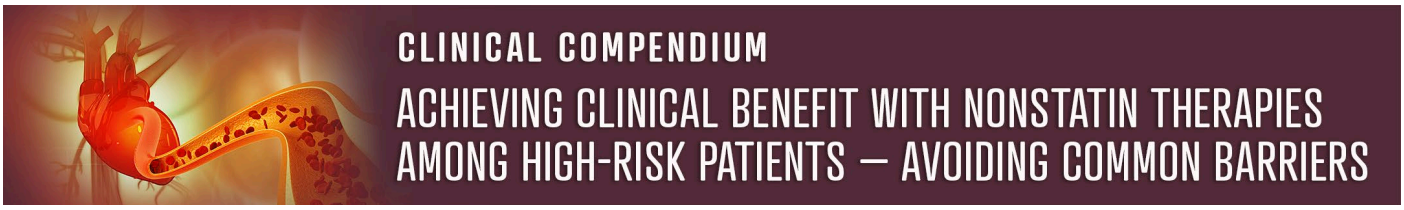

Editor's Note: This is a transcript of a presentation on January 28, 2025. It has been edited and condensed for clarity.
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Case 1– Risk Stratification and Assessment

A 48-year-old man is evaluated during his yearly physical examination. His medical history includes hypertension, type 2 diabetes mellitus, and moderately severe rheumatoid arthritis. The patient is Black and originally from sub-Saharan Africa. On physical examination, vital signs are normal; BMI is 23 kg/m^2. His 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) risk scores are 26% and 69%, respectively. A coronary artery calcium (CAC) scan performed last year indicated a score of 125 (>90th percentile). The patient's hypertension and type 2 diabetes mellitus are risk factors for atherosclerotic cardiovascular disease (ASCVD).

Question 1

Which one of the following findings in this patient is a risk-enhancing factor for ASCVD?

a. Body mass index
b. Elevated coronary artery calcium score
c. Race/ethnicity
d. Rheumatoid arthritis

Rationale

The correct answer is D/Rheumatoid arthritis.

- Hypertension and type 2 diabetes mellitus are traditional risk factors and components of the pooled cohort equations (PCE) used to determine 10-year ASCVD risk. More recently, chronic kidney disease and chronic inflammatory conditions including rheumatoid arthritis have been identified as-risk enhancing factors.[1,2] The patient's BMI indicates normal weight and is not a risk-enhancing factor for ASCVD.
- The addition of risk-enhancing factors to the 10-year ASCVD risk calculator provides a more individualized and comprehensive approach to ASCVD risk assessment. The presence of risk-enhancing factors may help guide the initiation or intensification of lipid-lowering therapy, especially among intermediate- and borderline-risk primary prevention patients.[1,2]
- An elevated CAC score is NOT considered a risk-enhancing factor. Instead, CAC measurement is a surrogate marker used as a clinical risk stratification tool to estimate the overall burden of coronary atherosclerosis. South Asian ancestry is a risk-enhancing factor, but this patient's African ancestry does not increase his risk.
- Risk-enhancing factors are primarily supported by observational data, indicating varying degrees of association with ASCVD. Typically, the more pronounced and severe the risk-enhancing factor, the higher the association with ASCVD.[1,2]

Faculty Commentary

JOHN E. ANDERSON, MD: We all have the traditional risk factors, but when we are talking about risk-enhancing factors, clearly the chronic inflammatory condition of rheumatoid arthritis is what concerns us. And this is a typical sort of thought process in primary care. You have somebody and you are trying to assess atherosclerotic cardiovascular disease risk (ASCVD) risk. What do we have to do, especially in the primary prevention patient? We know that this is really a high-risk prevention patient, especially when you see the elevated coronary calcium score and you see the other traditional risk factors. This is someone who could really benefit from aggressive lipid management. We all have goals from the American Heart Association (AHA), from the American Diabetes Association, for where we should have hypertension goals, where we should have glycated hemoglobin (A1C) and glycemic goals, and also where we should have lipid goals in these patients, whether they are high risk or very high risk. And clearly, what we have found is patients with chronic inflammation, like in this case rheumatoid arthritis, may be playing a real role. And Seth, you and I talked recently about a patient of mine with type 1 diabetes, well-controlled, who had Hashimoto's thyroiditis, sarcoidosis, and is now dealing with an unknown inflammatory arthritis being treated at the large university hospital. We did a calcium score and it was through the roof which enabled us to, at least for now, intensify statin therapy and add antiplatelet therapy. Again, as we are looking at these established risk factors, we need to be thinking about the other comorbid conditions, whether it's chronic kidney disease (CKD), a chronic inflammatory condition, persistently elevated low-density lipoprotein (LDL) cholesterol and we'll talk a little bit about lipoprotein(a) [Lp(a)] as well.

SETH S. MARTIN, MD: When it comes to coronary artery calcium scanning, that is a great direct assessment of the atherosclerotic burden, which is different than risk factors and risk-enhancing factors, but these can also add to the assessment. Clearly, this is a high-risk primary prevention patient, but an inflammatory condition, like rheumatoid arthritis, is considered a risk-enhancing factor that further motivates our prevention efforts to lower LDL cholesterol and mitigate risk.

References

1. Grundy SM, Stone NJ, Bailey Al, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi:10.1161/CIR0000000000000625
2. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Case 1– Risk Stratification and Assessment

A 48-year-old man is evaluated during his yearly physical examination. His medical history includes hypertension, type 2 diabetes mellitus, and moderately severe rheumatoid arthritis. The patient is Black and originally from sub-Saharan Africa. On physical examination, vital signs are normal; BMI is 23 kg/m^2. His 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) risk scores are 26% and 69%, respectively. A coronary artery calcium (CAC) scan performed last year indicated a score of 125 (>90th percentile). The patient's hypertension and type 2 diabetes mellitus are risk factors for atherosclerotic cardiovascular disease (ASCVD). The ASCVD risk scores and CAC measurement are recommended as key components of patient assessment.

Question 2

Which one of the following effects do 10-year and lifetime atherosclerotic cardiovascular disease risk scores and coronary artery calcium score have on evaluation of a patient's overall risk stratification and treatment?

a. Individually they provide minimal value
b. Collectively they provide modest value
c. Collectively they provide accurate predictive value
d. Collectively they provide complementary value for risk assessment

Rationale

The correct answer is D/Collectively they provide complementary value for risk assessment.

- The pooled cohort equations (PCE) are considered a robust tool for estimating 10-year ASCVD risk in US adults aged 40-75 years. The coronary artery calcium (CAC) score provides evidence of subclinical disease beyond the 90th percentile for age, gender, and race. Collectively, the validated assessment tools provide significant and complementary clinical insight allowing for informed decision-making among the clinician and patient.[1]
- The PCE is population-based and may thus over- or underestimate actual individual ASCVD risk. Such limitations can be minimized by evaluating the presence of risk-enhancing factors and/or the utilization of imaging modalities (eg, CAC, carotid intima-media thickness) among individual patients.[1,2]
- Individual patient ASCVD risk stratification remains inherently challenging. As such, no validated assessment tool or combination of tools provide precise prediction of future cardiovascular events.

Faculty Commentary

JOHN E. ANDERSON, MD: Why don't we look at case 1, question 2, and we looked at the ASCVD calculator and I use the ACC calculator. I think those of us in primary care who use these tools understand them to be fairly simple and easy, may take less than 1 minute, but what I've also found out, let me hear your feedback, is it gives you a framework for a one-on-one individualized discussion with the patient as well. And then also, if you add the coronary calcium scoring, you can really start to navigate risk in a more precise way. I would be interested for you to talk to us about what we know that's coming up on the horizon in terms of predictive tools that we may be seeing in guidelines soon.

SETH S. MARTIN, MD: These are all complementary tools that we can use to engage the patient in discussion around what's available to them to lower their risk and what fits best with their goals and preferences. What's on the horizon is the Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) equations. These have been published, not yet incorporated into treatment guidelines, but these are available in an online calculator. You can calculate 10-year risk for individuals who are 30 to 79 years of age and it also provides 30-year risk estimates for those that are 30 to 59 years of age. These equations were developed and released as part of the American Heart Association's cardiovascular kidney metabolic syndrome (CKM) advisory. These equations appear to be more accurate and are likely to be an important tool in future clinical practice. We can all stay tuned for them to be incorporated into treatment guidelines. At the moment, clinicians should stick with the pooled cohort equations because those are what treatment guidelines have incorporated already, but PREVENT is on the horizon. And in the meantime, I think it's important to recognize coronary artery calcium scores as a way to directly assess atherosclerosis. Atherosclerotic burden can really cut through some of the uncertainty of risk calculators or risk scoring and are a complementary tool to help refine risk and inform the clinician/patient discussion around best treatment and prevention strategies.

References

1. Grundy SM, Stone NJ, Bailey AI, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi:10.1161/CIR0000000000000625
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Key Concepts – Faculty Commentary for Case 1

JOHN E. ANDERSON, MD: A couple of key concepts coming out of this case.

- Number 1, traditional ASCVD risk factors and the more recently proposed and we discussed risk-enhancing factors are important to utilize for individual patient risk stratification and overall ASCVD risk assessment.
- Key concept number 2, ASCVD risk prediction has limitations and challenges, however, incorporating validated risk assessment tools, including the 10-year ASCVD risk calculator and common imaging modalities, as we discussed coronary calcium scoring, into risk stratification can better inform shared decision-making between patients and clinicians.

Case 2– Screening and ASCVD Risk Categorization

A 54-year-old woman with heterozygous familial hypercholesterolemia (HeFH) and recurrent ASCVD presents to clinic. The patient experienced a recent acute coronary syndrome (ACS) with coronary stents placed. The patient has an extensive family history of premature ASCVD, follows a Mediterranean diet, exercises daily, and is adherent with her daily rosuvastatin 40 mg and ezetimibe 10 mg, with no reported adverse events. Current laboratory results include LDL-C (109 mg/dL) and non-high density lipoprotein cholesterol (128 mg/dL). Additional screenings performed after the recent ACS showed an elevated lipoprotein(a) level of 205 nmol/L (normal range <75 nmol/L).

Question 1

Which one of the following risk categories for future ASCVD events is most applicable for this patient?

a. Low risk
b. Moderate risk
c. High risk
d. Very high risk

Rationale

The correct answer is D/Very high risk.

- According to the 2018 ACC/AHA Multi-Society Guideline on the Management of Blood Cholesterol, patients with a history of clinical ASCVD are categorized as either "ASCVD not at very high-risk" or as "very high-risk ASCVD." "Clinical ASCVD" includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.[1]
- Very high-risk is defined as a history of multiple major cardiovascular events or 1 major ASCVD event and multiple high-risk conditions.[1]
- This patient has recurrent ASCVD, recent ACS with additional stents, HeFH, elevated Lp(a), and an extensive family history of premature ASCVD, thereby meeting the criteria for "very high-risk."[1]

Faculty Commentary

JOHN E. ANDERSON, MD: Case number 2, we are looking at a patient with very high risk who's had an acute coronary event, who clearly is not at target. I'll turn this to the cardiology field. These are the kind of patients that are at very high risk of more events and we have to really be sure that we're avoiding any kind of clinical inertia when we're trying to treat these patients. I mean, this is of an urgent nature to get her risk factors modified, isn't it?

SETH S. MARTIN, MD: We need to avoid clinical inertia and get the LDL down as low as possible as fast as we can. The current guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) have this differentiation between very high risk and not very high risk in the secondary prevention setting and it's a pretty straightforward definition. Basically, if you've had recurrent ASCVD events, you're very high risk. Or if you have had 1 ASCVD event, but you have other high-risk conditions, such as diabetes, hypertension, smoking, and so forth, the common other high-risk conditions, if you have multiple high-risk conditions on top of an ASCVD event, then that would qualify as very high risk. And in that setting, based on current data and guidelines, we really want to get LDL cholesterol levels down below 55 mg/dL and non-HDL below 85 mg/dL. It's really critically important to recognize the urgency around risk reduction in a patient such as this, particularly when you have the combination of ASCVD and familial hypercholesterolemia. To me, that's really an alarm bell to treat this patient aggressively, as well as to dig into the family and make sure the family members are getting properly cared for, too.

JOHN E. ANDERSON, MD: I think this sense of urgency makes for a receptive individual. So, having that discussion about you had an event, I know you are on therapy, but you are not on enough therapy, and this is a moment when I think patients are going to be extremely willing to do whatever it takes to not cross the threshold of another event.

SETH S. MARTIN, MD: Having events is highly motivating and that's part of the reason it's important to act quickly to take advantage of that motivation before someone settles into a more stable state and may lose some of that motivation.

Reference

1. Grundy SM, Stone NJ, Bailey Al, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi:10.1161/CIR0000000000000625

Case 2– Lp(a) - Potential Clinical Impact

A 54-year-old woman with heterozygous familial hypercholesterolemia (HeFH) and recurrent ASCVD presents to clinic. The patient experienced a recent acute coronary syndrome (ACS) with coronary stents placed. The patient has an extensive family history of premature ASCVD, follows a Mediterranean diet, exercises daily, and is adherent with her daily rosuvastatin 40 mg and ezetimibe 10 mg, with no reported adverse events. Current laboratory results include LDL-C (109 mg/dL) and non-high density lipoprotein cholesterol (128 mg/dL). Additional screenings performed after the recent ACS showed a lipoprotein(a) level of 205 nmol/L.

Question 2

Which one of the following would be the most appropriate approach to this patient's therapy as a result of the new finding of elevated lipoprotein(a)?

a. Continue present therapy
b. Recommend additional therapeutic lifestyle changes
c. Optimize lipid-lowering therapy
d. Add high-dose niacin therapy

Rationale

The correct answer is C/Optimize lipid-lowering therapy.

- Elevated Lp(a) is considered an independent, linear, and causal risk factor for ASCVD and calcific aortic stenosis.[1-3] Given this patient's Lp(a) value of 205 nmol/L and extensive history of ASCVD, the elevated Lp(a) is a likely contributor.
- Clinical management of elevated Lp(a) includes optimizing lipid-lowering therapies to achieve lipid targets. Since this patient has recurrent disease, referral to a lipidologist with access to lipoprotein apheresis/investigational Lp(a) studies/agents should be considered.[1-4]
- Results from AIM-HIGH and HPS2 – THRIVE trials demonstrated no clinical benefit with niacin and concern for increased adverse effects.[5]

Faculty Commentary

JOHN E. ANDERSON, MD: When we look at case 2 and we look at question 2, talk to us about Lp(a). What is it, how prevalent is it, what do we think as cardiologists, what should primary care be doing to alter this risk in patients?

SETH S. MARTIN, MD: Elevated Lp(a) is common, depending on where you draw the cut point, the classical cut point around 125 nmol/L or 50 mg/dL is considered elevated in about 20% of people, so 1 in 5 people may have elevated Lp(a). It's an independent linear and causal factor for ASCVD, as well as calcific aortic stenosis. This patient's Lp(a) value of 205 nmol/L is clearly elevated and a likely contributor to their atherosclerotic disease history. The best management for patients with high Lp(a) is basically to control LDL and other cardiovascular risk factors, to do that in the most aggressive and optimal fashion. Since this patient's had recurrent disease, it's particularly important to be controlling those other risk factors. This would be a good case to consider referring to a lipidologist who has access to lipoprotein apheresis as well as investigational studies. There are now 5 different Lp(a) drugs in development, a number of clinical trials have been happening and so there could be a study opportunity for this patient. But, in the very near future, we are going to start getting the read-outs from the Lp(a) cardiovascular outcome trials, so very soon we will start seeing these major results and it's very possible that Lp(a)-directed therapies could be coming to practice which is ever more reason to be identifying your patients in the primary care setting with high Lp(a).

JOHN E. ANDERSON, MD: Much like with new agents to treat chronic kidney disease, it's incumbent upon us to screen both for kidney function, as well as for urinary albumin:creatinine ratios that frankly weren't done as much. What would your recommendation for primary care clinicians be in terms of how often do you have to screen? Is it a 1-time screen? And who would be at the top of your mind to roll into the category of screening?

SETH S. MARTIN, MD: Generally, a 1-time screening makes sense. We will learn over time when repeated testing for Lp(a) makes sense. Of course, if we have directed therapy, that will be a game-changer in terms of the need for follow-up Lp(a) testing. But, a 1-time measurement, I would be doing it quite broadly, but I would prioritize particularly patients who have had premature ASCVD recurrent events despite treating other risk factors well. The other thing that's interesting to note is that although traditionally niacin had been used because it does have some Lp(a) lowering and there was the thought that it could be beneficial, the modern data have not panned out in that regard, so in general it would not be advisable to use niacin, even in patients with high Lp(a). Again, the treatment strategy would be to optimize LDL and other risk factors at the moment.

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Case 2– Lipid Thresholds and Targets

A 54-year-old woman with heterozygous familial hypercholesterolemia (HeFH) and recurrent ASCVD presents to clinic. The patient experienced a recent acute coronary syndrome (ACS) with coronary stents placed. The patient has an extensive family history of premature ASCVD, follows a Mediterranean diet, exercises daily, and is adherent with her daily rosuvastatin 40 mg and ezetimibe 10 mg, with no reported adverse events. Current laboratory results include LDL-C (109 mg/dL) and non-high density lipoprotein cholesterol (128 mg/dL). Additional screenings performed after the recent ACS showed a lipoprotein(a) level of 205 nmol/L.

Question 3

According to the 2022 ACC Expert Consensus Decision Pathway (ECDP) on the Role of Nonstatins, what lipid threshold for initiating additional therapy and percent reduction target are most appropriate for this patient?

a. LDL-C ≥100 mg/dL and ≥30% to 50% LDL-C reduction
b. LDL-C ≥100 mg/dL and ≥50% LDL-C reduction
c. LDL-C ≥70 mg/dL and ≥50% LDL-C reduction
d. LDL-C ≥55 mg/dL and ≥50% LDL-C reduction

Rationale

The correct answer is D/LDL-C ≥55 mg/dL and ≥50% LDL-C reduction.

- According to the 2022 ACC Expert Consensus Decision Pathway (ECDP) on the Role of Nonstatins a patient with clinical ASCVD at very high risk on statin therapy for secondary prevention has a recommended LDL-C threshold of <55 mg/dL for initiating additional therapy and target LDL-C reduction ≥50%.[1]

Faculty Commentary

JOHN E. ANDERSON, MD: Seth, talk a little bit about some of the cardiovascular outcomes trials that we've seen in the nonstatin therapies. We have had a whole lot of these lately, haven't we?

SETH S. MARTIN, MD: With nonstatin therapies, we have gone from having the IMPROVE-IT trial of ezetimibe to then having multiple clinical trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, particularly the FOURIER trial of evolocumab and the ODYSSEY outcomes trial of alirocumab and then most recently, the CLEAR outcomes trial of bempedoic acid. We have been fortunate to have a number of key clinical outcome trials. Each one has shown benefit of these drugs on top of statin therapy, which has given us a number of new treatment options to drive LDL down to lower levels than we were able to achieve before.

With a patient who has clinical ASCVD at very high risk, as we have with our patient here, who's already maximized on statin therapy and the question is how much lower should we go with LDL, what should be our treatment threshold for adding on additional nonstatin

therapy? In the very high-risk patients, based on that consensus pathway, an LDL of 55 mg/dL, would trigger additional nonstatin therapies to be added. And our goal, from a percentage reduction standpoint, is to lower LDL 50% or more from baseline. We are getting down ideally the LDL levels below 55 mg/dL and there is no lower limit that drives safety concerns. So, really, the lower, the better.

Reference

1. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Key Concepts – Faculty Commentary for Case 2

SETH S. MARTIN, MD: Key concept number 1, the 2018 ACC/AHA multi-society guideline on management of blood cholesterol has categorized patients with clinical ASCVD as not at very high risk or very high risk. This is a key differentiation, and we treat the very high-risk patients even more intensively.

Key concept number 2, elevated Lp(a) is the most common genetic dyslipidemia, affecting approximately 20% of the global population and it's an independent, linear, and causal risk factor for ASCVD and calcific aortic stenosis.

Key concept number 3, the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies recommended aggressive LDL cholesterol reductions to levels less than 55 mg/dL, with levels exceeding this considered a threshold to add on nonstatin therapy to statins. And really, the lower the better when it comes to LDL.

Case 3– Lipid Thresholds and Targets

A 58-year-old man is evaluated in follow-up. His medical history includes coronary artery bypass graft (CABG) several years ago, well-controlled hypertension, and partial statin intolerance. The patient's lipid-lowering medications include ezetimibe 10 mg/d, icosapent ethyl 4g/d, and atorvastatin 10 mg 3 times weekly. This is the patient's maximally tolerated statin dose, and he is adherent to current therapy. He had not achieved target lipid levels with multiple statins and alternative dosing regimens. His current LDL-C is 114 mg/dL.

Question 1
According to the 2022 ACC Expert Consensus Decision Pathway (ECDP) on the Role of Nonstatins, which one of the following lipid thresholds for initiating additional therapy and percent lipid reduction targets are most appropriate for this patient?

a. LDL-C ≥100 mg/dL and ≥30% to 50% LDL-C reduction
b. LDL-C ≥100 mg/dL and ≥50% LDL-C reduction
c. LDL-C ≥70 mg/dL and ≥50% LDL-C reduction
d. LDL-C ≥55 mg/dL and ≥50% LDL-C reduction

Rationale

The correct answer is C/LDL-C ≥70 mg/dL and ≥50% LDL-C reduction.

- According to the 2022 ACC ECDP, this patient would be classified as having clinical ASCVD and "not at very high-risk" due to the CABG performed several years prior. The recommended threshold for initiating additional therapy would be LDL-C ≥70 mg/dL with a targeted LDL-C reduction ≥50%.
- Importantly, CABG or percutaneous coronary intervention (PCI) are considered "high-risk conditions" and not a "major ASCVD event." The patient also has 2 additional "high-risk conditions," persistently elevated LDL-C (>100 mg/dL) and hypertension, which is well controlled.[1]
- As a reference, Clinical ASCVD classified as "very high-risk" is defined as a history of multiple major ASCVD events (ie, recent ACS, myocardial infarction, ischemic stroke, symptomatic peripheral artery disease or 1 major ASCVD event and multiple high-risk conditions).[1]

Faculty Commentary

JOHN E. ANDERSON, MD: If we look at this case, we have a patient who has stable coronary artery disease, has had revascularization, stable hypertension, so this is a person at high risk, but not at very high risk having had an acute event years ago. So, there's an urgency here, we don't ever want to say there's not an urgency, but it's not an emergent type of profile. This patient's on 3 different agents, for whatever reason may have had some degree of statin intolerance, but it is now our job to figure out what's the next step. Do we intensify statin? Have we tried to intensify the statin several times and just met with either resistance or intolerance? Is it time to add another medication class, like a PCSK9 inhibitor? Again, sort of that shared decision-making with the patient.

SETH S. MARTIN, MD: Shared decision-making and I think it's important to listen to the patient. If they say this is the most I can take, I don't want to try anything more, we need to just take that as a signal, we'll lock that in as the statin dose and now let's look at what else we can do. And we are fortunate to have other options that we can add on. So, I think that's the sense I get from this case, that his maximally-tolerated statin dose has been established and now the question is what else can we do so that we don't leave that LDL hanging at 114 mg/dL.

Reference

1. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Case 3 - Therapeutic Considerations

A 58-year-old man is evaluated in follow-up. His medical history includes coronary artery bypass graft (CABG) several years ago, well-controlled hypertension, and partial statin intolerance. The patient's lipid-lowering medications include ezetimibe 10 mg/d, icosapent ethyl 4g/d, and atorvastatin 10 mg 3 times weekly. This is the patient's maximally tolerated statin dose, and he is adherent to current therapy. He had not achieved target lipid levels multiple statins and alternative dosing regimens. His current LDL-C is 114 mg/dL.

Question 2

Which additional nonstatin therapies are recommended by the American College of Cardiology guidelines to achieve target lipid values for this patient taking a maximally-tolerated statin dose and ezetimibe?

a. PCSK9 mAb
b. PCSK9 mAb and bempedoic acid
c. PCSK9 mAb and inclisiran
d. PCSK9 mAb, bempedoic acid, or inclisiran

Rationale

The correct answer is D/PCSK9 mAb, bempedoic acid, or inclisiran.

- A patient with clinical ASCVD, not at very high risk on statin therapy for secondary prevention, already receiving maximally-tolerated statin dose and ezetimibe, can be considered for the addition of a PCSK9 mAb, bempedoic acid, or inclisiran, to achieve desired LDL-C reduction.[1]

Faculty Commentary

JOHN E. ANDERSON, MD: And if we look at case 3, question 2, Seth, I'm going to turn this over to you. Talk to us a little about this era of nonstatin therapies and what we know from a cardiovascular outcomes standpoint.

SETH S. MARTIN, MD: We are very fortunate to have a number of options. This particular patient is not at very high risk but is still in the secondary prevention setting and an LDL of 114 mg/dL is not acceptable. We need to look at where else we can add on additional therapy. Once a patient's already on their max-tolerated statin dose and ezetimibe, then we can turn our attention to PCSK9 monoclonal antibody therapy, bempedoic acid, and inclisiran. When it comes to the PCSK9 monoclonal antibodies, we are basically talking about evolocumab and alirocumab where we have large clinical outcome trials showing a 15% relative risk reduction over just a short amount of time, a little over 2 years follow-up. So, impressive the amount of risk reduction that was achieved in just a short amount of time. And

then with bempedoic acid, we have the CLEAR outcomes trial. This was a mixed primary and secondary prevention trial, whereas the monoclonal antibody trials were more pure secondary prevention trials. But with bempedoic acid, we also have the outcomes benefit particularly in a statin-intolerant population in which that was conducted. Inclisiran has also now shown in clinical trials to lower LDL, and to do it safely. We are still awaiting the cardiovascular outcome trial for inclisiran.

Reference

1. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Case 3 - Limiting Nonstatin Barriers

A 58-year-old male with a prior coronary artery bypass graft several years ago, well-controlled hypertension, partial statin intolerance, and a recent history of medication nonadherence presents for care. Lipid medications include ezetimibe 10 mg/d, icosapent ethyl 4g/d, and atorvastatin 10 mg 3 times weekly. This is the patient's highest tolerable statin dose after failing multiple statins and alternative dosing regimens. His LDL-C is 114 mg/dL and is reflective of positive medication adherence to his current lipid-lowering agents.

Question 3

Which of the following best practices can be implemented to limit barriers to initiating and maintaining nonstatin therapies in this patient? *(Choose all correct answers)*

a. Identify common causes of clinical inertia within own practice setting
b. Implement a nonstatin prior authorization (PA) checklist
c. Limit the utilization of digital health tools
d. A and B only
e. All of the above

Rationale

The correct answers are A/Implement a nonstatin prior authorization checklist and B/Identify common causes of clinical inertia within own practice setting.

- Various organizations, including the National Lipid Association, have developed prior authorization (PA) checklists to help provide the necessary documentation to third party payors.[1,2] These checklists provide clear, concise, and essential information for improving the PA process.
- Clinical inertia is often present among both clinicians and patients. Common causes among clinicians include insufficient time, work overload, burnout, and inadequate knowledge of guidelines. Patient-related causes of clinical inertia include denial of disease or severity of disease, absence of symptoms, low health literacy, and "too many medications." Awareness of these factors can limit clinical inertia and improve clinician-patient communication and shared decision-making.
- Best practices for navigating the nonstatin PA process include involving clinic support staff to help with documentation/processing and utilization of a specialty pharmacy.
- Utilization of digital health tools such as apps or devices to assist with medication adherence, communication, etc., should be encouraged.

Faculty Commentary

JOHN E. ANDERSON, MD: Seth, if we look at case 3 and question 3, let's talk a little bit about medication nonadherence. Whether you want to have clinical inertia, medication nonadherence, I think it's important for us to understand our patients. One of the things I'll have my nurses do when they're doing a med reconciliation at the beginning of a visit is, especially if the patient has a complicated regimen, in a very nonjudgmental way, is like this is hard to do. Do you struggle with this? Are these medications being covered? Do you have a system whereby you remember this? Also, as we said with the statin intolerance, having that discussion with the patient. You have to be nonthreatening and understanding when you are talking to patients about this concept.

SETH S. MARTIN, MD: We want it to be a warm environment for patients to share their issues that they're having, whether it be concerns about side effects, an issue that they read about online or whether it's related to organization of their medicines. If they're on a lot of medicines, are they well-organized, using a pill box? Are they forgetting to take medication? All these are really important to address in the clinic setting. It's really fundamental.

JOHN E. ANDERSON, MD: I think we have talked about breaking down those silos, right? I think, well I'm not going to do a PCSK9, that's the cardiologist's job. Well, I'm an interventional cardiologist, that's the primary care's job. The thing is for us to identify when that nonstatin therapy is needed and maybe it's time to pick up the phone and have a conversation with your cardiologist or your primary care clinician so that we can make sure the patient is at the center of our discussion. And then if we need to go through a prior authorization, I get patients all the time wanting a prior authorization on a generic sleeping pill, no, right? But something as important as this, we are willing to jump through the hoops to get this for our patients.

SETH S. MARTIN, MD: It's worth the effort because cardiovascular disease is the number one killer. This is a central cause, we have such solid evidence, it's worth the effort to get the prior authorization and either to take ownership or to, like you said, call your local cardiologist, call your local lipid clinic, somebody in the area that has a lot of experience with this, has maybe built a team that they have even more support around the process because it takes time, but it's worth it, for sure. I think key documentation of the patient's prior therapies and making sure that is clear as it can be to support the prior authorization process and sometimes it helps for patients to advocate for themselves as well with their insurance plan when the patient really recognizes that this is a key next step for them. But I agree, John, it's absolutely, it's about teamwork, it's about taking ownership of this very important next step to advance our patients' care.

References

1. National Lipid Association. Access to therapy. PCSK9 inhibitors. Published 2020. Accessed February 3, 2025. https://www.lipid.org/access_to_therapy
2. Prime Education LLC. Nonstatin prior authorization checklist. Published 2021. Accessed February 3, 2025. https://pcna.net/wp-content/uploads/2022/03/Nonstatin-Prior-Authorization-Checklist_2.pdf

Key Concepts – Faculty Commentary for Case 3

SETH S. MARTIN, MD: Case 3, key concept number 1, risk stratifying patients with clinical ASCVD as not at very high risk or very high risk is essential to determine the lipid treatment targets and improve outcomes.

Key concept number 2, if patients with clinical ASCVD receiving maximally-tolerated statin therapy and ezetimibe are not at treatment goals, consideration can be given to adding a PCSK9 monoclonal antibody, bempedoic acid, or inclisiran.

JOHN E. ANDERSON, MD: And key concept number 3, clinical inertia and other barriers to initiating and maintaining nonstatin therapies exist and, as we discussed, there are various clinical strategies that can be implemented to navigate that prior authorization process to optimize prescribing and just really be sure that the patient is getting what they need.