Acute Coronary Syndromes: A Deeper Dive

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Outline

To give you an outline of the entire talk, which we've broken up into different sections, we'll talk a little bit about the definitions for ACS and the pathophysiology. Then we'll delve into the epidemiology and how that's changed over time. We'll then dive into specifics on STEMI as it relates to diagnosis, risk stratification, and revascularization, and then the same for non-ST elevation ACS. Then we'll talk a little bit about medical therapy and other management outside of these specific subtypes of ACS.

ACS: Definitions, Pathophysiology, and Epidemiology

DR. BOHULA: First of all, we'll dive into the definitions, the pathophysiology, and the epidemiology of acute coronary syndromes.

Acute Coronary Syndromes: STEMI, NSTEMI, UA: If we take a step back and think about acute coronary syndromes, we classically subdivide them into three different diseases or three different diagnoses which are ST-elevation MI, non-ST elevation MI, and unstable angina. We lump non-ST elevation MI and unstable angina together as non-ST elevation acute coronary syndrome. Really, all three of these should start with the presentation that it is consistent with ischemic discomfort. Then we further subclassify the specific disease states or diagnoses based on the ECG findings, so the presence or absence of ST elevations and by definition, if there are ST elevations, that's an ST-elevation MI or it falls into the other bucket, the non-ST elevation ACS in the absence of ST elevations. Then also we define it based on the presence or absence of biochemical markers of cardiac injury, so most recently that would be cardiac troponin. In patients who fall into the bucket of non-ST elevation ACS, in the absence of a positive troponin, they would classically be diagnosed with unstable angina. We think about this pathophysiologically as a spectrum of disease where really the ST elevations represent acute thrombotic occlusion of an epicardial artery, and the other two are non-total occlusion of this epicardial artery.

4th Universal Definition of MI: More recently, there has been a definition, which is the fourth universal definition of MI, which really makes a distinction between myocardial injuries, which is just quite straightforward a positive troponin or elevation in the cardiac biomarkers and acute myocardial infarction. In order to be classified as acute myocardial infarction, it needs to be more than just a positive troponin. They ultimately have to have evidence of acute myocardial injury, so a troponin that is elevated above the 99th percentile. But in addition, clinical evidence of acute myocardial ischemia, and really that is defined as symptomatology that's consistent with ischemia plus some other finding like ECG abnormalities or imaging abnormalities that are consistent with ischemia. Then the definitions go on to further subclassify according to the different types of AMI. So type 1 is an atherothrombotic event, which is plaque rupture or erosion. We also have type 2 events, which we will talk about a little bit more in a few upcoming slides, which is not an atherothrombotic event, but rather an imbalance between myocardial oxygen supply and demand, and it's again unrelated to acute atherothrombosis. Then there are other subtypes of MI, specifically for example type 4, which is a PCI-related MI and type 5, which is a CABG-related MI.

What is an MI in 2022: How do we think about MI in 2020? Well, we talked about cardiac injury and cardiac injury can be acute or chronic. Somebody can have evidence of elevated biomarkers chronically and we see that when we check labs, but we see that those elevations are flat, meaning that there's not an acute rise or fall. In the setting of acute cardiac injury we see a rise and/or fall in the cardiac troponin.

If we see chronic elevations, then think about structural heart disease and also maybe in the context of decreased clearance with renal disease. In the setting of acute rise and fall, then the question is: is it an ischemic mechanism? If it's not, then think about some of the other diagnoses, which can be mimics for AMI like PE, CHF, myocarditis, stress cardiomyopathy. Then further as you start to drill down on whether this is an ischemic mechanism and you do so by obtaining a history, ECG, echo, determine whether or not it looks like it's consistent with a plaque rupture event, in which case it would be a type 1 MI or whether it's this demand supply mismatch, a type 2 MI and then look for some sort of precipitants of anemia. Is it significant hypertension arrhythmia? Many different things can drive demand ischemia or type 2 MI.

Acute Myocardial Injury vs. Type 2 MI: Then there's also a distinction between acute myocardial injury, so not acute MI, but acute myocardial injury, which is not due to ischemia. That can be subclassified. For example, etiologies may be heart failure, myocarditis, cardiomyopathy, Takotsubos, things like PE, and even CNS disease. For example, stroke, subarachnoid hemorrhage. But this is you see an acute rise and fall in troponin, but really there are not the signs and symptoms that are suggestive of ischemia. That distinguishes it from a type 2 MI, in which case it is ischemic. It's not a plaque rupture event, but it is ischemiaally mediated by this supply/demand mismatch, and the patient does have symptoms that are consistent with ischemia.

Again, this can be from a couple of different mechanisms. It can be from decreased perfusion and that can be something like a coronary artery spasm or embolism or spontaneous coronary artery dissection or hypotension or significant arrhythmia, or increased demand, which again can also be from arrhythmia or hypertension. So actually, many other causes of demand. There are many different classifications of a positive troponin that we have to think about, but what we're really focused on here is the acute myocardial infarction or the acute ischemic insult.

Outline: The epidemiology has changed over time. Here's one registry from Kaiser Permanente in looking at the incidence of all MI, NSTEMI, and STEMI over time. What you see is that MI is decreasing over time and really that's dominantly driven by a reduction in STEMI, whereas NSTEMI rates have stayed roughly constant. These data go back to 1999.

Outcomes in NSTEMI: Even though the rates of NSTEMI aren't decreasing over time, one thing that's nice to see is that the outcomes in patients with NSTEMI have actually improved over time. This is looking at a whole slew of outcomes in patients who've had NSTEMI, including mortality rates, recurrent MI, heart failure, and stroke. What we see is that generally speaking, mortality has decreased over time and sort of other cardiovascular complications, recurrent cardiovascular events, have decreased over time.

Potentially one of the explanations is what we're doing to manage these patients, which is that we have now a larger and larger array of secondary preventative measures, including invasive management with coronary angiography, but then also other medical therapy and our utilization of that has increased over time, which I think we all suspect is a major driver of the improved outcomes in our patients with NSTEMI.

Case Fatality Rate in STEMI: Also, the outcomes with STEMI have improved quite significantly over time. What I'm showing you here is a number of different studies in STEMI over the years. What you can see is that in these trials, the case fatality rate in patients who are presenting with STEMI has dropped significantly. Most recently the data I'm showing you here is from HORIZONS-AMI with a 2.5% mortality, and that was in 2018. We think that this is probably driven by increased rates of reperfusion and in particular increased use of primary PCI, and then also improvements in medical therapy, so in the

antithrombotics that we use and other secondary preventative therapy that we'll talk about in much more detail in subsequent portions of the talk.

STEMI: Diagnosis, Risk, Stratification, and Revascularization

DR. BOHULA: Now we'll talk about diagnosis, restratification, and revascularization in our ST elevation MI patients. First we'll tackle diagnosis.

Case: I think it's best illustrated with a case, so we have a 65-year-old woman who has multiple risk factors, including type 1 diabetes, hypertension, and hyperlipidemia. She also has CKD. This woman's a little bit unusual in that she's had multiple kidney transplants. She now presents to our ED. She's had rest chest pain that started about two hours ago. Her initial workup is notable for some tachycardia with a heart rate of about 110 beats per minute. Her blood pressures are on the low side with a systolic of 80, diastolic of 50. She is a little bit tachypneic and she is requiring oxygen. Her creatinine is elevated, consistent with an AKI. Her high-sensitivity troponin T is also quite elevated and then we see that some of her risk factors are not well modified here, an LDL of 150 mg/dL and A1c of 8%. This is her presenting ECG, which is notable for ST elevations in leads 1, aVL, V1, all the way through V3 and there are some reciprocal ST depressions in leads 2, 3, and aVF. Here we're seeing acute ST elevations.

STEMI Pathophysiology: Thrombotic Occlusion: Going back to our pathophysiology, and we said she's presented definitely with ischemic symptoms, our ECG shows ST elevation, which put her in the camp of ST elevation MI. I think one of the take-homes of the sort of intervention for ST elevation is the notion that time is muscle, and that really the goal is rapid diagnosis and reperfusion. We talked about before how the diagnosis of ACS also involves evidence of myocardial injury with elevations in cardiac troponin, but in this case, we'll talk about this more. Really we need to make the diagnosis and to start the treatment plan.

Importance of Time to Reperfusion in STEMI: The treatment plan is reperfusion and we know from a number of different studies that it is very important to re-perfuse as soon as possible. These are data showing you delay to fibrinolysis and delay to PCI. The Y axis is in-hospital mortality. In both cases, the longer the delay, the higher the in-hospital mortality. Really the take home is as I said before, that the early reperfusion is key.

STEMI Diagnosis: To make the STEMI diagnosis, we want, as I mentioned, to have a clinical syndrome that's consistent with myocardial injury. Our woman is presenting with classic chest pain, which fits that requirement there. Then we're looking for EKG changes and generally speaking, that's ST elevations. One very important notion is again time is muscle. Early reperfusion is key. Early diagnosis is key. The EGK should be done as quickly as possible. The guidelines would suggest that should happen within 10 minutes of first medical contact. Ideally, and I think this is usually the case, it's done pre-hospital, so by EMS in the field so the diagnosis can be made as quickly as possible.

Diagnostic EKG Findings in STEMI: Now, a couple of points on the ECG findings in STEMI. What we're looking for are new ST elevations at the J point in two contiguous leads. The criteria are met if that ST elevation is at least 1 mm in most leads. The exception is in lead V2 or V3, where that ST elevation has to be greater. So in men that are of at least 40 years of age or older, that's 2 mm. In younger men less than

40, that's 2.5 mm. Then in women, it's 1.5 mm at least. Again, these are what meet criteria for ST elevations.

STEMI Diagnosis: Important Caveats: There are some very important caveats, which is if it sounds to you like this is a syndrome that is consistent with ischemia and you're concerned that for example you have an ST elevation MI but you're not seeing it by EKG, the recommendation is to recheck the EKG every 15 to 30 minutes. Because sometimes the ischemic symptoms may actually precede the EKG changes by some period of time. If it smells like an MI, but you're not seeing anything that is not diagnostic by EKG, continue to check those ECGs over time and you may ultimately be able to identify something that looks like an ST elevation MI.

I think the other thing which I alluded to before is that of course if we have epicardial artery occlusion, then we ultimately will see myocardial necrosis. But that may take time to be able to be appreciated in the blood. Of course, it's not immediate when you have an acute occlusion, that you will see evidence of a positive troponin. Really the diagnosis of course can be confirmed with an elevated biomarker, but we should not wait on management of the patient, i.e., reperfusion therapy, for those biomarkers. It really is sufficient to have the ischemic symptoms plus the EKG changes in order to make the diagnosis and to proceed with your intervention.

EKG Findings & Localizations of Territories: One thing that is actually quite helpful and important to know is that with ST elevations, those are actually very specific for vocalization of the arteries. Importantly, ST depressions and T-wave inversions are not localizing, but ST elevation can be extremely helpful in localizing the territory. This is a figure that I pulled form Bromwell's heart disease that really shows you where you expect to see the EKG changes, the ST elevation specifically, and what that translates to in terms of the infarct artery and also wall motion abnormality territories. Again, you can very nicely localize if you see ST elevations.

EKG Sensitivity for STEMI: Something to note, the EKG is not perfectly sensitive for ST elevation MI. We already talked about how sometimes there could be a little bit of a delay in appreciating ST elevations on EKG. Therefore, you get serial EKGs, but also depending on the infarct artery, the EKG is not 100% sensitive. It's very good for LAD lesions, also quite good for RCA lesions, but as I think we all have probably heard before, it's not very sensitive for left circ occlusions, so only about 60% sensitivity. It's not uncommon to have an electrically-silent, acutely, totally occluded left circ artery.

Really what we should be doing if you're worried, if you're suspicious, again, checking serial ECGs. But it's also a class IIa recommendation to do a posterior EKG to look for an electrically-silent left circ occlusion, which you may be able to pick up with elevations in V7, V8, and V9.

Atypical EKG Patterns: There are some atypical ECG patterns that can also obscure the diagnosis of STEMI left bundle branch block or paced rhythm, which generally speaking looks like a left bundle branch block. It can be quite challenging to make the diagnosis and on the next slide we'll go through the diagnostic criteria, which are the Sgarbossa criteria to make the diagnosis. In a more recent version of the ESC guidelines, they also note that sometimes even a right bundle branch block may confound the diagnosis of STEMI, so if you have that, again, very, very closely, they're not specific criteria outside of the ones that I've already mentioned to look for ST elevations, but just note that sometimes that can obscure your interpretation.

We've talked about the situation of a posterior MI and so again, keep in mind that if you're worried about a STEMI and you're not seeing it on your classic sort of anterior EKG, to look in the posterior leads to see if you see evidence of an isolated posterior myocardial infarction.

Sgarbossa's Criteria: To run through Sgarbossa's criteria, there are a few. I think one is that if you see ST elevation, in a normal left bundle branch block, which I have in gray on that sort of middle column there, in leads V4 through V6, aVL, and 1, we often see that there's negative deflection after the QRS. If you see ST elevations, which are positive and sort of concordant with the QRS, that is concerning, and so it has the criteria greater than or equal to 1 mm. That gives you 5 points, which right there gives you a very high probability of STEMI in the context of a left bundle branch block.

Also, ST depressions in the anterior precordial leads, which are V1 through V3, if those ST depressions are at least 1 mm, then that gives you 3 points, which again is high probability of a STEMI. Then the final criteria are significant ST elevations that are discordant with the QRS in the anterior precordial lead, so V1 through V3. The criteria there have to be at least 5 mm of ST elevation. That gives you 2 points, so not quite meeting that super high threshold of STEMI, but still is quite concerning if you see that. I think I would treat that as if it's a STEMI in the context of a left bundle branch block.

STEMI with LBBB: Here's an example of an ECG that meets criteria, two of the different criteria. We have in the anterior precordial leads the ST elevation that's greater than 5 mm. That would get you 2 points. Also, we have ST elevation that is concordant in the apical leads, V4 specifically, and that gives you 5 points. So right there we're at 7 points, with an extremely high likelihood of ST elevation in the context of the left bundle branch block. That's how you apply Sgarbossa's criteria to diagnose STEMI in the context of a bundle branch block.

Isolated Posterior MI: This is an example of an isolated posterior MI. The top panel is showing you your typical anterior ECG with a normal V1 through V6. We're not seeing any ST elevations, but we are seeing those anterior precordial ST depressions, which of course you worry is actually a posterior MI. In this case, they put on leads V8 and V9 and now you see that there are ST elevations in those leads, which then again is consistent now here with an isolated posterior MI.

Considerations by MI Locations: A few other things to think about in terms of diagnostics and also complication related to the specific locations of MI.

Anterior MI: When we think about anterior MI, this is really the highest-risk STEMI that we see. The reason I say that is that this is where we see most cases of cardiogenic shock, which can complicate approximately 5% to 10% of STEMI. We see cardiogenic shock most commonly and not surprisingly when we have a very large interior MI. With anterior MI you can also see a number of mechanical complications not super common, but nevertheless this is something that is certainly observed. Free wall rupture is one, LV aneurysm with an associated LV thrombus. You can have papillary muscle rupture and in this case with an anterior MI, that would most typically be an anterolateral papillary muscle rupture. Then an apical VSD.

Inferior Infarct: In the context of inferior infarct, there are a few things to look out for in terms of the most common complications. We definitely see rhythm disturbances, including sinus bradycardia, often times due to increased vagal tone. Depending on whether or not this is an RCA infarct and whether or not you hit the AV nodal branch, you may also see a high degree AV block or complete heart block. We can see

mechanical complications as well in the context of inferior infarct. In this context we often times see inferior basal VSD, which actually has a worse prognosis than apical VSD. Often times it's more difficult to manage and to close. Then we can also see papillary muscle rupture, which in the context of inferior infarct tends to be a posterior medial papillary muscle rupture. Then finally, we can see in addition to inferior infarct a concomitant posterior or RV infarction.

RV Infarction: We've already talked about diagnosing posterior infarction with a posterior ECG, adding leads V7 through V9. Now thinking about an RV infarction, actually it's quite common in our patients with inferior infarcts. It happens about a third of the time, typically presents with a classic clinical triad of hypotension, clear lungs, and elevated JVP.

There are a number of different clinical findings that we can see. We can see elevations of right-sided pressure with an elevated CVP or if you have right heart catheterization, elevations of RV and diastolic pressures. We can see the Kussmaul sign, which is paradoxical increase CVP or JVP with inspiration, which is a sign of noncompliant RV or an ischemic RV. Then we may or may not see some signs of low output on the right, so a low RVSP where RV can't generate high systolic pressures; a low RV pulse pressure where it's not generating a lot of stroke volume; low pulmonary artery pulsatility index, which is a very in vogue measure of RV function and that specifically is calculated as the PA systolic pressure minus the PA diastolic pressure over the right atrial pressure and we oftentimes use a threshold of less than 1 to be abnormal. The way that I think about this, it's the pulse pressure on the right side over the level of congestion on the right side, so smaller pulse pressure, higher congestion, lower number. That means that the RV is doing worse.

Then also evidence of low cardiac output, which may have a low or normal pulmonary capillary wedge pressure, particularly if the RV is having a hard time in getting blood over to the left side. You may see a low pulmonary capillary wedge pressure.

Right-Sided EKG: How do we diagnose an RV infarct? Well, in this case you would actually do a right-sided EKG, which carries the leads out around the precordium on the right and what you're looking for to make the diagnosis are ST elevations in the right-sided V4 lead.

Management of RV Infarction: How do we manage RV infarction? Well, I think a very important concept is that the RV needs preload. Really what you oftentimes need to do is give some fluids. Not too much, but enough to maintain RV preload and avoid things that can decrease RV preload. That's things like nitrates. That's venodilators like narcotics. That's diuretics. You also ideally if you can, if you have a way of doing it, lower RV afterload, so that may be something like pulmonary vasodilators. Think also about inotropic support for the RV and maybe even mechanical circulatory support if the patient's really in extremis or cardiogenic shock in the context of RV infarction. Reperfusion and then oftentimes these patients will, as we mentioned, if they have significant inferior MI with RV infarction that they may also have some degree of bradyarrhythmia or heart block. In that case, they can respond very, very nicely to increasing the heart rate and if possible, restoring AV synchrony.

Focused History & Exam: When a patient presents with an ST elevation, we do need to do a focused history and exam. Obviously, time is of the essence, but these things are important in order to, again, a very focused history and exam. So it is important to define the ischemic symptoms, the presence, nature, and duration of ischemic symptoms, to think about whether there is anything that could be an important contributor to their presentation. For example, is there concomitant drug use like cocaine use, which will

certainly determine how you're going to medically manage this patient? There may be things which could look like an MI or an ST elevation, which aren't necessarily the primary driver, so pericarditis, PE, aortic dissection of course potentially with extension into the coronaries and most commonly into the RCA.

These are things to think about when you're going in to see your patients with ST elevation. It's also important to think about whether there may be complications, so heart failure or mechanical complications and heart failure, for example, increases the risk for this patient. When we think about potentially managing them differently based on how high their risk is. Then mechanical complications of course are very important to identify because these can oftentimes be fatal in short order. You have to think about this and try to rule it out as quickly as you can.

Then also have to think about whether or not there are potential contraindications to primary PCI or fibrinolysis. For example, does somebody have a severe contrast allergy that would preclude primary PCI? Do they have active or recent bleeding, which for example may make it very challenging to consider fibrinolysis or possibly even primary PCI?

Initial Laboratory Testing: We mentioned that it is certainly nice to have biomarkers to confirm the diagnosis, so I think it's fine to send them at initial presentation of the course. But again, don't wait for those to be positive in order to make the diagnosis. It's also very helpful just to get a very basic set of labs, so electrolytes, renal function, CBC to know again what the starting hematocrit is and what their platelet count is, coagulations parameters just to make sure that they don't have again any obvious contraindications to intervention, and then eventually--and doesn't need to be sent off in the first set of labs--screening labs for secondary preventative risk factor modification like a lipid panel lipoprotein A, hemoglobin A1c.

Early Markers of Risk: When you see this patient, you want to think about the markers of risk. We'll go through a number of different risk scores that have developed to identify who's at high risk in order to prognosticate. But some things that are important are, as I mentioned before, anterior MI, which is higher risk in general than other locations. If you have a high sum total of ST elevations on MI, so if you add up all of the ST elevations, if it's high, that's concerning. That really just tells you that it's a larger infarct. If you have anterior ST depressions in an inferior STEMI patient where you worry about whether or not there's also a posterior MI or concomitant LAD ischemia, we already talked about diagnosis of an RV MI in patients with an inferior STEMI, which of course increases the risk in that patient. If they have heart block or if they have conduction disease with an anterior MI, what that tells you is that this is likely then a large MI. It's a way of sort of prognosticating based on an early read of the size of the infarct.

STEMI Risk Score: TIMI Risk Index: There are a number of different tools that we can use to risk stratify patients with STEMI. One of the early ones is the TIMI risk index. It's very, very simple. All it takes into account is age, heart rate, and systolic blood pressure, and you use that to then calculate the risk index. You can see a very large gradient of risk for mortality, 20-fold grading of risk across the sort of possible scores in these patients. So a very simple way of adjudicating risk in these patients, which the formula is listed there at the bottom. It's heart rate times the age divided by 10 squared over the systolic blood pressure.

STEMI Risk Score: TIMI Risk Index: Subsequent to that there was the development of the TIMI risk score, which takes into account a number of different variables. Eight variables are shown here and you get an integer score based on the number of variables present. That includes older age, lower blood pressure,

higher heart rate, evidence of heart failure or shock on presentation, anterior ST elevation--so again, anterior location of the MI--significant concomitant comorbidities, and low body weight or delayed presentation, so time to treatment of greater than 4 hours. You can see a very large gradient of risk for mortality at 30 days with the more risk factors that you have.

ACS Risk Score: GRACE Risk Score: There also is a risk score, the GRACE risk score, which is used quite commonly in practice, which looks at a patient's medical history, so their age, their history of heart failure, their history of prior MI, and their variables at presentation. What is the heart rate? What do their hemodynamics look like, their heart rate, their blood pressure? Do they have ST depression? What are some of the laboratory abnormalities? For example, what's their creatinine? Do they have elevated biomarkers? That really then defines the risk of all-cause mortality at six months. Often times, we think about a cutoff for particularly high-risk patients of being greater than 140 on this risk score, an intermediate of 110 to 140.

ACS Risk Score: ACTION GWTG: Subsequent to that there was another risk score, which was developed, which is now meant for both all ACS patients, so NSTEMI, STEMI, and it was developed out of the ACTION Get With the Guidelines Registry. Similar to the other ones, it takes in a number of variables, which are a little bit of demographics. But then also what are some of the presentation variables? So what does their blood pressure look like? What is the renal function? How high is their heart rate? Do they seem decompensated? Do they have a positive troponin?

Then also, some important modifiers in this one are: have they had a cardiac arrest, which of course, significantly increases the risk for these patients? Then again, it defines patients with STEMIs as being higher risk than patients with non-STEMI. You can see the gradient of risk based on a score that is calculated. So again, this is for in-hospital mortality. We saw GRACE with six-month mortality. This is in-hospital mortality.

Considerations for Reperfusion: The next steps are how we are going to re-perfuse this patient. There are a couple of different considerations that we should think about. First is: how long has it been since symptom onset? That helps us decide whether or not we're even going to pursue revascularization and, if we are, how we're doing to revascularize, i.e., are we going to use primary PCI or are we going to use fibrinolysis? How long is it going to take us to initiate an invasive strategy? That will also help us decide how we're going to revascularize. If it's a long time to initiation of invasive strategy, then likely we'll have to do fibrinolysis. If it's a shorter time, then you would pursue primary PCI and I'll show you the data supporting that notion. Finally, what's their candidacy for intervention in general and also for fibrinolysis?

Time from symptom onset: This is really a schematic that summarizes what the recommendations are. I'll show you some of the data behind this very shortly. But this is from the recent ESC STEMI guidelines. In the early phase of STEMI, so really in the first 12 hours, what's generally recommended, if possible is primary PCI Ia recommendation. If PCI can't be performed in a timely manner, which means within 120 minutes from STEMI diagnosis, you can consider fibrinolysis. I'll show you data to suggest that that's even more useful in the early period. You can also view it in the 3- to 12-hour window from symptom onset.

In patients who are 12 or more hours out from symptom onset, if they continue to have symptoms, if they're hemodynamically unstable, if they're having arrhythmias, then again pursuing primary PCI with the Ic recommendation. In patients who are relatively acute in the 12- to the 48-hour window but asymptomatic, then you have to consider the risk-benefit of primary PCI in asymptomatic stable patients,

so that they gets a IIa recommendation. Then generally speaking, in patients who are further out from their events, if they're asymptomatic--importantly, if they're asymptomatic and it's at least 48 hours from symptom onset, then intervention is not recommended. If they're symptomatic, again, if they're in shock, if they have hemodynamic instability, if they have other complications like arrhythmia, then pursue revascularization with primary PCI. Again, I think this is a helpful summary schematic to guide your choice of revascularization.

Then again, we have to think about the timelines in terms of our invasive strategy or otherwise. These are data from Lancet from 1994, so older data that really look at the benefit of fibrinolysis in STEMI patients across a whole bunch of different subgroups. Importantly, there's an overall benefit, and this is of fibrinolysis versus no intervention. There's definitely a benefit in terms of an 18% reduction in the odds of death at 35 days.

Part of the reason why I show these data is to show that that subgroup where they look at time from onset of symptoms, you see that there very much is a gradient where it seems like the benefit is really in those earlier time windows, as opposed to the later time windows where it starts to look like there's no difference between fibrinolysis versus control. Again, it seems as if there's a greater benefit for fibrinolysis in the early period.

If we think about the options we have for revascularization or reperfusion, the main options are primary PCI versus fibrinolysis. This is looking at data from 23 different trials. Primary PC is in yellow and fibrinolysis is in purple. What you see is the frequency of a whole bunch of different events that you can see in patients with STEMI, so death, recurrent MI, recurrent ischemia, stroke, and major bleeding.

What we see is for the most part across the board the rates of these events, these bad events, are lower with primary PCI than they are with fibrinolysis. The conclusion is that outcomes are generally better with primary PCI than with fibrinolysis, which is where the guidelines, as you just saw a couple of slides ago, favor primary PCI over fibrinolysis, generally speaking.

There is an important caveat, which is that if it's going to take time to get a patient to primary PCI, then it is worth pursuing fibrinolysis. This is a paper that was published some time ago now, in 2011, looking at that inflection point and looking at where that risk-benefit flips in terms of how long after the diagnosis of STEMI, so after the patient presents to you, where that inflection point is where it no longer is beneficial to delay primary PCI, but rather you should instead pursue fibrinolysis. In this paper, it's suggested that if the delay was more significant than 120 minutes, that fibrinolysis was favored. That's if the delay to primary PCI is more significant than 120 minutes, fibrinolysis is favored. That's really where that comes from in the guidelines, is this paper.

This is then the summary statement that comes out of the data that I showed you. This is the general schematic for how to triage for reperfusion. If you have a patient that develops chest pain, they call an EMS, and the patient is initially transferred to a PCI center, and the diagnosis is made--that less than 10 minute is less than 10 minutes to get an EKG, as I mentioned, so it should be very quick that an ECG is obtained--then per these guidelines then you want to have primary PCI. These are the ESC guidelines within 60 minutes of the diagnosis. That's at a PCI center.

If the patient is transferred to a non-PCI center or if they're in EMS and the diagnosis is made, then the question is: how long does it take them to get somewhere where they could get primary PCI? Because of

the data that I just showed you, if that's greater than 120 minutes, generally speaking, we'll talk about some caveats, then that patient should have fibrinolysis. We don't want to wait for them to have primary PCI. We do fibrinolysis, and that should happen very quickly within 10 minutes of recognizing that the delay for primary PCI is going to be prolonged.

If the patient goes to a non-PCI center and can be transferred and get PCI in under two hours, in less than 120 minutes, then the primary PCI strategy is preferred. Then the door to reperfusion time should be less than 90 minutes. That includes recognition of reperfusion.

Now I think just a few minor things to note; there are some differences between the ESC guidelines and the ACC/AHA guidelines. That time in a patient who is presenting to a PCI center, that time to reperfusion is less than 90 minutes in the ACC/AHA guidelines, as opposed to less than 60 minutes. Then the time for fibrinolysis with the ACC/AHA guidelines is less than 30 minutes once you've made the decision to proceed with that.

I mentioned that there are some caveats, where even if it's going to be delayed to get the patient to primary PCI, so greater than 120 minutes where you would still consider transferring them for primary PCI rather than fibrinolysis, that's in patients who are in acute severe heart failure or shock. If they have a contraindication to fibrinolysis, they can't do it, then obviously transfer them. Or if they're later presentations and that's because I showed you the data, there is not as much benefit for a late presentation using fibrinolysis. In that case, you're probably better off pursuing primary PCI. Even if it's going to take a longer time to get them to the primary PCI center, if they're late presentation, skip the fibrinolysis and send them to the PCI center.

Let's talk a little bit about what the contraindications are to fibrinolysis. We have a couple absolutes and we have a few relatives. An absolute contraindication is any prior intracranial hemorrhage, any known structural cerebrovascular lesion, any known intracranial neoplasm, a recent stroke, and so that is defined at less than three months if they have active bleeding or recent head trauma less than three months. Relative contraindications are generally the history of poorly-controlled hypertension. If they present with uncontrolled hypertension, you can treat that, get them in range, and then consider fibrinolysis. If they've had prolonged or traumatic CPR where they're at significant risk of bleeding, may be intrathoracic bleeding, recent major surgery, recent bleeding in the last two to four weeks, relative contraindication may be accessed at a non-compressible site, pregnancy, high risk for bleeding otherwise, so active peptic ulcer disease or anticoagulated patients. Again, keep in mind the last ones I listed are relative contraindications.

Let's say that your patient undergoes fibrinolysis; what's the next step? There are a lot of studies to help guide us in how we should be thinking about this. There were studies of what's called facilitated PCI, which is that they get fibrinolysis and rapidly then go on to PCI. I'm showing you data from a couple of different studies. This is early primary PCI after fibrinolysis sort of in the first couple of hours. The data would suggest from the ASSENT-4 trial that there are higher rates of death or CHF in those people who had fibrinolysis and then PCI very shortly after as compared to those who just underwent primary PCI. The FINESSE trial didn't show any difference in outcomes of death, VF, cardiogenic shock or CHF, but there was more bleeding with the addition of fibrinolysis. Generally speaking, the answer is we don't do facilitated PCI.

What we do is rescue PCI. If somebody gets a fibrinolysis for whatever reason, one of those indications I mentioned before, we don't see improvement. That's generally speaking defined a lack of ST resolution, the threshold being 50% within 90 minutes. These patients then were then randomized to rescue PCI, a sort of rapid PCI in the absence of improvement with fibrinolysis versus either repeat thrombolysis or conservative therapy. Rescue PCI showed improved mortality over the other strategies, the noninvasive strategies. If somebody's symptomatology is not getting better, if their ECG is not getting better, then definitely pursue rescue PCI.

Then there's another level of thinking about how we pursue PCI after fibrinolysis. The question would be: do we do PCI in everybody routinely? Not immediately after, not facilitated, but sort of routine early, which is generally speaking defined as 3 to 24 hours after fibrinolysis. Or do we go based on ischemia and delay beyond that 24 hours? What we found from a number of different studies is that the outcomes were better with routine early angiography as compared to the delayed approach. That really is now the strategy. In patients who require fibrinolysis, if their symptoms don't resolve, if their ECG doesn't resolve quickly, then we pursue rescue PCI. For all the rest of those individuals, then we pursue a pharmacoinvasive approach, which is routine early angiography.

This has made its way now to the guidelines. These are the ACC/AHA guidelines from 2013, where there's a IIa recommendation for pharmacoinvasive strategy and specifically as a part of an invasive strategy in stable patients with PCI between 3 and 24 hours after successful fibrinolysis. We talked about rescue PCI. That's again an IIa recommendation for urgent transfer for failed reperfusion or reocclusion. The definition there is again lack of ST resolution in 90 minutes, persistent symptoms, hemodynamic or electrical instability. Then we also talked about patients who present initially with cardiogenic shock or acute severe heart failure, that we're going to transfer them for PCI regardless of the time from MI onset, and that's a class I indication.

You do angiography, and you find that of course you identify the culprit artery or the infarct-related artery, but you identify multivessel disease. How do you manage that multivessel disease? There are a couple of different options. You could at the time of the initial primary PCI go after those non-culprit lesions or those non-infarct-related arteries, you could stage it and come back at a later date, or you could do really more of an ischemia-driven revascularization of multivessel disease, so only if there's ischemia or positive stress test, symptomatic clinical ischemia or evidence on imaging of ischemia.

We actually have now amassed a huge amount of data in non-shock patients around how to manage non-culprit vessel disease in STEMI. What I'm showing you is the most recent study, the complete study, which was in patients with STEMI who are not in shock. The intervention was either complete revascularization or culprit-only PCI on the initial window around the presentation. Ultimately, what we saw was that complete revascularization was superior in terms of cardiovascular death or MI. This was borne out by multiple studies that preceded this, too, that suggested that complete revascularization in patients who present with STEMI with the multivessel disease is favorable to culprit-only approach.

That led to the ESC to upgrade this recommendation for complete revascularization initially from a class III now to an IIa recommendation in the most recent guidelines, in the 2017 guidelines.

Interestingly, the story is a little bit different in patients who present with ACS and shock. In the CULPRIT-SHOCK trial, they randomized 706 patients with cardiogenic shock due to AMI, and importantly, this included both STEMI and non-STEMI patients. These patients had multivessel disease. What the question was is: what is better? Immediate multivessel PCI at the time of primary PCI versus a culprit-only approach at the index catheterization, so at the time of primary PCI with the consideration of staged PCI later for an endpoint of all-cause mortality or the need for renal replacement therapy.

Interestingly, maybe surprising to many of us, the approach of culprit lesion-only revascularization at the time of primary PCI was superior to a multivessel PCI approach at the time of index catheterization. Keep in mind also that patients could go on to have stage interventions, but just not at the time of the initial presentation. Those patients could be staged in the culprit lesion-only PCI arm.

Interestingly also, as I mentioned, these were not just STEMI patients. These were NSTEMI patients, but there was a consistency of signal within the two diagnoses of NSTEMI and STEMI.

I would say that this is now the guidance, which is that in patients without shock you do pursue multivessel revascularization that can be immediately at the time of primary PCI, that can be staged within the window around the presentation with STEMI, so maybe in the first 30 days either prior to discharge or they can come back shortly after and complete the revascularization. In patients with shock, at the time of the first intervention, only revascularized, the culprit lesion, and you can potentially later on come back and stage a PCI. But at the time of intervention, just really get in, get out, and deal with the culprit. That's it.

Case: Let's come back to our patient. We have a 65-year-old female, renal failure, hypertension. She's had chest pain for two hours. She has ST elevations. Then she's also in shock. We said her blood pressure was low. She was tachycardic. She had AKI.

When we look at what her TIMI risk score, it gets many points. She has low blood pressure, high heart rate, she's in heart failure/shock, and she had a big anterior ST elevation. She ultimately gets a score of 8, which puts her at risk, a 30-day mortality risk of 27%. She's extremely high risk.

She undergoes angiography, emergent angiography. We see we have multiple lesions in her RCA. Then she has a cath of her left coronary system and we also see that she has what looks like an acutely thrombosed LAD. She undergoes revascularization of her LAD, but importantly, she's got very significant systolic dysfunction.

At the time of her intervention, she has a right heart catheterization and her cardiac index is only one, despite escalating doses of vasoactives. She's also with this LV dysfunction and shock, and has got progressive hypoxemia. She actually gets put on VA ECMO. She's pretty quickly decannulated, so after revascularization she improves fairly quickly. Her creatinine does bump up pretty significantly, but then down trends. So ultimately, this woman who resolves from her shock and who has pretty significant residual RCA disease and who sort of made it out of the woods with her shock, undergoes ultimately a staged RCA PCI. Then she gets discharged about three weeks into her course and does quite well.

Take homes. I think the very, very important thing in STEMI is to make the diagnosis rapidly and then to pursue revascularization as soon as possible. Primary PCI is preferred and certainly that's the case at a

PCI-capable center. The goal is to have that primary PCI done within 90 minutes or if you're going to be a bit stricter about it with the new ESC guidelines, within 60 minutes. In patients who have shock, you want to focus on the culprit lesion, but you can stage it later. In patients who don't have shock, we'll complete the revascularization. It doesn't have to be at the index cath. It can be later.

Then we'll talk at little bit about this in upcoming slides, but there is a slew of medical therapy that we want to put these patients on at the time of presentation, anticoagulation, antiplatelet therapy, lipid-lowering therapy. Then in patients with shock, obviously we're going to avoid antihypertensive and negative inotropes. Then as I mentioned we'll talk about this later, but you want to then pursue aggressive medical therapy to prevent recurrent events.

NSTE-ACS: Diagnosis, Risk Stratification, and Revascularization

DR. BOHULA: Now we'll tackle some of the same topics but from the angle of a non-ST elevation ACS. We'll talk about diagnosis, risk stratification, and revascularization and non-ST elevation acute coronary syndromes.

Again, we'll start with a case. We have a 65-year-old woman who looks very similar to our last case, type 1 diabetes, hypertension, hyperlipidemia, has CKD in the context of multiple renal transplants. She presents again to the ED with intermittent rest chest pain this time that started about two hours ago.

Her heart rate is in the 90s. Blood pressure is much better on this presentation, 110/80. She's saturating while on room air. Her creatinine is a little bit above baseline. She has an elevated troponin at 15 ng/L. Her LVL and A1c again are poorly controlled, 150 mg/dL and an A1c of 8%.

Her ECG this time shows normal sinus rhythm, normal access, no evidence of prior MI, and no evidence of ST elevations here.

Again, as we're thinking about diagnostics, we said that these patients in order to meet criteria for ACS for the clinical syndrome, have acute coronary disease or acute coronary syndrome, they should have ischemic discomfort, which she has. We then define them the branch point of whether or not there are ST elevations by ECG. She does not have that. Then we look for biochemical evidence of myocardial injury. As we said, she does have an elevated high-sensitivity troponin.

In this woman, we have evidence of acute myocardial injury. We have clinical evidence of ischemia with her symptoms. Likely, she's probably going to fall into that type 1 atherothrombotic plaque rupture or erosion category. We didn't hear anything about a particular insult that would be driving a type 2 MI.

NSTEMI is a lot harder to diagnose than STEMI, so this has really evolved over time, as we have better assays and specifically high-sensitivity cardiac troponin assays. What we've learned and the benefits we've got is that with greater sensitivity we're now able to rule out MI in some patients with a single blood draw. I'll show you what that looks like in the studies. We also have better precision. If we can exclude a small change in troponin, we can also rule out a proportion of patients by looking at the troponin over time and over a relatively short window, shorter than we used to be able to do it, on the order of one to three hours. That's really saying: do they have any elevation at all on presentation? Do they have much change over time? We're able to rule out a decent number of patients, as you'll see, with quite good test parameters.

This is a study--and I'll show a couple of others--where they looked at the approach of using a single troponin measurement to rule out MI. They used in this first study a threshold for a high-sensitivity troponin T of less than 3 ng/L. What they found was that it had an incredibly high sensitivity of 100% and a negative predictive value of 100%. That's really quite good.

Other studies that followed had very similar metrics, a similar approach using a single value to rule out MI, again, with high sensitivity, high negative predictive value.

There is a strategy that has been tested of one hour--that's not just a single rule-out, but a one-hour rule out using again high-sensitivity troponin T. In this initial study of 436 patients, what they did is they ruled patients out if their initial troponin, high-sensitivity troponin T, was less than 12 or the change from 0 hours to 1 hour was less than 3. Then those patients would be ruled out. That actually was a huge number of the patients. It was 60% of patients and the sensitivity there was 100% and negative predictive value 100%. Very good with the strategy of ruling out 60% of patients and allowing them to go home.

Patients who ruled in either had a high value at presentation at zero hours of 52 or a significant delta between 0 and 1 hour of at least 5. Those patients were ruled in; that was 17% of the patient population, and that actually had a pretty good specificity of 90% and positive predictive value of 84%. Again, very good test characteristics. Then the 23% of patients that didn't fall into either one of those categories were then in the observation zone.

There was a subsequent study, a validation study with a larger number of patients. Really they had the similar findings, a similar proportion of patients who fell into each of the buckets, the rule-out, the rule-in, the observation, and also again very good test characteristics in terms of negative predictive value for ruling out, positive predictive value for ruling in, and then ultimately being able to identify those who were in the know in the observation zone.

This has made its way now into the guidelines. These are the ESC 2020 non-ST elevation ACS guidelines. It's a complicated chart, but essentially what it is, is using an approach similar to what I described in those other studies, where you have a patient who comes in, they have a clinical syndrome that's concerning for MI, they do not have ST elevations. Obviously, that puts you down a different diagnostic pathway. Here then in the absence of ST elevations, then in the absence of instability to you get blood sampling at zero time, at zero hours. Again, pretty quickly draw a second one at one hour. We look to see if somebody has a very low troponin, where you may be able to rule them out. If they have high troponin, you rule them in.

If they fall into neither of those categories, then we look at the delta at one hour. Again, you can pull some people out in terms of ruling them out if there's no significance, it's lower at first, and no significant. They get ruled out. Or if they have a big enough delta, then they rule in. All those others fall into a category we then check a three-hour troponin and again, if there's a significant change from one to three hours, they rule in. If not, then you can observe them.

This is sort of a helpful triage. Much of this can be done in the ED, given how long it takes for these things to be drawn and for the turnaround time, where you can decide whether you might rule somebody out in the ED, whether they definitely rule them in, or put them into the observation category.

This gives you just another way of depicting that to think about again I have a patient who I suspect has non-ST elevation ACS. I'm going to get a baseline zero-hour and one-hour troponin and I'm looking for a

value that is either very low at time zero where I can rule them out or it's low and there's very little change over time where I can rule them out or where on presentation initially it's high or the delta is high and then they're ruling in or those who fall into the middle category and then get a three-hour troponin test and then you can decide from there, depending on what the value is, how you're going to observe them and what additional testing you're going to do.

BWH Pathway: This has been operationalized, similar structure in terms of rule-in, rule-out at the Brigham, where I care for patients. Again, this will look very, very similar, but we have a patient who arrives where you worry that they are having some sort of ACS, but they do not have ST elevations. We get a troponin at zero hours and one hour. Again, we have specific thresholds for the initial value and for the delta that rule them in or rule them out. Then we have patients who fall into the observation at the Brigham. Then we determine what their heart score is, which is the likelihood that this patient is at risk for having ACS. In that situation then, we determine triage in terms of whether they will stay in the ED and be observed further, maybe have some assessment of ischemia or whether they might be admitted to medicine. Those rule-in patients get admitted to cardiology at the Brigham and then obviously, rule-out go home.

Management Strategy in NSTE-ACS: Then we move from diagnosis to management strategy. This also is certainly more complicated than the scenario in ST elevation MI. We obviously manage non-ST elevation with initial medical therapy, but many patients we can consider for an invasive strategy. Classic invasive strategy that we think about is an angiography, generally speaking within 48 hours with intervention if the anatomy is favorable. There is another approach, which would be a conservative management, which is selective angiography, either in people who have high-risk disease with provocative maneuvers like stress test, so they can go on for invasive angiography, or they have some other recurrent symptoms that push your hand into doing invasive strategy. Otherwise, patients who fall into the low-risk bucket avoid angiography all together and just get treated medically.

Benefit of INV vs CONS Strategy: Which is better? Well, there have been now a number of different studies looking at the potential benefits of the invasive strategy versus a conservative strategy. Generally speaking, the data fall in favor of an invasive strategy. Specifically, this meta-analysis is looking at rates of death, MI, early hospitalization in patients who are presenting with non-ST elevation. The benefit was on the order of 20% and I think it's particularly favorable for recurrent ACS events.

Troponin Treatment Interaction: I think there's a subset of patients where this is even more true when we look at the interaction of invasive versus conservative and patient characteristics. That's when patients are troponin positive. So when they have a non-ST elevation MI as opposed to unstable angina, those patients really do seem to do better with invasive management. The endpoint that's being shown here is death, MI, or ACS at 30 days. Those with an elevated troponin definitely seem to benefit from invasive strategy, as opposed to conservative strategy with selective angiography.

TIMACS : Then another question is how quickly we should pursue coronary angiography and intervention. This is a study of about 3,000 non-ST elevation ACS patients who were either cast early within 24 hours or sometime after 36 hours, where the median was about 50 hours. What you can see is that when you look at a couple of different endpoints, when you look at death, MI, or stroke or death, MI, or refractory

ischemia, there was benefit to early revascularization or early catheterization I should say over delayed catheterization. That was particularly true in subsets of high-risk individuals.

The ones that were most notable were those who had elevations in their cardiac biomarkers and those with particularly high risk score. I mentioned before the GRACE risk score, and oftentimes we use that to think about who we might intervene on earlier. I mentioned that threshold of 140 for the GRACE risk score. So those who have a GRACE risk score of over 140 tended to have more benefit from early catheterization and intervention if appropriate.

2014 ACC/AHA NSTEACS Guidelines: This is the 2014 ACC/AHA guidelines, which outline a strategy for when and who to cath. Those who are unstable, so refractory angina, significant heart failure, recurrent angina with minimal activity were at risk. The notion is that they should have immediate catheterization and intervention as appropriate. Those who were high risk, which is that population that I mentioned before in that subgroup analysis are those who have a troponin that is changing, significantly elevated, elevated GRACE risk score, or who have dynamic EKG changes.

The best recommendation is for early invasive within 24 hours. You can consider a little bit more delayed invasive approach in those who have significant risk, but aren't quite as high risk as some of the other categories that I mentioned. Then for those who are very, very low risk, you can consider more of an ischemia-driven approach, troponin negative, very low GRACE risk score, or where there's just a patient preference for ischemia guide and they're otherwise low risk.

2020 ESC NSTEACS Guidelines: The 2020 ESC non-ST elevation ACS guidelines are quite similar. The recommendation is to collect all the information, look at the ECG, the vital signs, physical exam, calculate the GRACE risk score, check troponins, and then based on really many of the same recommendations, there's a group who has a recommendation for immediate invasive. Those are the hemodynamically stable, cardiogenic shock patients with refractory symptoms, life-threatening arrhythmias, those who have mechanical complications, or are in heart failure or really significant ECG changes. Early invasive are those with dynamic changes who have an elevated risk score. You can consider those who had resuscitated cardiac arrest without ST elevations or cardiogenic shock. I think there are some trial data that maybe put that specific recommendation into question. Otherwise, you can take a more selectively-invasive approach for other patients.

Case: Coming back to our case, our 65-year-old woman, diabetes, CKD--in this case, much more of a chronic presentation, just a little bit of acute on top of it--she's got hypertension, she's got rest chest pain for a couple of hours. Actually, her ECG we said didn't have ST elevations, maybe some nonspecific ST changes, but definitely not ST elevations. She has also a couple of weeks of exertional chest pain. She gets a troponin that went from 15 up to 25 at one hour, so there's a delta of 10. She's ruled in at this point for NSTEMI. We start aspirin, heparin, beta-blocker, high-dose statin. Her GRACE risk score is 111. She ultimately has invasive strategy in the next 24 to 48 hours.

She ends up having a single thrombotic RCA lesion. She gets a drug-eluting stent. She has heparin and cangrelor during her left heart cath. She gets ticagrelor later and we'll talk about the data for that. Then ultimately she's continued on aspirin and statin in addition to the ticagrelor. She gets continued on her

home ACE and started on MRA. She has an echo that shows a low normal EF and then she has additional secondary preventative therapy that's added on.

Take Homes: The take-homes for this particular section are that making a diagnosis of non-ST elevation acute coronary syndrome can be challenging and it definitely requires integration of the clinical history, so looking for ischemic symptoms and documentation of dynamic cardiac injury. Also, it's quite helpful to use the rule-in/rule-out algorithms with a high-sensitivity troponin to assist with diagnosis and triage. Then you make the decision regarding what your strategy is going to be, invasive versus conservative, based on risk stratification.

Other Management (Medical Therapy)

DR. BOHULA: Here now we'll delve into other medical management or other medical therapy of our ACS patients. There are many, many different categories that we think about, but up front we oftentimes are thinking quite heavily about what anticoagulants we're going to use and what the antiplatelet therapies are that we should be giving and when we should be giving them.

Anticoagulants Acutely: In terms of anticoagulants, the most commonly used is unfractionated heparin. It's fast on, fast off, it's reversible with protamine, and it's weight based. It is sometimes challenging to do. The pharmacodynamics can be unpredictable and it requires assessment and measurement of the level of anticoagulation following a PTT. We do know that in studies comparing it to no anticoagulation there is a benefit in terms of a reduction in death and MI.

An alternative is low molecular weight heparin. It's much more predictable and not as easily reversed. It does have a favorable profile in terms of recurrent events, death, MI. Compared to unfractionated heparin, it may increase bleeding. Because it's not as reversible, I think generally speaking it's probably better considered in conservatively-managed patients.

Then bivalirudin is another option fast on, fast off. In comparison in a meta-analysis with heparin, there's an increased signal for MACE and also an increased signal for stent thrombosis with bivalirudin. Compared to heparin, lower bleeding rates. That's especially if it's not used in combination with the IIb/IIIa inhibitor. I think you can consider this in invasively-managed patients, especially if they're high risk for bleeding because of this lower bleeding signal, although I would say that generally speaking most are using unfractionated heparin. All right, so those are the anticoagulants.

Antiplatelet therapies. There is a whole array of things to consider, aspirin which target the thromboxane pathway. We have ADP receptor blockers, which is the P2Y12 inhibition. The typical ones in this class are clopidogrel, prasugrel, ticagrelor, and now cangrelor. We won't talk much about this, but there's another class of agents, the PAR-1 antagonists. That specifically is vorapaxar. Then also we won't spend much time on this, but there also is the category of the IIb/IIIa inhibitors.

ASA: Is Dosing Still Controversial: Aspirin is obviously a cornerstone of management in our ACS patients. The question is how we should dose it. We have data from the current OASIS-7 study published back in 2010 that inpatients who were then randomized to either low-dose aspirin 81 to 100 compared to 300 to 325, that there was no difference in death, MI, or stroke. Also, no difference in major bleeding, although in the subcategory of GI bleeding, those on higher-dose aspirin had higher risk. Really I think the conclusion is outside of the higher loading dose, a low dose of aspirin for maintenance is absolutely

sufficient. Otherwise, you're really not getting the benefit in terms of prevention of recurrent ischemic events, and you're probably increasing the risk of GI bleeding.

ADAPTABLE Trial: There was a more recent study in 2021 with Skylar Jones in the ADAPTABLE trial looking at patients with ASCVD, dosing them with either 81 or 325. There was a decent amount of crossover in the 325 to 81, but nevertheless, we didn't see a difference between the doses in terms of recurrent ischemic events, which also supports the notion that lower dose is absolutely sufficient for secondary prevention in these patients.

ACC/AHA Guideline Recommendations: The recommendations are to give non-enteric coated aspirin chewable 162 to 325 in patients with non-ST elevation ACS, but then a maintenance dose of 81 mg, and that's a level one recommendation.

P2Y12 Inhibitor Basic Pharmacology: Now we'll dive a little bit into the various options for ADP receptor antagonists or P2Y12 inhibitor agents. We'll talk about actually four, but what I'm showing you here are the three oral versions: clopidogrel, which is a thienopyridine, irreversible. It's a prodrug, onset of two to four hours. Pretty long half-life, so the duration of effect is 3 to 10 days. Prasugrel is another thienopyridine, irreversible. It is a prodrug, but this is not impacted by hepatic metabolism. Onset of action is quite quick, 30 minutes. Duration effect is prolonged, which means then that you have to withhold it for a decent amount of time before major surgery. Then finally, ticagrelor, which is not a thienopyridine. It's reversible and it's not a prodrug; it's an active drug. Onset of action is quite quick. Duration of effect is intermediate here, compared to the two other agents.

Clopidogrel in UA/NSTEMI: The first study we'll talk about is the CURE trial, which was patients with non-ST elevation MI or unstable angina, generally speaking, managed conservatively. Looked at a regimen of clopidogrel versus placebo and what we saw was there was a 20% reduction in death, MI, or stroke with the addition of clopidogrel, which is really the notion now that we have of treating non-ST elevation patients with a second antiplatelet therapy, even if conservatively managed.

CURE: Timing of Benefit: Importantly, the benefit was seen early and later with the addition of clopidogrel as compared to placebo in these non-ST elevation ACS patients. In terms of the safety profile, there is an increase in both major bleeding and minor bleeding with the second antiplatelet agent. That's obviously on top of aspirin. Adding a second agent does increase bleeding. I think this is very, very much a consistent message that we'll see in all the studies, which is more potent antiplatelet therapy derives more bleeding.

Clopidogrel Prodrug - Active Metabolites: Talk a little bit about clopidogrel metabolism. It's a prodrug. It's metabolized by the hepatic system and we'll talk a minute about the CYP2C19, which is probably the most important enzyme involved in the metabolism of clopidogrel. Because it's a prodrug, we do give a loading dose and it does take a little bit of time to reach a steady state.

Meta-Analysis of Clopidogrel Pretreatment: There was a question out there about whether there's a benefit, given that it's a prodrug of pretreatment. This is looking at the endpoint, so meta-analysis looking at the endpoint of recurrent MI before PCI and the data here support pretreatment with clopidogrel and also for events after PCI, so CV death or MI. Again, the data would support pretreatment with clopidogrel.

Interpatient Variability to Clopidogrel: Importantly, I mention that this is a drug that is activated through hepatic metabolism. Importantly, we see that there's a lot of variability in the effect to clopidogrel in terms of platelet aggregation after a dose.

CYP2C19 and Metabolism of Clopidogrel: There is this category of resistance. Interestingly, one of my colleagues Jess Mega [phonetic], looked at the genetics of this. As I mentioned, the allele that seems most important in the enzyme is CYP2C19. Those who have an alteration that leads to decreased function of the CYP2C19, we see less of a response to clopidogrel.

CYP2C19 & Clinical Outcomes: Importantly, that has important clinical outcomes, so this is an analysis also done by Jess Mega where she looked at patients who had ACS who had planned PCI and then were treated with clopidogrel and subclassified based on their genetics and whether they have the CYP2C19 reduced function allele or whether they did not. Patients who had this reduced function allele and who were given clopidogrel tended to have higher rates of CV death, MI, or stroke, and higher rates of stent thrombosis, suggesting that these patients were essentially resistant to clopidogrel and had worse outcomes. This has led to a black box warning with clopidogrel and the notion that if somebody is known to be a poor metabolizer, that you should consider alternative antiplatelet agents beyond clopidogrel.

Antiplatelet Therapies: We'll talk a little bit about some of the other antiplatelet agents beyond clopidogrel.

Clopidogrel vs Prasugrel: We looked at patients who we talked about non-responders and responders to clopidogrel. Responders are those who have greater than 25% platelet inhibition at 4 and 24 hours. The non-responders are those in blue and the responders are those in yellow. The Y-axis is the degree of inhibition of platelet aggregation, so higher on the Y-axis means more response to antiplatelet therapy. In patients who were then treated with prasugrel, we saw that basically everybody had inhibition of platelet aggregation. Even those who were clopidogrel responders had more inhibition of platelet aggregation with prasugrel. But where you really saw a huge delta was in those who were complete non-responders who got prasugrel, where there was a very big difference between the two different therapies.

TRITON-TIMI 38 Trial: This was studied in the TRITON study in patients with ACS undergoing PCI, a comparison of clopidogrel versus prasugrel for the composite death of CV death, MI, or stroke. There was a 19% reduction with the addition of prasugrel as compared to clopidogrel.

Timing of Benefit (Landmark Analysis): This was true in the early period and then also in the later period, so there was a benefit in the first couple of days and then beyond that as well when you do a landmark analysis.

Bleeding with Prasugrel: As I mentioned, prasugrel as we saw from the platelet inhibition studies, is a more potent antiplatelet therapy. So not surprisingly there is more bleeding, more TIMI major bleeding, more life-threatening bleeding, and more fatal bleeding with prasugrel. More potent antiplatelet therapy leads to more bleeding.

Who Shouldn't Get Prasugrel: The authors, Steve Wiviott and colleagues, were able to parse out who are particularly high-risk patients for bleeding. That included those who had a prior stroke, those who were elderly, greater than 75, and those who had low body weight. Those are people whom I would not recommend use of prasugrel in.

There was also a study looking at the benefit of pretreatment with prasugrel. No difference in terms of ischemic endpoints, but more bleeding with pretreatment. So that's not a recommendation to pretreat prior to PCI.

TRILOGY-ACS: No Benefit for Prasugrel in Medially Managed Patients Without PCI : Then there was a study, TRILOGY-ACS, that looked at medically managed patients who did not have PCI. There was no significant signal for the reduction in recurrent cardiovascular events with prasugrel versus clopidogrel. Prasugrel was generally not used for patients who were managed conservatively.

Ticagrelor: An Oral Reversible p2Y12 Antagonist: We'll talk a little bit about ticagrelor, which as I mentioned is the oral reversible P2Y12 antagonist, which is not a prodrug and which also similar to what we saw for prasugrel tends to be more potent of an antiplatelet agent than clopidogrel.

Ticagrelor Pharmacodynamics: This is just demonstrating that if you look at the degree of inhibition of platelet aggregation, greater inhibition is larger values on the Y-axis. What you see is ticagrelor comes on more quickly than clopidogrel, gives you more platelet inhibition, and actually also comes off more quickly than clopidogrel. It's just a more rapid onset, more potent antiplatelet than clopidogrel.

PLATO Trial Results: This was studied in the PLATO study ACS, both STEMI and non-STEMI comparison of clopidogrel versus ticagrelor for a composite MACE endpoint, and there was a significant reduction with the use of ticagrelor over clopidogrel.

Mortality Benefit with Ticagrelor: That was true for individual components of MI and also for mortality, and cardiovascular death.

Non-CABG and CABG-related Major Bleeding: Again, it's a more potent antiplatelet therapy. There was more bleeding with ticagrelor as compared to clopidogrel.

Ticagrelor Side Effects: Then another thing to know is that ticagrelor dose had side effects. It can cause dyspnea. You can see there in about 14% of patients they complained of dyspnea with it. There are some side effects, but it doesn't very frequently lead to discontinuation.

Prasugrel vs Ticagrelor: Do We Believe the Head-to-Head Data?: Then there was more recently an open-label study of about 4,000 patients with ACS undergoing planned angiography who were randomized in an open-label fashion to ticagrelor versus prasugrel. What this study, the ISAR REACT 5, suggested was that maybe prasugrel was actually superior to ticagrelor in this open-label study for the composite of MACE. Also, there was no difference in bleeding. Again, this is open to interpretation, but there may be some benefit of prasugrel over ticagrelor.

Cangrelor: Intravenous P2Y12 Inhibitor: Then finally, the final antiplatelet, the final P2Y12 inhibitor that we have, the most recent that has come through development, is an IV version called cangrelor. Very fast onset, very fast offset. It was studied in a trial called CHAMPION PHOENIX, where they looked at this agent followed by clopidogrel versus clopidogrel alone. There was a reduction in ischemic events or atherothrombotic events and no difference in bleeding. It's a nice option.

Switching from Cangrelor to Oral P2Y12 Inhibitor: If you're going to use this, which I have to say in the practice that I see now used very, very commonly in patients with ACS in the cath lab, they received cangrelor and eventually are transitioned to one of these agents. Generally speaking, the way that you do that is as soon as you stop the cangrelor, you give the loading dose of the oral antiplatelet.

2014 ACC/AHA NSTEACS Guidelines: P2y12 Inhibitors: The summary here from the 2014 guidelines is that if you're going to use clopidogrel, give a 300-loading dose if it's prior to PCI, 600 during PCI, and then follow that with 75 mg. For people who are only undergoing PCIs and not conservatively managed or medically managed, you can give prasugrel 60 mg loading dose, followed by 10 mg daily. Then ticagrelor, which you can use either in people who are medically managed or who get PCI, a loading dose of 180 mg, followed by 90 b.i.d.

There is a recommendation that it's reasonable to consider ticagrelor or prasugrel over clopidogrel and again, to not use prasugrel in patients who've had a prior stroke or TIA.

Post-Discharge Antiplatelet Therapy: How Long and How Strong?

DR. BOHULA: Moving on to the next topic, which is antiplatelet therapy: how long and how strong. Then we'll touch on some other medical therapy that we use for our patients.

Dual Antiplatelet Therapy (DAPT) Study Design: This has been a huge discussion about obviously there's no free lunch with antiplatelet therapy. There's always a bleeding signal whenever you give additional antiplatelet therapy. The question is really how long we should be using these therapies. The DAPT trial looked to address this. The design is a little bit complicated. It's patients who had a PCI, either for stable coronary disease or for ACS. They were then on open-label thienopyridine plus aspirin for 12 months. If they didn't not have any recurrent ischemic event or significant bleeding, then they were eligible for randomization after 12 months and they could then be randomized either to dropping the thienopyridine and just being on aspirin or continuing the thienopyridine plus aspirin and then continuing that on until 30 months, at which point then they stopped the thienopyridine and were observed for a three-month period after that.

Treatment Effects in ACS Patients: The primary findings are shown here, which is that there was a reduction in major adverse cardiovascular events with extended dual antiplatelet therapy out for 30 months. That included a reduction in cardiovascular death, MI, stroke, stent thrombosis. There was an increase, again not surprisingly, with additional antiplatelet duration for more major bleeding in these patients.

Trial Design: Another study that looks at a more stable population--these patients of the PEGASUS TIMI 54 study--which were patients who had a history of MI in the one to three years preceding. They were otherwise stable and had some risk factor for recurrent events, which are listed there in the box. These patients were then randomized in a 1:1:1 fashion to either high-dose ticagrelor 90 b.i.d.--what we now consider our standard dose of 60 mg b.i.d.--or placebo. They were followed for an extended period of time for primary efficacy endpoint of MACE and primary bleeding of TIMI major bleeding.

Key Efficacy and Safety Outcomes: What we see is placebo is in green and then high-dose ticagrelor in blue and then the 60 mg ticagrelor in red. There is a significant reduction in MACE, a trend towards lower rates of cardiovascular death, a reduction in MI, a reduction in stroke, again, with a higher rate of TIMI major bleeding.

Summary: The take-home was that adding ticagrelor to low-dose aspirin in stable patients reduced the risk of major adverse cardiovascular events. The benefit was really consistent for fatal and non-fatal events over the duration of the treatment. I didn't show you, but it was true and consistent in major clinical subgroups. But there was an increased risk of TIMI major bleeding, but not fatal bleeding or ICH. Because the benefit was somewhere between the two doses of ticagrelor but the bleeding looked a little bit less with the lower dose, that was really what won there, was the 60 mg daily.

Prolonged Intensive antiplatelet Therapy & Mortality in Second Degree Prevention :This is a meta-analysis now looking at prolonged intensive antiplatelet therapy for secondary prevention, including the DAPT study, including PEGASUS, including TRA2P, which was a study of vorapaxar, that PAR-1 antagonist. What the meta-analysis suggested is that there is an 11% reduction in all-cause mortality, a 16.5% reduction in CV mortality, and no difference in noncardiovascular mortality for prolonged intensive antiplatelet therapy.

COMPASS Design: In the right patient, in the lower bleeding risk patient, there is a benefit to prolonged therapy. Very briefly I'll touch on the COMPASS study, which was a study in stable CAD or PAD patients looking a regimen of either a low-dose aspirin, low-dose rivaroxaban, or very low-dose rivaroxaban plus aspirin. COMPASS Trial: Primary Efficacy Outcome: What the study showed was that there was a significant reduction in the recurrent cardiovascular events in these patients who are treated with very low-dose rivaroxaban plus aspirin as compared to aspirin alone, a 24% reduction there. COMPASS: Conclusions: The conclusions from the author were that this regimen of very low-dose rivaroxaban plus aspirin reduces MACE. I didn't show you the data, but it does increase major bleeding and ultimately, that clinical benefit supported the use of the combination of rivaroxaban plus aspirin. There was no significant benefit of that regimen of rivaroxaban alone.

Long-Term Antithrombotics - No Afib: In the absence of atrial fibrillation, these are the most recent guidelines from the European Society of Cardiology, which is that in patients who have non-ST elevation ACS in the course of their PCI you can use any of the agents for anticoagulation that we discussed, unfractionated heparin most commonly used, enoxaparin, or bivalirudin. Then depending on their bleeding risk, determine how long and how aggressively you treat them with antiplatelet therapy. Patients who are very high risk for bleeding are treated for a short duration with dual antiplatelet and then ultimately maybe just with a thienopyridine, specifically Plavix afterwards, so dropping the aspirin. Those are high risk and have a little bit longer duration of dual antiplatelet. Then drop one of the agents and here it suggests dropping the thienopyridine, but I think I've seen people also just drop the aspirin and leave the thienopyridine on. Those who are pretty low risk, you can consider extended-duration dual antiplatelet, which in the green is shown out there to 12 months, and that can be really any of the P2Y12 inhibitors. Then you can also consider an extended duration of dual antiplatelet therapy or even antiplatelet plus low-dose anticoagulant like rivaroxaban. You're more likely to do that if somebody is at a higher ischemic risk. It looks quite complicated, but I think in concept it's actually fairly simple.

ACE-I/ARB: A few other take-homes. There are obviously other therapies, and I'm not going to go into the data here, but just to quickly show you the recommendations in these patients who are post ACS there is a class I indication for ACE inhibition in patients who have evidence of heart failure, LV dysfunction. Also, for patients with STEMI who then have diabetes or anterior infarct. Similarly, the same patients if they can't tolerate ACE inhibitors, should be treated with an angiotensin receptor blocker.

Aldosterone Antagonists: Class I indication for aldosterone antagonists are MRA, as long as they don't have significant renal insufficiency or hyperkalemia and they're on therapeutic doses of an ACE inhibitor, if they have low EF, if they have symptomatic heart failure or diabetes.

Beta-Blockers: Then beta-blockers class I recommendation for those who have heart failure or low EF, and class IIa for continued oral treatment with beta-blockers during the hospital stay and then continued afterward, as long as there is no contraindication.

A Quarter of A Century of Treating LDL-C: Then finally, lipid-lowering therapy. We have tons and tons of data out there. Honestly, at first, we realized with the earlier studies that high LDL is bad. As we continued to try to drive the LDL down lower, the message became more and more refined, which is that lower is better. Then with IMPROVE-IT, we learned that it even lowers even better. Then with these very potent agents that we now have, the PCSK9 inhibitors, we learned that lowest is the best. So this has really been a long time coming, where now I think we understand that LDL is a toxin, and the less of it we have, the better.

Efficacy of LDL-C Lowering Even When Starting LDL-C ≤70 mg/dL (1.8 mmol/L): This is a meta-analysis done by Mark Sabatine, looking at even those people who start with very low LDL to less than 70 mg/dL, if we drive it down further, they have benefit in terms of reduction in major vascular events. It's really quite safe and also efficacious to drive the LDL down very low.

Cholesterol Guidelines: This has definitely been incorporated into the guidelines, the most aggressive of which is the ESC, the 2019 where they now have thresholds for those patients who have ASCVD, which are ACS patients, to have an LDL of 55 mg/dL or lower in those who are very, very high risk with recurrent ASCVD events. You can try to drive that LDL down to less than 40 mg/dL.

Cholesterol Treatment Algorithm (ESC 2019): The algorithms are similar between the different organizations, the AHA and also ESC, where it's really a stepwise approach that you first use high-potency statins, try to get the LDL down to the goal, which again, there are some subtle differences. The goals are different between AHA and ACC and then ESC. The goals are lower for ESC, a little bit higher for ACC/AHA. But nevertheless, a high-dose statin to try to get to the goal. If you're not at goal, ezetimibe. If you still haven't reached your goal, then reach for a PCSK9 inhibitor.

SGLT-2i and GLP-1-RA – MACE: I won't go into this. I suspect you will have talks specifically on these agents, but we also now have a couple of other cardioprotective agents that were initially designed as anti glycemic therapies, but we realized have to benefit in preventing recurrent cardiovascular events. Those are the GLP-1 receptor agonists and SGLT-2 inhibitors. This has made its way into the diabetes treatment guidelines and now even into the cardiovascular guidelines.

Management of Diabetes in Reports with ASCVD: If you have a patient, for example, who has diabetes, who has known ASCVD, then consider a GLP-1 receptor agonist. If they have heart failure, or CKD, consider an SGLT-2 inhibitor and probably consider both in both. Again, these are good agents, which offer cardiac protection in terms of atherothrombotic events, heart failure, and progressive renal dysfunction.

Case Conclusion: We'll come to the very end of our case presentation. This woman whom we have now seen a couple of times, 65, ACS, underwent PCI and has diabetes, CKD, hypertension, and hyperlipidemia. She doesn't have clinical heart failure. I think then as we've just gone through some of the secondary preventative therapies, what we should do for her is we said she wasn't particularly high risk for bleeding,

so she's on aspirin and we put her on potent antiplatelet therapy with ticagrelor. I think it's reasonable to consider continue that for at least 12 months. She has been put on a beta blocker and ACE and MRA to treat her hypertension and for post-MI risk reduction. We've put her on high-dose atorvastatin and ezetimibe and we actually got her LDL down to below the ACC/AHA guidelines, not below the ESC guidelines. You could certainly argue for being even more aggressive in a woman like this, maybe a PCSK9 inhibitor. Then she has diabetes and she has CKD, so we've added the SGLT-2 inhibitor. She has ASCVD and diabetes, so now we've added the GLP-1 receptor agonist.

Summary: In summary, the diagnosis of ACS can be complex. It's important to realize that ACS is not solely a positive troponin. Then for diagnosis for STEMI you need to rely on the clinical picture plus dominantly the ECG. For NSTEMI, you rely on the clinical picture plus troponin and the rule-in/rule-out algorithms. Then once the diagnosis is made, it's important to risk-stratify patients to determine how you're going to revascularize them. Then very, very importantly, you need to optimize them acutely, but also chronically. As I've shown you, we have many therapies now that can really benefit a patient in terms of reduction in residual risk for recurrent events. That really is our charge, is to continue to optimize our patients to prevent future events.

With that, thanks so much for your attention and I hope you were able to take away some important summative points from this talk.