ANDREW DUBLIN: OK, well, welcome, and a special welcome to the UCSF med students. I know they're just starting over here at John Muir. So hopefully, it's a great experience and you guys get a lot out of it.

So today, we're going to be talking about cardiac risk assessment and appropriate testing and the medical management of coronary artery disease. And I ended up-- I'm one of the cardiologists here at John Muir.

For those who don't know me, I'm an interventional cardiologist, as well as general cardiologist. Nowadays, in California, in particular, but really, across a lot of the country, there's not so many interventional cardiologists who only do interventional cardiology, and certainly not in our health care system. So I would say at least half of my time is general cardiology.

And as far as training goes, I went undergrad at Brown University and then medical school at Wayne State University in Detroit. So I've been having some flashbacks to my third year at Detroit Receiving and Harper and some of the hospitals out there. So nice to be here, I guess, in California, compared to Detroit.

And then I did my internship and residency at UC San Diego and a cardiology fellowship through the combined program with UCLA and Cedar-Sinai in Los Angeles. And then interventional cardiology, I went back across the country to Lenox Hill Hospital in New York City and did the natural cardiology there.

And then about four years ago, I came to John Muir. And I've been here ever since. So for this talk, I don't have any disclosures.

So let's talk about a little bit of the scope of the problem first. So not a lot of surprise, for more than a century, cardiovascular disease is the number one killer in the United States for pretty much every year, other than a bachelor year in 1918. So ever since then, it's really been cardiovascular disease, number one.

It's the underlying cause of around a 1/3 or more of all deaths in the United States. And on average, an estimated 770,000 Americans suffer a first heart attack each year. And then another 175,000 have what we consider a silent, or unrecognized, heart attack. That's based

on EKGs and data going backwards.

So for those of you who don't do a lot of angiograms or look at them, I think the pointer bar is not working too much. But these are the normal coronary arteries. So LMT is the Left Main. LCx is circumflex, so the branches of the circumflex.

LAD is the Anterior Ascending and Diag, the branches of the diag. But really, what this shows is nice smooth, clean arteries. And that's what we would all hope our arteries look like.

Now we know coronary artery disease doesn't start from the inside out. It starts from the outside in. So this doesn't mean that the patient has no coronary artery disease. It means they have no angiographic evidence of coronary artery disease, a very different concept.

What we're learning how to avoid is progression of the outer coronary artery disease now into the lumen, causing obstructive coronary artery disease. And we're not going to talk about acute coronary syndromes today. This is more of a stable ischemic heart disease lecture. But this angiogram could be a patient with either stable ischemic heart disease or acute coronary syndrome. The angiogram is specific towards that.

Now this is an angiogram of an acute coronary syndrome or an ST elevation myocardial infarction. So that right coronary artery is totally occluded. So we want to avoid that, obviously. We're not going to necessarily talk about the treatment and management of that today. But everything we're doing is really to avoid that.

I tell most of my patients that what I'm trying to do is make you feel better or make you live longer. If I don't make you feel better, and I don't make you live longer, I'm not doing a ton for you. And probably medicine's not necessarily what you're going to need. So if we can avoid this, we have the opportunity to make them feel better and make them live longer.

So the other thing I tell my patients is we're really not in the business of telling you this is going to happen or this isn't going to happen. We don't say you're clear for surgery. There's a lot of things that we used to say that we have gotten away from. And we're almost now in a risk prediction business.

And our job is-- the way I do my job as a patient's cardiologist is to put the odds in their favor instead of the house's favor. I mean, if you take Vegas as an example, we want to be the ones with the best odds going into it. And anything we can do to improve the odds, that's what we're doing.

Even in the best circumstances, patients could still have heart attacks, despite their optimal medical therapy, despite the optimum risk factor modification. And I think that's an important feeling for the patients to get. Set the expectations reasonably, and also make everyone rowing in the same direction.

So do we have a crystal ball? Can we say, you're going to have a heart attack? You are not going to have a attack. Obviously, we don't. But we do have good risk prediction models.

And the models that we use are calculators that have been developed over many patients, over many decades. And the important thing is these are estimations of cardiovascular risk in the individual without known cardiovascular disease. So it doesn't make a lot of sense to run a Framingham risk calculator on a patient that had a non-STEMI last year and had the stent in the right coronary. So these are without known cardiovascular disease. That's how you get the prediction.

Framingham is probably the most famous one and most commonly used. Most of you already should know that Framingham is a population in Massachusetts that's been studied for decades. And it's typically been looked at since the '50s and beyond to look at what's the incidence of coronary artery disease, what risk factors have been associated with it.

There's also the ACC/AHA pooled cohort. That's a hard cardiovascular disease risk calculator. There's a Reynolds risk calculator. So you can find a bunch of them. It's just get comfortable with one, know the ins and outs of it. And typically, that's what most people do.

Usually, they'll give something like a 10-year risk for a hard cardiovascular endpoint. So there's also lifetime risk calculators that you can use. And obviously, those are going to be different. Talking about what your lifetime risk is as a 40-year-old versus an 80-year-old. But what patients really can get a hold of is that 10-year risk. If you're talking about something like stopping smoking, obviously, you want to emphasize lifetime risk as well, so all together. But again, patients without known cardiovascular disease.

So I like the Framingham a lot. I think it does a great job and gets the message across to patients. It opens their eyes a little bit. Things that go into Framingham, obviously age, gender, total cholesterol and HDL cholesterol, not LDL cholesterol in the current version of it.

So it's important to talk about LDL, and we're going to talk about that a lot with treatment. But

that does not go into the Framingham risk calculator. Systolic blood pressure goes in, as well if you're on medications to treat hypertension. And then a smoker, which in this calculator is defined as any cigarettes in the last month. So that's what a smoker should be according to Framingham.

So let's look at a couple examples and see what really drives this calculator. So the first example is what I think we would all consider the ideal low-risk patient. I think it already says less than 1%, low risk. And I think most of you, if you just looked at this profile, that's what you would latch onto, I guess.

A 40-year-old male, total cholesterol of 130, HDL of 45, nonsmoker, blood pressure 120 on no meds. So if that patient came into your office, I don't think you'd be overly concerned that they're going to have a heart attack in the next 10 years, as you shouldn't be. So they'd be low risk.

So what is the only thing we change? We don't change anything out, but we give him 30 years of life and make him a 70-year-old, exact same total cholesterol, exact same HDL, nonsmoker, blood pressure great. He'd jump up immediately into intermediate risk, because age is the biggest driver of this entire calculator.

So it's a 10-year calculator, so between 40 and 50, very few people have heart attacks, no matter what their risk factors are. Between 70 and 80, a lot of people have heart attacks, even under the best of circumstances.

So looking at few more examples, now we've got that same 40-year-old, but now we'll give him some risk factors. So he's got bad cholesterol. His HDL is low. He's still a nonsmoker, but his blood pressure is 150. He's not taking any meds.

This guy probably comes into your office pretty frequently, I would imagine. Not frequently to see you because he has had a lot of medical problems, but a lot of people with this profile are in your office. So he'd be a 3% low risk over the next 10 years.

Now if you make him a smoker, he does jump up into the intermediate risk category. So smoking does confer quite a bit of risk, on top of the additional other risk factors. So he'd jump to 14% in the next 10 years a heart attack/stroke death.

But now we jump this person up 30 years again, the exact same risk factors, still a nonsmoker. And now he's already high risk, over 20% risk of having a heart attack in the next 10 years if

you're 70 and you have poor control of your risk factors. So that's what we call quantitative risk assessment. And that's really the first thing that should be done.

All patients, really, from the time they come in as an adult, a physician should have-- start looking at their risk calculators, whether it's lifetime risk or 10-year risk. It really helps them think about the disease process. And then it gives you the first opportunity to get them comfortable with a lot of the blood pressure, cholesterol.

Yeah, once you've done that, if a risk-based treatment decision is uncertain, then you can look at other things like high sensitivity CRP, coronary artery calcium scores. These really aren't go-to tests. They're not default tests.

They should be reserved for specific circumstances and specific patients, ones that maybe calculate to a low risk, but you have a feeling about them and think that they're probably at a little at higher risk than they're calculating to, a patient that you already have told them that they're an immediate risk, and they should be on therapy. But they're very resistant to medication.

This gives you another way to say, well, not only are you an intermediate risk, you've already developed coronary artery disease. You have calcium in your coronary arteries. And that's been shown that people generally will take statins and take other medications that you recommend if they have more of a visual evidence of the disease, as opposed to just the risk. So I use those as more of a selective target, not a broad-based approach for everybody.

So now what? We've established the risk. That's fine. We can predict it, but now let's lower the risk. I mean, that's really why people come to see us.

So just to the very basics, risk factors come in two flavors, non-modifiable and modifiable. Some things you just can't do anything about yet until genetic manipulation gets better And the fountain of youth is found. Until then, we're going to be stuck with age as a non-modifiable risk factor. The older you get, whether you're a man or a woman, the higher your incidence of coronary artery disease, the higher your risk for developing it.

Gender as well. So men typically start younger than women with developing coronary artery disease. But later in life, after menopause, typically then women will catch up. So don't think that this means that men should be treated differently than women. It's just that their risk occurs at a younger age, and for the most part. But women should obviously be treated

aggressively in risk factor modification as well.

Family history of premature coronary artery disease, defined as man less than 45 years of age, women less them 55 years of age. If they have a first-degree relative with that, then that confers additional risk on them, not that they can do something about that yet.

So that's the bad news. The good news is there's tons of things they can do to lower their risk. So I try and get them focused on what they can do.

The modifiable risk factors, I call better late than never. So diet is a big one. Everybody thinks they eat healthy and says they eat healthy. And, oh, I eat the Mediterranean diet, but they probably don't. In this culture, in this market, it's difficult to maintain that.

But are we just talking to say, oh, diet sounds like a good idea. Everybody should eat healthy. Or do we really have evidence that you can make a difference with coronary art disease based on your diet? And the reality is we do have evidence. So healthy diets are associated with lower cardiovascular events in patients without established disease. And there's a lot of others that suggests that even patients with established disease, changing your diet can impact your future.

So one of the big studies that came out in the last year or two was called PREDIMED. And it's a primary prevention trial, over 7,000 patients, 7,500 patients, being the patients at high risk for cardiovascular disease. And they were randomized to three different diets, the Mediterranean diet supplemented with olive oil, Mediterranean diet supplemented with mixed nuts, or a diet aimed at reducing fat intake, so a low-fat diet.

And I think a lot of people would have assumed low-fat diet would be either. But the reality is both of the Mediterranean diets, whether it was olive oil or nuts, outperformed the low-fat diet for prevention of the primary endpoint, which was a combined endpoint with myocardial infarction, strokes, or cardiovascular death.

This is a hard endpoint. It occurred significantly less often in the two intervention groups, 8 events per 1,000 person-years versus the latter. And that was statistically significant, so a substantial cardiovascular benefit from the Mediterranean diet. So I mean, I really push that pretty hard on patients. That's something that they can do. Even if it just means a little more salmon a couple times a week, it's going to have a benefit for them.

You can also tailor it a little more specifically to patients who have really high LDLs. You may want a diet that emphasizes vegetables, fruits, whole grains, work with nutritionists. There is a low-fat component to it. Limit the saturated fats to 5% or 6%. Calories from trans-fats are reduced. So you can tailor the diet a little bit. Obviously, if you have blood pressure issues, then you would want to keep your sodium less than 2,400 milligrams a day. And that will help with the blood pressure, specifically. The European Society of Cardiology, in 2012, basically recommended both for primary and secondary prevention, that this diet, which is sort of a description of the Mediterranean diet, be followed, oily fish at least once a week, less than 2,000 milligrams of sodium, low saturated fatty acids.

Moving on from diet and on to hypertension, or high blood pressure. So as JNC 7, we all know the definitions and how to treat it. I don't want to spend too much time on hypertension. But obviously, it's one of the things you run into most frequently and even get referrals for, because a lot of patients-- for some patients, this is really difficult to get on top of, no matter how many medications they take, no matter what they do with their diet. Some skinny people have high blood pressure, obese people. It can be really frustrating for a lot of patients. And assuming that the med compliance is good, which in this, really, we have pretty good med compliance. Although, you never know if people are taking everything you give them.

There was a lot of earlier segments for renal denervation, only in these resistant hypertensive patients. I don't know if any of you heard about it or got excited about it. I was actually extremely excited about it, because it was the first non-medication to show benefit in resistant hypertensives, other than diet and exercise, in forever in the early trials.

And so then it made it to the bigger trials. And the reason we do bigger trials is because sometimes they show us things that we didn't see in the early trials that it actually wasn't any better than a sham procedure.

So the way they did this trial was they-- actually, it's an invasive procedure. So you actually have to go in and denervate their renal nerve. And they actually did a catheterization on patients and didn't denervate their renal nerve and then compared it to patients who they did the catheterization and did. So some patients actually got a full catheterization with all the risks, protections, preparations, everything, and didn't even get the therapy. But what it showed was that they had the same blood pressure reductions as the people who got the therapy.

So this is basically not done right now. Maybe they didn't pick the right patients. And it's always the same thing with the trials. If it doesn't work, it's probably that you just designed the trial wrong, not that the therapy was bad. Therapy, the companies are going back to the drawing board to come up with a way that maybe they can still use this technology. So it hasn't been totally abandoned. But it's certainly years away from prime time now.

Diabetes as we all know, is a coronary artery disease equivalent. And in 2011, the AHA and ACC chose not to make a strong recommendation for a specific hemoglobin A1c target. So instead, they emphasized the importance of lifestyle modification and also coordinate care between primary care physicians, endocrinologists, cardiologists, just trying to get these people treated.

But they didn't say, you need to drive the A1c down to 7 or 6.5, or whatever. So the ACC did not come up with the things in that. Now we're 50% talking about diabetes because our lectures in and of themselves.

So obesity, obviously, we know, a big problem. Most of it, we measure from the body mass index. It's not a perfect system, but it's the best we have right now. And if you've done this on yourself, and you're me, you may be surprised what it tells you, that you're overweight when you considered yourself in pretty good shape. But being 25 to 29 on a BMI is not that difficult to get. I'll just say that.

[LAUGHTER]

Over 40 become morbidly obese. Over 30 becomes obese. So there's different definitions. And again, everybody's going to say, well, I'm just big-boned or thick whatever you call it. [LAUGHTER] And you take that into consideration. Everybody does have their own personal body type.

But we know that BMI has real value. And the real value is that it's a risk factor for coronary artery disease, that as your BMI gets higher, your risk of developing heart disease goes up significantly.

So in general, it's also central abdominal obesity that we know is a little bit worse than overall obesity, or what's called apple body . And it does contribute to hypertension, cholesterol, insulin resistance, diabetes, metabolic syndrome. But the increase in cardiovascular disease is present in obese patients without the metabolic syndrome and without these other things.

So it's really you have to treat the obesity to improve all your risk factors. But even in and of itself, it's still a risk factor. True for men and for women.

So the Nurses' Health Study looked at the relative risk of coronary heat disease. If your BMI were 21 to 23, it was 1.19. As it went up, 23 to 25, then we're up to 1.46 relative risk. By the time you got to 25 to 29, so I'm at two times relative risk-- and I said, I'm 25 to 29, but-- and then 3.56 relative risk if you get into the actual obese, greater than 29, 30. Note the risk of dying 15 years out was four times higher in women, particularly BMI 32, compared to less than 19.

So yeah, treatment of obesity will decrease hypertension, diabetes, cholesterol. It will make management easier. So there's tons of reasons to focus on weight reduction in a healthy way, not fad diets, not get the weight off as quick as possible. I'm not even going to talk about bariatric surgery. But that's something that, for the really morbidly obese, you should really look at.

So now moving on to physical activity. Regular physical activity, we know is beneficial. You get improvements in everything that you get with treating obesity better lipids, better blood pressure, diabetes.

ACC/AHA did make our recommendations specifically with physical activity, that it should be performed three to four times a week, on average, 40 minutes at a time, and involving moderate-to-vigorous intensity. So take that for what you will. That group should be exercising probably more than we are. For the most part, a lot of our patients we have to keep on [INAUDIBLE]. It's just a good reminder to remind them.

Now looking at secondary prevention in patients who've already got it, who have already been diagnosed with coronary artery disease. Prior to starting an exercise regimen, though, this is your couch potato who had a heart attack a couple of years ago and has finally seen the light. And he wants to start exercising.

Their recommendation is that they should undergo a risk assessment, physical history. And if they really are sedentary, then an exercise stress test prior to starting an exercise program so that they don't become a weekend warrior and tries to do the triathlon they didn't train for and dies of ventricular fibrillation because they were ischemic.

The 2005 meta-analysis looked at 11 randomized trials, 2,285 patients with coronary disease, most of whom had MI. And they were assigned to exercise or usual care without focusing on exercise. And a 28% reduction in all-cause mortality for the patients who were assigned to the exercise group. So it really made a huge difference.

We have cardiac rehabilitation programs that are one of John Muir's strongest offerings. And we have them at Concord. We have them at Walnut Creek. We have them at Brentwood. There's also one down in San Ramon. And these programs for patients who have had a recent acute coronary syndrome revascularization really should be mandatory. I mean, we try and get every patient into them.

Some patients who are younger, and they're working, and it's hard to do a 12-week session three times a week. But most patients that can do it, love it. They get time out of it. They're surrounded by people who are in similar circumstances than they are.

They're a bunch of semi-retired cardiologists that are not in the show. And it gets really almost universally good reviews. If you have any issues with it, let me know, 'cause what I've heard is universally good. Other patients with chronic angina, cardiomyopathy, peripheral arterial disease, also could be candidates for the cardiac rehab.

Smoking, no surprise, it's not good for you. But what happens if you do smoke, and now you want to stop, are you going to ever get back to the same risk as your friends who don't smoke? And the reality is that within three to five years, you can reach the same cardiovascular risk as nonsmokers.

So it's never too late to stop smoking. You didn't already do so much damage that it's not worth it to quit, that everything that you smoke causes acute inflammation. You can have acute plaque rupture with each cigarette, on top of the chronic inflammation you get from being an everyday smoker. So it really is something that you just have to talk about every time. And yeah, odds are you'll have a success.

And the only thing I think that's been proven to improve smoking apply a smoking deficient appliances, talking with your health care provider and getting encouragement from him. So it really makes a big difference. I'm sure you all knew that, but just as a reminder.

Again looking at 12,000 patients, smokers who had already had a heart attack or bypass surgery or revascularization, the relative risk of a quitter-- so it's kind of a funny way to say it--

but if you quit, you were at 0.64 relative risk, compared to if you didn't quit. So a lot of benefits for the quitters. I want to tell you why you want to be able to quit this.

So 2,600 patients survived to hospital discharge after a first MI. The longer you quit smoking, the better your chances of not having another heart attack were. And so really, I hope I've made that point clear enough. Everyone should be talking about smoking, that they should [INAUDIBLE].

Cholesterol, negative thing. This one, I mean, we could spend hours on. So I'm going to try and condense it. I'm obviously not going to get everything. One think I'll say is that of all the interventions we do, this gets the most pushback from patients, universally. And it can cost you hours of your time discussing the-- proving risks and benefits of statin therapy and of management of cholesterol.

And besides that, I had a patient literally come into my office two days ago and tell me, I read somewhere that 98% of patients who take statins don't need them. And it's like, wait, where could you possibly have gotten that number? [LAUGHTER] 'Cause they read it on the internet, and it's true to them. And so it's just you just have to be aware that there's a huge prejudice from a lot of patients to not take statins. And I'm going to give you some evidence that they are dangerous. But that doesn't mean we shouldn't be encouraging our patients to take them in the right situation.

So again, hopefully, this is mostly review, but elevated levels of LDL, triglycerides, low levels of HDL are associated with an increased risk of cardiovascular events. Now the surprise, one thing that is a surprise is that all the treatments that improved LDL have been shown to improve cardiovascular outcome.

So we've developed drugs that raise HDL. They didn't improve cardiovascular outcome. Triglyceride drugs, they don't improve cardiovascular outcome. So it doesn't mean you shouldn't do it for other reasons. But if you're looking at improving cardiovascular outcome, the proven therapy is LDL-lowering, and not any LDL-lowering. We'll talk specifically about that at the next line.

Among the drugs that have been tested in patients with elevated LDL, only the statins with one carrier, which I'll talk about in a second, have been convincingly shown to improve cardiovascular outcome. And they do it across a large level of baseline LDLs. People with LDLs in the 190s can benefit. People with LDLs in the 90s, if they have coronary artery

disease, can benefit. And so any high-risk patients with established cardiovascular disease, they really have a reason not to be on a statin.

And so the benefits, like I said, have not been shown for niacin, fibrates, bile-resins. Your LDL-lowering drugs like statins, they do have a modest benefit on-- effect on triglycerides. And, like Crestor, for example, can raise the HDL. So you can get some others with the profile benefits. But in general, the focus is on the LDL.

The reality is that statins probably have some of what we call pleiotropic effects or voodoo or magic, or however-- anti-inflammatory. I mean, pick your favorite where the patient will relate to and use that to convince them. It's probably not just an LDL story. It's probably something inherent in the statins. But we're still working to prove that.

The reason I say that is because if you give a patient 80 milligrams of Lipitor right before you do a PCI, they're gonna do better than if you don't give it to them. And they didn't lower their LDL with that one dose of 80 milligrams of Lipitor. So it's clearly more than just LDL-lowering. There is something else going on. And it's just our job to figure out what it is and try to communicate that as much as possible.

So again, patients with established coronary artery disease, at least a moderate dose of a statin is recommended, regardless of the baseline LDL. There's been large randomized trials of secondary prevention showing benefits of lipid-lowering with statin therapies on subsequent MI and stroke. Intensive statin therapy doesn't just reduce a first cardiovascular event but also recurring events as compared with standard therapy. So intensive statin therapy is better than standard statin therapy. So Lipitor, 40 milligrams, is better than simvastatin, 20 milligrams in these patients.

And you can go to a website and actually download high-intensity statins and moderate-intensity statins and keep a list if you want. Those are not the Crestor and Lipitor that they're talking about.

So in these trials, a positive relationship between the degree of LDL-lowering a magnitude of reduction has been observed. Now this is where I do respect the patients and respect when they're coming from. Very few patients over 75 are involved in these trials. So patients 85 years old, I mean, they have every right to ask you what's the statin doing for me?

And we can't necessarily give them as much of an answer as a patient who's 50. We know

what it's doing for the 50-year-old more than we know what it's doing for the 80-, 90-year-old, 95-year-old. I mean, we see them all. So look, I'm not trying to pooh-pooh the fears that concern a patient. It's just [AUDIO OUT].

So lower is better than, for the most part. But it's a little bit of a myth that cardiology communities put out there. We've never actually tested that hypothesis. So we don't generally take a goal LDL and try to get to it. We generally give a dose of a statin and then see where the patient ended up. And then that's where I say 70 is a good number, because in the PROVE IT trial, that's where most of the patient-- that's where the average LDL was on patients on hydrotherapy. So it's a little bit of a bait and switch. But that's the best that we have right now.

It's important to know that, nowadays, in all these trials, because statins are so well-established, the competitor is never a placebo. We're not comparing Lipitor to a placebo and saying Lipitor is better. It's always to another statin [INAUDIBLE] already established as being important. So at this point, it would really be wrong to do a placebo trial.

The PROVE IT-TIMI 22 and TNT, these trials have been out for going on probably a decade now. Large meta-analysis looking at [INAUDIBLE] adults, that's the same thing. And so basically, the recommendation officially, just so you know what the guidelines here, adults with known cardiovascular disease, 75 years or younger, should be treated with high-intensity statins. Those 75 years and older, it's reasonable to evaluate the benefits and risks. So take that for what you will.

Yeah, we know it lowers the risk of death 15% to 20%, non-fatal MIs by an even greater degree, and stroke reduction. This is 170,000 people in this secondary prevention meta-analysis. These aren't small trials that we're saying, hey, take a statin because it benefited 200 people. These are thousands and thousands and thousands of patients.

When do we know that you're crazy? If you don't take the statins after an acute coronary syndrome, we actually-- even though there is concerns with high-dose statin, atorvastatin 80, on long-term, in the short term, every one of the patients I treat starts out on Lipitor 80, atorvastatin 80, for the most part, if they come in with an acute coronary syndrome, because whatever they were taking before didn't keep coronary syndrome from happening. So generally, we'll intensify the regimen. And we may do it for only a few months just so we can get over that initial hurdle. But if they have side effects, obviously, we don't require that they

take it to [INAUDIBLE]. But we certainly give everybody a chance to succeed.

And patients who do not reach their LDL goal with statin-- so this is where I said there's one caveat to the statins are the only proven therapy. So after years and years and years of finally digging and trying to prove themselves as a good drug, ezetimibe, or Zetia, finally came out with a trial that showed benefit. A lot of controversy because it was used in the market for years before they ever had a trial that showed clinical benefit. But now that they can go back and say, see, we told you so. Look how beneficial it what.

So during the trial called IMPROVE-IT, that was just recently published last year, it was a post ACS trial, 18,000 patients, so a really big trial. And they compared patients on Zetia plus a statin to a statin alone. And so it was again not two placebos. And it was not Zetia alone. It was Zetia on top of the statin. So it reduced the combined endpoint of cardiovascular death, MI, unstable angina by 6.4%. So if you can't get to goal on your statin alone, Zetia is reasonable to use as endpoint.

So again, I told you I was going to tell you something that wasn't all good news. I don't know if you get the same journals I get. But in *Dia Pathology,* which I don't get that journal, but I get highlights from it, the [INAUDIBLE]. It was just a recent population-based study-- this is probably a few weeks old-- that shows statin therapy increased the risk for Type 2 diabetes by 46%. It's a massive number, even after adjustment for confounding.

So higher risk for diabetes than previously thought-- maybe 10% increased risk, 20% at the most. Now we know the majority of the people in the study [INAUDIBLE] simvastatin, and the risk for diabetes was dose-dependent. So the higher dose they were on, the more likely they were to develop diabetes.

But again, that doesn't mean you don't treat your patients with atorvastatin. It doesn't mean you don't treat patients with simvastatin. Diabetes is not coronary artery disease, heart attack, stroke, even though it's an equivalent risk. So if it's appropriate to treat your patients with a statin last month, it's still appropriate to treat them with a statin. It just means you have to be aware of what's out there, what you need to talk to your patients about, and what you need to monitor for.

So now let's talk about another one of my favorites, LP(a). So this got a ton of press and publicity and hype in probably late 2000s, 2000 naught, so whatever you call it, 2000, aughts.

So in 2010, the European Atherosclerosis Society said, we recommend screening for elevated LP(a) in people at moderate to high risk for cardiovascular disease via another calculator, and that the desirable level is less than 50. And this should be a treatment priority after you've dealt with the LDL. So again, they're not trying to usurp LDL. There's a thing after you've dealt with LDL. Look it up in your [INAUDIBLE].

Then they recommended that you measure it in high-risk individuals, especially those with premature coronary artery disease and family history, recurrent CVD events, despite statins. And then they went further and recommended niacin as the primary treatment. And niacin does lower LP(a) by about 30%. The problem is we have a lot of niacin trials that show it doesn't have cardiovascular benefit, even though it does do what it says it does.

But again, use only in LP(a) patients. And so again, with aim high and [INAUDIBLE], but they are not positive trials because they looked at the wrong patient. And you can make your own judgment about that. We don't have a trial that says yes yet.

So moving away from risk now, on to testing. So appropriate testing-- it's an interesting word, "appropriate," because appropriate use criteria are all the rage now. And obviously, nobody wants to do something that's inappropriate. So in 2012, the American College of Cardiology, and about 15 other societies. came out with guidelines for diagnosis and management of patients.

This is where it's important to be honest. We're talking about stable ischemic heart disease. We're not talking about coronary syndrome. We're not talking about unstable angina. We're not talking about chest pain, unspecified. We're talking about diagnosis of stable ischemic heart disease. So if you suspect that your patient has stable ischemic heart disease, then it is recommended that they undergo stress testing to both secure the diagnosis, because sometimes we're wrong, and to get prognostic information.

And the choice for which stress test to do depends on a lot of factors. And we always say if the patient has legs and they can exercise, a treadmill test is the best starting point, assuming that their EKG doesn't have left bundle branch block, ST-segment changes already. So there's well-published data on who should get stress testing, with exercise testing versus pharmacologic. But in general, the default tends to be a treadmill test, because you get much better prognostic information. If they go 10 minutes, even if they're ischemic, their odds of doing poorly are low. So even with coronary artery disease, just knowing that they want 10, 11

minutes gives you a lot of useful information.

So once the information is obtained, then the therapeutic approach is determined based on the results and individual patient characteristics, obviously. So low- and intermediate-risk patients whose symptoms are controlled on medical therapy, most often can be managed without intervention. And I'm an interventional cardiologist.

So high-risk patients or those with angina refractory to medical therapy, then obviously, we're going to start looking at revascularization. And that can be either with PCI or with CABG.

So one more test that I want to talk about is CRP, which we talked about a little bit before. But there are some people suggesting that evaluating CRP response after statin therapy and then implementing further treatment to reduce the CRP is a good approach. It's coming from subgroup analysis of PROVE IT-TIMI 22. So I don't tend to focus too much on that. I mean, I focus much more on the statins and CRP more as a marker. It's never been a proven therapeutic target before. Until it is, I would still use it as a marker. Potentially, that comes from-- that's something you've heard about.

So now I move away from testing and talk about medications again. So now this is specifically medical therapy for coronary artery disease or for stable ischemic heart disease. This isn't risk factor modification anymore.

So when you think about medical therapy for coronary artery disease, the first thing to talk about is antiplatelet therapy. So if you have coronary artery disease, however you came up with the diagnosis, there's not a contraindication, you should be on aspirin. The dose, anywhere from 75 to 325 milligrams are associated with the best risk/benefit ratio. Personally, I use 81 milligrams almost exclusively, because there's really no evidence that 325 milligrams of aspirin is any better than 81 milligrams for stable ischemic heart disease. And you're going to get a little more GI upset, a little more intolerant, a little more non-compliant. So I think 81 is just fine, personally.

Obviously, if you've had a gastrointestinal bleed on low-dose aspirin, then once it's treated, be on the PPI, try and get back on the aspirin, if possible. And obviously, you have to work with your gastroenterologist about that. But it doesn't mean that just because you've had one event, you can never be on aspirin ever again. Now if it's a massive bleed, obviously, that's different. So just teamwork, a team approach. If you're allergic to aspirin, then clopidogrel is a reasonable alternative. And there are people who are very allergic to aspirin.

One group of medications that we're not talking about are ticagrelor, prasugrel, so new dual antiplatelet therapy-type medications, thienopyridines. And the reason we're not talking about them, at this point, they have no role at all in stable ischemic heart disease. They're not treated-- the studies were not done in stable ischemic heart disease patients. They were done in acute coronary syndrome patients. So that's not part of today's lecture.

So if a patient has a Plavic allergy and an aspirin allergy, would I probably give them Brilinta? I would. But that's not part of the pathway we're talking about. So it would be off-label.

So antianginal therapy-- so now we've done the antiplatelets. Now we're on to antianginals. Really four classes of drugs that we use in the management of angina-- beta blockers, calcium channel blockers, nitrates, and then ranolazine is part of its own class.

Beta blockers are generally considered a first line therapy. They reduce anginal episodes. They improve exercise tolerance. They reduce heart rate and contractility, obviously. It's important to note here, all types of beta blockers have been equally active in the exertional angina. So there's no evidence that metoprolol is better than atenolol, better than Bystolic, better than t pick your-- Coreg-- whatever your favorite beta blocker is.

So in this indication, any beta blocker is fine. In addition, beta blockers are the only ones proven to prevent reinfarction and improve survival after you've had a myocardial infarction. That's all being further evaluated. But for now, beta blockers are a first line therapy. We don't use them in Prinzmetal angina or vasospastic angina, because they are ineffective, and they actually may make it worse. They can increase coronary vasospasm. So we're talking more about atherosclerotic coronary artery disease.

Calcium channel blockers, usually used in combination with beta blockers when beta blocker initial is not successful. Or if they really haven't intolerance to beta blockers, some patients have a lot of side effects from beta blockers. And we'll put them on amlodipine. They've got some channel blockers that have a heart rate component to it, and they'll do better.

They improve symptomatology by coronary and peripheral vasodilation and reducing contractility. We generally try and use the long-acting diltiazem or verapamil in there or second-generation dihydropyridine like amlodipine, felodipine, because short-acting dihydropyridine have been actually shown the mortality after a myocardial infarction. So generally, we'll stay away from those.

Nitrates, usually this is a sublingual used to treat the acute episode. You obviously have to teach the patient how to use it. There's a spray. There's a tablet under the tongue. We also have long-acting nitrate. And there is a one today, mononitrate. Dinitrate, you can use a couple times a day.

The problem with nitrates is that you tend to get a nitrate tolerance the longer you are on them. And so eventually, that may not be beneficial for them. It's usually, at this point, more of a third line agent, a lot of headaches with it. So one thing I will use this in especially for the patients who love to go on their hike up the hill. And that's the only time they ever get angina. Otherwise, they do fine. Then I'll tell them to take a sublingual before they go on the hike. And then oftentimes, they'll be able to do their hike and not get the chest pain and then do fine with that.

So if it's a specific circumstance where they know they're going to get angina, just on their own, just taking the sublingual before they get the angina and doing the activity, and maybe they won't get it. No different than giving them oral or dermal nitrate.

And then ranolazine is really the newest one used with beta blockers or as a substitute. I don't know if you guys use a lot of ranolazine. But you do have to be careful when you're initiating them on it. You have to bring them back and in to [INAUDIBLE] 500 twice a day. You have to bring them back in about two weeks and then give them an EKG, and make sure they're not having prolonged QT changes.

The drug wasn't developed as an anti-ischemic. It was actually developed as an antiarrhythmic But if doesn't really work as an anti-arrhythmic. It does work as an anti-ischemic. So the bad thing about it is it doesn't really have blood pressure effects. So if you have a patient who's already running hypertensive, and you don't think you have room for amlodipine, then the [INAUDIBLE] ranolazine can be a good choice, because they'll generally tolerate it a little bit better.

So now we've left the world of medications, and we're on to the world of revascularization for stable ischemic heart disease. So obviously, COURAGE trial was really a landmark trial in establishing how best to start treating patients with stable ischemic heart disease. It doesn't say how to finish treating them, but it says how to at least start treating them.

And yeah, it was published in 2007. 2,200 patients, if you haven't read it, a must-read medical

literature [INAUDIBLE] that there can be patients assigned to aggressive medical therapy alone or aggressive medical therapy plus PCI. Mind you, I think these were done with experimental stents. But really, the results are pretty irrefutable.

Patients were required to have objective evidence of ischemia. 87% were symptomatic. So, I mean, it was a really well-done trial. They called it COURAGE, because it took a lot of courage to not put a stent in a tight blockage when you know you could, and you don't know if you should. So a medium follow-up of 4.6 years. No difference between the two treatment strategies for death or MI. So they both happen about 19% of the time.

So it doesn't matter if you had an 80% lesion, if you got optimal medical therapy, or if you got more optimal therapy plus a stent, there were some differences in rates of angina. So that's why I say it doesn't tell the end of the story. It more tells the beginning. If you have a patient that's refractory to medical therapy, COURAGE doesn't tell you not to put the stent in. It just tells you not to do it as first line therapy. So we interventionalists, we like to find reasons to put stents in.

There was another trial called Fame 2. I'm not sure if you guys are familiar with this one. It obviously didn't generate as much of a [INAUDIBLE] as COURAGE did. It was a stable coronary artery disease trial. And it was looking at fractional flow reserve, which is basically a stress test on the specific blockage. You do it in the cath lab, so it's an invasive procedure. But you take a wire. You normalize it before you get to the blockage. Then you cross the blockage, and you measure the flow difference that you're giving adenosine to maximally. make some--

I'd remake and then measure the difference that we have in number at point A. If it's less than or equal to Point A, we call it physiologically significant, because you could have a 70% lesion that's not physiologically significant. Or you could have a 60% lesion that is physiologically significant. And it's partly due to how long is the lesion, and there's a lot of other factors.

So this trial looked at FFR positive. So if you had a positive FFR, then maybe a stent was better, as opposed to COURAGE, which didn't look at the physiological significant lesions. It just looked at all lesions. And the primary endpoint here was a composite of death, MI, urgent revascularization. And this trial was stopped early, which I'm not sure that that was the best thing for it.

They enrolled 1,200 patients. The reason they stopped it early was because the PCI group, the stent group, did so much better than the non-stenting group. But they didn't do better in

heart attacks. They didn't do better in deaths. They did better in urgent revascularization. So it's a softer endpoint. That's why I said I'm not sure it was the best thing for it. It was part of the combined endpoint for the way they designed the trial. They were kind of stuck. But it's a softer endpoint. I mean, it's not a heart attack. It's not death.

So what we can say is, in patients with stable coronary artery disease and FFR positive functionally significant lesion, then PCI plus optimal medical therapy decreases the need for urgent revascularization. That's not as powerful as saying it decreases your risk of death or decreases your risk of MI.

So now we move on to CABG or bypass surgery. And CABG can improve survival. So when you tell patients you want to make them live longer and feel better, in certain patients, you're going to make them live longer if you send them for open heart surgery. It's still true today in 2015 as it was 20 years ago.

So when we're talking about which patients benefit, left main, we know there's a survival benefit to bypass surgery, if you can use a LIMA as a conduit. And when it's your left made equivalent, that's basically if you have a 90% proximal LAD and a 90% proximal surge, you basically have a left main disease. So that's the left main equivalent.

Also, patients with acute coronary artery disease, especially if they have a reduced ejection fraction, they'll have a survival penetrate with bypass surgery. And then two vessel disease if the proximal LAD is more than 75% off, you might as well send them for CABG also.

So then who do we stents in? Those for whom CABG offers the survival benefit, but for whatever reason, they're a non-surgical candidate. So there are certain left mains that we want to open it, but the patient isn't going to get open heart surgery. So then we'll do PCI. Also, like we said, refractory angina as the maximal medical therapy. And then, depending on your opinion about Fame 2, that's another indication.

So in summary, lots of calculators are used to estimate cardiovascular risk in patients without previous diagnosis. The key to life is risk factor modification, both for primary and secondary prevention. A stress test is important to secure a diagnosis and also gives you prognostic information. Medical therapy includes the antiplatelet and anti-ischemics, as well as statins. And then there is a role for CABG and PCI and stenting in stable ischemic heart disease, but it's more limited than initially thought.