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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Love Story: Lipid Education for Women's Heart Health

Announcer:
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Dr. Taub:
Well, it's great to be here today as part of the Women's Health 2024 Beyond the Annual Visit lecture series. I'm Pam Taub. I'm a cardiologist and professor of medicine, as well as director of preventive cardiology at UC San Diego. And today I'm going to be talking to you about lipids, and we're going to do it through a little bit of a fun Taylor Swift theme, and that's going to be the love story of lipids. And you'll see some fun Taylor Swift-themed messages infused in the talk.

These are my disclosures and these are the learning objectives. So the talk is going to be around multiple aspects of lipid lowering and, as I mentioned, the Taylor Swift theme. So we're going to first start with Speak Now, and we're going to really look at how we're assessing CV risk in women and what the current status of CV events in women is in terms of the prevalence of cardiovascular disease.

Then we're going to go to our Love Story with LDL and talk about what the goals for LDL are and how we're attaining those goals. And then in Shake It Off, we'll talk about the ways to manage LDL-C, and in our Wildest Dreams we're going to talk about some of the latest research, including some of the newer non-statin therapies that we have available to us.

So now let's go to Speak Now, and I think this is a great time to really reflect on how heart disease is still the number one killer of women. And many of you may already be aware of the Go Red for Women campaign where we wear our red dresses to raise awareness of heart disease in women. But it's really important, even in 2024, that we not forget about heart disease in women. We're so focused on other conditions like breast cancer, which are also really important, but let's also raise awareness about how heart disease continues to be the number one killer in women.

And so, when we look at the statistics, they're very sobering. Cardiovascular disease accounts for 35% of all deaths in women worldwide. 8.9 million women died from cardiovascular disease in 2019, and women have worse outcomes and are less likely to receive guideline-directed medical therapy compared to men, and younger women are at the greatest risk for poor outcomes after having a myocardial infarction. And unfortunately, women are understudied, underdiagnosed, undertreated, and underrepresented in clinical trials. We're starting to do better, but we have a lot to do in getting equity for women in terms of clinical trials and also making sure they are appropriately treated. And so when we look at sex differences in coronary artery disease, women do tend to have more non-obstructive coronary artery disease. So when we do an angiogram, sometimes there's not an obvious lesion staring at us telling us that this person has atherosclerotic cardiovascular disease. So we need to keep that in mind when evaluating women.

We also need to understand better the pathophysiology of non-obstructive coronary artery disease, and that includes conditions such as microvascular disease and MINOCA [myocardial infarction with non-obstructive coronary artery disease] and INOCA [ischemia with

non-obstructive coronary artery disease]. And so we have to further research in this area, but also keep in mind that just because a woman does not have a significant obstructive lesion, that we can't dismiss them as not having disease; we need to understand these conditions better. And so there are some really unique factors that women have that really impact coronary artery disease manifestation and progression. And that includes a higher prevalence of autoimmune disease and more of an inflammatory milieu and other concomitant conditions, like obesity and hypertension that contribute to the progression of atherosclerotic cardiovascular disease. Conditions unique to women, such as polycystic ovarian syndrome, postmenopause, all of that can contribute to this inflammatory milieu.

And again, as I mentioned earlier, sometimes women have what we call microvascular disease, which is the large coronary arteries don't necessarily have disease, but it's really the microvasculature, the small vessels that we don't see on angiogram that have disease. And now we have very quantitative objective ways to assess microvascular function. So when we see women that have symptoms like chest pain but they don't have obvious disease on a coronary angiography or CT coronary angiogram, we need to be looking at testing for microvascular dysfunction. It is important to give people the correct diagnoses instead of telling people that these symptoms are made up or are due to anxiety. The better that we do with diagnosis and validating people's symptoms, the better progress we're going to make in terms of understanding pathophysiology and then ultimately coming up with treatments.

Another condition that women have that is really important in terms of driving atherosclerotic cardiovascular disease is diabetes. And what we see is that women who have diabetes are 4 times more likely to suffer, for instance, a stroke than women without diabetes. And hormonal changes in women can sometimes make the diabetes a little bit more difficult to control. And in all countries, women tend to have less intensive care for diabetes and they don't get access to some of the really important newer medications for diabetes, like the SGLT2 inhibitors or GLP-1 receptor agonists.

Another really important aspect of caring for women is understanding how some of the conditions both during pregnancy, before pregnancy, and after pregnancy can impact cardiometabolic risk. So for instance, women who have polycystic ovarian syndrome or obesity when they get pregnant, they do tend to have more pregnancy-related complications. Enduring pregnancy conditions, such as preeclampsia, gestational diabetes, confer risk for future cardiovascular disease. So when you follow women with gestational diabetes over 10 years, about half of them get diabetes. And so these conditions that are occurring in pregnancy can't be dismissed as conditions that are only going to impact the woman during pregnancy because these have long-term implications on overall cardiometabolic health.

Another condition that is more prevalent in women is heart failure with preserved ejection fraction. And sometimes it's very difficult to diagnose because the ejection fraction is normal, and sometimes the presentation of HFpEF can be confused with other conditions. So a lot of times patients with HFpEF are obese and they complain of shortness of breath, and it's easy to dismiss this to, oh, they're just inactive, they're obese and deconditioned, and that's why they're having shortness of breath. So it's really important to really do the workup in patients that have these symptoms to understand if they have HFpEF. And HFpEF also has the underlying substrate of some conditions unique to women, such as preeclampsia and autoimmune disease, which is more prevalent in women.

What we also see is, for instance with HFpEF, when women do have HFpEF, their outcomes are worse than men. And so some of it is a delayed diagnosis, but some of it is also less aggressive treatment of women with guideline-directed medical therapy.

When we look at the spectrum of conditions unique to women across the lifespan, we see that lipid lowering is really important for managing a lot of these conditions. So we want to be thinking about, in our younger patients, looking for conditions like familial hypercholesterolemia and optimizing LDL even before a woman gets into pregnancy age. And then when we look at women in middle age, we want to really be thinking about risk assessment, and that includes things such as looking at coronary artery calcium score, because if that's elevated, we're going to be more aggressive with lipid lowering. And in our postmenopausal women, we want to also be very aggressive in lowering the LDL cholesterol. And so across our lifetime we need to be thinking about ASCVD risk and how to optimize that and specifically really focusing on LDL lowering.

So women are complicated and I think the complexity is part of the elegance and uniqueness of women, and there are special considerations we need to be thinking about when we manage women.

So sticking with our Taylor Swift theme, now we're going to go to Love Story. And what that's really a reminder for us is how important engaging in meaningful relationships with our friends, our family, our community are in terms of our overall mental health. And one of the great examples of this is what we do in cardiac rehabilitation is we create community, and we really have patients engage with each other. So we all want to really engage in important and meaningful relationships. It's great for our overall health.

So now let's talk about the continuum of risk. We're mostly focused on secondary prevention. That's where a significant amount of our healthcare dollars are spent. And I call that the Band-Aid approach, and it's very unsatisfying because the event has already occurred.

What we really should be focused on is high risk primary prevention or patients who have subclinical atherosclerosis who haven't yet had an event and really focus on modifying their risk and preventing that first event.

And so when we look at our cholesterol guidelines, they do talk about certain biomarkers and certain imaging modalities that we can look at to identify these high-risk patients that have not yet had an event. And there's some very specific things related to women such as some of the pregnancy conditions I talked about like preeclampsia and gestational diabetes. And when we see there's a history of these conditions, that does put someone at higher risk and we need to be more aggressive. In addition, we need to be looking at other biomarkers that we don't often look at in routine clinical practice, and that includes high-sensitivity CRP and lipoprotein(a). Again, all of these risk enhancers help us identify patients that we need to be treating more aggressively. And if there is some uncertainty in risk, we can rely on things such as a coronary calcium score that will help us predict who is higher risk.

And so when we look at the people that are extremely high risk, those include patients that have had recent acute coronary syndrome, recent heart attack, stroke, and also patients who have symptomatic peripheral arterial disease. So we need to also really identify those patients that are very high risk, and that looks at both incorporating both major ASCVD events, including some underlying high-risk conditions. And the reason we want to identify these patients is our treatment goals are different for these patients. We want to be as aggressive as possible and bring that LDL down to much lower goals. So for instance, the guidelines for very-high-risk patients recommend an LDL less than 55. And less than 55 is the minimum threshold that we want to achieve. Typically in my clinical practice for these very-high-risk patients, I'm trying to achieve an LDL in the 30s, so as low as I can go. And so the 2022 ACC expert consensus decision pathway identified these patients that are very high risk as also being candidates for other therapies including bempedoic acid and inclisiran, which we'll talk about, because for these very-high-risk patients, statin monotherapy typically is not enough to get to that minimum LDL threshold of less than 55. And so these patients are typically going to need multiple agents to achieve their LDL goals.

We talked a little bit about coronary calcium scoring as a way to help us identify patients that are higher risk. What we've also learned from some recent studies is that when someone has a calcium score greater than 300, you want to consider that patient as a secondary prevention patient even though an event has not occurred. Because when you follow these patients over time, their risk of events is the same as those patients who've already had an event.

And so the 2022 expert statement does incorporate calcium scoring into risk assessment and tells us that we can consider adding more potent LDL-lowering agents for these patients that have elevated coronary calcium scoring. Here they talk about calcium score greater than a thousand, but I think in the future guidelines, that number is going to come down to probably calcium score greater than 300 based on some of the more recent data that I just presented.

One other point that is important to understand is sometimes people are getting calcium scoring confused with coronary CT angiography. So calcium scoring is looking at calcium deposition within the coronary artery. It's not necessarily identifying stenosis; it's just looking at calcium. Versus coronary CT angiography, which is not only identifying calcium, but it's actually looking at is there narrowing of the coronary artery, and it's looking at plaque deposition. And coronary CT angiography does involve giving the patient a contrast agent to identify coronary stenosis. And this is just an image of coronary CT angiography. And as you can see, we're getting really great delineation of the coronary arteries and we're able to assess for stenosis. And there are different sequences that are done with CT coronary angiography and you do get a very good plaque characterization with this modality.

So now let's go to Shake It Off. And I use this as a reminder to emphasize how important exercise is in terms of reducing our cardiovascular disease, and we all need to be engaging in at least half an hour of exercise. Again, these are minimum goals, and we all want to be those A-plus students, and we want to really go above the minimum goals. And it's also important in our exercise regimen to have diversity. Don't just do aerobic exercise. It's important to also do strength training to build our skeletal muscle. So need diversity in our exercise regimen. And so we need to be doing more exercise, and we can have great songs like Shake It Off when we do our exercise.

And so now let's talk about plaque stabilization. And so when we talk about atherosclerotic cardiovascular disease, we're talking about a disease in which LDL cholesterol is the fuel for the fire. That atherosclerotic plaque, the major component is LDL. And so everything we can do to reduce LDL is going to stabilize that plaque. We've seen in studies with statins, such as the REVERSAL study, that when you decrease LDL, you have plaque stabilization. When you really bring LDL to very low numbers, such as we saw with the GLAGOV study with the PCSK9 inhibitor where we got the LDL to levels of 30s, we saw plaque regression.

We see another great illustration of the lower, the better from the GLAGOV study. Here we are looking at the change in the atheroma volume. So the amount of LDL in the atheroma, you can see as the LDL gets lower, that atheroma or plaque gets smaller. And what you see here is the benefit doesn't stop when you get to an LDL of 70, that as you continually lower the LDL, you're seeing a benefit in terms of plaque regression. So the message is clear: the lower, the better in terms of reducing plaque volume.

So now let's have a little bit of a reality check, and we can't just shake it off because this is real-world clinical practice, and this is what's happening. And unfortunately, most patients are not achieving the LDL thresholds of even less than 70. As you recall. For the very-high-risk patient, we want to get to an LDL less than 55. And so in real-world clinical practice, we are not achieving these goals, and in many patients we're not even checking their LDL after they have a stent placed. So there's a lot of work to be done and we need to do better.

Here's a great study called the GOULD registry, looking at patients who had ASCVD and looking at how many of these patients actually achieved the minimum threshold of LDL. And these were patients that were enrolled from 2016 to 2018, and this was a study of over 5,000 patients. And what you see here, again, is in most of these patients, we are not achieving these LDL thresholds of less than 70 and less than 55. However, what we do see is when we use combination therapy, so for instance with PCSK9 inhibitor, statins, and ezetimibe, we do achieve a higher proportion of patients achieving these LDL thresholds. So what this tells us is statin monotherapy typically is not going to be enough in getting to these goals, and we need to be using combination therapy for our patients.

And so now let's talk about some of our Wildest Dreams and some of the incredible new options that we have for lipid lowering. And this has really been fueled by great research and great clinical trials showing the benefits of these therapies. So my wildest dreams as a cardiologist in terms of lipid lowering are coming true, and there are so many new things on the horizon that I couldn't even dream of 20 years ago. And so let's first talk about some of the nonstatin agents and the mechanism of action. So statins work on HMG-CoA reductase and lower cholesterol synthesis. Some of the newer agents like bempedoic acid act upstream to the statin, and bempedoic acid acts on ATP-citrate lyase and also decreases cholesterol synthesis. And when you decrease cholesterol synthesis, you also increase upregulation of the LDL receptor, and the LDL receptor is very important to clearing LDL from the bloodstream.

Some of the newer agents that we also have are agents that act on the PCSK9 platform, and this includes the PCSK9 monoclonal antibody that gobbles up the PCSK9 protein and the small interfering mRNA inclisiran, which prevents the synthesis of the PCSK9 protein. And PCSK9 is a bad protein which prematurely kills these really important LDL receptors. So by getting rid of PCSK9, we increase the lifespan of the LDL receptor. Another nonstatin agent is ezetimibe, which acts on the intestinal villi and really decreases the absorption of cholesterol. So a lot of different nonstatin agents that we have, and some of the clinical trials with these nonstatin agents are showing incredible efficacy. So we've seen with 2 different PCSK9 inhibitors, in the FOURIER and the ODYSSEY trial, a significant LDL lowering, over 50%, and it’s also associated with improved cardiovascular outcomes.

Getting back to what I talked about with the GLAGOV study with plaque stabilization, we've now seen in other subsequent studies, like HUYGENS and PACMAN-AMI, that after acute coronary syndrome, we are seeing beneficial effects in terms of plaque remodeling with these agents that lower LDL. So here we see in one of the studies that the fibrous cap is thickening, and the lipid core is also being reduced. And again, this is with these agents that potently lower LDL cholesterol and that's stabilizing that plaque. And when you have this plaque stability as well as regression in that lipid core, you are preventing that plaque from easily rupturing and causing an MI or a stroke.

And so in addition to the PCSK9 monoclonal antibodies, we now have inclisiran on the market, and that also has potent LDL lowering of about 50%. But one of the novel aspects of inclisiran is the ease of dosing. So inclisiran can be given twice a year versus the PCSK monoclonal antibodies that are given twice a month or once a month. This is just less frequent dosing and it's really great for our patients that struggle with compliance.

Another really important concept that we are appreciating in our patients is this concept of statin intolerance. We used to think that statin intolerance was not real, but we've seen now in clinical trials that statin intolerance is real, and there is this concept of both partial and complete intolerance. So there's some patients that can take very low doses of a statin, but typically those low doses do not allow them to achieve their LDL goals. And then there's the concept of complete intolerance where patients just can't tolerate any statin, and they have significant side effects such as musculoskeletal symptoms, muscle aches, joint pain, tendon pain that really impairs their quality of life. So we need to be providing other options for these patients with statin intolerance.

And one recent study that really highlighted another option for these patients is the Clear Outcome study with bempedoic acid. And in this study there was a significant percentage of patients that were women, so 48% women in this trial, which is really incredible because most of the secondary prevention trials have been 20% to 30% women. And there was a high percentage of patients that had statin intolerance in this study. And what we saw is a significant reduction in cardiovascular events in the group that had bempedoic acid compared to placebo. There was also a sub-analysis of patients that fell into the category of high-risk primary prevention and what we saw as an even more significant benefit for these patients in terms of risk reduction. And so again, getting back to what I said earlier, we need to identify these high-risk primary prevention patients that have not yet had an event, and we can really do them service by being aggressive in treating their LDL and preventing them from having their first event.

And based on this data, there was an update to the FDA labeled for bempedoic acid, and now it is approved for patients who are high

risk for a cardiovascular disease event but don't have established atherosclerotic cardiovascular disease. So this is a really great expansion to the label, which allows us to give a broader set of patients access to this important LDL-lowering drug.

So what is the future? As I said in my wildest dreams, I wouldn't have thought that we would have agents such as inclisiran that we could just give twice a year for LDL lowering. But things are going to get even better with new technologies, such as gene editing, where we can give a patient a drug maybe once or twice and there's long-lasting impact of that drug throughout their life. And so that is a very exciting future. And then in terms of lipid lowering, we really focus today on LDL, but there's lots of other aspects of lipid lowering that we need to be thinking about, including looking at lipoprotein(a), which is genetically inherited, and 1 in 5 people have an elevated lipoprotein(a). And we have drugs now in phase 3 clinical trials that are looking at lipoprotein(a) lowering, but we also need to be thinking about non-HDL and triglycerides as well.

And so we have really evolved in our management of LDL lowering from statin monotherapy to other oral agents like ezetimibe and bempedoic acid. And now we have the PCSK9 inhibitors, both monoclonal antibodies, and the small interfering RNA agent inclisiran. So lots of different options for our patients. And getting back to women, women especially are undertreated and are not getting access to a lot of the newer agents. And we need to be cognizant of that and really provide great access to these agents that are really important for LDL lowering and for decreasing future risk of cardiovascular events.

And so cardiovascular disease, despite all the advancements that we've made, it continues to be the number one killer worldwide and also the number one killer of women. And as I love to emphasize to my patients, LDL-C is still the most modifiable risk factor, and unfortunately, in real-world clinical practice, most of our patients with high-risk features and ASCVD are not achieving their LDL-C goal. And some of that is because we're stuck on statin monotherapy, and we really need to be shifting that paradigm from monotherapy to combination therapy with multiple agents, such as statins and adding some nonstatin agents to achieve our LDL goals. We are very comfortable doing this with hypertension and diabetes where we typically add on multiple agents. And so we need to also start doing that with lipid lowering, is adding on multiple agents. We also need to be thinking about other modalities for risk stratification, including coronary calcium scoring, which is a pretty cost-effective tool to look at patients that may not have obvious risk but have subclinical atherosclerosis.

And the newer data is showing that even a calcium score greater than 300 is a really important way to look at patients that have the same risk as those patients that have already had a heart attack. So a calcium score over 300, you should consider that patient a secondary prevention patient. And as we reviewed with studies, such as GLAGOV and HUYGENS, when we lower that LDL as low as we can go, typically into the 30s, we are making a big impact on that atherosclerotic plaque. We're increasing that fibrous cap thickness; we're decreasing that atheroma volume. So really try to get that LDL as low as you can in our secondary prevention patients.

Hope you enjoyed this overview of LDL lowering with a little bit of Taylor Swift interspersed in this talk.

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