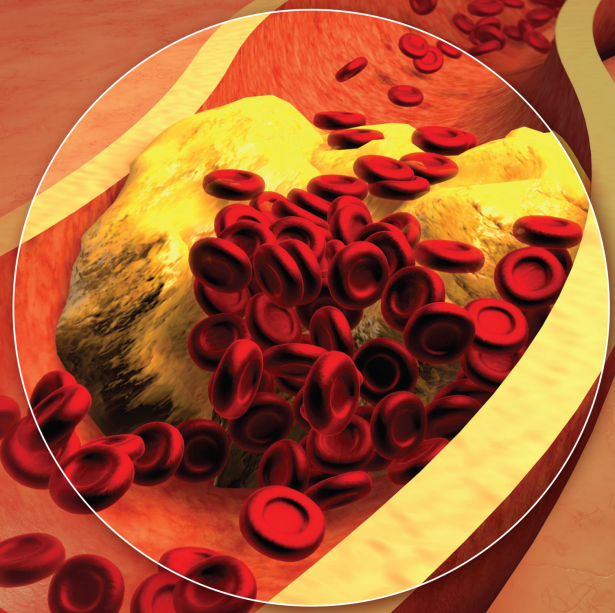
DYSLIPIDEMIA MANAGEMENT

Opportunities to Improve Patient Care



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1.5 AAPA Category 1 CME credits

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ACTIVITY OVERVIEW

Cardiovascular disease (CVD) is the leading cause of death in the United States (U.S.), affecting approximately 92 million American adults. Estimates indicate that 43.9% of the U.S. population will have some form of CVD by 2030. A large number of epidemiologic studies have shown that the risk of CVD rises significantly with increasing levels of low-density lipoprotein cholesterol (LDL-C). Correspondingly, decreases in LDL-C levels reduce the risk of nonfatal CV events as well as mortality over a wide range of baseline risk and LDL-C levels. Accordingly, LDL-C has largely replaced total cholesterol as both a risk marker and the main target of treatment for dyslipidemia. The management of elevated LDL-C is, therefore, fundamental in the primary and secondary prevention of CVD and related adverse outcomes. PAs have a critical role in the management of patients with dyslipidemia. This program will appeal to various learning styles and allow participants to reinforce their knowledge and acquire new skills that can immediately be applied to clinical practice.

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

- Evaluate available options for LDL-C management to identify appropriate therapy.
- Implement guideline-based recommendations for both risk evaluation and management of dyslipidemia.
- Integrate patient specific risk assessment and clinical considerations into the decision-making process.
- Create integrated patient care plans to optimize medication adherence and appreciate how less frequent dosing schedules may be associated with increased medication adherence.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The activity is designated for 1.5 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through May 31, 2023.

Estimated time to complete this activity: 90 minutes.

HOW TO RECEIVE CREDIT

There are no fees for participating and receiving CME credit for this activity. Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central.

In order to receive credit, participants must complete the post-test and evaluation. You will be able to access your certificate of completion in Learning Central as soon as you complete the post-test with a minimum score of 70%. Your certificate will be available under "Transcript" for your records.

DISCLOSURE POLICY STATEMENT

All individuals in a position to control the content of this activity have disclosed their relevant financial relationships with commercial interests. Disclosures from the author(s) are listed below.

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CLINICAL DIALOGUE

Andrew Herber, PA-C: Hello, and welcome to this *Clinical Dialogue* and *eCase Challenge* program, "Dyslipidemia Management: Opportunities to Improve Patient Care." I'm Andy Herber, a physician associate in hospital medicine at the Mayo Clinic in Rochester, Minnesota.

Joining me in this conversation are two expert PA faculty, Viet Le and Dan Thibodeau. Viet is an Associate Professor of Research, cardiovascular researcher with Intermountain Health Heart Institute, Intermountain Healthcare in Murray, Utah and faculty at the Rocky Mountain University of Health Professions' PA program in Provo, Utah.

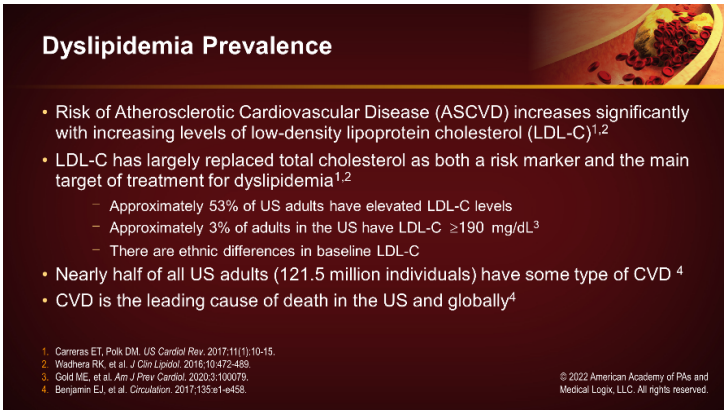
And Dan is an Associate Professor for the physician assistant and doctor of medical science programs at Eastern Virginia Medical School. My thanks to both of you for your participation in this important continuing medical education activity. Let's get started.

So, Viet, how common is dyslipidemia, and how does it affect the risk of cardiovascular disease?

Viet Le, MPAS, PA-C, FACC, FAHA: Well, let's address how common it is. Approximately 53% of U.S. adults, so that's nearly 100 million individuals have elevated low-density lipoprotein cholesterol, or LDL-C levels.

Three percent of adults in the U.S. have an LDL cholesterol greater than or equal to 190. Obviously, there's going to be some ethnic differences in terms of the baseline LDL cholesterol. But, you know, the risk of atherosclerotic cardiovascular disease, it increases significantly as LDL cholesterol also increases.

LDL-C, has largely replaced the total cholesterol as a risk marker and the main target for treatment for dyslipidemia in the guidelines.

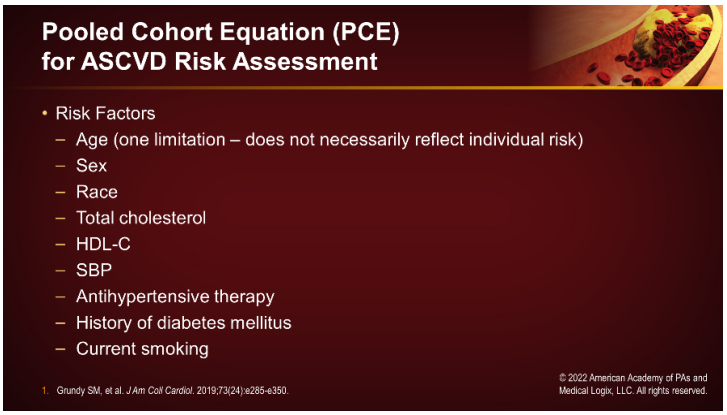


Andy Herber: Great. Dan, can you help us with some guidelines on that?

Dan Thibodeau, MHP, PA-C, DFAAPA: Sure. Well, Andy and Viet, it's a pleasure to work with you once again. So, when we think about risk of all of our patients, certainly we're going to think about ASCVD risk as our basis for looking at why we want to start therapy on individuals who have not had any CVD events in the first place.

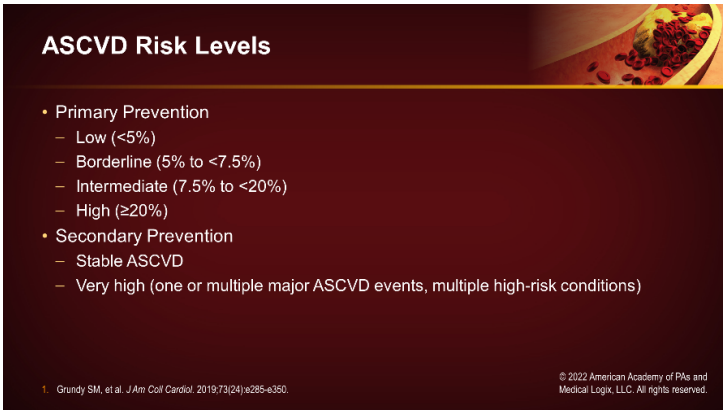
The 2018 Cholesterol Clinical Practice Guidelines allow us a recommendation that give us a 10-year risk assessment, and it's based on the traditional ASCVD risk factors. And we use this through what we call a pooled cohort equation, or PCE. You can reference this online to look at those risk calculators.

We have different risk factors, which include age, and that doesn't necessarily reflect individual risk, but sex, race, your total cholesterol, your HDL-C's, your systolic blood pressure, and then three important questions: Are you on any antihypertensive medicine? Do you have a history of diabetes? And do you smoke? And based on those factors, your patient will be given a risk profile, a 10-year risk assessment.

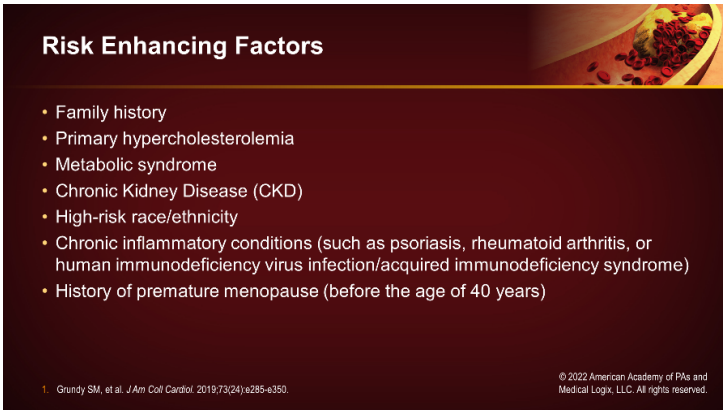


And so basically, the calculation will give us a percentage score. Anything below 5% is considered low risk. Five to just less than 7.5 is borderline. Seven and a half to less than 20 is intermediate. And then anything above 20% is considered high risk.

Now, for those individuals considered very high risk, these are individuals who already have documented one or multiple ASCVD events or they've had one major event with multiple high-risk conditions. And so those individuals we'll classify as very high already.



But we also have other risk-enhancing factors that we need to really talk with our patients about, family history, primary hypercholesterolemia, conditions like metabolic syndrome, chronic kidney disease, some individuals' race and ethnicity, African-American populations, Asians, Alaskan natives as examples.

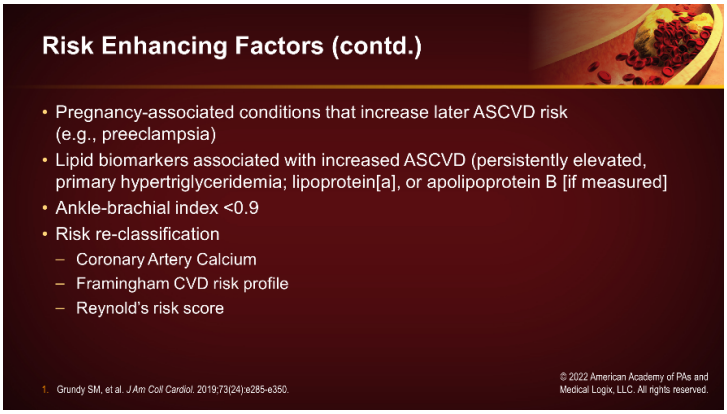


And then those individuals who have chronic inflammatory conditions. So, some of your skin conditions, like psoriasis, rheumatoid arthritis, HIV/AIDS.

We need to also think about women, those individuals who have a risk of premature menopause or they've had a pregnancy-associated condition that have increased their ASCVD risk. So an example of that would be the preeclamptic patient who's well documented during their pregnancy.

We also have to think about individuals that have lipid biomarkers that are associated with an increased ASCVD risk. We're talking about persistently elevated primary hypertriglycerides, elevated levels of C-reactive protein, lipoprotein A or apolipoprotein B, or if they've had an ankle-brachial index of less than 0. So those are some other individuals that have an increased risk.

We can use reclassifications using coronary artery calcium measurements. And then there's other risk calculators that we can use. Just to name a couple, the Framingham CVD Risk Profile and the Reynolds Risk Score are very similar to the pooled cohort scores where you're inserting certain factors related to risk, and then it'll pop out a 10-year risk level.



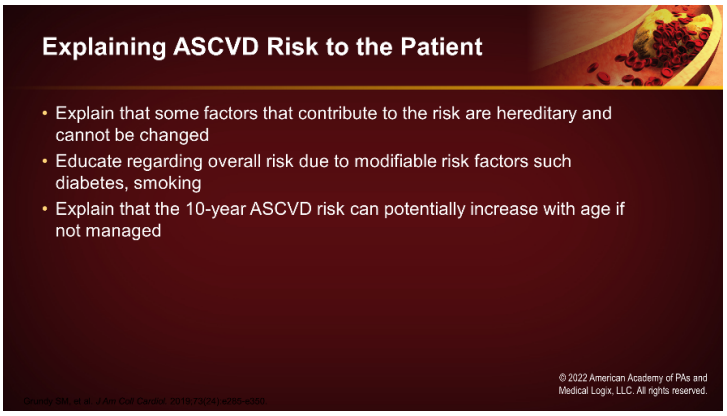
Now, all of these guidelines for the primary prevention of cardiovascular disease are very well outlined in a 2019 American College of Cardiology/American Heart Association publication. And they really address the patient comprehensive approach to things like lifestyle, your estimated risk of ASCVD and when to decide on initiating pharmacotherapy.

Andy Herber: Dan, thanks for breaking that down for us. Can you kind of further explain how you explain risk to your patient?

Dan Thibodeau: Sure. Well, one of the things that I tell patients often is, there are some things that are just not your fault. There are just factors that you were born with, and there's nothing we can do about it.

You really have to educate them on the effects of overall risk because they have diabetes, smoking history, those types of modifiable risk factors we can really educate the patient on, and then talk about some of their other disease patterns that they have that we can try to at least improve on.

When it comes to the overall idea, though, of explaining risk, one of the challenges is actually really educating the patient and letting them know that as each year progresses, and they have a 10-year risk score of a certain percentage, each year they have that risk, and there is the potential for that risk to increase as they get older. That's certainly true if none of their other risk factors or their modifications have changed at all. It actually worsens.



We can say, "Well, we can't do anything about your sex or your race, but we certainly can work on lowering your blood pressure, getting your HDLs improved and your overall total cholesterol at a more appropriate level."

Andy Herber: So, Viet, there's got to be some benefits to lowering LDL cholesterol, right? And then do we have any guidelines in primary prevention as far as lowering LDL cholesterol?

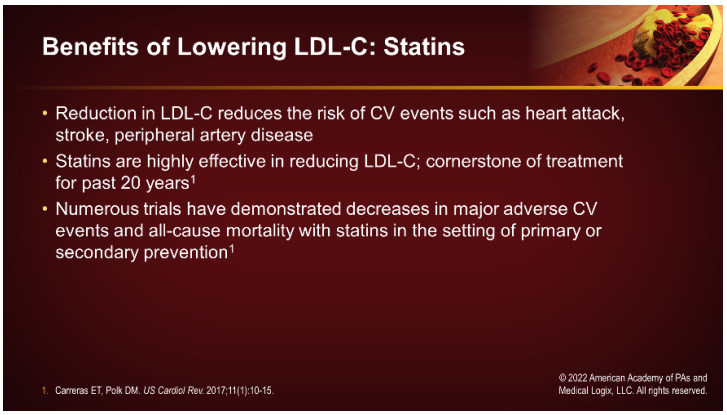
Viet Le: Yes. The same guidelines that Dan spoke about with regards to the 2019 cholesterol guidelines, ACC/AHA, discusses really how to approach this in primary prevention. But what are the benefits?

I mean, I tell my patients that LDL cholesterol is the framework of atherosclerosis, plaque. You can't have plaque or atherosclerosis unless you have an abundance or enough LDL cholesterol.

So the benefit of lowering LDL cholesterol is really striking at that risk of heart attack, of stroke, of peripheral arterial disease, the things that LDL cholesterol tends to help create in our bodies.

So, the current guidelines based on doing risk stratification, whether someone's eligible or has enough risk for developing atherosclerosis. Looking at lowering cholesterol, it really starts with the gold standard of statin therapy.

So, statins are the mainstay of treatment, and have been so for over 20 years. They're highly effective in reducing LDL cholesterol in primary prevention, as well as secondary. Leading to relative risk reductions by up to 30%. Although it must be acknowledged that 70% residual risk remains, even with the gold-standard statin therapy.

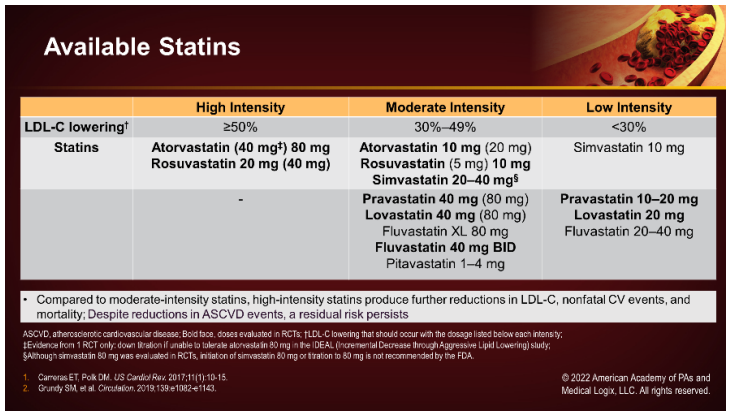


So, statins are really just the starting point of optimizing reduction of atherosclerotic cardiovascular disease events, or ASCVD.

The available statins on the market now include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. So there are numerous trials that demonstrate reduction

in major adverse cardiovascular events, often you'll hear it called MACE, and allcause mortality.

Low-intensity statins reduce LDL cholesterol by just under 30%, or less than 30% on average. Moderate-intensity statin therapy, by comparison, generally reduces cholesterol between 30 to 49% from their baseline. And then lastly, high-intensity statin therapy reduces LDL cholesterol by at least 50% or greater on average.



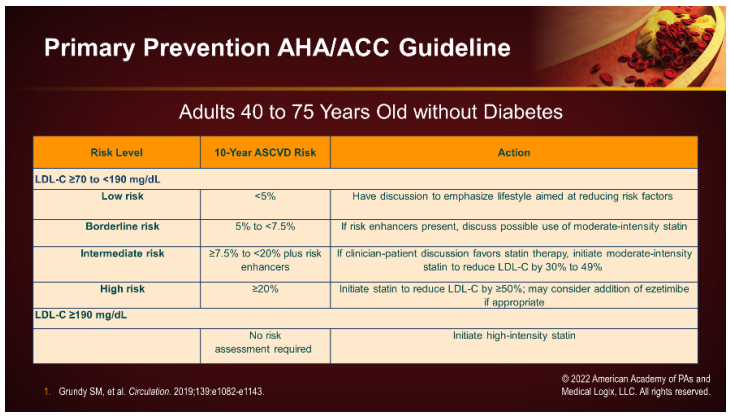
So it's important to note that, compared to low- and moderate-intensity therapies, high-intensity statins further reduce LDL cholesterol, nonfatal cardiovascular events and mortality events. So, decreases in LDL cholesterol reduce the risk of nonfatal as well as fatal cardiovascular events. That's an important point to recognize.

And we look at LDL cholesterol. When you lower it, you also lower those events in primary as well as secondary prevention. And it works across the broad range of baseline risks and LDL cholesterol levels. So, again, you know, my example of 70 versus 170, if you have an event with those baseline therapies, any reduction in cholesterol by those percentages reduced risk further.

So, the guidelines set a range or a threshold for LDL cholesterol. And really, it's important to look at stable cardiovascular disease versus high-risk. And these are individuals that have had an event and then a second event and/or they happen to have had a heart attack or a stroke and have multiple risk factors that places them at a much higher risk for having a second or third or fourth event.

So these thresholds are set both in primary and secondary prevention.

Now, in the primary side of prevention, those folks that have an LDL cholesterol that begins or is baseline greater than or equal to 190, they also have a target for an LDL cholesterol less than 100.



In secondary prevention, when you're looking at stable cardiovascular disease, you want at least an LDL cholesterol reduction of greater than or equal to 50% from their baseline. And that's a class 2B to further reduce it to less than 70 mg/dl.

In the very high-risk cardiovascular disease folks, it is class 2A, so it moves up a level in terms of indication, to target an LDL cholesterol to less than 70. And that really means before adding non-statin therapies, which we'll discuss a little bit down the line here.

So, in primary prevention, when you look at ages, what do we do with folks that are between 20 to 39 years of age? Well, you estimate that lifetime risk of ASCVD or atherosclerotic cardiovascular disease.

Well, you know, as Dan spoke about, in the 2019 guidelines, you estimate a lifetime risk of ASCVD, or atherosclerotic cardiovascular disease, and use that pool cohort equation. If they happen to have an elevated lifetime risk, you encourage lifestyle aimed at reducing risk. But honestly, I would say encourage lifestyle in all folks.

You consider statin therapy, however, beyond lifestyle if they have a family history of premature atherosclerotic cardiovascular disease.

Then we look at the main categories of primary prevention, and these are folks that do not have diabetes but are aged 40 to 75 years. And really, everyone should be engaged in a discussion concerning risk, because this is when it begins, or at least we see the majority of events. And you discuss this before starting treatment.

Obviously, it becomes important in shared decision-making and informing the patient. But you review those major risk factors that Dan spoke of before, such as smoking or elevated blood pressure or LDL cholesterol.

And then addressing that pooled cohort equation, you look at that 10-year risk of ASCVD. And if it happens to be in that borderline range where it's less than 7.5% but greater than 5%, you look at those risk-enhancing factors and decide whether or not risk is high enough to consider statin therapy.

So, really, you want to address those calculated 10-year risks using that pooled cohort equation. If they happen to fall into that borderline range of less than 7.5% but greater than 5%, you look at those risk-enhancing factors as a way to decide whether or not someone requires statin therapy or is eligible.

Discuss the potential benefits of lifestyle modifications. But I think that that's fair in anyone that you address in primary care or in cardiovascular space. But looking at the statins, you really want to understand, well, actually, help the patient understand risk versus benefit, because there are going to be potential side effects or adverse effects, drug-drug interactions, and you want to make sure that the patient feels comfortable benefits far outweigh any risk or adverse events that could happen.

If their LDL cholesterol's greater than or equal to 70, but just under 190 looking at those ASCVD risk scores again, low risk, less than 5%, those individuals really aren't eligible for statin therapy, or they're at low enough risk that they may still decide to use it, but the benefit is lower.

When we look at borderline risk, so those are the individuals with, you know, risk-enhancing factors might make the difference, but they're calculated between 5 to less than 7.5%. So discuss the possible use of moderate-intensity statin therapy. It may make sense in someone that has a family history of early coronary disease or who smokes.

When you look at intermediate risk, this is by and large the biggest group of individuals. When they hit greater than or equal to 7.5% but fall just under 20%, then these individuals really in a patient-clinician discussion, a moderate-intensity statin therapy makes the most sense for these individuals to reduce their events. And really, you want to shoot for an LDL cholesterol between 30 to 49% reduction.

Finally, there's the high-risk individuals. To reiterate Dan's discussion before, high risk is greater than or equal to 20%. And these individuals, really we should have a discussion of high-intensity statin therapy to reduce LDL cholesterol by at least 50% and greater.

Finally, circling back to patients with a baseline LDL cholesterol of greater than or equal to 190, the discussion is initiating high-intensity statin therapy.

A third group that the 2019 guidelines address in primary prevention are those individuals with diabetes. The mainstay of the guidelines for diabetes is 40 to 75, and in LDL cholesterol, greater than or equal to 70.

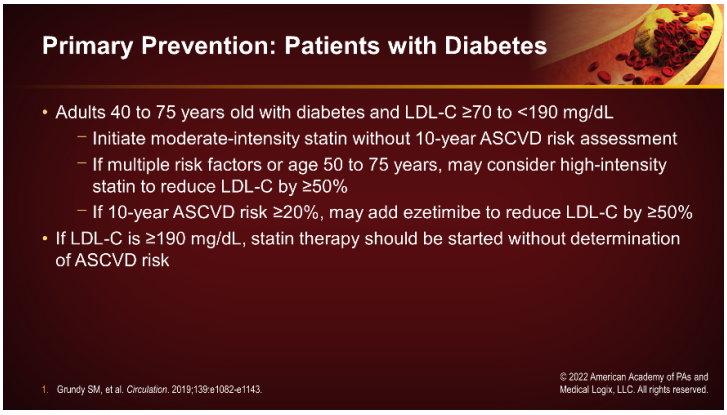
These folks really should start on a moderate-intensity statin therapy without doing a pool cohort equation or ASCVD risk assessment.

If they have multiple risk factors and/or they've reached the age of 50 to 75, you know, you can consider high-intensity statin therapy to reduce LDL cholesterol to greater than or equal to 50%.

So, again, the main point with primary prevention, I always have to come back to those folks with LDL cholesterol greater than or equal to 190. Because many of them are unaddressed, they will have these higher cholesterol levels, but do not have statin therapy.

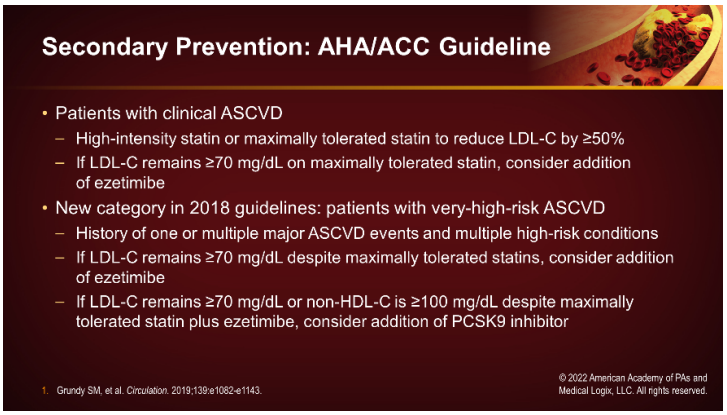
The guidelines are very clear on this. You don't have to do risk assessment. Just initiate high-intensity statin therapy. And if their LDL remains greater than or equal to 100, remember that threshold, then consider adding ezetimibe.

And other part of that is, if the LDL cholesterol's greater than or equal to 100, and they're already on a statin and ezetimibe, then really consider adding a PCSK9 inhibitor.



For the secondary prevention these are those that have clinical atherosclerotic cardiovascular disease, they've already had a heart attack or they've had symptoms that led to revascularization, so stent or bypass, they may have had a stroke, or they have peripheral arterial disease.

Now, the newest category that was added in the 2018 and 2019 guidelines for statin therapy or cholesterol management was really the very high-risk atherosclerotic and cardiovascular disease patients.



Andy Herber: Great, Viet. That's awesome. My question to you, though, and a little bit of follow-up here is, people are nervous about heart attacks and strokes. So, if we're shooting for under 70, somebody might say, "Hey, why can't I be at 20?" Is there too low of LDL cholesterol, how do you counsel that patient who, you know, essentially wants to be bulletproof by taking statin therapy?

Viet Le: No, that's actually a very, very good question. It's a pragmatic clinical question. And really, the FOURIER trial with a PCSK9 inhibitor has answered that and continues to answer that. There were 500 individuals in that trial that had maximally tolerated statins plus/minus ezetimibe, and then the PCSK9 inhibitor. And many of these individuals, 500 of them, reached an LDL cholesterol less than 20.

And they've now been followed nearly four years. They did an initial report at two and a half, and there's no complications, at least cognitively or metabolically, for having an LDL cholesterol artificially achieved to that level.

Dan Thibodeau: To dovetail off that, Viet, part of that extension of the FOURIER trial was EBBINGHAUS that actually looked at overall cognition in individuals that received PCSK9s with a LDL-C lower than 50. And there was no change in cognition even with low numbers.

Andy Herber: So, Dan, despite, how great these statin therapies are, sometimes it's not enough for patients. Can you talk about those?

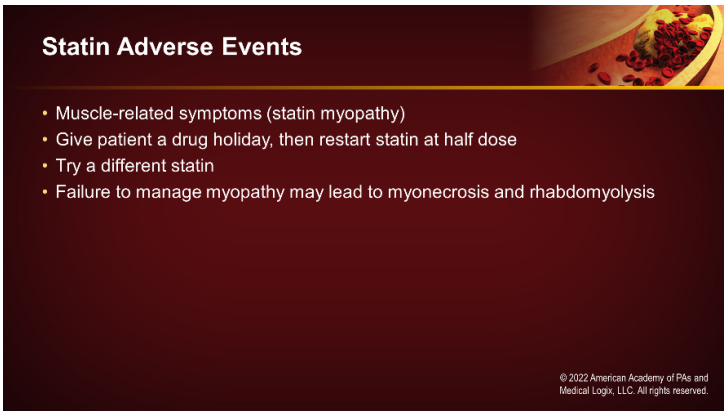
Dan Thibodeau: Right, Andy, there are. Despite maximally tolerated statins, patients have up to at least a 70% risk of ASCVD still, even though they're on statins.

And so up to two-thirds of cardiovascular events still can occur in these types of individuals. And many are at high risk for cardiovascular disease who don't always achieve that LDL-C target that we look for.

One of the things that we need to remind ourselves on when we initiate statin therapy is to look for the adverse effects. And specifically, with statins, we want to make sure we look for that muscle-related symptoms, that statin myopathy.

Most of the time, we recommend drug holidays, take them off of it, reinitiate it after a month or six weeks, and see if that is truly an adverse effect related to the statins.

If it is, we might need to consider lowering the dose. But if it's severe enough, if we start getting more than just muscle soreness and we start getting myalgias, myositis and, worst-case scenario, rhabdomyolysis, which is rare, then we would need to stop this and look for alternative therapies.



Some individuals may just have to try a different statin. The pharmacological properties are a little bit different, and so some individuals may do better with atorvastatin versus simvastatin versus another pharmaceutical option in that regard.

So I think we have to explore other reasons why individuals might have adverse effects or just symptoms that we may associate to statin muscle-associated pain.

Andy Herber: So, guys, when you talk about the muscle-associated pain, do you check a CK or an AST or an aldolase or something? Or is it just kind of purely diagnosed from clinical judgment?

Viet Le: When it comes to folks that come in with myalgias, I do a very intensive history-taking on this. I don't often order a CK for this, you chase down what's causing the CK, and it's not statin. There's something else driving that.

Dan Thibodeau: I think the vast majority of people who have had the complaint of muscle-related pain that you suspect might be related to statins, it's usually more on the mild side. It usually doesn't bump their liver enzymes that much, if at all.

I think you just have to have a practical approach, stop the statin, follow the symptoms and then reintroduce the statin at a different time or at a lower dose.

Andy Herber: Great. Thanks. So, guys, what about the patients that come into your office that are maybe statin-averse or have had complications with statins in the past, and they have high LDL they're high risk? There's got to be other options other than statins, right?

Dan Thibodeau: Well, Andy, there's a combination of the use of statins as well as non-statin drugs that are recommended as part of these guidelines that have been well established and published, the most recent one being in 2019.

But the overall use of combination therapy is actually quite low. And so only about, up to maybe 9% of the population is on a combination therapy, and so we probably don't do as good of a job as we could in using more than one drug for the reduction of our LDL.

So, currently, what we have related to non-statin therapies include ezetimibe, which is a cholesterol absorption inhibitor. We have our two PCSK9s, alirocumab and evolocumab. And these are antibodies that are directed against the PCSK9 marker. There is inclisiran, which inhibits PCSK9 synthesis, and bempedoic acid, which inhibits the cholesterol biosynthesis.

So, Viet, we know that there are guidelines that are related to non-statin therapy, and I'll let you talk a little bit about that. And then we'll go through some of these drugs.

Viet Le: Usually it's moderate-intensity statin therapy that can be increased to high-intensity, and then adding ezetimibe. Those two really by and large can get most people under 100 mg/dl, and in those with cardiovascular disease, at least close to the 70 mg/dl mark and lower.

Secondary cardiovascular disease prevention, if it's not achieved by statin alone, and that LDL cholesterol is still greater than or equal to 100, it makes sense you would add ezetimibe or a PCSK9 inhibitor to get that LDL cholesterol to below 100 for most, but again, class 2B is to drop that less than 70 mg/dl. That's probably the most important in very high risk ASCVD.

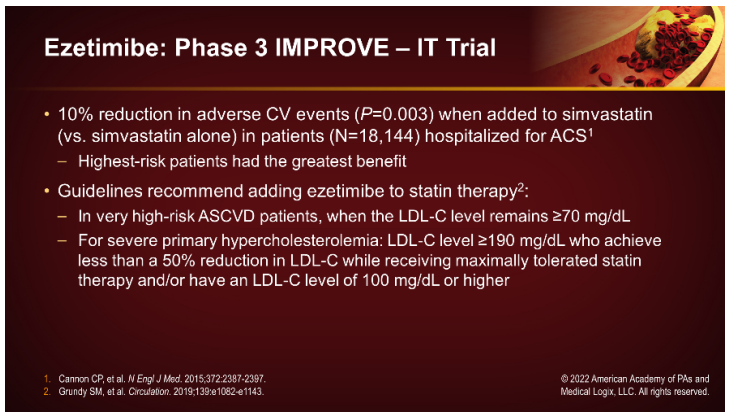
So coming back to ezetimibe, ezetimibe showed in the IMPROVE-IT trial, which was really compared to simvastatin alone, right, so simvastatin versus simvastatin with ezetimibe.

We saw a further 10% risk reduction that was relative. And that was statistically significant.

Any LDL concentrations that were below those recommended levels, really occurred without any incremental increase in adverse effects.

So based on that, really, the guidelines recommend adding ezetimibe as first-line, non-statin therapy to high-intensity statin therapy. LDL remains greater than or equal to 70.

And then that group of primary prevention folks, where their cholesterol was greater than or equal to 190 at baseline, you don't need to calculate the risk for those individuals, as we've previously stated, but adding ezetimibe is helpful in those individuals.



So I'll turn it over to Dan, the PCSK9 inhibitors and those data.

Dan Thibodeau: Right. And so as Viet said, we still have those individuals that are either not maximally at the level we want them to be, they have primary and secondary prevention numbers that are just not there, or we still have individuals with high risk, and we have not achieved it with our maximally-tolerated statin, as well as ezetimibe.

So the other option that we can add to this are the PCSK9 inhibitors. And they have become particularly important with our patients who have that higher-risk profile, or we just haven't gotten there to LDL levels below 70. Or like I mentioned before, they are on a maximally-tolerated statin plus ezetimibe but we still haven't quite lowered their overall cholesterol LDL levels below 70.

And so, let me talk about a couple of these, the alirocumab and evolocumab. Start with alirocumab. This, like evolocumab, PCSK9s, briefly, will adhere to the PCSK9 receptor site. That allows the LDL cholesterol globules to absorb into the hepatocyte for a rapid reduction of LDLs. And so, they work very effectively.

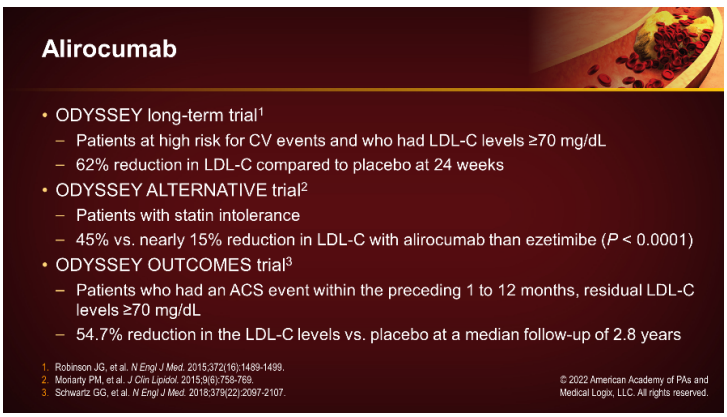
These are injection therapies for both.

So individuals were placed into all kinds of different studies. One in particular was the ODYSSEY LONG TERM trial with alirocumab. And this showed a 62% reduction of LDL-C levels when compared to placebo at 24 weeks.

And at 78 weeks, this significantly lowered the incidence of major CV events when we compare it to placebo.

There is also the ODYSSEY ALTERNATIVE trial. And these were with individuals that had statin intolerance. And so, patients either got alirocumab, ezetimibe, or atorvastatin. And the results showed a significantly reduced LDL-C with alirocumab compared to ezetimibe. We're talking 45% versus nearly 15%, when compared to the ezetimibe trial.

Additionally, there was the ODYSSEY OUTCOMES trial, and those are individuals who had an ACS event within the last one to twelve months prior to the initiation of therapy. They had residual LDL levels greater than 70, and non-HDL levels greater than 100. They also had the possibility of apoprotein-B levels greater than 80. And this was after at least two to sixteen weeks of maximally-tolerated therapy with either atorvastatin or rosuvastatin so those are your high-intensity statins.

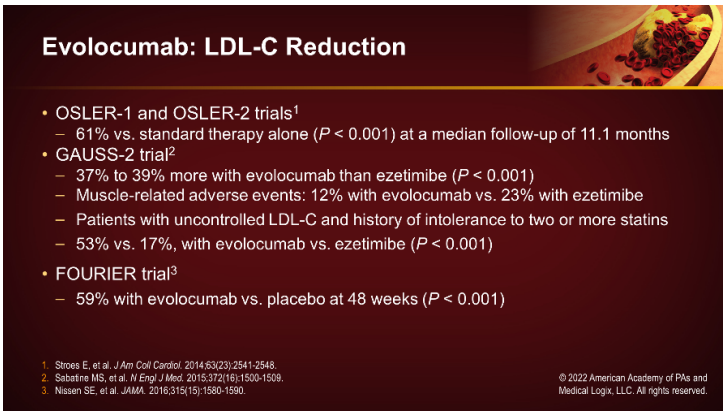


So, the follow-up median was almost three years, and it showed close to a 55% reduction of overall LDL levels.

One of the other PCSK9s that came out during the same year in 2015 was evolocumab. Multiple studies through this as well with equal promising numbers, similar to alirocumab. You had the OSLER trials 1 and 2, which used evolocumab, standard therapy, or alone. And the follow-up after just under a year, reduced the LDL-C levels by 61%.

The GAUSS-2, which was a phase three trial for statin-intolerant patients, once again, LDL-C reduced by 37 to 39% more than with evolocumab than ezetimibe alone. Muscle adverse events were only 12% with evolocumab and 23% with ezetimibe.

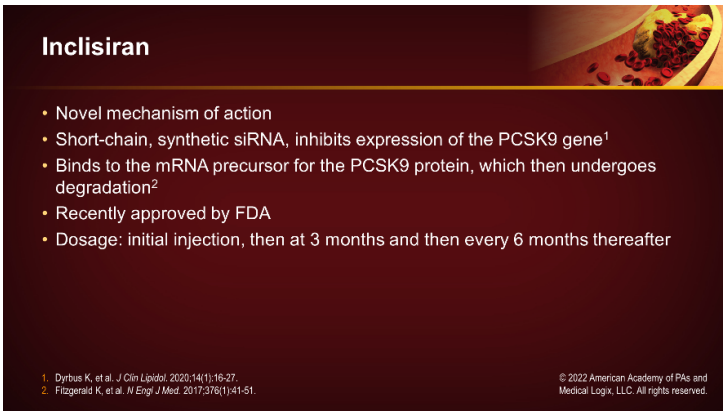
So, there are other multiple studies that were done with evolocumab. FOURIER trial, which Viet mentioned earlier, 27,500 patients with ASCVD disease, as well as LDL-C levels greater than 70, with patients being on maximally-tolerated statins. And you had a 59% reduction of LDL-Cs with this trial as well.



I mentioned also the EBBINGHAUS trial, looking at the issue of reduction in cognition, which did not show to be statistically significant with the lower levels.

So Viet, I know you're going to talk about inclisiran and I'll let you go ahead and explain that.

Viet Le: So, when we look at inclisiran, this is a small interfering RNA. So it's not a monoclonal antibody, but it does affect PCSK9. PCSK9 interferes with the LDL receptor; it binds on it and degrades the LDL receptor.



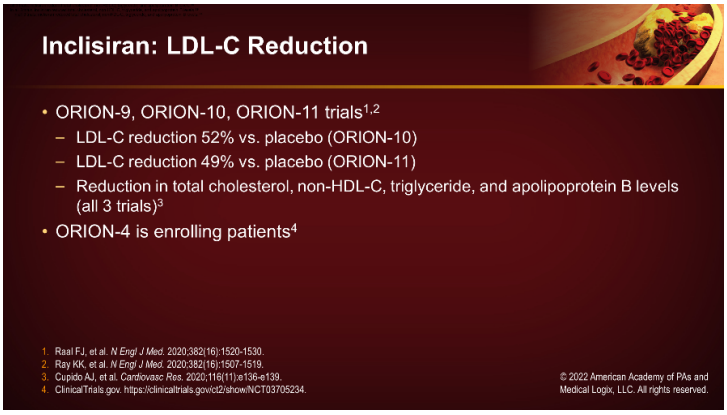
And so, in the same vein as alirocumab and evolocumab, when you affect PCSK9 synthesis, you see the very similar reductions in LDL cholesterol as with ODYSSEY and FOURIER. So, you know, going through the ORION-9, the ORION-10, the ORION-11 trials, I was a sub-investigator on the ORION-10 and still a sub-investigator on the ORION-4 trial, which is an outcomes trial.

What we saw was very just extraordinary reductions in LDL cholesterol, in this case, 52% versus placebo, and that's in the ORION-10. In the ORION-11 trial, 49% versus placebo.

It's an injection that occurs once every six months, other than the initial start of that medication, which requires a 90-day kind of a booster.

We don't have an outcome trial just yet; ORION-4 is still enrolling.

Inclisiran is now FDA approved as of December 2021 and was previously approved in Europe in December 2020.



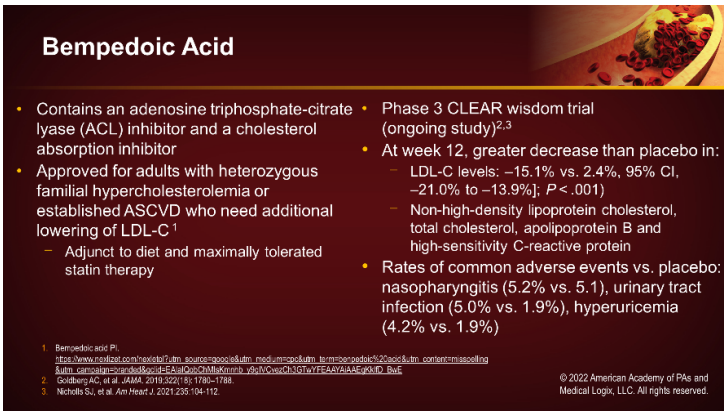
And then lastly, now we have bempedoic acid, and I'll turn that over to Dan.

Dan Thibodeau: And this was approved for the treatment of adults who have heterozygous familial hypercholesterolemia, or that they have established ASCVD. And these are individuals who require the lowering of the LDL, on top of their diet, as well as a maximally-tolerated statin therapy.

So this was evidenced through the CLEAR WISDOM trial.

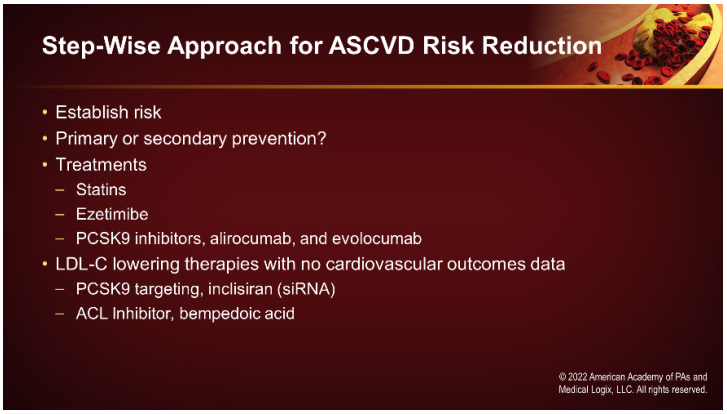
And the primary outcome showed that from a 12-week baseline, was a reduction by 15% compared to 2.4% with placebo.

One thing I will add about bempedoic acid is that the side effects are similar to PCSK9s, where nasopharyngitis, possible urinary tract infections. One thing that's a little bit different with bempedoic acid is hyperuricemia, so you'd have to be careful in individuals that may have higher uric acid levels, your patients who have gout may not be optimal patients for these medications.



Andy Herber: What's the stepwise approach here? You can't add it all at one time. You add one, check their labs again in three months, then add another one, or is it shorter duration than that?

Viet Le: It's an important question. I think, first of all, again, establish risk. Is there primary prevention or secondary prevention? It's statin, ezetimibe and then consider the PCSK9 or inclisiran. And then bempedoic acid actually kind of falls last on my list only because I think, you know, we're still waiting for clear outcomes or clear wisdom.



Dan Thibodeau: Yes, and I think having a methodical approach is definitely what we want to try to accomplish here.

Of course, we're doing this with the understanding that these are not the only medications that they're being treated for. They have hypertension, they have diabetes, they have other diseases that they obviously are getting medicines for as well, so we have to be cognizant of that bigger picture.

Andy Herber: Viet, we talked all about how great these medications are. Any reasons why patients aren't adherent to these strategies, if they can essentially save their lives?

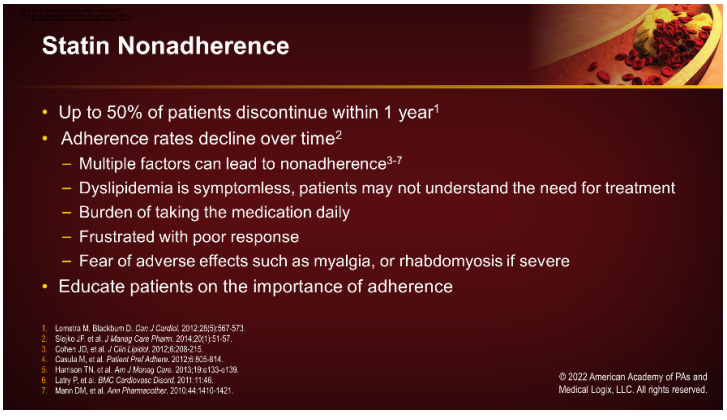
Viet Le: It's unfortunate that the adherence rates are so low. Up to half, 50% of patients discontinue their statins within that first year. And that's regardless of whether they've had a heart attack or stroke, or this is just primary prevention.

And that adherence rate continues to decline over time. I think perhaps there's a missing educational gap there that leads to a patient discontinuing a medication because they just don't understand what it's for and what it's doing for them. Maybe they understand the risk, but it's just too low, it's stacked against taking this medication once a day indefinitely.

We have to do a better job of educating our patients on the mechanisms of LDL cholesterol, the events that are of importance, and then how our statin therapies or lipid-lowering therapies address that.

They may be frustrated with poor therapeutic response. Maybe the side effect profile is much higher than any perceived benefit.

They may forget their medications.



Fear of adverse events, I think is actually pretty high. We have to address those perceived fears of events, or adverse events.

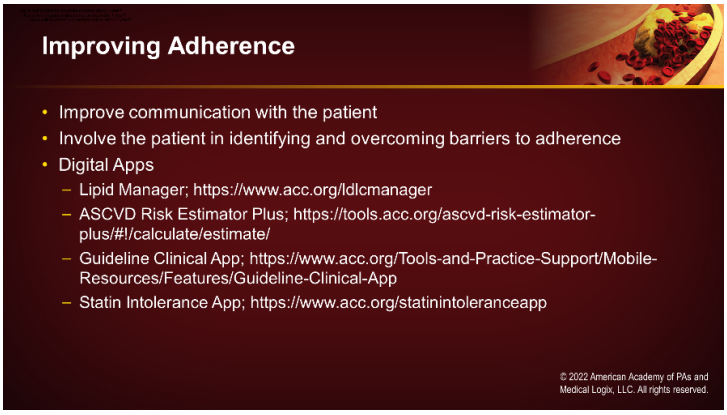
Dan Thibodeau: It reminds me of a quote I use from C. Everett Koop, when he said, "Drugs don't work in people who don't take them." And so we have to really educate patients on the importance of adherence, and really have a frank discussion with them as well about why they want to discontinue.

There was a retrospective, real-world study, when they looked at alirocumab or evolocumab versus statins, a small study with 34 patients, but it showed that the adherence rate for PCSK9s was 79% compared to 31% in the statin group. They took those individuals about two more, 238 patients receiving PCSK9s and they had patients who had required additional therapy despite being on statins and ezetimibe, and they followed up at 17 months, and no patients discontinued the PCSK9 inhibitor.

Andy Herber: Is there anything that patients can do to help with adherence or to help kind of keep them on track?

Viet Le: The neat part about this digital age is that we have a lot of apps, you know, "there's an app for that." In this case, the American College of Cardiology has created several useful apps.

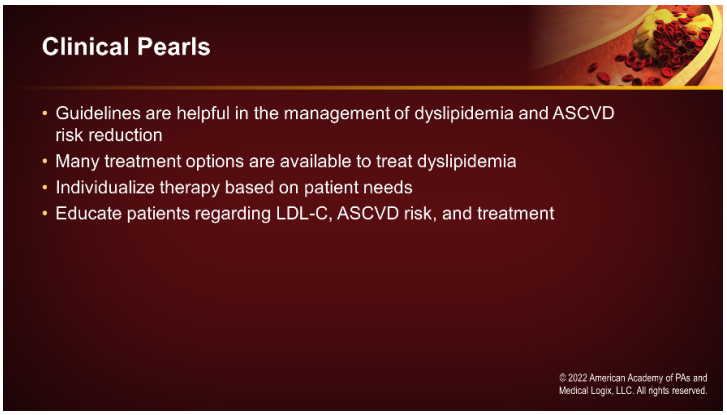
There are others outside of the American College of Cardiology, but the ones that we've, you know, both Dan and I have used include the LDL Cholesterol Manager, ASCVD Risk Estimator, the Guideline Clinical App, and the Statin Intolerance app. These are helpful for both clinicians and patients. I encourage my patients to download these apps so they can also see what kind of scoring or calculation we do as clinicians.



Andy Herber: Awesome. This has been an outstanding conversation. I appreciate both of you guys taking the time. Is there any kind of words of advice, or some pearls for maybe a new graduate PA, or someone who's changed professions and now is in the clinic? Is there something you want them to know going forward? You know, what are your take-home points for them?

Dan Thibodeau: Yes, very, very simple recommendations. First of all, guidelines are there for a reason. They're very helpful. I would get to know what those guidelines actually say and recommend. It is very algorithmic, very helpful in the management of dyslipidemia and ASCVD risk reduction.

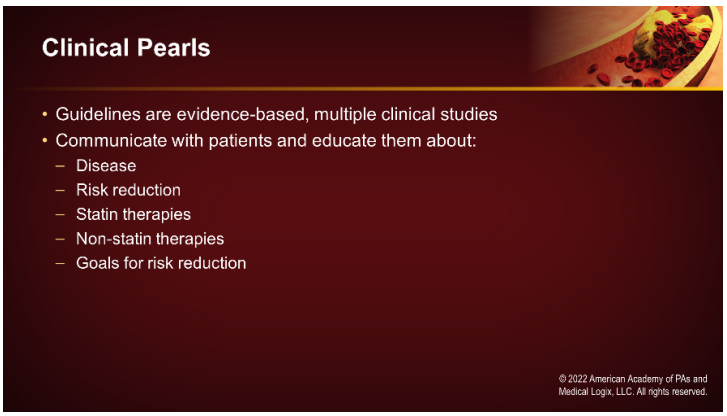
And just that, hey, look, we all recognize there's a lot of tools in this toolbox and it's just really understanding how to use those tools effectively for each individual patient and what works for them. For some, it can be just statins, and others it can be multifactorial reasons for why we choose the therapies for our patients. But at the end of the day, it's a very simple fundamentals of education, education, and education on the patient.



Viet, what are your thoughts on that?

Viet Le: No, I think you hit it right on the mark. You know, I think start with the patient in front of you. As you said, the guidelines have a lot of brilliant minds put together, looking at multiple, multiple research and clinical studies. And so, they're well set.

But to your point, educate. As the patient understands the disease and/or the risk of disease, then they may ask, "Well, how do I reduce that risk?" And that facilitates a better conversation regarding statin therapies, non-statin therapies, and what goals should be set going forward to reduce their risk.



Andy Herber: Fantastic stuff. Well, I'd like to thank both of our expert faculty, Dan Thibodeau and Viet Le, for their great insights and discussion. And I would like to thank you, the best virtual audience ever, for participating in this *Clinical Dialogue*.

CLINICAL PEARL

The risk of atherosclerotic cardiovascular disease, ASCVD, increases significantly with dyslipidemia, which is marked by increased levels of LDL cholesterol. Lipid-lowering therapies can reduce elevated LDL cholesterol and can lower the risk of cardiovascular disease and related events.

PAs should be familiar with the clinical practice guidelines for lipid-lowering therapies. As the first step, guidelines recommend assessing ten-year ASCVD risk, calculated by assessing ASCVD risk factors and using the Pooled Cohort Equation, or PCE, as a starting point.

You should review the family history and medical history with the patients and should recommend lifestyle modifications.

In terms of pharmacologic treatment, statins have been the standard therapy for lowering LDL cholesterol in primary and secondary prevention. The dose and type of statin will depend on the patient's age, risk factors and baseline LDL cholesterol levels.

Nonadherence is a significant problem. Due to nonadherence, patients may not benefit fully from treatment. PAs should be mindful that some patients can be intolerant to statins due to adverse effects, such as statin myopathy, or are unable to take the required dose and will need other treatment options.

Guidelines recommend a combination of statin and non-statin therapies that include agents that have different mechanisms of action. PAs can help patients to achieve maximum treatment benefits by communicating with them, using strategies to promote adherence and involving them in shared decision-making.

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eCASE CHALLENGE

Introduction

This *eCase Challenge* will examine key considerations in the management of dyslipidemia, particularly with regard to the recommendations specified in the 2018 guidelines from the American Heart Association/American College of Cardiology (AHA/ACC).

Case Presentation

Alex is a 49-year-old Caucasian male, and a news anchor at a local TV station. He works long hours, including late nights and weekends. He has a 14-year-old daughter and a 9-year-old son. Lately he has been feeling tired and has often felt out of breath when walking to work, which he attributes to his long days and lack of sleep. He often eats a quick lunch at his desk and does not exercise. His wife has often insisted that Alex should see a doctor since his last annual check-up visit three years ago.

Upon evaluation, his medical history, and physical and laboratory assessments reveal the following:

Biometrics:
- Height: 5 feet 7 inches
- Weight: 180 lbs.
- BMI: 27.1 kg/M²

Vital Signs:
- Resting pulse: 82 bpm
- BP: 130/88 mmHg
- Respirations: 15/minute

Pertinent Laboratory Results:
Total cholesterol = 210 mg/dL
Low-density lipoprotein (LDL-C) = 165 mg/dL
High-density lipoprotein (HDL-C) = 40 mg/dL
Triglycerides (TG) = 180 mg/dL
A1c = 5.9%

Past Medical History:
- None

Past Surgical History:
- None

Family History:
- Mother (74-years old): Osteoarthritis
- Father (76-years old): Diabetic, suffered an MI when he was 65 years old.
- Brother (60-years old) diagnosed with type 2 diabetes at 58 years of age.

Social History:
- Smoker (1 pack/day since 20 years of age, 29pk/yrs.)
- Alcohol use: moderate (2 drinks per day)

Current Medications:
- None

Known Allergies:
- None

Case presentation continues

Alex is advised about improving his eating habits and is encouraged to exercise regularly. Smoking cessation is recommended and benefits and therapies are discussed. He is given information on the details of the AHA/ACC recommendations for a healthy diet, which emphasize intake of fruits, vegetables, whole grains, and healthy sources of protein. AHA 2017 HTN guidelines are discussed in reference to his blood pressure today (meets stage I, ≥130/≥80) and he is asked to keep a daily blood pressure diary. He is also made aware that his A1c of 5.9% suggests pre-diabetes and that following the recommendations for improving his healthy lifestyle habits (i.e., healthy diet and exercising more regularly) will help reduce his risk of developing diabetes. He is counseled that taken together, his triglycerides, blood pressure readings, and elevated A1c suggest metabolic syndrome. Based on Alex's overall evaluation and laboratory reports, his clinician decides to start moderate intensity statin therapy. Alex receives educational material on stopping smoking. He is given a follow-up appointment after six weeks.

Question 1

Which of the following statements is correct regarding ASCVD risk assessment?

A. Age is the primary determinant of ASCVD risk level in individuals 40 to 75 years old
B. 10-year ASCVD risk of 7.5% to <20% is considered borderline risk
C. ASCVD risk assessments in patients 40 to 75 years old should consider the calculated 10-year risk and the presence/absence of family history
D. Risk assessment is unnecessary in patients who do not have ASCVD

The correct answer is C.

Although age is a risk factor used in the calculation, it does not necessarily reflect the total individual risk.

Compared to the previous 2013 guidelines from AHA/ACC, the latest 2018 guideline recommendations emphasize more personalized and detailed approaches for assessing the risk of ASCVD in individual patients. Guidelines note that for adults 40 - 75 years of age, 10-year risk assessment should be performed by using pooled cohort equation (PCE), and by reviewing major risks that include family history. Risk-enhancing factors include:

- Family history of premature ASCVD (males, age <55 y; females, age <65 y)
- Primary hypercholesterolemia
- Metabolic syndrome (three or more of the following):
    - Increased waist circumference
    - Elevated triglycerides (>150 mg/dL)
    - Elevated blood pressure
    - Elevated glucose
    - Low high-density lipoprotein cholesterol
- <40 mg/dL in men
- <50 mg/dL in women
- Chronic kidney disease
- Chronic inflammatory conditions (for example, psoriasis, rheumatoid arthritis, or human immunodeficiency virus) or acquired immunodeficiency syndrome
- History of premature menopause (before 40 years of age)
- Pregnancy-associated conditions that increase later risk of ASCVD (for example, preeclampsia)
- High-risk race/ethnicities (for example, South Asian ancestry)
- Lipid biomarkers associated with increased risk: persistently elevated primary hypertriglyceridemia and (if measured) elevated high-sensitivity C-reactive protein ≥2.0 mg/L,

lipoprotein(a) ≥50 mg/dL or ≥125 nmol/L, or apolipoprotein B ≥130 mg/dL, or ankle-brachial index <0.9

Levels of 10-year ASCVD risk are defined as:[1]

- Low risk: <5%
- Borderline risk: 5% to <7.5%
- Intermediate risk: 7.5% to <20%
- High risk: ≥20%

Patients with persistent, moderate hypercholesterolemia (LDL-C levels of 160 to 189 mg/dL) may be candidates for cholesterol-lowering drugs. Statin therapy should be considered if the individual has an LDL-C ≥160 mg/dL and a family history of premature ASCVD, or very high LDL-C (≥190 mg/dL).

For younger patients (20-39 years of age), the lifetime risk of ASCVD should be calculated to encourage adoption of a heart-healthy lifestyle designed to reduce risk. For individuals without ASCVD, traditional risk factors should be evaluated every 4 to 6 years.[1]

For patients with diabetes who are 40 to 75 years old and have LDL-C ≥70 to <190 mg/dL, moderate-intensity statin should be started without an ASCVD risk assessment.[1]

Case presentation continues

At the follow-up appointment, laboratory work up shows that Alex's LDL-C level has not changed much since his last visit. Alex admits that he has not been taking the statin as regularly as he should have. He has sore muscles but mentions that it could be due to the fact that he has started to go to the gym. His clinician re-iterates LDL-C contributions to the development of cardiovascular disease and re-emphasizes how both statins and healthy lifestyle changes reduce both LDL-C and may reduce cardiovascular disease events. They both agree that rather than increasing statin dosing, being more consistent in taking moderate-intensity statins is the next best step. Alex is given a follow-up appointment after six weeks.

Question 2

According to the ACC/AHA guidelines, what should be the goal for reducing Alex's LDL-C levels?

A. 10-29 % reduction
B. 30-49% reduction
C. ≥50% reduction
D. ≥70% reduction

The correct answer is B.

The AHA/ACC guidelines for the management of blood cholesterol provide specific recommendations for primary prevention for patients like Alex with intermediate ASCVD risk.[1] Guidelines recommend that for individuals 40-75 years old the goal should be reduction in LDL-C by 30-49% through moderate intensity statins.[2] Statins have been the cornerstone of lowering LDL-C for more than two decades and are highly effective for reducing LDL-C. Numerous clinical trials have shown that both in secondary and primary prevention settings, statins significantly decrease the occurrence of major adverse CV events as well as all-cause mortality.[3]

Statin therapies are classified as low, moderate or high-intensity based on the average LDL-C lowering observed in clinical trials:

- **Low-intensity: reduce LDL-C by <30% on average**
  - Fluvastatin 20-40 mg
  - Lovastatin 20 mg
  - Pravastatin 10-20 mg
  - Simvastatin 10 mg
- **Moderate-intensity: reduce LDL-C by 30% to 49% on average**
  - Atorvastatin 10-20 mg
  - Fluvastatin 40 mg bid
  - Fluvastatin XL 80 mg
  - Lovastatin 40 mg
  - Pitavastatin 2-4 mg
  - Pravastatin 40 mg
  - Rosuvastatin 5-10 mg
  - Simvastatin 20-40 mg
- **High-intensity: reduce LDL-C by >50% on average**
  - Atorvastatin 40 mg (up to 80 mg)
  - Rosuvastatin 20 mg (up to 40 mg)

Compared to moderate-dose statins, high-intensity statins produce additional reductions in LDL-C, nonfatal CV events, and mortality.[4,5]

Guidelines also note that if high-intensity statin therapy is contraindicated, or patients experience statin-related side effects, moderate intensity statins can be used with a goal of 30-49% reduction in LDL-C levels. Patients with diabetes who are 40-75 years old and have LDL-C ≥70 to <190 mg/dL should be started on a moderate-intensity statin without an ASCVD risk assessment.[1] When patients with diabetes have multiple risk factors, a high-intensity statin can be considered to reduce LDL-C by ≥50%.

Case presentation continues

Two weeks after the previous appointment, Alex calls and tells his clinician that he took the statin regularly as prescribed for 10-12 days and then quit because of muscle pain. Around the same time, Alex had started bicycling three-times a week. It is not clear if Alex is intolerant to the statin or not, his soreness could be due to additional physical activity. His clinician considers next steps for managing Alex's high LDL-C. During a discussion with his clinician, it is emphasized that Alex also may have several risk-enhancing factors – an elevated triglyceride level of 180 mg/dL, possible metabolic syndrome, and primary hypercholesterolemia (LDL-C 160-189 mg/dL, his baseline was 165 mg/dL) which may add to his ASCVD risk.

Question 3

Which statement regarding adherence to statin therapy is CORRECT?

A. The primary reason for statin nonadherence is failure to achieve desired LDL-C goals in 4 weeks
B. Up-to 70% of all patients who start statin therapy discontinue treatment within 6 months
C. Statin-associated myopathy is a major cause of treatment nonadherence
D. After the first 4 months of taking statins, rates of adherence increase over time

The correct answer is C.

Adherence to statin treatment is critical for maximum treatment benefit. However, as many as 50% of patients discontinue statins within one year of treatment initiation and after that adherence rates continue to decline over time.[6] In the Understanding Statin Use in America and Gaps in Education (USAGE) survey of more than 10,000 patients, the most common reason for discontinuation

of statins in former users was side effects (in 62% of patients).[7] Among those who discontinued statins, 60% cited muscle-related side effects as the primary reason for stopping their treatment.[8]

Both patient- and clinician-related factors can contribute to nonadherence.[7] Patient-related factors include limited knowledge about dyslipidemia, a lack of understanding of the need for treatment and how the treatment works, frustration with poor therapeutic responses, a negative attitude toward medication, forgetfulness, and fear of adverse effects.[9,10] Because dyslipidemia does not have any obvious symptoms, patients often fail to understand the need for treatment or the fact that therapy may not show immediate benefits.[11] This can lead to frustration and nonadherence.

In a survey of patients who failed to fill their first prescription for a statin, the most common reasons given for this "primary" nonadherence were general concerns about taking the medication (63%), a decision to try lifestyle modifications instead (63%), not believing that the medication was needed (28%), not believing that their condition was life threatening (25%) and fear of side effects (53%).[12]

A systematic search of papers published between January 1984 to May 2017 (19 studies), reported that potential predictors of statin adherence included traditional risk factors for CVD such as being male, age and hypertension. High BMI and alcohol misuse were associated with nonadherence.[13]

Clinicians may not have open communication with the patient and may fail to provide pertinent education about dyslipidemia, need for treatment, and the rationale for how the treatment works. In addition, lack of involvement in helping the patient identify and overcome barriers to adherence, and a lack of consistent adherence monitoring are also factors relating to nonadherence.[11]

Patient-centered approaches that can improve adherence include providing information and education about dyslipidemia, explaining the underlying reasons for prescribing statins, and describing the benefits and risks of therapy.[11] Other steps to improve adherence include providing written information on dyslipidemia and its treatment to supplement verbal information, as well as the use of electronic reminders to facilitate patient adherence with dosing schedules.[11,14]

Question 4

What do the 2018 AHA/ACC guidelines include about the use of non-statin therapies for primary and secondary prevention?

A. High-intensity statins plus ezetimibe can be used for secondary prevention if more intensive treatment beyond statins is needed
B. Moderate-intensity statins plus ezetimibe should be used for all patients with ASCVD regardless of LDL-C levels
C. Non-statins are not appropriate for use for primary prevention in patients with intermediate risk
D. High-intensity statins plus ezetimibe should be used to reduce LDL-C by ≥30% in all patients for secondary prevention

The correct answer is A.

Guidelines recommend adding ezetimibe to existing statin therapy in patients for whom statin alone is not sufficient to reduce LDL-C levels that remain at ≥70 mg/dL.

Large-scale clinical trials have demonstrated benefit of adding nonstatin therapy such as ezetimibe to statins, which can further reduce LDL-C levels by an additional 20%.

Ezetimibe, a cholesterol absorption inhibitor, was evaluated in the phase 3 IMPROVE-IT trial (N=-18,114) in patients who had been hospitalized for an ACS within the preceding 10 days and had LDL-C levels of either 50 to 100 mg/dL (if they were receiving lipid-lowering therapy) or 50 to 125 mg/dL (if they were not receiving such treatment). In this study, simvastatin (40 mg) in combination with ezetimibe (10 mg) was compared with simvastatin monotherapy with placebo. Primary end point was composite of cardiovascular death, nonfatal myocardial infarction, unstable angina (that required rehospitalization), coronary revascularization (≥30 days after randomization), or nonfatal stroke. Compared to simvastatin alone, the combination of simvastatin and ezetimibe was associated with a significant 10% relative reduction ($P = 0.003$) in the primary endpoint. At seven years, event rate for the primary end point was 32.7% and 34.7% in the two groups respectively (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% CI, 0.89 to 0.99; P=0.016). Adverse event rates (muscle, gallbladder, hepatic, cancer) were similar in the two groups. [15]

Case presentation continues

Based on a shared decision-making process that included a discussion of his multiple risk enhancing factors and acknowledging his probable statin related myalgias, Alex and his clinician added ezetimibe to his statin therapy, rather than increase the statin dose at his last appointment. At four weeks after starting this treatment, before he can be seen on follow-up, Alex presents to the emergency department with new exertional chest pains while riding his bike and is admitted for NSTEMI-ACS (which includes unstable angina) and receives a stent to his mid left anterior descending artery. His current LDL-C is 140 mg/dL. Implementing a guideline-directed treatment strategy for patients such as Alex who fail to attain the LDL-C goal on statin and ezetimibe, on-follow-up seven days post discharge, his clinician decides to add a PCSK9-targeting therapy.

Question 5

Which of the following describes PCSK9-targeting therapies correctly?

A. The three currently available PCSK9-targeting therapies act by binding to LDL receptors

B. Injectable PCSK9-targeting evolocumab and alirocumab are administered once every 6 months

C. Injectable PCSK9-targeting inclisiran is administered at baseline, then 3 months after the initial dose and every 6 months afterwards (twice a year after initiation)

D. Injectable PCSK9-targeting inclisiran is administered every month

The correct answer is C.

The guidelines state that for a high-risk patient with an LDL-C ≥70 mg/dL or a non-HDL-C ≥100 mg/dL while on maximally tolerated LDL-C–lowering therapy, the addition of a PCSK9 inhibitor can be considered. When a PCSK9 inhibitor is added to statin, additive reductions in LDC-C levels of 43% to 64% can occur.[1]

In addition to ezetimibe, nonstatin therapies include alirocumab and evolocumab— antibodies directed against proprotein convertase subtilisin kexin type 9 (PCSK9), inclisiran— a short-chain, synthetic siRNA, which inhibits the expression of the PCSK9 gene, and bempedoic acid— an adenosine triphosphate-citrate lyase (ACL) inhibitor. Unlike statins, which typically need to be taken as once-daily oral doses, PCSK9 targeted therapies need to be administered less frequently. Inclisiran (approved in 2021) is

administered at baseline, then at three months, and every six months afterwards (twice a year after initiation). This newly approved therapy has shown promise through clinical trials and is another option for patients who need addition of a nonstatin therapy for lowering LDL-C

Both alirocumab and evolocumab (both approved in 2015) have shown effective reduction in LDL-C when added to stain therapy.[16-22] They are self-injected and are administered once every two weeks or once per month.[23,24] Alirocumab was assessed in three phase III trials. The ODYSSEY OUTCOMES trial (N=18,924),[22] ODYSSEY LONG-TERM trial (N= 2,341)[21] and ODYSSEY ALTERNATIVE trial.[20]

In the ODYSSEY OUTCOMES trial of alirocumab, enrolled patients had an ACS event within the preceding one to twelve months, residual LDL-C levels ≥70 mg/dL, non–high density lipoprotein cholesterol (non-HDL-C) levels >100 mg/dL after two to sixteen weeks of intensive or maximally tolerated therapy with atorvastatin or rosuvastatin. After a median follow-up of 2.8 years, there was a 54.7% reduction in the LDL-C levels vs. placebo. The primary endpoint of major adverse CV events (time to first occurrence of CHD death, nonfatal MI, unstable angina requiring hospitalization, or ischemia stroke) occurred in significantly fewer patients in the alirocumab group than in the placebo group (9.5% vs. 11.1%, respectively; $P = 0.0003$).[22]

The FOURIER trial (N=27,564, patients with ASCVD, with LDL-C ≥70 mg/dL on maximally tolerated statins) examined CV outcomes among patients treated with evolocumab.[17] At 48 weeks, the mean percentage reduction in LDL-C levels with evolocumab, as opposed to placebo, was 59% (from a median baseline value of 92 mg/dL to 30 mg/dL; $P < 0.001$). Compared to placebo, the addition of evolocumab to statin therapy significantly reduced the risk of the primary endpoint (a composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization; $P < 0.001$). Other trials of evolocumab included OSLER 1 and 2, and Gauss 2 and 3.[16,18,19]

Efficacy of inclisiran was demonstrated in phase 3 ORION-9 (N=428, patients with heterozygous familial hypercholesterolemia who were on statins and ezetimibe),[25] ORION-10 (N=1561) and ORION-11 (N=1617) trials.[26] In the ORION-9 trial at 17 months, the percentage change in LDL-C (the primary outcome), was -39.7% vs. +8.2% ($p < 0.0001$) for inclisiran vs. placebo. In the ORION-10 and ORION-11 trial, the reduction was 52.3% (95% confidence interval [CI], 48.8 to 55.7) and 49.9% (95% CI, 46.6 to 53.1) respectively.

Case Conclusion

After starting on a PCSK9-targeted therapy in accordance with AHA/ACC guidelines, at three months Alex's LDL-C level is <70 mg/dL. He will be monitored closely to ensure that he is adhering to therapy, his LDL-C levels are appropriate, and that he is progressing well with his lifestyle modifications.

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CME POST-TEST: Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central. See page 2 for further information.

Question #1

Which of the following is correct about efficacy of statins?

A. High-intensity statin therapy lowers LDL-C levels by ≥70%
B. Moderate-intensity statin therapy lowers LDL-C levels by 50% - 69%
C. Moderate-intensity statin therapy lowers LDL-C levels by 30% - 49%
D. Low-intensity statin therapy lowers LDL-C levels by <20%

Question #2

Which of the following is a correct statement about ASCVD risk and its management according to the AHA/ACC guidelines?

A. For adults 40-75 years of age, and LDL-C ≥70 and <190 mg/dL ASCVD risk should be assessed
B. Risk assessment is not necessary and moderate intensity statin therapy can be initiated for adults with LDL-C levels ≥ 150 mg/dL
C. For individuals 0-19 years of age with or without familial hypercholesterolemia, lifestyle changes only should be recommended
D. For individuals 20-39 years of age, lifestyle changes should be encouraged to reduce ASCVD risk, and statin therapy should be initiated regardless of family history

Question #3

Which of the following is a correct statement about management of ASCVD risk in patients with diabetes according to the AHA/ACC guidelines?

A. High-intensity statins are recommended for all adults with diabetes regardless of the ASCVD risk level
B. For adults with diabetes who are 40-75 years of age, ASCVD risk should be assessed in order to consider high intensity statin therapy
C. In adults with diabetes and multiple ASCVD risk factors, moderate intensity statin therapy should be initiated
D. In adults with diabetes and multiple ASCVD risk factors, low intensity statin therapy should be initiated

Question #4

Which statement regarding side effects of statin therapy and adherence is CORRECT?

A. As many as 50% of patients discontinue statins within the first year of treatment
B. Rates of adherence to statins increase over time
C. Statin myopathy symptoms are usually severe
D. Statin myopathy does not typically affect long-term adherence, as it is self-limited

Question #5

In contrast to taking statins daily, approved PCSK9 targeting therapies (e.g., PCSK9i, siRNA) need to be administered less frequently. Which of the following is correct?

A. Alirocumab is administered either 140 mg every 2 weeks or 420 mg once monthly
B. Alirocumab is administered either 75 mg every month or 140 mg every 3 months
C. Inclisiran is administered at 3 and 6 months after initial dose
D. Evolocumab is administered either 75 mg once every 2 weeks or 300 mg once every 4 weeks

Question #6

Which of the following is the correct definition for ASCVD risk?

A. Low risk: <2%
B. Borderline risk: 5% to <10%
C. Intermediate risk: 7.5% to <20%
D. High risk: ≥30%

Question #7

Which of the following do the 2018 AHA/ACC guidelines advise with respect to primary prevention of ASCVD in adults 40 to 75 years old with LDL-C ≥70 mg/dL?

A. High-risk patients should be treated with a statin aimed at reducing LDL-C levels by 25%
B. Patients with diabetes with LDL-C levels ≥70 mg/dL should be started on a moderate-intensity statin without first having an ASCVD risk assessment
C. Patients without diabetes who are at low risk of ASCVD but have risk enhancers may warrant treatment with a high-intensity statin
D. Patients with severe primary hypercholesterolemia (LDL-C ≥190 mg/dL) should have their 10-year ASCVD risk assessed to determine a target LDL-C level before starting therapy

Question #8

Which statement concerning the 2018 AHA/ACC recommendations regarding statin therapy for the secondary prevention of ASCVD is correct?

A. Non-statin therapy can be beneficial to patients with ASCVD who have LDL-C level of ≥70 mg/dL despite maximally tolerated statin
B. Patients with ASCVD should receive a high-intensity statin to reduce LDL-C by 50% unless they are <50 years old, in which case a moderate-intensity statin should be used
C. Patients with ASCVD who develop muscle symptoms (myopathy) from statins should immediately discontinue such treatment permanently
D. Patients with ASCVD who experience statin myopathy should immediately switch to an alternative agent rather than trying a lower dose of their current therapy

Question #9

Which of the following is true about statin nonadherence?

A. Typically, up-to 25% of patients will become non-adherent to statin therapy
B. Statin myopathy is a leading cause to nonadherence
C. Adherence rates differ with age groups over time
D. Not achieving LDL-C goals in 4 weeks is the main reason for statin non-adherence for majority of patients

Question #10

Which of the following can be effective for improving adherence?

A. Low intensity statins
B. Bempedoic acid
C. Ezetimibe reduced dose
D. PCSK9 inhibitors

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