[MUSIC PLAYING]

IFTIKHAR KULLO: Hello, my name Iftikhar Kullo. And I'm a professor of medicine in the Department of Cardiovascular Disease, and also a consultant in the department. Today, I'm going to give an update on familial hypercholesterolemia, which is a relatively common Mendelian disorder that is associated with a high risk of adverse cardiovascular events.

This is the outline on my talk. I'll be first starting with the historical perspective and describe the genetic basis of this disease. I'll describe the presentation of clinical criteria and the associated ASCVD risk, the burden of FH in the community, the merit of cascade screening, and then how we can manage these patients with drugs.

Let's start with this case, which illustrates the dramatic and often unexpected presentations that can be manifest with FH. This is a 35-year-old woman, who presents with ST elevation anterior myocardial infarction. And on physical examination, she has the stigmata that are characteristic of familial hypercholesterolemia, including tendons xanthomata, particularly near the Achilles tendon, as well as arcus senilis, as seen here in this picture.

When we take a family history, we note that her mother died at age 50 of coronary heart disease. And her son later turned out to have high LDL cholesterol of 271 milligrams per dL. Her lipid profile is shown here with a total cholesterol of 338 and LDL cholesterol of 285, an HDL of 31, and a triglyceride level of 114 milligrams per dL. Her lipoprotein(a) was significantly elevated at 190 milligrams per dL.

The first reports of FH interestingly came from dermatologists in the early part of 1930s. And they noticed an association of xanthomata, high cholesterol, and myocardial infarction. And the first report was published by Mueller, a Norwegian physician in 1938.

In 1964, Khachadurian performed segregation analyses in a large Lebanese family that suggested that it was a single gene defect responsible for the very high cholesterol levels in this family. In 1967, Frederickson at the NIH further elucidated the role of lipoproteins in atherosclerosis.

And in 1974, Brown and Goldstein presented their important work describing the molecular bases of FH and incriminating defects in the LDL receptor as being the most important cause of FH. And they of course went on to win the Nobel Prize for this work.

As a genetic disorder, FH manifests locus heterogeneity, allelic heterogeneity, as well as varying penetrance. Now what do these terms mean?

Locus heterogeneity simply means that different loci across the genome can cause FH. And we know that several genes rather than a single gene are responsible or can cause FH.

Allelic heterogeneity means that there is not a single mutation in a gene that's responsible, but several mutations in one gene can be responsible. In fact, in the LDL receptor, more than 2,000 mutations have been described, of which about 60% are deemed pathogenic.

There's also varying penetrance. In other words, a person or a patient can have the mutation. But the LDL level may not always be very high due to other factors that I'll describe in a moment. And of course, it's autosomal dominant. And you can see the characteristic pedigree where nearly half of the affected first degree relatives are affected by FH.

Now let's watch this animation, which depicts LDL levels in the circulation, or particles in the circulation, and binding to the LDL receptor on hepatocytes being internalized, and then being targeted for degradation in a clathrin-coated vesicle that ends up in the lysosome.

And here we see that the cholesterol component is degradated, whereas the LDL receptor gets recycled back to the surface where it then can function again and remove LDL particles from the circulation. If there's a sparsity of LDL receptors, then the LDL levels go up. And if there's an excess of LDL receptors, then the LDL cholesterol levels will go down. So it's a very tightly regulated system by the liver.

Now on this cartoon are illustrated the three genes that are incriminated commonly in FH-- the LDL receptor gene, the apolipoprotein B gene, and PCSK9. Now loss of function in the first two genes results in impaired LDL uptake by the liver, and therefore increased LDL cholesterol levels.

Interestingly, in PCSK9 it's actually again a function of mutation that leads to decrease LDL receptors and increased circulating LDL cholesterol levels. And this is because the LDL particle after it binds to the LDL receptor is internalized, as I showed in the previous animation. And then the cholesterol is degraded but the protein receptor itself is recycled back to the hepatic surface.

Now PCSK9, when it's bound to this LDL and receptor complex, targets the LDL receptor for degradation as well, with the result that the density of LDL receptors on the hepatic surface goes down and LDL cholesterol levels go up.

Now what's the typical clinical presentation of a patient that we are suspecting to have FH? Often these individuals will have a strong family history of early onset of adverse cardiovascular events. Or the patient himself or herself may have had premature ASCVD, most commonly myocardial infarction.

On exam, they will have features that are pathognomonic-- xanthomata, arcus senilis. Often patients may have aortic sclerosis or stenosis because of the high LDL levels. And this is particularly prominent in those that also have concomitant increase in the lipoprotein(a) levels.

One should consider additional testing, such as measuring the lipoprotein(a) level, if not already done so, assessing subclinical disease burden, for example, by coronary artery calcium scanning, echocardiography to assess the aortic valve, and then stress testing to assess if the patient has inducible ischemia.

Now the presentation is modified by several factors other than the LDL cholesterol. And those are listed here. And they include metabolic factors, environmental factors, whether drug therapy was instituted and at what time, the characteristic of the particular mutation in LDL receptor, other genetic factors-- that would be called modifying factors-- and whether there's elevated lipoprotein(a) level.

Now the clinical diagnosis is established based on criteria. And the two commonly used criteria for FH-- the first is the Dutch Lipid Clinic Network criteria, which essentially gives a score for several factors that are listed here, including the extent of plasma LDL elevation, whether there's family history of ASCVD or high cholesterol, whether there are signs on physical exam of xanthomata or arcus senilis, whether there's a personal history of ASCVD, or whether a positive genetic test is available.

Another set of criteria are the Simon Broome criteria. Here, the important central criterion is total cholesterol that's elevated to greater than 219 in an adult or greater than 216 in a child, an LDL that's greater than 119 in an adult or greater than 155 in a child.

And then for definite heterozygous FH, tendon xanthomata in patient or patient's first degree relatives, or the availability of a positive molecular genetic test. It's probable heterozygous FH if there's a family history of myocardial infarction at an early age, or there's history of elevated cholesterol levels in the family members.

Now homozygous FH is a severe form where there are two mutations present, either in the same gene or in different genes that I alluded to earlier. Here, the plasma LDL-C levels are often greater than 500 milligrams per dL, although a criterion of greater than 400 milligrams can be used if there's presence of concomitant aortic valve disease or there's onset of tendon or cutaneous xanthomata at an age less than 20 years.

A threshold of 300 milligrams per dL can also be used if these levels are present in the face of lipid lowering treatment, or there's family history of hypercholesterolemia, or presence of tendon or cutaneous xanthomatas at age less than 10 years.

As I mentioned, often these individuals have two mutations in the FH-related genes-- LDLR, APOB, or PCSK9. And this picture shows the dramatic deposits of cholesterol in the skin, manifesting as xanthomata around the tendon areas.

Now the prevalence of FH has varied from 1 in 600 to 1 in 200, depending on how the disease was ascertained. We undertook a study called the Screening Employees and Residents in the Community for Hypercholesterolemia in Olmsted County.

We took our cohort of employee and community health individuals that has about 138,000 adults or individuals in it, and we identified about 6,500 individuals that had an LDL cholesterol greater than 190 with a triglyceride level that was less than 400. We then excluded individuals that had secondary causes of hyperlipidemia. And we ended up with nearly 6,000 individuals, which is a remarkable prevalence of about 4% in this cohort.

We next went on to assess how many of these individuals actually met criteria for FH. And 1 out of 14 individuals with an LDL cholesterol of greater than 190 had met the clinical criteria for FH. However, only half of these had an ICD-9 code that was related to cholesterol.

And an LDL level of greater than 100 milligrams per dL on treatment was achieved only in about half of the individuals. So these did clearly outline the gap in awareness, detection, and control of FH. And thus much more needs to be done in this realm.

One way we can improve in this area is by cascade screening. And this is a typical family with FH, where the proband was tested for cholesterol levels after her father died suddenly at age 65. She indeed had elevated LDL cholesterol and met the criteria for FH. And then other first degree relatives were screened. And one of her two siblings also turned out to have FH, as did one of her children and her brother's children.

So one can see that if we identify the proband and then go on to cascade screen the relatives, we can identify additional relatives that may benefit from early treatment. Now how should we do this cascade screening? Well, one group favors LDL cholesterol measurement. Another group favors doing the actual genotyping.

I would favor the latter because the data that are shown in this slide were mutation-negative relatives of patients with FH were compared to mutation-positive relatives. And you can see there's a substantial overlap in LDL cholesterol levels in these two groups. Of course, they're higher in those that are mutation-positive. But nonetheless, the overlap is significant.

And hence, LDL cholesterol levels by itself may not be able to identify an affected first degree relative. So in the CV genomics clinic, one of our goals is to indeed identify first-degree relatives of the proband that might have FH.

So once we have the patients seen in the CV genomic clinic, we will have a genetic counselor draw the family pedigree and counsel individuals regarding genetic testing. The relatives are then contacted directly via the index case. And all the relatives can be then seen in the clinic and offered a DNA and lipid profile. When FH is confirmed, appropriate therapy is recommended. And this can be done in the CV health clinic. Or the patient can be referred back to their primary care provider.

Now such an approach allows an unambiguous diagnosis in relatives and for further cascading. And in the Netherlands this program has worked quite effectively in terms of cost per life of years gained. It was a very acceptable $8,700.

This program has been in place in that country for more than 10 years, during which time 20,000 cases have been detected, a really spectacular success in public health genomics. Unfortunately in countries such as the US, where the health system is not centralized, cost effectiveness for cascade genetic testing has not been assessed.

How do we manage patients with FH? Well, there are two categories of drugs, broadly-- those that affect on hepatic metabolism and those that act on the intestine. Let's start with the liver here.

And of course, the central modality would be statins. They inhabit HMG-CoA reductase and reduce cholesterol production in the liver, which then in turn leads to increased LDL receptor expression on the hepatocytes.

Mipomersen is a new drug that is an antisense for apolipoprotein B 100. And that then leads to a decreased production of VLDL-like particles. And microsomal transfer protein inhibitor lomitapide also acts similarly by reducing the production of VLDL atherogenic particles.

A new class of drugs that target the PCSK9 protein that I alluded to earlier has emerged and been shown to have significant LDL reduction properties. Two drugs-- alirocumab and evolocumab have been approved by the FDA in 2015 for patients who have FH and are not at goal, in spite of maximal medical therapy, or have statin intolerance. These drugs act by inhibiting PCSK9 and thereby reducing the degradation of LDL receptor, which are then able to recycle several times-- in fact up to 150 times-- and therefore efficiently lower LDL circulating levels.

Two drugs that act on the intestine are ezetimibe, which inhibits the NPC1L1 protein and reduces cholesterol absorption, and then colesevelam and other bile acid resins that bind bile acids and then in turn lead to increased expression of hepatic LDL receptors.

So once we have an individual who has suspected FH and ruled out secondary causes of elevation and LDL cholesterol, we then attempt to establish a clinical diagnosis based on the features I alluded to earlier. We may consider additional testing.

And then the patient should be referred to the CV genomics clinic where genetic testing and cascade screening can be started, counseled on lifestyle changes. And then lipid lowering therapy is focused on statins. And then ezetimibe can be added if the goaled LDL cholesterol is not reached.

Newer drugs that are available include the PCSK9 inhibitors, as well as mipomersen and lomitapide. Bile acid sequestrants and niacin can occasionally be used. And then the role of lipoprotein apheresis has diminished recently, because of the availability of the PCSK9 inhibitors.

Now in children, statins do not appear to affect growth, maturation, and educational levels. The drugs can be started as early as eight years. And both pravastatin and simvastatin have been studied, as well as pitavastatin, in particular in children of Asian descent.

Our goal is to reduce the LDL cholesterol to less than the 95th percentile or less than 130 milligrams per dL, or have a greater than 50% reduction in baseline LDL levels. Ezetimibe or colesevelam can be started from age 10.

In the rare patient with very severe FH or homozygous FH, lipoprotein apheresis is an option. Now at Mayo Clinic, we have initiated a CV genomics clinic to manage patients with familial hypercholesterolemia.

The patients are assessed by a genomic cardiologist, as well as colleagues in the CV health clinic. And then they meet with a genetic counselor for pedigree drawing, counseling about genetic testing, and obtaining pre-authorization for genetic testing.

Once these results are back, they are reviewed by the genomic cardiologist. If there's a pathogenic variant, then obviously the diagnosis of FH is confirmed and the cascade screening of relatives can begin.

Occasionally, we'll see a variant of uncertain significance. And we are in the process of developing functional assays that will help us better understand the significance of such variance.

If no pathogenic variance is identified, patients can still be considered to have FH because genetic testing is negative in 20% of individuals that meet the criteria for FH. We're exploring the use of whole exome sequencing in such families to discover new genetic etiologies for FH.

So to summarize FH in 2016, we continue to unfortunately have low awareness detection and control for this condition. Some of this may be addressed by the availability of a new ICD-10 code for FH. There is lot of data suggesting that cascade screening by genetic testing may be cost effective and prevent adverse cardiovascular events in family members that are affected but asymptomatic.

Intensive LDL cholesterol lowering should be started as early as possible. In fact, in children who are affected with high levels, treatment can be started with a statin, ezetimibe or colesevelam, as early as age eight to 10 years. Novel therapies have a promise for high-risk severe FH patients. And those include PCSK9 inhibitors.

I want to end by acknowledging my laboratory colleagues, as well as funding agencies. And I would like to thank you for listening to this talk. And I hope that the information presented will be useful in your practice.