Welcome to a new podcast series presented by the American Heart Association to help disseminate the key points as well as the nuances of the 2018 AHA/ACC Cholesterol Guidelines. My name is Pradeep Natarajan and today I'll be your host. I'm the Director of Preventive Cardiology at Massachusetts General Hospital and Assistant Professor of Medicine at Harvard Medical School.

Today we will be discussing the important new changes in the 2018 Cholesterol Guidelines, released November 2018, and compare them to the 2013 Cholesterol Guidelines. Many of these changes will be covered in detail in other podcasts for this series. The purpose of these guidelines is to address the clinical management of blood cholesterol and related disorders and most importantly risks for atherosclerotic cardiovascular disease. These guidelines focus on risk stratification and pharmacological cholesterol lowering. A strong emphasis on non-pharmacologic strategies to lower cholesterol remains in these guidelines, but specific dietary and physical activity guidelines for improved health and reduced disease risk are covered in detail in other guidelines. And, as always, these guidelines are meant to guide practice for most clinical circumstances and obviously don't replace clinical judgment. So, as you all know, cardiovascular disease risk remains the leading cause of death in the U.S., of which the bulk represents atherosclerotic cardiovascular disease. LDL cholesterol elevations through both genetic and non-genetic mechanisms have long been recognized to be associated with future risk of atherosclerotic cardiovascular disease and, importantly, reduction of LDL cholesterol through multiple approaches, is associated with reduce risk for atherosclerotic cardiovascular disease.

The 2018 guidelines represent the latest update from the 2013 guidelines and there were several new changes introduced in the 2013 guidelines from its 2001 predecessor. The 2013 guidelines really took a purist view of the evidence. This resulted in the elimination of treating to LDL cholesterol and non-HDL cholesterol targets, but now focusing on four groups eligible for statins. The
results are a de-emphasis of non-statin medicines, given the lack of support of clinical trial data evidence at the time, and the recommended approach to estimate cardiovascular disease risk was advanced from the Framingham Risk Score to the Pooled Cohort Equations.

Speaker 1: 02:34 The key changes in the latest guidelines stem from new cardiovascular outcome clinical trial data for non-statin medicines, specifically ezetimibe and PCSK9 inhibitors, and the use of cost-conscience, clinically sound approaches to use these medicines. So this actually includes returning to LDL cholesterol targets in certain scenarios and more emphasis is placed on the patient-provider discussion for statin suitability among primary prevention patients at elevated estimated atherosclerotic cardiovascular disease risk. So this, actually, also includes the use of additional clinical factors, now termed risk enhancing factors, and in some scenarios, coronary artery calcium scoring to help adjudicate.

Speaker 1: 03:18 so, let's start with screening and measurement, but really, first, a quick word on terminology. LDL cholesterol is the dominant cholesterol fraction of circulating atherogenic lipoproteins. Non-HDL cholesterol, which is simply the total cholesterol minus the HDL cholesterol, associates with athero-risk more strongly because it captures additional atherogenic apo B containing lipoproteins. And while these guidelines focus on LDL cholesterol, in scenarios where a non-HDL cholesterol remains elevated despite appropriate LDL cholesterol levels, atherogenic lipoproteins really may be incompletely addressed, non-HDL cholesterol goals were included with LDL cholesterol goals in the 2001 guidelines, but given the overall decrease in emphasis in targets in the 2013 guidelines, there was also a decreased focus on non-HDL cholesterol generally and there was increased focus on proportional LDL cholesterol lowering. Now in 2018, we retain focus on proportional LDL cholesterol lowering and now reintroduce targets in some scenarios. But in the highest risk setting, those with atherosclerotic cardiovascular disease with features worrisome for heightened risk for recurrent events, non-HDL cholesterol should also be targeted, and we'll come back to this shortly.
So, in the prior guidelines, a fasting lipid panel was preferred, based on subsequent work indicating that fasting and non-fasting states really don't result in substantially different LDL cholesterol values, either a fasting or non-fasting lipid panel measurement, for the purposes of evaluating LDL cholesterol, are suitable. If triglycerides are above 400, the calculated LDL cholesterol is unlikely to be accurate. But, interestingly, recent work suggests that when LDL cholesterol is very low, the calculated LDL cholesterol by the conventional Friedewald formula, may often be inaccurate. So, based on these observations, when LDL cholesterol is less than 70, a direct LDL cholesterol measurement is reasonable. Or, you can use a modified LDL cholesterol calculation equation, such as the Martin Hopkins equation, and that may be more reliable in these settings for calculating LDL cholesterol.

So the four statin eligible groups are largely similar in the latest guidelines compared to prior. So high intensity statins, which are statin regimens aimed at lowering LDL cholesterol by at least 50 percent, are recommended for patients with clinical atherosclerotic cardiovascular disease or severe hypercholesterolemia.

At least moderate intensity statins, which are statin regimens aimed at lowering LDL cholesterol by at least 30 percent, are recommended for patients who don't have clinical atherosclerotic cardiovascular disease, but have diabetes or have an elevated ten year risk for atherosclerotic cardiovascular disease. We'll focus on guideline changes for all of these groups, except for diabetics without athero, which really largely remains unchanged.

So what exactly is clinical atherosclerotic cardiovascular disease under the umbrella of secondary prevention? These are individuals with acute coronary syndrome, a history of a prior MI, angina, prior revascularization, peripheral arterial disease, stroke, TIA, aortic aneurysm. So technically, non-obstructive coronary atherosclerosis is not considered clinical atherosclerotic cardiovascular disease, but this phenomenon is considered elsewhere under the primary prevention umbrella that we'll get back to.
So, consistent with the 2013 guidelines, the 2018 guidelines emphasize that all patients with atherosclerotic cardiovascular disease should be on a maximally tolerated statin to get their LDL cholesterol down by at least 50 percent. There is now an important and new subset of atherosclerotic cardiovascular disease termed 'very high risk atherosclerotic cardiovascular disease.' This acknowledges that despite at least 50 percent lowering of LDL cholesterol, there's likely to be a subset of patients who remain at unacceptably elevated risk for recurrent events warranting intensification of LDL cholesterol lowering.

So, since the last guidelines, cardiovascular outcomes clinical trials show that in addition to statins, ezetimibe and to date two PCSK9 monoclonal antibodies further lower LDL cholesterol and further lower recurrent cardiovascular disease event risk. Data also suggests a greater absolute clinical benefit for patients who have a greater burden of atherosclerosis, who've had recurrent events, who have additional cardiovascular disease risk factors and have higher on statin LDL cholesterol levels. The term 'very high risk atherosclerotic cardiovascular disease' encapsulates these features. These are patients with more than one major atherosclerotic cardiovascular disease event, such as recent ACS, prior MI, history of stroke, or symptomatic peripheral arterial disease, or those with a single major event but other clinical features suggestive of high risk as further outlined in the document. For these individuals, the goal is to lower LDL cholesterol by at least 50 percent and get LDL cholesterol to less than 70 and get non-HDL cholesterol to less than 100. It's recommended to pursue ezetimibe first prior to a PCSK9 inhibitor to achieve these targets. There's a 2B recommendation for ezetimibe only when there's atherosclerotic cardiovascular disease, but without very high risk features, to achieve these same targets.

Now let's take a quick pivot to cost and value. This actually is an important new theme in the 2018 guidelines. In the 2013 guidelines the word cost is used only once and it's used to support the favorable economic impact of statins on cardiovascular disease risk reduction, but the word
'cost' is now used nearly 70 times in the 2018 guidelines. LDL cholesterol lowering proportionately lowers atherosclerotic cardiovascular disease risks across a broad range of LDL cholesterol concentrations and across a broad range of baseline atherosclerotic cardiovascular disease risk. But, clinical benefit, as measured by absolute risk reduction, is maximized when you’re starting with higher LDL cholesterol or starting with higher atherosclerotic cardiovascular disease risks, for first events or recurrent events.

Speaker 1: 09:18 Since, at the time of drafting the guidelines, cost effectiveness analyses indicated that the cost of clinically available PCSK9 inhibitors were too high for the anticipated value as derived from clinical trial data, the authors of the guidelines actually plainly state that the current PCSK9 inhibitors have low value at 2018 costs. And as such, to maximize clinical benefit and, as a result, value, the guidelines support their use now only in those with very high risk atherosclerotic cardiovascular disease or familial hypercholesterolemia. And this really is a tricky balance between societal costs, out-of-pocket costs, public health, individual health and introduced for the first time in these guidelines.

Speaker 1: 10:00 Now let’s shift over to sever hypercholesterolemia. This is LDL cholesterol at least 190 and particularly when atherosclerotic cardiovascular disease is not present. For patients 20 to 75 years of age with severe hypercholesterolemia, as before, a maximally tolerated statin is recommended to a goal of LDL cholesterol 50 percent lower. If this is not achieved or LDL cholesterol is above 100, the addition of ezetimibe is reasonable, now with a stronger recommendation compared to 2013. And if patients 30 to 75 still have an LDL cholesterol above 100, despite statins or ezetimibe, and also have heterozygous familial hypercholesterolemia, a PCSK9 inhibitor may be considered. This is a 2B recommendation. The recognition of familial hypercholesterolemia as a distinct actionable entity and the incorporation of PCSK9 inhibitors for primary prevention are new for these guidelines.

Speaker 1: 10:54 While there are clinical criteria for FH, the diagnosis really is best established molecularly through genetic testing.
But, severe hypercholesterolemia, particularly when higher LDL cholesterol levels are present, still carries a very high risk for atherosclerotic cardiovascular disease, even when familial hypercholesterolemia genetic variants are absent. So, in patients 40 to 75 years of age, their baseline LDL cholesterol is above 220, and despite statins and ezetimibe their LDL cholesterol remains greater than 130, PCSK9 inhibitor could be considered. And this is also a 2B recommendation.

Speaker 1: 11:32 Since cost effectiveness of PCSK9 inhibitors for FH hadn’t been extensively evaluated prior to the drafting of these guidelines, the guidelines state that the value of PCSK9 inhibitors, in this setting, remains uncertain. A large bin of patients who may be eligible for statins are those without atherosclerotic cardiovascular disease, diabetes, or severe hypercholesterolemia. And, as before, among these patients, to begin to establish statin eligibility, we use the Pooled Cohort Equations to estimate ten year risk, but the labels for the risk categories are now different, partly to address prior concerns of expanding statin eligibility in the 2013 guidelines. High risk is now 20 percent where previously it was 7.5 percent. Now intermediate risk is 7.5 to 20 percent. Borderline risk is 5 to 7.5 percent and low risk is less than 5 percent. So, previously, for individuals with a ten year risk greater than 7.5 percent, a moderate to high-potency statin was recommended. Now, for individuals with a ten year risk greater than 20 percent, a high-potency statin is recommended. But, for individuals with a ten year risk between 7.5 to 20 percent, it is acknowledge that LDL cholesterol should be lower and it's acknowledge with the level one recommendation that statins reduce risk for atherosclerotic cardiovascular disease among these individuals, but the decision for a statin should ultimately be made in the context of a risk discussion and patient preferences.

Speaker 1: 12:56 And these guidelines also now introduce the term 'risk enhancing factors' to help favor the initiation or intensification of statins for intermediate risk and select borderline risk adults. So, risk enhancing factors are clinical factors that independently associate with cardiovascular disease risk but are not in the Pooled Cohort Equations.
So, these factors without the specific term was actually in the 2013 guidelines but with a weaker recommendation class. So, now there is a stronger recommendation for use and the list is further expanded.

Speaker 1: 13:26 So, previously, and again in 2018, there's first-degree, relative with premature atherosclerotic cardiovascular disease, an LDL cholesterol greater than 160 but not quite greater than 190, and one measured and elevated CRP, and a low ankle-brachial index. But now, additional factors include the presence of metabolic syndrome; chronic kidney disease; chronic inflammatory conditions, like psoriasis, rheumatoid arthritis, and HIV; a history of menopause prior to the age of 40, a history of preeclampsia, South Asian ancestry, and were measured an elevated lipoprotein little a, and elevated apolipoprotein B.

Speaker 1: 14:03 Now, substantial epidemiological research has led to a stronger recommendation for coronary artery calcium scoring to help with statin prescription adjudication in some scenarios. And, epidemiological data suggests that the burden of coronary artery calcification in asymptomatic individuals is strongly associated with ten year risk. And, most notably, data from, again, multiple studies, also indicate that when coronary artery calcium score is 0, there's a very low rate of events for the subsequent five to ten years. So, in 2013 there was a 2B recommendation for the use of elevated coronary artery calcium score essentially as a risk enhancing factor.

Speaker 1: 14:40 Now, there's a 2A recommendation for a slightly different use. It's now recommended for use when there is equipoise regarding statin prescription for intermediate risk and select borderline risk patients after there's been a clinical risk calculation, evaluation of risk enhancing factors and shared decision-making. And, based on low event rates in epi studies, for coronary artery calcium score of 0, then it may be reasonable to hold off on a statin and reassess in five to ten years. But, if coronary artery calcification is present, it's reasonable to initiate a statin.

Speaker 1: 15:13 The guidelines do acknowledge specific scenarios where coronary artery calcium of 0 may not be suitable as a basis
for withholding statins. This includes cigarette smoking, family history of premature athero, and diabetes. The guidelines do highlight four specific scenarios where knowledge of a score of 0 may be helpful. It includes patients who are reluctant to start a statin but want to better understand their risk, patients with prior statin-associated symptoms concerned about whether they even need to be re-challenged on a statin, older adults who have a low burden of clinical risk factors but their elevated ten year risk is driven by their advanced age but who remain uncertain about taking a statin, and middle-aged adults who have borderline risks but also have risk enhancing factors.

**Speaker 1:** 15:57 So, this brings us to the conclusion. In summary, statins are appropriate for clinical atherosclerotic cardiovascular disease, diabetes, severe hypercholesterolemia, and elevated ten year risk for atherosclerotic cardiovascular disease. For patients with atherosclerotic cardiovascular disease with recurrent events or additional risk factors for recurrent events, now termed very high risk atherosclerotic cardiovascular disease, intensification of lipid-lowering therapy with ezetimibe and PCSK9 inhibitors, as necessary to achieve an LDL cholesterol less than 70 is now appropriate. Intensification with these agents for familial hypercholesterolemia to achieve LDL cholesterol less than 100 is also now appropriate. High risk for a first event is now ten year risk greater than 20 percent and a statin remains indicated, but for those at intermediate risk and select borderline risk, further LDL cholesterol lowering with statins will lower risk, but there's now increased emphasis on incorporating risk enhancing factors and shared decision making to determine statin suitability. And if you or the patient still remain unsure about statins in this setting, a coronary artery calcification score of 0 may be used defer statin initiation.

**Speaker 1:** 17:04 I hope you found this helpful. Thank you for taking the time to improve your practice. Take care.