Lakshmi Mehta: 00:16 Hi, I'm Lakshmi Mehta from the Ohio University. I'm here today with Dr. Carl Orringer, and we're here to talk about the 2018 cholesterol guidelines and how does familial hypercholesterolemia fall into that new guideline. This is an American Heart Association initiative to reach out to the masses about the cholesterol guidelines.

Lakshmi Mehta: 00:35 Dr. Carl Orringer is a associate professor of medicine at the University of Miami Miller School of Medicine. He's director of preventative cardiovascular medicine there as well, and he's had four decades of experience in dyslipidemia as well as he's a former national lipid association president. Welcome.

Dr. Orringer: 00:53 Thank you, Lakshmi.

Lakshmi Mehta: 00:54 Wonderful. So let's get started. What is the prevalence of familial hypercholesterolemia?

Dr. Orringer: 00:59 It used to be taught that the prevalence was about 1 in 500, but more recent data have suggested that the prevalence is 1 in 250 and that is pretty well accepted world-wide. There are certain pockets where it's even less than that, but in general the overall prevalence is about 1 in 250.

Lakshmi Mehta: 01:14 That's quite high. There are lots of people that are out there that are undiagnosed, it sounds like as well.

Dr. Orringer: 01:20 That's true and so that gives us a lot more opportunity to intervene and to make a difference in people's mortality and morbidity.

Lakshmi Mehta: 01:26 Terrific. The physical exam findings can be interesting in FH. Can you describe some of them?

Dr. Orringer: 01:34 The classic findings that we see are premature corneal arcus and tendon xanthomas. The truth today, however, is that most patients who have severe hypercholesterolemia do not have those findings. As a general rule, those with severe hypercholesterolemia have no findings but if you
look for the corneal arcus and if you look for tendon xanthomas, you will find them on occasion. Especially in patients with LDL cholesterols of 190 or greater.

Lakshmi Mehta: 02:00 Not all fall into that text book classification on physical exams, so how should we diagnose FH?

Dr. Orringer: 02:06 It most often comes up either on a routine blood test, it shows an LDL cholesterol greater than or equal to 190 milligrams per deciliter, or it shows up by a family member or the patient having had an early cardiovascular vent. We’re talking about men under the age of 55 or women under the age of 65, or having family members who had that same disorder, or having family members who have had sever hypercholesterolemia.

Lakshmi Mehta: 02:30 Do you recommend a certain screening tool for these patients?

Dr. Orringer: 02:34 In general, it is important to recognize, first of all, that most patients who have LDL cholesterols of 190 or greater actually do not have familial hypercholesterolemia. In fact, a study that recently was published showed that only about two percent of patients with LDL cholesterols of 190mg/dl or greater have a well defined monogenic cause for the hypercholesterolemia. In fact, there are probably polygenic causes or polygenic and environmental causes that caused the severe cholesterol elevations.

Dr. Orringer: 03:06 When you find a patient with LDL cholesterol 190mg/dl or greater, the first objective is to repeat it to make sure that the value is accurate. Then, you would like to rule out secondary causes. If the LDL cholesterol greater or equal to 190 is still present, you would like to rule out secondary causes, and a simple way to do that is to check a TSH to rule out hyperthyroidism. You'd like to get a BUN in creatinine to rule out chronic kidney disease. You'd like to also get liver testing to rule out those rare cases of obstructive liver disease that are associated with severe hypercholesterolemia, and then you would also need to consider whether various drugs that raise cholesterol levels may be a factor.
Dr. Orringer: 03:44 In most patients, however, these are not factors and therefore we are dealing with a patient who is at increased cardiovascular risk, and we have to figure out the best ways to deal with that risk.

Lakshmi Mehta: 03:54 Sometimes it's helpful if you know that their family has this high LDL of 190 or greater, then that might assist you in to being a little bit more focused, but certainly screening for secondaries is mandatory for most people.

Lakshmi Mehta: 04:05 The new cholesterol guidelines looks at LDL greater than 190 and, from what you're saying, most of those patients don't have FH but still were treating the same. How do you go about that approach.

Dr. Orringer: 04:17 There have been studies to show that regardless of whether patients have monogenic disorders causing their LDL cholesterol greater than 190 they are at increased cardiovascular risk. When they are found to have well established monogenic genetic disorders, the risk is particularly high because they have been exposed to very very high levels of LDL cholesterol beginning in utero. Nevertheless, most patients who we see do not have primary genetic disorders, but they have a risk that is about five fold higher than those of LDL cholesterols of less than 130 of having future atherosclerotic cardiovascular disease event. Therefore, we must talk to these patients about appropriate ways to prevent them from developing these events.

Dr. Orringer: 05:01 We carefully look at not only their cholesterol, but their other risk factors because those who have more risk factors are more prone to the development of ASCVD events. But once we address those, we really focus with great intensity on lowering LDL cholesterol.

Dr. Orringer: 05:16 The first approach in lowering LDL cholesterol is to give them proper dietary counseling because, despite the fact that their LDL cholesterols are very high, some patients will respond surprisingly well to heart healthy dietary patterns. We first like to instruct them on approaches to healthier dietary choices, but in fact, the evidence very clear that statin therapy reduces risk. And the more that LDL cholesterol is lowered, the greater the risk reduction.
Dr. Orringer: 05:44 We don't have perspective controlled randomized trials in these patients, primarily because the patients are at such high risk that we have to use the best information that we have from other studies. But in fact, there are observational studies that indicate that treating these patients with statin therapy makes a big difference and that higher intensity statins are associated with greater risk reduction than are moderate intensity or lower intensity statins.

Lakshmi Mehta: 06:09 Is there a certain LDL range that you would like your patients who either in the new guidelines that they need to reach or just in the particular FH patient that we should reach as clinicians?

Dr. Orringer: 06:22 The safe heart registry, which is a registry of 2,404 genetically determined patients with heterozygous familial hypercholesterolemia followed in Spain, showed that an LDL cholesterol of greater than or equal to 100mg/dl is associated with an increase risk for future atherosclerotic cardiovascular disease event as an independent risk factor. Even in multi-variate analysis, an LDL cholesterol of 100mg/dl or greater was associated with increased risk, thus we definitely like the lower LDL cholesterol to less than 100mg/dl in patients who have not had previous coronary events and have severe LDL cholesterol elevation. Or if they've had previous events, we would like to see their LDL cholesterol less than 70mg/dl if at all possible.

Lakshmi Mehta: 07:06 In the new guidelines, the LDL of greater than 190, when clinicians place a patient on a high intensity statin, if they don't have "FH", but they're placed on that high intensity statin, do they need to check LDLs after that and do they need to target less than 100?

Dr. Orringer: 07:23 The first thing that's important to point out is that anytime a patient is started on a statin, it's very important to monitor their LDL cholesterol response to that statin. The percentage reduction in LDL cholesterol. We're looking for at least a 50% reduction in LDL cholesterol with the use of a high intensity statin, or if for some reason they cannot tolerate a high intensity statin, a 39-40% reduction in LDL cholesterol with a moderate intensity statin. It is
important, of course, to monitor these patients because if their LDL cholesterol remains above 100, and we've done the best that we can with dietary therapy and with statins, we then have to consider the use of non-statins.

Lakshmi Mehta: 07:58 What are the choices in non-statins for these FH patients?

Dr. Orringer: 08:02 The guideline first recommends the use of ezetimibe as the initial go to drug if statins are unable to lower LDL cholesterol to its efficient extent. That is less than 100mg/dl. Ezetimibe makes a good added therapy choice because it is generic, therefore inexpensive. It's well tolerated. It's one pill a day, and it has been shown in trials of patients who have heterozygous familial hypercholesterolemia to lower their LDL cholesterol levels more than statins monotherapy. We do have good data to show that the addition of ezetimibe makes sense in these patients and is well tolerated. And it does lower LDL cholesterol more.

Lakshmi Mehta: 08:42 After ezetimibe, what do you do?

Dr. Orringer: 08:44 Those who have persistent elevations in LDL cholesterol level, we have two choices in terms of drug therapy. One is the use of bile acid sequestrants. Now bile acid sequestrants are available either in a generic for or in brand name form. The generic bile acid sequestrants have inconvenient dosing forms, are difficult to tolerate with regard to gastrointestinal side effects, and generally are pretty poor in terms of adherence long term.

Dr. Orringer: 09:10 There's a brand name bile acid sequestrant, colesevelam, which was shown in a study of heterozygous familial hypercholesterolemia patients to lower LDL cholesterol by an additional 18% and was well tolerated, but it is not generically available and also has inconvenient dosing forms, having to be used either in a powder form or in six pills per day. It's difficult in terms of pill burden.

Lakshmi Mehta: 09:34 What's the role of PCSK9 inhibitors in LDL apherisis in FH patients?

Dr. Orringer: 09:40 PCSK9 inhibitors have been shown in two studies of patients with heterozygous familial hypercholesterolemia
to safely lower LDL cholesterol to an extent of at least greater than 50% additional LDL lowering on top of that which is obtained from statins or statins plus ezetimibe. There are no ASCVD outcome studies, using PCSK9 inhibitors in patients with familial hypercholesterolemia, but it is reasonable to assume that these drugs helpful in these patients, especially in those with persistently elevated LDL cholesterol levels.

Dr. Orringer: 10:13 In the guideline, we use this as a level 2b recommendation because we don't have higher level evidence for the use of these agents in these patients, and there are no ASCVD outcome studies to support our stronger recommendation for these agents. In addition, we don't know how cost effective these agents are in patients with familial hypercholesterolemia. It is likely that those patients who have familial hypercholesterolemia and ASCVD who represent some of the highest risk patients would likely be at a cost effective level, but we really don't have the information right now to support a higher level of recommendation.

Lakshmi Mehta: 10:50 Sounds like you just gave us some thoughts for future research. What about LP little A in an FH patient? Does it matter that they're LP little A is elevated? They're already at high risk. Does it affect how you're going to treat them?

Dr. Orringer: 11:03 Lipoprotein A is a particular type of LDL particle that is associated with increased risk of thrombosis and increased risk of progressive atherosclerosis in addition to increased risk for valvular aortic stenosis. Patients with familial hypercholesterolemia have a greater prevalence of high lipoprotein A levels and when LP little A is significantly elevated in those patients, they are particularly high risk for progressive ASCVD.

Dr. Orringer: 11:30 It is a good idea in patients who have heterozygous familial hypercholesterolemia to obtain a lipoprotein A level to determine if they happen to be in a group in which aggressive and severe early age progressive atherosclerosis is to be expected.

Lakshmi Mehta: 11:46 What about LDL apherisis?
There are some patients with familial hypercholesterolemia who cannot lower LDL cholesterol enough with diet plus maximally tolerated statins plus ezetimibe, possibly with a bile acid sequestrant and PCSK9 inhibitors. Those patients then might be candidates for LDL apheresis. That's a technology that has been used in the United States, Europe, Japan and other countries in patients with severe hypercholesterolemia who are drug resistant. This requires the use of various different types of systems that basically filter the blood of these patients with severe hypercholesterolemia and basically eliminate very very high levels of APO B containing particles.

LDL apheresis treatments may lower LDL cholesterol as much as 70-80% per treatment. The treatments are generally given every two weeks. In rare cases, it has to be given more often, and on occasion, it can be given less often. But the advent of PCSK9 inhibitors has reduced the need for LDL apheresis by probably 75% so fewer and fewer patients are requiring LDL apheresis because we have these effective new treatments that can help most of these patients.

It's a great treatment option that's a nuisance to go for every two weeks, but we've seen great results at our institute with LDL apheresis.

Let's switch gears to special populations. How should we manage FH in children?

One of the key things in the treatment of patients with familial hypercholesterolemia is to identify those who are at risk for the disease so that we can intervene earlier because, in fact, the likelihood of complications related to familial hypercholesterolemia remains clearly related to the level of LDL cholesterol and the duration of exposure. The sooner that we can intervene to help ameliorate that process, the better of we're going to be in terms of prevention. It is important to recognize that familial hypercholesterolemia may be diagnosed in children. It's usually diagnosed in those children with LDL cholesterol of 160mg/dl or greater on two or more occasions, especially in the setting of other family members with very
high cholesterol levels or family members with very high cholesterol levels and premature ASCVD.

Dr. Orringer: 14:01 When we detect children who have these disorders, our first approach is dietary intervention. We always try to give them a dietary trial to see whether dietary therapy will make a difference in terms of lowering their LDL cholesterol to less than 160mg/dl. In which case, we could continue them on diet at least in terms of watching them over time to see if their numbers go up.

Dr. Orringer: 14:22 However, there are some children who have LDL cholesterol levels that are persistently greater than 160mg/dl despite a good dietary trial and in those cases, especially when there's a family history of severe hypercholesterolemia or there's a family history of early ASCVD, those patients can be started on statins between the ages of 8 and 10. There are multiple statins that have been used in children. They are safe, they are effective, they do not alter growth or hormonal factors and they are generally well tolerated. One pill a day in generic. It is an option that we can use for selected children.

Lakshmi Mehta: 14:55 Before we get to the pregnant population, you had mentioned screening. Could you briefly talk about cascade screening or genetic screening in these patients?

Dr. Orringer: 15:04 Cascade screening refers to looking at first, second, or third degree relatives of those who have been diagnosed with familial hypercholesterolemia. That is what is generally recommended when a patient is found with a diagnosis. Another type of cascade screening is reverse cascade screening. That is if you happen to come across a child with sever hypercholesterolemia and LDL cholesterol of 160 or greater, it's important to screen their parents, because now you're going to have a much greater likelihood of finding someone who has the disorder rather than when you're trying to screen the general population.

Dr. Orringer: 15:34 Screening should be done primarily using the patient with diagnosed familial hypercholesterolemia and then using that patient as the branch point for all the others who you are going to be screening.
One of the key things in this whole discussion of screening is making sure that you would use pretty established criteria to diagnose the disorder. Diagnosis of familial hypercholesterolemia is important because there are multiple different systems to do it. There have been systems that have been developed by the Dutch. There have been systems that have been developed in England. There were earlier systems that were developed in the United States. In fact, all of them have strengths and all of them have weaknesses.

The system that I like the best that I find is easiest to apply clinically is what was recommended or suggested in the 2015 American Heart Association scientific statement on familial hypercholesterolemia in which they simply suggested that an individual who has an LDL cholesterol of 190mg/dl or greater where secondary causes have been ruled out, combined with a first degree relative with premature ASCVD or a first degree relative with severe hypercholesterolemia, that is generally sufficient to make the diagnosis.

If you were to do genetic screening, there would be some of those patients or many of those patients who might not have monogenic familial hypercholesterolemia. On the other hand, the risk is so high that it makes sense for such patients to be considered to be at very high risk and therefore proceeding ahead with good dietary therapy and maximally tolerated statins and then when necessary the use additive non-statins.

The simple AHA criteria may expand the net a little bit too much, but in fact, it's a great way for clinicians to be able to identify patients at risk and get them started on proper treatment.

One of the challenges we see in, fine, you've diagnosed someone with FH, you've got them on a treatment, but it's a young female of child bearing age. How do you handle when they're not yet trying to get pregnant? And then when you're trying to do pregnancy counseling? And what do you do during pregnancy?
Dr. Orringer: 17:35 What we generally do is, when we identify a young woman who's in the child bearing years who has severe hypercholesterolemia, the first discussion is that we have an effective treatment that could help to reduce your risk over time. It is going to be long term risk reduction.

Dr. Orringer: 17:50 Different things are going to happen in the interim and one of them is that you may want to become pregnant. I always tell patients who are considering conceiving, is that they should take their statins right to the time that they inform me of their decision. Then I tell them they shouldn't be off their statins for at least two months prior their attempted conception. They remain off their statins during pregnancy and during breastfeeding and then they can restart their statins after that. The use of statin therapy is always associated with effective birth control.

Dr. Orringer: 18:21 If a woman who is taking a statin becomes pregnant, we ask her to immediately stop the statin, and we like to inform her OBGYN physician that they need to check specifically for any abnormalities of the fetus. There have been many women who have become pregnant while taking a statin who delivered completely healthy children, but there may be an increased risk for fetal abnormalities in those taking statins. For that reason we like to have women off statins for at least two months when they are planning to conceive.

Lakshmi Mehta: 18:52 Taking homozygate FH female off of a statin can be problematic. How do you treat their lipids during that time?

Dr. Orringer: 19:00 If you have a homozygous FH patient who becomes pregnant or wants to become pregnant, we continue their apheresis treatments right through pregnancy. That's an approach which has been well tolerated in selected patients. Of course you don't have large numbers here, but homozygous FH patients can go through apheresis very safely and there's no adverse effects on the fetus.

Lakshmi Mehta: 19:20 Thank you. Looking at the 2018 cholesterol guidelines, do you see gaps in knowledge there or treatment of FH patients?
Dr. Orringer: 19:31 Sometimes you have to use the best available data that you have. We do not have ASCVD outcomes data on patients with familial hypercholesterolemia so we have to use the best available data. We know that statins reduce risk, and we know that higher intensity statins reduce risk more than moderate intensity statins or lower intensity statins. We know that statins are generally well tolerated, and we know ezetimibe reduces LDL cholesterol on top of statins more effectively than statin monotherapy, and we know that PCSK9 inhibitors can provide an additional 50% or greater LDL cholesterol lowering effect.

Dr. Orringer: 20:05 We pretty much work empirically in these patients with the concept that lowering LDL cholesterol more is greater. We would love to have outcomes trials on ASCVD, risk in patients with familial hypercholesterolemia, but in the absence of those, we will do what we can to lower LDL cholesterol to the greatest extent possible. Evidence gaps clearly relate to ASCVD outcomes in these patients.

Dr. Orringer: 20:27 An interesting question is: Should all patients with severe hypercholesterolemia who do not achieve a certain level of LDL cholesterol lowering receive PCSK9 inhibitors since they are extremely effective in reducing LDL cholesterol? I think the role of PCSK9 inhibitors in these patients remains to be determined, not only in terms of their effect on outcomes but also their cost effectiveness.

Lakshmi Mehta: 20:52 One final question: Can you give us a few key points or take home messages in treating FH based on the new guidelines?

Dr. Orringer: 20:59 The first and foremost point is, when you encounter a patient who has an unexpectedly high LDL cholesterol level by screening or based upon a family member having an early event, and you get their blood, and it turns out their LDL cholesterol 190mg/dl or greater, these patients need to be jumped on in terms of, first of all getting them onto heart healthy diets and then the maximally tolerated statin. You want at least a 50% reduction LDL cholesterol with the statin, but if you get a 50% LDL cholesterol reduction, or their LDL cholesterol remains at 130, you know you’ve got more work to do. That LDL cholesterol minimally should be less than 100mg/dl, and if they have
ASCVD, it should be considerably lower. Everything you can do to lower LDL cholesterol in these patients makes a lot of sense.

Lakshmi Mehta: 21:44  Well, thank you, Dr. Orringer, for taking the time with us today to talk about FH and the cholesterol guidelines.