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NATIONAL LIPID ASSOCIATION

Optimizing Cardiovascular Risk Reduction in High-Risk Patients Through Lipid Management

A CE/CME Activity

Overview

In this video webcast of a satellite symposium held during the National Lipid Association's Fall Clinical Lipid Update 2017, **Peter Howard Jones, MD,** and **Joseph J. Saseen, PharmD,** provide their insights into the evolving lipid management of patients at high risk for cardiovascular events. To better facilitate the integration of recent data into real-world clinical practice, Drs. Jones and Saseen discuss 4 case scenarios of patients at different levels of cardiovascular risk. There is no fee for this activity.

Content Areas:

- Primary prevention (with and without complications)
- Secondary prevention
- Heterozygous familial hypercholesterolemia
- Statin intolerance

Faculty

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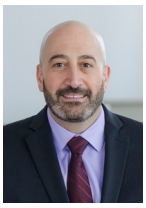

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Table of Contents

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Objectives & Accreditation

Activity Title
Optimizing Cardiovascular Risk Reduction in High-Risk Patients Through Lipid Management

Activity Format
Internet Enduring Material

Fee
There is no fee for this activity.
Release Date: September 30, 2017
Expiration Date: September 30, 2017

Overview
Peter Howard Jones, MD, and Joseph J. Saseen, PharmD, provide their insights into the evolving management of patients at high risk of a cardiovascular event despite maximally tolerated statin therapy. Drs. Jones and Saseen review current ACC and NLA guidelines, including recommendations related to the use of nonstatins such as ezetimibe and PCSK9 inhibitors. To facilitate the integration of these guidelines into real-world clinical practice, Drs. Jones and Saseen discuss 4 case scenarios of patients at different levels of cardiovascular risk. These discussions blend evidence from clinical trials with their individual experiences.

Target Audience
This activity is designed to meet the needs of physicians, physician assistants, pharmacists, registered nurses, nurse practitioners, advanced practice registered nurses, and registered dietitians with an interest in clinical lipidology.

Type of Activity
Knowledge

Learning Objectives
At the conclusion of this activity, all participants should be able to:

- Discuss real-world implications of new data on proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors;
- Explain the effect of PCSK9 inhibition in specific clinical scenarios (eg, diabetes, familial hypercholesterolemia, statin intolerance);
- Identify patients who may benefit from the use of nonstatins therapies, including PCSK9 inhibitors—either as monotherapy or in combination with a statin—in order to optimally reduce the risk for atherosclerotic cardiovascular disease (ASCVD);
- Evaluate lipid management treatment plans to reduce ASCVD risk in patients at particularly high risk;
- Discuss strategies to improve the knowledge, skills or performance of the health care team.

Criteria for Success
To participate in the activity, go to http://www.cardiocarelive.com/. To receive credit, participants must (1) read the target audience, learning objectives, and disclosure statements, (2) complete the educational activity online, and (3) complete the posttest and activity evaluation. To receive *AMA PRA Category 1 Credits*™, participants must receive a minimum score of 70% on the posttest.
If you have questions about this CME activity, please contact the NLA at cme@lipid.org. Please claim credit by September 30, 2017.
For pharmacists: Upon receipt of the completed activity evaluation form, transcript information will be available at www.mycpemonitor.net within 4 weeks.

Commercial Support
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Credit Designation

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Credit provided by the National Lipid Association

In support of improving patient care, this activity has been planned and implemented by The National Lipid Association and Annenberg Center for Health Sciences at Eisenhower. The National Lipid Association is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Dietitians
The National Lipid Association is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR). Registered dietitians (RDs) and dietetic technicians, registered (DTRs) will receive 2 continuing professional education units (CPEUs) for completion of this program/ materials. CDR Accredited Provider #NL002

Pharmacists
Universal Activity Number
0624-9999-17-044-H01-P (Knowledge)
This Activity has been approved for 2.00 contact hour(s) (.1 CEUs) of the Accreditation Council for Pharmacy Education

Nursing
The maximum number of hours awarded for this CE activity is 2 contact hours.

Faculty/Planner/Staff Financial Disclosures

Faculty/Planner Financial Disclosures

Jones, Peter

Consultant	Amgen, Merck & Co., Inc., Sanofi/Regeneron

Saseen, Joseph

N/A	Nothing to Disclose

Staff Disclosures

Annenberg Center for Health Sciences at Eisenhower

N/A	Nothing to Disclose

NLA

N/A	Nothing to Disclose

NLA CME Reviewers

Dixon, Dave

N/A	Nothing to Disclose

Disclosure of Unlabeled Use and Investigational Product

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Disclosure Declaration

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Disclaimer

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Estimated Time to Complete

This activity consists of one session, which should take approximately 120 minutes to complete.

Hardware/Software Requirements

Participants will need a computer with a recent version of Adobe Flash installed, as well as an internet connection sufficient for streaming media.

1. Introduction and Evolving Paradigms in LDL Hypercholesterolemia

Good evening everyone. Thank you very much for being here this evening. I want to welcome you to the CME Symposium—Optimizing Cardiovascular Risk Reduction in High-Risk Patients Through Lipid Management. My name is Peter Jones. I work at the Houston Methodist Hospital at Baylor College of Medicine. I do weight management, but I also work in the Center for Cardiovascular Disease Prevention. I've been a lipid specialist all of my career, and I've also been a member of the NLA from its inception about 16 years ago.

Presenters

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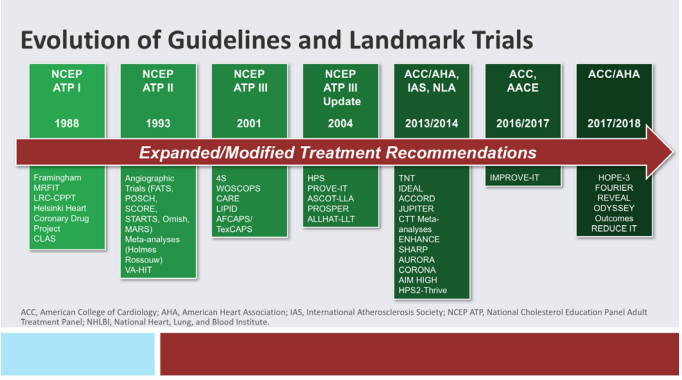
I'm going to be joined this evening by my copresenter, Joseph Saseen, PharmD, who's a professor and vice chair in the Department of Clinical Pharmacy, and a professor in the Department of Family Medicine at the University of Colorado Anschutz Medical Campus, and that's in Denver.

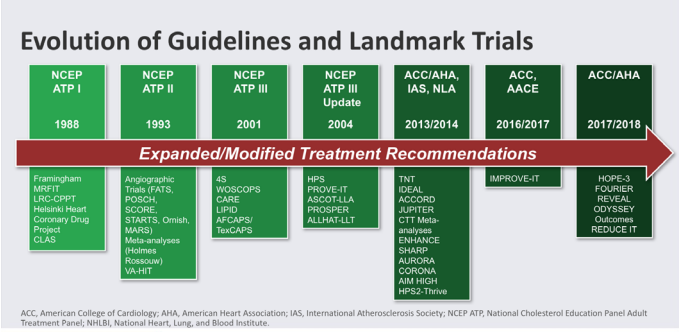
It's my job to just sort of set the stage for what we're going to try to talk about tonight, because as you heard in some of these skill questions, we all know how to use, supposedly, maximally tolerated statins in the right patients, but the question is, how do we move beyond that to lower LDL in high-risk patients? So in the evolution of guidelines—and I think you all are well aware of this, and I was around during the ATP1 when we didn't have a lot of information—we went on a lot of scientific evidence that LDL cholesterol lowering would be a good thing. It was some single drug treatments—bile acid resins and niacin—that suggested that we might be on the right track. And, of course, as we got more information with the statin class of drugs, ATP2 and ATP3 came along, not only incorporating intensive LDL lowering with statins, but also sort of targeting LDL cholesterol as the biomarker we wanted to lower, and also making a treatment goal for these patients.



It was updated to ATP3 in 2004 with more information, as we got that about higher intensity statin vs lower intensity statin in higher risk patients. Then, of course, the ACC/AHA came in 2013 with updates to the ATP lipid guidelines and using randomized clinical trial evidence. We'll talk a little bit more about their statin benefit groups. But around that time, the ESC, International Atherosclerosis Society, even the Canadians, came out with their recommendations. Most of them did still use the biomarker LDL cholesterol as the target of therapy and use it as goals. And the National Lipid Association also had their recommendations come out for how to manage high-risk patients in 2014.

Last year, there was an update from the ACC called the Expert Consensus Decision Pathway, which was designed to consider nonstatin drugs added to maximally tolerated statins and under what situations. Hopefully you saw that. The ACC Expert Consensus Decision Pathway will be updated this year, very soon, and the AACE guidelines came out with even more intensive LDL goals this past year as well, based on information. We know that ACC/AHA is in the process of updating their guidelines. That probably

will be another year or 2 before that comes along, but the NLA did update their recommendations for how to use nonstatin drugs, just a couple of months ago. We'll talk about that. I think some of it's in the back of your take-home handout as to how to use nonstatin drugs in the right patient population.



So in 2014, the NLA recommendations part 1, made it very clear that we felt that LDL cholesterol was not just a target of what we're treating to reduce cardiovascular disease, but you had to achieve certain levels in order to maximize that benefit. Of course, you know that it was both LDL cholesterol and non-HDL cholesterol that the NLA focused on as the primary targets of our treatment. And apolipoprotein B was a secondary target, but you can see the levels there for LDL and non-HDL in low, moderate, and high risk, and of course, in the very high-risk patients, which are usually those with established cardiovascular disease.

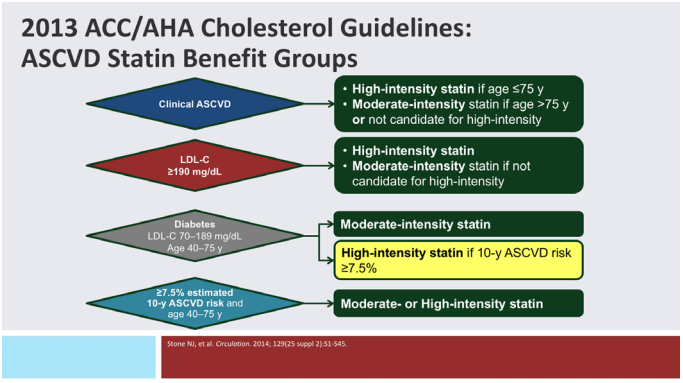
2014 NLA Recommendations—Part 1

Risk Category	Treatment Goal (mg/dL)		
	Non-HDL-C	LDL-C	Apo B
Low, Moderate, or High	<130	<100	<90
Very High	<100	<70	<80

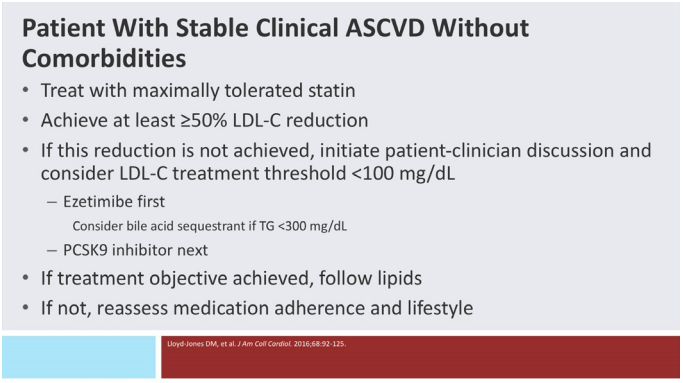
Primary Target: Non-HDL-C and LDL-C
Secondary Optional Target: Apo B

Jacobson T, et al. *J Clin Lipidol.* 2014; 8:473-488.

The 4 statin benefit groups you all are familiar with. The one with established heart disease is group 1, clinical ASCVD. The other 3 groups are essentially primary prevention patients. But high-intensity statins are clearly to be used in the highest risk patients, so high-intensity statin to achieve at least a 50% reduction in LDL from baseline. The age group between 40 and 75 years, moderate-intensity statin if you're over the age of 75 years with clinical ASCVD. The FH population in group 2, high-intensity statin is preferred. In group 3, which is primary prevention diabetes in the 40- to 75-year-old group, again high-intensity statin would be used if they're high-risk. Primary prevention diabetes in moderate-intensity if they're less than 7.5% using the pooled cohort equation. Then, of course, the last group, group 4, is pure primary prevention. They are determined solely on the pooled cohort equation estimate of 10-year risk being more than 7.5%, and that moderate- or high-intensity statin could be your choices depending on age and other factors. So, you all are familiar with that.



So as you look at what the ACC did last year with the Expert Consensus Decision Pathway, they said, "Yes, we're going to look at these 4 groups, these 4 statin benefit groups, and decide if any of these groups deserve the consideration for nonstatin, add-on drugs." And the first group they started with was stable ASCVD, which is the number 1 statin benefit group and they divided them up into 2 groups. One without comorbidities and one with comorbidities. And, of course, the same idea here is that you treat with maximally tolerated statins and that you try to get at least a 50% reduction in LDL from baseline. That's consistent with the ACC/AHA guidelines.



But they said if that reduction is not achieved and the LDL cholesterol is still above 100 mg/dL, then you might consider nonstatin drugs. So this was an introduction of the concept of LDL thresholds. So, what they're doing is bringing back LDL to the ACC/AHA and saying it's not about just using a statin, walking away, fire and forget. It is looking at what the response has been and deciding where the LDL went and if it's still above a certain level, a threshold, that you might consider additional treatments. So, they said ezetimibe, where you get a 20% or 25% LDL reduction, might be a consideration to add to maximally tolerated statin. And then a PCSK9 inhibitor could be considered, again determining patient-physician interaction, baseline LDL, and where you want it to go.

So, I think everybody sort of agreed that's a fairly logical way to do it, but it means you have to bring LDL back into the picture. You have to follow it and you have to know what you're doing in order for that to occur. Then there was the other group, which is ASCVD with comorbidities. And in this one the comorbidities could be ASCVD with diabetes, post-ACS, patients who have recurrent events on optimal statin treatment, those who have FH with established cardiovascular disease, uncontrolled risk factors; you know those difficult to manage—hypertension, continued smoking. Patients with high Lp(a) are those with CKD, stage 3 or 4.

Patient With Clinical ASCVD and Comorbidities: Diabetes Mellitus, Recent Acute ASCVD Event, ASCVD Event on Statin, Baseline LDL-C ≥190 mg/dL, Uncontrolled Risk Factors, Elevated Lp(a), Chronic Kidney Disease

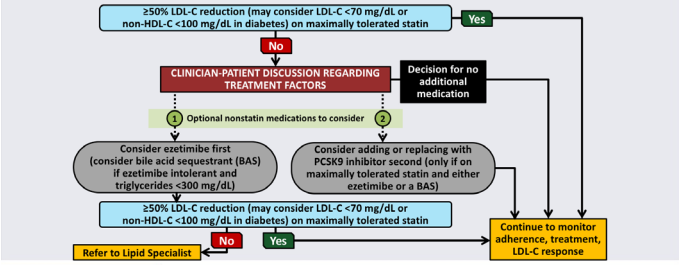
- Treat with maximally tolerated statin
- Achieve at least ≥50% LDL-C reduction
- If this reduction is not achieved, initiate patient-clinician discussion and consider LDL-C treatment threshold <70 mg/dL or non-HDL-C <100 mg/dL if diabetic
  - Ezetimibe first
  - PCSK9 inhibitor next
- If treatment objective achieved, follow lipids
- If not, reassess medication adherence and lifestyle

Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68:92-125.

And again, this is treated with maximally tolerated statin. Expect at least a 50% reduction, but if that's not achieved, then take a look at where their LDL is. And if their LDL is above 70 mg/dL, then you might consider the addition of a nonstatin drug. Again, considering ezetimibe, with a 20%-25% LDL reduction, or possibly a PCSK9 inhibitor, depending on where that LDL is and where you would expect it to go.

So, this is what those pathways look like. If you look at the paper, it's sort of complicated, and I don't want it to be that way. It sort of starts at the top. Here's the patient. Those, for instance, with comorbidities and ASCVD and then "Yes," everything is achieved. Your LDL got what you wanted to do, less than 70 mg/dL, and everything on the tolerated statin, and you just continue it. But if it's "No," you go down through the middle. You consider the possibilities. They didn't get below 70 mg/dL. They didn't get greater than a 50% reduction. Then you consider ezetimibe or PCSK9, and then you look again at where they went. Did they achieve the expected response you wanted? In other words, did they go less than 70 mg/dL, for instance, and then you consider maintaining that treatment. If not, they get the option to refer to a lipid specialist and that's what we are.

2016 ACC Expert Consensus Decision Pathway: Clinical ASCVD With Comorbidities



Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68(1):92-125.

Then, of course, group 2 is FH patients. Those with LDL more than 190 mg/dL, without clinical ASCVD. So, in this Expert Consensus Decision Pathway, treat everybody with maximally tolerated statin, which should be high-intensity statin. They suggest that lipid specialists should probably be dealing with these patients. Again, you look for primary prevention in FH. You should consider whether their LDL cholesterol gets below 100 mg/dL at least in this situation. Many times it does not, for those of you that treat FH. Then they said you could consider the addition of ezetimibe or PCSK9 depending on where their LDL was above 100 mg/dL, and where you wanted it to go. They thought it should be at least less than 100 mg/dL in primary prevention in familial hypercholesterolemia. Now remember, the age group here is between 40 and 75 years with FH. Of course, you have other drugs to consider with FH at the bottom. Those are more complicated, using compound heterozygous, or double heterozygous, sometimes the homozygote FH which we have

mipomersen, lomitapide, and even LDL apheresis. That's why they want lipid specialists to always be involved with the FH patients for long-term management.

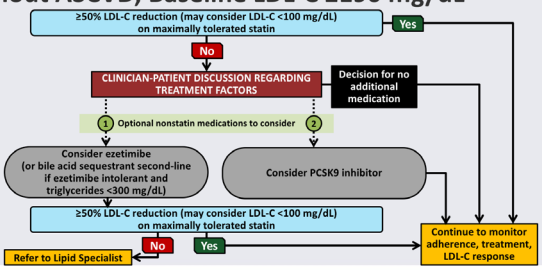
Patient Without Clinical ASCVD and Baseline LDL-C ≥190 mg/dL

- Treat with maximally tolerated statin
- Strong recommendation for referral to lipid specialist
- Achieve at least ≥50% LDL-C reduction
- If this reduction is not achieved, initiate patient-clinician discussion and consider LDL-C treatment threshold <100 mg/dL
  - Ezetimibe
    - Consider BAS if TG <300 mg/dL
  - PCSK9 inhibitor next
- If treatment objective achieved, follow lipids
- If not, reassess medication adherence and lifestyle
- Consider mipomersen, lomitapide, and/or LDL apheresis in appropriate patients

Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68:92-125.

And again, this is the decision tree you see in the paper, just wanted to show you what it looks like. I think most of you have seen that for FH primary prevention.

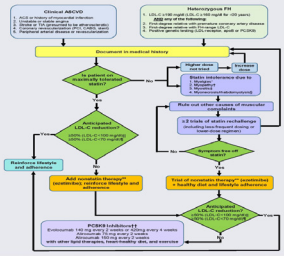
2016 ACC Expert Consensus Decision Pathway: Without ASCVD, Baseline LDL-C ≥190 mg/dL



Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68(1):92-125.

Now this is not the best way to look at this. That's why we have it in the back of your handout. This is what the NLA expert panel came out with last year and we've updated it. But essentially, it's divided up into 2 sections. One up on the top up here on the left is clinical ASCVD. Over here is FH. Those were the 2 groups we felt would be considered for the addition of PCSK9 monoclonal antibodies, and the decision is based on threshold levels of LDL cholesterol. It does

2017 NLA Expert Panel on Treatment of Clinical ASCVD and Heterozygous FH With PCSK9 Inhibitors



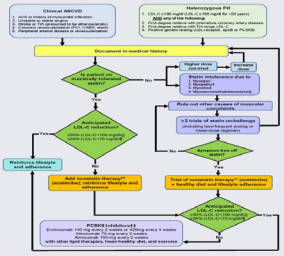
Saeed A, et al. *J Clin Lipidol.* 2017;11(3):596-599.

consider patients who are at very high risk. So, in the NLA, it was ASCVD with comorbidities. With a heterozygote FH, we did update that here recently with the update in the *Journal of Clinical Lipidology.* It's online. It's not out yet, but it's online.

If you look at the 2017 expert panel update, they divide FH into 3 groups: primary prevention, secondary prevention, and then a third group is younger patients. Now remember, the expert consensus decision pathway by the ACC doesn't talk about treating FH with any of these nonstatin drugs under the age of 40 years. So, the NLA felt that there was a need, under the age of 40, to consider the possibility that there could be high-risk FH patients, who are primary prevention, who deserve nonstatin drug treatments on top of optimal statin therapy. So, we do go through that.

Now, of course, the NLA talks specifically—it's in the purple section here—on statin intolerance which, unfortunately, never really gets put into anything. They talk about maximally tolerated statin. Well, what if that's zero mg statin? What if it's 10 mg of atorvastatin, 3 times a week? Well that's obviously a person who cannot tolerate high-intensity or even moderate-intensity statin. So, determining statin intolerance is a difficult issue, and the NLA does have criteria for how to manage statin intolerance and what to do, and of course, most of you know that, but you should try to maximize as much statin as you can in all patients at high risk. But even if maximally tolerated statin is very, very little statin, there is a need for nonstatin drug use in some of these high-risk patients.

2017 NLA Expert Panel on Treatment of Clinical ASCVD and Heterozygous FH With PCSK9 Inhibitors

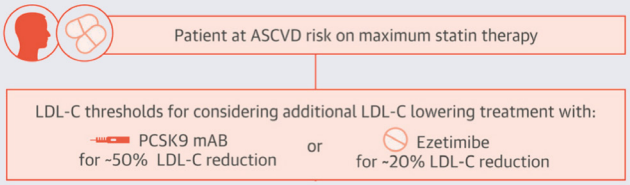


Saeed A, et al. *J Clin Lipidol.* 2017;11(3):596-599.

Jennifer Robinson put together a little bit of information. This was published last year in *Journal of the American College of Cardiology,* determining when to add nonstatin therapy, and she looked at it from the concept of number needed to treat. And her idea was

using thresholds again, but she said what you need is to see where you want to go and then look at what you expect from the treatment you get. If you're starting with an LDL of 190 mg/dL and you want their LDL to go below 100 mg/dL, you're not going to get it with ezetimibe. That's only going to give you a 20% or 25% reduction. If that 20% or 25% reduction gets you to a reasonable goal for that patient, that's a cost-efficient way to do it, and a number needed to treat can be very low if your threshold is, say 130 mg/dL, and you want to go lower.

Determining When to Add Nonstatin Therapy



Robinson JG, et al. *J Am Coll Cardiol.* 2016;68(22):2412-2421.

But the higher your baseline LDL, the more you need a greater reduction from baseline, and the PCSK9s can become very reasonable in number needed to treat with a higher baseline. It's a really good paper to consider, and it does consider these thresholds, and I think, intellectually, we all understand that. Your LDL is 105 mg/dL and you want it to go below 100 mg/dL, well ezetimibe would be an easy way to do that. But, of course, many of us consider lower is better, and why not just go as far down as you can go? Well that's probably reasonable, too, based on clinical decision and what your patient determines. But what she was using is number needed to treat, which is one way to look at it.

The evolution of lipid treatment is really getting quite amazing and it will in the next decade be more amazing than what we have. Statins have been probably one of the most amazing preventative drugs we've ever come up with, but we still have bile acid resins. We still have cholesterol absorption inhibitors, ezetimibe. We do treat triglycerides with fibrates and omega-3s. But with the PCSK9s, and the use of a technique like monoclonal antibodies—and soon some of the drugs will be with antisense and small interfering RNA—we will be able to treat very specific lipid problems and get profound reductions using these novel delivery techniques. And the PCSK9s are sort of evolving that treatment for us over the usual once a day oral pill kind of approach that we've gotten used to over the years of lipid treatment.

Dyslipidemia Medications

	LDL-C	HDL-C	TG
Statins	↓18–55%	↑5–15%	↓7–30%
Bile acid sequestrants	↓15–30%	↑3–5%	↑0–10%
Nicotinic acid	↓5–25%	↑15–35%	↓20–50%
Fibric acids	↓5–↑20%	↑10–20%	↓20–50%
Cholesterol absorption inhibitor	↓13–20%	↑3–5%	↓5–11%
Long-chain omega-3 fatty acid drugs	↓6–↑25%	↓5–↑7%	↓19–44%
PCSK9 inhibitors	↓40–72%	0–↑10%	0–↓17%

Jacobson T, et al. *J Clin Lipidol.* 2014; 8:473-488.
Shimada Y, et al. *Eur Heart J.* 2015; 36:2415-2424.

And there's still plenty of unmet need in patients with high LDL and a lot of this unmet need isn't that we don't necessarily have the right drugs, it's just that patients sometimes don't get them.

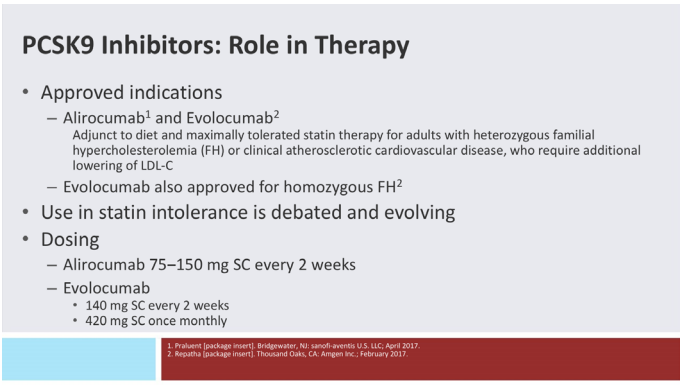
Amazingly, patients with type 2 diabetes, most of them, particularly primary preventions, that statin benefit group 3, aren't really taking enough statin. Amazingly, too, patients discharged from the hospital, this is 58% of Medicare patients and 70% of commercially insured beneficiaries, don't even fill their prescription after an MI for their high-intensity statin. So, they don't fill it. There's about 30–40% that don't even fill it. Amazing how that doesn't quite get incorporated into the patient's treatment paradigm. I'm sure it's not that bad for antiplatelet drugs and other things that they leave the hospital on, but the statin and, of course, the FH patient population is in our wheelhouse and they are very high-risk patients and they need intensive treatment. And I think we are the ones that identify these patients and start them early and incorporate a more intensive approach because their risk of cardiovascular disease is very high, and they have very premature cardiovascular events.

Unmet Needs of Persons with Elevated LDL-C

- In US adults with T2DM, <20% of statin prescriptions are for high-intensity dose[1]
- 58% of Medicare beneficiaries and 72% of commercially insured beneficiaries hospitalized for MI fill a prescription for a high-intensity statin within 30 days of discharge[2]
- Persons with heterozygous FH are at 100-fold greater risk for a nonfatal cardiac event than general population[3]
- Persons with homozygous FH are at high risk of a fatal CV event before age 20 y[4]

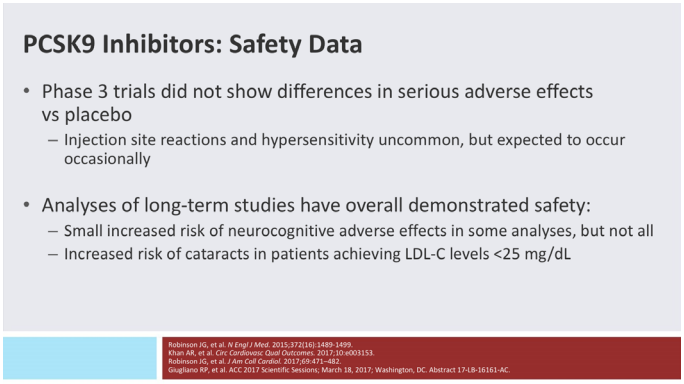
1. Beaubrun AC, et al. *Eur Heart J.* 2016;37(Suppl):1012-1013. Abstract P4987.
2. Rosenson RS, et al. *J Am Coll Cardiol.* 2017;69(22):2698-2706.
3. Nair DR, et al. *Curr Opin Cardiol.* 2014;29(4):381-388.
4. Nordestgaard BG, et al. *Eur Heart J.* 2013;34(45):3478-3490.

So the PCSK9s have given us the opportunity to have add-on drugs that are well tolerated, with very appreciable LDL reductions. So the 2 of them, as you know monoclonal antibodies, alirocumab and evolocumab, that was approved to be used on top of maximally tolerated statins in patients with ASCVD and heterozygote FH. That's the indication. There's no specific mention of statin intolerance, just maximally tolerated statin, in patients who need additional LDL lowering, and again there was no definition about what additional LDL lowering meant either. That's why the Expert Consensus Decision Pathway and the NLA had to come in there and sort of make some sense out of what additional LDL lowering really meant, and where the benefit would probably be.

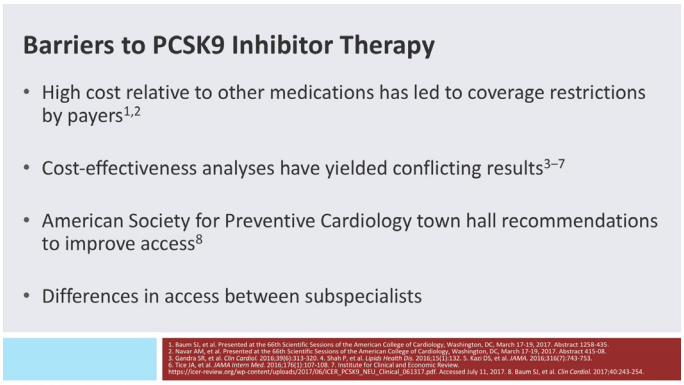


We do know that the dosing… I think most of you are familiar the dosing of these, right? Has everybody at least prescribed 1 patient with a PCSK9? You've got 2 doses of alirocumab and 2 doses of evolocumab. The evolocumab is once a month with 1 dose, and it's every 2 weeks for the other 2 dosing compounds.

And the safety is not as much as we would like. There's a lot of phase 2 data, the ODYSSEY Long-Term, and the OSLER studies gave 2-year safety data, compiling information on patients. The FOURIER was a 2.2 mean year, follow-up study. Positive, but still only 2.2 years. But it does look like they're safe. The only problem is occasional injection site reactions, but we don't think there's any abnormalities like new-onset diabetes. A question about neurocognitive function abnormalities with low LDL does not appear to be the case with EBBINGHAUS as a subgroup analysis of the FOURIER. There is still a question about cataracts from low LDL, but that needs to be determined longer term. I think we do have reasonable safety data on these drugs, but we hope to get more to make you feel more comfortable.



Probably the most challenge with these is barriers to access. Have any of you tried to fill out a prior authorization for a PCSK9? It's the most frustrating thing in the world to do and it mostly deals with documentation. The NLA has published our own barriers to prior authorization to PCSK9s in the *Journal of Clinical Lipidology.* There's been town halls by the American Society of Preventive Cardiology to try to improve access and teach providers how to make that prior authorization less painful. And it looks as though lipidologists do get some preference to the prior authorizations. Cardiologists, too, and endocrinologists, but the general internal medicine and family practice seem to have a much harder time getting authorizations, even if they fill out the documentation well.



So, it is a challenge, and these are something that you have to work on. It's not impossible to get. We've gotten our institution up to 100%. We don't get anybody denied but, boy, it does take a while to get it. If you give up, they are denied, but if you don't, you'll get there. So, we're now going to go through and sort of—with that background—we're going to go through some cases, and we're going to have 4 cases, we're going to back and forth between Joe and me. Joe is going to present the first one for you.

Case Study Mateo

Joseph Saseen: All right, let's get into this patient case. So, imagine that you're the provider for Mateo. What do we know about Mateo? Mateo is a 68-year-old man who is admitted to the hospital for a myocardial infarction. We also know that his LDL cholesterol is 118 mg/dL and his triglyceride value is 184 mg/dL. Before his hospitalization, he reported that he somewhat exercised, a 30-minute brisk walk, 5 days a week. He also reported that he follows a low saturated fat diet, but also reports to limited adherence with that diet. And also, he's been treated with a statin, simvastatin 40 mg daily for over 3 years. Think about what you would do with Mateo.

Case Study: Mateo

- 68 yo male admitted for myocardial infarction
  - LDL-C 118 mg/dL
  - Triglycerides 184 mg/dL
- Treatment prior to hospitalization
  - 30-minute brisk walk 5 days per week
  - Diet low in saturated fats (limited adherence)
  - Simvastatin 40 mg once daily (x 3½ years)

What change would you make to his treatment plan?

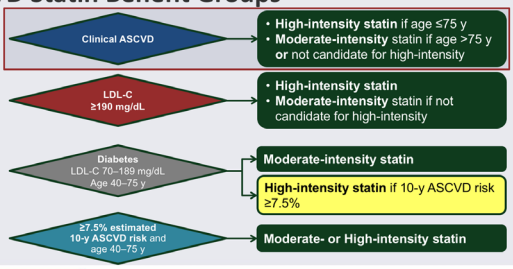
What change would you make to his treatment plan? Would you switch to a high-intensity statin regimen? Or would you add a bile acid sequestrant? Or add ezetimibe, add fenofibrate, or perhaps add a PCSK9 inhibitor? What would you do based on this limited information for Mateo?

What change would you make to his treatment plan?

1. Switch to high-intensity statin regimen
2. Add bile acid sequestrant
3. Add ezetimibe
4. Add fenofibrate
5. Add PCSK9 inhibitor

But the real trend here is to switch to high-intensity statin therapy. And I believe, probably some of the reason for that is very clearly listening to Dr. Jones, and going over some of the recommendations. And if we just look at the ACC/AHA recommendations, clinical ASCVD, which is Mateo, he's admitted to the hospital with a myocardial infarction. So now he's a secondary prevention patient. What's recommended clearly, based on excellent evidence, is high-intensity statin therapy. So, recognizing his current therapy is simvastatin 40, going up to high-intensity, at least is in line with what's recommended.

2013 ACC/AHA Cholesterol Guidelines: ASCVD Statin Benefit Groups



Stone NJ, et al. *Circulation*. 2014; 129(25 suppl 2):S1-S45.

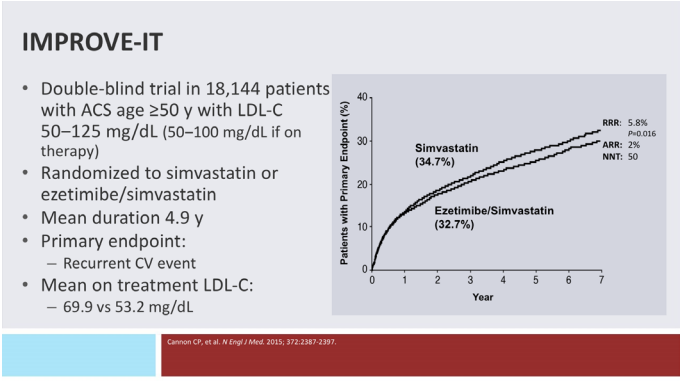
Perhaps some people chose the other options because they wanted more robust reductions than what you would get by just stepping up the intensity in statin therapy, so I might understand that to some extent. Let's go through those guidelines a little bit clearer though. It's based on what I call overwhelming evidence supporting high-intensity statin therapy. The ACC/AHA group also believes in that. They have this labeled as a class I-A evidence recommendation, that being using high-intensity statin therapy in people like Mateo with clinical ASCVD. They have another corollary recommendation, based on good evidence, that if there's some risk factor or known intolerance to high-intensity statin therapy, then maybe you can get away with his current regimen, which is moderate-intensity. But very clear, it looks, based on this information, that Mateo has just been on moderate-intensity statin therapy and then suffered his cardiovascular event, now changing his comorbidity to be in a secondary prevention patient.

ACC/AHA 2013 Blood Cholesterol Guideline: ASCVD

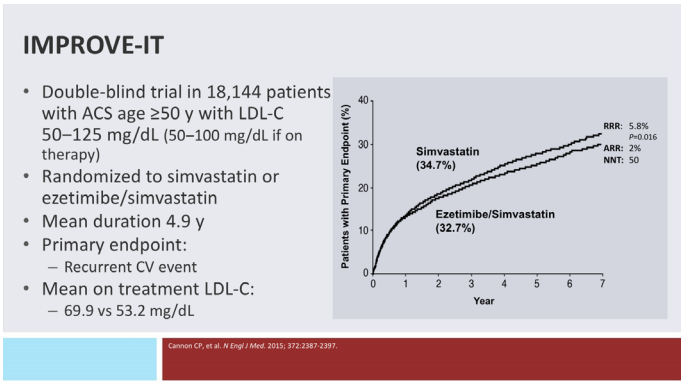
Class I Recommendations	Level of Evidence
High-intensity statin therapy should be initiated or continued as first-line therapy in men and women ≤75 years of age, unless contraindicated	A
If high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, **moderate intensity** statin therapy should be the second option if tolerated	A

Stone NJ, et al. *Circulation*. 2014; 129(25 suppl 2):S1-S45.

We do have new information, looking at ezetimibe, 11% of people may have been thinking that IMPROVE-IT, maybe these data apply to this kind of patient. How does the IMPROVE-IT data apply to a patient like Mateo? Well, this study was very large and robust, 18,000 patients, looking like Mateo, a recent ACS event, which is his now-predominant medical condition. It was a randomized study that looked at patients treated with a baseline of simvastatin 40 mg/day. There were some changes in study methodology, but then had randomization to either placebo or ezetimibe for multiple years. Now, the median duration was about 5 years but they extrapolated findings out to 7… a little over 7 years, and they met their primary endpoint, which was recurrent cardiovascular events. We can see, based on the curve to the right on this graph, that if you look at patients developing the primary endpoint of a recurrent cardiovascular event throughout the years, that there were fewer patients that were treated with ezetimibe suffering from that recurrent cardiovascular event.

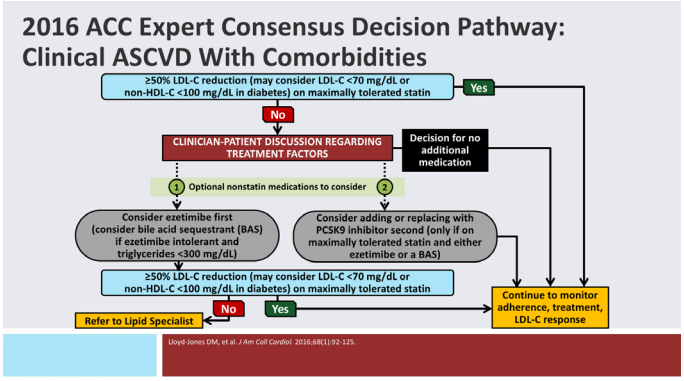


This was a significant finding. Now, we might think the clinical relevance may be small because the relative differences between these 2 treatment arms were probably not as much as we would like to have, but when we look at these data, they are evidence that adding ezetimibe to a patient like Mateo may improve his condition. Now, he may not completely look like the improved population, because I think it's important to appreciate what the LDL values were in this population. Patients treated just with simvastatin alone had LDL values, after a period of years, of about 70 mg/dL, vs less than 55 mg/dL, about 53.2 mg/dL is listed here for the patients treated with ezetimibe. So, perhaps Mateo is a little bit more of an exaggerated patient or maybe he's not as adherent with his statin regimen as patients that were in the IMPROVE-IT trial.



Another way to look at this is the number needed to treat. The number needed to treat was respectable, being 50, but really, this is a figment. The number needed to treat looks good because we have a big difference with an endpoint that is commonly seen in this population. I can't get away from the fact that after 7+ years, the endpoint went from 34.7% down to 32.7%, a net difference of 2%, giving a number needed to treat at 50, but still high values for achieving that endpoint in both groups.

That was incorporated into ACC Expert Consensus Decision Pathway. This is how it was written in 2016. And very clearly, this pathway applies to Mateo. Now, you may think he has clinical ASCVD because he's admitted to the hospital, but what is his comorbidity? We didn't have a whole bunch of background, but don't forget that recent ACS, or a recurrent event while on statin therapy, is considered that comorbidity, so this algorithm does apply to him and it would, if you worked down, one thing that we should not get beyond is the need to use maximally-tolerated statin therapy, and I think that just has not been achieved in Mateo. If it were, then ezetimibe would be recommended based on this 2016 statement as first therapy after maximizing statin therapy with

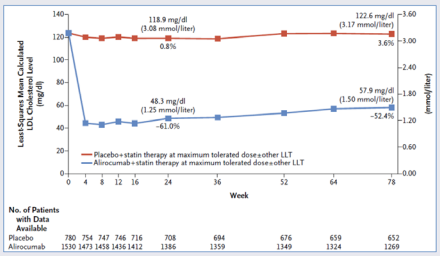


a PCSK9 laid out here as another option, a second option to think about.

Now, I do want to state that this was published in 2016, 1 year after IMPROVE-IT. Why is that important? Well, very clearly, that ACC Expert Consensus Decision Pathway is positioning PCSK9 inhibitors as second-line to ezetimibe. But what do we know about the PCSK9 inhibitors? We have alirocumab data from the ODYSSEY Long-term trial, that really shows, in a large population, these drugs are highly effective. Much more effective from an LDL-lowering perspective than ezetimibe. We see consistent reductions that were produced with this particular PCSK9 of about 50%–60% in lowering that LDL value, so very much comparing a strong LDL-lowering therapy when we're looking at PCSK9s to ezetimibe.

Alirocumab (ODYSSEY Long-Term): LDL-C Levels Over Time

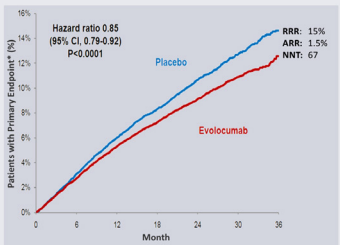
- 2,341 patients at high CV risk with LDL-C ≥70 mg/dL despite maximally tolerated statin ± LLT
- Randomized to
  - Alirocumab 150 mg q2w
  - Placebo
- Primary endpoint
  - Δ LDL-C at 24 wks



The one thing that PCSK9 inhibitors did not have were outcomes data, at least until earlier this year. What happened after 2016 was publication of the FOURIER data. This is evolocumab compared to placebo in patients who were clinical ASCVD patients, so secondary prevention, on top of a baseline of maximally tolerated statin therapy, which was mostly high-intensity statin therapy in the majority of patients.

Evolocumab (FOURIER): Primary Endpoint* Results

- 27,564 patients with ASCVD
  - LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL treated with optimal therapy (high-intensity preferred, minimum atorvastatin 20 mg daily or equivalent)
- Randomized to
  - Evolocumab 140 mg q2w
  - Evolocumab 420 mg q month
  - Placebo
- Primary composite endpoint
  - CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
- Median follow-up: 2.2 y
- Mean LDL-C values at 48 weeks:
  - Placebo ~89 mg/dL
  - Evolocumab 30 mg/dL



*Composite of CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization.

Now this is a very large trial of over 27,000 patients, so it was highly powered to achieve their primary endpoint of recurrent cardiovascular events. And if you look to the graph to the right, we see that those treated with evolocumab, in the red line, had fewer cardiovascular events than those in the blue line. And if we want to look at these results, they're, perhaps, a little bit more overall impressive when we compare them to IMPROVE-IT because of the magnitude of difference, seen only after about 2.2 years. Also important to note is the LDL values in these patients were comparing the placebo-treated patients, on top of a baseline of maximally tolerated statin therapy, an LDL of about 90 mg/dL, which dropped down to 30 mg/dL, with evolocumab as the PCSK9 inhibitor treatment, with the number needed to treat is 67. It's hard to compare numbers needed to treat across studies but I think it's important to sort of look at these in the big picture of things.

So, when we think back on Mateo, we can appreciate that he is a patient who is in need of further cardiovascular risk reduction therapy, but I want to ask Dr. Jones, maybe more specifically, in a patient who presents to you, who's had a recurrent cardiovascular… or cardiovascular event on statin therapy, how does that overall change your approach to managing their lipids?

Peter Jones: Yeah, I mean, the question I was going to ask about Mateo is he says he presents with an MI and he'd been on simvastatin for 3 ½ years. You would assume that that was his first MI, so he was being treated primary prevention and then had an MI, right? So, your first thought is, okay, well, maybe we started too late in his treatment. Maybe we didn't treat intensely enough, or his LDL was still 118 mg/dL in primary prevention. Maybe he should have been lower. But if this was… What if I told you that this was Mateo's second MI? And that he was put on simvastatin the first time, 3 ½ years ago, and now he's had another event? That will make you think a lot differently about what you might want to do. I do think he needs to be on high-intensity statin. His LDL is 118 mg/dL on simvastatin 40 mg/day. You're going to put him on 80 mg/day of atorvastatin or 40 of rosuvastatin if he can tolerate it. So where will his LDL go? How much lower? From 118 mg/dL?

Six percent, 8%, 10% maybe? Doing that? That's about all you'll get, so he'll still be above 100 mg/dL on that. So, the question is where's that threshold? What do you do next? And that's the question that I think you consider is, you'd like his LDL to be as low as possible. Certainly, if you get his LDL to around 100 mg/dL on high-intensity statin, he would probably benefit from ezetimibe, he'd get a 20%–25% reduction. You'll get him down there close to 70 mg/dL on ezetimibe. But he also has a baseline LDL on high-intensity statin after an MI, which fits the FOURIER study, and so his baseline LDL is very close to that. You give him a PCSK9, he'll get down to 30 mg/dL or 40 mg/dL, and he'll get a benefit from that in a couple of years.

So, it really is a decision as to what you're trying to accomplish and what you think is in his best interest. If was his first MI, maybe at his age you might say, well, yeah, high-intensity statin, maybe ezetimibe, see if I can get him down to 70 mg/dL. But if this is his second MI and the high-intensity statin and his LDL's around 100 mg/dL, maybe I'll look at FOURIER and sort of say, geez, I'm going to jump the ezetimibe and go to PCSK9. What do you think?

Joseph Saseen: I guess when I look at this patient right now, I have a few things that are suspicious in my brain. I know that during an acute coronary event, your LDL sometimes drops down so I'm wondering is this 118 mg/dL really on statin therapy? Does he have a nonadherence problem? He may not be taking his medication.

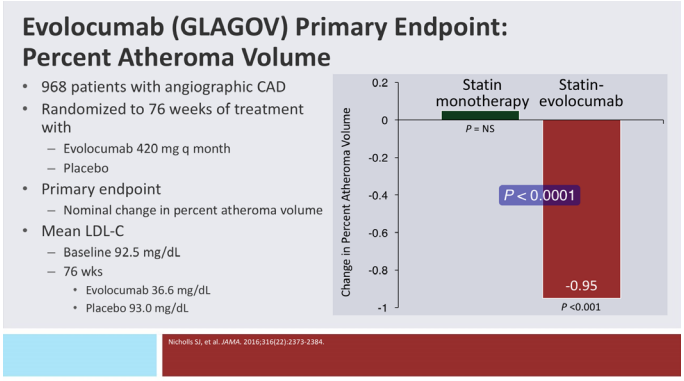
Peter Jones: Yeah, we don't even know what his baseline was. We don't even know how he responded to simvastatin. I mean, he could have had a great response to simvastatin, he could have had a terrible response to simvastatin. All we know, he's got 118 mg/dL on 40 mg/day of simvastatin.

Joseph Saseen: Yeah. It's possible, if he's taking his simvastatin, that his baseline's 200 mg/dL and it's dropped down a little bit because of his acute coronary event, so digging back—I call it a chart digest—going back and getting a little more information might be reasonable. But, given that, I think it's very reasonable to go to high-intensity statin therapy. If I had my magic wand, I would place him right now. I'd switch his simvastatin to atorvastatin 80 mg/day.

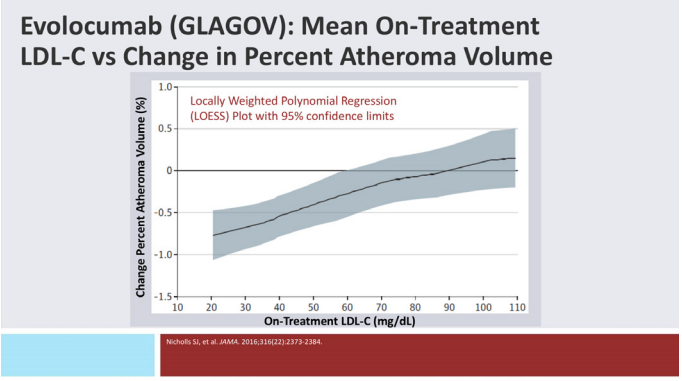
Good data, long-term data, the MIRACLE study, other studies support that treatment during acute coronary syndrome. I think it's sort of a given that we have to give that a chance to work or chance to fail, whichever perspective you want. I think, when you think PCSK9 inhibitors in this person, I'm not closing the door on it, but I think I might be a little premature. There's some tempting data though from angiographic studies. Have you heard? What's your take on some of the GLAGOV data?

Peter Jones: Well, you've got them. You've got them. You might as well go ahead and show it because this is the other point about, maybe with a recurrent event where you might say, geez, we didn't see this with statin treatments. So you present the GLAGOV.

Joseph Saseen: Yeah, the GLAGOV data, if you haven't heard of it, it preceded the FOURIER. It came out, it looked at almost 1,000 patients with angiographic CAD and evaluated evolocumab vs placebo in these patients, with a primary endpoint looking at percent atheroma volume. And you can clearly see on the right that there was regression, or decreased atheroma volume, with the addition of evolocumab, but not with placebo. So, this is actually suggestive that these robust reductions that we get with PCSK9 inhibitors, displayed on the bottom right, treating patients to LDLs in the 30s, that maybe we can get significant reductions in plaque burden or plaque volume. Matter of fact, you could even plot it off and this is just another way of depicting some of the data from GLAGOV and look at the percent change in atheroma volume vs the LDL achieved in these patients, these 1,000 patients, and the lower the LDL value that was achieved, the more reduction or decrease in atheroma volume we have. So, I guess this builds sort of a good hypothesis that, something that I believe in, which is lower is better, and maybe it could



be a PCSK9 effect or it could be just a fact that these are strong drugs. So, it does sort of open that door that maybe it's an LDL effect that lower can result in these beneficial effects.



Peter Jones: I agree. This makes me [lean] a little bit more to the more complicated, recurrent-event patient on optimal statin treatment, to maybe think of a PCSK9 and the lower LDL you can get earlier in that kind of patient situation, than maybe somebody who has had the first MI, for instance. But, you know, as I said, if he wasn't that kind of case, this was his first MI, you might give him a chance to go to high-intensity statin, maybe ezetimibe, and see what he does. Depends on the complexity of his coronary disease, but if it was recurrent events on the statin, I think the GLAGOV sort of supports that in a very short period of time, you get regression, which you're not going to get by just a little bit more intensifying his statin treatment.

Joseph Saseen: And we have time for some questions from the audience.

Joseph Saseen: So, the question is, "Is it the statin or is it the LDL that provides the benefit in event lowering?"

Peter Jones: Well, I do think your question is really getting down to the issue. Do statins do more than just lower LDL? And there's always been this pleiotropic effect issue of statins reducing inflammation and changes. There still is that possibility, yes, and it's hard to separate the LDL-lowering from other effects statins may have. I think the randomized clinical trial data suggests higher intensity statin does give you incremental benefit than lower intensity statin, maybe because it's LDL, maybe because there are other factors we haven't been able to suggest. I will say the PCSK9 monoclonal antibodies do not change inflammation, so they do not lower CRP, but they cause regression in a real short period of time, so that is LDL, okay? So I think most of the stuff from statins is LDL, but I think they're proven drugs, they're safe, they work. You should maximize them as much as possible and then decide on moving to nonstatin drugs with further focus on LDL as the ultimate goal.

Peter Jones: It's patient decision, what you expect, what you want in the short-run, long-term, that makes the decision of how you add these nonstatin drugs. In the patient situation, baseline LDL, comorbidities, all determine probably which nonstatin drug you would add. Yes?

Attendee: Yes, they also mention bile acid sequestrants. So the question is, in your past experience, how many medications do you add on to somebody like this to get them to goal? One agent, 2 agents, 3 agents, 4 agents? When does it become impractical, at what point?

Peter Jones: Well, that's a great question because prior to PCSK9s, this is the kind of guy with recurrent events who would be on the maximal statin he would tolerate, then you'd add ezetimibe, then you'd add a bile acid resin. And, yeah, if you gave all 3 of those, he could get his LDL below 70 mg/dL. If you did, from 118 mg/dL, got him to high-intensity statin, added ezetimibe, added a bile acid resin, you could probably end up at 60 mg/dL on him. That's what we used to do. The patient would scream and yell about all the pills they were taking and they hated it and the question is, would they comply with it? Being able to come up with another treatment that gave profound LDL lowering and simplified treatment, increases patient adherence, obviously. There's a cost issue to it, but from the patient's standpoint, I think they were all over this. It was not very hard to get patients to switch from taking all the colesevelam and others that they were taking. Some were even taking niacin, too. We had 4 drug treatments in the FH patients, for instance, to try to get them anywhere reasonable. So, these drugs have helped patient compliance and I think *that* will end up with the result because they'll have consistently low LDLs because they comply with their treatments long-term.

Joseph Saseen: And my comment based on that is, at what point would you accept multiple drugs to control lipids? I think it depends on your patient. I have hope for this guy that I do believe that maybe 2 drugs might get him to an acceptable level. It may be rosuvastatin 40 mg/day or, at least, atorvastatin 80 mg/day might be needed with perhaps ezetimibe. It may get an acceptable level. I have much more tolerance for multiple lipid-lowering drugs for those patients with FH because of their more exaggerated background or baseline LDL. So the big thing here I really want to see is, what was this patient's baseline LDL. I think that would help.

Attendee: Thank you for a great presentation in this great case. Where would you fit the results of the CANTOS trial, as we know them as of this moment? Didn't lower LDL, did in fact decrease inflammation, and did reduce cardiovascular events. Do you ever see a time in the future where there's a marriage of both lowering LDL and using an anti-inflammatory?

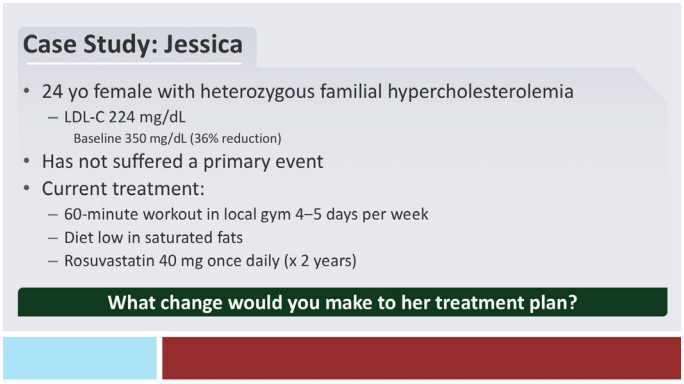
Peter Jones: Yeah, that's a great question and it's a little outside the realm of what we're going to talk about here this evening, but you're correct. We'll hear about CANTOS in a few weeks, at the ESC meeting, exactly what the impact was, but it's a monoclonal antibody to interleukin-1b given over 3 to 4 years after an event. It did reduce cardiovascular events through reducing a target on inflammation. Of course, this is being looked at through other mechanisms of reducing inflammation with a trial that Paul Ridker is doing with methotrexate as a chronic treatment in patients. So, we may end up marrying certain treatments to reduce cardiovascular events that don't work through LDL, but they work on modulating atherosclerosis, which is a complex disease. Of course, it even rolls over into diabetes, when you start introducing drugs that reduce heart failure and death and they don't really change the glycated hemoglobin (A1c) much more than some of the other drugs, but they reduce heart failure and death. They do it through different mechanisms, but they are used in high-risk patients and give benefit. So, yeah, that's a complicated issue as how that will get incorporated into these high-risk ASCVD patients with recurrent events. It will probably be there, but it's going to get complicated for those of us that manage these patients. You're right.

Joseph Saseen: Yeah. All I can say is it's going to be exciting to see how cardiovascular disease changes with some of these new data. That's not the last of that story.

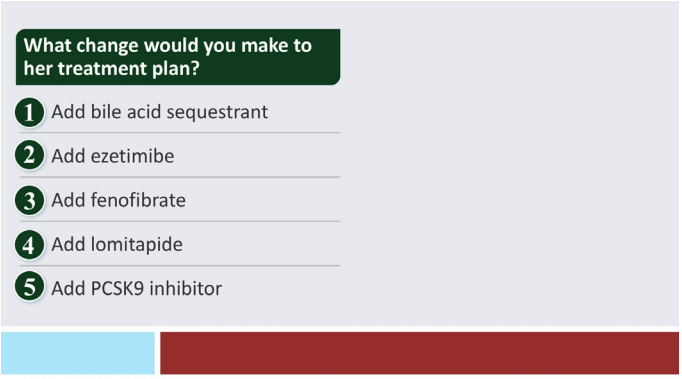
Peter Jones: It is… it's not the last of inflammation impacting vascular risk. Okay, second case.

Case Study Jessica

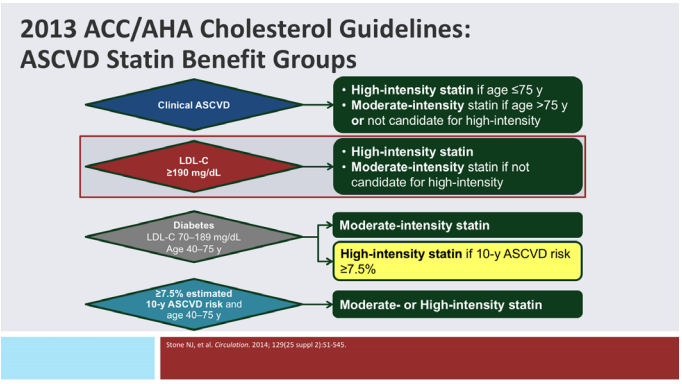
This is a young woman, Jessica, 24 years old, primary prevention heterozygote FH. Her LDL is 224 mg/dL on a statin from a baseline of 350 mg/dL. So she's not a subtle heterozygote FH patient. Her current treatment is rosuvastatin 40 mg/day, which she's been doing for 2 years and she does the right exercise and low-fat diet. Obviously, she has been talked to about her pregnancy protection, which you all should do if you're going to put young women with FH on statins, but I think her PCP has done a pretty good job up to this point—or somebody—in talking to her about early intervention in FH to get a lifetime risk reduction.



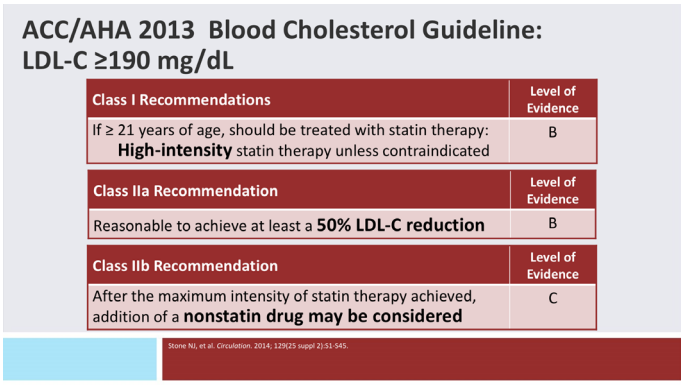
So the question is, what changes would you make to her treatment plan? So, see where LDL was, where it is, the reduction she got on 40 mg/day of rosuvastatin, which is a high-intensity statin. So, would you talk to her about adding a bile acid sequestrant, ezetimibe, fenofibrate, lomitapide, or a PCSK9 inhibitor?



So, let me just sort of say… Most of you would add a PCSK9 inhibitor. I will tell you that in the ACC/AHA, she fits in group 2, except for her age. They don't really say anything under the age of 40 years old for heterozygote FH. It's usually ages 40-75 years and if they're primary prevention or secondary prevention, you use high-intensity statin, so she is an FH, with a baseline LDL more than 190 mg/dL. She's primary prevention, but doesn't really fit the age range. Does anybody, Joe, have a recommendation for age range in what to do with high-intensity or more in statins, add-ons, anything? I mean, this is what they said—maybe you could consider a nonstatin drug after you used high-intensity statins in FH, but they sort of said it was up to… It was a low-evidence recommendation.



Joseph Saseen: Yeah, I think this is just maybe an area that hasn't been studied as well. Age 21 years and up, I'm comfortable. If you think about when you can use high-intensity statin therapy. The one thing that jumps out about this person is that it's a woman of childbearing potential and it wouldn't hold me back and maybe when you're in your 40s there's less of a risk of that, but 21-years-old and up is a point where I would really feel pretty comfortable in using high-intensity statin therapy in this kind of woman, because of her presentation and because of her maybe blunted response to her current treatment.

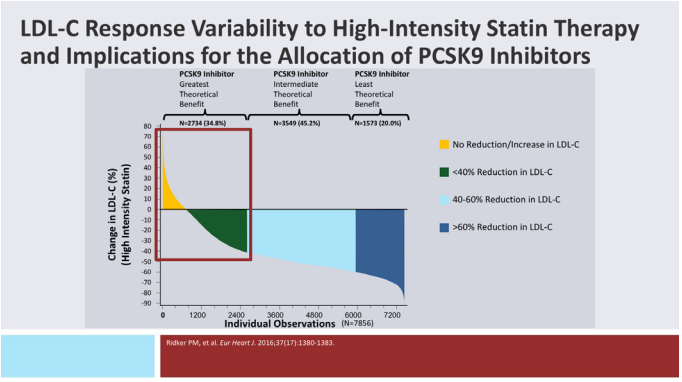


Peter Jones: Yeah, we'll talk about that blunted response in a moment. Any trouble with ezetimibe or a bile acid resin being added to a woman of childbearing potential?

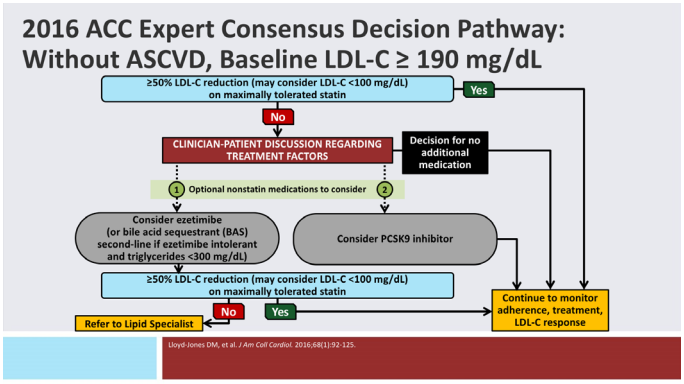
Joseph Saseen: Absolutely no problem with the bile acid sequestrant. That's a nonsystemic drug that should be viewed as very safe and even compatible with pregnancy. Ezetimibe, probably is okay in pregnancy, but it was approved when we had pregnancy ratings and it's considered a C, so it's a little bit more concerning than a bile acid sequestrant, which is labeled as a B where we know it is safe. I still would be okay in using these drugs, especially with a bile acid sequestrant, but I think it would require me to do some other things and due diligence with education in other treatments.

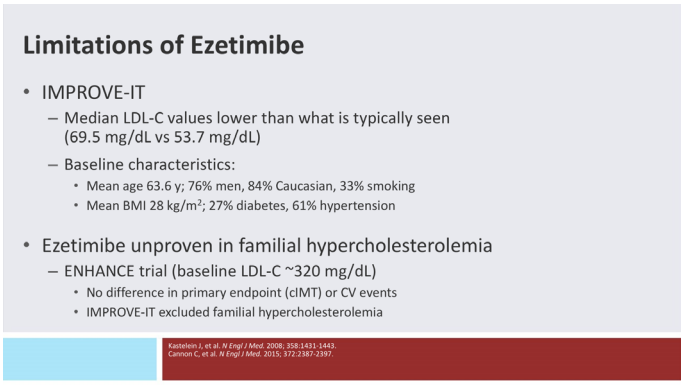
Peter Jones: I mean, the problem is, she is not a subtle FH patient. She's probably got a monogenetic… You've probably listened to some of the gene discussions this evening. To have a baseline of 350 mg/dL, she probably is a monogenetic. You get to that high a level, and they do have very high risk of heart disease early in life. The fact that she responded a little less than you expect to 40 mg/day of rosuvastatin is not unexpected with statins. I mean, some of you've probably seen that happen. You give a patient a statin and you see these waterfall plots and not everybody gets the mean 50% or 55% reduction. Some get more, some get less. And there's some that don't even respond much at all to statins, which we don't understand completely, but they are hyporesponders to statins. She seemed to get less of a response than you would expect.

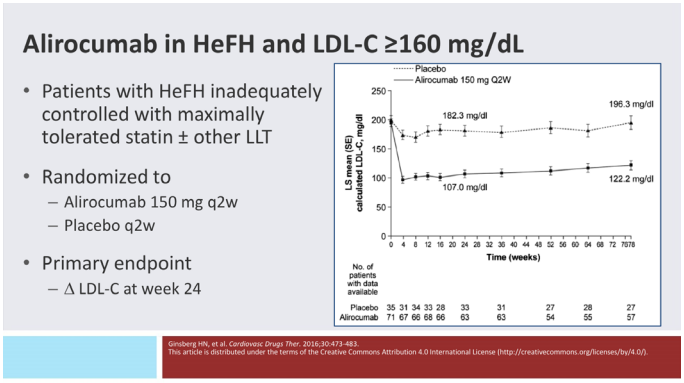
This was an interesting paper by Paul Ridker. What he was saying, using these kinds of LDL response variabilities, you might consider this in allocating a PCSK9. So, he was saying that maybe, in this group down here, the one on the waterfall plot that gets less than 30% reduction on high-intensity statin. Yeah, you're giving them the high-intensity statin, so yeah, maybe they're getting some anti-inflammatory effect, but they're not getting the LDL effect. So, what do you do? You can add ezetimibe. You could add bile acid resin, but depending on where they are, they need substantial LDL lowering and maybe with an FH patient, that kind of hyporesponder, would be something that you might consider. So that was an interesting thought. He said, less likely to use PCSK9s if you're a normal responder and you get the really good response to high-intensity statin.

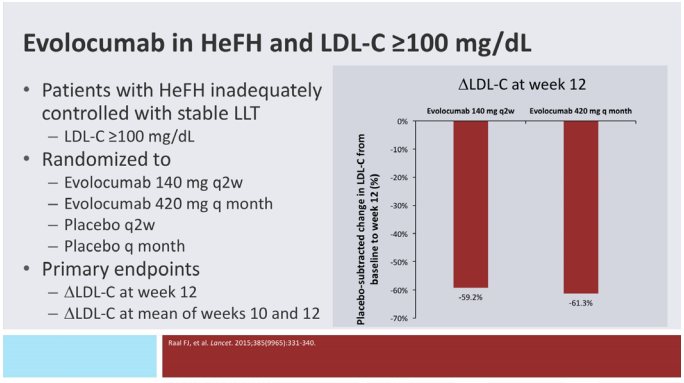


The question I have for her, and this is with the Expert Consensus Panel, without ASCVD, they did say you could consider a PCSK9 inhibitor and ezetimibe. But again, most of this is in patients who fit the older patient groups with FH, and there's not a lot of data in young people with FH to use the PCSK9s. I will say that the data for outcomes with ezetimibe are in older patients. I mean, it's with patients with ASCVD, which is the IMPROVE-IT trial, and even when they tried to add it in patients with FH, which was a carotid intima media thickness study which failed, which was the ENHANCE study, it didn't seem to help much adding on top of high-intensity statin so there's a lot of limitations about PCSK9… I mean, about ezetimibe, there. There is data that PCSK9s work in heterozygote FH very well. Plenty of data with alirocumab lowering LDL at least 50% from baseline and the same with evolocumab reducing LDL at least 50% from baseline in heterozygote FH.









So, one of the questions I think, Joe, that I was wanting to know is that is hyporesponsive in FH, should that make you think… If they take a high-intensity statin and get less response, could part of that response … Is that meaning maybe you should be checking Lp(a)?

Joseph Saseen: You know, I was going to ask you the same question actually. This might be the kind of patient where you would check Lp(a) to see that may explain some of the lack of response. Clearly, this lady has had some response. Not as much as we would predict. And there is some normal variability amongst patients. Not everybody is going to get what you predict. Her reduction is less than 40%? Okay. That's definitely in that range where I'm thinking, hey, maybe she has high Lp(a). That would explain some of her blunted response. It doesn't mean that you wouldn't still treat her and treat her aggressively, but it is something that I think has some merit and for clinicians that actually see these kind of patients, they will more commonly measure Lp(a) to help gauge their intensity to treatment and maybe to modify some of their treatment approaches overall.

I think it's really easy in this kind of person to say—at least my perspective—I look at her, I'm like, I really want to advocate strongly for a PCSK9. I'll fill out the prior authorization. I work at a great institution, we have a great team of people, that overall health care team approach to getting these prior authorizations for PCSK9 patients that really need them and meet criteria. This is a woman who would look like it. Some prior authorizations may require the use of ezetimibe, so I'm always concerned. I remember the ENHANCED trial and those were patients with familial hypercholesterolemia and the results were not perfect, not perfect studies on it, but they were disappointing. So, I accept sometimes that I might start ezetimibe to, I hate to say, go through the motions, but if I add it on, I would not think it's going to get me to the endpoint I want. It would basically be to help me get that prior authorization for one of the PCSK9 inhibitors approved.

Peter Jones: Well, you know, getting back to the fact that she's 24 years old and we didn't get into the history of whether she's married, whether she wants kids and all that, but pregnancy issues become a concern. So, we talked about ezetimibe, what you felt about the safety of that. Bile acid resins are clearly safe. Monoclonal antibodies, what do you think about the safety?

Joseph Saseen: That's a great question. This is one where there's phase 4 data, mandated by the FDA to look closer at pregnancy and women that develop pregnancy while treated with a PCSK9 inhibitors. We need that data and there was a change with the FDA a few years ago that we're not going to see pregnancy categories for new drugs any more. There's a great little explanation provided to clinicians for you to make the choice.

So, what we know about, these are very focused treatments. Monoclonal antibodies for PCSK9, which doesn't seem to have any other physiologic purpose that you would predict would cause embryonic damage.

Peter Jones: They don't cross the placenta, right?

Joseph Saseen: Yeah, they shouldn't because of the molecule size and that they're monoclonals. So, we would think that, just like insulin and large molecules, subcutaneous injection for stability, it shouldn't cross the placenta so you would expect it to be safe for pregnancy and a lot of clinicians believe that despite some of the lack of current data.

Peter Jones: So that would make you feel a little bit more comfortable if you wanted to take that step. So, her LDL's 224 mg/dL. If you were to add ezetimibe, okay, it might get her below 200 mg/dL, okay. So she ends up at 180-190 mg/dL. Okay. Everybody feel comfortable about that? You may. You could add a bile acid resin on top of that and you might get her from that 180-190 mg/dL down to 140-150 mg/dL. But now she's got to take that handful of drugs we were talking about before in order to get down to that range. And she might. But they're all reasonably safe in pregnancy. If she had a high Lp(a), would that push you more towards not using ezetimibe and a bile acid sequestrant? Would you then move more towards the PCSK9 for her?

Joseph Saseen: I would.

Peter Jones: Would everybody feel more comfortable? I mean, I think Lp(a) probably should be measured in all FH patients anyway, but, I mean, she would probably be one you'd definitely want to measure because of her somewhat, seemingly not as good of a response to rosuvastatin 40 mg/day to see if she… and if her Lp(a) was really high enough, yeah, she's got a high risk for heart disease, but also, you know, aortic

stenosis and an earlier treatment paradigm safe for her at her age, might be a PCSK9 monoclonal antibody.

Joseph Saseen: It's certainly a way to help the approval… Well, you would think that would help with the approval of your PCSK9 inhibitor.

Peter Jones: Correct. Now, would anything else help you with wanting to be more intense with her treatment and getting a lower LDL, such as using a PCSK9? Would you do a coronary calcium score on her?

Joseph Saseen: So, personally, as a pharmacist, we don't do much of those in my practice. I'm thinking this is probably a woman that you could, depending on the cost and her available… I'm not sure it would make me want to be more aggressive because I already want to be aggressive in this woman.

Peter Jones: Yeah.

Joseph Saseen: Would you order a calcium score?

Peter Jones: I don't know. I mean, if it's zero, is it going to change what you do?

Joseph Saseen: No.

Peter Jones: If there's something else that would make you be more intensive, maybe. I think some of us would want to be that anyway. So, I think that's probably where we would go. I just want to make a comment about the NLA update to the use of PCSK9s in a patient just like Jessica. They did go in that group between 18 and 39, less than 40 years old, young patients. And they did say that PCSK9s should be used if they have some other comorbidity with their FH. So if their FH is clearly monogenetic gene, they always have high risk and you should get lower LDL. So, if there's definite gene defect, you probably should consider it in a younger person. If they have high Lp(a), that would be another comorbidity. And if they have evidence of noninvasive vascular disease that you could consider that a higher risk, younger patient for PCSK9 under the age of 40 years.

Attendee: So, I don't know that we have a lot of data, but my question is, if she decides she wants to get pregnant for that 9-month period and/or the 6 months she might breastfeed, would you stop all medicines? Would you continue one? Would you continue all?

Peter Jones: Well, the question with the statin is, as we all know, she should stop it before she gets pregnant. As I always told my younger FH patients, women, I said, "I want to be the second person that knows you want a child." And that's when we stop the statin and then you try and then you get pregnant and then you go through breastfeeding and then we start. I used to continue bile acid resins and stuff while they were pregnant, at least during that part if they could tolerate it without the constipation, but the PCSK9s we talked about, we don't know whether you should stop them. It probably does not come out in breast milk. It probably does not pass the placenta. You probably could continue that, but not the statin, so far, is what I would recommend.

Joseph Saseen: I think that's a good way of looking at it and I think this is where you really poll the patient and have their choice respected. We had a great lecture yesterday from Ann Goldberg… or this morning actually, from Ann Goldberg and Lipid Academy. And this exact question was posed and what her preference was, and I'll just share her preference, because she has a lot of experience with this kind of thing, is that she routinely stops all therapies but the bile acid sequestrant during pregnancy and throughout breastfeeding, to be conservative. Now, if a patient was willing to accept potential, very low, potential risk of the PCSK9 inhibitor, I would be inclined to consider that. I think if you think of the finite period though, stopping therapy and just bridging with a very weak agent like a bile acid sequestrant, or a moderate, I guess, agent, like a bile acid sequestrant, might be the most conservative and probably okay approach for that period of time.

Peter Jones: The only problem is that some of these women want to have 5 kids! And I'm sitting here like, "Okay. This is getting to be a long time here, you know!"

Joseph Saseen: And potentially pass on that gene, right? So, I mean, there's another family planning aspect that's beyond this presentation, that if she really has heterozygote FH, that her offspring may actually inherit one of those genes.

Peter Jones: Yeah, so you counsel them if you want to have 5 kids, you increase the chances that one of them is going to get your gene.

Attendee: So, if you chose to put them on bile acid sequestrant during pregnancy, you're monitoring them. Are you monitoring their triglycerides and stuff? Because you know how trigs will go up during pregnancy? Do you pull them off then or how do you handle that situation?

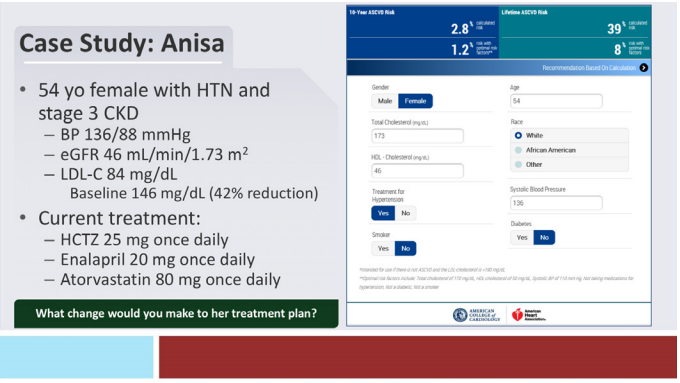
Peter Jones: Well, it is going to be something you'll have to monitor during pregnancy, particularly there's a lot of things you have to monitor: weight gain, impaired fasting glucose, gestational diabetes, preeclampsia. There's a lot of other factors that will contribute to their future risk of heart disease, as you well know, because preeclampsia and impaired fasting glucose and gestational diabetes are bad, future cardiovascular risks for women. So, you're going to have to monitor all those things, but, yeah, I think you wouldn't want the triglycerides to go up, and hopefully they wouldn't gain weight and develop insulin resistance and get hypertriglyceridemia, but that would be something you would have to follow.

Peter Jones: Well, I think it depends on what their baseline is and then what happens after that. I mean, if it's continually going up, I think, you know, if it goes to 200, 300, 400 mg/dL, yeah, you're going to have to stop it at 300, 400 mg/dL. It may contribute and you probably should back off of it if it gets to those kinds of levels because if those are fasting levels, then post-parandially, they even go higher. So you probably need to consider stopping it if they go above 300 or 400 mg/dL on a bile acid sequestrant.

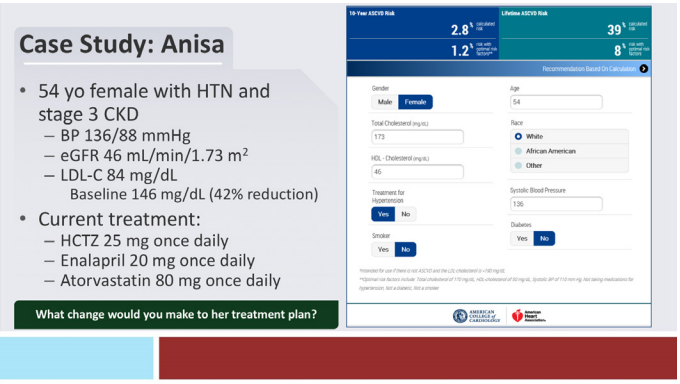
Joseph Saseen: Absolutely. Great discussion about lipid disorders in pregnancy. Our next case is also one but I don't think we'll have *that* conversation.

Case Study Anisa

This is Anisa. She's a 54-year-old female with hypertension and stage 3 chronic kidney disease. Her blood pressure is 136/88 mm Hg, estimated GFR indicates stage 3 is 46 mL/minute/1.73 m². Her LDL is 84 mg/dL. Baseline, we have it available. It was 146 mg/dL. So, she has had a 42% reduction from her measured baseline. Currently, she's treated with hydrochlorothiazide, enalapril, and high-intensity atorvastatin, that being 80 mg once daily.



On the right, we see the 10-year ASCV risk score. So, who here has calculated 10-year ASCV risk in a patient? Okay. Now, when we look at her risk score, if we put in her numbers, we're going to be probably a little surprised that her 10-year risk is only 2.8%. However, one common sort of problem that we have with calculating 10-year risk score is the cholesterol values that you put into them should be at baseline and we put in actually her on-treatment, her on-atorvastatin 80 mg/day treatment. So, I'm not surprised that her 10-year risk is being calculated at a very low value. If we actually had her pretreatment, her prestatin values, we could put them in there and get a more accurate picture of her baseline risk because I'm sure that it's greater than 2.8%. So, don't be fooled that when you have low numbers, it might be because you're using an on-treatment cholesterol value into the calculator.



But the question for Anisa right now, this CKD patient, stage 3 CKD, 54 years of age, hypertension and LDL down to 84 mg/dL on atorvastatin 80 mg/day is, "What change would you make to her regimen? Would you continue atorvastatin 80 mg/day and call it a day, or would you maybe change atorvastatin to rosuvastatin 40 mg daily? Would you

add a bile acid sequestrant, add ezetimibe, or would you add a PCSK9 inhibitor? Which would you choose for Anisa?"

What change would you make to her treatment plan?

1. Continue atorvastatin 80 mg once daily
2. Change atorvastatin to rosuvastatin 40 mg once daily
3. Add bile acid sequestrant
4. Add ezetimibe
5. Add PCSK9 inhibitor

We have a majority. So most people are adding ezetimibe, but a quarter of patients are deciding to call it a day, continue atorvastatin 80 mg once daily and then with a little uptake of maybe using a PCSK9 inhibitor. Majority, though, is comfortable in adding the ezetimibe. And I think when you look at this patient, what is driving your decision? What is it about this patient that concerns you? I think that we always have to think of patients broadly. She does fit into, from the ACC/AHA approach, she is in a statin benefit group. She's in the primary prevention without diabetes population, which was introduced by Dr. Jones in the introduction and it really would tell us for patients like this patient, Anisa, she's between the ages of 40 and 75 years, and her 10-year ASCVD risk is not 2.8%, it is higher. So, I'm making a very broad assumption that if we put in her baseline values, that she would be at the 7.5% or greater. And in that case, you have the option of moderate- to high-intensity statin therapy.

ACC/AHA 2013 Blood Cholesterol Guideline: Primary Prevention—No Diabetes Mellitus and LDL-C 70–189 mg/dL

Class I Recommendations	Level of Evidence
The pooled cohort equations should be used to estimate 10-year ASCVD risk to guide statin therapy	B
Adults age 40 to 75 years with 10-year ASCVD risk >7.5% should be treated with a **moderate to high intensity statin therapy**	A

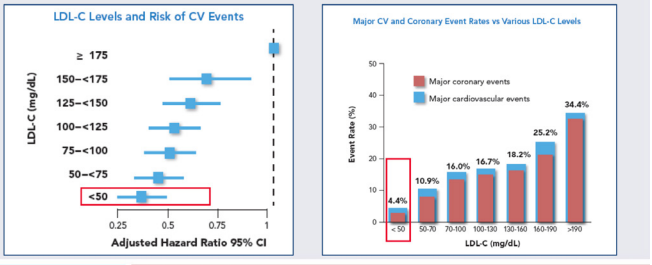
Class IIa Recommendations	Level of Evidence
Reasonable to offer **moderate intensity statin** to adults age 40 to 75 years with a 10-year ASCVD risk of 5 to <7.5%	B

Stone NJ, et al. *Circulation.* 2014; 129(25 suppl 2):S1-S45.

I guess when you take a step back, we can't be mind-readers and look at everything in the past, but this is a woman who is primary prevention and her provider chose to either start with high-intensity statin therapy or titrate her up to that to get this LDL value of currently 84 mg/dL. Now she might be a little bit of a hyporesponder, too, because you would expect with atorvastatin 80 mg/day, you probably would at least realize a 50% reduction, but there was an… I'm interpreting and overall seeing an aggressive approach that I'm thinking is probably appropriate for this patient and, you know, there's other recommendations at when you would just be okay with moderate-intensity statin therapy. That could be patients who have a little bit lower 10-year risk scores. I'm not thinking that is actually the area that fits this particular patient. I think one thing that might be driving her aggressive approach might be her baseline CKD, but before we go down that route, I want to sort of throw out another possibility.

Perhaps this clinician was comfortable in aggressively treating Anisa because of data from meta-analyses, like this particular one, that we are showing you right now, that really shows a relationship that, based on clinical trials, the lower the LDL achieved, the lower the risk of cardiovascular events. We see that very clearly on the left that patients treated to an LDL of less than 50 mg/dL, in this forest plot, that they have lower risk ratios than patients treated at 2 higher LDL values. That gives us some information. If you want to look at the actual numbers, the percents from the same meta-analysis, of cardiovascular events, if you look at red, that's just major coronary events, but in blue, which would be appropriate for a woman especially to also include stroke, we see those percentages, too. And if we treat, perhaps, based on these data, on good meta-analysis, the most aggressive approach and achieve an LDL of less than 50 mg/dL, it's associated with a risk of about 4.4%, compared to her right now being about 16%.

Very Low Levels of Atherogenic Lipoproteins and the Risk of Cardiovascular Events: A Meta-Analysis of Statin Trials



Boekholdt SM, et al. *J Am Coll Cardiol.* 2014;64:485–494.

Now, these are meta-analyses. They're not going to give us all the answers, but I think that relationship of maybe treating more aggressively may give you more predicted reduction in cardiovascular events. You know, we went back and forth on agreeing on this. I think now, we have PCSK9 inhibitor data, and even with IMPROVE-IT, that it supports that LDL-lowering hypothesis. Perhaps that explains Anisa's aggressive approach. But, I guess, I sort of tip my hat a little bit. When I look at this patient, she does have stage 3 CKD. The NLA's approach, when you look at risk stratification, is to identify CKD—significant CKD like this patient—as a risk factor that will lead to a high-risk category and a more aggressive approach. In your practice, how do you consider CKD in your aggressiveness?

Peter Jones: Well, it is an important part of your consideration. Why has she, at 54 years old, got an EGFR of 45 mL/min/1.73 m²? I mean, I would like to know her urinalysis. She's got protein already. Are there some other issues going on? This is not going to be a good thing for her, starting young at 54 years old. They do have higher risk of cardiovascular disease and, you know, it's not captured in the pooled cohort equation. None of that with where her kidneys are, and why they're at that point, is captured in this. I think this is… we talked about what other factors besides, okay, she's got hypertension. Oh, and then she's got CKD. So, she's primary prevention with comorbidities, but she doesn't have diabetes. You know, I'd like to know, does she have protein in the urine? Is this something I'm going to worry about in the short run? Not just for her kidney function, but overall cardiovascular risk. Even at 54 years old, deciding on more intensive treatment for her, is this one were coronary calcium might be a measure?

Joseph Saseen: It might help you. Yeah.

Peter Jones: Anybody think that that might be something? If she had zero, you might just stick with 80 mg/day of atorvastatin and if she had positive coronary calcium at 54 years old, you'd be more intensive? That's something to worry about?

Joseph Saseen: And if you're convinced to already treat more aggressively, you don't need another test. Maybe that's more for the people, I call it "on the fence," when you're not quite sure. Or maybe the patient's giving you some… You really want to treat more aggressively and they're giving some resistance. Sometimes it helps with that shared decision-making. Or, because I'm always an advocate, if you've already made your decision to be aggressive, you don't need another test probably. But I think it does help some people to give you more information.

Peter Jones: It does.

Joseph Saseen: To make your treatment decision.

Peter Jones: It can. I guess the question is, if you keep her on the statin dose and don't add anything, I mean, that's probably fair. But if somebody wanted to add ezetimibe as a treatment, that would certainly get her another 20%–25% lower on LDL, which is really quite impressive. She'd be well under 70 mg/dL if she responds appropriately. Any data that ezetimibe is okay in CKD?

Joseph Saseen: Yes, and let's share some of that. And when you talk about CKD, when you think about drug safety and CKD, as a pharmacist, this is where my attention goes up, right? CKD, I want to assure safety. When we think about just statins in general, we had this historic, sort of reluctance to include CKD patients into long-term trials because of fear of an increased risk of muscle-related side effects, and because of that, a lot of trials systematically excluded people with kidney disease. One way to look at statin safety, if we just start there, in CKD, one pharmacologic perspective that's nice about her current treatment, which is atorvastatin, is [it's] the least dependent on renal elimination, less than 2% of that drug is eliminated unchanged in the urine, vs everything else is greater. And the other high-intensity option being rosuvastatin might be fine, but that is eliminated 10% unchanged in the urine. So sometimes we look at drug elimination in patients with impaired kidney function and that characteristics of drug elimination help influence our choice, so I'm happy with atorvastatin, but we do have some data with CKD.

You may think, oh… For those of you who are may be thinking PCSK9 in this patient, there's some data that's evolving. These data come from the ODYSSEY trials, a pooled analysis that looked at alirocumab vs placebo or ezetimibe and if you look at the

populations on the left, there are patients with ASCVD, with estimated GFRs of less than 60 mL/min/1.73 m² and if you look at overall, these are pooled data. This is not a definitive answer. It's sort of preliminary data, but there is a trend that there may be lower cardiovascular risk, similar to what we might see in patients with ASCVD and diabetes. This is not definitive by any means, but at least it's some suggestive data that perhaps CKD coupled with ASCVD may be in the right direction. This patient does not have ASCVD. They just have CKD, but I think this is what we have available right now with major adverse cardiovascular events with the PCSK9 inhibitors. The one question that Dr. Jones asked, though, is do we have data with ezetimibe. Yeah, we do and it's good safety data.

Relationship Between MACE* and Lower LDL-C in Chronic Kidney Disease

Pooled analysis of 10 ODYSSEY trials comparing alirocumab vs placebo or ezetimibe in patients on maximally tolerated statin

Population	n	Hazard ratio (95% CI) per 39 mg/dL lower LDL-C
Overall ASCVD	3503	0.75 (0.62 to 0.90)
Polyvascular Disease	943	0.71 (0.49 to 1.01)
ASCVD + DM	980	0.65 (0.49 to 0.86)
ASCVD + eGFR <60	660	0.69 (0.48 to 1.00)

*Composite of CHD death, nonfatal MI, fatal/nonfatal ischemic stroke, unstable angina requiring hospitalization.

Ray KK, et al. *J Am Coll Cardiol.* 2017;69(11):55. Abstract 1126-316.

So, the one study that welcomed patients with CKD was the SHARP study, almost 10,000… or a little over 9,000 patients in the study all had CKD, a third were on dialysis. Two-thirds were predialysis or just had impaired kidney function, impaired chronic kidney disease. And these patients, who are primary prevention patients, after a period of years, placebo was compared to ezetimibe with simvastatin 20 mg/day and there was overall benefit at reducing cardiovascular events. But the question about safety is really important because that really was the early part of this study. This study, at the end of the day, at the end of it, actually compared 2 drugs to nothing and showed benefit, as far as cardiovascular event lowering, but the first year of this study was a safety analysis and it really did prove that both simvastatin 20 mg/day alone and simvastatin with ezetimibe were considered safe, to the point where, at the end of the study, when both those drugs were used together, we didn't see an increased risk of predictable, or at least fearful, adverse events that may be increased by the presence of CKD, like extra myalgias, or a high access rate of patients dropping out.

The Study of Heart and Renal Protection (SHARP)

- 9438 patients with CKD
  - Not on dialysis: SCr on 2 occasions ≥1.7 mg/dL (men) or ≥1.5 mg/dL (women)
  - On dialysis: hemodialysis or peritoneal dialysis
- Age ≥40 y with no history of MI or coronary revascularization
- Randomized to
  - placebo
  - ezetimibe/simvastatin 10/20 mg daily
  - simvastatin 20 mg daily

  1 y to assess safety; after 1 y, rerandomized to one of the other two groups
- Total median follow-up 4.9 y

Baigent C, et al. *Lancet.* 2011; 377: 2181–2192.

So, from a safety perspective in CKD, atorvastatin looks like a good drug, so does ezetimibe as far as safety. I would even throw in there, if you're looking for another statin that's really proven in CKD, we can go pharmacologically based on atorvastatin, but we also can look at simvastatin 20 mg/day, which was used in this particular study as being studied long-term in a CKD population.

Peter Jones: So, one question I have is, is the monoclonal antibody excreted in the kidney?

Joseph Saseen: I want to say no. I'm not 100% certain on that. Usually monoclonal antibodies being large molecules are not excreted unchanged in the urine at all, so I'm suspecting a very low incidence of that.

Peter Jones: So, if she were to progress slowly over the years, or if the estimated glomerular filtration rate reduces, you wouldn't need to necessarily… if you went to a PCSK9 or thought that was useful—and I'm not using her, but if you were to use it in someone with CKD—that probably wouldn't need to be dose adjusted, for instance. Same thing with ezetimibe because they had some patients who had stage 5 CKD and it didn't seem to have any safety issues in them either so, you know, I think those are good.

Joseph Saseen: So, the question is, any concern about using the maximum dose of atorvastatin lowering HDL?

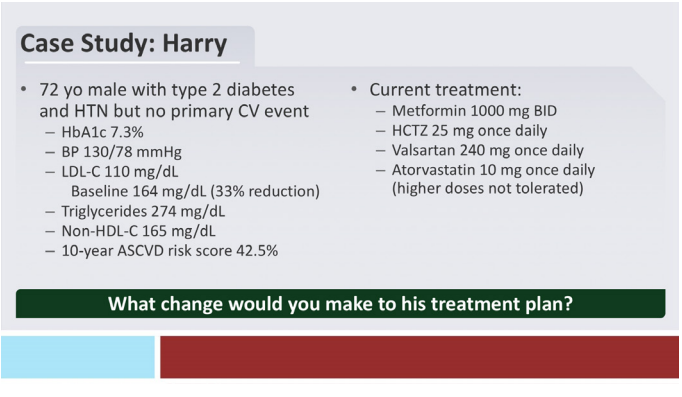
Joseph Saseen: Yeah. I'll tell you my take on that. That is a true thing that happens with atorvastatin that we don't see with other statins, sort of, we have more

HDL effects with lower doses than we do with higher doses, so I think it's one of those nice pharmacologic facts that, I hate to say it, doesn't really mean much because we know that atorvastatin 80 mg/day, based on multiple studies, does provide that cardiovascular event lowering, so it's one that maybe that reduction doesn't mean anything because it's superseded by the overall cardiovascular benefit. That's the way I look at that data.

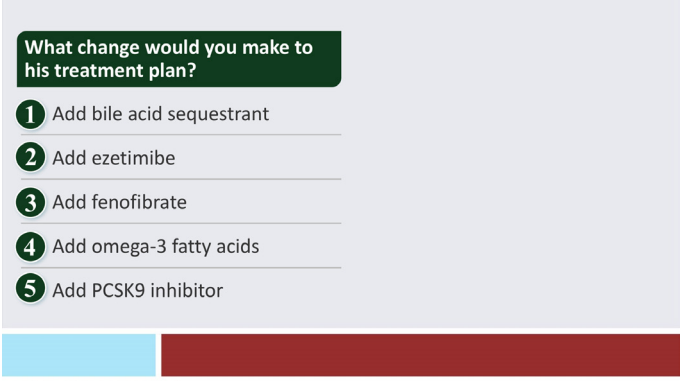
Peter Jones: I agree. We're still not sure what HDL cholesterol means in the big picture, on that end.

Case Study Harry

Okay. We're going to move to our last patient here, Harry. Okay, so, Harry's going to be a 72-year-old male with type 2 diabetes and hypertension, but no cardiovascular event, so he's primary prevention diabetes. A1c 7.3%, blood pressure's pretty good, LDL is 110 mg/dL. His baseline was 164 mg/dL and he had a 33% reduction on atorvastatin 10 mg/day. We'll get to that in a second. His triglycerides are 274 mg/dL. His non-HDL cholesterol is 165 mg/dL, so you obviously see the discordance between LDL and non-HDL in him as a diabetic. And if you wanted to do his 10-year ASCVD risk, it's obviously terrible, because it's primarily driven by his age, 72 years old. So, he takes metformin twice a day, takes hydrochlorothiazide, valsartan, that should be 320 mg/day, right? Not 240 mg/day. And atorvastatin 10 mg/day because he says he could not tolerate any higher dose than that. Now, let's assume that he's new to you and that's the history you get.



So what change would you make in his treatment plan? One, add a bile acid resin. Two, add ezetimibe. Three, add fenofibrate. Four, add omega-3s. Five, add a PCSK9.



I'm really intrigued by what you're going to say about this one. I expected to see it sort of all over the place here.

Joseph Saseen: And it is.

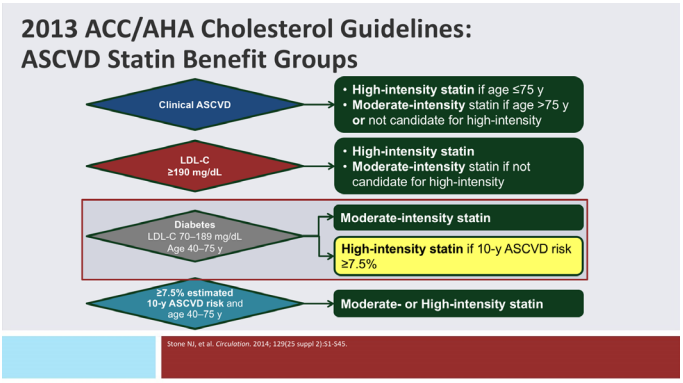
Peter Jones: It is. You know, because the unanswered question I didn't ask you is, who wants to go through a 2- or 3-month period of time trying to figure out whether he truly is intolerant to a higher intensity statin, which is what he really needs. So, he says, "I can't tolerate it." But he's new to you and he says I can only take 10 mg/day. So, *should* you, if he's new to you, try to see if he can take a higher intensity statin? Yeah. I mean, that would be… If he's new to you, that's what you probably should try to do and that's always a painful thing to try to because the patients are, whether they have a nocebo effect or a true intolerance is hard to figure out, but it takes time to do that. But, I think you should at least try that and see if you could get him on a higher intensity statin.

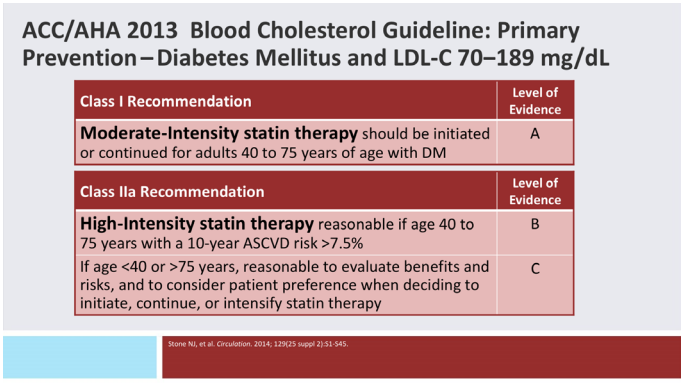
But let's assume he's not new to you, and you did try all that, and you've been following him for a few years and all you've got is 10 mg of atorvastatin and he's told you, "That's all I'm going to take." And you've got those patients, right? “That's it, doc, not going to do anything else.” So, obviously, the interesting thing here is he's got not only LDL that's not optimal, it's 110 mg/dL, but he's got discordance with high triglycerides. It's not uncommon with diabetes to have that kind of triglyceride-rich lipoproteins. They're high non-HDL cholesterol. And some of us tend to try to lower both if we can, LDL and non-HDL, and that's what fibrates and omega-3s have always tended to be used for, so I'm not surprised that some of you wanted to use the omega-3s in him. Don't have a lot of outcomes data in this particular type of patient yet, on adding those on top of a statin, but hopefully we will.

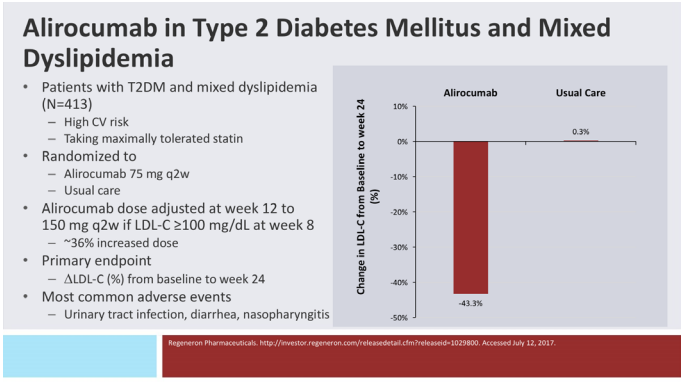
We've tried the fenofibrate in diabetes. Unfortunately, the fenofibrate trial in diabetes was not in this exact patient, which is the one they should have done it in. They did it with lower triglyceride levels at baseline, but they should have done it with baseline 275 mg/dL and they may have seen a benefit. But, you know, fenofibrate, depending on his renal function, is something that you have to consider as well, but that would have been a possibility.

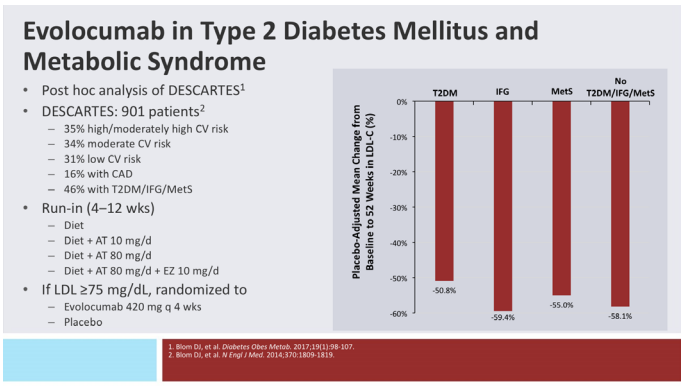
Bile acid sequestrant, glad you didn't do that one. Because the question was asked about bile acid sequestrant and high triglycerides. This would be the one where, yeah, you're probably going to push him to 275-300 mg/day or more if you were going to try to use a bile acid sequestrant, although colesevelam does lower A1c, and if they could, if he did have a lower triglyceride value, you could use a bile acid sequestrant for 2 things: lower A1c and improve the LDL cholesterol. So, his hypertriglyceridemia makes that a little bit more challenging. I do think ezetimibe would certainly get him below 100 mg/dL in primary prevention, so he could certainly go from 110 to 90 mg/dL or so on that.

The PCSK9 in primary prevention diabetes, this is a difficult area to know what to do. You'd probably do the ezetimibe first and see where he was and then you'd have to consider whether you might consider PCSK9. But let me just say that he fits into that diabetes group right there, where he should be on high-intensity statin and he's not, because he's on maximally tolerated 10 mg a day. But that's what he should do and there's plenty of evidence that that's what these kinds of patients should be on. The question is, does the PCSK9s have any data in type 2 diabetes? Do they worsen diabetes? Do they worsen A1c? The answer is, we don't think so. They lower LDL significantly and that's been shown with alirocumab and evolocumab in patients with diabetes or metabolic syndrome.









The question I have for you, and I have maybe for you out there in the group, if we couldn't maximize his statin and we used ezetimibe and his LDL went down to 85 or 90 mg/dL, would that be sufficient for you in primary prevention in this kind of guy?

Joseph Saseen: Personally, I'd be happier than I am right now and I really would want that non-HDL. So this is a patient where I want that LDL in that range.

Peter Jones: Right.

Joseph Saseen: And I really want the non-HDL to get closer, too. I'd want it less than 130 mg/dL.

Peter Jones: So how are you going to go that with him? You might add ezetimibe, and that may get

his LDL down, but it's not going to make as big an impact on his non-HDL cholesterol. So, what does he need to do?

Joseph Saseen: You know, this is probably somebody, and it's maybe not even a lipid thing… I think we really need to make sure that we control his glycemia better and that will have some benefit. It may not make his triglycerides perfect, but it will have a beneficial reduction in triglycerides and I'd like to give that a chance to work. His A1c is not that high, but I think this is a patient where I would want to be more aggressive with LDL-lowering and I'd also want to reduce triglycerides. I wouldn't commit to a drug, I'd commit to other management strategies through diabetes.

Peter Jones: Yeah, it's sort of… We start stepping outside of the box here when you look at these high-risk patients. He doesn't have established heart disease, but he's an older man. He can certainly have preserved ejection fraction with diastolic dysfunction which is what the sodium glucose cotransporter-2 (SGLT-2) inhibitors probably helped by using those kinds of drugs in these patients in reducing some of their cardiovascular events. So, the question is, do you start stepping outside the box to reduce cardiovascular events using some interesting and novel treatments that aren't necessarily lipid lowering? So that's just one other…

Peter Jones: GLP-1 agonists have also been shown to reduce… so if you start working on the diabetes side with known drugs you also complement what you're trying to do on the lipid side. We don't have a lot of data on SGLT-2s affecting lipoproteins, but we do on the GLP-1s. They do tend to have benefits in lowering triglycerides to some degree. I'm not sure the SGLT-2s have proven that they improve triglycerides much at all. Anybody have any questions about this particular guy?

Attendee: Not necessarily about him, but in all these guidelines, it sort of says, comorbidity is diabetes, but we don't really differentiate type 1 vs type 2.

Peter Jones: Correct.

Attendee: And, you know, with insulin, our type 1s are living into ages that are approaching higher risk, so we do just treat all diabetics the same, 1 and 2?

Peter Jones: I think the ADA and AACE generally say that you should and what happens there is that most of the… You know, you get the real type 1s. They tend to be a little bit younger and they've had longer duration diabetes, so this gets into your primary prevention diabetes whether you're new-onset diabetes or you're 15 years into your diabetes. I mean that's a big difference in overall risk. I mean, a longer-term diabetic, even if they haven't had an event, tends to be a much higher risk in the short run than a new-onset diabetic. Type 1 diabetes have a lot of nonvascular problems. They're blind and their kidneys and their neuropathies and everything tend to be really bad as well, but they do get vascular disease, too, and so they should be in that same… And then I don't know whether any of you see what I call a "1.5 diabetics." They're obese and they require a lot of insulin and they're almost insulin deficient, but they're obese, and they're just a difficult patient to manage, but they're all very high-risk and I think they should be considered, even as primary prevention, a group that needs intensive treatment. If they can be on high-intensity, they should be.

And he's not, which is the biggest problem for him and we're now trying to make adjustments on top of that. I think if his baseline LD… If he was totally statin-intolerant and his LDL was a lot higher, so, in other words, he got a 30% reduction in taking 10 mg/day of atorvastatin, what if he took zero? And his LDL was 140, 150 mg/dL? We might be talking about this differently, right?

Joseph Saseen: Yep. Yeah, we might.

Peter Jones: I mean ezetimibe, bile acid. You wouldn't use a bile acid resin with his situation. Ezetimibe is barely going to drop him reasonably. You consider him high-risk and you'd want him certainly well below 100 mg/dL, you might consider the PCSK9 if he was totally intolerant to statins. Would you agree?

Joseph Saseen: And I'd switch to rosuvastatin in a heartbeat. I mean, it looks like he's only… not tolerating higher doses of atorvastatin, which usually is a pretty well-tolerated agent. It is a little bit more lipophilic than rosuvastatin, so might be worth… I mean, I'm an advocate of try another statin almost always. So, if it's only one that they've had a problem with, easy-peasy. We have lots of patients that have a

problem with one that we switch to another one and had success. It's not always… It's not foolproof. You still may have some problems with that, but I think some of the pharmacologic aspects of rosuvastatin might be very desirable in a patient like this and it may allow you to go up on the dose.

Peter Jones: Yeah, you could try the Monday, Wednesday, Friday, with a 10 mg dose of rosuvastatin. You could also use 10 mg once a week. I mean, those are things for really statin-intolerant patients. Those are all options, but he's at least taking 10 mg a day. But if he was zero, there would be other options we would consider. Maybe a PCSK9 and him being such a high risk, might become an option under those situations.

Joseph Saseen: Maybe check a few other things like his thyroid function. Some people might be inclined to check a vitamin D if you go down that statin-intolerant kind of pathway. At least he's taking his current statin based on this information.

Peter Jones: Any other questions about this case or anything in general that we have sort of brought up with our 4 cases today? I think we tried to cover most of the statin benefit groups and how you might consider the addition of nonstatins.

Attendee: Can you comment on which of the inhibitors we would use, dose, as far as your choice in the inhibitors?

Peter Jones: Of the PCSK9s?

Attendee: Yeah, there were 2. Which one do you prefer, why, the dose, how do you determine, "I'm going to start on this dose," and then things like that please.

Peter Jones: Yeah, well those… the efficacy tends to be similar. If you use the top dose of evolocumab and alirocumab, they're pretty similar in their dosing so you use 150 mg of alirocumab, 140 mg every 2 weeks of evolocumab. You should expect the same response. [Coughs] Excuse me. And the delivery mechanism is exactly the same between the 2. The evolocumab does have a once-a-month option that patients, if they wanted to only remember to take it once a month, it's a larger volume, but they could take it once a month and you can get similar efficacy there. The alirocumab does have a lower dose. The question is why would you ever use the lower dose? If you wanted lower is better? Well, sometimes, if you get too low an LDL, sometimes having an option of reducing the dose might be a reason to do that, but I'm not sure most of us ever deal with getting too low an LDL that we would worry we want to reduce our intensity of treatment. Joe?

Peter Jones: Unfortunately, you might get told which one to use by the payer. Yeah.

Joseph Saseen: Yeah, that's a reality. We have an interdisciplinary team. Our nurses and our prior-authorization pharmacists know that information a lot better. We have communications. It's not always the pharmacists or the provider that's calling the insurance company. We use our total team resources to do that, but I've heard some people say that in diabetes that alirocumab might have less of an LDL-lowering effect. I think that's sort of a little bit blown out of proportion, because I overall… Given most patients, I think they are comparable in their overall efficacy at lowering LDL cholesterol. Some other providers might say, "I'm going to go with evolocumab because it has the long-term data out now from FOURIER." I'm happy to get either one for my patient and I am okay if insurance dictates which of the 2.

Peter Jones: If you're an outcomes guy, there's one with outcomes. That's the FOURIER and that's evolocumab. If that's the way you want to go. And a lot of times it is driven. You'll say… You'll write a prescription for one and then the payer comes back and says, "We only have the other one on the formulary." And you go, "Oh, okay. Well, then it's fine. I'll take the other one." Does that answer your question? Okay.

Attendee: Yeah, quick question about the JUPITER study. Just want to talk about that a little bit since we know in that study, many of the people who took rosuvastatin, who had metabolic syndrome, were tipped over into diabetes. So, wanted you to comment on that because many of those folks, I'm sure, if you plugged into that ACC/AHA guideline would have high risk. So, comment on that please and I know we know pitavastatin doesn't tend to do that so let me hear from you and the pharmacist. Thank you. Okay.

Peter Jones: Yeah. Statins in general do tend to have a higher risk of progression to new-onset diabetes. That has come out. JUPITER sort of brought it to the forefront. Meta-analyses have confirmed that. It's not just with rosuvastatin. It is with high-intensity statins more than low-intensity statins in general, and it is more with patients that have components of the metabolic syndrome, so the more they have impaired fasting glucose, central adiposity, higher triglycerides, low HDL, all those components are more likely to be moving towards diabetes.

So, in essence, you're saying that there are patients who are on standing on the precipice anyway of moving to diabetes and maybe the statin gave them a little extra nudge. And I think that may be true. There is some genetic evidence to suggest that working through the LDL receptor, that there may be a higher risk of diabetes. So, they've looked at things that stimulate the LDL receptor. Patients may be at higher risk, so it doesn't seem to be the case with ezetimibe—it doesn't tend to do that. Bile acid resins, as you know, colesevelam increases the LDL receptor, lowers LDL but actually reduces A1c, so there may be something specific to the statins. We don't know about PCSK9s, monoclonal antibody inhibition. It does not appear, so far, to push people towards diabetes, new-onset diabetes. But, honestly, I don't think there's enough data yet to know that for sure. Over time, it took us a while to figure it out with diabetes. I mean, with statins.

So, it does happen with statins, but remember, statins are going to reduce events in these high-risk people and overwhelm the small number of people who would just be nudged towards diabetes, whether they were headed in that direction anyway.

Joseph Saseen: My bottom line, just real quick points. I agree with what's been said. There is an increased risk. It is small. The benefit still outweighs risk. It is a dose-dependent phenomenon, and even at the high dose, it still is a small increase. I'm not convinced it's different across the statins. I think it's related to the potency, until I see data that indicate otherwise to me. I know there's… You mentioned pitavastatin but pravastatin has also been said, maybe that doesn't have… I'm not sure that's true or not.

Peter Jones: I agree.

Joseph Saseen: I would rather view it as a class effect, but still a small one. And the last thing that was mentioned, if patients don't have any risk factors for type 2 diabetes, I'm not worried about the statin doing anything harmful. It's those that have other risk factors that may be pushed into it. And I heard it worded at Lipid Academy this morning, from one of our esteemed experts, that it's really… It's nudging people into diabetes that eventually probably will be there anyways.

Peter Jones: Right.

Joseph Saseen: I think that might be a good way to position that with patients because that's going to be our barrier, when they bring it up and they hear about it and they don't understand it.

Peter Jones: Because what you want to do is, those who are on the precipice anyway, you should be talking to them about exercise, diet, weight reduction, those kind of things anyway, if you're going to use a statin, because you need to keep them off that edge and move them away from metabolic syndrome and insulin resistance.

Joseph Saseen: Great question, that I was asked today and I'm going to give you the same answer. The question is, "What is the explained mechanism of increasing propensity for new, onset diabetes?" I have not seen a clear one. I think we're still working on it.

Joseph Saseen: There's slight increases in both in people without a history of diabetes. The one thing that I have noted is that you don't see a worsening of diabetes control in those with established diabetes, just those people without diabetes at baseline. So, it's a small increase in both. That's why the FDA says to monitor glycemic parameters occasionally on statin therapy, via either fasting blood glucose or A1c.

Peter Jones: Yeah. They've tried to do studies on statins, whether it affects insulin release by the pancreas. First-phase insulin release. Some have said, "Maybe, yes it does." Some say, "No, it doesn't." Others tried to look at peripheral insulin resistance at the muscle level. Some said, "Maybe there is a little there." Some said, "No, there's isn't." So, there isn't really a statin mechanism to insulin action, either

peripherally or released by the pancreas. So, it's not clear what the mechanism really is. So, it happens, but we're not quite sure.

Joseph Saseen: Next Nobel Prize will be figuring it out.

Peter Jones: I don't think it increases glucose production. It's either going to be insulin release or insulin sensitivity peripherally, rather than gluconeogenesis. I think they've said it's not gluconeogenesis in the liver. It's one or the other. There's some who support both of those, insulin sensitivity at the muscle or insulin release, and then, just as many that said, "No, we didn't find it."

Peter Jones: Wonderful. Listen, guys, thank you so much for spending your evening with us. I hope it was enjoyable and I hope you got something out of the program. Thank you, Joe, for joining us this evening.

Joseph Saseen: Thank you.

Peter Jones: All right. Thank you.