 site in a reversible fashion. It has a shorter half-life. You have to give it twice a day instead of once a day. Ticagrelor inhibits platelets directly after the patient ingests the drug. It then undergoes hepatic metabolism through the CYP3A4 pathway. This creates an active metabolite which is similar in potency to the native drug. Ticagrelor has an onset of action which is fast. The onset to peak activity is like prasugrel, typically two hours. It has high antiplatelet activity. The platelet inhibition for prasugrel is approximately 70% while ticagrelor inhibits 95% of platelets. This provides a very high level of antiplatelet activity for this oral drug.

Let’s talk a little bit about the data behind these three drugs: clopidogrel, prasugrel, and ticagrelor. Let’s start with clopidogrel. The PCI Cure trial, which provided a 300 milligram loading dose and 75 mgs per day of clopidogrel for patients who went to the cath lab and received a stent, demonstrated the effectiveness of this class of drugs. There was a significant difference in death and MI for the patients who received clopidogrel versus placebo. New information regarding clopidogrel is that you don’t want to use that old 300 milligram loading dose. You want to use a 600 milligram loading dose followed by 75 milligrams per day thereafter. That’s the new dose for patients who have unstable angina/ NSTEMI who are going to the cath lab. This dosing regimen is based on the CURRENT trial. There was a nice 15% reduction in the bad outcomes of death, MI, and stroke in 30 days in the patients who got double loading dose of clopidogrel, a 600 milligram load, and then 150 milligrams per day for 6 days followed by 75 milligrams per day for long term therapy. If you’re going to use clopidogrel in the invasive arm of the Guideline you have to double up the loading dose. That’s what the literature supports. The reason that’s so important is because that higher dose of antiplatelet agent overcomes some of the variability in clopidogrel platelet inhibition, which then causes less stent thrombosis. There was a stent thrombosis reduction in the patients who got double loading dose of clopidogrel (600 milligrams) versus single dose (300 milligrams), which was a 46% relative risk reduction. Stent thrombosis in an ACS patient is not a good thing. You go from good coronary blood flow to no flow in a short period of time and patients present quite ill, and subsequently can have bad ischemic outcomes including myocardial infarction and potentially death.

The TRITON TIMI 38 trial evaluated prasugrel, a newer antiplatelet agent (Figure 3). This is prasugrel versus clopidogrel and the trial is a cath lab trial. In the trial the cardiologist performed the cardiac cath, and then looked at the culprit coronary artery.
When it was evident the patient needed a stent, the cardiologist started the patient on prasugrel or clopidogrel, and then they did the procedure. The trial followed patients for 450 days, so almost a year and a half. You have a nice statistically significant reduction in death, MI, and stroke in patients treated with prasugrel versus clopidogrel. A higher level of antiplatelet activity leads to a lower level of death, MI, and stroke.

Bleeding however was an issue with this higher potency antiplatelet agent. If you have a higher potency antiplatelet drug you are going to have more bleeding. With prasugrel you can see significant increases in Thrombolysis in Myocardial Infarction (TIMI) major bleeding, with a significant increase in life-threatening bleeding, and fatal bleeding. The risk of bleeding was found to be greater in patients who were older, age 75 or greater, have a low body weight of typically less than 60 kilograms, or have a history of prior transient ischemic attack (TIA) and stroke. If you’re going to use prasugrel you should ask these three questions of your patients. Have you ever had a TIA or a stroke? How old are you and how much do you weigh? Sixty kilograms is pretty small, so often this represents older women. This will eliminate probably about 30% of the patients in the ACS category based on these three criteria, but it’s critically important to remember these patient exclusions if you’re going to use prasugrel.

The PLATO trial, which looked at the newest antiplatelet ticagrelor, is shown in Figure 4. These patients were treated “upstream” and not just in the cath lab after identifying the coronary anatomy. These patients were treated in the ED as well as in the cath lab waiting room, and then taken to the cath lab to perform the procedure. For patients treated with ticagrelor there was a significant 1.9% absolute reduction in death, MI, and stroke at one year in these patients compared to patients receiving clopidogrel. The PLATO trial is one of the few non-fibrinolytic ACS trials over the last two decades that actually demonstrated a mortality benefit. A higher level of antiplatelet activity leads to a reduction in negative ischemic outcomes.

Bleeding was not as much of an issue in the PLATO trial compared to TRITON TIMI 38. There are likely multiple reasons. Ticagrelor has a shorter half-life than prasugrel. The antiplatelet effect wears off more quickly. The bleeding with Coronary Artery Bypass Grafting (CABG) was not statistically significant. Non-CABG bleeding demonstrated a slight increase with a p-value of 0.025, but there was no problem with life-threatening bleeding. There was no increase in intracranial hemorrhage with ticagrelor, unlike prasugrel, and you didn’t have the problems associated with prasugrel treatment in patients with advanced age, low weight, or prior TIA or stroke.

For patients you wish to treat “upstream”, before undergoing coronary angiography, you shouldn’t use prasugrel. There are no data on upstream utilization in NSTEMI patients. You also have to be careful not to use prasugrel in patients with TIA, stroke, or age over 75. Ticagrelor can be used prior to the cath lab, and therefore can be used in the non-invasive pathway with just medical therapy. You’ll also have a potential mortality benefit with ticagrelor compared to clopidogrel, with minimal increase in bleeding risk, which is important in terms of weighing the benefits if this drug.

You must select your management strategy based on the appropriate diagnosis, unstable angina/NSTEMI. If you’re going for conservative therapy, start your anticoagulant using enoxaparin or the unfractionated heparin. You then initiate clopidogrel or ticagrelor. Both of them are 1B in medical therapy. If you are going the invasive route you initiate your anticoagulant therapy, first unfractionated heparin, and then you can add pre-cath either clopidogrel or ticagrelor, or if you are going to be in the cath lab looking at the artery and seeing the lesion, then you can use prasugrel as well. All three of the antiplatelet agents can be used if you are in the cath lab looking at the artery, but only clopidogrel and ticagrelor should be used if you are initiating the drug upstream prior to cardiac catheterization.
Now let’s address STEMI – increasing speed to treatment is the most important thing that we can do as emergency physicians. We also have to be able to give appropriate treatment as well. Often times we have time to give drugs while we’re waiting for the cath lab to get activated or while waiting for the patient to be transported from an outside facility. There are a number of different things that we can utilize upstream prior to cath in STEMI patients as well, according to the guidelines.

If a patient shows up in the ED typically they have been given aspirin by the paramedics before getting there or they may have taken aspirin at home. If they haven’t been given aspirin, we should give it immediately. An anticoagulant, usually heparin is what most hospitals utilize because these patients are going to the cath lab to receive invasive strategy. Maybe in the cath lab they will be switched to bivalirudin which has been shown to be very beneficial in STEMI patients but doesn’t for the most part get utilized upstream. Then patients typically receive the P2Y12 inhibitors such as clopidogrel, prasugrel, or ticagrelor. All three are indicated in this patient population.

The glycoprotein IIb/IIIa inhibitors are generally used on knowing the coronary anatomy after being taken to the cath lab. The cardiologist in the cath lab observes the culprit lesion and if significant may use glycoprotein IIb/IIIa inhibitors. For the most part you will see that these drugs are not utilized upfront in the emergency department. Beta blockers are typically utilized in most patients, being particularly useful in patients with hypertension, tachycardia, but certainly not in patients with bradycardia or heart failure. High dose statins have also found a role upfront in STEMI patients. You can also utilize it upfront in non-STEMI patients as well. There are some decent data supporting this therapy.

Here are the data on the antiplatelet agents, because we’re spending most of the time on these drugs. For TRITON TIMI 38 in patients with STEMI, a nice reduction in death, MI, and stroke at 15 months was observed. This provided a relative risk reduction of 21% in the patients who got prasugrel over clopidogrel. If you have your choice, this is the patient population to utilize it in. Unlike the NSTEMI population, you don’t see the bleeding problems in the STEMI patients as they tend to be heavier, younger, and have less stroke and TIA. In PLATO the 8,430 STEMI patients had a nice reduction in death, MI, and stroke at 12 months in the patients who received ticagrelor versus clopidogrel.

We didn’t talk about fibrinolytics but if you’re going to use them you need to initiate your anticoagulant, which can be either heparin or enoxaparin or fondaparinux, and then you give clopidogrel 300 milligrams, the low dose, because that’s the only dose that’s been evaluated in STEMI patients with fibrinolytic therapy. You give it in patients who are less than 75 years old only.

If you’re going to use primary PCI however, you initiate your anticoagulant therapy which is typically going to be unfractionated heparin, maybe transition to bivalirudin in the cath lab, and then you can load with a second antiplatelet agent, either clopidogrel, prasugrel, or ticagrelor. It doesn’t make any difference. All three are indicated in the STEMI patient population according to the 2013 STEMI Guideline.

ANDRA L. BLOMKALNS, MD: My discussion will emphasize NSTEMI and unstable angina and cover it in more depth both from a diagnosis and treatment perspective. This discussion will be based on the focused update - the 2012 ACCF/AHA Guideline for treatment of unstable angina and NSTEMI. There are approximately four times as many NSTEMIs as STEMIs, although I would say in my clinical practice it seems like an even greater ratio than 4 to 1. We’re going to address aspirin, beta blockers, and platelet antagonists.

Let’s discuss a case. You have a 73-year-old male who presents to your ED with chest discomfort. The symptoms began earlier this morning. He had some sweating, some shortness of breath, felt a little dizzy. He’s not really symptomatic at the present time. The patient has a history of coronary heart disease and had a stent placed previously. Recently he began requiring insulin. He has dyslipidemia and hypertension.

He takes a daily baby aspirin, amlodipine, and atorvastatin in addition to insulin. His ECG, which you obtained in less than 10 minutes of his arrival to the ED has LVH with strain. You’re lucky and find another one which looks exactly the same. There are no acute ST-segment changes. You’re feeling this is not a STEMI but clearly this gentleman is having pain consistent with the ischemic chest pain he has had in the past. His chest x-ray is fairly unremarkable with exception of cardiomegaly. He is not in distress and has a normal cardiac exam. There are no rales on the pulmonary exam and he does not appear to be fluid overloaded. The patient has a slightly elevated white blood cell count. His electrolyte profile has a glucose of 230 and a slightly elevated creatinine. There are no ketones. His troponin I is positive, and substantially elevated at 0.35. His BNP is 750.
This is a high risk NSTEMI patient. He has a positive troponin and new symptoms of myocardial ischemia. The patient doesn't need one platelet antagonist, he needs two. The patient first needs aspirin. Your choices for the second antiplatelet agent are clopidogrel or ticagrelor. Prasugrel should be used in the cardiac cath laboratory after the patient’s coronary anatomy is defined. I really want to emphasize the correct doses for the antiplatelet agents (Figure 5). We’re good with the four baby aspirins for our patient. If there are no contraindications then give clopidogrel 600 milligrams or ticagrelor 180 milligrams. These antiplatelet agents should be given as early as possible.

For clopidogrel, there is a gene, CYP2C19 that is required to metabolize clopidogrel from the inactive to the active form. Genetic testing is available that might help identify patients with defects in this enzyme pathway, although testing is not currently recommended or routinely available in most hospitals.

The COMMIT trial was a glycoprotein IIb/IIIa inhibitor trial which also evaluated beta-blocker therapy. It wasn’t that long ago we were giving metoprolol 5 milligrams and wait 10 minutes, 5 milligrams and wait 10 minutes, and then 5 milligrams and wait 10 minutes. However, this approach is very nursing intensive. The recommendation is now to give metoprolol in its oral form (25, 50, or 100 milligrams) if the person is hemodynamically stable. That is a determination you really have to make because the long term benefit of this therapy is realized only several weeks or months later. If the patient is hemodynamically stable, not suffering from bradycardia or in severe heart failure, then give the patient an oral beta blocker.

All of the anticoagulant and antiplatelet therapy we have discussed can cause bleeding, sometimes very significant bleeding. Anticoagulant therapy, including unfractionated heparin and low molecular weight heparins, require discussion. I find that whether you use unfractionated heparin or low molecular weight heparin is largely institution dependent.

Bleeding associated with anticoagulant and antiplatelet therapy is obviously among the worst bleeding we see in the ED. Older people, people who have been on anticoagulants such as warfarin for a long time and have exhausted all of their factors, and patients with comorbid conditions like hypertension, stroke, peptic ulcer disease, malignancies, and liver disease, are more susceptible to bleeding.

CRUSADE was a national quality improvement registry with two hundred thousand patients with unstable angina/NSTEMI across the United States (Figure 6). Patients who bled after receiving anticoagulant and antiplatelet therapy had substantially increased in-hospital mortality.

Cardiac biomarkers are critical for decision making in patients with unstable angina/NSTEMI. **Troponin and brain natriuretic peptide (BNP) are death markers.** Anticoagulant and antiplatelet agents used for unstable angina/NSTEMI are more effective in preventing negative outcomes in patients who are troponin or BNP positive, or in other words at high risk of ischemic complications from ACS. You likely noticed that the patient described previously has a BNP of 750. Does he have heart failure? He doesn’t have other signs of heart failure, but the elevated BNP may be an acute manifestation of myocardial dysfunction. It’s now considered a recommendation to get BNP in these patients. The higher the BNP is the higher the likelihood of death. That’s either getting a BNP or an N-terminal pro-BNP.
I want to take a minute to talk about special populations as I think the people in the trials generally are patients without co-morbidities, and these sicker patients tend to be the ones that actually come to our ED. For older people, that’s 75 and above, we should be a little bit more careful. Currently we give drugs based on ideal body weight and not actual body weight, which can be part of the problem. Make sure you look at your package insert. A lot of this depends on patient functionality. You can treat an elderly person with everything. You can pull out all the stops, particularly if they plant a garden and still go to soccer practice with their grandchildren and thus are active. Your decision may be different if the patient is in a terminal condition, non-ambulatory, and non-verbal in a nursing home. Their functional status should be considered.

For post-CABG patients, I think sometimes we think they’ve already had everything done. What else can we do? For new NSTEMIs, these patients should be treated just as aggressively and probably need a cardiac catheterization because their anatomy is extremely complicated.

Excellent, you’ve treated our patient with aspirin, clopidogrel, or ticagrelor. He’s hemodynamically stable. You’ve given him a beta blocker, 50 milligrams of metoprolol given orally. You decide on clopidogrel and you give him 600 milligrams, eight little tablets, and all is good. You proudly call your cardiologist and say I did all this and I gave him 600 milligrams of clopidogrel or 180 milligrams of ticagrelor. He’s like, “What?” I think there is a concern in emergency medicine that we might do something that can’t be undone or is not the preference of our specialists. What I want to say to you is that no matter what antiplatelet agents you give the patient they can continue on with a very reasonable course. It doesn’t matter if you started the patient on clopidogrel and then the patient needed to be changed to ticagrelor or prasugrel because of cardiologist preference. There are ways to do that and many trials have evaluated patients who were switched from one agent to another.

For the patient presenting to the ED at the beginning of my discussion, these are the treatment steps which the emergency physician should pursue. First give aspirin for everybody as soon as possible, and then treat with clopidogrel or ticagrelor using an appropriate loading dose of 600 milligrams for clopidogrel and 180 milligrams for ticagrelor. Obtain a troponin and BNP level. Use an elevated BNP level as leverage for a sicker patient to receive more complex care. Metoprolol, the beta-blocker should be given orally as intravenous beta-blockers have increased mortality in some patients. Unless you need to treat acute hypertension or acute severe tachycardia, an oral beta-blocker should be used. Treat the hyperglycemia to about 180. That is my recommendation because hyperglycemia actually increases your inflammatory mediators. Of course assess your bleeding risk for each individual patient as in-hospital mortality is directly associated with in-hospital major bleeding.

**Top Eight Things to know about ST-segment Elevation Myocardial Infarction**

- 2013 ACCF/AHA Guideline for STEMI is a comprehensive revision of 2004 Guideline
- STEMI is 25% of 2 million US patients with ACS yearly
- STEMI is defined by characteristic ischemic symptoms, persistent ST-segment elevation, and release of cardiac biomarkers
- “Door to Balloon Time” or “Door To Needle Time” has been revised to “First Medical Contact (FMC)-to-device time”
- Importance of calling 911 - patient delay in reporting symptoms negatively impacts care
- Primary PCI remains the treatment of choice for STEMI
- The 2013 Guideline includes advances in reperfusion therapy, organization of regional systems of care, transfer algorithms and evidence-based antithrombotic and medical therapies
- Hypothermic cooling protocols are stressed to treat patients with cardiac arrest before or at the time of cardiac catheterization

Table 2.

**DR. GIBLER:** Let’s discuss the STEMI guidelines. You can see there are the top eight things to know about the management of ST-segment elevation myocardial infarction (Table 2). The 2013 Guideline is an update of the 2004 Guideline. Of the 2 million U.S. patients with ACS yearly, STEMI represents 25% of the patients. STEMI is defined by characteristic ischemic symptoms, persistent ST-segment elevation, and release of cardiac biomarkers. The door to needle time has been revised to first medical contact to device time. This is so that emphasis can be placed on the role of the pre-hospital providers and their importance in getting patients to the cath lab quickly. It is critical for the patient to dial 911 early after symptom onset.

For STEMI, PCI is the primary treatment of choice. Even though fibrinolytic therapy works well, PCI is the most important treatment for patients. It has been found to be the 1A classification for treating these patients.

The first part of these recommendations concerns the development of a system of care. Communities should create an EMS system of care, and there are a number of resources to potentially help with that, such as Mission Lifeline and the Door to Balloon Alliance. Paramedics should perform 12 leads in the field because that’s what’s best for patient care. It can be done even while they’re getting the patient ready to transport to the ED so that it can be evaluated by the emergency physician prior to patient arrival. The positive STEMI on 12-lead ECG in the field has been shown to decrease by 30 minutes the time to treatment for these patients.
Reperfusion therapy should be administered to all eligible patients prior to 12 hours. If they’ve had pain for 12 hours or less they are candidates for reperfusion therapy such as PCI. Obviously the earlier the patient receives reperfusion therapy for STEMI the better the patient’s outcome. If you can get them within an hour, two hours, or three hours of symptom onset you’re going to maximize the salvage of myocardium. Primary PCI is the recommended method of reperfusion. The goal should be (and a lot of cities are trying to develop this) to bring these patients to PCI capable hospitals that have the cardiologists present 24 hours a day.

When fibrinolytic therapy is indicated it should be given in 30 minutes or less. Reperfusion therapy is reasonable to consider for patients with STEMI having symptom onset within the prior 12 to 24 hours who are having ongoing ischemia. The toughest thing to determine for patients is when their chest pain started. Often it’s what time did their chest pain start that brought them in to see you. It might be off and on, off and on, off and on for 6, 10, or 12 hours and then all of a sudden you have complete occlusion and then the patient comes in to see you. When did their actual chest pain start associated with complete occlusion of their coronary artery? The time of occlusion could have been 30 minutes before they saw you in the ED. Never think that you can’t or don’t need to reperfuse these individuals because of time delay greater than 12 hours. If there is question about the time of occlusion, cardiac catheterization for PCI may be the best choice for these patients.

This is a flow diagram that’s in the guidelines that shows very clearly this whole concept of treatment within 90 minutes (Figure 7). Getting the patient reperfused within 90 minutes using PCI is ideal management. The patient who presents to a hospital without PCI capability is given two hours to have PCI performed at another institution with PCI capability. That includes the 30 minutes for evaluation. The concept for PCI is you take 30 minutes, you evaluate the patient and contact the receiving hospital, and then you have them transported by ground or air ambulance to that hospital.

What about the therapy for these patients with STEMI? Obviously aspirin is required. After PCI, aspirin should be continued indefinitely. A loading dose of one of the P2Y12 inhibitors including clopidogrel or ticagrelor should be given in the ED. Prasugrel is also indicated for STEMI but should not be used in patients of low weight, the elderly, and patients with previous TIA or stroke. All of these agents should be given as early as possible at the time of primary PCI to patients with STEMI. The glycoprotein IIb/IIIa inhibitors are basically cath lab drugs.

For patients with STEMI undergoing primary PCI unfractionated heparin remains the primary therapy at most institutions. It’s effect can be easily and effectively monitored during and immediately after the PCI. Enoxaparin, a low molecular weight heparin is also an excellent alternative for heparin in STEMI patients. Difficulty in monitoring for the low molecular heparins has limited their use in some institutions.

What about giving fibrinolytics to these patients who have received anticoagulants? Fibrinolytic therapy can be given along with unfractionated heparin in the absence of contraindication. When PCI is not available fibrinolytic therapy is reasonable for patients with STEMI if there is clinical evidence of ongoing ischemia in the setting of STEMI and a large area of myocardium at risk.

What about patients with cardiogenic shock? There is actually a trial called SHOCK which compared fibrinolytic therapy to patients receiving PCI in patients with cardiogenic shock. PCI was found to be the treatment of choice. For these patients, irrespective of the time delay, transport to a PCI capable hospital is critical. Early revascularization with PCI or CABG should be performed in patients with cardiogenic shock or significant myocardial pump failure with STEMI. This is irrespective of the time of symptom onset. These patients need to go to the cath lab. Therapeutic hypothermia is the standard of care for patients who experience a return of spontaneous circulation (ROSC) after ventricular fibrillation arrest resuscitation. These patients need to be transported to an institution which can provide therapeutic hypothermia.
In conclusion, STEMI represents a significant portion of patients presenting with ACS and acute myocardial infarction. Regional systems of care are important to develop and should includeprehospital 12-lead ECGs by paramedics to decrease time to treatment in-hospital and identify patients with STEMI to be transported to PCI capable hospitals. Primary PCI is the best treatment for patients with STEMI. Again the caveat is that PCI must be performed in two hours or less if you are referring that patient to a PCI capable hospital, or 90 minutes or less if your hospital is PCI capable. Finally antiplatelet and antithrombotic therapy continues to evolve for these patients and is critical to initial opening of the artery and reperfusion maintenance.

**DR. GIBLER:** What I’d like to do is now go through three quick cases with Drs. Hoekstra and Blomkalns. We have a 60-year-old female who presents to the ED of a rural critical access hospital with chest discomfort, nausea, and vomiting. She has had pain for two hours. Her past medical history is remarkable for smoking, elevated low density lipoprotein cholesterol, hypertension, and moderate obesity. Her 12-lead ECG is positive for an inferior STEMI with lateral reciprocal changes. How would you evaluate and treat this patient, and what options are available for reperfusion therapy?

**DR. HOEKSTRA:** I’ll start. Critical access hospitals typically mean they are a long way away from anything else, particularly early percutaneous coronary intervention. The reality is the time that it takes you to get this patient from the critical access hospital to the cath lab is going to be a key indicator of what you utilize for your reperfusion therapy. If it’s going to be more than 120 minutes before possible PCI, you typically are going to be looking at giving fibrinolytic therapy in your ED and then transporting to a hospital capable of percutaneous coronary intervention. If it’s going to be less than 120 minutes you’re typically going to be looking at a very quick ambulance ride or a helicopter transport to get the patient to the cath lab. If your system is running the way it should be and you’ve actually set up a system of care, you should know the answer to that question already before the patient shows up.

You should have a protocol in place that says if a STEMI walks in our door this is the number that we’re going to call for the EMS people to activate to come get this patient and take them away and this is the cardiologist we’re going to call at the receiving facility to let them know that they are coming. You should not be asking permission to send the patient but are just letting them know the patient is coming. You should have a specific protocol with anticoagulant and antiplatelet drugs needed to give to the patient before transport. Sometimes it’s going to depend on weather. Sometimes it’s going to depend on what EMS is available, a helicopter or ground ambulance. There are a number of different things that can help you make that choice.

I will throw in one more idea in addition to transportation and protocol development. How soon did the patient show up with pain? If you have a patient that presents within the first two to three hours of their acute myocardial infarction, there still is time for fibrinolytics to be effective. If they show up 6 to 12 hours after the onset of their pain, lytics really don’t do much. That may also help influence what you do with a patient like this.

**DR. BLOMKALNS:** The only thing I’d like to add is that this is probably not the patient to give the beta blocker to with the inferior MI. The patient’s blood pressure might be preload dependent and you might be dealing with some issues of hypotension and relative bradycardia on presentation. Nitroglycerin or beta-blockers may bottom out this patient’s blood pressure. Also, I think people view the helicopter, and for those of you who have flown on one, you understand this, as instantaneous transport. They think if you call the helicopter from time zero, the helicopter lands, the patient magically materializes on board, and it flies away. You probably know that it takes a lot longer than that. The helicopter lands and it cools down and it has to start back up. It does this and you have to still transport the patient back after converting all the drug and fluid infusions to equipment compatible with the helicopter’s equipment. No matter how fast you try to do that it takes time. To say that someone could be transferred within less than an hour anywhere is not realistic.

**DR. HOEKSTRA:** Most of the transfers for PCIs that are happening in this country have an average first door to second balloon time of about 120 minutes. It’s really tough to get those under 90 minutes even in a well-functioning system because of the issues that Dr. Blomkalns is talking about.

**AUDIENCE MEMBER ASKING QUESTION 1:** If it’s going to take 120 minutes at best to get to a referral hospital, what you’re saying is that we should sort of abandon the 120 minute business and give these people fibrinolytics. You’re essentially saying that it’s impossible to get them into PCI within the recommended time.

**DR. HOEKSTRA:** Yes, and the question is what is the recommended time? There’s a study looking at this very point.
DR. GIBLER: It’s a strong recommendation that if it’s going to take longer than 120 minutes to undergo acute coronary intervention with a transfer, fibrinolytics should be strongly considered. It often takes three hours, four hours, or longer. You have to know your system. The Guideline authors have placed caveats to indicate these recommendations are for an idealized system and understand there is going to be some variability. Fibrinolytic therapy is very good therapy for patients, but you have to use your own judgment on that versus transfer.

DR. HOEKSTRA: The other thing to remember is the 90 minute versus 120 minute window came from a couple of studies that looked at a large number of questions and a large number of patients and looked at where the lines of optimal treatment crossed. Any given patient however is a little bit different. That’s why I was talking about the short time to reperfusion versus a long time to reperfusion. If you get somebody within the first couple of hours when their mortality curve is quite steep (in terms of benefit with reperfusion) this is a patient who could benefit with fibrinolytics. If you get the patient later in the three to six hour time frame, PCI is going to be the only way to go because the lytics are not going to do much for that patient. You’ve got to use clinical judgment in looking at the individual patient and not just the time from symptom onset.

AUDIENCE MEMBER: In this lady who comes in two hours after she’s had symptoms, you have to figure maybe on top of that another two hours or more getting her to an interventional hospital.

DR. GIBLER: Yes, this would be a good fibrinolytic candidate. If the patient is coming in to the hospital early on, you just have to know your referral network if you’re considering transferring the patient. Everybody thinks that once that patient leaves their department and goes somewhere that they’re magically opened up, but when you actually look at the data on that it’s really, really tough for hospitals to adhere to that 90 minutes once the patient comes in their door. Is there a head-to-head study of PCI, 120 minutes versus fibrinolytic use at 30 minutes, or is this just a best guess based on combining studies and data? I think what has been shown very, very clearly is that 90 minutes with PCI beats fibrinolytic therapy. The reason why is that fibrinolytic therapy tends to open coronary arteries over a 90 minutes period, not instantaneously as PCI does. In the first 30 minutes you get about a third of the arteries are open, in the next 30 minutes another third of the arteries are open, and in the last 30 minutes another third are open. With this time frame, there still is about 85 or 90% artery patency with optimal fibrinolytic therapy. If you do PCI theoretically you have the culprit artery 100% open and it happens immediately. That’s the reason why that comparison is there. It’s based on a 90 minute comparison with PCI. In addition, patients treated with fibrinolytic therapy have a higher incidence of intracranial bleeding and major other bleeding compared to patients undergoing PCI.

AUDIENCE MEMBER ASKING QUESTION 2: Why is the clock for PCI started in the field and the fibrinolytic clock doesn’t start until after the ED arrival?

DR. HOEKSTRA: Clearly the clock is arbitrary, right? We don’t really know when patients said they started having pain. I mean there have been studies certainly saying “when did your pain start?” For patients saying their pain started “just a minute ago” can encompass a minute or perhaps five and a half hours ago. It’s just that whole range of time. Patients aren’t very good at telling you when they started having pain, and certainly in the metrics for an EMS system will be when they transported the patient, and the metrics for a hospital is when they receive the patient. I think the clocks are different because the people using the times for quality control are different. If you think about it, the average time from a field ECG to the arrival in the emergency department is about 20 minutes. You can’t give fibrinolytics in the field because the trucks don’t have them and paramedics don’t give them.

DR. GIBLER: Actually, I was a principal investigator on a fibrinolytic in the field trial in the late 1980’s, early 1990’s. The Nashville pre-hospital fibrinolytic experience was combined with the Cincinnati experience for publication of results. The bottom line is exactly what Jim was saying. We found that the pre-hospital 12 lead ECG drove in-hospital therapy. It drove down the time to in-hospital therapy. It’s very complex training paramedics to give fibrinolytic therapy in the field. It takes an enormous amount of training. You only see these patients sporadically which means that training decays very quickly. We found that the pre-hospital 12 lead was the most effective part of that whole trial.

DR. GIBLER: Case two, a 70-year-old man with ongoing chest pain for two hours. You had a 12 lead ECG sent to you from the pre-hospital setting by a paramedic which shows ST elevation, myocardial infarction in his anterior septal lead. It’s a big infarction. The interventional cardiologist at your institution is currently caring for another patient in the cardiac catheterization laboratory at a nearby hospital and tells you to have the patient go directly to the cath lab, bypassing your ED. He or she will be in shortly to take care of that patient. What do you think?
DR. HOEKSTRA: This is a question that is really being asked a lot right now. Should my paramedics seeing an ECG in the field bypass the ED and go straight to the cath lab? A lot of cath lab hospitals are doing this, often it is not necessarily for quality reasons as much as patient acquisition reasons. The paramedics love doing this because they get to go to the cath lab and watch a procedure. They think they’re doing the right thing because it’s faster to do it this way. We’ve got to be really careful. Taking somebody from the field straight to the cath lab, can save you a few minutes and it might save you as much as 30 minutes. While it can save you a few minutes it has significant pitfalls associated with it.

This patient with an anterior MI goes straight to the cath lab and gets up there and finds out that there’s nobody there or maybe there’s a nurse there who is a cath lab nurse or maybe a cath lab tech, but no doctor. What’s just been committed? It’s potentially an EMTALA violation, as no provider has performed a screening medical exam on this patient. An unstable patient is sent to a part of the hospital where they can’t take care of unstable patients. That’s a problem. Number two, what if this patient had cardiogenic shock? Is this the right place to take care of somebody with cardiogenic shock in a cath lab with a nurse and a doctor that’s flying in looking for the pulse in the groin? Probably not. What if they need an airway? What if the patient doesn’t really have a STEMI and they’ve got something else going on? The ST-segment elevation are due to a left bundle branch block that we’ve all seen a bunch of times?

If you’re going to do this kind of straight to the cath lab approach, you’ve got to do it right. You have to have specific protocols in place, everything from security meeting them at the door and providing way finding for the EMTs to get to the cath lab, to making sure that there is a doctor in the cath lab when they get up there to receive the patient and take care of them, also making sure the patient is not unstable. Certain things have to be told to the emergency physician by telemetry about that patient before that doctor can feel comfortable saying the patient sounds stable enough that they are okay to go to the cath lab. Blood pressure, pulse, oxygenation, and things like that are really important before you pull that trigger and let the patient go upstairs. If you can do those things appropriately, and if you have that protocol in place and you can practice it a few times, then I think it’s perfectly reasonable to do so. If you just do it indiscriminately without all those things being in the right place and that protocol being established, you can get yourself in big trouble. This would be a perfect example of that.

DR. BLOMKALNS: I think it’s a mistake to send people directly to the cath lab. I mean that’s one of the critical things that we’re trained to do, is to be able to decipher all the possible things that can be wrong with this patient that may have nothing to do with their myocardium.

DR. HOEKSTRA: The places I know that approach these patients such as this always have a doctor up in the cath lab before the patient is ever sent there.

DR. GIBLER: It might be a fellow, a cardiology fellow. This is someone that can start the intervention.

DR. GIBLER: In the last case, a 45-year-old male collapses at his son’s football game. Bystanders begin performing CPR while 911 is called. Paramedics respond in five minutes to find him unresponsive and pulseless. After electrical defibrillation for ventricular fibrillation he has a ROSC with a weak but definite pulse at a rate of 110. He remains unresponsive. A 12-lead ECG is performed in the field and shows a large anterior STEMI with inferior ST depression. In other words, this is a big MI. Panel, what would you recommend for this patient when the paramedics call for your instructions? You can carry that further if the patient comes to you and you’re a PCI institution.

DR. BLOMKALNS: All right. Obviously this patient is going to do best when he goes to the cath lab as quickly as possible. I think hypothermic cooling is absolutely a critical intervention that can be performed with relatively little difficulty. You also have the option of just one of those countercurrent gel-like blankets which work fast. I think you can start cooling that patient down almost immediately.

DR. HOEKSTRA: Yes. I think there are a couple of questions about this one. One is what kind of hospital would this patient be sent to for care? Obviously he would be sent to a cath lab facility because this is also a big anterior MI. You worry about cardiogenic shock. You want to have him in the right place. He is obviously going to need ICU stabilization and other complex care. This is a patient who should bypass the non-cath lab facilities and probably go someplace where not only do they have a good cath lab but they also have a pretty good ICU. The second thing is cooling. I don’t know what you guys are doing, but for a STEMI patient who comes in unresponsive, we’re starting to cool that patient before they go to the cath lab and also in the cath lab. It’s not unreasonable to do both at the same time. While you’re working on the artery you’re also cooling the patient down at the same time.
AUDIENCE MEMBER: Just a practical question. Somebody comes in with chest pain and you see the STEMI. He already has received 75 mg of clopidogrel daily treatment and has taken 81 mg of aspirin daily as well. Do you deduct the 75 milligrams from the 600 milligram loading dose, and the aspirin dose from 300 milligrams?

DR. HOEKSTRA: This is actually a really good question because now what you have to ask yourself is here’s a person having a STEMI who is already on aspirin and already on clopidogrel. What’s the problem? Well, the first thing I would think about is resistance to clopidogrel due to the patient’s inability to produce the hepatic CYP2C19 necessary to effectively convert clopidogrel to its active form. He or she is probably one of those patients who is fitting into that category. Remember the slide that I showed you on clopidogrel where there are responders and non-responders? He’s probably a person who is a non-responder. The first thing I would do is switch him to a higher potency drug. I would continue the aspirin and I would put him either on ticagrelor or prasugrel as my P2Y12 inhibitor, and I would give him a full loading dose of the new agent.

DR. GIBLER: Yes. If he’s on daily aspirin you’ve probably taken care of the platelets as it relates to the aspirin dose, but I agree with switching him to a more potent antiplatelet drug. It makes sense because he essentially is infarcting despite the antiplatelet drug that he had been taking, which in this case was clopidogrel.

AUDIENCE MEMBER: Let’s suppose that this person had a stent placed before. Now, I would pose the same question. How would you approach this patient?

DR. GIBLER: I’m going to ask our interventional cardiologist in the audience to answer that question.

AUDIENCE MEMBER: If somebody occludes while on clopidogrel you have to go to one of the other agents. When you look at two studies, TRITON TIMI 38 which was the prasugrel study, they did not allow anybody to be on clopidogrel when they started the trial as opposed to PLATO where 46% of the patients were already on clopidogrel, and were then switched safely to ticagrelor. Ticagrelor has a mortality benefit compared to clopidogrel and it has been well studied. That’s the way I would go.

AUDIENCE MEMBER: For our interventional cardiologist colleague, if they’ve already had PCI in the past, and have a stent in place, you just go look at the artery involved and open up their closed stent?

AUDIENCE MEMBER: Yes, and as a cardiologist, I would then place whatever other stent in the patient that was necessary.

AUDIENCE MEMBER: Panel, you have mentioned the 90 minute and the 120 minute time periods. I just want to clarify. For a non-PCI facility transferring to a PCI facility, you still have the 120 minute goal, correct?

DR. GIBLER: Correct. If you are transferring out of your institution to a PCI capable institution, the recommendation is for two hours. It takes you about a half hour to make the diagnosis to make the diagnosis and arrange transport, and hopefully get somebody in there very quickly to take that patient out. If the patient is presenting directly to a PCI capable institution, it’s a 90 minute window to receive PCI.
The Evolving Landscape of ACS in the Emergency Setting: Focus on Antiplatelet and Anticoagulation Therapy

CME POST TEST

After you have read the monograph carefully, record your answers by circling the appropriate letter answer for each question.

1. For patients with ST-Elevation Myocardial Infarction (STEMI), “Door to Balloon Time” or “Door to Needle Time” has been revised to:
   A. “First ECG to Balloon Time”   C. “First ECG to Cardiac Catheterization Time”
   B. “First Medical Contact (FMC)-to-Device Time” D. “Door to Open Artery Time”

2. Patients with ST-Elevation Myocardial Infarction (STEMI) represent more than 70% of all patients with Acute Myocardial Infarction.
   A. True    B. False

3. For patients with ST-Elevation Myocardial Infarction (STEMI) Primary PCI should be performed in which of the following circumstances:
   A. Ischemic symptoms <12 hours with first medical contact time of \( \leq 120 \) minutes
   B. Clinical and/or ECG evidence of ongoing ischemia 12-24 hours after symptom onset
   C. Ischemic symptoms <12 hours and contraindications to fibrinolytic therapy, irrespective of delay from first medical contact
   D. All of the above

4. Fibrinolytic therapy is never indicated for patients with ST-Elevation Myocardial Infarction (STEMI).
   A. True    B. False

5. Which of the following antiplatelet agents should NOT be administered as early as possible or at time of primary PCI in patients with STEMI and a history of prior stroke or transient ischemic attack?
   A. Clopidogrel   B. Prasugrel  C. Ticagrelor   D. Aspirin

6. According to the 2012 Guidelines for NSTEMI and unstable angina, which of the following markers is a strong predictor of mortality in patients with STEMI and NSTEMI?
   A. NGAL (neutrophil gelatinase-associated lipocalin)   C. MPO (myeloperoxidase) – BB fraction
   B. BNP or pro-BNP (brain natriuretic peptide)   D. HgbA1C (hemoglobin A1C)

7. According to the 2012 ACCF/AHA Focused Update of the Guideline for patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction, in addition to aspirin, a loading dose of P2Y12 receptor inhibitor therapy is recommended for UA/NSTEMI patients for whom PCI is planned. Which of the following regimens is NOT acceptable without first performing a cardiac catheterization?
   A. Clopidogrel 600mg   B. Clopidogrel 300mg   C. Prasugrel 60mg   D. Ticagrelor 180mg

8. Which of the following is TRUE of ticagrelor:
   A. Increased cardiovascular mortality compared with clopidogrel
   B. Increased incidence of alveolar hemorrhage in patients with COPD
   C. Decreased stent thrombosis when compared to clopidogrel
   D. Increased mortality in patients who subsequently undergo CABG

9. In the 2013 STEMI Guidelines from the ACCF/AHA, the following are acceptable anticoagulants with patients undergoing fibrinolytic strategy EXCEPT:
   A. Unfractionated heparin   B. Enoxaparin   C. Factor Xa   D. Fondaparinux

10. For a patient who has had a recent MI with PCI intervention presenting to your ED, all of the following antiplatelet regimens would be considered acceptable EXCEPT:
    A. Aspirin 650mg daily   B. Ticagrelor 90mg twice daily   C. Prasugrel 10mg daily   D. Clopidogrel 75mg daily

11. For NSTEMI/UA, studied separately in comparison to clopidogrel, prasugrel and ticagrelor were superior in reducing clinical events but at the expense of increased risk of:
    A. Thrombocytopenia   B. Non-CABG associated bleeding   C. Hemolytic anemia   D. Clopidogrel resistance
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JANUARY 2014