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Closing the Gaps: Global Implementation of Lipid Guidelines

Announcer:
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Dr. Lina Badimón:
I am Lina Badimón. I am Professor of Medicine at the University of Vic-Central University of Catalonia in Barcelona in Spain. And it's my pleasure to introduce the program of Women as One Global Lipid CME 2026: *Closing the Gaps*.

So we are going to be presenting different chapters in which the situation in the control of dyslipidemia will be analyzed in depth. My chapter, Chapter #1, will deal with foundations and global context.

So, with no more ado, I'd like to introduce my presentation, Chapter 1, that is going to be dealing with foundation and the global context of the area that we are dealing with, so women's health.

Cardiovascular disease is the number one killer of women worldwide. In Europe, for example, cardiovascular disease is also the leading cause of death, causing 3.9 million deaths every year. This is 45% of all deaths. And this is within Europe, we have also discrepancies between Western and Eastern Europe, but nevertheless, these are the average numbers. Cardiovascular disease, the ASCVD-associated diseases, mainly are coronary heart disease, stroke, and others that have a little lower contribution. So, 2.1 million deaths a year are happening in women. This is 49%, and 40% in men. So we are talking about a heavy toll in women's health.

This is why last year, well, two years ago, *The Lancet Regional Health - Europe* issued a commission to understand disparities in cardiovascular health. In this commission, we had four areas of interest. One was women, the other ones were racial and ethnic disadvantages, the other was mental health, and the fourth was elderly populations.

But if we concentrate on women, that is the topic of today, there were some areas that we wanted to really investigate and work for the next years, as these were associated to social aspects and also to medical aspects. So in women, we realize that there is a limited access to healthcare, and this is always depending on the country you are living. I mean, if we are not in Europe or in United States, the conditions are even worse. Women usually have a low income, and then also they have insufficient social support. And in the medical arena, it is a lack of diversity among cardiology clinicians, and women are underrepresented in clinical trials, and this have an effect on how we understand women's health.

This article was published as an outcome of this commission, and we were touching different aspects. Although fewer women develop ischemic heart disease, they are at a greater risk of dying from disease than men, and that's very important. Also, the biggest difference in outcomes is observed after STEMI, both in terms of mortality and acute complications, because for many years it was considered that women have less risk because they develop cardiovascular disease later. What they did eventually was that women were less well treated.

So the significant gaps that persist in understanding why these differences are present and what can we do to eliminate them are still in

the open air, and we have to keep investigating how we can reduce them.

There are several contributing factors identified. Obviously, we have been studying this for the last years. So, in addition to risk factors, the conventional risk factors, there are non-conventional risk factors, and there are gender- and sex-specific factors.

And regarding treatment, there is difficulty in access to care. Women complain of nonspecific chest pain more than men do, for example, and women experience delays in hospital presentation and treatment as well. And there are treatment complications associated to the fact that we know much less about the disease in women. So after PCI, women have a lower likelihood of optimal flow restoration, and they also present a higher bleeding risk. At the lower part of the circle, actions can be taken to mitigate disparities, and we will do better actions when we know much more.

But there are areas in research that needs to be taken care of, and areas also in public health. So in the research realm, we need to enroll more women in clinical trials. We need to improve data collection and sharing these data systems among investigators interested, and we need independent statutory bodies to address gaps in sex-specific research and also produce awareness in the population.

And in the public health realm, we need to have nowadays digital health interventions focused on women, patient education, and intensive primary prevention in women, and we have to tailor strategies of management on differences and also in the complications that women have after interventions. So, for example, sex-specific aspects related to atherothrombosis are that women have frequently worse outcome after intervention.

So I am showing you here two examples, one in Europe, one in the US. So the International Registry of Acute Coronary Syndromes is a registry that compared transitional countries, so Eastern countries in Europe with Western countries. And this ISACS-TC trial had 41 centers in 12 countries. So the objective of this specific study was to analyze the risk of 30-day mortality after STEMI in women. As you see here in the histogram, the risk of 30-day mortality is higher for women than for men in older stages of age, lower than 60, 60 to 74, and older than 75. But younger the age, the risk of having a complication was higher. So the group of less than 60 was associated with higher 30-day mortality rates in women, even after adjustment for medication, primary PCI, and coexisting morbidities. This was in this registry published in 2018.

But 2 years afterwards, there was this study coming from the Brigham, in which the group was even younger, so less than 50 years of age. And the study was in men and women presenting for their first MI. And you see in the graph, women is the red line, men the blue line. So men experience less risk. So women who experience their first MI under the age of 50 and survive the hospitalization had a significantly higher rate of long-term all-cause mortality than men.

Why is that? Well, we don't completely understand, so maybe we have to really start thinking that we have to investigate the causes of disease in women. We have advanced in this area as well, but not as much as we need.

We have to think that the heart has coronary arteries that produce ASCVD events, but also there is a lot of microvessels in the muscle irrigating the myocardium, and these are small vessels that have also some difficulties when sustaining perfusion. So women have microvascular dysfunction, meaning that there is dysfunction of the endothelial cells, both in the coronaries and also in the small arteries. These microvessels that produce impaired coronary microcirculation and also have abnormal coronary vasomotion, and these may happen without plaques, without atherosclerotic plaque. This is the concept of MINOCA that is happening more often in women than in men, because this dysfunction is more often happening in women.

So when the plaques are in the epicardial coronary arteries, these are atherosclerotic plaque, also, we have found differences between women and men. Maybe men and older women have a same phenotype of ruptured plaques with a thin fibrous cap, with a necrotic core, and rich in inflammatory markers, while females are more often associated to a phenotype of eroded plaque with thick-cap fibroatheroma with inflammatory markers, and rich in vascular smooth muscle cell-derived proteoglycans. So it's a different type of plaque, because also the risk factors may be a little bit different, or affecting differently the vasculature. Therefore, these concepts need to be investigated in depth.

When we talk about cardiovascular risk factors, the topic of today, the topic of dyslipidemia, and how we control dyslipidemia in women, I think we should span our interest also to these other risk factors, traditional risk factors that associate with cardiovascular disease that also affect women, like diabetes. I mean, is important in women. Smoking. I mean, in Europe there are countries in which smoking in women is still high, too high. Overweight and obesity, it happens quite often in women. Physical inactivity as well. Hypertension. And obviously dyslipidemia, that we will discuss afterwards with these three excellent speakers we have today.

But there are emerging and non-traditional cardiovascular risk factors like preterm delivery, hypertensive during pregnancy, disorders during pregnancy, gestational diabetes, but then also women have more often autoimmune diseases. Also the situation with cardio-oncology, breast cancer treatments, and also quite often depression.

And in our work within the mission, the Commission of *The Lancet*, we wanted to really make emphasis on pregnancy-related cardiovascular risk factors, and also cardiovascular risk factors associated to the reproductive system that usually affect the whole life of women. As we mentioned before, breast cancer, but also early menopause and premature ovarian insufficiency, the hormone replacement therapy, or changes in hormones due to the menopause, due to the menstrual cyclicity, because we have changes in hormones continuously every month. The regularity of this menstrual cyclicity also has an impact. Vasomotor symptoms, early menarche, polycystic ovarian syndrome, functional hypothalamic amenorrhea. Many young women nowadays suffer from this problem. And also hormone-based contraception. That this is happening quite often now, and these hormone treatments needed for contraception may affect, as well, women's health in the future and when they reach the menopause.

And in relation to the pregnancy times, so final parity, infertility, placental abruption, preeclampsia, gestational problems, diabetes, miscarriages, stillbirth, low birth weight. So there are many different issues that can have an effect on women's health.

So again, we like to separate psychological stresses from social determinants of health, and women are in need of social support. As I said before, it also depends on the countries, and this we will have to analyze in depth within our commission.

There is income inequality, quite important in some countries, and a lack of education. And regarding psychological stressors, we have violence and partner abuse, post-traumatic stress disorder, and depression. Therefore, there are many different issues that can affect women's health.

So, what do we have to consider? We have to consider that diabetes has a greater impact on cardiovascular risk in women than in men, as there are these sex-specific risk factors I already mentioned. There are risk-enhancing factors, like, for example, I didn't mention chronic kidney disease, and I did mention the autoimmune inflammatory diseases that women have more often than men.

The impact of the changes in the life course on lipid profile, the cumulative cholesterol exposure, is very important in women with familial hypercholesterolemia because they have this exposure during life, but in addition, during the fertility years or the breastfeeding years, usually the treatment is stopped, and obviously they keep accumulating cholesterol and affecting their arteries. So we have to study much better for how long these women should not be taking the treatment. Do we have hormonal and chromosomal effects influencing ASCVD? And we have to always remember that women also suffer from non-obstructive coronary artery disease that have a significant effect, and this might happen with and without atherosclerotic plaques in the epicardial arteries.

I'm finishing with this slide. Many of these concepts I'm introducing will be discussed later on in relation to dyslipidemia, but we, the European Society of Cardiology and the European Atherosclerosis Society, in 2023 wrote a consensus document with a call to action. And putting into perspective all the concepts I already mentioned, what we did is to really emphasize that we need to assess risk factors in women, all risk factors in women, and if they are not controlled, we have to start treatment early. Not because women are not in the menopause, the cardiovascular risk factors should be untreated. They should be treated. But we have to minimize the time off treatment after pregnancy and breastfeeding. We have to manage elevated risk factors as per guidelines from midlife. And we have to treat risk factors for non-obstructive coronary artery disease.

I think all these conditions may affect both sides, the medical part and the social aspect should also be considered, because they are important. Underdiagnosis, delayed diagnosis, undertreatment are common in women, and we really have to take care of this as well.

So, thank you very much for your attention. As I say, these dyslipidemia concepts and how the guidelines are being implemented, and how now women diseases or women cardiovascular risk factors are being already considered in the guidelines, both European and American guidelines that appeared this year, and I think all these concepts will be presented very, very excellent in the next chapters of this program.

Dr. Erin Michos:
Hello, I'm Erin Michos. I'm Professor of Medicine in the Division of Cardiology at Johns Hopkins University, and I'm pleased to talk about risk stratification and how that applies to lipid management.

So, of course, for everybody it's important to follow a healthy lifestyle throughout one's lifetime, but when considering drug therapy, estimation of risk facilitates matching the intensity of therapy to one's absolute risk, maximizing the anticipated benefits of therapy with potential harms of overtreatment, although our lipid-lowering therapies have a really good safety profile.

So in March 2026, we released the new American College of Cardiology/American Heart Association guidelines for management of dyslipidemia, and they recommend with a Class I indication that for primary prevention—so for individuals who have no known atherosclerotic cardiovascular disease and also no known familial hypercholesterolemia, because those groups already have a Class I indication for intensive lipid lowering—so, for other primary prevention patients, it's recommended to calculate risk using the new PREVENT Risk Score from the American Heart Association. And specifically you want to use the PREVENT ASCVD risk calculator.

There's also a risk calculator for heart failure and total CVD, but we use the ASCVD calculator for the lipid guidelines. And you'll estimate a 10-year risk of ASCVD for ages 30 to 79, but notably a 30-year ASCVD risk for ages 30 to 59, which I think is really important because we want to think about long-term risk. Often women have low risk in the short term, but may have high lifetime risk, and we want to focus on decreasing their total cumulative burden of atherogenic particles.

So, after you calculate 10-year risk, then you want to further personalize it by considering risk enhancers—and I'm going to go over those. And we have female-specific risk enhancers. And then if there's still some uncertainty about the benefit of lipid-lowering therapy initiation, or also the treatment target for LDL cholesterol, you can measure a coronary artery calcium score for adults that are men over the age of 40 or women over the age of 45. And then when you have all that information, you can reassess, recalculate their risk, and assess their need for lipid-lowering therapy. And you want to keep doing this over and over again in someone's lifetime, because risk is not stagnant at one point in time.

Now, notably, the risk cut-points and the thresholds for initiation of lipid-lowering therapy are different now when you use the PREVENT ASCVD score compared to the older guidelines that use the pooled cohort equations. So now low risk is considered less than 3% 10-year risk, borderline is 3% to 5% 10-year risk, intermediate is 5% to 10% 10-year risk, and high risk is greater than 10% 10-year risk.

Now, the European guidelines also endorse risk assessment. They use a SCORE2 risk estimation tool. There's also modifications for older persons and persons with diabetes. This also includes sex-specific risk calculation tools that estimate 10-year risk for fatal and non-fatal cardiovascular disease, and these are calibrated to different regions in Europe. And you can see the cut points for risk on the SCORE2 shown here on the slide on the right.

Now, once you calculate risk, going back to the US guidelines, high-risk individuals, more than 10% 10-year risk, have a Class I indication for intensive lipid lowering, but the guidelines now also recommend statin therapy for those that are intermediate risk, more than 5% 10-year risk and above, after having a clinician-patient risk discussion.

Now, for individuals at borderline risk, 3% to 5% risk, this is where you want to consider those risk enhancers that I'll go over, because it is a IIa indication for initiating statin therapy if you're borderline risk and have risk enhancers. But even low risk, less than 3% 10-year risk, the guideline gives a IIa indication that low-risk individuals who have an LDL cholesterol above 160 or have a high lifetime risk, a 30-year risk greater than 10%, it's also recommended to consider statin therapy to reduce their cumulative burden of lipoprotein particles, even if they're low risk in the short term.

So, let's talk about these risk enhancers. The guidelines endorse these female-specific risk enhancers which I've shown on this slide, but specifically they're outlined in Table 14 of the US ACC/AHA guidelines, and they include adverse pregnancy outcomes, specifically having a hypertensive disorder of pregnancy, gestational diabetes, small for gestational age, preterm delivery, or recurrent pregnancy loss, or other reproductive markers, such as having early menarche before the age of 10, early menopause before the age of 45, and notably premature ovarian failure before the age of 40, or polycystic ovary syndrome, which has now been renamed polyendocrine metabolic syndrome.

The guidelines also give a Class I indication to measure lipoprotein(a) at least once in all adults as a risk enhancer. We know that individuals that have Lp(a) levels above 125 nmol/L have a 1.4-fold increased risk. Levels above 215 nmol/L, a twofold increased risk. And the guidelines state, if lipoprotein(a) is elevated, LDL cholesterol should be intensified and other ASCVD risk factors aggressively controlled. The guidelines also say, for those that are borderline risk that have high-sensitivity C-reactive protein above 2 mg/L on at least two occasions, this also is a recommendation that favors statin therapy for those individuals.

So, here's the table from the guideline that lists all those risk enhancers. They're the ones I already mentioned, including the reproductive risk markers, lipoprotein(a) elevation, CRP elevation, but there's others that are called out, having a family history of premature ASCVD, a high-risk ancestry like South Asian ethnicity, chronic inflammatory diseases. We know that things like lupus and rheumatoid arthritis have a strong female predominance. The guidelines also recommend considering statin therapy for those with persistently elevated triglycerides or an LDL above 160 mg/dL. So, again, for those that are borderline or intermediate risk, if they have these risk enhancers, that would favor statin therapy.

And this is similar to what the European Society of Cardiology guidelines also say. Instead of calling them risk enhancers, they call them risk modifiers, but they also have the sex-specific female risk modifiers shown here on the slide in the pink that are very similar to the US guidelines, as well as other shared modifiers that both males and females may experience. And the presence of these sex-specific and other modifiers should be considered to up-classify individuals who are at borderline risk into the intermediate-risk category.

The US guidelines now also give a Class I indication for select adults at borderline risk or intermediate risk. If there's some uncertainty about lipid-lowering therapy, you can measure coronary artery calcium score in men above 40, women above 45. That's because

calcified plaque is late-stage plaque, so a coronary calcium score of 0 is less informative in younger adults. But notably, this does not apply to patients with severe primary hyperlipidemia with LDLs above 190. You should start intensive lipid-lowering therapy very early in life.

So, if you do measure coronary calcium, the guidelines do give risk-based thresholds for lipid-lowering therapy. For example, if the calcium score is above 1,000, to target an LDL goal less than 55 mg/dL. Calcium scores above 300, an LDL at least less than 70, an optional goal, which I aim for, less than 55 mg/dL in these very high-risk individuals. For those with a calcium score above 100, an LDL goal at least less than 70. But anybody who has a calcium score greater than 0, that means there's atherosclerosis, and targeting an LDL goal at least less than 100, and I try to aim for less than 70 in these individuals as well.

And again, a calcium score of 0 should not be used to defer therapy in the very high-risk patients with severe primary hyperlipidemia or those with diabetes, or a strong family history, for which you would want to do statin or other lipid-lowering therapy, even if the calcium score is 0.

So, in summary, the new guidelines from the ACC/AHA have a lot of things that move the needle forward for cardiovascular health in women, including this focus on long-term 30-year risk, considering age and sex percentiles for coronary calcium scores, including these reproductive risk factors, and the guidelines also give some guidance around lipid-lowering therapy during pregnancy and lactation, which I think will be discussed by a future speaker. Thank you.

Dr. Michelle O'Donoghue:
Hi, I'm Dr. Michelle O'Donoghue. I'm a cardiologist at Brigham and Women's Hospital in Boston, and an investigator with the TIMI Study Group.

So, I'll be talking a little bit more about different strategies for lipid lowering, as well as touching upon what the current guidelines are recommending.

Importantly, as shown on this slide, we know that, irrespective of how you lower LDL cholesterol, it appears to translate into a pretty reliable reduction in cardiovascular risk. So, what I mean by that is, whether you use statins, diet, niacin, fibrates, ezetimibe—any of these types of lipid-lowering strategies—based on how much you lower the LDL cholesterol, we know that that pretty reliably translates into the same relative risk reduction in major vascular events.

Similarly, for people who carry genetic polymorphisms, so really a genetic experiment of lifelong low LDL cholesterol levels. Again, that translates pretty reliably into a lower risk, a lifetime risk of cardiovascular risk. So, whether it's PCSK9 or other types of genetic targets that may confer lifelong lower LDL cholesterol, here, because that is present really from birth, that translates into an even larger lifetime lower risk of developing coronary artery disease.

But importantly, one of the recurring themes of today's presentation is that we know that lipid-lowering therapy is underused even in our higher-risk patients with established atherosclerotic cardiovascular disease. These are data from an observational registry of more than 5,000 patients with ASCVD. I'm looking to see how many changes in lipid-lowering therapy occurred over a period of 2 years. So, these are higher-risk patients. We'd expect their LDL cholesterol to be at least less than 100 mg/dL, and based on more recent recommendations, perhaps even less than 70 or 55 mg/dL.

But if you look at the cohort on the left here with LDL cholesterol levels that were above 100 mg/dL, only about 1/2 were on intensive lipid-lowering therapy, and even fewer were on other types of therapies, like ezetimibe and PCSK9 inhibitors, and just less than 1/4 had any form of intensification that occurred over that 2-year period.

And on the right-hand side, even for those who have lower LDL cholesterol levels at baseline, 70 to 99, but still not yet at target, intensification was even less frequently done, and vanishingly very low uses of the PCSK9 inhibitors and other types of non-statin lipid-lowering therapies.

So, PCSK9 was really a breakthrough target, a very interesting story in terms of the genetic experiment of identifying people who appeared to have genetic mutations in PCSK9 gene that conferred either lifelong low or high levels of LDL cholesterol, and a lot of it has to do with just recycling of the LDL receptor on the hepatic cell surface. The PCSK9 protein targets the LDL receptor for destruction, and really we want to have more of those LDL receptors on the hepatic cell surface, because they soak up that bad LDL cholesterol from the circulation. So, by targeting PCSK9, either with a monoclonal antibody, or there's also a small interfering RNA that's available, with less PCSK9 around, we have more expression of the LDL receptor on the hepatic cell surface, and that leads to a drop in LDL cholesterol.

Specifically, these are data from the FOURIER study of patients with established atherosclerotic cardiovascular disease, showing that evolocumab reduced LDL cholesterol on average by about 59% and that those effects were sustained over time.

Looking at the primary endpoint from the FOURIER trial, again with patients with established ASCVD, use of a PCSK9 inhibitor monoclonal antibody reduced the risk of cardiovascular events by 15%. And we see that the curves continue to diverge with time, suggesting that there's greater benefit with longer-term use.

One of the interesting observations as well from the FOURIER program was looking at the shape of the relationship between achieved LDL cholesterol and the annualized incidence of cardiovascular events. As you move here from right to left, you're looking at people who achieved lower and lower levels of achieved LDL cholesterol, and it doesn't matter how low you went to, that continued to lower your risk. So, even for people who achieved values that were less than 30 mg/dL, 20 mg/dL, really lower LDL cholesterol values than we're used to usually trying to achieve in clinical practice, you can see, though, that pretty reliably this continued to reduce their risk of cardiovascular events.

And what about safety? Now, sometimes people become concerned about achieving very low LDL cholesterol values, but data from FOURIER were very reassuring in this regard, including when we had a very long-term follow-up through the open-label extension, when some people treated with evolocumab for up to 8 years. There, regardless of how low you achieved their LDL cholesterol, the colors there in burgundy and red were people who achieved less than 20 or 20 to 40 mg/dL for their LDL values, but there appeared to be no higher incidence of any types of adverse events of interest, including neurocognitive events or hemorrhagic stroke.

So, those are patients with established ASCVD. There's a lot more focus now on prevention. You know, how can we stop athero in its tracks before patients have overt disease? So, on one end of the spectrum, if you have those with no athero, then those with stable atherosclerosis but without symptoms, those with stable atherosclerosis with symptoms, and those with a prior atherothrombotic event. So, really that concept of perhaps 1.5 prevention, so not exactly those who are completely primary prevention with no athero whatsoever, but for those who are at higher risk of progressing, should we start before there's clinically overt disease?

Well, these were the data from the VESALIUS trial that really looked at that population. It studied evolocumab in patients who are at risk for a first event. And what it demonstrated with intensification of lipid-lowering therapy with evolocumab was that there was a 25% relative risk reduction in major adverse cardiovascular events in this lower-risk patient population. And now looking at all-cause mortality, here there's a 20% reduction with evolocumab that became most apparent with longer-term follow-up.

So, I think very notable here that we have a population who have not yet had an event, and yet we're able to really modify the trajectory of their disease and prevent not only a first event but prevent the risk of death—of early death—for those patients, so I think that's an important finding as well.

We have a wide arsenal of non-statin lipid-lowering therapies that is continuing to expand. Of course, ezetimibe has been around for a long time. That interferes with cholesterol absorption, leads to about a 20% reduction in LDL cholesterol. Data from IMPROVE-IT showing that there's a proportional reduction in major adverse cardiovascular events. There are two different monoclonal antibodies that are currently available, alirocumab and evolocumab, targeted against PCSK9. There are others that are emerging as well.

Data from both ODYSSEY Outcomes, FOURIER, and now as well VESALIUS, demonstrating reduction in cardiovascular events, and these lead to about a 50% to 60% reduction in LDL cholesterol.

We'll hear a little bit more from Dr. Taub about bempedoic acid. This is a newer non-statin lipid-lowering therapy that works upstream from the statins within the liver and doesn't appear to have the same types of muscle side effects, and so may be appealing for a statin-intolerant patient in particular. That leads to about, again, a 15% to 20% reduction in LDL cholesterol.

And finally, inclisiran, which is a small interfering RNA that prevents synthesis of the PCSK9 protein, and also leads to about a 50% reduction in LDL cholesterol, with clinical outcomes trials that are still ongoing, but have the advantage of less frequent administration, with only subcutaneous administration twice a year after the initial loading period.

I think people are very excited as well that there are oral PCSK9 inhibitors that are in later stages of development. These are phase 2 results from two different compounds that are in development, but demonstrating again very robust reductions in LDL cholesterol.

So, what do the guidelines currently say? Well, based on the most recent ACC/AHA dyslipidemia guidelines, Step 1 is really assessing risk, and we can do that with a PREVENT risk score. So, 10-year risk can be calculated. Online calculators are available. If you have a patient with borderline risk, we'll talk a little bit more about some of the risk enhancers that can be used to help determine who is appropriate for lipid-lowering therapy. And for those patients who are at intermediate or higher risk, that's where lipid-lowering therapy really should be strongly considered. For those patients who are again in more of a borderline zone, that's where calcium scores may also be useful for helping to determine who might be a good candidate for more intensive lipid-lowering therapy.

It's important that we really think about risk markers that are specific to women. So, here's in particular our reproductive risk markers.

Adverse pregnancy outcomes are a consideration as well, so hypertensive disorders of pregnancy, gestational diabetes, small-for-gestational-age births, preterm delivery, recurrent spontaneous pregnancy loss. Those are the types of questions we should be asking our patients, and probably are not doing that all too often in our clinics, but they are important risk markers that again may ultimately come into decision-making when it comes to lipid-lowering therapies.

Other questions we should be asking our patients are about age of menarche. Early menarche is a risk factor, early menopause, as well as polycystic ovarian syndrome, and irregular menses. For patients who are pregnant or are lactating, there are special considerations. For a patient who's planning to get pregnant who's on statin therapy, the recommendations are to stop statin therapy 1 to 2 months before attempting to become pregnant. For a patient with homozygous FH who is very high risk, there you can consider continuing lipoprotein apheresis during their pregnancy. And similarly, for patients with very high triglycerides, higher than 500 mg/dL, you can continue the use of fibrates or high-dose omega-3 ethyl esters during pregnancy, during the second or third trimester, to reduce their risk of pancreatitis.

Additional considerations would be for patients who are at very high risk, who need to have some lowering of LDL cholesterol during their pregnancy. It's a IIa recommendation that bile acid sequestrants can be considered. And for pregnant individuals with FH or history of a clinical ASCVD, it may be reasonable to continue statin therapy to lower LDL cholesterol and ASCVD risk. There we have less data, so it's only a IIb recommendation.

So I won't walk through this in detail but really thinking about lipoprotein goals. That was one of the big advances with this iteration of the guidelines, was bringing back the targets, so to speak. So there are three big buckets of targets, and you just need to think about where your patient fits in as to whether you're trying to target an LDL cholesterol less than 100, less than 70, or less than 55 mg/dL, depending on their risk.

For primary prevention patients, by and large, if their 10-year risk is less than 10%, then a less aggressive goal of less than 100 mg/dL may be appropriate. But for your higher-risk patients, even if they're primary prevention, and certainly the data from VESALIUS would support this strategy as well, you may want to be more aggressive and target LDL cholesterols of at least less than 70 mg/dL.

So this figure is really thinking about the concept of cumulative lifetime LDL toxicity. So what I mean by that is, let's focus more on preventing disease before they have clinically overt coronary heart disease. So what each line here is indicating is looking at somebody's LDL cholesterol across their lifetime, whether it's 80 mg, 120 mg, 200, or 400. That line becomes steeper and steeper as their LDL cholesterol becomes higher and higher, and that red line is indicating the point at which they develop overt coronary heart disease. So, by initiating lipid-lowering therapy, we can really change the slope of that line, really delaying the onset of coronary heart disease.

So it's really thinking about lifelong cumulative LDL toxicity and thinking about additional risk factors. You know, so for women, there's somewhat of a protective effect early on, but we know that there is sort of a catch-up period, so to speak, after menopause, where very quickly women's risk starts to approximate that of a man.

So with that in mind, we really want to think about dialing back and starting more aggressive lipid-lowering therapy at an earlier point in time. Thank you.

Dr. Pam Taub:
I'm Pam Taub. I'm a cardiologist and Professor of Medicine at UC San Diego, and I'm going to be talking about how we manage statin intolerance and sex differences.

And so when we think about lipid management across the lifespan of women, we need to think about all the distinct different stages that women have, and how there are changes in lipids at different stages. So, for instance, pregnancy is a time when lipids do increase, and so that's not the ideal time to be checking lipids in the middle of pregnancy. We also need to be thinking about in menopause how there is an increase in LDL, and this is also where there's an increase in the prevalence of cardiovascular disease.

In addition to thinking about these stages, there's also some other things that happen. So, for instance, in young adulthood, that's when we see, for instance, conditions such as polycystic ovarian syndrome. And so it's really important that we think about these unique stages in the lifespan of women and how we manage lipids during each stage.

What we also know is that statin intolerance is very common. We used to think that this was just something that people were making up, but we've seen now in very well-conducted studies that it is common, and the National Lipid Association introduced this concept of both partial intolerance and complete intolerance. And complete intolerance is a patient that cannot take any statin therapy, where their maximally tolerated statin dose is zero. Partial intolerance is also very common, and this refers to patients that can only take very small doses of statins. For instance, it may be atorvastatin 10 mg every 3 days, or rosuvastatin 2.5 mg 3 times a week. So we need to also

understand that partial intolerance exists.

And when we look at who has statin intolerance, we see that this is much more prevalent in women compared to men, and so we need to be giving our patients other options.

There are so many novel non-statin options that are available and that act through different mechanisms of action. So, for instance, we have ezetimibe, which acts through preventing intestinal absorption of cholesterol.

We also have two drugs that act on the PCSK9 platform. So PCSK9 is a protein that prematurely degrades the LDL receptor, and the LDL receptor is really important for clearing LDL cholesterol. And the PCSK9 monoclonal antibodies like evolocumab and alirocumab basically gobble up the bad PCSK9 protein, and inclisiran prevents the synthesis of the PCSK9 protein. So we have multiple options now acting on the PCSK9 platform.

And we also have bempedoic acid, which acts on the cholesterol synthesis pathway, but upstream to where statins act and decreases cholesterol synthesis.

So those are the options that are currently available, and we have a lot of other drugs that are in development, including drugs that inhibit angiopoietin-like 3 and also CETP inhibitors.

But what we're seeing is that most clinical trials don't enroll a significant number of women. So if we look historically at some of the clinical trials, we see that many of them only are enrolling about 25% women. The most recent study, the CLEAR Outcomes study with bempedoic acid that was published in 2023, actually did a great job and enrolled about 49% women. So we're starting to do better in our clinical trials of lipid-lowering therapies in enrolling women, but historically we have not done very well.

So the bempedoic acid CLEAR Outcomes trial was a study that had 49% women, and in this study we looked at bempedoic acid in a very high-risk population or patients with ASCVD. And in this study, treatment with bempedoic acid was associated with a 13% relative risk reduction in cardiovascular events.

We do also need to keep in mind that there are lipid changes that are occurring during the lifespan of women. So, as I mentioned earlier, in pregnancy we see a lot of changes in lipids, specifically an increase in LDL-C and triglycerides.

We also see changes in lipids after menopause, and this was a slide provided by one of our speakers, Dr. Michos, and what we see really nicely depicted is what's happening after menopause. So menopause is a very vulnerable time for women. A lot of hormonal changes are occurring, but we're also seeing an increase in LDL-C, an increase in triglycerides, as well as a decrease in HDL-C. We also see in menopause that there is abdominal obesity that starts to happen, accumulation of visceral fat. So there's a lot of cardiovascular changes occurring around the time of menopause that increase cardiovascular risk.

Briefly, I want to touch upon lipoprotein(a), which is a very common entity. One in 5 people have elevated lipoprotein(a), and it increases risk of cardiovascular events. But what we want to keep in mind is in women after menopause there can be a 20% to 30% increase in lipoprotein(a). So we know from the recent guidelines we should be checking lipoprotein(a) at least once in everyone's lifetime, but in women who've had previously borderline Lp(a) levels, you may consider checking it again after menopause, as there is this increase that's seen in menopause.

We also now have some great data from the guidelines of risk enhancers. And one of the very nice things that the guidelines call out is reproductive risk markers, including premature menopause, preeclampsia, gestational diabetes. And this is really important for us to keep in mind when we're evaluating women and really assessing for some of these reproductive risk enhancers.

So, in summary, we know that statin intolerance, either total or partial, is common in women. We do have many non-statin options. And we also need to understand that there are specific lipid changes that are occurring during the lifespan of women that impact cardiovascular risk. And we need to utilize risk enhancers, especially some of the reproductive risk enhancers that are unique to women, to appropriately assess cardiovascular risk.

And I'm going to be talking about lipid management, and really focusing on implementation across US and global settings. When we look at the current state of lipid management, the real-world data is very sobering. So, for instance, only 1 out of every 2 patients after a PCI even have LDL-C measured, and so if we don't even have this fundamental data, how can we even get more aggressive with implementation?

And this is very consistent across many studies that show not only are we not measuring LDL, but in terms of implementation of high-intensity statins, that's also very dismal. So this was a large insured US cohort, and what you see here is only about 23% of patients that had ASCVD were on high-intensity statins.

We also see that clinical inertia is real, and this is real across both primary prevention and secondary prevention, with only about 42% of patients being on guideline-directed statin therapy.

We also have seen in more contemporary registries, like the GOULD registry, which looked at over 5,000 patients with ASCVD, that in terms of achieving our LDL-C goals, when you look at patients that are just on monotherapy with statins, very few patients achieve their LDL-C goals.

However, when you start thinking about combination therapy, that's adding on other agents, such as ezetimibe, PCSK9 inhibitors, more patients achieve their targets, and this is a really important theme, which is that combination therapy is very important. We need to move past the concept of statin monotherapy.

In Europe, The DA VINCI study also looked at LDL-C goal achievement in a large cohort. And this study also showed that combination therapy was necessary to achieve LDL-C goals, and specifically PCSK9 combination therapy seemed to be very potent, with 67% of patients achieving LDL-C goals.

What we've also seen from the recent publication looking at the SWEDEHEART registry is that when you start combination therapy upfront, so for instance, in this study they looked at patients who started both ezetimibe and statins upfront after an MI, and they compared it to patients that had later initiation of ezetimibe, and they found that when upfront initiation of statin and ezetimibe occurred, that MACE over a 3-year period was lower. And this really reflects that when you start upfront combination therapy, you achieve your LDL-C goals earlier, and it's also sustained. So, really speaking to the importance of combination therapy from an implementation perspective.

We've also seen some great data with inclisiran, which not only overcomes adherence issues because it's very easy to administer every 6 months, but it's also very well tolerated. What we see here is when you compare inclisiran versus standard of care in patients after ACS, those patients that received inclisiran achieve their LDL-C goals earlier.

So, why is there so much clinical inertia and difficulty achieving LDL-C goals? And some of that has to do with a lot of misperceptions about statin therapy, and we need to come up with better ways to get statins and other non-statin therapies to our patient, and this is where we need to leverage team-based care. We need to use EMR tools to identify patients that don't even have LDL-C measurements, and figuring out systemic ways to make sure that LDL-C is measured, and also making suggestions on different therapies, and that includes combination therapies. And this is where a multidisciplinary team is very important, and we need to leverage the expertise of multidisciplinary teams, including dietitians, pharmacists, nursing, to help with implementation.

So, in summary, we still have an implementation gap in real-world clinical practice. Women are often the most undertreated group, and if we utilize multidisciplinary teams and system-based solutions, we can overcome some of these implementation barriers. We have had so many incredible breakthroughs in lipid management, but our next breakthrough is really delivery, not necessarily discovery.

Dr. Erin Michos:
So, this is a female patient referred for cardiovascular risk assessment. She's a 58-year-old woman of South Asian ethnicity. She has no history of heart disease. This is a primary prevention patient, and she's currently asymptomatic. So, she's here in the office for cardiovascular risk assessment. She has a history of hypertension. She takes losartan, but no diabetes or smoking history. However, she did have adverse pregnancy outcomes with a history of preeclampsia in her first pregnancy and gestational diabetes in her third pregnancy. She also had early menopause at age 44 and a family history that's notable for a mother who had a myocardial infarction at age 60.

On exam, her BMI is 26. She has an elevated waist circumference. Her blood pressure at 136/78 could still be optimized some more, but otherwise her exam was normal. And her current lipids—and again, she's not currently on any lipid-lowering therapy—she has a total cholesterol of 210, triglycerides of 160, HDL of 42, an LDL of 136 mg/dL, and a lipoprotein(a) of 82 nmol/L which is in the intermediate-risk range. Her A1c is still in the normal range. She had normal kidney function, but she had an elevated high-sensitivity CRP at 2.8 mg/L.

So, per the guidelines, we start with a risk assessment. So, using the PREVENT ASCVD risk score, she falls into the intermediate-risk of a 3.1% estimated risk over the next 10 years, but her lifetime risk over the next 30 years was estimated to be at 17%. So, keep in mind her LDL is only 136 mg/dL. Does she need a statin?

Well, as I went over in my first presentation, that if somebody is at borderline risk in the next 10 years, if they have risk enhancers present, that does favor statin initiation, and she has quite a few risk enhancers, and I highlighted them on this table. She has a family history of premature atherosclerotic cardiovascular disease in her mother. She has a higher-risk ancestry with the South Asian ethnicity. She had early menopause, preeclampsia, and gestational diabetes, so several reproductive risk markers. She has a high-sensitivity

CRP greater than 2. I mean, the guidelines say you should confirm it on another measurement. She also has elevated triglycerides. So she has a number of risk enhancers.

Now, she does have a little bit elevated Lp(a), not quite in the risk-enhancing range that was used as a 125 nmol/L threshold, but still it's elevated. It would be another reason to intensify her LDL-lowering therapy and treat all of her other ASCVD risk factors more aggressively

Now, what if she was a decade younger and her 10-year risk was, you know, less than 3%, low risk? The guidelines really highlight the importance for early intervention and do say that even in individuals who are at low risk, if they have heterozygous familial hypercholesterolemia and LDL above 190, or if they are above age 30 and have an LDL above 160, a strong family history of premature ASCVD, or a high 30-year risk of ASCVD greater than 10%, this would also favor initiation of statin with a IIa indication, even if their 10-year risk was low. So she meets criteria per the guidelines for statin therapy.

We've talked to her about optimizing her lifestyle, would like to control her blood pressure a little bit better, but after engaging in shared decision-making, unfortunately the patient was reluctant to start a statin. She was worried about side effects. She had been reading things on the internet, and although we counseled her on the excellent safety and efficacy profile, she was still quite hesitant.

So, after discussion, we decided to get a little bit more data, and we got a coronary artery calcium score, and her score came back 24, which doesn't sound that high, but in a reproductive-age woman this was at the 81st percentile for her age and sex. And seeing often is believing. You know, once she was confronted with her own images that clearly demonstrate she already has the atherosclerosis process, she was much more interested in engaging in preventive therapy, and she agreed to initiate a statin. We additionally started with a moderate-intensity statin at 5 mg of rosuvastatin daily.

With that, her LDL came down to 83, which was reduced from her previous of 136, but given that she had a lot of risk enhancers, strong family history, already had atherosclerosis based on a high calcium score for age and sex, I wanted to get her numbers even better. So we intensified her rosuvastatin to 10 mg daily to aim for this.

She's currently tolerating a statin, but as you heard from the other speakers, we do have other non-statin therapies that could be offered to her alone or in combination with statin to help achieve these risk-based targets.

Dr. Michelle O'Donoghue:
So, for the second case, we'll discuss a 62-year-old African American woman who has a prior history of coronary disease, who had a stent placed 6 years ago, but she's now hospitalized with an ST-elevation MI and undergoes placement of a new stent.

Her past medical history is otherwise notable for a history of type 2 diabetes, for which she's on metformin and a GLP-1 receptor agonist, a family history of premature coronary disease, and hyperlipidemia. She's on rosuvastatin 20 mg but she's been intolerant to higher doses.

On exam, her BMI is 24 kg/m², and she's normotensive. She otherwise has a normal cardiac exam.

Her lipid panel is most notable for an LDL cholesterol of 118 mg/dL and an elevated Lp(a) at 130 nmol/L. Her A1c, her eGFR, and hs-CRP are all within normal.

So where do we go from here? Well, we know data from PROVE-IT that were published now a couple of decades ago, but looking at a strategy of more intensive statin therapy with atorvastatin 80 mg compared to pravastatin 40 mg within 10 days of acute coronary syndrome, intensification of statin therapy led to a 16% relative risk reduction in major adverse cardiovascular events. But notably, when you look at this figure, you can also appreciate that the curves diverged quite early, suggesting that there really is early benefit from more intensive lipid-lowering therapy in patients after ACS.

This has also been supported by more recent intracoronary imaging data. So, these are OCT data from a randomized clinical trial of statin monotherapy versus statin plus more intensive lipid-lowering therapy with evolocumab. And what I think is quite notable here is that even by week 4, the more intensive lipid-lowering strategy here with a PCSK9 inhibitor led to favorable changes in fibrous cap thickness, as well as a reduction in lipid arc, so really suggesting that you can help to stabilize the plaque very early on after an ACS with more intensive lipid lowering, and including more thickening of the fibrous cap.

So, what do the guidelines say? When we look at the most recent iteration of the ACC/AHA ACS guidelines. If you have a patient with an ACS who's already on maximally tolerated statin therapy—here you're looking at the middle of this figure—the Class I recommendation is to achieve an LDL cholesterol less than 70 mg/dL, and there's a Class IIa recommendation for intensification if their LDL cholesterol is between 55 to 69 mg/dL.

Here, for this particular patient, we know that their LDL cholesterol is actually above 100 mg/dL, so really necessitates intensification of

our lipid-lowering therapy. And here the patient is unable to tolerate a more intensive statin regimen, so we need to think about non-statin lipid-lowering therapies.

So, really just breaking that down a little bit further. Step one is maximally tolerated statin therapy after an ACS, and then step two, add a non-statin lipid-lowering therapy as needed to achieve an LDL cholesterol less than 70 mg/dL, or ideally less than 55 mg/dL.

So, how do you pick which therapy to reach for next? Well, choose your non-statin lipid-lowering therapy based on how much you need to reduce their LDL cholesterol. Really, it's basic arithmetic, in essence, because we know that ezetimibe and bempedoic acid reduce LDL cholesterol by about 15 to 20%. PCSK9 inhibitors can achieve about a 50 to 60% reduction in LDL cholesterol. So, think about what their LDL cholesterol is now, and where you need to get to.

But importantly, you really want to recheck the lipid panel 4 to 8 weeks post-discharge, and then intensify as needed, if not at goal, because, as I showed before, we know that early changes in plaque were followed as seen. So, we really want to make sure that we're intensifying as needed.

What about the Lp(a) part of this story? Well, if it's above 125 nmol/L or above 50 mg/dL, depending on which type of assay you use, for a patient who has clinical ASCVD, such as the patient in this particular vignette, we want to achieve LDL cholesterol and non-HDL goals on maximally tolerated statin therapy. But for a patient who's not at goal, like this patient, we preferentially would want to add a PCSK9 inhibitor, a monoclonal antibody in this instance under the guidelines, because we know that the PCSK9 inhibitors can also achieve about a 25 to 30% reduction in Lp(a). We don't know whether or not lowering Lp(a) through that pathway is going to add any incremental benefit, but nonetheless we think that intensification with the PCSK9 inhibitor will offer benefit overall for that patient, regardless.

So, in summary, target an LDL cholesterol less than 55 mg/dL. If they're already on maximally tolerated statin therapy, initiate a PCSK9 inhibitor in this instance to achieve sufficient LDL lowering. PCSK9 inhibitor may also offer the benefit of lowering Lp(a), albeit again we don't know whether or not that offers any additional clinical benefit. Continue to reinforce favorable lifestyle changes. Continue diabetes management, including the GLP-1 RA, once stabilized post-MI. Recheck a fasting lipid panel four to eight weeks post-MI, and up-titrate lipid-lowering therapy as needed. Importantly, also don't de-escalate therapy, so if their LDL cholesterol level ends up being below the target goal, that's fine. Do not de-escalate. And also consider family cascade screening for the elevated Lp(a), as we know that that can run in families.

Thank you so much for joining us today. You know, this was just a wonderful review, I think, of a lot of the contemporary data, the guidelines, thinking more about non-statin lipid-lowering therapies to help achieve goals, but I welcome your thoughts as well.

Dr. Lina Badimón:
Yeah, I'd like to thank everybody. I mean, it was a very good program. These chapters were really clear to help to treat better dyslipidemia, and to take care of women, that is what is very important nowadays.

We have to congratulate ourselves that all these measurements are already within the guidelines, and this will help a lot to treat women much better. So, I'd like to thank you for all your work, and I hope this program is liked by everybody. Thank you.

Dr. Michelle O'Donoghue:
Thank you so much for joining us today, and for anybody who would like to download resources, they will be available for you. Thank you.

Announcer:
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