Coronary Artery Disease

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DR. DEEPAK BHATT: Hello. I'm Dr. Deepak Bhatt from Brigham and Women's Hospital and Harvard Medical School. It's really a pleasure for me to speak to you about coronary artery disease of course in the context of cardiometabolic health. This is an extremely important topic, very common, something that really everyone involved in the cardiometabolic space needs to know about. Before I get started, these are my disclosures which include several different relationships with industry. I may also during the course of my talks present data that are off-label and may also discuss investigation uses of various drugs and devices.

ACS: Initial Evaluation, Diagnosis, and Treatment

Let me go ahead now and start with a brief discussion of acute coronary syndrome (ACS), initial evaluation, diagnosis, and treatment. Other speakers in this area will go into more detail with respect to ACS and some of the data (some of the trials); I want to provide a rather high-level overview of ACS, what it is and what really you need to think about conceptually when dealing with patients with acute coronary syndrome.

Epidemiology & Burden of Disease

Let me first just start with some basics as far as epidemiology and burden of disease as far as coronary artery disease goes. To step back, it's a leading cause of mortality and loss of disability-adjusted life years worldwide with nearly 7 million deaths and 129 million disability adjusted life years annually. It's really a huge impact both in terms of mortality and morbidity. Just to focus on the U.S. for a second, an estimated 20.1 million adults aged 20 and older have coronary artery disease, and someone has a myocardial infarction (MI) approximately every 40 seconds. We're not talking about rare diseases here. We're talking about common ones worldwide. The mortality and incidence do differ by country, and in the most recent decades, has fallen in high-income countries; but a large portion of this burden falls on low- and middle-income countries and even in high-income countries. There's a lot of heterogeneity of reports recently about the rates of for example MI going up in rural areas of the United States as opposed to urban areas. And with the COVID pandemic, who knows exactly where things stand. In fact, there are a lot of patients coming in with coronary artery disease and its complications. My own sense is that coronary artery disease, and all its manifestations in the foreseeable future, are here to stay.

Here's some prevalence data as far as coronary artery disease by age and sex in the US in the 2015-2018 era showing, I think, what everybody knows that the prevalence of coronary artery disease goes up with age. I'm just showing what it is in men and in women. There is a lot of CHD and in particular in older age groups. It's very, very common.

Something I want to make sure you're aware of are the relatively recent American College of Cardiology and American Heart Association Chest Pain Guidelines. These came out at the American Heart Association annual meeting in 2021. I think they're really important. I think it's something that everyone involved in the care of patients with coronary artery disease needs to know about whether we're talking about emergent or urgent types of patients, acute coronary syndrome type patients or more stable angina type patients or the asymptomatic patients. Regardless of where our patient might fall on the CD continuum, these guidelines are really useful. But in particular for patients who are having chest pain and there are some perils and they're summarized in this nice color-coded graph that's directly taken from the official guideline set.

Each of the different letters here in CHEST PAIN stands for something important that you ought to know about. I'll just start with the first and/or to the last and do it by first to last. I don't mean in terms of importance just in terms of where it fits here on the acronym. For the CHEST or the C that refers to chest pain. It means more than pain in the chest. That's the first point here. It's an important one. Of course we're always talking about chest pain but a lot of patients are describing, hey, I have pain in my chest. They might be using words like pressure in the chest, heaviness in the chest, or symptoms that aren't even in the chest, so it's really important to know about that.

High sensitivity to troponins are in, that's really what your hospital should be using worldwide. Really this is now the evolving standard of care really in most regions of the world that use this standard of care. Early care is important. Seek early care for acute symptoms. Share the decision-making. That means patient input, some things are kind of obvious. If somebody comes in with a ST elevation myocardial infarction, in general if you're in a region in the world where you can get them to the cath lab quickly, that's what you ought to do. But on the other hand, patients with unstable angina, troponins are negative, there's no dynamic ECG changes, they're pain free now - imaging, should you go right to the cath lab, there the patient references really do matter. If they really hate the invasive procedures well, then obviously go with a noninvasive test. If they've been coming in with chest pain to the emergency department every couple of months, that might make sense to go right to that cardiac catheterization to provide a more definitive answer, so important to share decision-making with the patients in situations like that. But again take it into an extreme if someone is coming in STEMI and cardiogenic shock, that's not the time to talk about medical management. That's the time to get them to the cath lab or in contraindications obviously.

The T is for testing not routinely needed in low-risk patients. This is an attempt to stop doing testing that's really of marginal value that's being done, maybe just to provide a little bit of reassurance in the patient, or maybe for perceived medical-legal coverage. But the reality is that this type of low-risk testing is just hurting the system and escalating care costs and not improving actual care to patients. If they're low risk in general you don't need to test those patients.

The P refers to pathways, so use clinical-decision pathways. A refers to accompanying symptoms. Women may be more likely to present with accompanying symptoms, so that is very important to realize. I'll come back to that point in a second. Identify patients that are most likely to benefit from further testing, that sort of ties into T, don't test the not really low risk patients, but identify the ones that do need further testing. It's not that testing is not that important, obviously this.

The N is to remind us that noncardiac is in, atypical is out that ties together with the A here the accompanying symptoms. The most common symptom that's described is chest discomfort of some sort with this chest pain, pressure, heaviness, something like that. But a proportion of patients, I mean and also men describe something else and it might even leave with this something else that's a little bit more common in women than men. And they say, "Oh, yeah, I have that shortness of breath," and they're also having chest pain but it might lead with shortness of breath, so it's important to realize the different types of symptoms that can occur. But usually chest discomfort is part of it even if that's not what the patient is leading it or they're emphasizing. And atypical sign meaning that it might not be noncardiac, well, just call it non-cardiac pain if you don't really think it's cardiac as supposed to atypical which sometimes then leads to uncertain pathways of under treatment or sort of just code for saying, "Hey, we think this is bogus chest pain, but are we going to get this patient out the emergency room?" Instead of

just saying,, “Yeah, you don’t think it’s cardiac chest pain but you think it’s something else that warrants further workup or it doesn’t warrant further workup or just warrants observation and time to see what happens.” Maybe time over hours, weeks, months, so at any rate, important to realize that aspect of care. And then assessment for disruption risk assessment should be used at many emergency departments and incorporated such systems and once they it probably have to. Alright. That’s really important as far as the slides go because there’s a ton of important information encapsulated here.

Symptoms and Signs: Chest Pain

Other things from the same guidelines - obviously, you want to elicit some things and signs of chest pain and it might be a described chest discomfort or pressure, squeezing, gripping, heaviness, tightness, exertional, stress-related, retrosternal these are all potential descriptors. When present, it’s a higher probability of ischemia, left-sided, dull aching, less so with stabbing, less so with light-sided tearing, ripping and burning, much less so with sharp fleeting, shifting, positional. The probability of ischemia is somewhat influenced by these symptoms. You want to elicit a careful history.

Angina Severity: Canadian Cardiovascular Society

Now, in terms of angina severity, it is important to know about that. It is Grade 1, 2, 3, and 4 angina per the Canadian Cardiovascular Society. Grade 1 means angina only with strenuous exertion, so during strenuous, rapid or prolonged activity like walking or stair climbing. Grade 2 is angina with moderate exertion, so there’s some limitation of activities when performed rapidly, post-meal and cold, under emotional stress soon after waking up, climbing more than one flight of stairs, etc. This is more for the more-severe angina. Then there’s Grade 3 angina with minor exertion, so difficulty walking even short distances, one or more flights of stairs, or at a normal pace. These are of course concerning symptoms. And Grade 4 is rest angina even with no exertion are most often that characterizes symptoms that are unstable. These are the different classes of angina. In particular with 3 and 4, we get really worried.

Commonly Asked Questions about ACS

Alright, let’s move now specifically to acute coronary syndrome. What is acute coronary syndrome? Well this refers to a sudden reduction in blood supply to the heart muscle due to ST elevation myocardial infarction that you might hear others call STEMI, non-ST elevation myocardial infarction or non-ST segment elevation myocardial infarction often just called N-STEMI and then unstable angina. These are broadly speaking the three broad categories of acute coronary syndrome.

Does the nomenclature matter? It does, because it affects how patients are initially diagnosed and treated. Speaking of which, how do we see if patients are diagnosed? Well, in addition to clinical history that most often includes as I mentioned sudden onset of severe chest discomfort, in addition to that is history pump electrocardiography and high sensitivity troponin measurements are critical to diagnose for the ACS to be present and whether there’s STEMI, NSTEMI or unstable angina which then guides the exact therapeutic strategy.

What causes ACS? Well the most common cause of ACS is rupture of atherosclerotic plaque or thrombus formation. Other less frequent causes include plaque erosion, calcific nodules, coronary spasm, spontaneous coronary dissection sometimes called STAB, coronary embolism, and myocardial infarction with nonobstructive coronary artery sometimes called MINOCA.

Do all patients with ACS need a cardiac catheterization? Although the majority of patients such as those with electrocardiographic or ECG or EKG changes. Yes, elevated troponin levels. Yes, ongoing chest pain, hypotension or ventricular arrhythmias, then generally yes, you tend to go with cardiac catheterization. And then based on their coronary anatomy, usually percutaneous revascularization, sometimes surgical revascularization, and sometimes just continued medical therapy and the ratios or the rates of that usually about 60% of the time PCI, surgery about 10% and the remainder 30% or so just initial continued medical therapy. Importantly, low-risk patients without these features are most often initially managed with medications only and non-invasive testing to risk stratify them if warranted. But again it depends exactly how low risk they are. In some cases, no testing might be alright as well.

Initial Diagnosis and Management of ACS

This algorithm essentially summarizes everything as far as initial diagnosis and management of ACS. The first step in the branch point is electrocardiogram, which most places will say the standard of care is or should be ECG performed within 10 minutes of a patient's arrival to the emergency department. If ST segment elevation is present or not present, that determines the next steps. If ST signal elevation is present, then treat the patient with antiplatelet and anticoagulant therapy. Most often that's aspirin and unfractionated heparin though it might be aspirin and low molecular heparin such as enoxaparin. And then I must say the predominant practice in most regions of the world is aspirin or unfractionated heparin.

And then they should go to a cardiac catheterization laboratory assuming one will be available within two hours, usually the numbers are in a quarter within 90 minutes of hospital arrival. But if it involves a transfer to another hospital, probably up to two hours or so is considered acceptable. And if that's the case, if that answer is yes, you can get them in the cath lab within two hours and they should go there whether it's in your hospital or another hospital that's within two hours of being able to do the procedure. And then perform coronary angiography, see if there's any obstructive coronary artery disease. Most often defined is about 70% or so stenosis or greater. And then if there is such an obstruction that's present, they should be treated with PCI. And these ACEs that would be a drug-eluting stent.

If the STEMI within two hours, if the catheterization lab is available, that's definitely the way to go. If it's not going to be available within that time frame, then you really do want to treat as soon as you can with fibrinolytic therapy, alteplase; tenecteplase are the lysis of choice. But if you happen to be in the region of the world where those are too expensive, then streptokinase is still acceptable. Then the patient after getting the lysis would be transferred to a PCI capable facility within the next 24 hours. More than likely within that period of time, they should then usually within the 6- to 24-hour frame undergo catheterization and most often still are still going to end up getting PCI.

Now, if they happen to have undergone the coronary angiography and an obstruction is not present well then they've got myocardial infarction with nonobstructive coronary artery disease or MINOCA. And then medical therapy, risk factor, control is warranted and there's no role for coronary revascularization.

Now with the INSTAMI side of the equation, there are things like antiplatelet anticoagulant therapy most often once more aspirin and unfractionated heparin. In some places they may also get pretreated with an oral ADP receptor antagonist such as clopidogrel or ticagrelor. And then in general I think it's probably better not to do that unless you're going to be delayed to go into the cath lab for several days because

there are regions in the world where that's going to happen. But if you're going to go to the cath lab relatively quickly in that NSTEMI patient really then I wouldn't recommend pretreating with the oral ADP receptor agonist and just go with aspirin and anticoagulant to get most of unfractionated heparin, but depending on the location, delayed cath lab, maybe enoxaparin is a low molecular weight heparin. But what needs to happen after the ECG has shown there is no ST elevation to see if there is an elevated high sensitivity troponin. And that should be measured and it should be repeated I'd say within three hours.

Some algorithms would really say, the most recent algorithms are doing that repeat within two hours or an hour probably is even better in terms of efficiency of getting patients through the troponin measurements really are key. And it is a high-sensitivity troponin. There are some regions in the world where that hasn't totally been penetrating local practices, but it really should. If the troponin is elevated either on the initial measurement or that repeat measurement, say within that first three hours, then the patient is diagnosed with a non-ST segment elevation MI. And if they've got that then basically they should go to the cath lab barring contraindications. And if there is an obstruction present then it should be treated with PCI most often or with CABG. Again, I gave you the ratio before.

Now with STEMI most of the time, they're going to get alluding 90 plus percent of the time very rarely sort of you're going to be employed unless they're mechanical complications or things like that. and just medical therapy on those MINOCA patients when they come up in the 60% PCI, 10% bypass surgery, 30% medical therapy early is more for the NSTEMI type of patients. And there their catheterization should typically be performed within 24-48 hours though potentially faster if they are higher risk. Now in the patient where they are high risk features, they're going to the cath lab sort of like with the STEMI where as soon as possible. It's typically the way to go.

Now, if the patients are troponin-negative where they've got unstable angina again assuming they don't have elevation and if they have certain high risk features, if it's heart failure, dynamic ECG changes, ongoing chest discomfort, hemodynamic instability, if it's hypertension, if those things are present again, they need to go to the cath lab sooner rather than later perhaps urgently and their treatment is quite similar to the NSTEMI patient. If they don't have any of those features, they would get medical therapy and risk factor control and then undergo noninvasive evaluation, increasingly that's computed tomography, angiography or CT angio. Historically, that's always been a stress test.

But which one to choose fully depends on local expertise and physician with actual patient preference. But I do think noninvasive CT angio is going to continue gaining around here because it gives an assessment immediately if there's any severe left main disease or proximal three-vessel disease or things like that. But you don't really do all sorts of prognosis. And if that noninvasive evaluation - however it's done - CT angio, stress testing, in fact significantly abnormal and typically the patient would undergo catheterization and if it isn't, then continued medical therapy and risk-factor control. That's the overall way of treating acute coronary syndrome.

There are a lot of branching points here and overlap in terms of different ways of treating ACS sort of providing a high-level overview. I mean there is a bit more finesse to a lot of these. There can be issues dealing with ST elevation equivalence, obstruction of the left circumflex artery for example or large angle, it may not manifest ST elevation but there might still be unoccluded arteries. There are other ECG findings that can sometimes be very concerning. Marked anterior ST segment depression for example, might be really quite worried about that. In fact, left bundle branch blocks through the years have been thought of as a STEMI but that's more if there's a new left bundle branch versus left bundle branch. Even

if there are very specific criteria that increase the likelihood that it really is a STEMI equivalent based on left bundle branch, - - criteria and so forth. This is really a very high-level overview just to give you a sense of the different treatment pathways.

Treatment of STEMI Algorithm

Just to get a little bit more into the treatment of ST elevation MI because that is time-sensitive information everybody needs to know. If an acute ST elevation MI is diagnosed in the field, well then you want to bring the patient to a PCI capable hospital if that's a possibility in that region of the world. And in 80-90% of the U.S. that's a nonissue, other than some rural areas of the U.S. This is typically what should be done. If there isn't a capability of diagnosing STEMI in the field by these medical services, well then you just bring the patient to the closest hospital for chest pain evaluation by ambulance. A lot of patients drive in, but that's not a good idea; it should be by ambulance.

If there is however a hospital nearby capable of PCI, then in general that's what the patient is going to get primary percutaneous coronary intervention and get a drug-eluting stent these days. If there isn't such a hospital capable of PCI, is there a STEMI network hospital? Many hospitals even if they say, a community hospital that don't have primary PCI capability are a part or should be part of a hospital network, so they can immediately stabilize and transfer those patients for primary PCI especially if that can be done in the two-hour timeframe, two hours from symptom onset to actually doing the interventional procedure.

If none of that is possible because it's a rural area of the U.S. or region of the world, that doesn't have access for geographic or economic reasons to a cath lab, then full-dose lytic should be given assuming there are no contraindications. But I would say to consider based on a trial - consider a half dose of lytic if the patient is 75 years or older and they're using sort of the current standard lytics. By that I mean the ones that were listed here: alteplase, reteplase or tenecteplase. If you're using those in folks over 75 or older there I would recommend the half dose assuming that there is going to be the possibility to transfer that patient within the next 24 hours to a PCI capable hospital.

Let's talk a little bit about etiology here as far as plaque rupture. That's the predominant cause of acute coronary syndrome especially for ST elevation MI and also for a non-ST segment elevation MI and really it's that plaque rupture that leads to acute coronary obstruction. If the obstruction is complete, we tend to think of that as ST elevation if it's incomplete. In terms of the degree of obstruction we think of that as causing non-ST elevation MI. That's not all entirely true, nothing in life or medicine is ever black and white. That's the general 30,000 foot textbook teaching of it.

Causes of ACS

As I mentioned, the predominant cause of ACS is plaque rupture by that I mean a lipid was inflamed plaque rupturing exposing its inner contents to flowing blood leading to blood clot formation typically fibrin and platelet with strongest forms occluding the artery. That's what causes an ST segment elevation MI most of the time though if it's not completely obstructive at will then more often result in an non-ST segment elevation MI.

Increasingly, plaque erosion where there is a denuded endothelial surface caused by flow disturbances near the plaque and then formation platelet responds. This increasingly plaque erosion has been recognized as the cause of STEMI and especially NSTEMI. A higher proportion of STEMI or plaque rupture

versus plaque erosion is the same with NSTEMI but the ratio is a bit less extreme, so we're increasingly seeing plaque erosion as a cause of NSTEMI. That is a little bit more common in women than men.

Calcified nodules are another less common cause of acute coronary syndrome. Maybe 5% or so of acute coronary syndrome are due to calcified nodules. And then there's lipid rich plaque with calcium deposits and protruding eccentric nodules or calcification that can lead ultimately to thrombus formation and an acute coronary syndrome. Once more if it's obstructive that will be a STEMI but more often I think that's going to present as NSTEMI or stable angina.

These are I guess some of the more common causes of ACS. But there are a number of other causes as well to always consider coronary spasm can result in an acute coronary syndrome that can occur independent of or in conjunction with other types of ACS. It can be multifocal or multivessel, so either in multiple parts of an artery or in multiple arteries or just in one spot. The possibility of spasm may increase with the presence of damaged endothelial cells. You can get a couple of mechanisms of play, that is you get some plaque erosion, some thrombus formation, some spasm. These are always just clearly distinct even though I've drawn them here as distinctive, not always in real life such distinct entities. The spasm can be epicardial. It can also be a microvascular spasm or a bit of both.

As well another cause is spontaneous dissection and this occurs in somewhere maybe 1-4% of ACS just like coronary spasm. It's at that low single digit range. And this is something it's important to recognize. We're seeing more of it as we're doing more coronary angiography. Here in general if the patient stabilizes and is pain-free, you want to manage it medically, you've got to be careful about instrumenting these arteries with wider catheters, imaging instruments because sometimes if you get in the wrong place such as the false lumen, you can make the situation a lot worse. Obviously for patients having 10 out of 10 chest pain then you've got to do what you've got to do in terms of trying to wire and stent the artery. But a lot of times these can be matters medically.

The ones that end up needing procedures tend to be really sort of high risk patients and do worse than the ones that don't need procedures. As far as procedures go, if you're doing a procedure PCI generally what's done. But sometimes these patients do end up going to bypass surgery. That can be tricky sometimes and the surgeon has to probe and try to find the true lumen and anastomose with. I'm not as straightforward as one of the male CABG.

And then I'll mention embolism. Again it's a little single digit percentages for the course. And the most often source of an embolism is a cardiac source, atrial fibrillation, LV thrombus that sort of thing. But there can be non-cardiac sources as well. Once more I'll just underscore that probably it depends on the exact population. We've got probably around 5% of ACS are MIs with non-obstructive coronary artery, some of which would be caused by what I listed in these slides, some of which are having other causes.

Etiologies of ACS

DR. BHATT: Just to summarize what I said here are the different etiologies of ACS. Again I just mentioned all these in the previous slides. But here is some more information about the pathophysiology, some of the characteristics in terms of which ones are more common in women versus in men, that sort of thing. If anyone wants a real deep dive into this or a deeper dive into this recent review article with Renato Lopes and Harrington in JAMA provides additional information.

Let me say one other thing here too. This is some work drawn upon from the 2020 European Society of Cardiology ACS Guidelines. I really think these are quite user friendly guidelines too and just like the chest pain guidelines I mentioned before from the HCCHAB guidelines can be quite instructive. I have a nice figure so you don't have to read all the text. You can just come through the figures and tables.

But one thing that I'm going to mention in the context of SCAD or spontaneous coronary artery dissection. We learned a lot about it. It used to just be SCAD but now there are different types that have been delineated type 1, 2, 3. It sort of depends on the exact angiographic features as you can see on the slide. For example, long diffused and smooth stenosis is type2. Focal or tubular is type 3. Multiple radiolucent lumen is type 1. That is most relevant for folks that are angiographers. But important for you to just know that there are multiple types that our knowledge is evolving here with scan. Important to figure out is it an obstructive situation with the scan or non-obstructive because if you have an obstructive scan, reduced coronary flow, ongoing symptoms.

As I mentioned you have to consider revascularization, you might consider intravascular imaging needs to be done with care. Things like IVUS or intravascular ultrasound or OCT or optical coherence tomography can be utilized to figure out if this is really dissection. But those catheters if you're on the false lumen can extend the dissection, making a bad situation worse. Be really careful, really know what you're doing and have a little bit of luck on your side. OCT in particular , this is a bit technical but that involves forceful injections typically of contrast. Again if you're on the false lumen you're forcefully injecting contrast that can really cause a dissection unravel. These patients can do a lot of bad things but assuming they don't require any sort of invasive imaging or procedures, tpically they're on optimal medical therapy and these things actually heal in many cases without any sort of procedural care.

Recommended Antithrombotic Therapies for ACS

As far as ACS goes, lots of different therapies to consider acute coronary syndromes are highly prevalent antithrombotic strategies or a big part of their care, with lots of clinical trials in that space again. In this view our article in JAMA can get into some of the details. There's a lot of data to review and digest. But in general aspirin should be given to everyone. On presentation, typically the dose is 325 or four 81, so chew and swallow. I would say if the patient is already chronically on aspirin, in my own practice, I still do give them this load or reload of aspirin because sometimes patients say they're on aspirin but they weren't really taking it. Sometimes they're on acetaminophen but they confuse that with aspirin, so unless I've seen them take it, I'm never 100% sure, so aspirin.

And then the P2Y12 receptor antagonist in general I would say is best to give after the coronary anatomy is known. But if you're in a place where the time for the catheterization lab is going to be a few days, then it does make sense to pretreat. If you're pretreating the options of clopidogrel or ticagrelor. Prasurgel in general you shouldn't use as a pretreatment strategy unless the patient has STEMI and you're really quite sure you're going to do PCI whereas it will give you a bit more flexibility because they're indicated in ACS that's managed medically or that's managed with PCI or surgery for that matter.

Some things to know about, there are some patients with aspirin allergy. Desensitization is a good idea in those patients. That should be done in a monitored setting. If someone shows up with a STEMI there's not going to be time to desensitize them. If you do have folks in your practice that have true aspirin allergies, good to be sensitized before they're having a STEMI or they're in extremes.

As far as the P2Y12 inhibitors, much like aspirin, they can cause bleeding but when combined with aspirin, the risk of bleeding obviously goes up quite a bit. With respect to prasugrel, it's got a black box warning in patients with history of stroke or PIA due to an increased risk of intracranial hemorrhage, so one particular caution there. With ticagrelor, it can cause dyspnea side effects. You should be aware of that. It doesn't actually make the lung function worse but patients can have a subjective sense of dyspnea. Sometimes just tell them they're with it and they'll get used to it and it will go away. But sometimes it remains problematic and then they've got to be switched to clopidogrel or prasugrel as may be appropriate. Those are some thoughts about antithrombotic therapy.

In general doing antiplatelet therapy in the ACS patient should be continued for 12 months. But if there is a really high bleeding risk, the duration may need to be abbreviated. And if they're really high ischemic risk and little bleeding risk, then that duration should be increased beyond 12 months.

In their short term phase, other sorts of antithrombotic consideration is parenteral anticoagulation. Most often it's unfractionated heparin that's used, a bolus and infusion, per institutional dosing nomograms. Many places also use low molecular weight heparin such as enoxaparin. That's a little bit easier in terms of not having to check the PTTs and monitoring. Especially in places where there's going to be some intense monitoring that's possible it does make life easier. But if you are using low molecular weight heparin you have to realize you have to be aware of the kidney function. If someone has markedly abnormal kidney function probably best not to use low molecular weight heparin. The other thing to be aware of with both types of heparin unfractionated or low molecular weight is the potential for heparin antibodies. If someone has a history of heparin antibodies, you really want to not use these sorts of agents unless you're quite sure that they've cleared their heparin antibodies or there's no other alternatives.

What about oral anticoagulation? That is a much more limited role in the context of ACS but it can have a role in certain ACS patients subgroups such as those with atrial fibrillation or that maybe after STEMI have a left ventricular thrombus. Atrial fibrillation in the standard of care now I'd really say are the NOACs, the non-vitamin K oral anticoagulants. Warfarin has really become much less popular even if the patient has a mechanical heart valve or maybe antiphospholipid antibodies. Some data suggest maybe warfarin is better than the NOACs. But in general afib should be getting a NOAC. The dosing should be per the label, factoring in kidney function and age if appropriate for these specific NOACs and per specific label.

As far as LV thrombus, historically that's been warfarin. There have been some small, nonrandomized studies looking at the NOACs and the LV thrombus and they seem okay too, so hopefully more work will go on in that area.

Exactly what to do with the antithrombotic therapy really requires a lot of thought. Unlike some things that other speakers mentioned statins, pretty much everybody with coronary disease should get them or contraindications or intolerances. But here for the antithrombotic regimen upfront and early in the acute phase, yes, you ought to do what you ought to do. But in terms of longer term antithrombotic therapy such as dual antiplatelet therapy you have to look at patient characteristics, their history of ischemic events and bleeding events, their exact clinical presentation, ACS patients benefiting more from antithrombotic therapy and intense antithrombotic therapy and prolonged antithrombotic therapy than say patients with a chronic coronary syndrome or stable angina.

Think about comorbidities such as chronic kidney disease, diabetes, peripheral artery disease, heart failure, these tend to push towards more protracted durations of dual antiplatelet therapy. Think about the need for oral anticoagulation. There you want to avoid being on triple antithrombotic therapy for too long. And also think about other aspects of care that could reduce bleeding such as use of radial artery access instead of femoral artery access for catheterization and PCI, just a few of the important things to consider in weighing ischemic and bleeding risk and deciding upon the antithrombotic regimen.

Other Recommended Medical Therapies for ACS

DR. BHATT: Other recommended medical therapies for ACS patients this also applies for those with stable atherosclerotic disease. High intensity statins really should be initiated in all patients on presentation. Choices are things like maximally tolerated statin dose, atorvastatin 40 or 80 mg a day or rosuvastatin 20 or 40 mg a day. I mean I really like to push it to say atorvastatin 80 or rosuvastatin 40. But if there's any concern of intolerance, then I back off a little bit on the dose. But I tend especially in the ACS patient to start with very intense statin therapy, obviously on top of lifestyle modification and that sort of thing and recommendations for that, but when right there at the hospital, lifestyle modification started kicking right away. Medical therapy is particularly important and it should be lifelong therapy. If intolerance is developed, try switching statins using lower doses, every-other-day regimens. And if none of that seems to be working in your hands, refer the patient to a preventive cardiology clinic.

Ezetimibe is another great agent proven to be effective in ACS and even more broadly generic now, very well tolerated, really a very few in the way of side effects because it's not systemically absorbed. If patients are having myalgias or other sorts of things like that on ezetimibe we have to wonder about a nocebo effect where they're having side effects that would occur even on placebo. It doesn't mean they don't think it's real but I want to be sort of pushing back the ezetimibe and reassuring them the symptoms are unlikely due to that. If patients are truly statin intolerant it's a great drug. But here I'm really talking about it as an add on, on top of statin for intense LDL reduction, trying to get the LDL at least below 70 per the guidelines. But I would push that to even below 50 based on the data.

Other therapies to consider beyond those therapies which the majority they see as patients should be getting are PCSK9 inhibitors. If they're already on maximally tolerated statin and the LDL is above 70 especially if it's above 100 despite that, above 100, it's actually quite cost effective even at the current rather high prices. In the 70-100 range it's not simply cost effective, but the data would still support its use and really not much in the way of side effects other than a local injection site reaction.

Icosapent ethyl is something else to consider. There are patients who have non-fasting triglycerides greater or equal than 135 mg/dL despite a maximally tolerated statin dose should be considered for icosapent ethyl. Things to be aware of there are that it does have fish products in it. It's manufactured and therefore if patients have a history of anaphylaxis to fish or seafood or something, you want to be really careful about using this sort of drug. If it's sort of a mild reaction, that's one thing. If they have true anaphylaxis, you want to be very, very careful. In general, I would think twice before using.

Other sorts of side effects to be aware of are an increase in atrial fibrillation and hospitalization for atrial fibrillation with icosapent ethyl. The absolute risk assessment in the trial that led to its approval was modest, but if it does occur you need to be aware of it. Also serious bleeding did increase. It wasn't statistically significant but the P value was pretty close. You do need to be aware of the potential for increased bleeding including potentially serious bleeding. For someone who's really frail, already having

problems with bleeding within appropriate therapy. But for most patients that are having ACS and/or candidates for that, well then they would be fine candidates for icosapent ethyl as well.

Beta blockers, of course I have to mention that in an ACS talk. But in particular for the patients with left ventricular dysfunction or significant residual coronary artery disease with angina, these are really important drugs to use. I would say that as a class, they're quite good. Carvedilol may have some specific benefits even beyond other beta blockers. But most importantly I'd say make sure they're on a beta blocker versus no beta blocker if they meet the criteria I just mentioned. But whether every patient when I say should get beta blockers, if they normally function, they have complete revascularization. The data isn't so clear about that. There are ongoing trials.

ACE inhibitors and angiotensin receptor markers, very important, patients with left ventricular disease function or diabetes, should everyone with ACS get one? Certainly if they have hypertension it's a good drug to use for that purpose as well. I would say the majority of patients should get them. But certainly if there will be dysfunction diabetes, aren't contraindication should be on an ACE or ARBs. ARBs are a little bit better tolerated. There's more historical data for ACE inhibitors. You can make an argument for either one. But it probably does make sense to go the ARB route since they are so well tolerated and are generic now anyway.

Mineralocorticoid receptor antagonists, aldosterone or eplerenone is really what we're talking about or spironolactone. There we really want to get patients that have left ventricular dysfunction on these agents. That's really quite important to do that. The patients with LV dysfunction of course or very high response, this is something relatively cheap to do and highly effective but still very underutilized. You have to be aware of the potential with these drugs. They have hyperkalemia. With spironolactone in particular everyone is aware of the side effects of gynecomastia and so forth. Sometimes that leads to underutilization of this drug and class of drug. Just monitor the patients carefully for side effects, check their potassium and follow up.

Ten-Year Trends in MI: Discharge Medications

Alright. That's all I'm going to say about ACS therapies here. Here are some 10-year trends in MI. Lots of progress is made in terms of medical therapy but still room for improvement in some areas such as what I mentioned as far as aldosterone antagonists.

Comparing Influenza Vaccine vs Control: MACE

Another thing I'm just going to mention in ACS, you might be surprised to see in an ACS talk is influenza vaccination. This is a meta-analysis. The trials were so small but the number of events was small, looking at influenza vaccine versus control and the end point of MACE for major adverse cardiovascular events showing a significant reduction with influenza vaccine versus control. It appeared that that benefit was particularly marked in those with a recent ACS more so than in those with stable coronary artery disease. If your patient gets admitted with ACS, this meta-analysis supports that you should even if you aren't doing it for any other reasons, you're doing it just to prevent influenza. But if for some reason that's not convincing enough, you should do it to try to reduce the risk of a recurrent ischemic event.

This led to several guideline changes, as far as CV mortality that was heading in the right direction, not statistically significant, not enough events, but a risk ratio of 0.81 looked pretty good to me. More recently, a randomized clinical trial has proven what we saw in that meta-analysis that is a reduction in

ischemic events with influenza vaccine versus placebo. What was largely an MI population where a few patients that were sort of high - - was mostly MI population. Significant reduction in MACE and even all cost death was significantly lower. How many things do we do in medicine that are reducing death, so it is really important to make sure not to forget about influenza vaccines in patients who are eligible to be vaccinated.

I just showed you mortality but here specifically cardiovascular death and myocardial infarction which is lower even though the P value wasn't significant. Are these other effects here that are being captured or some of the deaths really pulmonary deaths or something else, maybe. But from the patient's perspective it doesn't really matter if the mortality is lower, you ought to do it.

Alright. Well with that I want to wrap up the part about acute coronary syndrome. I hope that this overarching review was useful. As I alluded to the other speakers getting into other aspects of ACS in more detail, it's an important topic and hopefully one that you have a good sense of. Thank you so much for your attention.

Stable CAD: Testing and Evaluation

Well now I'd like to speak to you about stable coronary artery disease and focus a bit on testing and evaluation. I think the European Society Cardiology put forth a useful framework in terms of chronic coronary syndrome. That is ACS which I spoke about previously. Eventually it transforms into chronic coronary syndrome. There are some patients who never have an ACS that just have chronic coronary artery disease. This is all along the continuum of CAD. In the chronic phase of therapy, there's still substantial risk. The risks aren't as high as during an ACS period. The patients with chronic coronary syndrome especially if they've had any - - before but even if they aren't, there are patients that are still at significant risk of future ischemic events. And we can lower that risk with risk factor modification using lifestyle changes, using medical therapy and in some cases revascularization as well. The role of revascularization is very prominent in ACS. It's also important but less prominent in chronic coronary syndrome.

These are once more from the chest pain guidelines. I mentioned that in a prior talk on ACS but these guidelines really apply to ACS. They can apply to stable chest pain syndrome. The point here is that at the base of the pyramid, there are a lot of asymptomatic patients with CAD. In general, the testing that's recommended is no testing. But in patients that are at low risk there, you might defer testing. You might do ECGs. You might CAT scans. But really these guidelines are trying to push away from that type of testing and deferring it if the patient keeps coming back with symptoms or something that's different. But some of this really low risk even just getting the ECG and so forth, it's not clear. It's always so helpful and sometimes this leads to cascades of testing that ultimately result in invasive testing every now and then, a complication. A very symptomatic really should the testing is the current recommended. If they are low risk in general if you can try to defer testing or keep it as non-invasive and minimal stick as possible.

Now if they have an intermediate risk, their anatomic or functional testing can be quite useful. If they are high risk, same story but there you might consider or really ought to consider invasive coronary angiography. If you have an ACS really there, invasive coronary angiography in general is the way to go with some of the caveats and finesse that I mentioned in the prior talk on ACS. But the bottom line is the higher the risk, the closer they are. But the apex of the pyramid the more likely you want to test and do

invasive testing. The lower down the pyramid they are the less likely you want to do any testing. But if you have to do some testing, you want to make it non-invasive.

Timing of PCI Based on Clinical Syndrome

In some proportion of patients and based on that testing will be treated with PCI or percutaneous coronary intervention and the breakdown is shown here. it will vary a lot depending on the exact population of the practice patterns in that region or country. But in general, for stable angina 20% of the patients will be treated with PCI. If they've got an abnormal test that leads to an angiogram and there's a severe stenosis on the angiogram. And in general the role of PCI here is after the patient is already on maximally tolerated medical therapy if they still have substantial symptoms that persist.

A PCI in this context definitely improves angina, reduces the need for future urgent revascularization and severe single vessel disease. Other certain advantages and disadvantages to PCI versus CABG in multivessel disease and the left main disease, I'll come back to that. But depending on the anatomy, either PCR or CABG might be appropriate even in those contexts. If there's no PCI performed, well there's antianginal medications and that might require dose escalation over time. There might be a time where the medications which were effective are no longer effective in that patient and then they need elective or even urgent revascularization. You have to keep reassessing the patient over the following months and years after that initial presentation whether it's to the office or wherever you might have seen them.

Then there's NSTEMI or unstable angina, about 50-60% or so of those patients are treated with PCI. There is usually a lesion on the angiogram. Sometimes you can see that it's ulcerated on the angiogram. In general, you want to perform PCI urgently in the next 24-48 hours. Within 24 hours is ideal. But sometimes other factors come into play, cath lab availability, weekend staffing levels, etc. PCI should be performed emergently if there's ongoing symptoms or dynamic ECG changes. By dynamic I mean they're having chest pain, the ST segment has dropped, chest pain goes away, ST segment is normalized as opposed to someone with just constant ST segment depression or maybe it's in the context of LVH or that's just their baseline ECG. That also is high risk in some of these totally normally ECG but they're not quite the same as dynamic changes.

PCI in this context reduces the composite of death or myocardial infarction. In some meta-analysis it also reduces death but certainly reduces important ischemic events. And if PCI isn't performed, a stress test prior to discharge is I think a good idea. If there is significant ischemia, coronary angiography and revascularization based on the coronary anatomy. Another alternative these days with these patients could also be CT angiography. It sort of depends what your trying to get at, is it an anatomical diagnosis you want to make that is you trying to exclude left main or proximal three vessel disease or you're trying to see are there symptoms really do to coronary artery disease and they're getting them on the treadmill and exercising will be quite useful because if there are no symptoms and they've just gone say 10 mets or metabolic equivalence on the stress test, well, probably the rest chest pain they came in with isn't really due to coronary angina. It's not 100% of the time, that's a generalization. But that sound stress testing can be useful.

And then in the STEMI patients as I alluded to in my ACS about 90% of those folks are treated with PCI, percutaneous coronary intervention drug-eluting stent implantation. Typically there's an occlusive lesion on the angiogram - a 100% blockage. Generally you want to open up the artery within 90-120 minutes of

their arrival to the emergency department. Within 60 minutes is considered ideal. That minimizes the amount of myocardial damage. In this context PCI reduces all cost mortality. If PCI isn't performed for whatever reason, lack of cath lab availability, rural area, if there's a snowstorm impossible to transfer the patient, that sort of thing, then you want to treat them with fibrinolysis and then promptly transfer them to a center that can perform PCI and they probably will still undergo PCI but not on quite the same emergent basis.

Second Generation Drug-Eluting Stents and Decreased Risk of MI and CV Death: Theoretical Framework

Now stents, there's been a lot written about stents. This slide summarizes some of the evolution and thinking about stent. There were bare metal stents that were first present. Those were replaced by first-generation drug eluting stents because they reduce stent restenosis, which is the stent clogging up and needing a repeat procedure. But they did compare with the bare metal stents slightly increase stent thrombosis, the stent clotting up which when that happens can be a life threatening emergency that lead to myocardial infarction or even death. And that was a real issue with the first generation drug-eluting stents prolonging death duration just on that basis in many patients. Now the reduction stent restenosis is good because sometimes restenosis can be malignant. Usually it just requires a repeat procedure, sometimes it's asymptomatic. But sometimes it actually prompts in acute coronary syndrome. The reduction in stent restenosis with first generation drug-eluting stents really good from a patient's perspective is less likely need to repeat procedure. The repeat in stent thrombosis while in absolute term is much less frequent. Potential sequelae are much worse.

Overall then the first generation drug-eluting stents compared with bare metal stents had a neutral effect on death or myocardial infarction because of the competing benefits and risks of decreasing stent restenosis by a lot. But stent restenosis wasn't such a horrible thing. I've heard every now and then it was counterbalanced by increasing stent thrombosis by just a little bit but when it happened really bad stuff could happen. These two counterbalancing effects lead to first-generation drug-eluting stents still being an improvement over bare metal stents but really just in terms of decreasing the need for repeat procedures and not influencing rate of death or MI.

Now the second-generation stents versus first-generation drug-eluting stents reduce stent restenosis probably by a little bit more, certainly by a lot compared with bare metal stents and also appeared to reduce stent thrombosis versus the first-generation drug-eluting stents with even in some cases a peer versus the bare metal stents. So, therefore it's conceivable had we ever done, adequately powered large enough trial that can happen, you know, the second-generation drug-eluting stents versus the first-generation drug-eluting stents or bare metal stents might actually reduce the risk of death or MI, but regardless of whether that is true, you believe it or not, that may have now become worldwide, the standard of care. If patients are getting PCI, they're getting second-generation drug-eluting stents. Certainly the ones in the United States that are FDA approved, they're all excellent. There's some in other regions of the world with the data quite robust. But the commonly used ones worldwide are really very safe and very effective.

Fractional Flow Reserve Measurement for the Physiological Assessment of Coronary Artery Stenosis Severity

I've been talking about stenting and coronary angiograms but there are ways of being more precise than just looking at an angiogram saying, yeah, this lesion looks severe, I'm going to stent it. This one doesn't look so bad and we'll leave it alone. There are ways of quantifying lesion severity in the cath lab such as fractional flow reserve or FFR which is used to measure the physiological severity of a coronary artery stenosis. The angiogram provides an anatomical assessment that's a 70% narrowing. But the FFR provides a physiologic assessment. Essentially what it does is measure the drop in pressure across the lesion and the drop in pressure is significant that correlates highly with ischemia. And the right clinical scenario makes it more likely that the patient's symptoms are really angina. If that lesion is stented makes it more likely they'll have resolution of angina. Those relationships are all perfect. There's a lot of ongoing research to refine everything that I just said. But again the 30,000-foot view is more or less correct.

The cutoff numbers for FFR that are used in clinical practice are 0.8 or less. An FFR of 1.0 is totally normal. But 0.80 or less means that lesion is causing ischemia either if that is at rest or if it's accruing after vasodilators are administered. Though I should say that the initial work that was done with FFR really uses 0.75 as a cutoff. If it's 0.75 or less, then you know it's really bad, but if it's 0.80 or less in clinical practice we say close enough to 0.75 we use that as a cutoff. That's the fractional flow reserve.

Now the IFR, instantaneous wave-free ratios, is another way of assessing coronary flow and it's a little bit more sophisticated in terms of the algorithms used. But the magic number is 0.89 or less so, just important to realize your reading reports slightly different numbers there for IFR and FFR and their cutoff of what is considered abnormal, a 0.89 or less for IFR, 0.80 or less for FFR.

What I'm going to say here is getting more into the technicality. This is probably more important for interventional cardiologists to understand and for referring physicians. But the fluid dynamics and computation dynamics can get pretty tricky, pretty quickly if you've got serial lesions in an artery, lung lesions, that's just a lot of math that goes into this actually. But we in the cath lab can sometimes sort this out by using FFR and IFR. This is just an example of what the FFR tracing looks like. And then abnormal FFR here you see a 0.43 in the case of a patient with serial lesions. Sometimes one lesion interferes not in a bad way, but interferes mathematically with another lesion. You can imagine if there's a really tight lesion up top well then there will be a lesser blood flow in the downstream lesion. Therefore the downstream lesion might be assessed as not being a significant narrowing because there's not a lot of blood flow going through it. But once that top lesion is fixed it would be then evident that the bottom lesion also is either. There is some complexity. This is with all testing.

Stable Coronary Disease: Evaluation

Let me move on now to talk about an algorithm for treating the stable coronary artery disease. The first step is, are there symptoms obviously. We're talking about people with symptoms. Are the symptoms stable? If the answer is no, send them to the emergency department. And by send them I mean send them by the ambulance not their spouse or the patient driving themselves. But if the symptoms are stable, well then you want to figure out are the symptoms resolved with medical therapy? For risk reduction such as initiation of things like statin and aspirin or did the symptoms resolve with treatment that's directed towards angina. These are beta blockers, nitrates and calcium channel blockers. If the answer is yes, you can just continue medical therapy and periodically assess for recurrent symptoms or any sort of change in exercise.

Now the reality is many patients and physicians especially in the U.S. aren't going to be satisfied with the, yeah, sounds like you have angina, I'm just going to empirically treat you. I mean usually there's some testing that goes on. There's a stress test. You get a sense of how well the patient can do on a treadmill and I think that's very reasonable that you add. Sometimes these days there'll be a CT angio just to reassure the doctor and the patient that they're not sitting on tight left main disease or proximal three vessel disease or something like that.

Now if on the other hand their symptoms are not resolved and let's say there's ischemia present on the stress test, either a stress test with exercise if the patient can exercise with pharmacological stress, then as I mentioned these days absolute CT angio. If that's abnormal, then you would want to have the patient undergo invasive coronary angiography not just cardiac catheterization. If there is nothing of severe lesion there, you can reassure the patient to continue lifestyle modification, medical therapy. You don't want to say, oh, you have normal coronary arteries. You're in great shape because most often the circumstance, there's going to be some degree of coronary artery disease, so you don't want to overly falsely reassure them. But you can tell them, oh, your symptoms are likely not due at least to epicardial coronary disease. Microvascular disease, this is another sort of scenario. But at least you can say it doesn't look like it's something that we can stent or do bypass surgery that will make you feel better.

On the other hand if there are lesions that are present there if it's greater than 80% stenosis, typically a performed PCI. If that 40-80% range is sort of ambiguous there, you might want to beat things like FFR or IFR and in fact IFR will be preferred there if it's 0.89 or less generally performed PCI. If not, don't perform PCI. If stenosis is less than 40%, don't perform PCI or any invasive testing. But you might still emphasize to the patient hey, maybe it's just a 20% lesion, I'm not going to do anything about it procedurally. But it does still increase your risk of MI versus someone that had truly no angiographic coronary artery disease. The patient who's stress test wasn't abnormal there, again you would also use continued medical therapy. But periodically, reassess for worsening of their symptoms or new symptoms. That reassessment is important because if the symptoms are getting worse on medical therapy, there you don't want to just sit on things and say, oh, this is stable coronary artery disease. That can be a red flag if the symptoms are worsening despite escalation of medical therapy.

CABG for Patients with Diabetes and Multivessel Disease

I'd said I get back to the issue of surgery and I am right now. In particular for patients with multivessel disease, it's not just a matter of PCI. One has to also consider CABG even more so if they have diabetes but even if they don't have diabetes, if they have complex multivessel disease. If the patient has multivessel CAD and they're angiographically suited for CABG or PCI, in general if you're a good surgical candidate, I would say go with CABG especially if it's complex lesions but they are less likely to need repeat procedures, less likely to have residual angina if the procedure was being done for angina in the first place.

If you have a left main lesion with additional complex multivessel disease, again if they're a good surgical candidate even in the current era, I would do CABG. If they have multivessel disease in the context of diabetes, again I would in general favor CABG. But, if they have multivessel disease without diabetes or even if diabetes has very discrete lesions, there it's a discussion with the heart team, with your surgeon, with the interventionist, with the patient, and with their family, to discuss patient preferences. And there CABG I think would still often be favored if there's complex anatomy. But if it's relatively straightforward

anatomy, relatively easy to stent lesions then probably PCI makes good sense as well. If the patient has high stroke risk or advanced age, there in general I would tend to favor PCI over CABG.

When you ask patients, a lot of times they push the discussion towards PCI even when sometimes - - to have bypass surgery. It can be a challenge sometimes convincing patients, but sometimes bringing in the surgeon to that discussion can help. But sometimes when they hear they're going to get a median sternotomy that far is even more. But nonetheless it's useful to try to present all options as a heart team.

Testing: ECG

Let's talk a little bit more about testing in the context of coronary artery disease in patients with chest pain obviously history, physical exam. ECG is the first step. If they've got a STEMI or NSTEMI that's suggested by the ECG, well you've got to follow the ACS type guidelines. In particular if it's STEMI you need to act very quickly. You've got to also consider things like pericarditis. Sometimes that can be tricky to differentiate from STEMI especially if you're not a cardiologist or even if you are a cardiologist, other testing can be helpful as well.

In patients where there's non-diagnostic or normal ECG, sometimes it can be useful to do fancy aversions of ECGs, getting posterior leads for example, leads V7 through V9 if a posterior MI is suspected. Repeating the ECG can be important if there's persistent arrest symptoms or for patients troponin becoming positive. If there is a new arrhythmia then you want to follow the arrhythmia specific guidelines for things like atrial fibrillation. ECG is very important in the patient with chest pain. Even one presenting at the office, just to make sure it's not worse than what you think that it is really stable chest pain and not an ACS lurking about.

Testing: Biochemical Tests

Blood tests are important. The usual good stuff, CBC, obviously the patient is very anemic that can prompt angina, need of course to check lipid levels, LDL, cholesterol, triglycerides as well, check the creatinine. You want to know what that is in case you'd be giving them contrast dye from a CT angio or from a cardiac cath for example. If you go, you should suggest ACS. I mentioned in my ACS talk that I should repeat the troponin, and use high sensitivity troponins. In general, repeat that test within three hours. Some algorithms even push that to one to two hours. If there's thyroid disease, it's suspected, check thyroid function obviously. And screen for type 2 diabetes in these patients because sometimes even though they don't think they have diabetes, in fact they do.

Evaluation Algorithm: No Known CAD

This is from the chest pain guidelines that were issued at the American Heart Association 2021. This is the algorithm for patients with no known coronary artery disease. If they come in with acute chest pain and/or intermediate risk, again no known coronary artery disease and you probably want to look at whether they have prior testing. If they have and it's been inconclusive for example, they're getting a coronary CT or going right into an invasive coronary angiogram could provide lots of reassurance and diagnostic certainty. On the other hand, if they haven't had prior testing, you probably want to start with either stress testing of some form of exercise, ECG or stress testing with some form of imaging potentially with a noninvasive coronary CT angio.

There are a lot of branch points as you can see on the algorithm. But important things to see, has the patient had prior testing or not. Because if they have had prior testing and they're coming back again with chest pain, we really have to rush things up a little unless it's a very recent negative stress test. In there you might just opt to discharge and though in real life that can take some courage to always be so easy. But that's what the guidelines here are recommending.

In those patients where there's inconclusive evidence, a lot of what I've mentioned before can be useful. One thing I didn't mention was FFR with CT. I mentioned invasive FFR but you can also get a non-invasive CT angiogram that calculates non-invasively again using computational fluid dynamics, the FFR. That can be useful too because if the CT shows some minor plaque, the FFR is normal, probably that patient's chest pain isn't due to epicardial coronary artery disease. On the other hand if the CT shows an 80% mid LAD, the FFR is abnormal there in that LAD, then it's more likely it's all true-true related but that's the cause of their chest pain, so lots of different branch points and perils here in this algorithm.

Evaluation Algorithm: Known CAD

Now that's the patient with no known CD. Now is the algorithm for patients with known CAD presenting with acute chest pain, intermediate risk, again known CAD. Partly depends on whether they have non-obstructive CAD or obstructive CAD. As you can see here various roles for CT angio, for stress testing, in this case with imaging more so than just with exercise, ECG testing alone here for FFR CT or stress testing and ultimately these patients that have severe abnormalities on the non-invasive testing most often end up in the cath lab. And then based on the anatomy they undergo revascularization. Though everyone should of course get guideline-directed medical therapy.

Testing: Choosing the Right Test

These chest pain guidelines that I'm referring to going into the important topic of choosing the right test. Again if the patients are at low risk, no testing is necessary. But there are options for CAC or coronary artery calcium or atherosclerotic cardiovascular disease risk stratification. That can be useful just to decide how intense your secondary prevention might need to be. In patients that are intermediate to high risk, there in the younger patient by younger less than 65 years of age or there's less obstructive CD suspected, their coronary CT angio is a favor. And if they're intermediate- to high-risk in an older patient, at 65 years of age or older or there's more obstructive CD suspected, their stress testing is favored.

There's still a role for all of these different forms of testing. No one needs to be upset if their favored test is not going to get used anymore. There's a role for all these sorts of testing. The key thing is choosing the right test for the right patient. If the patient is capable of exercise and exercise being part of that stress test, the stress test obtained is a good idea. But if they can't exercise, things like PET scans can be quite useful. There's a role for pharmacological stress testing obviously in patients who are unable to exercise. Sometimes if you're looking for things like microvascular dysfunction, again PET can be useful. If you're looking for LV dysfunction or scar through some form of imaging, it can particularly be used. Again, it's not just a matter of the same tests for everybody. There's some thought and also usually what local expertise is available that goes into all these decision making, so not trivial decisions.

Just further expanding on these concepts. a number of factors listed on this slide that favor use of noninvasive coronary CT angio or stress imaging. This is probably the one thing to say but I suspect what may happen despite where our guidelines here are recommending is the proportion of patients I bet

take both modalities of testing. And there might be something we said for that in terms of complementary information about anatomy and about function. But from a cost perspective, I'm sure that statement that I made would be frowned upon. The other thing is that the technology gets better with CT angio and FFR and assessing not just anatomy but also extrapolating the physiology that could potentially make you take on an even larger role. There has been a lot of innovation with respect to incorporating FFR into CT.

Testing: Coronary CTA

One other point I should mention is if there's any concern about anomalous coronary arteries for example, if there needs to be evaluation of the aorta and pulmonary arteries as well, let's say if someone were thinking of pulmonary embolism, that also might favor CT angio. The optimal windows for coronary artery pulmonary embolism for aortic dissection aren't necessarily all the exact same. But there sometimes is value in favoring CT with the ability to get some assessment of all those different potential causes of chest pain at once.

Other points to mention about coronary CT, a lot of the visualization of the coronary lumen and wall using intravenous contrast agents of course, there's high accuracy for detection of coronary stenosis. Stenosis that is in the sort of moderate range may not always be functionally significant even in the 50-90% range. Sometimes it can be an overestimate. Non-invasive or invasive functional testing is recommended for further evaluation when angiographic stenosis is detected by coronary CT. It's not necessarily just one and done as far as testing goes. We really do need to think about things in an integrated sort of way. Sometimes if you place this large enough that it has a dedicated cardiovascular image, you would think it would be very useful in terms of recommending which test to use.

Testing: Chest X-ray

Now I'm just going to mention these are tests that are - - would be done. But I just mentioned here the chest x-ray which is still recommended. The humble chest x-ray is still recommended for patients with presentations that aren't classic presentations not within the size and symptoms of heart failure, where there's suspicion of pulmonary disease. The chest x-ray hasn't gone away and I still think it is a useful part of the overall evaluation of a patient with chest pain where you haven't sorted out yet, is it the heart or not the heart.

Alright. With that let me conclude this part about stable coronary artery disease and testing. That really touches upon a lot of the highlights but there's an enormous amount of information. I would say if you really want to get into some of the specifics of how to deal with chest pain, I think the most recent chest pain guidelines are good because they deal with stable chest pain, unstable chest pain, testing algorithms in a way I think is very digestible and user friendly.

Now I'd like to speak about the treatment of coronary artery disease. This could be a day or week-long lecture, but I'm going to try to sum up some points that I think are relatively recent and interesting.

Primordial, Primary, Secondary Prevention

First let me just talk about prevention broadly in the secondary, primary and primordial prevention. Secondary prevention refers to treating patients with established cardiovascular disease whether it's

coronary disease, cerebrovascular disease, peripheral vascular disease, heart failure, patients that have known disease trying to prevent the next event which could potentially be a fatal event.

Then there's primary prevention which is treating the risk factors. Risk factors eventually lead to cardiovascular disease. And then there's primordial prevention that is institution of healthy behaviors that prevent the development of risk factors in the first place consisting of things like fetal and infant health, avoidance of smoking and tobacco products, vaping and that sort of thing, avoidance of high caloric diets, preferably plant-based, relatively lower calorie diet, avoid physical inactivity in fact nor saying daily physical activity, maintenance of an ideal body weight, avoiding obesity or overweight states and avoiding environmental pollution to the extent that can be done on an individual level. Certainly on the society level, that's something we're going to give a lot more thought to especially with everything that appears to be going on with climate change accelerating, lots of consequences and potentially cardiovascular and cardio-pulmonary health. These approaches some with the individual patients, some that are more in a public health level, some both, can go a long way to prevent risk factors and ultimately prevent some proportion of cardiovascular disease.

This red is always a lifestyle modification. The blue is lifestyle modification and in many cases medical therapy. The grey is lifestyle modification, medical therapy, typically polypharmacy and sometimes procedural care as well such as revascularization.

Lifestyle Management

Let's talk a bit about lifestyle management. This is really important. A healthy diet is important. Diet high in vegetables, fruits, whole grain, I think a plant-based diet is best to the extent the patient can adhere to that. saturated fat in general is believed, it should be less than 10% of intake. There are some sort of controversies about fat. I mean I think if you're getting your fat from vegetables, fruits, whole grains, that's a bit different from getting your fat from red meat which is quite unhealthy.

Alcohol should be limited. I wouldn't say that alcohol is cardio protective. That's a popular belief. It's not evidence-based; most of the data showing associations are highly confounded. What's clear is that drinking more than a glass a day raises the risk of things like atrial fibrillation and heart failure, that sort of thing. Really we shouldn't encourage patients to drink for the purposes of cardiovascular health. If the patient likes to drink, we should encourage them not to drink more than a drink a day. It used to be two drinks a day for men and one for women, probably the two for men, I mean it all depends on the person's size and metabolism, and so forth. But probably better to say not more than one as a general advice for both men and for women.

The World Health Organization rather, WHO, is actually labeled alcohol as a carcinogen, so beyond the lack of established cardiovascular benefit, the clear association of atrial fibrillation and alcohol, even a drink a day being a trigger for atrial fibrillation as one gets older. Either is the associations with cancer that are quite robust, especially certain types of cancer. Bottom line, plant-based diet, avoid alcohol to the extent possible, very unpopular I know, sorry. Maintain a healthy weight, that's critically important, it sort of ties in with diet and exercise. But increasing physical activity is a good idea. Shooting for 8,000 to 10,000 steps a day is not a bad thing for someone that isn't for orthopedic reasons able to exercise vigorously at a minimum. I think that's still better than nothing.

Smoking cessation, if somebody is smoking or vaping, try to get them to stop. Regular physical activity, 30-60 minutes a day of moderate physical activity, most days I'd say every day is good. But even if that can't happen, every other day is pretty good. Probably some incremental value as well to resistance training, there are things like weight lifting beyond just aerobic exercise. But the bottom line is anything is better than nothing. More is better than less. No, at a certain point more isn't better, that is sort of marathon running, triathlete sort of thing, that's not clear that there's incremental cardiovascular protection provided by that. Those folks really - - troponin. It might actually be sort of a U- or J-shaped curve at a certain point. I don't think more is better. But within the range of what most of us in the sedentary modern world are doing, almost everyone can benefit from an increase in physical activity.

Cardiac rehabilitation, very important for those that have indications. And certainly in the US the indications and coverage in payment for various indications has increased. Patients that are candidates for cardiac rehab, you definitely want to refer to them in the context of what I've been discussing, coronary artery disease really works well with these patients with symptomatic coronary artery disease would be candidates for cardiac rehabilitation.

Psychosocial factors are probably important as well, trying to reduce stress. That's easier said than done. But I'd say at a minimum trying to get a good night's sleep, there's a lot of associations between sleep quantity, sleep quality and higher associated rates of cardiovascular disease. But getting enough sleep can be good for mental health, for stress, etc. Anything that works for a patient to decrease stress, not easy in the modern world but might help reduce risk of cardiovascular disease. If not directly at least indirectly because people that are stressed tend to eat lots of junk food, sleeping may be disturbed and there can be sort of compounding risks that's going on there.

And as I alluded to a little bit earlier, trying to reduce air pollution would reduce cardiovascular and cardiopulmonary risk. Interestingly, even environmental noise has been associated in some studies with higher risk of CVD and there's some potential for confounding noisy neighborhoods that probably also have lots of air pollution. But nonetheless there might be some independent risks there. If somebody is very noisy, disrupting someone's sleep, that could potentially directly increase cardiovascular risk.

IMPROVE-IT: Primary Results

Alright. That's all I'm going to say about lifestyle, very important. Let's move on to medical therapy. Statins for everybody, that sort of goes without saying. But beyond statins, what else can we do? E Ezetimibe plays an important part of the armamentarium, very underutilized. Here, the IMPROVE-IT trial showed a significant reduction in LDL cholesterol and a significant reduction in ischemic events that parallels that, not just the magnitude but achieved very safely and now I would say achieve very cheaply since ezetimibe is generic. Even though this is an ACS trial, there's other data supporting that these data apply in a non-ACS setting to patients with stable atherosclerotic disease as well. If the patient's LDL is optimal on high intensity statin, make sure to get on ezetimibe.

FOURIER

The FOURIER trial showed that the PCSK9 inhibitor evolocumab, an injectable cholesterol lowering agent lowered LDL cholesterol by a lot, 50-60% reductions in LDL cholesterol and corresponding robust decrease in ischemic events with evolocumab versus placebo. In that patient who's maxed out on station, ezetimibe, if the LDL is still beyond what the guidelines recommend, PCSK9 inhibition is quite

useful. FOURIER studied patients with stable atherosclerosis involving the coronary with peripheral circulations.

ODYSSEY OUTCOMES: LDL-C On-Treatment Analysis

Odyssey outcome studied patients with an acute coronary syndrome. Here with alirocumab versus placebo once more 50-60% reduction in LDL cholesterol with this injectable cholesterol lowering drug, a PCSK9 inhibitor, large significant reductions in LDL here just as in FOURIER and a similar significant reduction in ischemic events. Two separate trials, different populations, different investigators, same bottom line, highly effective safe class of medicines.

Primary Efficacy Endpoint: MACE

Now Odyssey outcomes was an ACS trial and therefore the population in some respect you could say was higher risk. When we examined the endpoint of mortality in Odyssey Outcomes, we see there in particular in patients with an LDL greater than 100 despite the doctor and patient doing everything they can to get it to 100. There also appears to be a reduction in all-cause mortality. Not just non-fatal ischemic events but also all-cause mortality.

All-cause Death in 3 Predefined Categories of Baseline LDL-C

The higher risk the patient, the longer they're treated, the more likely the benefits will accrue, including potentially reductions in heart endpoints such as all-cause mortality.

"Cholesterol-Years" for CV Risk Prediction and Treatment

This brings me to this concept of cholesterol years. I think everybody in the audience probably knows about tobacco years, the number of years the patient smokes tobacco, the number packs they smoke, so that's the pack years. Here we're talking about cholesterol years, so the number of years their cholesterol has been elevated and how high it's been elevated. Sort of an area under the curve, it's really a more conceptual framework. The higher the number of cholesterol years, the greater the area under the curve, the more important it is to start therapy sooner. For example in someone with familial hypercholesterolemia, FH, severe hypercholesterolemia from birth, you want to get those people on pharmacotherapy as soon as possible. There's not just a matter of lifestyle modification. That's also good to recommend. But you really need to get them on potent pharmacotherapy or they are someone that's lucky that has good genetics, has a good lifestyle, lifelong low LDL cholesterol, it may not be so critical to get them on pharmacotherapeutic at least early on in life. Now if they live long enough, I think even over there, there might be a role. It really depends.

Patients in between with more moderate degrees of hypocholesterolemia, depends on the actual level of their cardiovascular risk factors. There's some thought that needs to go into this. But the bottom line is you don't want to have patients running around with elevated cholesterol for years. What happens perhaps more often in primary care practice, the patient comes in, LDL cholesterol is elevated above guidelines to treat that patient. But there's a discussion, decisions made to just imply lifestyle modification, come back in 6 to 12 months. And then the patient forgets, doesn't come back for 6 to 12 months, but then let's try lifestyle modification, forgetting that we already tried that for 6 to 12 months ago and nothing has happened. Lifestyle modification is important. But it is important if that's the initial strategy to reassess. I think a lot of times what happens is patients should be on statins, don't ever get

started on their statin. Don't be letting the lifestyle modification go on too long. If the patient needs guideline indication for statins, skip them on their statin sooner rather than later.

Promising Therapies for Hypertriglyceridemia

DR. BHATT: Okay, that's - - about LDL cholesterol. Let me talk a little bit about triglycerides. Some - -, they're back in again I think. There are a lot of different therapies that lower triglycerides like fibrates, high doses of Omega 3 fatty acids, a bunch of new therapies. But not always though do drugs that lower triglycerides lower cardiovascular risks. Important to realize that some drugs, a large triglyceride might lower cardiovascular risk but not every drug not necessarily lowers triglycerides will lower cardiovascular risk. You should use the drugs that lower cardiovascular risk if you're treating triglycerides obviously.

Targeting RNA to Lower Triglycerides

DR. BHATT: There are some exciting new compounds on the horizon. Well I shouldn't say on the horizon being tested. You have to see what the randomized clinical trial show. Molecular approaches that target RNA, that lower triglycerides by an enormous amount or specifically triglyceride-rich lipoprotein or you have to see if there's a corresponding reduction in cardiovascular risk, offsetting toxicities. This could be a really important class of medications.

A Revolution in Omega-3 Fatty Acid Research

What have we got now? Well let's talk a little about omega-3 fatty acids. There's been a lot of research that goes on and one particular omega-3 fatty acid icosapent ethyl has been shown to be highly efficacious. It's a highly purified icosapentanoic acid, that's in the middle of this diagram here. But for folks that want to do things more naturally, they can certainly get levels of ALA or alphalenoleic acid to natural sources of vegetarian and vegan, things like chia seeds and flax seeds and walnuts, some green leafy vegetables that's reasonably high in that content. That's one way naturally of getting EPA. Not very efficient in humans these various enzymatic conversion steps but it is one way for people to eat fish, marine oily fish is another way of getting EPA for that matter also BHA. Those are some "natural" sources. But for most people, they're going to have relatively low levels of EPA.

Now EPA is eventually converted into other different omega-3 fatty acids, ultimately DHA. But EPA and DHA when they're given exogenously say in supplements or prescription medications, very different what their actions might be. There are different enzymatic steps for example with EPA that are converted to things like SPM, specialized pro resolving mediators that are very potent anti-inflammatory agents or other things that are produced from EPA. Likewise DHA produces a number of downstream mediators, some of which are potent anti-inflammatories as well. But these are very different compounds and interaction is very different. Some of the confusion in the field has been trials that have combined EPA and DHA, for the most part being neutral whereas every trial of EPA today has been positive, so not all omega-3 fatty acids are created equal with respect to cardiovascular protection. It's important to understand that.

Primary and Key Secondary Composite Endpoints

And really the omega-3 fatty acid that has been proven to provide benefit is eicosapentaenoic acid in the form of prescription icosapent ethyl or IPE sometimes it's called. That was studied in the REDUCE trial showing significant reduction as in ischemic events including significant reduction as in cardiovascular

death, in MI, in stroke, in coronary revascularization, in hospitalization for unstable angina as individual endpoints as well as composite endpoints. For patients that have elevated triglycerides even mildly elevated or above 135-150 this has been proven to be an effective therapy on top of dietary modification, on top of statin therapy.

Cardiovascular Risk Reduction: T2DM

I just want to say a word about patients with CAD with diabetes: these are very high-risk patients. And a number of the different therapies I mentioned may be appropriate for them. A statin is obviously, ezetimibe as well, PCSK9 inhibitors potentially if their LDL is still high. Icosapent ethyl if their triglycerides are high despite statin therapy. Lipid management is a big part of it. Blood pressure management as well. In general you want to be pretty aggressive with blood pressure management in these patients but not to the point where they get symptomatic not being aggressive in folks that are frail or have multiple comorbidities. But in general for young healthy people that fall in this camp of diabetes and coronary artery disease, you want to generally get the blood pressure below 140/90, maybe less than 130/80.

Screening for cardiovascular disease should be considered not necessarily with tests that are found these days when we're talking about invasive or even non-invasive tests with the asymptomatic patient. But certainly you want to screen for cardiovascular disease by saying, hey, do you have angina? Don't say angina of course. Ask for various chest discomfort symptoms but also ask for claudication to screen for peripheral artery disease, ask for symptoms that might be consistent with transient ischemic attacks, so screening for cardiovascular disease in all arterial territories.

Lifestyle modification is important. Glycemic control is important to prevent microvascular complications. With SGLT2 inhibitors and at least some of the GLP-1 receptor agonists, also preventing certain types of cardiovascular and cardio renal outcomes. SGLT2 inhibitors in particular to prevent the risk of heart failure and kidney disease progression and GLP-1 receptor agonist to reduce ischemic outcomes and to also preserve kidney function, are very important additions to our armamentarium. And, yes, they're branded and can be expensive right now. But the benefits they provide not only for glycemic control but cardiovascular/cardiorenal outcomes are quite impressive. Speaking of that, just today as a matter of fact, it was announced that an EMPA-KIDNEY study looking at SGLT2 inhibitors chronic kidney disease will stop for overwhelming efficacy by the data safety.

Every day, there's more data coming out with respect to the SGLT2 inhibitors and the GLP-1 receptor agonist, though the data don't apply to every GLP-1 receptor agonist. Some do have some positive cardiovascular outcome data, some don't, sort of the same situation with the omega-3 fatty acids. Some of them do have cardiovascular benefits like I mentioned some don't.

What about antithrombotic strategies? For the patients with diabetes and CAD, they probably have at least beyond an aspirin. But potentially one has to consider depending on the severity of their cardiovascular disease, do they need to be on dual antiplatelet therapy? Might they be a candidate for dual pathway inhibition, aspirin plus vascular dose of rivaroxaban at 2.5 bid, so there are a lot of different things to consider there in terms of optimal antithrombotic strategy. Of course you have to consider their bleeding risk.

And then one has to consider social determinants of health as well. I mentioned for example the cost of some of these diabetes drugs or some of the other regimens that I mentioned, PCSK9 inhibitors,

icosapent ethyl, certain forms of dual antiplatelet therapy that involves ticagrelor, - -, these are all currently branded medications with financial cost associated with them. You need to factor all those things in pill burden, etc., so lots of different things to consider. While this is specifically in this age, a statement pertaining to the patients with diabetes and CAD really everything I said other than the glycemic management part of everything I said also applies to those with CAD, not without diabetes.

CAD and T2DM

But I do want to focus a little bit more on those with diabetes because out of those patients out there, 34 million have diabetes. Most of that is type 2 diabetes of course. And in this population, cardiovascular disease is the leading cause of morbidity and mortality. That's true also in type 1 diabetes. We really want to be aggressive in our lifestyle modification and where appropriate pharmacotherapy and where appropriate polypharmacy in these patients.

Noninsulin Diabetes Drug Development

DR. BHATT: Incredible evolution of drug therapy when one is talking about diabetes drugs. Obviously insulin is a big advance. But here I'm talking about non-insulin diabetes drug development. Just look at the advances especially in the past few years with the SGLT2 inhibitors and GLP-1 receptor agonists, reductions in cardiovascular events. As I alluded to, they are large in many cases, large in relative terms, large in absolute terms with expanding indications. It seems to be coming every few months.

Potential Indirect CV Effects of GLP-1R Agonists

I talked a bit about GLP-1 receptor agonist a slide or two ago, I just want to mention them a little bit more to say there are multiple mechanisms of action that are being described that I think have already been shown and will increasingly be shown to have protective effects on the heart and on the kidney. These are drugs that are established not only in diabetes but are being studied in heart failure with preserved ejection fraction, in obesity, in a variety of different disease states. I think we're going to hit a lot more about GLP-1 receptor agonists in years to come though they already have a role in clinical medicine.

Management of Stable CAD in Patients with T2DM: Antithrombotics

Now with respect to management of stable CAD in patient diabetes, it's a little bit about antithrombotics, diabetes is in general prothrombotic state. Aspirin alone is reasonable to consider in patients with diabetes. Certainly if one were talking about the primary prevention setting that is diabetes without known atherosclerosis, aspirin is a reasonable option to consider if the patient is having multiple risk factors for ischemia and is at a low bleeding risk. The guidelines are sort of actually down to the endorsement of aspirin primary prevention. But based on the central, there's still a legitimate role in some patients with diabetes even if it's without known atherosclerosis. But certainly if they have known atherosclerosis diabetes, aspirin alone can be considered.

Clopidrogel alone can also be considered. It is something that's validated in the CAPRI trial in secondary prevention. That is in patients with in that case prior MI, ischemic stroke or symptomatic peripheral artery disease. And then the subsequent analysis which show that in patients with diabetes from the CAPRI trial even greater absolute risk reduction with clopidogrel monotherapy versus aspirin monotherapy with no increased bleeding risk in fact lower risk of GI bleeding for clopidogrel versus at

least 325 of aspirin whether that would hold true of 81 of aspirin is not known. But there's certainly no reason to think there'd be increased bleeding risks, so a good safety and a modestly better efficacy with clopidogrel monotherapy versus aspirin monotherapy.

One can consider aspirin plus clopidogrel based on the CHARISMA trial, one can consider aspirin plus ticagrelor based on THEMIS or THEMIS PCI. In fact that's now an FDA approved indication. THEMIS being the largest trial ever done in patients with diabetes and stable coronary artery disease. Certainly dual antiplatelet therapy in patients that have high CV risk and not an increased and at risk of bleeding would be appropriate candidates to consider for dual antiplatelet therapy. In some situations, such as acute coronary syndrome, recent stenting, you have to do it. But I'm talking about the more chronic setting.

Finally aspirin and low dose rivaroxaban based on the ENCOMPAS trial is something to consider. I'll point out this as 2.5 bids of rivaroxaban. The data at least don't exist for there are no acts and even with respect to rivaroxaban that dose 2.5 mg bid is less than say the afib dose which is in some of normal kidney function is 20 mg once a day. If you're going to use this make sure you're using the right NOAC at the right dose.

Management of Stable CAD in Patients with T2DM: Blood Pressure

Other things to mention as I had alluded to is blood pressure control of less than 140/90, perhaps less than 130/80 if there's additional risk factors for stroke or microvascular complications present. ACE inhibitors/ARBs should be first-line therapy because of decreased cardiovascular risk in those with CAD. Long-acting thiazide diuretics are recommended. Chlorthalidone is perfectly good. Hydrochlorothiazide is more commonly used but probably chlorthalidone will be a bit more effective. There can be a slight increase in glucose with thiazide diuretics as you're likely aware of.

Calcium channel blockers can be good in controlling symptoms of angina. It can also provide some cardiovascular risk reduction in those with hypertension as well and it's something that's part of the armamentarium. Aldosterone antagonists such as spironolactone or - - particularly effective in patients with prior MI or LV dysfunction. Finerenone is a non-steroidal drug that's broadly speaking in this class that was relatively recently having a randomized clinical trial data presented. This is a good option for patients with kidney disease on the basis of diabetes. Obviously it's a branded drug and there's a cost associated with it. But it does seem to be another new tool in our tool kit and based on some trials such as FIGOROA, - - analysis, it does appear that a large number of patients with chronic kidney disease could be eligible for that form of therapy, so another dataset to be aware of. And then beta blockers. It's not clear that they have an effect on mortality and uncomplicated CAD patients but certainly in those with LV dysfunction or just multivessel disease, it's not revascularized angina, arrhythmias such as afib, frequent ventricular, you think they can be quite useful.

Management of Stable CAD in Patients with T2DM: Lipids

As far as lipids go, I've alluded to some of this. High intensity statins pretty much for everyone baring contraindications. Ezetimibe should be strongly considered especially if the LDL remains above 70. PCSK9 inhibitor is on top of the ezetimibe, but if the LDL is still above 70, nice and not recommended anymore. There's still a lot of prescriptions for niacin that are written but it is not recommended anymore. Likewise fibrates, not recommended as a general strategy but when the triglycerides are very high, above 500 then they might be quite useful to reduce pancreatitis risk. They don't clearly reduce cardiovascular risk.

There's some ongoing trials, again with fenofibrate. And then there's icosapent ethyl that I mentioned before. I showed the data from REDUCE in there. If the triglycerides are above 135 despite maximally tolerated statin and dietary intervention, there you really want to consider icosapent ethy, barring any contraindications.

Management of Stable CAD in Patients with T2DM: Glycemic Control

Glycemic control is something that is extremely important to prevent microvascular complications. Its effect on macrovascular complications probably is an effect, though rather modest. Certainly meta-analysis in dealing with randomization studies suggests that there's an effect even in macrovascular outcomes. They're probably in the 9, 10, 11% relative risk reduction. The microvascular complication seems like neuropathy or retinopathy, nephropathy, that's where glycemic control really shines. What should the target be? Less than 7% of patients who are young and healthy might be less strict in frail patients, older patients, with multiple comorbidities. Patients that have had multiple bouts of symptomatic hypoglycemia there, you want to be a bit more careful not cavalier.

Management of Stable CAD in Patients with T2DM: Glucose-Lowering Medications

DR. BHATT: What things can be used? I talked about the SGLT2 inhibitors where they have cardiovascular benefits. Reductions in hospitalizations for heart failure benefits even in high risk populations and all-cause mortality, lower weight by a bit. They don't really cause hypoglycemia to any great extent. In general, you need to of course be careful of patients with insulin or - -. They do lower blood pressure by a little bit and do lead to less progression of chronic kidney disease.

The GLP-1 receptor agonists do have CV benefits for some of them in terms of reducing MACE. It's not a class effect. And they're also associated with weight loss and essentially really very little to know in the way of hypoglycemia. Two very well tolerated safe drugs. Expensive but providing cardiovascular and kidney benefits.

Metformin in many places in some guidelines remains the first-line agent. There's a possible cardiovascular benefit if you go to old small randomized data or newer non-randomized registry type data, so just from the REACH registry. But the evidence is nearly as strong as SGLT2 inhibitors or some of the GLP-1 receptor agonists but there's no associated weight gain or really much with hypoglycemia risk. It's a good drug. Many patients with diabetes and CD need more than one drug anyway so it ends up being a bit of a theoretical discussion. You start metformin first and you start with these other evidence-based cardiovascular benefit type agents first.

Now the TZDs probably have the CV benefit, they're not on heart failure. They do include fluid retention and potentially then heart failure. But they do appear to probably have an effect or benefit on atherosclerotic type endpoints. Not much in the way of hypoglycemia. There can be associated weight gain, edema can be an issue that can contribute to the risk of heart failure, some association as well bone fractures.

The DPP4 inhibitors have been neutral with respect to MACE type outcomes. We did see in SAVOR-TIMI 53 an increase in hospitalization for heart failure specifically with saxagliptin. Some of the other DPP4 inhibitors there were signals of increases in heart failure. Some of them depending on which guideline you look at or which label you look at, there is heart failure risk in there.

Insulin and sulfonylureas are likely neutral on cardiovascular outcomes. Probably the data is a little bit, you can sort of make an argument in whatever way you want. But probably the most contemporary data showing new trial outcomes, they can be associated though importantly with weight gain and hypoglycemia. I do need to be careful with them.

Management of Stable Angina in Patients with CAD: Medical Therapy

Other issues in terms of management of stable angina patients with CAD in terms of medical therapy. And this really applies to non-diabetes patients. There are no antianginal medications that reduce morbidity or mortality in stable CAD. That's important to realize. And they tend to have a similar impact in reducing angina. Beta blockers there's a perhaps slight preference among some folks for vasodilating ones like carvedilol. I think they tend to have less adverse metabolic effects that might be more relevant in someone with dysglycemia or diabetes.

The calcium channel blocker can be quite good but avoid nondihydropyridines in patients with LV dysfunction or with concomitant beta blockers. Long-acting nitrates can be useful. But long term use I don't know that I see really causes endothelial function. But there can be tolerance that develops to them and they sort of lose effect. And then ranolazine, there are no hemodynamic effects from that so that's a real plus of that agent, so it's a second or third line agent. It's pretty good. There's also interestingly a moderate reduction in hemoglobin A1c that's been observed.

Management of Stable Angina in Patients with CAD: Revascularization

What about stable angina revascularization especially in the patient with diabetes? I alluded to some of my thoughts. This is from the DHA scientific statement both surgical and percutaneous revascularization outcomes are impaired in the setting of diabetes. There's an increased risk of procedural complications and recurrent ischemic events. But nevertheless in the right patient is still the right thing to do. With multivessel disease, left main disease, complex coronary artery disease, essentially echoing what I was saying before the recommendation is for CABG versus PCI unless the patient is a poor surgical candidate.

But that's only if the surgeon is going to be using an internal-mammary artery to the LAD. If that' isn't part of CABG then really it doesn't make sense to do CABG. It makes sense to do PCI. Typically achieve more complete revascularization and resolution of angina with CABG versus PCI. But obviously the price for that is longer length of stay, more procedural complications, so patient's opinion and choice really matter, as I alluded to earlier, shared decision-making is very important. And the newest-generation drug-eluting stents have narrowed the gap but not eliminated the gap between CABG and PCI with respect to the need for repeat revascularization.

Also in some trials analysis, lower rates of spontaneous myocardial infarction with CABG versus PCI probably because PCI is just stenting that 90% mid LAD lesion whereas that left internal memory or LIMA bypass graft is bypassing that 90% mid LAD lesion but it's also bypassing the 30-40-50 proximal LAD lesion that might three years from now lead to plaque rupture in an MI. Some differences just between those modalities of revascularization bypassing the disease, artery versus stenting, is the most severe segment. Again if the patient has very focal disease, PCI should be performed as fine. If it's a very diffused disease, probably CABG will be better unless it's so diffused that the distal targets where the surgeon wants to anastomose the graph is diffusely disease. These are decisions and discussions that are

often best made with a heart team. That is the cardiac surgeon, an interventional cardiologist, the referring cardiologist as well.

The Evolution of SGLT2i in HF Management

Alright. Let me talk a little bit more about SGLT2 inhibitors. It's hard not to talk about them. They're an exciting class of medicines with respect to the data in diabetes, heart failure, and chronic kidney disease. At this point I'd say the data set is overwhelming growing by the day in a number of trials that are listed that have shown the benefits of SGLT2 inhibitors in patients with diabetes, with normal ventricular function, reducing the risk of future heart failure and in patients with heart failure either with or without diabetes, either with or without reduced or preserved ejection fraction, showing reductions in future need for hospitalization for heart failure. In the higher risk subsets that's even showing reductions in cardiovascular or all-cause mortality.

Effect of SGLT2i on CV Death and HF Hospitalizations in Patients with HF

Speaking of which, here a meta-analysis, we see a 25% reduction in cardiovascular death or hospitalizations for heart with SGLT2 inhibitor use in patients with heart failure.

Effect of SGLT2i on All-Cause Mortality in Patients with HF

In that same population of meta-analysis, a 14% reduction in all-cause mortality was highly statistically significant. These are potentially life-saving drugs in the right patients. In some proportion of these patients of course have CAD. Not all of them do, some of them have heart failure on a different basis. But some proportions have CAD.

Total CV Death, Nonfatal MI, or Nonfatal Stroke

An interesting thing I'm mentioning just for the sake of interest from the SCORED trial is an investigation not currently FDA approved. But here with this SGLT2 inhibitor, it's actually SGLT1/2 inhibitor versus placebo, there's a significant reduction in heart failure as seen with the other SGLT2 inhibitors. But also significant reductions of MI and also significant reductions of stroke which hasn't been seen with the other SGLT2 inhibitors, so potentially an atherosclerotic effect needs to be studied further in the basic science lab and future randomized clinical trials, but still an important and interesting signal of anti-atherosclerotic benefit.

EMPACT MI: Evaluate the Effect of Empagliflozin on HHF and Mortality in Patients with MI

Speaking now of SGLT2 inhibitors, there are ongoing trials such as EMPACT MI in evaluating the effect of SGLT2 inhibitors on cardiovascular endpoints in patients presenting with myocardial infarction. Lots of more data to come here with early initiation of SGLT2 inhibitors in the context of ACS. Here with empagliflozin, but I should mention there's also a trial with dapagliflozin, ADAPT MI that's ongoing, similar sort of randomization and population.

Redefining Residual Risk in the Current Era

That's a quick overview of coronary artery disease. I touched upon various ways of reducing risk with lifestyle modification and with medical therapy. But to summarize really reducing residual risk in the current era, there are a lot of folks who one must consider. Addressing residual cholesterol associated risk in that patient who's already on maximally tolerated statin, in some cases that will be zero milligrams

but hopefully in most cases that will be a high intensity statin. We feel we are still above 100 there really want to watch it down with ezetimibe based on improvement, but also based on FOURIER, on ODYSSEY, PCSK9 inhibitor, if ezetimibe doesn't do the trick.

In the patient with residual inflammatory risk, there are targeted inflammatory therapies will probably be indicated in the future, the data for colchicine that exists right now looks pretty good but the largest ongoing trial that needs to complete in my opinion before we can under a final decision whether colchicine should be part of standard of care for secondary prevention in coronary artery disease patients. There are targeted anti-inflammatory drugs such as canakinumab that was shown to be effective in the CANTOS trial even though the company decided not to commercialize the drug for that indication.

There are other anti-inflammatory drugs where large outcome trials are ongoing. My guess is there ultimately might be a role for an available dedicated anti-inflammatory drug. But we see there's residual thrombotic risk. Unfortunately there's no simple biomarker to say, hey, this patient has elevated thrombotic risk, we still have to use clinical descriptors of ischemic risk and bleeding risk to target who should get out residual thrombotic risk reduction. But we know from trials such as PEGASUS - -, the dual antiplatelet therapy can have an important role in stable coronary artery disease patients with high ischemic risk and low bleeding risk and we know from ENCOMPASS the dual pathway inhibition aspirin and low dose for rivaroxaban. I can also have an important role in reducing that residual thrombotic related risk.

Residual triglyceride risk, we've opened the door widely with reduced age showing the icosapent ethyl is highly effective in patients with elevated triglyceride and increased cardiovascular risk including those but not limited to those coronary artery disease. The PROMINENT trial is ongoing with fenofibrate. That trial is fully enrolled from what I understand, so the results will hopefully be out in the near to intermediate term, so that might provide yet another option to address triglyceride associated cardiovascular risk.

Lp(a) related residual risk seems to be important as an independent predictor of adverse cardiovascular outcomes. There are a number of trials testing targeted Lp(a) reduction. Those trials were positive. No offset in toxicity. This could be a really important therapeutic class. Right now we don't have a lot that we can do, but there is some data suggesting that PCSK9 inhibitors are particularly clinically effective in patients that also have inhibition, elevated cholesterol Lp(a).

And then finally there's a residual risk attributed to diabetes and maybe even prediabetes in the - - proportion of patients that have CAD and I'd discuss in detail the value of SGLT2 inhibitors and GLP1 receptor agonists in that context.

Pyramid of Risk

Finally then to wrap things up here, to sort of end where I started, we want to think as public health advocates about primordial prevention and emphasizing healthy behaviors, to all our patients and communities. We want to really emphasize primary prevention, identify risk factors aggressively, initiate aggressive lifestyle modification and where appropriate, don't be shy, about pharmacotherapy especially if it's a generic pharmacotherapy, even if it involves poly pharmacy as it often does especially for hypertension and sometimes for LDL control. And then finally, secondary and tertiary prevention,

preventing recurrent cardiovascular events in patients with established cardiovascular disease with tertiary prevention to have actual prior ischemic events. That's extremely important. There you want to throw the kitchen sink at patients, really emphasize lifestyle modification but certainly poly pharmacy is going to be part of that. There's no getting around that. And then a proportion of those patients' procedural care, things like revascularization can be life-saving. You really want to take care of patients across all levels of risk here in the pyramid but be particularly aggressive and intense as we get close to the apex of that pyramid.

Well thank you very much for your attention. I hope that this review of various aspects of the diagnosis, management, treatment of coronary artery disease has been useful to you.