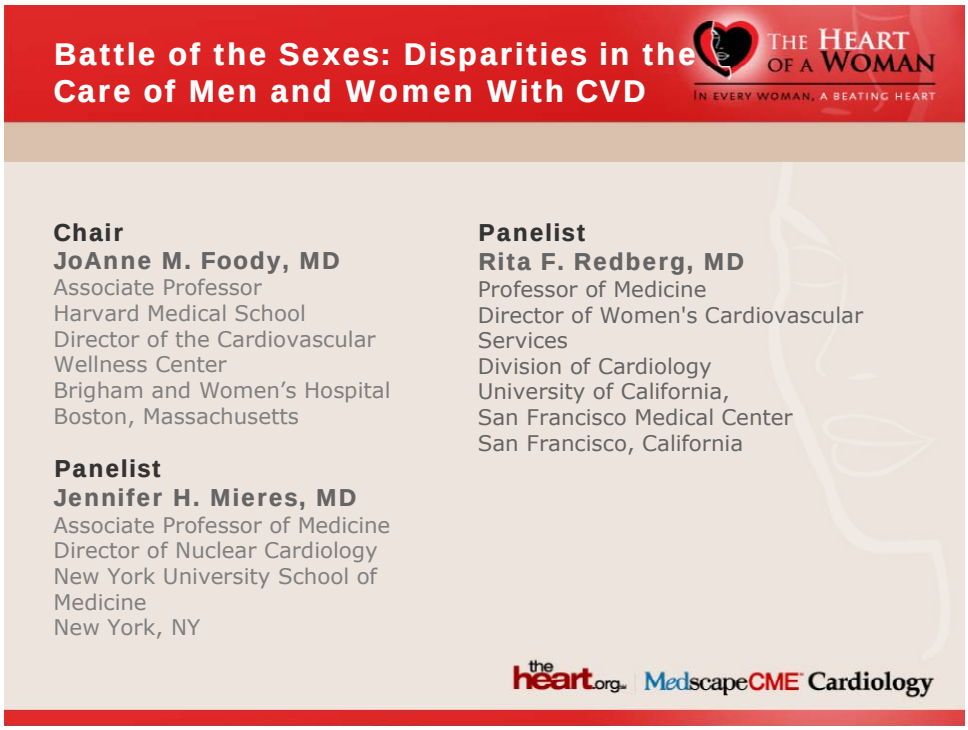
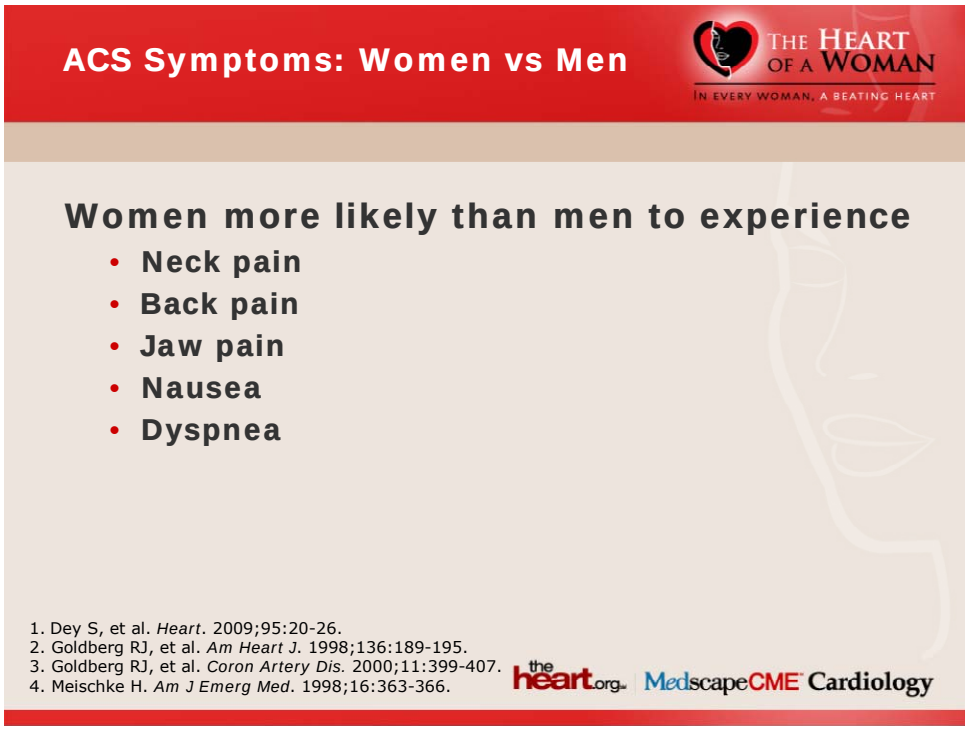


Slide 1

Joanne M. Foody, MD: Hello. I'm Joanne Foody, Associate Professor of Medicine at Harvard Medical School and Director of the Cardiovascular Wellness Center at the Brigham and Women's Hospital in Boston. I'd like to welcome you to our first program in the Heart of a Woman series, entitled: "Battle of the Sexes: Disparities in the Care of Men and Women with Cardiovascular Disease."

Today I am joined by 2 colleagues, Rita Redberg, Director of Women's Cardiovascular Services at the University of California, San Francisco Medical Center; and Jennifer Mieres, Associate Professor of Medicine and Director of Nuclear Cardiology at New York University School of Medicine. Today we're going to discuss a topic that is near and dear to all our hearts, that is disparities in the care and management of cardiovascular disease [CVD].

In getting started, I'd like to first ask you, Rita, if you can review some of the important issues regarding the epidemiology of CVD in women.

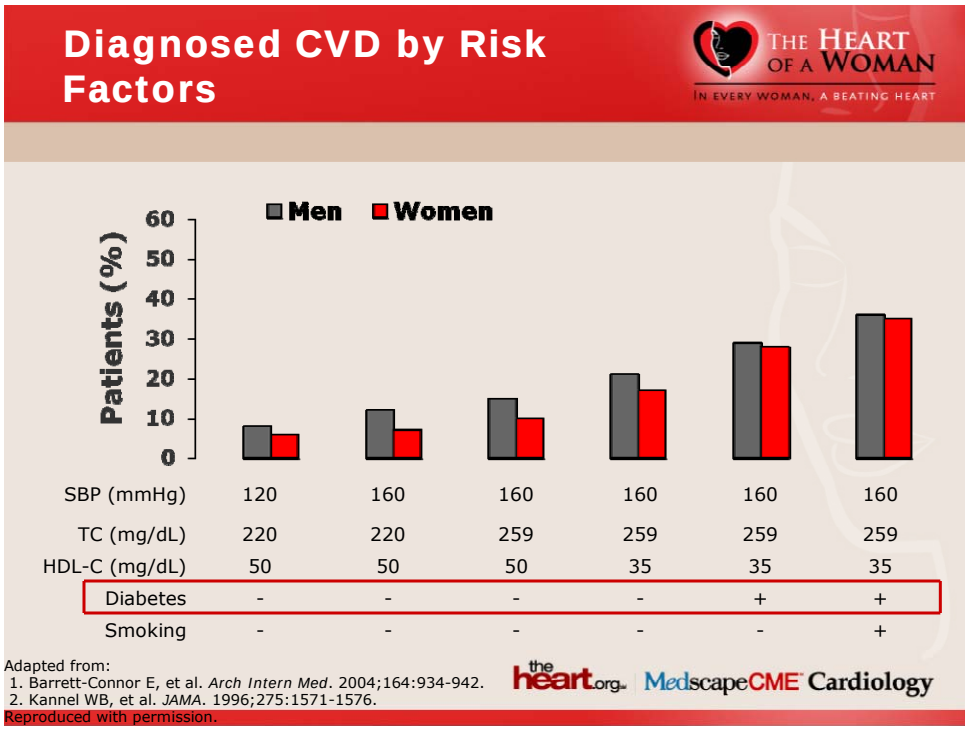


Slide 2

Rita Redberg, MD: Sure. First off, as we know, heart disease is the leading cause of death in women. For a long time, because women are about 10 years older than men on average when they get heart disease, we haven't been as concerned or as aware of heart disease in women. Although, still the majority of women are going to present with chest pain just as men often do, and woman also get atypical symptoms. We have to really be concerned and aware -- especially in women with risk factors, if they have other right-sided pain, shoulder pain, nausea, vomiting, fatigue -- and balance that awareness with what we know about heart disease and epidemiology.

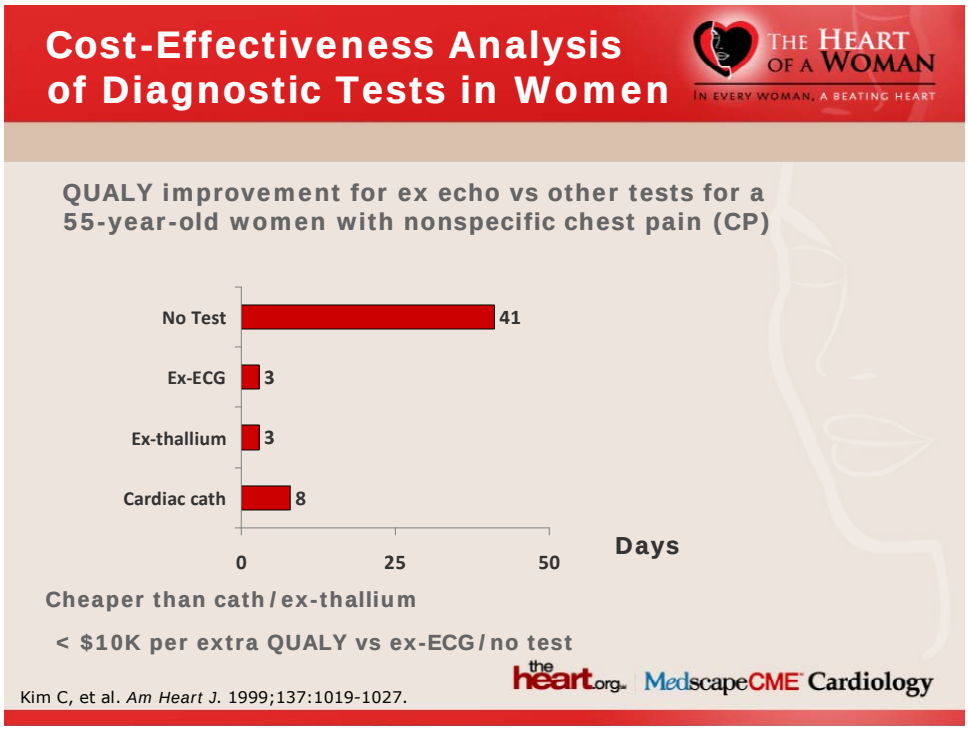
We're learning a lot more about the actual atherosclerotic process, and it looks like women have much more diffuse plaque than men do. Women have smaller arteries. The more we learn, the more we see there are a lot of subtle differences that can help us in diagnosis and then apply that to management and treatment of women with heart disease.

Dr. Foody: Clearly there are a lot of underlying differences that we see, whether it be age of onset or differences in fact in the disease process. Jennifer, as far as your experience with respect to diagnosis, how does this play out?



Slide 3

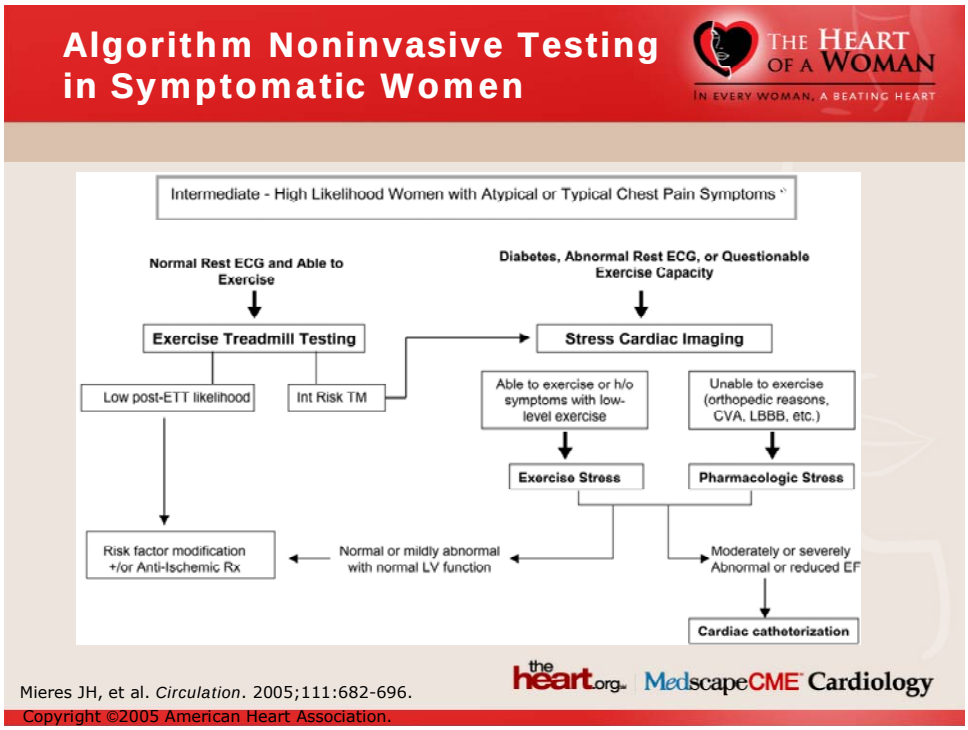
Jennifer H. Mieres, MD: Before getting to diagnosis, it's important, as Rita said, to point out that men and women share many similarities in terms of risk factors. We're all familiar with the risk factors (hypertension, diabetes) but I think as we've studied gender-specific aspects as it relates to CVD, we've discovered that some risk factors are much more potent. Diabetic women, for example, may have a larger plaque burden and more diffuse atherosclerosis and may actually present with less classic symptoms. I think to reiterate what Rita said, we've come a long way, we're understanding more, and in the last decade we've made tremendous strides.



Slide 4

Along those lines, in the area of diagnosis; prior to probably the 90s, we have applied a traditional male model for diagnosing physiologically significant coronary artery disease [CAD]. Whereas when we started studying the sex-specific differences, we've discovered that some of our traditional noninvasive tests are not as accurate in women. For example, the exercise treadmill: We know based on a study, actually a meta-analysis published by Rita and colleagues, that we can see differences and that maybe the plain treadmill stress test may not give us as much information and may not be as accurate in women as it is in men. For many decades that was sort of our standard, the first test we've used. We're doing studies and we're learning more that maybe when you combine imaging studies, whether it's stress echo or stress nuclear, with exercise or with pharmacologic stress, we can improve our diagnostic accuracy for detecting physiologically significant CAD in women. It's an area in evolution, but I think we've made significant strides.

Generally speaking, when a woman comes in to see you, the history of course is most important, looking at the risk factor profile, and then determining from our algorithm of a variety of noninvasive tests, which pathway she should follow. In my practice and I am sure in your practice, when women come in with symptoms and we suspect CAD based on risk factors, we pretty much go to imaging. We combine exercise with imaging; we look for a reproduction of symptoms; we look at all the other parameters, but we go directly to imaging. I think that the guidelines are evolving to support that pattern.

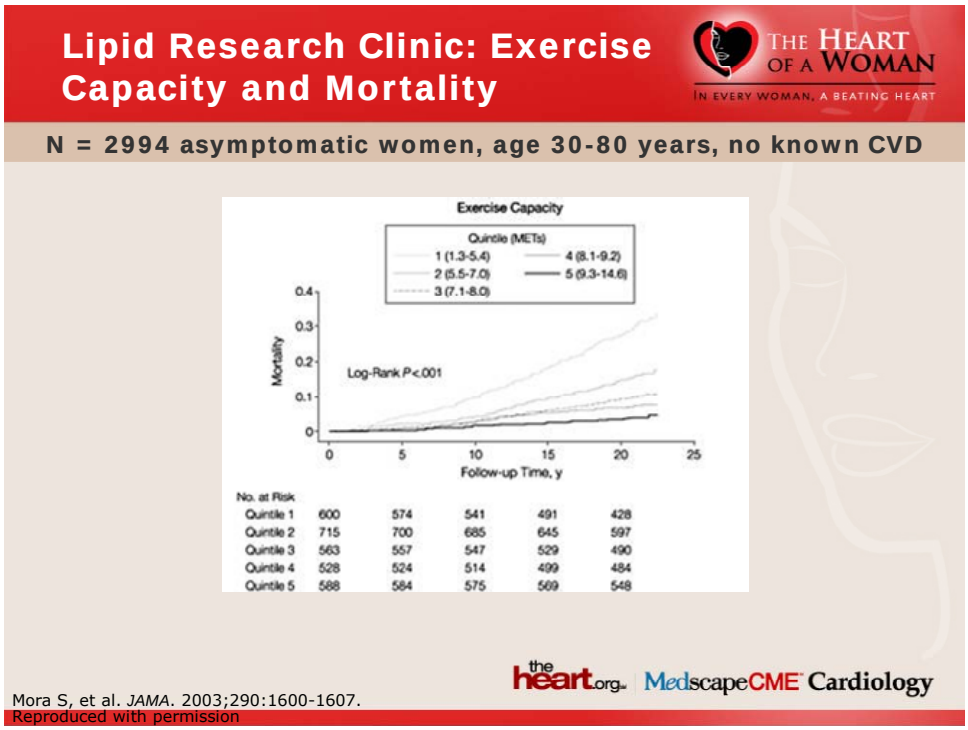


Slide 5

I know from the noninvasive consensus statement that we published in 2005, we felt that incorporating the baseline ECG, assessing the functional capacity for women -- because we can get a lot of information just from the history, finding out whether a woman can do her daily activities of living -- we can determine functional capacity, baseline ECG, and the clinical history, to decide whether she should go for imaging with exercise or imaging with pharmacologic stress. I think you'd agree with me that we have made strides and now we have specific algorithms that we can use to determine whether there is psychologically significant CAD.

Dr. Foody: Excellent. Rita, you've done a lot of work in this area as well. In speaking to these new algorithms, what is your typical approach if you take a woman who is presenting with symptoms that may be suspicious for coronary disease?

Dr. Redberg: As Jennifer said, I do have a much lower threshold for starting with imaging in women because, as you alluded to, we did a cost-effectiveness analysis, 10 years ago now, because as we know treadmill testing is just less sensitive and less specific in woman -- particularly middle-aged women where they're much more likely to be in that intermediate probability category where we're really not sure and we most need testing. The treadmill test is more likely to give us false positives or false negatives, and this is costly both in terms of additional testing and also in terms of anxiety with false-positive diagnoses.



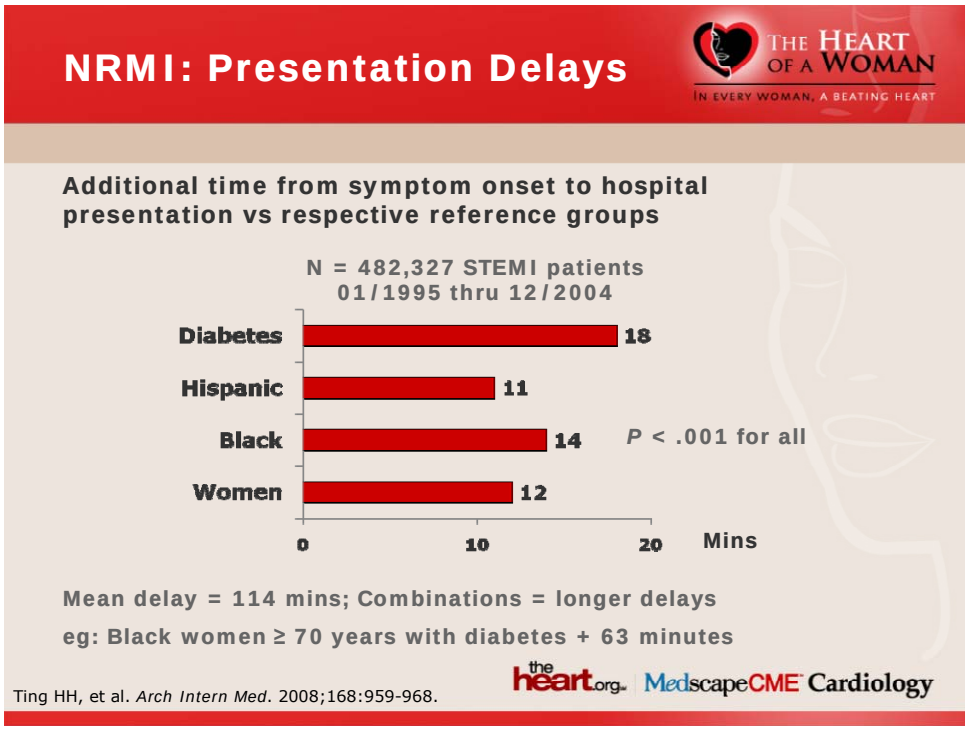
Slide 6

I like to start with a stress imaging test. I prefer exercise if a woman can get on a treadmill because we get a lot more information (besides whether or not there is ischemia), we get the functional time, and how many minutes a woman goes on a treadmill. The Lipid Research Clinic's data a few years ago found for every additional minute on the treadmill you have a much better prognosis. So you get a lot of prognostic, as well as diagnostic information, from an exercise imaging test. Certainly for women that can't exercise, pharmacologic testing, with imaging obviously, is also excellent. I often start exercise imaging sooner with women than with men.

Dr. Foody: These are really important points when we think about the unique aspects of diagnosis in women; it's nice that we do have these newer guidelines to ensure that women get appropriate testing, given, as you said, their lower pretest possibility in some instances, as well as the issue of false positives.

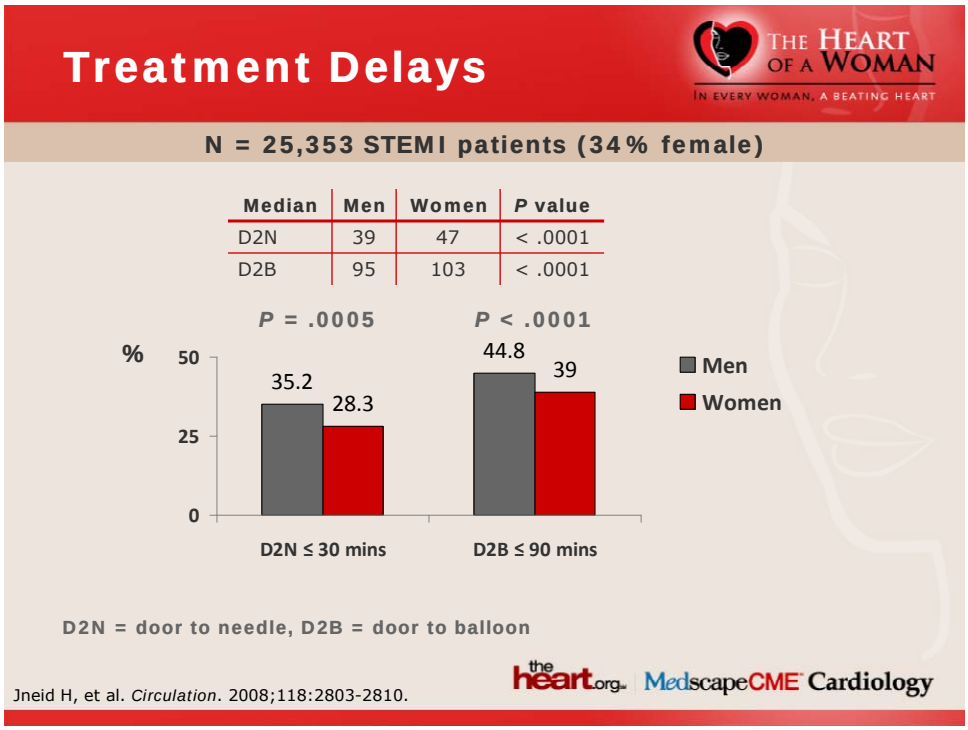
As much as we try to prevent disease in many of our female patients, we know that many women are succumbing to acute coronary syndromes [ACS]. At this point, I'd like to really move into this area because I think ACS really highlights a large proportion of the disparities for women.

Jennifer, in your experience when you think about ACS for women, in totality, what are the major barriers or disparities that you are faced with?



Slide 7

Dr. Mieres: I think you can divide this into 2 parts. First of all, we've been pushing the fact in trying to make women aware that they're vulnerable to heart disease, but more importantly they have to be active and they have to be partners with their healthcare professionals. When you think of the emergency room [ER] and patients presenting with ACS, what we've seen as we've studied the gender-specific aspects, is that heart disease is not on many women's radar screen. They're not thinking they're vulnerable to a heart attack. Symptoms may develop. They delay presentation so they go to the ER much later than men. They arrive late because of under-recognition from their part that something important is going on.



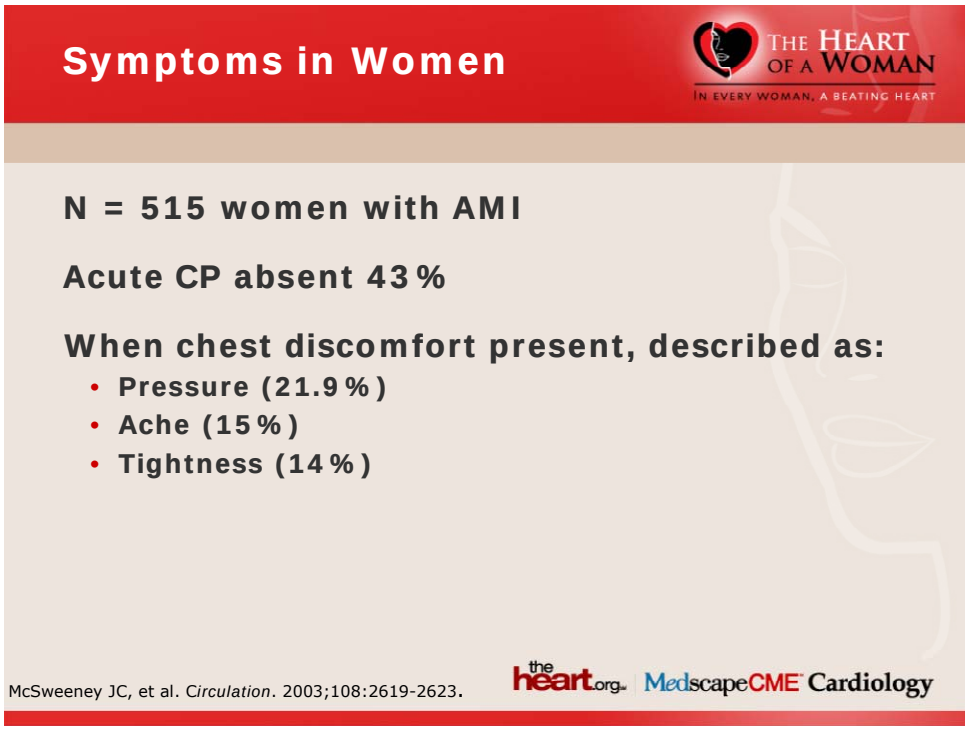
Slide 8

They get to the ER and again symptoms of chest pain, which is the classic symptom, may be combined with other symptoms or the chest pain may not be as severe; they speak to the triage nurse, and then again heart disease is not on the radar screen of the triage nurse. Again, there is under-recognition and delayed diagnosis. By the time a heart attack or ACS is picked up, the medical professionals realize that it is in process, it may be too late for some of our life-saving and more aggressive strategies. The combination of under-recognition of symptoms and delay in diagnosis because of late arrival and non-classic symptoms can account for some of the disparities in terms of the death rate from ACS for women compared with men.

I think that we have made significant strides over the past decade because we know that if you recognize that it's an ACS and you can get a woman to the cath lab; in the case of an acute MI [myocardial infarction], you can open the vessel, put a stent in, and we know that even though there are technical challenges with the size of the vessel, that if you can do it in a timely fashion, the outcomes can be better. We have to spend more time getting women to recognize the symptoms, recognizing they're at risk, and we need to focus a little bit more on our colleagues in the ER. I think we preach to the choir. We as cardiologists, we know what's going on. We need to expand our boundaries and spend some time educating or alerting ER physicians, ER nurses -- the triage nurse is the first person our patients are going to see -- that women are vulnerable; they may have less classic symptoms, but we have to get them onto that acute chest pain pathway. You come in, time is muscle, do an ECG, and put the team into

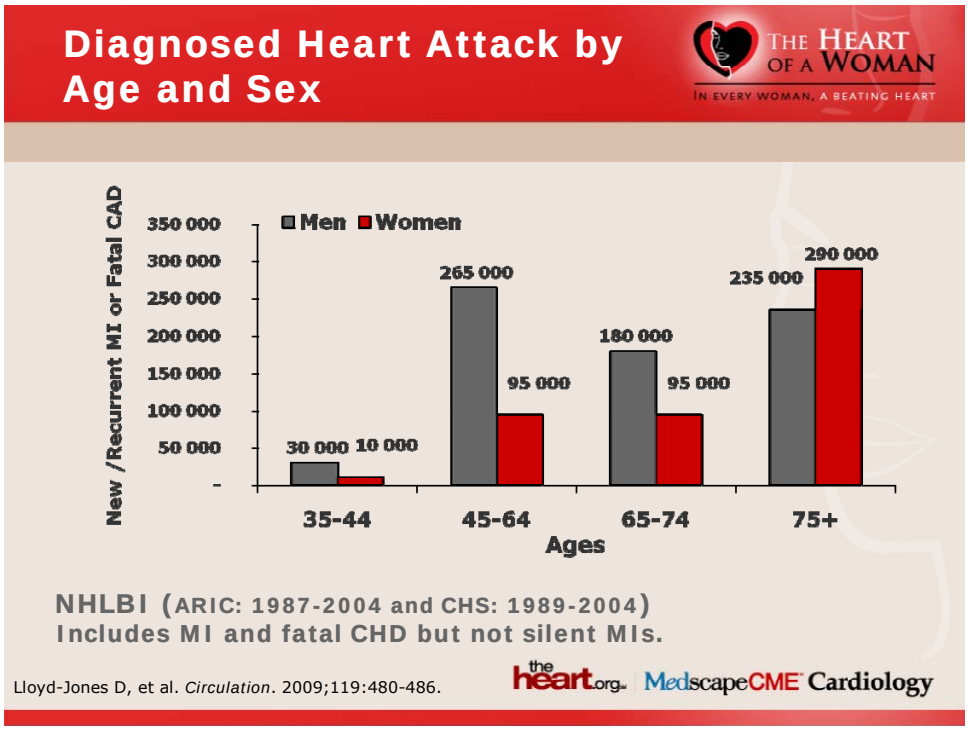
rapid fire.

Dr. Foody: Absolutely. Let's talk a little bit about symptoms. There's a lot being said that women don't have typical symptoms for heart disease. Rita, given your experience around that could you characterize the symptoms or presentation for women?



Slide 9

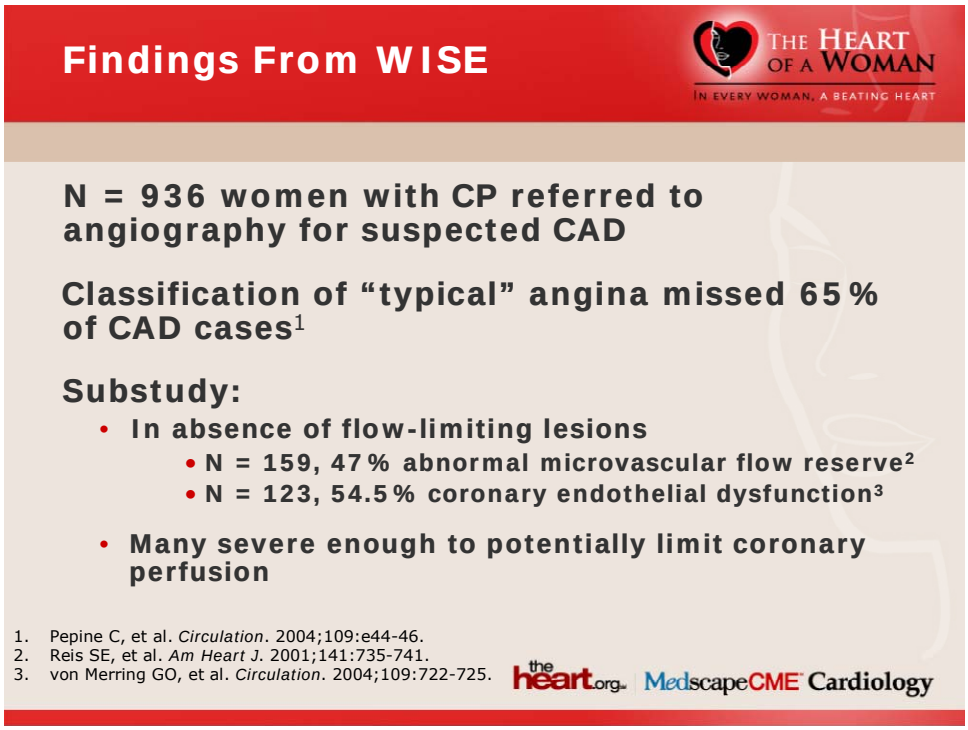
Dr. Redberg: Certainly it's true. In the last decade, we've helped women a lot because they're more aware that heart disease is the leading cause of death and to consider heart disease even if they're not experiencing classic chest pressure that feels like an elephant sitting on your chest. It's particularly true for middle-aged women. Again it gets back to the epidemiology because heart disease is still less prevalent in middle-aged women than it is in middle-aged men. That's part of what's going on with the ACS.



Slide 10

We know women have worse outcomes when they're diagnosed, but it's more challenging because it's still more likely in a middle-aged woman, who comes in with even a classic story of chest pain, that it's not actually due to ACS. In all the ACS trials, women have less obstructive disease than men do and that's particularly true in middle age. As women get older, the epidemiology is more like men's; the prevalence is more like men's. It's really a double-edged sword because we know women are going to do worse, particularly if it takes us longer to diagnose them. On the other hand, it's a harder diagnosis to make because it's also very possible that it's not coronary disease. Of course, we try to err on the side of quickly ruling out coronary disease because we don't want them to sit, but we are also aware that women have a lower incidence of obstructive coronary disease when we take them to the cath lab for ACS.

Dr. Foody: Absolutely. It really is a disparity. Jennifer, I think some of your work around chest pain centers and imaging may really help inform that. What's been your experience?



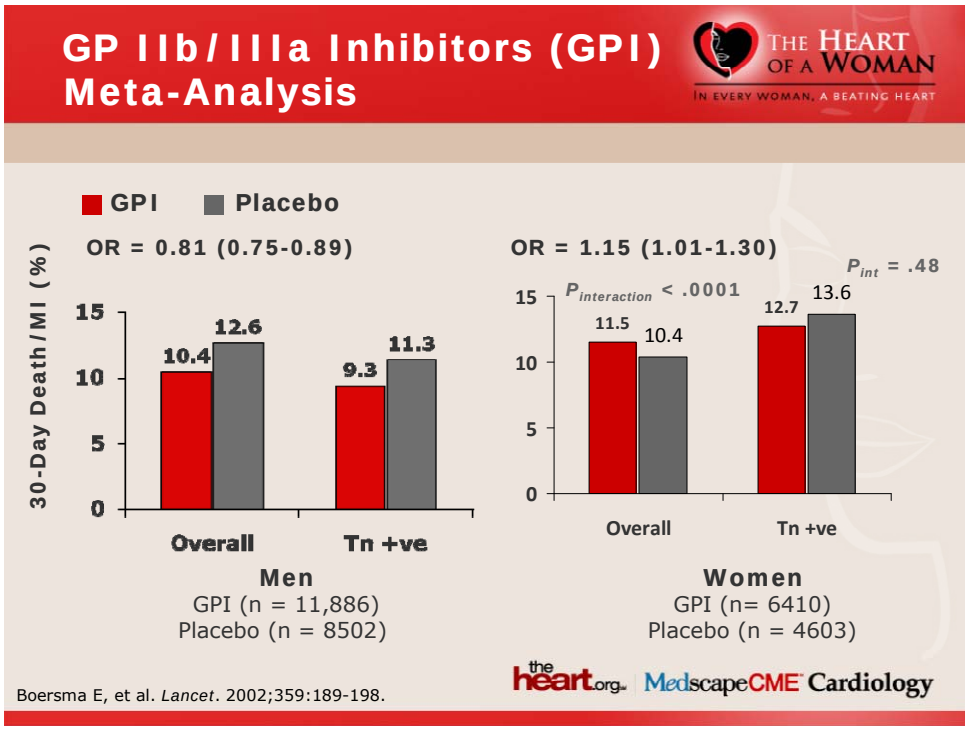
Slide 11

Dr. Mieres: We've learned a lot again from some of the recent publications, such as the WISE (Women's Ischemic Syndrome Evaluation) study, even though this was a unique cohort of over 900 women, we learned a little bit about the distribution of atherosclerosis and the burden of plaque. I think one of the key points that came out of that study was that when we take a woman or man to the cath lab and we use standard angiography, using your luminogram, so to speak, may not give you a true and accurate assessment of the burden of atherosclerotic plaque. In the WISE study, where they did intravascular ultrasound, they recognized that women may have more diffuse vessel wall disease so that even though a woman comes in with chest pain, you take her to the cath lab, and you do your standard angiography, you are not seeing the true picture and the burden of atherosclerosis is probably greater. They alluded to that, but we need to come up with different methods to detect and assess the burden of atherosclerosis.

We're in this era where there's new technology coming on the market. We're able to look noninvasively looking at the coronary vessels using CT [computed tomography] angiography; we need more evidence, but it might give us an idea as to the plaque burden. Not only can you see the lumen, but you could also see the integrity of the vessel wall. It's a very exciting area, but I think the WISE study definitely gave us some insights that women have atherosclerosis, but the distribution may be different.

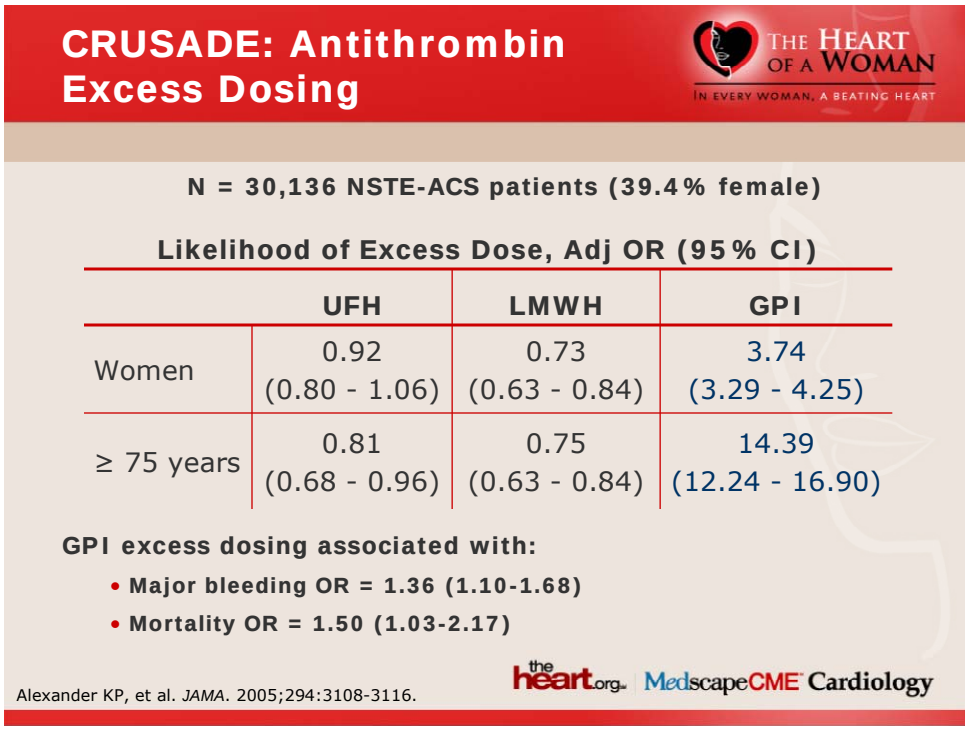
Dr. Foody: Now in those instances where we are dealing with an ACS with thrombosis, work

done by Andrea [speaker means Alexandra Lansky], for example, highlighted that if women are intervened early and receive evidence-based therapies, that they do just as well in general as men. In contradistinction to that, we have some evidence suggesting that there are other risks for women; bleeding risks for example, and procedural risks. What is some of the new information regarding some of the disparities around treatment? Rita, if you'd like to comment.



Slide 12

Dr. Redberg: I think it's another example of the double-edged sword because certainly women benefit from the evidence-based therapies, but the risk stratification is important because we know for example from a meta-analysis of all the trials on glycoportein IIb/IIIa inhibitors in ACS actually showed increased death and mortality in women compared with men. There was a clear difference. When you drill down, the difference was really driven by the women who had negative troponins. That wasn't true for the men. The men with negative or positive troponins both benefited from IIb/IIIa inhibitors and the the thought is that it really is related to women's risk being lower, and women with negative troponins are going to be your lowest-risk group. That's obviously one way to risk stratify. There are TIMI [Thrombolysis in Myocardial Infarction] risk scores, GRACE [Global Registry of Acute Coronary Events] risk scores, and other ways to stratify women besides clinical assessment.



Slide 13

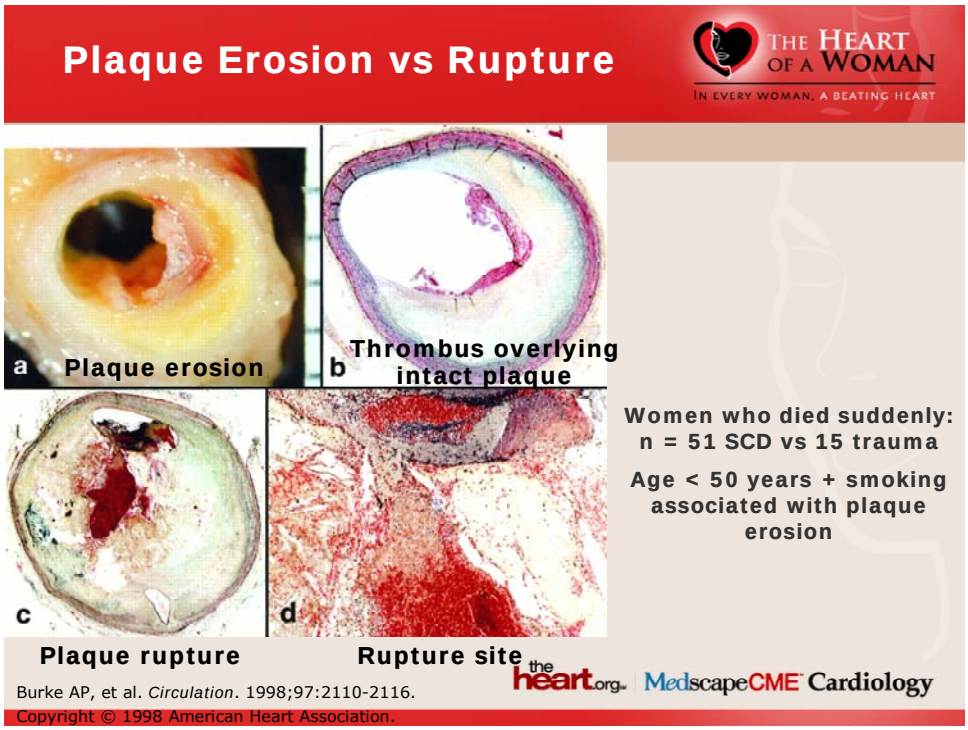
What it meant was the risks for the bleeding complications [outweighed the ischemic benefits], because women bleed more in general than men. Women with ACS are going to have about twice the bleeding complications than men. Once we add the platelet inhibitors, women bleed even more. Then we have the additional issue that women are more likely than men not to get the right dosing of the platelet inhibitors. That also contributes to increased bleeding. Obviously we can work on education and on dosing women correctly, but even at the correct dose women are going to bleed more than men.

It's important to risk stratify because for those lowest-risk women with the negative troponins, we probably don't want to be as aggressive, certainly not with IIb/IIIa inhibitors, because the risk is going to exceed the benefit. For the sick women, where we know the outcomes are going to be worse, they definitely need all of our guideline therapies and they need the interventions quickly. As Jennifer said, it's taking us longer to diagnose women than men, and then the outcomes are worse.

Dr. Foody: Absolutely. This is particularly an issue in young women, where we've seen a lot of information emerging that young women with MI do much worse than either older women or men of the same age. Jennifer, in speaking to that, are there any particularly issues or concerns in that group?

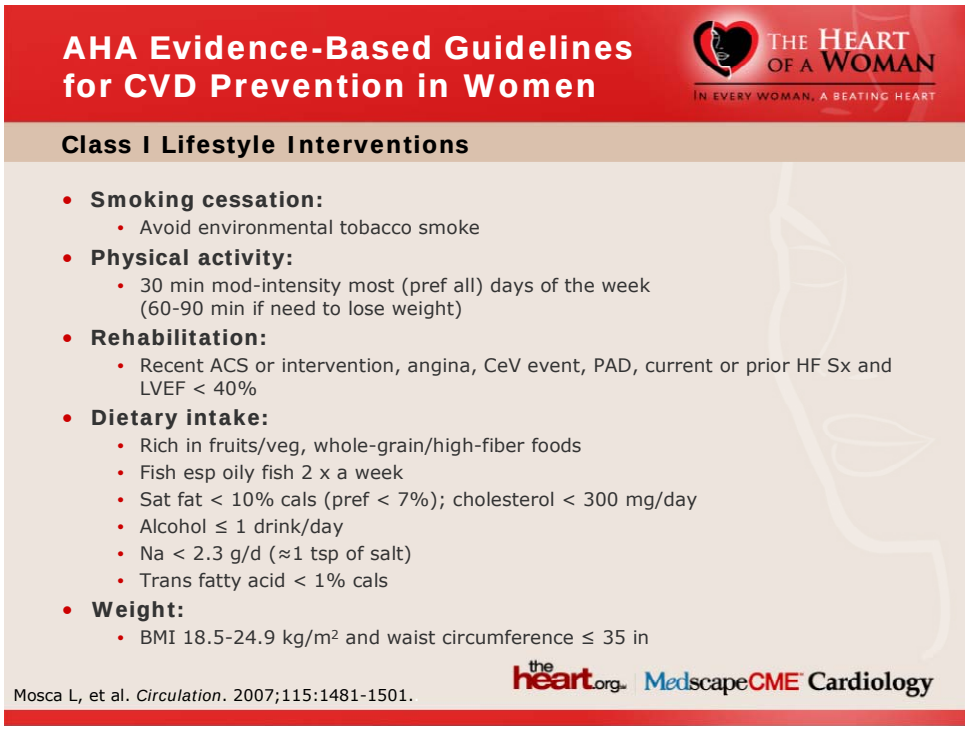
Dr. Mieres: I think young women definitely are at a disadvantage because they show up to the

ER and no one's thinking of heart disease. Especially women under 40, they may come in with vague symptoms or even with classic symptoms, and they get ignored because the paradigm or thinking is that a 40-year-old woman is not having a heart attack. Again, the delay in diagnosis definitely becomes a problem.



Slide 14

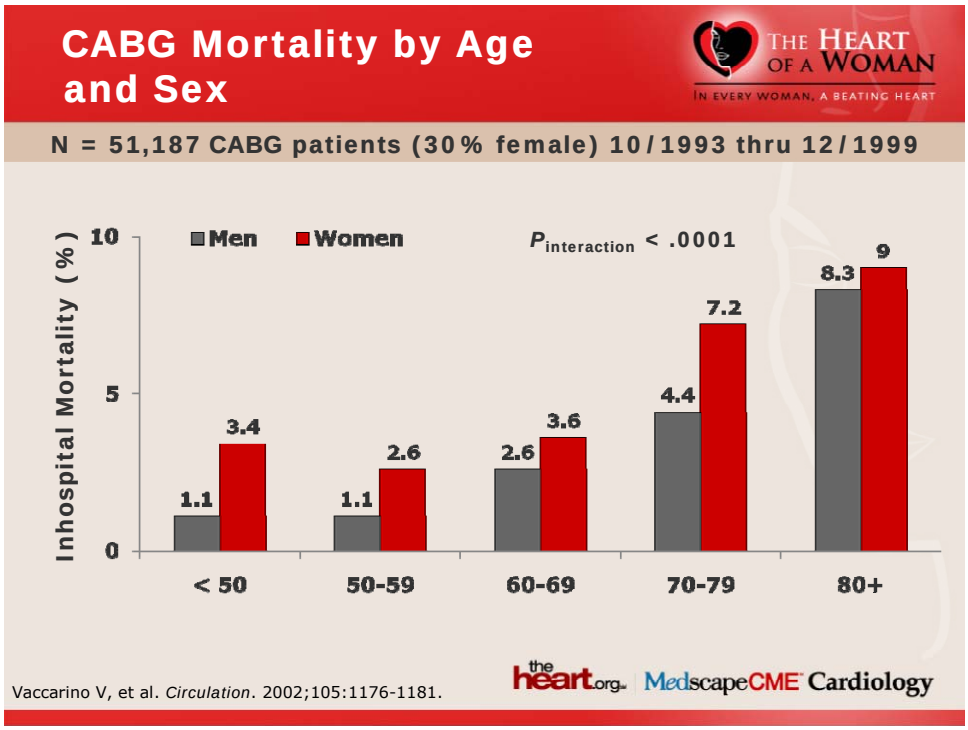
Also, some work published in the late 90s looking at the morphology of plaque and the burden of atherosclerosis, showed that younger women who've died suddenly have less plaque, but much more plaque erosion, and that cigarette smoking was a strong risk factor [for plaque erosion] and was strongly linked to ACS and sudden cardiac death in those patients. I think we need to educate younger women to let them know they're vulnerable, especially if they have risk factors and especially if they smoke. We also need to educate the ER and the whole medical community on the link between smoking and ACS especially in younger women. The key is early diagnosis. Get them to the cath lab and implement preventive strategies as well.



Slide 15

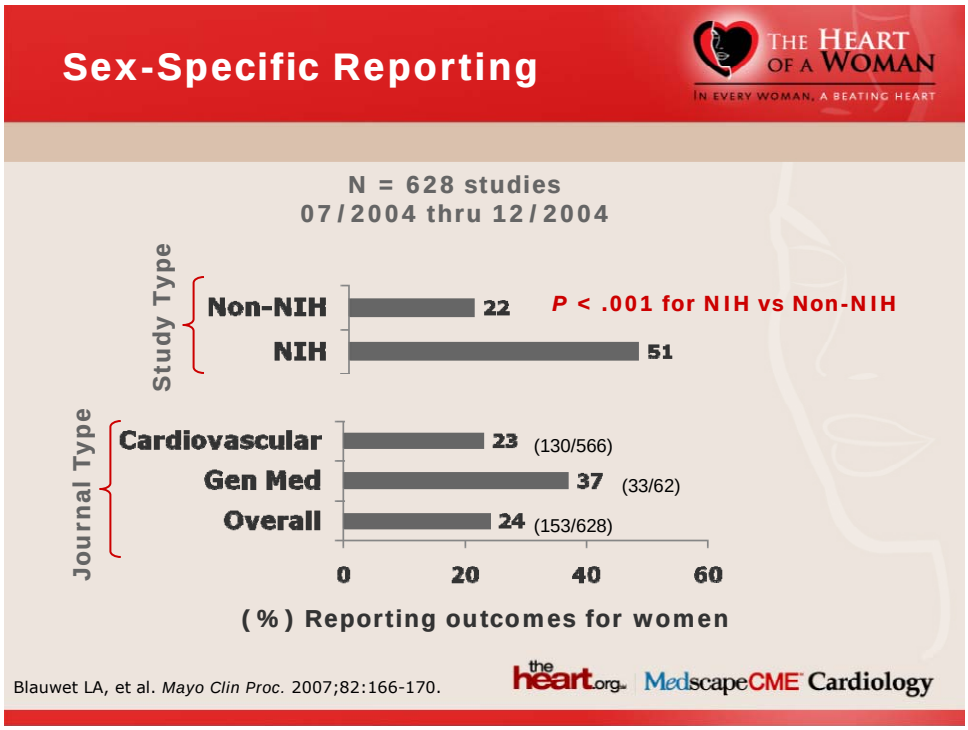
I want to talk about the fact that we have cardiovascular prevention guidelines for women which were published in 2004. I think you may have both been authors on that. That has given us a road map in terms of what works for prevention from a medical point of view, again highlighting for the first time that lifestyle changes are so important; smoking cessation being a part of that; and second-hand smoke… There was an update to the primary and secondary prevention guidelines published in 2007. In addition to diagnosis and treatment strategies, we have got to get women on board with the lifestyle changes, as well as physicians and the medical community, to really manage risk factors aggressively. Get the cholesterol to goal; get the HDL-C [high-density lipoprotein cholesterol] up; LDL-C [low-density lipoprotein cholesterol] to goal; treat high blood pressure; diabetes; and be aggressive in treating these. I think if we were to do that we would definitely come close to reducing the mortality from heart disease.

Dr. Foody: These are wonderful points. Both of you have highlighted the need for more education, not only for our patients, but also for providers, around this issue. One of the other areas is research and the way we look at questions regarding CVD in women. I know Rita you feel very strongly about this issue and just wanted to get your thoughts on next steps and future directions in this area.



Slide 16

Dr. Redberg: You're right. I do feel strongly about this because, as I said and as we've talked about for the last 20 minutes or so, there are differences between men and women, but we don't know about any of those unless we actually look at sex-specific results. I think it's important for journal editors or me and others to report data separately for men and for women. A lot of the things that we've been talking about we would never know if we just looked at the data as a group. There are a lot of differences. We were just talking about young women.



Slide 17

Ten years ago now, Viola Vaccarino published a quite striking study showing that women less than 50 years old have 3 times the operative mortality from bypass surgery -- 3% compared with 1% for men. We'd never know that unless we looked at sex-specific data. Honestly, we still don't really know what's going on. I think that heart disease in young women is just a more virulent form of disease and that's why their outcomes are worse than it is when it presents in men at that age group.

It's so important that we get sex-specific data. When we're talking about new drugs and new devices it's important that we get sex-specific data because the risk-benefit ratio is going to be different in women than it is in men, and we just don't know it. A lot of drug problems are more common in women. We talked about bleeding; there are other issues. The long QT and torsade de point are more common with some of the antiarrhythmic drugs in women than they are in men. The devices are often made for people that are sized like men, not like women, and so we really need to have sex-specific data, not just more women in clinical trials, which will obviously help. On average about 30% of clinical trial subjects are women, not the 50% as are represented in the heart disease population. With important trials, it's important that even if there wasn't a significant result in women, and if the data are available and reported separately, then someone else can come along and do a meta-analysis that would have the power to compare women and men. I think that's what you [Dr. Mieres] summarized in the imaging statement.

Dr. Foody: Absolutely. I think whether it's in imaging, or whether it's in therapeutic interventions, clearly we need more information. We can definitely say that one of our big messages is that first we have to educate more women, as well as providers, around heart disease, but importantly we need more information. We need more data to fill in the gaps around this. Hopefully programs like this will provide some impetus for that, as well as provide each of us the opportunity to look at our own patient populations and explore some of these issues and look at what the disparities are that we see.

For now I want to thank both of you for your participation in today's conversation. Again, thank you for all the work you've done in this field and the work you're about to do in this field.

Dr. Mieres: Thank you.

Dr. Redberg: Thank you.