Transcript Details

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Establishing Best Practices for Collaborative Care for Patients with ASCVD Between Academic and Rural Providers

Announcer:
Welcome to CME on ReachMD. This activity titled, “Establishing Best Practices for Collaborative Care for Patients with ASCVD Between Academic and Rural Providers,” is jointly provided by UK HealthCare CECentral and Partners for Advancing Clinical Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Gluckman:
Welcome to today's continuing medical education program entitled, “Establishing Best Practices for Collaborative Care for Patients with ASCVD Between Academic and Rural Providers.” This activity is provided by Partners for Advancing Clinical Education and the University of Kentucky HealthCare CECentral, and supported by an educational grant from Novartis.

My name is Ty Gluckman. I serve as Medical Director at the Center for Cardiovascular Analytics Research and Data Science at the Providence Heart Institute in the Providence Health System in Portland, Oregon. And it's an honor today to be joined by my co-faculty, Dr. Rishi Wadhera, Associate Professor of Medicine at Harvard Medical School and Associate Professor of Health Policy and Management at the Harvard School of Public Health in the Division of Cardiology at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

These are the disclosures for the two of us.

And these are the learning objectives. And in short, we're going to essentially be reviewing information related to non-statin medications that can be used to help achieve LDL cholesterol goals, highlighting the current and emerging role of lipoprotein(a) assessment, and describing barriers to equitable care for individuals living in rural communities.

So I'm going to kick things off by focusing, initially, on management of patients at risk for or with atherosclerotic cardiovascular disease. And I suspect a lot of this is already known to you, but I'm going to be highlighting, hopefully, some information that's new to you as well. And I love this image or pictorial, but it really nicely illustrates the continuum of atherosclerotic cardiovascular disease risk faced by the patients that I see, that you see, likely every day, if not every week in clinic. So to the far left, you can see that there are individuals, and hopefully for a lot of us, we have no atherosclerosis, we're considered a primary prevention patient population, only to highlight in this pictorial the fact that elevated levels of circulating LDL cholesterol can predispose as one moves from left to right, the development of atherosclerotic plaques, that even if someone has primary prevention, defines an individual at higher atherosclerotic cardiovascular disease risk. And as the plaque progresses and the atherosclerotic cardiovascular disease process progresses, it puts people at increased risk for premature atherosclerotic cardiovascular events, or non-premature events that can be the result of plaque rupture, erosion, or fissuring, where you can have, in the case of the coronary circulation, a myocardial infarction, cerebrovascular circulation, a stroke, or critical ischemia involving the peripheral circulation.

And when we think about the relative impact of LDL cholesterol, it's important to realize that there are a lot of factors that drive the risk for atherosclerotic cardiovascular disease events. This is one of the very pivotal important studies called the INTERHEART study. This

was published now two decades ago, and looked at nearly 30,000 individuals across multiple countries. In looking at those individuals with a first myocardial infarction, what were the drivers, or the population attributable risk related to that first myocardial infarction? Now, I would acknowledge to the far left that those individuals who had diminished intake of fresh fruits and vegetables and exercise was a driver of risk. But many of these other risk factors are what we would consider traditional risk factors; needless to say, abnormalities in lipids, and in particular, elevated levels of LDL cholesterol was associated with a heightened population attributable risk. And what you can see to the far right is when you take all of these factors in totality, it accounts for about 90% of the population attributable risk for a first myocardial infarction.

And this is an interesting sort of way of thinking about cholesterol, in a way that we think of maybe more analogous to tobacco exposure, we think of pack years of exposure to tobacco. But what about cholesterol years of exposure? Because, in short, it is the cumulative exposure to higher levels of cholesterol, LDL cholesterol in particular, over time, that defines susceptibility to development of atherosclerotic plaques and the events that follow with that. And you can see, as is illustrated by an arbitrary horizontal line of a threshold for onset of atherosclerosis, that those individuals who have the highest elevation of LDL cholesterol, those with familial hypercholesterolemia from birth, they may have very high levels and a very relatively short duration of exposure before they cross that threshold and have events. In contrast, as you move from left to right along the X axis, you can see that individuals who have lesser degrees of elevation of their LDL cholesterol may require a longer duration of exposure to cross that threshold, and many people, fortunately never cross that threshold at all.

So all of this comes down to who warrants LDL cholesterol-lowering therapy, and we're really talking about pharmacotherapy as intensive lifestyle changes through diet and exercise should be ubiquitous and recommended to all individuals. And going back to 2013 and the subsequent 2018 blood cholesterol guidelines, they really defined four key groups that warrant LDL cholesterol lowering. And these are mutually exclusive groups. So as I approach these patients when I see them in clinic, I'm thinking about this sort of systematically. Does the person sitting in front of me have clinical atherosclerotic cardiovascular disease? Have they had a heart attack? Have they had a stroke? Have they had arterial revascularization in the cerebral vasculature, the coronary vasculature, or the peripheral vasculature? If the answer is yes, you go down that pathway. If the answer is no, do they have primary severe hypercholesterolemia defined as an LDL cholesterol greater than or equal to 190 mg/dL? Of these individuals, a subset will have a familial etiology, or familial hypercholesterolemia. If the answer is yes, you go down that pathway. If the answer is no, do they have diabetes mellitus? Type 1 or type 2, doesn't make a difference. If the answer is yes, you go down that pathway, if the answer is no, you're left with a group that still may warrant treatment to lower their LDL cholesterol, but it's defined by their risk threshold, or the predicted risk for adverse cardiovascular events over a time horizon, usually of 10 years. But some of the risk estimators have the ability to estimate over a longer time horizon, so-called lifetime risk, which can be 30 years or longer in terms of being looked at overall.

Of note, there have been some updated changes to the guidelines over time. In particular for clinical atherosclerotic cardiovascular disease, the concept of further stratifying that group into those at very high risk versus those at not very high risk. Let me be clear, all patients with atherosclerosis are high risk, but essentially, are there people that warrant even more aggressive LDL cholesterol lowering? And the concept of risk enhancers or other factors that may inform the decision-making about whether we're more aggressive for these individuals. And in the 2018 blood cholesterol guidelines, they introduced the concept of two goals, both a percent reduction in LDL cholesterol from baseline if you happen to know their LDL cholesterol level at baseline, as well as a LDL cholesterol treatment threshold, whereby you want to be below that treatment threshold. Put a different way, if their LDL cholesterol remains at or above that treatment threshold, additional LDL cholesterol lowering is going to be warranted with pharmacotherapy.

And one key takeaway, probably a key pearl of this slide, is we traditionally in cardiovascular medicine have sought to match the intensity of risk factor modification to the baseline risk. In short, we want to be more aggressive for people that are at higher risk and there is a lesser degree, if you will, of intensity of our preventive efforts in those people who are lower risk. A world of relativism, if you will.

So I briefly touched base on this, but just to highlight that in 2018 in the blood cholesterol guidelines, they further segmented individuals with atherosclerotic cardiovascular disease into those deemed to be very high risk versus not very high risk. The former of those at very high risk were defined as people having two of the items or more in the red box, major ASCVD events that are listed there, or one of the items in the red box and two or more of the items in the gray box overall. And large population analyses have suggested that at least 50%, and in some cases a higher percentage, of patients with atherosclerotic cardiovascular disease are very high risk. But doing this importantly helps to define in that guidance document and subsequent guidance issued by the American College of Cardiology, more intensive LDL cholesterol lowering in those that are deemed to be very high risk.

In addition to this, and this is by no means a complete list, increasingly, we have recognized you doing a coronary calcium scan to define whether someone has coronary calcium present as a marker of atherosclerosis and the atherosclerotic burden, is probably the

most widely utilized test to further refine the risk profile of individuals out there. So in particular, for individuals in whom treatment decisions are uncertain, despite the fact of assessing someone's risk or trying to determine what their risk profile looks like, the use of a coronary calcium score can help you refine risk such that a coronary calcium score of 0 may suggest that the estimated risk by plugging numbers into a calculator or estimator of risk may be an overestimate of their true risk.

On the flip side, the presence of coronary calcium defines individuals as having atherosclerosis and defines essentially a population definitely in need of cholesterol-lowering therapy, and may even draw decisions about how intensively you lower their LDL cholesterol.

Some additional details are provided here. But in general, in someone who has elevated coronary calcium, you don't repeat testing over time. In contrast, for those individuals that have a coronary calcium score of 0, for whom a decision is made to withhold a decision of initiation of lipid-lowering therapy, most commonly initially with a statin, you could repeat the coronary calcium scan 3 to 5 years there afterwards. Of note, this approach of looking for a coronary calcium score of 0 is really not recommended in patients with diabetes, those with severe hypercholesterolemia, those with a family history of premature coronary heart disease, those with tobacco use or abuse, and those with another high-risk condition.

And I've put this together. It's sort of a distillation of what came out of both the 2018 blood cholesterol guidelines and an Expert Consensus Decision Pathway on non-statin therapy that was put out by the American College of Cardiology in 2022 and it allows you to understand the dual goals for each of these populations. I've attempted to color code the respective populations that we highlighted before in blue, red, green, and yellow that match up to those four groups on a few slides back. But just to note that each of these populations have dual goals, and essentially, if you're unable to achieve both goals, then you have the need to intensify your treatment regimen overall. I will acknowledge that it relies upon knowing their baseline LDL cholesterol to determine the reduction in their LDL cholesterol from a percentage perspective. I rarely, if ever, have people withhold their therapy to get a new baseline. Rather, you may be limited in a situation where 12 years ago was when they had their baseline lipid panel, that you simply may not be able to calculate or estimate what their reduction in LDL cholesterol is because you don't have a baseline for comparison.

So I would be remiss in any presentation, even though it's focused on pharmacotherapy, if I didn't highlight the importance of lifestyle intervention. And this is an accumulated or aggregation of lots of different analyses highlighting the variety of ways in which you can lower LDL cholesterol and the magnitude of LDL cholesterol reduction that can be achieved with these interventions. Now, you may be saying, Ty, it's a challenge for my patients to do one of these things, let alone all seven of these things. But it just does reinforce that lifestyle is the cornerstone and the base that we would be adding all pharmacotherapy to. And if done intensively across the board, you can achieve upwards of a 30 to 45% reduction in LDL cholesterol that mirrors what we achieve in general with moderate intensity statin therapy.

Let's fast forward beyond lifestyle intervention. And again, drug therapy is not a replacement for but a compliment to lifestyle intervention, only to highlight that we have a lot of tools in our toolbox that can target the means by which to lower LDL cholesterol. Statins have historically been and continue to be our base therapy for this patient population, but there are a number of non-statin therapies that I'm going to be reviewing in a few moments that represent adjunctive therapy on maximally tolerated statin therapy for those that require additional LDL cholesterol lowering. And again, reflective of what I shared previously, patients in particular With atherosclerotic cardiovascular disease and severe hypercholesterolemia are amongst the higher risk populations. Those are people that we push their LDL cholesterol levels to even lower levels, and therefore, depending upon where you're starting, statins may fall short, even with high-intensity statin therapy of achieving those dual goals, and as such, non-statin therapy may well need to be added.

I'm reiterating what I just shared. And this is a pooled analysis that was published now almost a decade ago, looking at a number of primary prevention trials in blue with a control, most often placebo arm, illustrated by a filled in circle, the intervention group represented by the open blue circle, and then the secondary prevention trials, which are represented by squares, the same theme. And you can see these are on-treatment trials. So as you look along the X axis, these are mmol/L of LDL cholesterol. You essentially can take that number and multiply it by roughly 40 to be equated to mg/dL. But as you pharmacologically move from right to left, lowering LDL cholesterol with statin therapy in secondary prevention and primary prevention, you can see along the Y axis, it's associated with a reduction in the rate of coronary heart disease, death, or myocardial infarction.

The key takeaway for me, above and beyond what I've already shared, is that the slope of the secondary prevention trials is steeper than the primary prevention. In short, for the same magnitude of LDL cholesterol reduction, you get a greater magnitude of event reduction observed in secondary prevention compared to primary prevention. It doesn't take the wind out of the sail for me of using statins in primary prevention, where there's a wealth of data, as reflected here, substantiating cardiovascular benefit with their use in those populations.

Which brings up the issue of intensity of statin therapy. And it's important to realize that not all statins are created equal in terms of their

expected or on average reduction in LDL cholesterol. And this may seem a little bit arbitrary, but I think it makes sense with how I think about, as a clinician, segmenting the different forms of statin therapy. We have high-, moderate-, and low-intensity therapies. And high-intensity statin therapy is a regimen that, on average, will achieve approximately a 50% or greater reduction in LDL cholesterol. I do want to underscore the word on average, because essentially, as I'm going to show you here in a moment, you only really know the treatment response of the patient sitting in front of you or that you're managing in clinic when you recheck their lipids after being exposed to that intervention or that therapy. And this goes for all of our lipid-lowering therapies, our LDL cholesterol-lowering therapies. But you can see here that atorvastatin and rosuvastatin at 40 to 80 and 20 to 40 mg, respectively, are the two drugs and two doses for each drug that on average will achieve this effect. Moderate-intensity statin therapy, on average, will achieve a 30 to 49% reduction in LDL cholesterol. And you can see a wider array of drugs and doses. And then low intensity would achieve, on average, a less than 30% reduction in LDL cholesterol.

And I like this slide a lot, but this is actually pulling data from the JUPITER trial, which was a trial of at-risk, moderate- to high-risk individuals, primary prevention being looked at, exposing those individuals to the drug rosuvastatin at 20 mg per day. This was a primary prevention trial. And this is taking half of the people in the trial that were exposed to rosuvastatin. This is a waterfall plot. Each one of the lines, and you can't see these as lines, but each one of these different areas in the color scheme that I'll get to in a second, represent individual patients of the 7,856 individuals. And what you can see here is of those 7,856 individuals, you can see to the far right, in yellow, there was a subset of individuals who exposed to 20 mg of rosuvastatin actually had a greater than 60% reduction in LDL cholesterol. The lion's share of people in green had a 40 to 60% reduction in LDL cholesterol, about what you might expect on average for people being exposed to high-intensity statin therapy. But perhaps surprising to each of you watching, some people had a less than 40% reduction in LDL cholesterol, as illustrated in red. And in blue, there were some people who had no reduction in LDL cholesterol and actually saw modest increases, or in some cases, more pronounced increases, in LDL cholesterol.

Now that may seem quizzical and at odds with what you would normally think about, but it's only to highlight that there is – just because you have an average treatment effect doesn't mean that every person exposed to the therapy will experience that average effect. You're going to see variability in response, and it needs to be followed up with lipid testing to determine whether they sit in the blue, red, green, or yellow groups, figuratively, for a given therapy.

And this is a call out here that was illustrated in 2013 blood cholesterol guidelines, the 2018 blood cholesterol guidelines. One of the challenges we have is some individuals may say, 'I'm going to put you on lipid-lowering therapy. I'm going to set it and forget it.' And the reality is that's never what the guidelines have said. First and foremost, if you initiate drug therapy, change the dose of a drug, switch to a different drug, add a drug. The recommendation is to recheck a lipid panel 4 to 12 weeks later, principally, to figure out what is the magnitude of the LDL cholesterol-lowering effect for the drug that you've initiated, changed the dose, added to, overall. It's primarily to figure out where on that waterfall plot they sit, and is this a patient who has achieved their dual LDL cholesterol goals, or does something more needs to be done.

And then lastly, if they achieve their dual LDL cholesterol goals, the recommendation is every 3 to 12 months thereafter, rechecking the lipid panel. And now the focus is less about the expected or actual achieved LDL cholesterol-lowering effect; it's more about monitoring for adherence. And if you have a patient whose LDL cholesterol has been in the same range, and all of a sudden, on a repeat check abruptly goes up, it should prompt you to ask the question, did they stop taking their medication? Did they run out of their medication? Are they having any tolerability issues related their medication overall? So this is my special plug for testing initially and repeat testing on a surveillance basis for different purposes overall.

I do want to just sort of round down this section by highlighting the fact that statins, which represent the mainstay of the therapy for all the four key risk groups, has a highly favorable benefit to risk ratio, with a number of the points outlined here in terms of the ability to lower LDL cholesterol, reduce coronary atheroma, reduce ASCVD events. And there are a lot of myths and misunderstandings about statin therapy. And I want to acknowledge that from a population perspective, they may occur infrequently. But if you're dealing with a single patient who's challenged by issues, that is your patient that you're interfacing with on that given day, the reality of the data is the preponderance of data does not support a data that would suggest statins have any effect on cognitive function, renal function, risk for cataracts overall, or risk for hemorrhagic stroke, certainly in the absence of prior stroke overall.

I do want to acknowledge that there are potential risks related to statin use. Modest risk of new onset diabetes about 0.1% annually, and acknowledging the fact that most people go on to develop diabetes were at risk for it overall, and they had metabolic syndrome or a clustering of risk factors that predisposed them to develop it. Muscle symptoms can occur, namely myalgias or statin-associated muscle symptoms, but there is a very strong nocebo effect that exists. Very rarely you may see clinically relevant liver injury. The FDA does not recommend surveillance, monitoring of liver function tests, or a hepatic panel in the absence of symptoms or signs to suggest that absent a baseline ALT prior to initiation of therapy overall. So highly favorable. And I know we're going to be focused on non-statin

therapy here going forward.

And it is important to realize that unfortunately, despite individuals being treated with statin therapy and segmented along the bottom, along the X axis, you can see some trials, some historical trials, that are secondary prevention, some high-risk primary prevention, and some moderately lower-risk primary prevention trials looking at the residual event rates of coronary heart disease events in those in the blue bars who received statin therapy. Calling out simply these trials where the Delta moving from red to blue was associated with a significant reduction in the rate of adverse coronary heart disease events was meaningful. But still, people who are exposed to statin therapy faced increased risk for these coronary heart disease events, and there's an opportunity to bring their risk down further.

So I want to pivot now into moving beyond statin therapy, and we've sort of hopefully laid the base case for the value of statin therapy, and certainly maximally tolerated statin therapy, and again, more often recommending higher intensity statin therapy for those in particular, at highest risk. But I want call out the different therapeutic options that we have available in the non-statin group, and we're going to walk through these systematically, but they largely work within the liver, at various different parts of the liver, and through different mechanisms of action, an exception being ezetimibe that works within the intestines to decrease cholesterol uptake there, which ultimately has a feedback back to the liver.

And I'm going to walk through these systematically, first, starting with ezetimibe. It's a daily oral agent. It was approved for LDL cholesterol lowering as monotherapy. It achieves about an 18% reduction in LDL cholesterol, but when added to statin therapy, most of us see somewhere in the range of a 20 to 25% reduction in LDL cholesterol. And it's not to be used in those with moderate or greater degrees of hepatic impairment. As I had mentioned, it works to decrease intestinal cholesterol uptake. And most of the data stems from an acute coronary syndrome trial called the IMPROVE-IT trial, published now a decade ago, looking at over 18,000 individuals hospitalized within acute coronary syndrome exposed to simvastatin alone as moderate-intensity statin therapy, or simvastatin plus ezetimibe, and the addition of ezetimibe to moderate-intensity statin therapy was associated with a significant reduction in the 3-point cardiovascular event rates observed in this trial. And while ezetimibe cut its teeth and defined its benefit in an acute coronary syndrome secondary prevention trial, in most of the recommended guidance out there, it has become the first preferred non-statin therapy because of its oral formulation, good tolerability and safety profile, ability to lower LDL cholesterol on top of statin therapy by about 20 to 25%, and its generic formulation, even acknowledging that it hasn't been necessarily studied in primary prevention in these other populations, at least from an event-driven trial standpoint.

I'm going to pivot now over to the PCSK9 inhibitors, and specifically focusing on the monoclonal antibodies, two of which are FDA approved, alirocumab and evolocumab. These are approved to lower LDL cholesterol, but also to reduce the rate of major adverse cardiac events in patients with atherosclerotic cardiovascular disease. These drugs, which are injected subcutaneously either every 2 weeks or every 4 weeks, achieve on average about a 45 to 64% reduction in LDL cholesterol on top of statin therapy. And these are largely well tolerated, although there is a risk potentially of hypersensitivity reactions and a low risk of developing diabetes, as is illustrated in the third bulletpoint on the right lower corner as well. These drugs work to interfere with PCSK9. In short, mechanistically, this leads to an upregulation of the number of LDL receptors on the surface of the liver. I always remember back to my training more LDL receptors means greater clearance of LDL cholesterol from the bloodstream.

Clinical trial data points to two trials. On the left, the ODYSSEY OUTCOMES trial. This was an acute coronary syndrome population, secondary prevention, randomizing on a background of standard of care lipid-lowering, LDL cholesterol-lowering therapy, alirocumab, compared to placebo, as illustrated by red and blue, respectively. The rate of the composite endpoint in this case of coronary heart disease, death, non-fatal heart attack, non-fatal ischemic stroke, and hospitalization for unstable angina, was associated with a 15% relative risk reduction by treatment with alirocumab in this trial, and really established the PCSK9 inhibitors as one of two trials substantiating the clinical benefit, the cardiovascular event reduction associated with additional LDL cholesterol reduction in this population.

This trial, ODYSSEY OUTCOMES, was actually preceded by the FOURIER trial on the right, which was a stable atherosclerotic cardiovascular disease population exposed to evolocumab or placebo, an alternate PCSK9 inhibitor monoclonal antibody, on top of standard of care therapy and secondary prevention, showing a 15% relative risk reduction in the composite that's illustrated on the left along the Y axis, cardiovascular death, non-fatal heart attack, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization.

You can see that in both of these trials, on the left nearly 19,000 patients, on the right over 27,500 patients. These were huge trials that substantiated the benefit of the PCSK9 inhibitor monoclonal antibodies.

What about inclisiran? Inclisiran is a PCSK9 inhibitor, but it works through a small interfering RNA rather than a monoclonal antibody to achieve that effect. The effect ultimately is targeting PCSK9, leading to an upregulation of LDL receptors and greater clearance of LDL

from the bloodstream. Inclisiran is FDA approved today for atherosclerotic cardiovascular disease patients, for those with primary hyperlipidemia, or those with heterozygous familial hypercholesterolemia as an adjunct to diet and maximally tolerated statin therapy in those that require additional LDL cholesterol lowering. It achieves on average of 50% reduction in LDL cholesterol. It is a unique dosing as a small interfering RNA. And for those familiar with this, mechanistically, these often can result in drugs with longer half-lives. So as a result of this, the drug is administered subcutaneously in healthcare settings, clinical settings, as compared to the monoclonal antibodies which are administered at home, inclisiran is administered in a healthcare setting initially at Day 1, then 3 months there afterwards, and then can be dosed every 6 months thereafter. So offers a unique approach, requiring administration in healthcare settings, but a less frequent dosing interval, again, targeting PCSK9.

As of today, we do not have available to us cardiovascular outcomes trial data. There are two key cardiovascular outcomes trials that are underway as we speak, but that data is not available. And so what I'm illustrating here is the magnitude of LDL cholesterol reduction that's achieved that can be sustained despite every-6-month dosing in a fairly flat way over time, with a large differential in the magnitude of LDL cholesterol reduction by inclisiran in blue, compared to placebo in red.

And then listed last year is the ATP citrate lyase inhibitor, bempedoic acid. This is a prodrug that is activated in the liver, not active in muscle. It's an oral agent, and so as a complement to ezetimibe as the only other oral non-statin that we've talked about today, with the PCSK9 inhibitors being administered subcutaneously, it's a daily oral agent. It's approved for atherosclerotic cardiovascular disease patients, those with increased ASCVD risk, primary hyperlipidemia, and those with heterozygous familial hypercholesterolemia. It achieves only about a 17 to 18% reduction in LDL cholesterol, so a lesser amount than the other drugs that we've highlighted. And in particular for those that are able to tolerate higher intensities of statin therapy, you see, on average, lesser magnitudes of LDL cholesterol lowering. For those that cannot tolerate any statins, you'll see modestly higher levels of LDL cholesterol overall. It may increase serum uric acid levels. There's a risk of potential tendon rupture. This is an incomplete list of potential side effects, as it has been for all of the drugs, but just calling out some of the key points for this drug and the other drugs as well.

We have a cardiovascular outcomes trial data for bempedoic acid, namely, the CLEAR Outcomes trial. And this was a unique study in that attempted to enrich the population with those that had statin intolerance. The definition of statin intolerance most often used is the inability to tolerate at least two statins with one at the lowest approved dose by the FDA. And 1/4 of individuals in this trial were on low-intensity statin therapy, but 3/4 were not receiving statin therapy, and they actually attested to, and their clinicians attested to, the fact that they were statin intolerant. And so on a backdrop of not having statin therapy in 3/4 of individuals and low-intensity statin therapy in the remaining 1/4. And this was also a mix of 70% secondary prevention, 30% high-risk primary prevention, those with diabetes mellitus, and an additional cardiovascular risk factor, bempedoic acid was associated with a 13% relative risk reduction in the primary composite, four-component MACE composite in this trial.

On the right-hand side, you can see there was a stratified analysis that was prespecified, looking at the difference between primary and secondary prevention populations, and you see an outsized treatment effect with a 30% relative risk reduction in the primary prevention group. Not surprisingly, this was associated with a lesser magnitude of benefit in the secondary prevention group overall, with a just under 10% relative risk reduction in that group. So overall, a positive trial, with most of the benefit being consolidated in the 30% of individuals that were high-risk primary prevention patients.

So I actually showed you the top portion of this slide at the very beginning. This is actually the full image from the publication. And I think it nicely harmonizes pretty much everything we've talked about. As we move from left to right to primary prevention to higher risk primary prevention to secondary prevention, the base, or bedrock, in green, is a healthy lifestyle through diet and exercise. Statin therapy, moving to higher intensity to match the baseline risk of the individual as we move from left to right. The incorporation of non-statin therapy in a regimen as an addition to maximally tolerated statin therapy where needed to achieve those dual LDL cholesterol goals based upon the underpinning of matching the intensity of LDL cholesterol lowering to the baseline risk of the individual and is illustrated at the bottom, and that's reflected on the slide that had the dual LDL cholesterol goals. You're trying to achieve increasingly greater magnitudes of LDL cholesterol reduction in those at highest risk.

And I didn't highlight this earlier, but in 2022, the American College of Cardiology Expert Consensus Decision Pathway on non-statin therapy moved the LDL cholesterol treatment threshold, we might be able to substitute in the word goal of being less than 70 in secondary prevention down to less than 55 in that very high-risk ASCVD group. So you can see the sort of spectrum of LDL cholesterol targets that one would be shooting for as you move into higher risk populations overall.

Despite everything I shared, and hopefully it's been logical, I might even submit convincing to you, about the sort of evidence base to support everything that we've presented thus far, there's a lot of unmet needs. And this is illustrated by this publication from 2023. This is an observational analysis of north of 300,000 patients with clinical atherosclerotic cardiovascular disease from 92 US health systems. Admittedly, the data was looked at between 2017 to 2018, of which 180,000 plus patients had an LDL cholesterol level at baseline. And

in those 182,000 plus individuals, they looked at, A, how were these individuals being treated relative to statins and statin intensity? And what degree did they achieve their LDL cholesterol goals? Which, at that time previously, for an all-comer ASCVD, was less than 70. I'm acknowledging we've moved the bar, and now for at least half of those patients, it's going to be moving down to less than 55. But the commentary here is, if we move to the far left, you have a sizable percentage of individuals that are illustrated, more than 20% of people with a lipid panel available, who are not being treated with any statin therapy at all. And when you look at people being treated with low- and moderate-intensity statin therapy in the middle, and high intensity, the remaining individuals on statin therapy, roughly speaking, were almost 50/50, a little bit greater for high-intensity statin therapy. But there's an opportunity to do much better in terms of, A, getting people on statin therapy, and B, pushing people to high-intensity statin therapy where tolerated; in short, because it increases the likelihood that you're going to achieve LDL cholesterol levels more in keeping with what we want to achieve, lower is, in fact, better for this population.

Now, this is secondary prevention. What about primary prevention? So I've illustrated here in sort of three tiers of bar graphs, severe hypercholesterolemia to the far left. These are people with LDLs great or equal to 190, of which a subset have familial hypercholesterolemia, diabetes mellitus type 1 or type 2 in the middle, and those with a 10-year ASCVD risk using the American College of Cardiology and the American Heart Association's ASCVD Risk Estimator that relies upon the so-called pooled cohort equation. And if their 10-year risk was greater, equal to 7.5%, warranting statin therapy, at least moderate-intensity statin therapy.

And this was an observational analysis of nearly 450,000 patients who didn't have atherosclerotic cardiovascular disease from 90 US health systems. And what can you see or say about this? Well, A, in green that's no statin therapy. So nearly 60% of people with severe hypercholesterolemia in this cohort weren't receiving any statin therapy. In those with diabetes, nearly 40% weren't receiving statin therapy. And in those with an estimated 10-year risk greater or equal to 7.5%, nearly 60% were not receiving statin therapy. And in red, there is a reflection of those receiving statin therapy, but at an intensity that is lower than otherwise one would recommend for this population.

So despite having lots of tools in the toolbox, we've got our work cut out for us just to do the basic blocking and tackling with statins and statin intensity. I haven't presented, but I can assure you that there are large gaps in care related to underutilization of non-statin therapy as well. If the patient is unable to achieve their LDL cholesterol goals on maximally tolerated statin therapy, which conceptually could be low intensity, or they can't be on any statin therapy, it's important to realize that there are a lot of non-statin therapy options available to you that are importantly associated with improvement in heart outcomes.

So what's the ask? I'm going to end this section by highlighting that, as it relates to LDL cholesterol management, it's about identifying patients at highest risk of ASCVD events and matching the intensity of our treatment to their baseline risk. It's a recognition that lipid-lowering therapies as monotherapy, or in combination, they're underutilized, and, I would argue, significantly underutilized. So we have a lot of opportunity to just use the therapies that we have that are FDA approved today.

It's an acknowledgement that there are barriers or headwinds to utilization. Some of our therapies are generic. Some are not. But working as a team with different clinical stakeholders and leveraging support programs where they exist to overcome some of these barriers that exist. I would argue, though, one of the key barriers is even you can't treat what you don't measure. So if you don't know their LDL cholesterol level, it's hard to act further to intensify their treatment regimen.

In yellow, initiating lipid-lowering therapy at appropriate intensity in high-risk patients. In black, considering combination therapy in those that don't achieve their dual goals. And then, based on their risk assessment, initiating lipid-lowering therapy earlier than we otherwise do.

With that, I'm going to pivot over to a different topic, but clearly a related topic, and that's a focus on lipoprotein(a), that is related to but distinct from items that we've talked about thus far, and its influence on ASCVD risk.

So what is lipoprotein(a)? Lipoprotein(a), or LP(a), is distinct from LDL cholesterol, and comprises a relatively small amount of total cholesterol in the LDL cholesterol pool. In those individuals who have elevated levels of lipoprotein(a), it may contribute upwards of 30% of the LDL cholesterol measured in a standard lipid profile. Obviously depends upon the relative contribution and levels of lipoprotein(a). It consists of a single apolipoprotein B particle covalently bound to apolipoprotein A, and the levels are largely genetically determined. So this is a condition where, when you measure it, what's defined or what's measured is often what occurs early in life since birth, overall. The data or the measurement or the value can be presented either in mass units, mg/dL, or molar units, nmol/L, the ladder is generally preferred. And you can convert between them by multiplying by about 2.4. So if you get a mg/dL, you can multiply by 2.4 to get nmol/L. Or if you get nmol/L, you can divide by 2.4 to get mg/dL.

In general, levels greater than or equal to 50 mg/dL, or 125 nmol/L, are associated with increased risk for adverse cardiovascular events, namely atherosclerotic cardiovascular disease events, as well as calcific aortic stenosis. And it's estimated that roughly 1/4 to

1/5 of individuals have elevated level of LP(a). Now, the magnitude of that elevation can vary significantly, and we'll show some data about that in one second.

This is an observational analysis of over 460,000 individuals from the UK Biobank study who had their LP(a) level measured and were followed for a meeting of 11.2 years. You can see that there is heterogeneity that may relate to genetic heterogeneity amongst the populations distributed by race, on the left-hand side, with black individuals having, on average, higher levels of lipoprotein(a) compared to other races presented there. Women, on average, will have a modestly higher LP(a) level compared to male counterparts. And this is illustrated here with data representing nmol/L of LP(a). And then this is of no surprise in an observational analysis, those that have clinical atherosclerotic cardiovascular disease, because of the bias of looking at that population, not surprisingly, include a population that's more likely to have higher levels than those that don't have atherosclerotic cardiovascular disease.

In this analysis, when these individuals were looked at over time, you asked the question, what's the distribution of LP(a) levels in the populations? On the left-hand side, it's representative of individuals with clinical ASCVD when they were enrolled in the UK Biobank study, and in this cohort. On the right-hand side, these are people without clinical atherosclerotic cardiovascular disease. And it's really important to highlight they use a cut-point here of 150 nmol/L. As I had mentioned beforehand, many of us use the 125 nmol/L as sort of the lower end of hitting that threshold of increased cardiovascular risk. But the red group illustrated, in both figures, represent individuals with levels at or above 150 nmol/L in these populations. The vast majority of the population is to the left of that. These are people who have much lower levels of LP(a), and these individuals very leftward shaped bell distribution, skewed all the way to the left. But there are, as is illustrated here, 20% of individuals in this cohort with clinical ASCVD who had levels at or above 150 nmol/L, and on the right-hand side without ASCVD, about 12% of individuals fit that mold.

What was the risk faced by these individuals? And again, this is an observational a non-interventional trial, you can just see those with higher levels of LP(a) greater or equal to 150 nmol/L, as illustrated in pink and red, had a higher rate of adverse cardiovascular events, atherosclerotic cardiovascular disease events, compared to those with lower levels of LP(a). And that's true on the left in those with ASCVD and on the right in those without ASCVD. Not surprisingly, the event rate is that much higher in those with ASCVD on the left, by the very nature of the fact they've already had an event or being declared as having ASCVD, it's already a higher risk population out of the gate.

This is a very busy slide. I actually like it a lot because it's busy and it's not meant to confuse you. It's only to say that we've had varying recommendations in the US, as illustrated by the US flag, in Canada as illustrated by the Canadian flag, and in the Europe by the European Union, that there is not concordance across, even in the United States, professional societies about who should be tested for LP(a), or lipoprotein(a). Some organizations recommend uniform testing for everybody once in their lifetime. Others recommend consolidation of it to people, for example, in orange, who have a family or personal history of premature atherosclerotic cardiovascular disease, those at particularly higher risk overall. And again, this heterogeneity hasn't helped in reinforcing the importance of understanding someone's LP(a).

The other big headwind that I'm going to get into in a moment is we have never had therapies that have been approved by the FDA specifically to lower LP(a), and therefore some clinicians may say, how important is it to measure it if, in fact, I don't have treatment to target it specifically? I will say two quick things related to that. In general, an elevated LP(a) is a risk enhancer, so if you have a patient who you're treating with moderate-intensity statin therapy, their LP(a) level is elevated, they have a family history of premature family events or family members have had premature events, that may be a motivation to switch to high-intensity statin therapy or add additional non-statin therapy, because that person is probably at higher risk than a counterpart who doesn't have that family history, doesn't have an elevated LP(a) level overall.

This is illustrating, in practical terms, how often or infrequently LP(a) testing is done. This is but one of many analyses. This was done at the University of California Health Systems, multiple hospitals in multiple parts of California, looking at 5.5 plus million individuals from six academic medical centers, just looking at how often LP(a) testing was performed over roughly a decade. It was performed in 0.3% of all adults, only 3% of those with a family history of cardiovascular disease, and in less than 4% of those with a personal history of cardiovascular disease.

And so again, I'm going to acknowledge we don't, as of today, have FDA approved therapies that are approved principally to lower LP(a). We do have both statins that we can use at higher intensities if they're not otherwise warranted, and we have non-statins, particularly PCSK9 inhibitors, that also can lower LP(a). Although they're not FDA approved for that purpose by intent, these are drugs and other non-statins that can be added to people's treatment regimen to get back to the concept of matching the intensity of LDL cholesterol lowering to the baseline risk of the individual, particularly if they have higher, and in particular, high levels of lipoprotein(a).

This is a survey from the University of Pennsylvania trying to get better at understanding attitudes and barriers to lipoprotein(a) testing.

This was a small analysis looking at clinicians in internal medicine and cardiology. Some of the biggest drivers of not testing were, 'I'm not familiar with lipoprotein(a),' 'I'm concerned that insurance may not pay for it or there's some billing concerns,' 'I'm concerned that we don't have clinical trial outcomes data to support it,' 'I'm concerned that we don't have available pharmaceutical or pharmacologic therapies to address this overall.' And so you can see here that these are reasonable explanations in some respect, but part of this is to help enlighten and become more familiar with lipoprotein(a) and share where the field is going overall. And again, I would say that there is support for testing to stratify cardiovascular risk with a threshold of 50 mg/dL, or 125 nmol/L.

What about the effective available therapies of LP(a)? I talked about this earlier. Now I want to reinforce, other than LDL apheresis, which could be used to remove lipoprotein(a), we largely do not initiate most of the other pharmacotherapies that we've listed here. And we didn't talk about niacin, although, as a B vitamin, it can reduce lipoprotein(a) and is available in a supplement form. To a large degree of the therapies that we've highlighted earlier that target LDL cholesterol, there's varying degrees of LP(a) reduction, with the most notable observed amongst the drug therapies in the PCSK9 inhibitors, namely the monoclonal antibodies and small interfering RNA. This may come as a surprise, but statins actually can increase modestly, lipoprotein(a) despite that fact they reduce cardiovascular risk. But it is important to realize that if you're measuring it for somebody who is on background statin therapy. Let me be clear, that is not a motivation to stop statin therapy. In someone with elevated levels of LP(a), just because they're on a statin, they have an indication for statin, you should not be stopping statin therapy under those circumstances.

And importantly, there are a number of investigational therapies that are being tested that target principally LP(a). These include antisense oligonucleotides, small interfering RNAs, or small molecules. They're at varying degrees of development. Some of these have had presented and published phase 2 trial data showing striking reductions in LP(a) levels. And the sort of proof is in the pudding is, will that reduction in LP(a) levels translate into reduction in hard cardiovascular events in phase 3 trials. The furthest along of that is the HORIZON trial on the first line, evaluating the first of those therapies, pelacarsen, with a projected trial completion in 2025. The next of those large phase 3 outcomes trials with olpasiran in 2026 in the OCEAN-Outcomes trial. And you can see other therapies listed lower down below that, at a point of actually in the phase 2 trial, a point with anticipated data report out either last year or into the coming years for future data, assuming that they move forward with phase 3 trials.

And just sort of to round things out and round things up, this is just a slide put together in the *American Journal of Preventive Cardiology* that highlights that there are greater than 112 million Americans that have been looked at with claims data. This was over about 7 years showing that only 0.3% received LP(a) screening, and most of the LP(a) testing is consolidated within a very small number of healthcare clinicians overall. So small testing rate, but when testing is done, it's done by an even smaller percentage of clinicians.

If you're looking for available ICD-10 codes to link your billing to, I have not had the challenge of getting it reimbursed or authorized by payers. But if you do, these are some of the codes that you could use. The CPT code for the LP(a) test is listed there. And there are some direct to consumer assays, but I would argue almost every commercial lab, university lab, hospital lab, has the availability to do this test routinely.

Finally, when to refer to a lipid specialist. This is sort of a potpourri that, if you said, I need to raise my hand and essentially phone a friend for help, complex dyslipidemias, particularly where you suspect genetic underpinnings, complex therapies moving beyond standard non-statin therapy, managing drug-drug interactions, managing special populations, those with HIV, polycystic ovarian syndrome, end-stage kidney disease, a pediatric population, those that have been resistant or unresponsive to prior therapy. Maybe they sit to the far left on that JUPITER trial waterfall plot, and you can't explain why they're having a paradoxical response to therapy that you're treating them with. Drug therapy resistance, statin intolerance, looking to people where we even have to be that much more aggressive of getting their LDL cholesterol down, and you feel like you may have run out of tools in your toolbox that you feel comfortable prescribing. And then in determination about what compliment of additional therapies or interventions may be required.

With that, that's going to pull us now to the next part of our presentation, and it's an honor to pass things over to my colleague and look forward to hearing more about individualizing care for patients in rural communities. Thank you.

Dr. Wadhera:
Thanks so much to my colleague, Dr. Gluckman, for that terrific talk. We're going to switch gears now and discuss individualizing cardiovascular care for patients in rural communities.

Rural communities in the United States experience significantly higher cardiovascular mortality rates than urban communities, and those gaps are widening. You can see on the figure here that rural communities shown with the dark blue line have experienced a significant rise in cardiovascular death rates since 2010, while urban communities have experienced a significant decline in death rates, and as a result, disparities are widening.

A key question is why we see these gaps in cardiovascular mortality rates between rural communities in urban communities, and why

are these gaps widening? And so what I'm going to do is walk us through the multi-dimensional factors that contribute to rural urban disparities in cardiovascular health. Starting with cardiometabolic risk factors and social risk factors, moving on towards health insurance and access to care, and then ending with some of the challenges that rural communities face from a health system and infrastructure standpoint.

Let's start with cardiometabolic risk factors. Adults living in rural communities experience significantly higher rates of hypertension and diabetes than their counterparts that live in urban communities. On the left here, you can see that the prevalence of hypertension in rural communities, as shown in the yellow, is significantly higher when compared with large metropolitan statistical areas or urban areas, as shown in the red. If you shift gears and look to the right here, you can see that diabetes-related mortality rates after experiencing an initial decline have increased over the past decade. Diabetes-related mortality rates are highest in rural communities, as shown in the yellow, and they are increasing more steeply than in urban communities.

These general patterns in terms of differences in the burden of cardiometabolic risk factors are similar for hyperlipidemia. On the left, you can see that the prevalence of hyperlipidemia is 5 to 8 percentage points higher in rural communities when compared to urban communities. And although we have seen this sort of decline in total cholesterol levels in the US population as a whole, rural communities have lagged behind over time.

Obesity rates have also increased more dramatically in rural areas compared to urban areas, and these patterns are similar across the United States. The blue here shows you obesity rates in rural communities, and the red obesity rates in urban communities. And you can see that whether you live in the Northeast, the Midwest, the South, or the West, obesity rates are significantly higher in rural communities.

Beyond the common cardiometabolic risk factors that we think of that confer a higher risk of cardiovascular disease and adverse cardiovascular health, it's worth thinking about how differences in lifestyle and behavioral risk factors contribute to worse cardiovascular health in rural America. On the left, I show a picture of someone who's exercising. We know that rates of moderate to strenuous physical activity are generally lower in rural areas compared to urban areas. Rates of tobacco use and smoking are almost two times higher in rural areas when compared to urban areas. And then it goes without saying that the opioid epidemic has disproportionately affected rural parts of the United States, and we've seen a dramatic rise in cardiovascular death rates that have been associated with drug overdose.

Beyond cardiometabolic risk factors, lifestyle risk factors, and behavioral risk factors. It's really important to acknowledge that there are major differences in the burden of socioeconomic risk factors in rural parts of the country compared to urban parts of the country. Poverty is a major risk factor for poor cardiovascular health and poor health overall, and we know that poverty rates are significantly higher in rural parts of the country, no matter what age group you fall in. This figure shows poverty rates in rural America compared to urban America from childhood to adulthood. And you can see that high poverty rates disproportionately affect children, working-age adults, and seniors in rural parts of the country. And when poverty and rurality intersect, health outcomes are worse. And I think that's exemplified really well in this figure, which shows that high poverty rural areas have the highest mortality rates in the country, shown in the solid blue line. Those rates are higher than rural areas that have low poverty rates, which are shown in the dashed blue line.

Beyond poverty. It's also worth thinking about the other socioeconomic risk factors that we know are inextricably tied to cardiovascular health, and those are low levels of educational attainment, food insecurity, and housing instability. And food insecurity and housing instability in particular are on the rise in rural America.

So we've talked about cardiometabolic risk factors, social risk factors, lifestyle and behavioral risk factors. Now I want to shift gears and focus a little bit on access to care. We know that insurance coverage is very important to access medical care and healthcare services, but uninsurance rates are significantly higher in rural parts of the country compared to urban parts of the country, and that is true both overall and across different racial and ethnic groups, as you can see in the figure over here.

One of the biggest policy reforms that's happened over the last 15 years has been the expansion of the Medicaid program, which is a federal and state administered program that provides insurance coverage, public health insurance coverage, to low-income Americans. Medicaid was expanded under the Affordable Care Act beginning in 2014. And you can see on the map shown on the left, that many, many states in blue have adopted Medicaid expansion, but several states have still not done so. And I think this is important to point out, because 20 million individuals, and specifically low-income, working-age adults, gained insurance coverage under Medicaid expansion. But uninsured individuals in rural areas are disproportionately likely to live in states that have not expanded Medicaid, so those red states that you see on the left there. And so insurance coverage remains a barrier to accessing care in rural communities.

But even beyond insurance coverage, what happens when you do have insurance coverage, are there other challenges that rural individuals face when trying to access care? And this slide shows one of them. And the simple truth is that primary care provider supply

is lower in rural areas when compared to urban areas. This figure shows the number of PCPs per 100,000 population in urban areas in the red compared to rural areas in the blue. And you can see there's a gap there. Rural adults have less access to primary care providers, and actually that access issue has not improved over time; it's getting worse. The gap between urban and rural areas in terms of access to primary care providers has been widening since 2010.

Rural adults also have less access to specialty care. And that that's again shown in this figure on the left, you can see the number of how many rural adults have at least one PCP visit per year relative to urban adults. But then when you look to the column to the right of that, you can see that the number, the proportion of rural adults who have at least one specialty visit per year in the blue is significantly lower when compared to urban adults shown in the green. So again, we're seeing gaps in insurance coverage, we're seeing gaps in primary care, access to primary care, and we're also seeing gaps in access to specialty care.

And then when you look beyond outpatient care and think about access to acute care services, we're in the midst of a rural hospital closure crisis. The number of rural hospitals that has closed over the last decade, we've seen an acceleration in closures in rural areas, as shown on this map. And there's great evidence that suggests that when rural hospitals close, mortality rates and mortality specifically for acute cardiovascular conditions, goes up.

When we think about quality of care and access to procedural care for patients who do show up to a rural hospital, there are large disparities in access to acute cardiovascular care, whether it be cardiac catheterization or PCI for an acute myocardial infarction, or a thrombolysis and endovascular therapy for ischemic stroke. And those gaps in access to advanced care translate into higher 30-day mortality rates for conditions like MI and stroke, as you can see in the figure on the right.

Now, there's been a lot of discussion, both locally at the state level and nationally, about how telehealth could be a valuable tool when it comes to addressing the rural urban gap in access to care that I've just highlighted in the preceding slides. The pandemic really accelerated use of telehealth services. As you can see in this figure, there was sort of this huge boom in telehealth use in both rural and urban areas, and then sort of a slight decline as the pandemic went on, and now we're sort of in the steady state, where telehealth use is still much higher than it was before the pandemic. But when you look closely at this figure, you can see that there are major gaps between telehealth use in rural and urban areas. Rural areas use telehealth less than urban areas, and that's a little paradoxical. We would expect or hope that the adoption of telehealth use would be greater in areas like rural communities that disproportionately experience barriers in accessing care.

And one of the reasons that gap exists in telehealth use between urban and rural areas is because we live in a digital divide. Rural Americans have lower access to high-speed broadband internet than urban Americans, and you can see that on the map shown on the left. And on the right, I've shown some data about how broadband subscriptions vary by income, age, and race, and ethnicity in urban and rural areas. Across the board, we see that rural adults have less, on average, less access to high-speed internet, which is an important mechanism by which many folks access telehealth services. So you need the access to internet to get telehealth in many parts of the country.

And then there are broader things going on when it comes to reimbursement policy that also impacts telehealth utilization. Over the course of the pandemic, we saw payers approach to a telehealth change, in that they were more likely to reimburse those services. We saw that certainly from Medicare's perspective, but also from private payers' perspective, where there was this philosophy that we should pay or reimburse providers that are providing telehealth services to expand access to care. And so reimbursement policy has a huge impact on whether telehealth is going to be utilized. And right now, we're in this midst of a transition in which reimbursement policy for telehealth is changing, in that some payers are starting to dial back on reimbursement for these services.

I think it's important to point out, beyond the differences in burden of cardiometabolic risk factors, beyond these disparities and access, that there are valuable opportunities for collaboration between rural hospitals and urban academic medical centers. And many of these collaborations already exist in the form of regional systems of care, but these collaborations are really important to streamline the delivery of cardiovascular services, specifically advanced cardiovascular services to patients who are acutely ill with heart attack, with cardiogenic shock, or ischemic stroke. And so these collaborations, whether it be regional systems of care that help expedite the transfer of patients with acute coronary syndromes from rural hospitals to tertiary care centers, or telehealth services like Telestroke that can help streamline and enhance care delivery in rural hospitals, these collaborations are really, really important to get patients the care they need to have the best possible outcomes.

So I'll just end by highlighting that the rural/urban gap in cardiovascular health is driven by multiple factors, and so we need multi-dimensional investment to improve cardiovascular health in rural communities. And those investments will involve expanding insurance coverage, improving economic opportunity and educational attainment in rural communities, investing in training programs that attract healthcare providers, both primary care providers, specialists, and advanced APPs to rural areas. There are also some structural

disadvantages that rural communities face that need to be addressed, like broadband expansion so that these communities can adopt telehealth. Addressing the rural hospital closure crisis, so that people living in rural communities have access to acute care services that they need when they're suffering or experiencing a medical emergency. And then part of that can be addressed through stable and consistent funding for rural hospitals, which on the national policy scale, many policymakers are attempting to solidify.

Thank you for joining us for today's program. We hope this session provided valuable insights that you can apply in your clinical practice. To claim your CME credit, please remember to complete the post test and submit the online evaluation form. Again, thank you for your participation and have a great rest of your day.

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