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TRANSCRIPT - GR 04 04 25 **"Ischemic Heart Disease 2025"** guest speaker Noel Bairey-Merz, MD, Cedars-Sinai

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Internal Medicine Grand Rounds

- So it's my pleasure to introduce Noel Bairey-Merz. Noel Bairey-Merz is this year's Groelman lecture. But 1st let's introduce the Groman lecture itself. Dr. Jake Goldman received his Md. Degree from the University of Maryland, and his training over Uin in Baltimore City and the University of Nebraska
- undertook basic endocrine research in collaboration with his brother at Hopkins, subsequently started a private obgyn practice in the DC. Area was on the staff of Washington Hospital Center. 45 years later he retired to his second career in farming in Gordonsville.
- Marjorie Groman received her Bs degree from the University of Maryland. She then underwent Diabetic Cranium University, and donated his mentorship before his.
- These are the past Goldman lectures. You see, we had a couple of years hiatus for the little pandemic that got in the way, but otherwise these are incredible luminaries in the cardiovascular field, and it's really an honor to have Dr. Gray Mars here with us today. So
- she graduated with an undergraduate degree from the University of Chicago, followed by an Md. At Harvard, did her Residency and Chief Residency at Ucsf, followed by a
- cardiovascular fellowship and chief fellowship at Cedars Sinai. She remained there ever since is now the Irwin Sheila Allen endowed chair in Women's Heart Research and Director of the Barbara Streisand, Women's Heart Center, Professor of Cardiology and Biomedical Sciences at Cedar Sinai, and professor of residence at Ucla.
- She is a world renowned, expert in women's heart disease.
- aging menopause, etc. She has been the pi for the wise study which actually, I participated in in the 19 nineties as a site in Pittsburgh. And that's been going for almost 30 years. She's the co-pi of the warrior study that we just presented last week's Accustore Grant on aging.
- and is a co-investigator. 400 full peer reviewed manuscripts and a well over 250 reviews, chapters, and editorials, and given over 600 National International invited lectures.
- Her past honors include for the Bernadine Healy leadership Award for the Acc. And women's cardiovascular care. She's been president of the Association for University Cardiologists.
- She's a master of the Acc. And won a distinguished clinician scientist, award from the Acc. Over a decade ago. She's an editor of the Esc. Cardiovascular Medicine Textbook, and on the editorial board of the European Heart Journal Circulation, and several others. She's also won the Nanette Wenger award from the American Society of Preventive Cardiology.

- This is her. The topic of her talk today is playing on the bottom, and she'll be a lot of data.
- Well, many thanks for the invitation and the honor of being the annual Groman lecture Awardee. And what I'm going to talk about today is centered on
- ischemic heart disease in women. And we said yesterday, thank goodness for the study of women, because, increasingly, this is turning out to be a man's disease as well. So hopefully, I'll be able to convince you of that. These are my conflict of interest, and dominantly related to a board of directors on ep topic, not of relevance today.
- So for a more general medical audience, I thought I would start with a case 54 year old postmenopausal female presents to the emergency department with prolonged chest pain, 12 h at rest.
- She has a past medical history of gestational diabetes, hypertension, and dyslipidemia, family history, father with a stroke at 59, mi at 66, and she's currently managed on hormone replacement, therapy, oral progesterone, estradiol vaginal tablets and hydrochlorothiazide and a 12.5.
- So you're called to the Ed. She's hypertensive but not tachycardic. She is the average American. Her Bmi is 31 physical exam. Is unremarkable pulmonary exam. And these are the older high sensitivity troponins. And I've provided you with the reference range there less than 0 point 5. So she had arrived, calling
- and troponins and fasting lipids. Who knows why they did them then? But it looks, you know, not bad, but not good.
- At that time they were doing breast myocardial perfusion rather than the Ccta. To decide who goes up to the Cath lab. And, in fact, she did have, in addition to her non-st wave changes in 3 and a half. She did have an anterior wall. Perfusion, defect that you should advise her to take it upstairs. Normal Lv. Function by echo be up 64%. No wall motion abnormalities.
- And when they take her upstairs to have the angiographic study, her lvep is 9 normal up to 12. She has no obstructive coronary disease, no vasospasm, no monoclonald.
- So let's just go and do a pre-test by a show of hands with the diagnosis. Who thinks it's coronary basal spasm.
- He thinks it's myocarditis. He's had a myocke right? We all agree. She's had a heart attack open artery. Myocke how about coronary? Microvascular dysfunction? All right, all right. What causes it? Atherosclerosis?
- How about ischemia due to endothelial and non-endothelial dysfunction.
- all right how about all of the above.
- All right, there's that paper. This is what gets you in these stem careers how to diagnose it. Conservative, hey? She had symptoms. She had evidence of ischemia and no obstructive safety. Non-invasive
- myocardial blood flow reserved with a pet or MRI advanced imaging. Is that how you would make it? Yeah.
- How about invasive doing coronary, flow, reserve testing in Doppler or Lombardy or I/O.
- So how about any of the above? Yeah, right? And number one would be a presumptive diagnosis right? It wouldn't be definitive. But you'd be right
- all right. Last, but not least, how to treat it.
- Anti atherosclerotic therapy lady aspirin, high intensity, statin pacer, arbitr

- caretakers, basic scientists, both for everything. How about anti-seemic therapy? Alpha beta blockers, calcium channel blockers, nitrates rinolazine not so much and we don't know if she has persistent symptoms. Yet what about non-cardiac therapy? There are no evidence-based guidelines currently for this group.
- Alright. Number 4, all of the above. Yeah, okay, alright. So that's your pretest.
- And one more test.
- Is this a Monet or a Manet? Okay? Who thinks it's a Monet? You got a vote?
- Who thinks it's a Manning.
- Monet or Mayonnay some things. It's a Monet thinks it's a manet. Okay, here we go.
- You guys are definite stem guys and gals. Your stem. That's my name, and it's really embarrassing, because that was his wife.
- Now, this is the mayonnaise, and more. If you got this one right, because in your college dorm. You probably bought this poster and put it over the bed right? So this is. This one is much more famous.
- Now, if you want to, therefore, to go back and train in our history and get better at this right? Us stem people. We have to have rules about how we're going to make decisions, so you might say. Well, matinee uses a lot more color, and it's not as edgy.
- it's more loosey, goosey.
- the mayonnaise. He always used black. He loved black, and it's tighter. The painting is tighter, it's less loosey goosey. Okay, now, what relevance does this have to what we're going to talk about? I will share this with you. It's a teaching tool. So we're going to talk about ischemic currency 2025, or, thank goodness for the study of ischemic heart disease in women.
- and we're going to go through an epidemic of death low hanging fruit which was issued gender. We can still talk about that here.
- Number 3 is critical investigation, which is sex. And then we'll talk about results of our labor and hopefully translating that into policy in our future. So this is a slide that a lot of people have seen multiple times, but it really bears repeating. We never sex stratified the data until 19 seventies. When we finally
- started sex stratifying. And these are Cbd mortality for our nation.
- And what was a shocker was in 1984, the gross crossed. So the male mortality that had continued to decline predominantly in findings in men. 4 men and 5 men was really not helping women right. The war that we were thought we were winning in cardiology.
- not only from public health, but up to diagnosis and treatment. We then fast forward 10 years until the movie and Dr. Bernadine Healy, writes Neontel syndrome, that she thinks the reason women are not reaping these same rewards is they don't look like men.
- And then 12 years for Women's Ischemia Syndrome Evaluation to be commissioned by National Heart, Lung and Blood, the Aha. As well as the Acc. As well as the Society for Women's Health research, all start campaigns, 12 years to take action. But it did happen.
- One of the things that we looked at early on in the Y study was this paradox. This was commissioned, and we did a systematic review. This was published in Jama, and then you can see this is now remote history, 2,005. But at the time no one had bothered to sex stratify the data, and what we saw was in these cohort studies, these registries that all had poor lab adjudicated Angiography

- that it turned out open arteries in the setting of Minoka were 2 to 3 to 4 times more prevalentine. And when you ask the internationalist. When's the last time you got an N. Stemi or a Frank Stemi or an Acs with open arteries, they couldn't think of one.
- They couldn't think of one despite this, the data that was sitting under our nose. So we so it's, you know, definitely contributing to what we consider that epidemic of death.
- So let's go forward low hanging fruit. And again, gender. We're defining it here in all of our biomedical research defines gender as that sociocultural attribute that aligns with the sex and not always. But that's why we're using it. And this is how we use it as defined by the office of research and women's health at the Nih.
- And so what were some issues of gender? Well, when people have obstructive coronary disease, it's easy to see, because we had dominantly studied men, and, as I said before, in men for men and by men, I mean, how do we do stress testing the Bruce protocol, guess who made that Dr. Bruce guess who runs on the treadmill, Bruce.
- So there were so many aspects of what we had done that were really fabulous. We were again winning the war on cardiovascular disease in men.
- What we hadn't recognized was there was a dark side of the moon, and that when we recognized that women could present with Acs and Stemi and Stemis with open arteries. We had to start looking further, and so, in fact, small vessel dysfunction was what wise was commissioned, therefore, and what we identified. And it turns out to explain a lot of these gaps.
- This is an editorial that we published in the European Heart journal. And again it talks about this issue of gender.
- those real cultural attributes. So why, in the obstructive coronary disease pattern? Why is Barbara dressed up like a man. Barbara starts in from the movie because at that time in Europe turn of the century. That's how you became Literate was that only men could learn how to read and write.
- When you look at Barbara on the right, looking like the female, then you see that this is more of the microvascular pattern. And here's what happens when physicians recognize disease when they can make a diagnosis, they can deliver a therapy. And so you see the therapies, low dose aspirin, beta blocker, asin statin. These are our guidelines, right? This is our secondary prevention. And so you see that the majority of those people are men
- in the stick figures where you look on the other side with Barbara looking like a woman. It's probably about 25 to 30% of ischemic heart disease, and it's dominated by women. There are men.
- And then what you see. Finally, last, but not least, is that surplus of death right? The epidemic of death that we were seeing in women. So we think this recognition, this issue of the sociocultural attributes of looking like a woman, was contributing to the surplus of death.
- Here's what happened. And again, in the 1st 10 years of this journey, guidelines were increasingly becoming important, and for those of you that discharge patients from your Ccu or your step down unit. They're typically now a reminder. Doctor, low dose aspirin.
- beta Blocker, if appropriate, acr and high intensity statin. And these were the Acs guidelines at the time they still are. This is sort of a challenging. It's not our work. I

would have had a better graphic. So what I've done is color, coded it. And following guidelines, implementation, the lives that were saved were female lives.

- and that really, again tells you they were not getting recognized, not diagnosed, so, therefore, not treated. The top 2 lines are, are the male patterns. No, no value. If we thought women and men should do the same. This is the blue lines right? And and we might even say women should do better historically. But this is the work that's laid out for us.
- All right. So why? Why do these things differ, therefore? And then we need to delve into sex differences. Right? It's not this recognition of Monet or mane. It's not pattern recognition, although that's critically important.
- But let's now talk about why these things might be different. So here's a number of registry studies that just demonstrate the prevalence of normal and non-obstructive coronary arteries is much more common in women than men, and these are all clinically indicated angiograms. These were not registry studies of asymptomatic folks.
- And this is what drives typically chest, pain, shortness of breath, or even sudden cardiac death will biennial coronary angiogram with an invasive cardiologist, and, as I said in the beginning, a man problem, too. So here's more contemporary data from our Va heart study. This is coronary angiographic
- of every angiogram done in our Veterans. Administration Hospital. Even though we have many women in the military. Now, one out of 5 soldiers is female, the ones that are getting coronary angiograms at this time, still dominantly are men.
- And so what you can see now is no obstructive coronary disease is now common even in men, and this is likely the result of the diabetesity epidemic as well as over-the-counter, low dose aspirin in primary care, physician intensive statins, just handing statins out like to hand up the Ssris, which is a good thing. It's a good thing.
- Yes, please. So we're seeing a demographic change in the amount, the accumulation, and then small vessel, dysfunction being preferential over obstructive coronary disease.
- We now know also, like I said, there's the dark side of the moon that we just now sort of put our foot in the water, and we acknowledge that it's there.
- atherosclerotic disease on the left, something we know we love, we know how to treat. We feel very gratified, and often it's a plumbing issue right now, increasingly, we can do optimal medical therapy, which is what I call liquid plumber. But when they get to us too late. We throw in stents right? And we do things like bypass surgery.
- Vasospastic disease is also in the textbooks, and sometimes called prince metals angina that turned out in our wives of women that have a higher amount of vasospastic disease, meaning Raynaud's migraine headaches only about 3%.
- But if you find a prince battles patient, they will thank you for their calcium channel agent, and they will come and renew it every year, and if you try to take it away from them. They will go see another doctor. So it's not common, but it's relatively easily treated. So the dark side of the moon was this microvascular dysfunction.
- and in this editorial that we wrote we said, these can overlap
- these can overlap, and when you think about your patient that has triple vessel disease that has either been declined the Biposurgery because they won't quit smoking, or you know, somebody didn't want to do stents, and they keep showing

up often. That's collaterals, and that's a code word. If you want to explain it to the cardiologist

- for small vessels right? That there are small vessels that will bail you out if needed. So this is probably prevalent throughout these different phenomenons of cardiovascular disease.
- and it turns out, even though we throw stents in, and we do most of the bypass. In these epicardial coronaries they normally contribute less than 10% of the coronary vascular resistance. So they really are not the dealmakers that we think the epicardial coronaries are. Of course, the Epicardials are important, especially if they become plugged up acutely.
- but hemodynamic significance really doesn't occur until at least 70% of the woman is obstructed.
- Coronary microvasculature, on the other hand, is responsible for greater than 70% of the resistance under physiological circumstances. So we really should know about the small vessels, and we should be paying attention to them. Why studies with our longer term follow up
- have been demonstrated to sort of 2 basic endotypes. There probably are many more endotypes, but the impaired visibility, meaning the small vessels, do not open up when you go up a flight of stairs. You have a deleted argument, or you're just needing to do a little more work, and this is adversely impacted and predicts death
- as well as major adverse cardiac events, such as heart attacks and heart failure. The increased vasoconstriction is the other endotype. You test for both of these. This one pretty much dictates hospitalization for angina and persistent symptoms, and if we think back to our patient we'll be asking, does she have persistent angina? Can you guess which of these endotypes?
- No, you have to do the testing, but they clearly have not only different prognoses, but they likely have different pathways of treatment. This is longer term follow up again, done by some of my fellows demonstrating that most of the patients have atherosclerosis.
- They have no obstructive coronary disease, but they do have coronary atherosclerosis. So certainly a lively contributor to this type of physiology is coronary atherosclerosis. Yet up to 25% do not have coronary atherosclerosis evident. And so those are again, perhaps a different endotype. And then this is showing the impaired
- microvascular dilation predicting cardiovascular adverse events and death, when the increased constriction predicts hospitalization, we've demonstrated. And again, this was when intravascular ultrasound was new in the coronary arteries. Over 80% of these I know the subjects have coronary atherosclerosis. Again suggesting this is a potential treatment target.
- the mechanisms. Again, this is genuine ischemia, magnetic resonance spectroscopy, which is not a clinical tool. This is pure research available in selected centers. At the time of the wide study the University of Alabama was able to do this work, although we can do it now, and it just really demonstrates that myocardial ischemia is frequent in subjects with signs and symptoms, but no obstructive coronary disease.
- and that these are not false positives. You can find textbooks that say that women have a high rate of false, positive Ecgs on stress testing. And it turns out there are 2 positives. So you can always correct textbooks on board or even go online Wikipedia

- mechanisms. So coronary flow reserve, again, is the one that is the most impactful in terms of abnormal dictates, increased events, including death. And this is a sex specific threshold. So for coronary flow reserve. In most other settings the threshold for abnormality is 2.5, but it's probably a little lower for women. 2.3 2.
- We then embarked on a number of what we call randomized pharmacologic probe trials. And again, what we do is we take a pharmacology that has a known effect. Quinipril ace inhibitors are known to improve endothelial function, and we got our 1st hit, which improved coronary flow, reserve, and reduced angina for new inhibitors or anti-anginol in the setting of small vessel dysfunction.
- These others a hormone replacement therapyterone, added to the ace sednafil is a Pd. 5. Inhibitor, Rinolazine, a novel now not so new. Not sure how it works. Anti-anginol drug
- and none of these other ones were particularly positive in terms of improving outcome. So this, then, led to, and, as we heard earlier, we just presented this warrior trial at the American College of Cardiology. Scientific Sessions last week.
- Warrior stands for women's ischemia treatment reduces events in non-obstructive coronary artery disease. The investigators are listed. As you see, we have planned an appointed care strategy, trial of 4,422 subjects with angina, and no obstructive coronary disease by angiography.
- and they were randomized to an intervention of intensive sun and acerr
- versus primary care. Guideline directed risk factor management which actually was mutual care, and the reduction of mace all cause death, non-fatal, mi stroke or hospitalization for angina or heart failure.
- It would be unethical to treat these patients to take away treatment for dyslipidemia treatment for hypertension. So again, this was a pragmatic trial done again at point of care.
- The structure is here. Patients were randomized, but it was open, labeled, the outcomes were blindedly evaluated, the intensive medical therapy included again high intensity statins. So Rasuva, 1020, 40, Atorva, 1020 40, 80,
- and these were provided to the patients and mailed to their home, maximally tolerated Ras blockade with an ace, or, if intolerant, an R. And you can see the doses there, and we had replicated, or we were hoping to replicate what we had seen in our pilot studies.
- submitting and putting preparing slides before last week. I don't have the slide here, but it turns out it was a neutral trial. We under enrolled because of the pandemic, so we were underpowered. We had a higher than expected and planned contamination rate, or what you would call crossover. So we had low adherence, relative low adherence
- in the Imt. So it's considered a non definitive trial with not arguing for or against this as a therapy at this time, and the manuscript will be forthcoming.
- So that was a lot of evaluation. What has happened since we went forward with this campaign? Here's the results of our labor, and in the 1st 10 years
- curve down, male mortality continued to decline, but the curve was definitely bent. We take partial credit for this meaning. We can't really prove observational associations, but we certainly saw a 43% decline in cardiovascular disease deaths in women. So where does this leave us? Well
- again? Thank goodness for the study of ischemic heart disease in women, because a lot of what we're talking about and we've been doing for the last 25 years has direct relevance to the new, relatively new type 2 mi, and it's defined by

- a rise and fall in cardiac biomarkers evidence of ischemia. But it doesn't have unstable CAD, and it's due to a mismatch in myocardial lysogen supply and demand. And, as you can see, to the right of this graphic abstract, it's more common in women, not exclusively women, but definitely more common in women
- and likely small vessel. Continued investigation as to mechanistic pathways and treatment are going to offer some knowledge about what can we look like to? Mi.
- you know. Look it up.
- What do we? What should we do with type? 2. Mi, no, yet guidelines. And we don't really know what to do. And we would see again, you know, a lot of variety in treatment patterns.
- So thank goodness for the study of women. This has also led to new chest, pain, guidelines and icd codes addressing this new epidemic in women and men.
- So there are codes now for Inoca. There are codes now, for Mynoga may or may not be useful in terms of making a specific diagnosis, because, as we know, different things contribute to this, but it was done, I believe likely, because of it, will increase awareness right? When a physician can code for something, it means
- something. A diagnosis was made, and it may lead to less therapeutic inertia.
- And so we'll see. This was an editorial that we wrote with Dr. Martha Kawati, who led the new testing guidelines and the different types of diagnosis that we answered questions in those introduction questions. The new guidelines endorse those in the 2 a category meaning we should pursue establishment of a diagnosis.
- So policy in our future. Where are we doing? Well? Not that great are we? Both curves are now starting to grow up. So we're back. We're we're going back to the future. This started before the pandemic. So while the pandemic may have accelerated it.
- this certainly can't be blamed on the pandemic, and we're seeing this along with erosion in control of risk factors as well as again the diversity epidemic.
- So as we say, more, more work ahead for sure. All right. Well, let's get back to our patient. So she went up to the Cath lab as I shared with you. And it turns out she had mid lad bridging with a focal plaque
- at that site on Ilas, and you can also see that that, as well as an very abnormal coronary fuel reserve of 1.8.
- She also has a dentist, induced vasoconstriction and chest pain distal to that bridge. And again, probably focal plaque. You can only see certain things of the ibis, because it's a fairly large catheter
- with nitroglycerin. She has resolution of the basic constriction, and then she has one more treatment target. She has an abnormal left, ventricular and diastolic feeling pressure right? And her bowel function was normal. I already showed you the echo or ejection. Fraction is normal. So why is her Lvdp elevated right? Probably due to ischemia due to this coronary, microvascular dysfunction.
- So we make a diagnosis of ischemic heart disease. That is still a good. Icd 10. Code to use 9 and 10 with coronary, microvascular dysfunction and coronary vasospasm.
- We also said in our notes, it's mid-led bridging. It's not a significant bridge in a functional term, your cardiologist would say, leave that alone, but it turns out it's a nidus for a focal plaque, and then a focal amount of vasoconstriction.
- We diagnosed her with an N stemi, and she subsequently had late gadolinium scar on her cardiac MRI, and that elevated lvedp. You can either call it diastolic dysfunction or not, diastolic dysfunction remains a little bit of an enigma about how

to term it, and whether or not it's truly etiologic or just a symptom of everything else that's going on.

- We treated her with aspirin, low dose, and ace inhibitor, which we had showed previously, was beneficial. She didn't have persistent angina and responded to Carbadolol, and we often use very low doses in our women
- to ameliorate symptoms. They don't have to be fully beta blocked if their symptoms improve, and we think it's probably related to autonomic nervous system control, which is other than endothelial control. Endothelial, dependent
- self control. The autonomic nervous system is pretty important in the small vessels, something when nitroglycerin is needed, we tend to not use long acting nitrates because of the problem of nitrate tolerance, and because most of the small vessels, the pre-arterials before the capillaries don't have any smooth muscles, and nitroglycerin is a smooth muscle drug
- hormone replacement was carefully discontinued. We have an endocrinologist that will help us get them off the hormones, and if you want to talk about hormones, it's fine. I always get questions. If you have established cardiovascular disease, it's a black box warning, so use it, use it at your own risk. And she was referred to cardiac rehab.
- So we do Seattle angina questionnaire scores. We use the sac 7, which is quite quick. People can do that in 5 to 7 min. And so she had a baseline of 67, which means she has multiple episodes per week and one year after treatment, she's up to 74, which is close to clinically significant improvement in a randomized control trial.
- and she had no further myocardial infarctions or hospitalization for angina, which often turns out to be one of the most important treatment outcomes in this group that often are highly symptomatic.
- All right. So you get to. You're going to do well on the test. But remember, there's going to be an art history test as well. So okay, so what was the diagnosis in this paper?
- Myocarditis? No coronary oops? Oh, no, I think something happened in translation? The answer is coronary microvascular disorder. I don't know a problem. And one of the things is that that was the diagnosis that she has right. And therefore it's also important
- again, to recognize that Minoka mimics myocarditis can be a fairly common minor mimic. And that's where. And you're very strong here in cardiac MRI. That's your best test. But no, she had microvascular dysfunction. Let's see how many of these messed up. What causes it? Atherosclerosis Ischemia
- all of the above. Yeah, okay, my, the mess up. It should be all of the above, but somehow it's the other 2. But that's correct. I'm sorry I should approve these before I sent them by email.
- How to find it? You knew the answer. Okay, that one didn't get scrambled. And and part of it is these new chest pain guidelines endorse advanced imaging as well as invasive
- as 2. A. So what does 2 a mean? You can consider it. There's some data to suggest that that could be helpful. It's not a class one, and you should do it. And so I, in my own practice, if they're over 65. If they have the risk factor burden that we saw in warrior, we treat them anyway, they need to be treated, and if they have persistent angina. Then we might go on

- and try to find a better treatment target. But I think the Conservative is reasonable in patients that are at otherwise how to treat it. You also did well on this. Okay, that one didn't get scrambled and we don't know really right? We don't know. And I've been meeting with your Cardiology group here, encouraging all of you to do research. And you are doing research. And I'm delighted about that.
- And we need to test these newer metabolic agents that seem to be making a difference in heart failure with preserved ejection fraction. And there are multiple lines of evidence that do suggest that this microvascular dysfunction is a precursor to another female dominant disease.
- Okay, so here's your test. Alright. So who thinks the one on the left is a Monet.
- Alright. How do you think is
- right? Okay, so that's correct. The one on the left. And why is it? Why is it a Monet?
- Brighter, more color, and not so edgy. This is the only way I got the color. Yeah, all right. What about the one on the right, Amone, or Mayonnaise? You can put Amone.
- All right, man, edgy black. It was black. Okay? So now you can recognize obstructive coronary disease and a heart attack.
- and you can recognize the heart attack and no obstructive coronary disease. Right? So it's just pattern recognition. And I was, you know, particularly delighted to do both cardiology and medicine, because if you don't recognize what's going on. You won't call a cardiology. Consult right? Okay. I'm glad to have been able to do this with you. So that's the Monet.
- and that's the mandate.
- All right. So let's let's summarize ischemic heart disease is prevalent. It's the leading health threat for women and men. It remains, and it's going back up. So we are all guaranteed jobs. There are sex and gender differences in heart disease, presentation. The sex differences probably drove the study. The gender differences of mostly studying and sort of missing the boat. About these sex differences.
- myocardial infarction with no obstructive coronary disease now called Minoka and type 2 mi, which is a component of that Minoka is an umbrella term, are increasingly common in women and men.
- Right diagnosis can include empiric as well as advanced and invasive diagnostic methods and emerging data supports statinase. And our large outcome trial was neutral. So more work is clearly needed. There was a large trial and outcome. Trial started also around the same time in Sweden called Beta Heart.
- Beta, yeah, something like that. And it was a randomized, controlled trial of minoca to Beta blockers in Statin, and they were probably smarter than us, and when they couldn't enroll in the pandemic they just stopped. So they were, and they were also under enrolled.
- Let me thank my co-investigators here on the left, and then our clinical team, because we do see these patients, and again chatting with some of your junior faculty about starting programs. When you are seeing these patients, you have 2 advantages. You are the clinician who can make those bedside observations and bring that back to the research team work with your basic scientists and clinical imagers.
- But, more importantly, the patients trust you and are, I think, more willing to be enrolled. We've never had problems enrolling women in the study, even though everyone else seems to have problems. So you know, do your due diligence. And

then, of course, this is our funding in the tiny small print. But we need to thank our patients in the middle

- because they volunteer for these projects. Many of them say things like, I'm doing this for my daughter. I'm doing this for my mother. I am doing this for the future, so thank you for paying attention. Happy to take questions. But remember your pattern recognition.
- Thank you very much for a wonderful presentation. So we have time for questions.
- Nice. We know that you didn't have a data study, but it looks like you're still inclined to use quinopril quality of data, suggested the quinopril. Time was positive.
- We don't. We don't have the secondary analyses yet. We closed. We locked the data set and unwinded, and started analyzing. 3 weeks before the Acc. We had submitted a promissory abstract. So that is one of many additional analyses
- in an initial forest plot. We didn't really find any subgroup that did better or worse. We did have a sensitivity analysis which would adjust for all of the crossover as well as site to site. We had 71 sites, and that did suggest a 25% mace reduction in the intensive medical arm.
- Confidence intervals obviously look very wide. And it wasn't a primary analysis. So we can't go to town with it, but it does suggest that what we had as our pharmacologic probe trials.
- had we been able to deploy, the intervention
- would have probably paid off, and we remain, I mean, who's not to like about the good benefits of high intensity statins A's and arps for run of the mill. CAD. Yeah, thanks. Thank you very much. It's an inspiring talk, as usual in the patient that you showed that had minoca.
- is there a role for more aggressive antiplatelet therapy with a p. 2, y. 12. Inhibitor or adapt, we tend to like, not think about those situations and get a stent. But yeah, this is another a great suggestion. And we, in addition to that, being a knowledge gap, right? I mean, there are no other trials in this space.
- despite it now encroaching probably 50% of women and men.
- So trials are needed for sure, and I think trials probably could be funded now that men are in the game as well. Right? Yes, but the additional evidence that I have again as a bedside clinician
- when I started seeing younger women, and by that I mean 45, 55. Sometimes they have lupus, sometimes they had some chest radiation, and I started ordering what we call a prothrombotic workup factor, 5 linen Mtphr Prothrombo mutation and lupus anticoagulant. It's just a quick screen. I just, you know, 4, and we have a little sat.
- And in these patients we get a hit in 25%, and when you send them to the regular hematologist, they say this is nothing, you know, being heterozygous for Factor V. Lyme, this is nothing, and I'm like, but they just had an open, artery heart attack, and I have a hematologist. Now. We train together at Ucsf, and she will do additional testing and advise us. And so I am doing that.
- I'm not putting everybody on that yet.
- Yeah, I was just going to ask that. Yeah. So this is from Dr. Pole. Thank you for this wonderful presentation from the primary care perspective. What initial screening tests do you recommend for women presenting with tangible chest pain. I'm assuming Pet or MRI would be follow-up studies if initial testing raises the possibility of Cmd.

- yeah, this is a really good question. And about a 3rd of the patients would have sort of exertional angina like you as a clinician, you know, would say, Wow, that's angina. That's what I learned about two-thirds have all sorts of, and one of the things is another separate line of inquiry that Dr. Pooja, one of our former fellows now at Emory.
- is adenosine is one of our, you know, lock and key receptors and adenosine does all sorts of things. You know. God, in her wisdom only gave us a few lock and keys. Adenosine is one of the pain pathway receptors. And so we think that these patients also likely have pain, pathway, abnormalities to account for all this, Atyp, and we're not supposed to say typical chest, pain.
- non-cardiac. What is perceived as non-cardiac chest pain, but as a primary care. Physician. You are probably hearing. They have chest pain for hours
- for hours, and their components are negative. What's going on? How can they have so much pain? So it's actually really hard, I think, to know what test to order based on those clinical demographics, and I'm not sure every patient that came into my primary care practice would benefit from an MRI or a pet.
- and what I might consider doing. I know you have a women's heart center here. You might consider engaging them and getting some advisement, and I'm not saying you shouldn't pursue.
- you know. Important stuff, meaning. Don't ignore women with chest pain, and don't rely on the specialist, but I'm not sure I would do all that testing. I think I would probably be more judicious of whom to test.
- It's hard to get those tests authorized as well.
- Thanks for a great talk you had mentioned earlier that primary care settings through a lot of statins, and then I thought the next S. You were going to say were Sglt 2 inhibitors. I was curious what data is emerging in terms of treating more intensely with Sglt. 2 inhibitors with Myoka. Yeah, great question. We actually were invited. We do these pharmacologic probe trials actually, quite affordably, because we've got the platform where they're all fairly well phenotyped. And then we can randomize them for the 16 weeks trials and use mechanistic outcomes, coronary flow, reserve, and pri in the in the MRI, and we were invited by Nova Nordisk for Semglutide and by lexicon for and before the pandemic, and we submitted to their investigator initiated platform, and everything went down in the pandemic. And now we're just kind of trying to see if they're still interested. And I do know that one of your cardiologists is doing an Sglt pilot right, and probably other people are interested in this as well. I would guess it's been a very pleasant surprise that these new diabetes drugs are so cardiometabolically important. And it's turning out ischemic heart disease probably is a metabolic problem in addition to an inflammation problem. So hopefully, additional treatment targets that we can all use right. I'm a big believer in liquid plumber.
- And I've got 2 questions. One is, you know, I come from the nephrology divisions.
- The cardiac mortality is very high, and most of them die from non ischemic you know events. And and I was wondering whether I mean I mean, there was a lot of delay in investigating women, but I'm wondering when we send our patients to cardiology for investigation, whether they closely looked for small vessel disease, because they don't find much large vessel, and they die from there. And so that's 1 question.
- And the second question that I have is trying to figure out what is causing this increased fasom in these small vessels. You know, and we are focusing more on

the blood vessel itself. But could we do something outside the blood vessel like, and you you kind of alluded to the bigger snow as one possibility.

- But I'm wondering whether, because, you know, platelets are really full of articles and just going back to his question in something. I was wondering whether whether anyone has looked at information and mediators of information that can cause, you know spasms.
- So let me one of the things the early thing that you said let me address that. So you know, dialysis patients at least the last time I looked, and you can correct. But they die of sudden death or heart failure. Yeah, exactly. And the other thing is, don't they? Typically have? Lvh yes, yeah. So one of the things to sort of remember, I mean clinical pearl, maybe glass B, but an lph, patient is starting to have microvascular dysfunction because they have hypertrophied in an abnormal way. And it typically is worse than how much angiogenesis they can recruit. So they typically start to have ischemic urgency from inadequate capillary and and flow to the heart muscle. And it's, I think, the underlying tenet of why Ldh. Has been bad for you and contributes to sudden cardiac.
- So that's another just kind of you know. Why we have to treat hypertension. And why would people have Lvh, we need to pay attention to that, and really go at them with the aces and the r's, which are better drugs. That was number one, number 2 was what contributes to the vasoconstriction. We're actually starting to work with your genomic group because they think they have a genetic signal.
- That is predisposing people to that part of it that said it wasn't. It did not predict death, the way that the lack of dilation of the small vessels is. And here's the last thing I would comment. I think your question.
- There are both anatomical and functional problems to the small vessel. The left ventricular hypertrophy problem is dominantly anatomical. We have a mismatch between the numbers of small vessels to the amount of myocardium that needs the oxygen.
- And then you have the other problems of Ldh elevated. Ldp, right? So you've got a gradient problem. You know what wants to flow downstream, and if the pressure centrally is high, it doesn't flow. And then functional problems are more autonomic nervous system and failure, meaning the infrastructure of the Myocardium is just fine, but the little arteries are not dilating up, or a function of the so I hope that helps. But I bet there's a lot of small vessel dysfunction in in dialysis patients.
- I you know I don't do nephrology dialysis patients. So that would be a literature search. Oh, in Cmd. Oh, yes, yes.
- Good that we have done that. Yeah, they have, you know. It's 2 thirds of them have atherosclerosis, so it's hard to sort of imagine that they wouldn't have elevated il 6 hscrp, and they do. It hasn't been like a deal maker for us, you know, when you put it into the regression, not everything else fades.
- It's it's a multi multi factor process. Yeah. Yeah. But you know, would colchicine help.
- When so many of the lupus patients don't have pericarditis, they have anginal pain, that's what it is. Don't put them on prednisone.
- And so inflammation. Right? Yeah. Good thoughts. What is your threshold for? For glp-one S. Now especially based on the select trial, right? Underlying mild obesity and underlying heart disease is indication, the amorphic effects, blood pressure lowering, anti-inflammatory effects.

- What is your threshold? Yeah, my concern about the glps today is there's no off-ramp, and I'm compelled by that there was a Jama review, not a review. It was a study that 26% of patients that were using it for non-diabetes indications, only 26% were still on it at one year and it's a combination of it's they're not well tolerated.
- They're expensive. And the insurance company. I I have one patient. You know, we lost 30 pounds since a 1 c normal. I said, we pay for it anymore. I mean, he was diabetic.
- Yeah. And and there are some pretty bad side effects, and also people just get tired of being nauseous all the time. So well, I actually, because I don't treat diabetes. I'm actually not prescribing them currently. And I'm waiting for an off ramp and the oral semblutide that was also prevented at the Acc. The Pbd study stride. Yeah, that was positive. And so, you know, if we started to get better tolerability, because what patients are doing now in the heart space, or even just in the weight management space is their weight cycling and I don't think that's healthy. I know it's not healthy. The literature is very strong that it's not healthy quick question. We have time for one more. Yeah, that was really interesting talk. Thanks. I had a question kind of about the patient example that you talked about. You mentioned that they were on hormone therapy, and that they were taken off, and that it's a little bit of a black box. Is there any data on like Cmd. And people who are on gender affirming care, or anything like that, are they at higher risk? All right, thank you.