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Optimizing Outcomes in Familial Hypercholesterolemia: Diagnosis, Treatment, and Management

Announcer Intro:
Welcome to CME on ReachMD. This activity, entitled “Optimizing Outcomes in Familial Hypercholesterolemia: Diagnosis, Treatment, and Management”, was developed through the joint providership of the University of Cincinnati and CORE Medical Education, LLC. and is supported by an educational grant from Esperion Therapeutics, Inc. and Regeneron Pharmaceuticals, Inc.

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Dr. Russel:
Familial hypercholesterolemia is a group of inherited genetic defects that lead to the severe elevation of serum cholesterol concentrations. Clinically, familial hypercholesterolemia is diagnosed by a high serum level of low-density lipoprotein – LDL cholesterol – and genetically is characterized into two subgroups: homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia. This activity reviews the evaluation and management of familial hypercholesterolemia and highlights newly available advances into the treatment of patients with this disease. Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is CME on ReachMD. I’m Dr. John Russel.

Joining me to discuss the latest in the management of familial hypercholesterolemia is Dr. Christie Ballantyne. Dr. Ballantyne is Director of the Center for Cardiovascular Disease Prevention at Methodist DeBakey Heart Center, and Chief of the section of Cardiovascular Research, Director of the Atherosclerosis Laboratory and Professor of Medicine at Baylor College of Medicine. Dr. Ballantyne, welcome to the program.

Dr. Ballantyne:
Pleasure to be here.

Dr. Russel:
So why don’t we start today by looking at the big picture. What is the definition of familial hypercholesterolemia, and how prevalent is this condition?

Dr. Ballantyne:
Well, as you might guess by the name “familial”, this is a genetic disorder. You have extremely high levels of LDL cholesterol, beginning at birth. Usually we’ll see a family history of premature coronary heart disease. There’s also accelerated atherosclerosis, men in their 40’s, women in their 50’s. It’s around one in 250 in the population for heterozygous, and one in 250,000 for homozygous in the United States. And one of the keys we’ll get into is really early detection and early treatment.

Dr. Russel:
So as a family physician, how would this manifest itself in my practice? How would I recognize it? How would I diagnose it?

Dr. Ballantyne:
That’s a really important question because everybody who’s in primary care, and if it’s one in 250, you’ve got people in your practice

with this disorder. So, let me give a kind of a case example here. 30-year-old Hispanic man has a history of high cholesterol. Mother has a history of very high cholesterol. His sister also has a cholesterol over 300. And when you see him, he's thin and normal examination. His cholesterol's over 300, his LDLs 218.

So what we see is the typical pattern of each generation – so that's what we call an autosomal dominant pattern. It's something that goes from, your mother or father down, and then you're 50% chance your kids will have it. So the family history is really key in terms of the diagnosis. There is multiple genes that can cause this. It's usually the LDL receptor, but there is four genes that can cause this. I don't think it's that important to know them. There are some physical findings that are important to know. One of them is the corneal arcus, and that's not specific, it's also called arcus senilis. But the other one is tendon xanthomas and a lot of times, unless you actually palpate the Achilles tendon, and you really need to look carefully at the extensor tendons in the hands, you may miss this. And we're seeing less of it now, so really the key thing for diagnosis is measurement of an LDL level, and if you see an LDL over 190, you should be thinking familial hypercholesterolemia. I like to use the diagnostic criteria – it's the American Heart Association Giddings because I think it's most practical. It's if you have a high LDL, and if it's for children over 160 – if, there's a first degree relative, so, you know, parents, siblings, if there's another high LDL in that family, then you've made a diagnosiswith it, If there's premature heart disease. You can also do genetic testing – that makes a diagnosis. But it's a very simple, pragmatic way of making this by clinical criteria, family history, high LDL, family history of high cholesterol or premature heart disease, individuals with a high LDL. That's heterozygous. Now, when it's super high LDL, like you're seeing over 400, you may be thinking they might have two bad copies of the gene. And if you see an LDL that's over 560, something in that range, you really gotta be thinking this is something, looks like it may be extremely severe, probably two bad copies of the gene here, and you should be thinking about homozygous FH, and that's something that very frequently, you see that situation that's a referral, patient. Now there are a couple of older criteria. The WHO Dutch Lipid Clinic,there's a Simon Broome criteria. I personally, even though I'm a lipid specialist, I don't like to use these criteria, 'cause they're specific but not very sensitive, and I think that's one of the absolutely key things, we don't want to miss this, folks. It's very easy to treat if you identify it, so I think that's just one of the most important things, and there is an expanding role for genetic testing now. It's a lot more available if you wanna do this. It's less expensive. There are resources – there's a great organization called the FH - familial hypercholesterolemia – Foundation. They've got a wonderful website that'll give information to your patients about genetic testing with it. The main thing to keep in mind is unfortunately, we are part of a big registry, and what we saw in the registry is the age of diagnosis was in the 40's for this. That is very, very late in life to be picking this up. I mean this has been going on lifelong, and it's one of the key things for people in family practice, internal medicine, primary care, GYN – is that in prevention, you know, what we often do in cardiology – I'm a chief of cardiology, and we have all kinds of dramatic things, with, you know, acute MI and stents, heart transplants, , left ventricular assist devices. We have dramatic things, but it's like a fireman who's trying to put out a fire. That's dramatic, and he's rescuing a child, but what really works is, you know, if you have smoke alarms, if you build your house well, if you have safety features. It may be boring, but it's incredibly important prevention. So our biggest problem is too little, too late, and that's why it's so important that everybody who's in primary care, just know this is a common disorder, it's not super rare, it's easy to diagnose, and it's critical to diagnose it early and start treatment early.

Dr. Russel:
So, Dr. Ballantyne, you mentioned that this might be about one in 250 people I see in my office who have the heterozygous familial hypercholesterolemia. How does this go about being treated?

Dr. Ballantyne:
Now we start off with statins, and I think our audience is familiar with statins. We'd like to use high-intensity statins, and our goal would be to get a – a 50% reduction, and so those tend to be rosuvastatin and atorvastatin. And then we have to move to other therapies, 'cause their startup was such high levels of LDL cholesterol. An older one would be bile acid binding resins. That gives about an 18% LDL further reduction then we have ezetimibe, and that, on top of a statin, may give you 20-25%. We do know that from the IMPROVE-IT study, it did give some event reductions. It was rather modest. This study started off with a low LDL, so it wasn't a very big LDL reduction – 70 to 54, and it reduced events by 9%. Now, we have the PCSK9 inhibitors. We've got two of them. We've got alirocumab and evolocumab. They're much more potent. They have the efficacy of reducing LDL on top of a statin by 50-60%. And we know that they do reduce events. This was shown in the FOURIER study and in the ODYSSEY outcome study, where they both reduced events by, an additional 15% in people with coronary heart disease. Now these have also been further studied in the pediatric population with heterozygous FH. They've been previously studied in adults. We now have the data in children, and we see also that there is very good efficacy in children. There was an ODYSSEY KIDS study, where they lowered LDL around a 45%, and there was a study with evolocumab. It was the HAUSER study lowered LDL once again, about 45%. So these are good reductions. In the adults, we saw just a little bit more than that. But they're approved in, indicated for heterozygous FH, for both adults and in the pediatric population. We have a new player that came out just last year. So we're familiar with statins. This is a drug that also blocks cholesterol synthesis, but it's a different step of the process. Instead of inhibiting HMG-CoA reductase, it inhibits ATP citrate lyase and it has another pharmacological

feature where it's a prodrug, gets activated in the liver to the active compound, and so therefore, may give fewer muscle side effects. And as we know, some of our patients on high-intensity statins do complain of muscle side effects. It can raise uric acid, something to be watching out for, if a patient has a history of gout or high uric acid. So, on top of a high efficacy statin, bempedoic acid gives a rather modest reduction of 18%. If someone is not on a statin or on a, very low dose – basically not tolerating even a full starting dose, you get more efficacy. You're getting around 23-24%, LDL reduction, and it works best in combination with ezetimibe. That's available now as a single tablet. The two of them together, ezetimibe and bempedoic acid, and this was giving about a 38% reduction. So that approach is giving almost a 40% reduction, similar to a moderate intensity statin, not high intensity statins. As I said, we're trying to get over 50% reduction. It's approved for heterozygous FH, or established ASCVD who require additional LDL cholesterol-lowering therapy. Do not have outcomes yet with this agent. As I mentioned, we do have outcomes with the PCSK9 inhibitors and with ezetimibe. We do not this agent yet, but there is a large outcomes trial that is being done for individuals with statin intolerance.

Dr. Russel:
So you mentioned some therapies, some that are very familiar to us, some that are newer to us. Are there any new drugs in the development pipeline?

Dr. Ballantyne:
Yes, there is, an entirely new approach, and it's, one that I think, you know, this is the world of biotechnology we live in. I was, surprised when we first came up with the monoclonals, 'cause that was a very different approach in taking a tablet, but what had happened was they – by genetics, found out that people who lacked PCSK9 had low LDLs and were protected from heart disease. So biotech comes in, well we can block the protein with a monoclonal. Now, I think we live in the world of, uh, messenger RNA therapeutics that we're all familiar with the vaccines, where you give the vaccine and you overproduce, something. This approach that's been developed is basically you never make the protein because you interfere with the messenger RNA, and so we have molecules that are called small interfering RNAs, and there has been one that specifically blocks the production of the PCSK9 protein. That is called inclisiran. It's also an injection, but one of the unique things here is because of the way this works, it's as something we have in our body called the risk it ends up having a long activity. You give it a first dose, then one at three months, then one every six months. And it's a unique, newer formulation they have, GalNAc formulation that targets the liver or there's a receptor, and I see a little galactosamine in the liver. So you can give a relatively small dose, and what's very unique here is that once you get baseline, three months, six months and every six months. And in one of the trials, they did with heterozygous FH is that, they got an LDL reduction of about 50%, and that's what we're seeing, and there's been several large, phase 3 studies. This drug was approved in Europe. It's not approved yet in the United States. It's undergoing, review by the Food and Drug Administration, so it has good efficacy, It has this unique aspect of only giving it every six months. And in a safety profile, through the phase 3 program, it looks to be quite good. You do get some occasional injection site reactions. We see that with the monoclonals and with these therapies, but we didn't see any problems in regards to either liver or muscle.

Dr. Russel:
So doctor, now that we've discussed the patients who have heterozygous familial hypercholesterolemia, can you tell us about the treatment of the patients who have the much rarer homozygous familial hypercholesterolemia?

Dr. Ballantyne:
So, these are really tough to treat patients, with it, so we start off with the same things, but remember, they're gonna have, extremely high levels of LDL cholesterol, because they have two bad copies of the gene, and so we start off with statins and ezetimibe, but they may not work very well, because, both of them are kind of increasing LDL receptors. We have the option of PCSK9 inhibitors. There's also apheresis, lomitapide, and there's a new one called evinacumab. So let me just talk a little bit more. Now the PCSK9 inhibitors, basically you can use those in the same dosing. There's also a new indication where you could give the evolocumaba larger amount every two weeks – 420 milligrams, so that's normally the monthly dose, for it. They're both approved to be used in homozygous FH, you may be able to give a higher dose in these patients to try to get more efficacywith it. Now, LDL apheresis some of the patients don't respond well to these other agents, and so this is the way that basically, you can run the blood over a column and remove the LDL particles. Its indications would be if someone has an LDL over 300and you've been treating them in – this is the case where we don't always have the genetic diagnoses, so you may think, well maybe they're heterozygous or homozygous, but if they're behaving like a homozygous individual, they don't respond to the treatments, then the apheresis is also indicated for heterozygous patients too. And then particularly, if someone is heterozygous and they've got heart disease, they've had a heart attack, their LDL is remaining over 160, then also apheresis is indicated for those individuals. We do know that apheresis works. It lowers your LDL by, you know, 55 to 70 percent. It lowers LPA, but it's transient, so you have to do this. Sometimes people do it once a week, mostly it's every two weeks, it's fairly time-consumingin that people have to go, they sit down, you gotta have good venous access, so usually you'd have to put in something for, for access. It does improve – stabilizes, atherosclerosis. We know that there's benefits for it. It is something that is done

in specialized centers, with it. We have a drug called lomitapide. This blocksspecific thing, its MTP inhibitor. It is something that you take orally. It lowers LDL 45-50%. It blocks the production oftheLDL, so it's not removal. It does have some GI side effects, particularly if someone's eating, fat, it'll give you, diarrhea. You have to watch the liver function test, 'cause it may increase fat in the liver by the way it works. Takes some careful monitoring, with it. So those are therapies. We have a new one. and once again a new concept. Came out of genetics. They found out that there were people who lacked ANGPTL3, and most of you probably never heard of this. I've always been taught everything's about the LDL receptor, and then if you didn't have any LDL receptors, pretty much, you know, out of luck unless you were doing apheresis or other things. And here we have a therapy that even if people don't have any LDL receptors, it reduced LDL by 47%. It's an infusion – a monoclonal, fully human versus 2% with the placebo, so that's about a 50% net difference. So it got LDL to less than 100 in 47% of the patients, so that's really remarkable, with this. So it's a new therapy. It's an infusion. It just got approved this February. You have to go once a month, and it takes an hour, and it blocks, this ANGPTL3, that's angiopoietin-like 3, that's an inhibitor of lipoprotein lipase so it's really a different mechanism of action. And what we think is that normally, you get homozygous FH because you don't have LDL receptors, so everything gets blocked up and piles up. Basically you get LDL and these remnants, that when you give this ANGPTL3, that what it ends up doing, it basically causes the VLDL to be removed by the liver, so you never make LDL. Very different mechanism of action. Highly effective, so it's an exciting new opportunity for these individuals who have a really tough-to-treat disorder. And in general, I would recommend that when you have a patient who's not responsive. If you're primary care and you think it's homozygous FH, usually that's a good patient to refer to a lipid specialist.

Dr. Russel:
So doctor, if I have a patient who I think has a familial hypercholesterolemia, are there some guidelines that help me to kind of work through how I should be managing this patient?

Dr. Ballantyne:
Well, yes, there are, and that's one nice thing, we have the, ACC/AHA multi-society guidelines that came out recently, so let's kind of go back to that case that we talked about. So remember he was a 30-year-old Hispanic man. He has a cholesterol over 300, his sister also has a cholesterol over 300, his LDL's 218. So by the family history and his lipid measurements, we've made a clinical diagnosis of familial hypercholesterolemia. Now one of the things that's in the guidelines that make it very straightforward, anyone who's got an LDL over 190, you should be using a statin in those patients. So, whether you know for sure it's FH, or not FH, you oughta be treating LDLs over 190. Alright? So, if you think they have heterozygous FH, you need to be looking at, okay, I started with a statin, but now what else do I need to do here?

So this is the case – in our guidelines, it clearly states that – people in these situations, we should be looking at adding ezetimibe, bile acid resin, or PCSK9 inhibitor. So I think our guidelines are pretty clear cut. Now, one of the things that comes up, if somebody is not responsive, then it's why we have specialists, then you can also say, you know what, we've done all the things that are – we start off with, then let's refer you over to a lipid specialist, to see what else might be going on.

Now, that's the case of, pretty straightforward patient. Let me give you another case. So this was a 57-year-old woman, lifelong history with very high cholesterol. It was diagnosed at age two. They said that she had some xanthomas. She had a cholesterol over 1,000. Had bypass at age 24. Aortic valve replacement at age 53. She'd been on statins, LDL apheresis, had myalgias on statins, she got hypotension on apheresis, she's had all kinds of problems, so they stopped the apheresis. not able to take a statin. She's on lomitapide. She's taking warfarin and aspirin. She's got atherosclerosis, and on that regimen right now, she has, an LDL of 400+. Now, genetic testing showed a heterozygous mutations in the LDL receptors gene. But if we look at this case, remember I said if you have an LDL that's over four or five hundred, you should be thinking about homozygous familial hypercholesterolemia. So, anybody who's got an LDL over 1,000 and this kind of history, and not responding, you should be thinking, clinically this is homozygous FH. Now, basically this is an area that – go back to those guidelines here. She's got aortic valve disease, too, so this is clinically homozygous FH. This is my area of specialty, so I got repeat genetic testing, and in fact, she did have two different mutations in the other receptor, so that means she's a compound heterozygous, which is same thing – two bad copies, of the LDL receptor. And this is somebody who now, we've gotta think about doing more, for this kind of a patient. So, what else is indicated? Well, now with homozygous FH, we talked about higher dose PCSK9 inhibitors, and then the other options we have are apheresis and evinacumab, and this is someone, in fact, I saw in by video consult yesterday, and we're gonna try one of these infusions with this. She lives remotely, and that's one of the things that comes up is that we have to arrange for her to get an infusion locally, 'cause she's several hours away, from where I am practicing here. So we have new options. Very frequently, this kind of patient, is someone who's – there's gonna end up being issues with prior authorization for any of these type of things that we're talking about here. And it's good to refer them to a lipid specialist when you have that really super high one tough-to-treat that you think might be homozygous FH.

Dr. Russel:
Dr. Ballantyne, we certainly covered a lot of new information today. Very exciting stuff. What are some of the takeaway points you'd like

our audience to know about this topic of familial hypercholesterolemia?

Dr. Ballantyne:
So let's keep to the simple points, is that when you see a very high LDL, over 190, be thinking, gee, this could be familial hypercholesterolemia. Take the family history. Is it in the brothers or sisters? If someone's adopted, then, you know, this might be it. So the main thing is, what we wanna do is we wanna start early, and we wanna treat effectively. So we do too little, too late – that's our big problem in clinical practice. Recognize the high LDL. You can do genetic testing. We've got lots of agents now, beyond statins – ezetimibe, bempedoic acid, PCSK9 inhibitors – we have a new one for homozygous FH – evinacumab. Lots of options, so get started early. If you can't get there with the ones that you're used to using, then go ahead and refer the patient to a lipidologist. That's perfectly, you know, when I'm a specialist in my area, but I'm a cardiologist, and I refer to my colleagues who do EP and other things, just 'cause I don't – can't know everything, and our – so, it's – it's okay to refer people. When you see this, recognize it, get started, and make sure they're followed up well. And very importantly, particularly for family practice, remember it's familial. Don't just treat the individual. Screen the family. That's really important, 'cause you can make a big impact and find other people, get started earlier, and you can help prevent heart attack, stroke and premature death from heart disease.

Dr. Russel:
Well, those are some great points for us to keep in mind as we come to the end of today's program. I'd like to thank my guest, Dr. Christie Ballantyne, for helping us better understand the latest in the management of homozygous and heterozygous familial hypercholesterolemia. Dr. Ballantyne, it was great speaking with you today.

Dr. Ballantyne:
Thank you very much. Pleasure, to be on with you.

Announcer Close:
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