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DARRYL CHUTKA: This is *Mayo Clinic Talks,* a curated weekly podcast for physicians and health care providers. I'm your host, Darryl Chutka, a general internist at Mayo Clinic in Rochester, Minnesota. As primary care providers, we're all quite familiar and comfortable with statins, basically, the cornerstone of treatment for hyperlipidemia. They first became available in the late 1980s, and they're truly an amazing class of medications.

In 2015, the FDA approved a new class of drugs for treating hyperlipidemia, the proprotein convertase subtilisin kexin type 9 inhibitors, also known as the PCSK9 inhibitors. Medications in this class can dramatically lower LDL cholesterol and can be used with or without a statin. But are these drugs needed? They're quite expensive and require administration by subcutaneous injection.

With us today to discuss the pros and cons of the PCSK9 inhibitors is Dr. Stephen Kopecky and Dr. Scott Wright, both cardiologists at the Mayo Clinic in Rochester, Minnesota. Scott, Stephen, welcome.

SCOTT WRIGHT: Thank you, Darryl. It's a pleasure to join you and your audience, and to join Steve.

STEPHEN KOPECKY: Same here.

DARRYL CHUTKA: All right, Scott, let's start with you. How do these new drugs work, the PCSK9 inhibitors?

SCOTT WRIGHT: I'm glad it's OK to use the abbreviation, Darryl. I have trouble pronouncing the full name. They work very elegantly in this regard. The body has a mechanism to clear LDL cholesterol from itself by having clearance receptors on the liver. The receptors would last an incredibly long time, except for the fact that the body has a mechanism to remove those receptors and recycle them.

And the removal process involves having LDL bind to the PCSK9 protein, so that when the protein and LDL are taken into the inside of the liver cell by the receptor, that's a signal to kill the receptor, so that the liver has to synthesize a new receptor. So when the liver binds LDL alone, the receptor brings LDL inside the cytoplasm, and it puts the receptor right back out on the surface. When it has the PCSK9 protein attached, it destroys the receptor and synthesizes a new one.

The drugs work by binding the protein and not allowing it then to bind with LDL and be taken up by the receptor. As a consequence, the liver keeps synthesizing receptors, but the old receptors hang on so that you have, in my view, an overexpression of the clearance receptors, so that you suck more LDL out of blood into the liver, where it's then excreted from the body.

So it's an elegant way to lower LDL in a way that's really self-regulated. But these drugs interrupt the self-regulation of the receptor density, and thus favorably, reduce LDL. And genetic studies show in patient populations where there's a loss of function of PCSK9, the same thing happens. So we're pretty confident about this mechanism.

DARRYL CHUTKA: So why should we use these drugs instead of the statins?

SCOTT WRIGHT: Well, it turns out that about 70% of our total LDL is likely maintained or averaged or modulated by the whole PCSK9 process. So these drugs are the most effective way we have of lowering cholesterol.

But you're right. We have statin drugs and other lipid lowering drugs. And they've been quite effective for 20 or 30 years at lowering cholesterol by blocking the synthesis of LDL inside the liver and by promoting more production of the clearance receptor to remove LDL from the body.

Unfortunately, in many patients, probably 2/3, the ability of the statin drugs to lower LDL is just not enough to reduce their risks for subsequent events, meaning if you're a high risk patient. If we treat 100 of those, 50 to 60 will have residual risk, meaning recurrent events despite being on treatment. So we need more therapies to lower LDL further to reduce their risks.

It's not that we need more drugs necessarily, but we need to really lower LDL. The goal here is not how many drugs do you use or what drugs do you use, but it's how low can you get the LDL so that the risks for that individual patient are reduced as much as humanly possible.

DARRYL CHUTKA: One reason I've heard that this class is out here is because there are some patients who can't tolerate the statins. And I know, Steve, you work in the preventive cardiology area. And I've sent you some patients personally, who've had intolerance to the statins. How common is this?

STEPHEN KOPECKY: Well, if you look at the randomized trials, Darryl, the statin intolerance is maybe 1% of 20,000 patient trials. But if you look at how those trials were done, they excluded people that were statin intolerant. Some of the early studies actually gave you statins for, like, two months, if you were a screen failure. You weren't intolerant. You were just a screen failure. A little difference in nomenclature to the FDA and the European agencies, but the bottom line is the same-- people can't take them.

If you look at the general population now, 10% to 12%. If you look on some of the internet pages, some Facebook pages, that's 15% to 20%. Clearly, it depends on the population, the RFH patients, the patients with familial hypercholesterolemia, the ones that have a genetic reason for this marked elevation. About 2/3 of those are statin intolerant. If you use the definition, they cannot get to the goal LDL on the hydrostatin.

DARRYL CHUTKA: OK.

STEPHEN KOPECKY: So it's a real entity.

DARRYL CHUTKA: All right.

SCOTT WRIGHT: Yeah, Steve was very insightful early on in this to really provide a countercultural argument. Most of us who were trialists or lipidologists were saying that statin intolerance was more of a perception than a reality because the research studies did show 1% to 2% had intolerance. But Steve was an early recognizer that this incidence rate is 10% to 20%.

I don't know about in your practices, but every time I prescribe a statin, one out of 2 times, the patients ask me about side effects or worries about taking it. I think there's a real phobia to taking statins among the general population that's probably unwarranted, but it's there and we have to manage it. What do you think, Steve?

STEPHEN KOPECKY: Well, if you look at some objective data, it's hard to get objective data with statin intolerance because we don't have a diagnostic test. If you have a heart attack, you do an electrocardiogram and a troponin, and it gives you the answer. You have aortic stenosis, do an echo, and it will give you the answer. We don't have that single test that tells us, yes, there's a statin intolerance, or no, it's not.

But if you look at some objective data like when we give patients the exact same medication back that caused their symptoms, we take it and put it in different capsules, give it right back to them, and don't tell them if it's those same statin or a placebo. Half of the patients get the same symptoms back.

If we give them the placebo, a quarter of the patients get the same symptoms back. So you would think that 100% would get the same symptoms if it's a real drug and none if it wasn't. So there's a lot of issues. And I think the reason is that it's a multifactorial issue in that some patients get statin intolerance because of low CoQ10 levels. CoQ10 has been shown to go down, and you can raise it and help it in a small percentage of patients.

Also, patients that have more pain in the dental chair more likely to have statin intolerance. They feel symptoms more. So there's many issues out there. And I think we have to treat every patient individually, which is what we should always do anyway.

DARRYL CHUTKA: Yeah.

SCOTT WRIGHT: It seems, Steve, that competitive athletes seem to have a higher risk of this. Is that true?

STEPHEN KOPECKY: Well, there has been studies. In Germany, they looked at a good group of very high level competitive athletes. 3/4 cannot take a statin. And I have patients that before they run a big marathon, they call me and will say let's stop the statin about six weeks before because their times go up. And if they are on the statin during the marathon, restart the statin after they finish the marathon and they get by it just quite well.

DARRYL CHUTKA: That's interesting. I've got a fair number of patients who have a perceived statin intolerance, and I see them pretty reliably once a year. And I'll find a certain percent have stopped their statin sometime during the past 12 months and ask them why. And they say, well, my shoulder was giving me pain. And so they stopped the statin.

And I said, well, did your shoulder pain get better when you stopped it? And they said, no. So we see a lot of perception that there's problems with the statins. But I think overall, they've been a really good class of medications.

STEPHEN KOPECKY: Yeah, very true. In those types of patients, what we generally do and you probably do is say, OK, let's stop your statin for a month. We know it's safe to do. Studies have shown that. But write down, do a stick figure drawing of your body, and tell me where the pain is-- shoulders, hip girdles, whatever. Write down a number, and a month later, pull it out and see where you are.

If it's gone, then OK, I can say it was the statin. But if it's still basically the same, it wasn't the statin. And then let's keep you on it. Let's try to have you stay on it. The thing is there are many different statins, and they all have different efficacy in different patients. They all have different side effects in different patients.

The efficacy has been shown multiple times. In fact, there's a great-- in the Physician's Desk Reference for Rosuvastatin, there's a graph showing the wide variation in statin response to five different statins. And some people may get a better response on 20 of pravastatin than on 40 of Rosuvastatin, in terms of LDL reduction. And the same is true for side effects. So we tried different ones.

And I've learned some things from you and your colleagues in preventive cardiology that if a patient is what looks like really having problems with the statin, giving even a tiny dose of Rosuvastain starting at once a week, maybe then going to twice a week, and gradually titrating it up to what they can tolerate, you can still accomplish a fair amount of reduction in LDL cholesterol.

STEPHEN KOPECKY: Exactly right, and then you add some Ezetimibe on top of it later on, which works much better when there's a statin on board. You can achieve some meaningful reductions in LDL.

DARRYL CHUTKA: Yeah.

SCOTT WRIGHT: Then when you add a PCSK9 drug, you really lower the LDL.

STEPHEN KOPECKY: You certainly do.

DARRYL CHUTKA: So let's talk about using these drugs. The adherence of statins is not all that great. I mean, some studies have shown that up to 50% have stopped the statins within their first year. These are medications that are expensive. They have to be administered by injection. Are patients going to take these drugs reliably?

STEPHEN KOPECKY: Well, it's interesting. As I mentioned, in familial hypercholesterolemia patients, we have a lot of patients that are intolerant to high dose statins. So they get a little bit. And I'm impressed with how many people are intolerant to PCSK9 inhibitors.

Now admittedly, this is a select group where 2/3 are statin intolerant to start with. But it may be the rapidity with which we drop the LDL. There's evidence of that. So maybe the slower approach may be better. But clearly, these patients, I mean, we have to believe them. Because they, like you say-- we don't live with them. They don't take the pills, we don't know about it.

DARRYL CHUTKA: Scott, the other problem, these are not cheap medications. How are we going to deal with this? How is the health system going to deal with handling this high cost of this class?

SCOTT WRIGHT: You're exactly right. I mean, when the drugs came out, they were $14,000 to $16,000 a year. Now they're $5,000 to $6,000 a year. But let's be honest, those are very expensive therapies. And really, the most unbiased, cost effective analyses suggest that $4,500 to $6,000 a year is probably the right target range for a cost benefit analysis.

But quite frankly, for many of our patients, that's still a lot of out-of-pocket expenses. And it certainly drives the adherence issues. And I think the frequent injections of generally twice a month or every two weeks leads to reduced adherence to the drugs.

There's no question the drugs work. The monoclonal antibodies to PCSK9 drop LDL or lower LDL dramatically within just a few days of administration. It may be that that rapid reduction in LDL triggers some of their perceptions of intolerance. But it's a challenge.

Now so we have two issues to fight or to overcome with patients. One is the cost issue, and the other is the frequency of administration. I don't know about you, Darryl or Steve, but in my practice, when I have a diabetic patient and it's time to start either a GLP 1 injectable or insulin, they're resistant to any injections.

Now when they get used to it, they're happy to be on it, and they'll take a second injectable drug because a lot of patients take insulin and a GLP 1. I think the same is true with the philosophy and the mindset with the injectable monoclonals. But it's a big commitment. It's a lifetime commitment to be on them.

And I think there's a compelling need for really new and novel therapies, which either can be administered less frequently or work through different mechanisms to lower PCSK9. And I've actually been involved in research with some of those and presented some data. And I think there will be some new drugs potentially out in a year or two, which can be given once or twice a year that will lower LDL comparably to a monoclonal antibody.

The second issue, though, is the cost issue and can we afford it. We've moved from an era where if you look at the top 10 selling drugs in 2000 versus 2018, the costs are tenfold higher now than they were 15 years ago or so.

And the number of people covered by them is substantially less, right? If you think about it, H2 antagonists were one of the top selling medications in the early 2000. Statins were there, covering millions of lives of patients. Today, it's injectables or biologics for rheumatologic disorders or special diseases. And the therapies are hundreds to hundreds of thousands of dollars a year.

When you talk about PCSK9 and think about the implementation of PCSK9 therapy, the question really is, can a society afford covering 30 million people at $6,000 or $10,000 a year? And the answer is twofold. One is no society can truly afford that, and secondly, no society can truly not afford to adequately treat cardiovascular risk.

The answer really is this. Most patients don't need a PCSK9 drug. Most can be managed with high dose statins and Ezetimibe and lifestyle modification. We haven't heard Dr. Kopecky yet talk about diet, but I haven't yet to see Steve find a diet that he didn't like or embrace, because he's a big advocate for lifestyle modification.

And I really am a big advocate for starting statins early, intensively, and trying to help patients have success in the first few weeks. And once they see they can drop their LDL, they stay on them, I think, more effectively. So I think statins-- PCSK9 drugs will be used at a fraction of patients, and they'll be used in subpopulations, high risk individuals like FH patients, as well as patients who have had acute coronary syndromes or have multivessel coronary disease for whom the next event could be fatal.

And there, I think they do have a very good cost effective analysis. And in that regard, I think society can afford to cover it. I'm hopeful that as new products come out, maybe the prices will come down due to competition. And things will become a greater value for our patients.

DARRYL CHUTKA: Yeah, and despite the relatively high cost of these drugs, at least compared to the statins, are they cost effective in terms of maybe preventing hospitalization, preventing a cardiac procedure, preventing an MI and its subsequent complications? Maybe in selected individuals, these are very cost effective drugs.

SCOTT WRIGHT: I think so, in certain individuals. In the FH population, no question. Homozygous FH patients are dying of cardiovascular disease by age 40. Heterozygous FHs are having life altering coronary events by age 50 or 60. They're losing a lot of years of productivity, and not to mention the cost in terms of family and society.

So yes, we certainly can afford to treat it there, and I think high risk patients with atherosclerotic disease, type 2 diabetics, people with multivessel disease. These drugs make a lot of sense there. But for primary prevention, I think it has to be selective-- maybe the FH population and just maybe a small percent of others.

DARRYL CHUTKA: OK. Well, Steve, we've had a lot of experience now with the statins, and we know that they can reduce cardiovascular mortality. Do we have enough experience with the PCSK9 inhibitors? Do they do the same thing?

STEPHEN KOPECKY: They clearly do. And but remember, they should be added to because they work differently than a statin, differently than Ezetimibe. So they should be added to those first two drugs if the patient can tolerate it. And they clearly are, like Scott was saying, they clearly are beneficial, and they clearly can reduce events, especially in the higher risk patients that can't get to their goal.

Thing is what no one's really wanted to see is someone to go straight on a PCSK9 inhibitor. And we're not seeing that. The guidelines have been very clear-- don't do that.

DARRYL CHUTKA: OK.

SCOTT WRIGHT: But I think that's where we should go. What's not really widely known is that statins raise PCSK9 levels. So statins have a counter regulatory mechanism to offset their LDL lowering. And I think the FDA with its insistence that everybody getting treated with a PCSK9 has to be on high dose statins in clinical trials before they can approve the use of a PCSK9 is really pushing it in a direction that's unwise.

I think high dose statins have more side effects, and I think we see more LDL lowering with a low to intermediate dose of a statin and a monoclonal antibody than we get with a high intensity statin and a monoclonal.

DARRYL CHUTKA: Well, these drugs are remarkably powerful. Especially when combined with the statin, they can plummet the LDL cholesterol. How low should we go? What's safe in patients?

SCOTT WRIGHT: Zero.

DARRYL CHUTKA: Zero?

SCOTT WRIGHT: Right, you have a mechanism in your body--

STEPHEN KOPECKY: I completely disagree.

SCOTT WRIGHT: You have a mechanism in your body to take LDL from or to take cholesterol out of HDL and convert it to LDL. So normal tissue, any tissue can get LDL if it needs it, right? Now zero is probably a little too low, but I routinely try to lower it 30 or 40 milligrams per deciliter in my patients who are post ACS or high risk. I don't think there's a lot of harm in lowering LDL.

If you look at native populations in parts of the world where there's tough access to get meat or enriched fat products and people that have sort of hunter gatherer lifestyle, so eating a lot of grains and rice, their natural LDLs are 30 to 40. So I think we know that low LDLs are safe. And I don't worry when the LDL drops to 10 or 20. Steve may, but I don't.

DARRYL CHUTKA: Well, let's get our opinion from Dr. Kopecky.

STEPHEN KOPECKY: Yeah. Well, I think it's always helpful to, like Scott was saying, ask Mother Nature. Look around Mother Nature. There's no human population that has an LDL below 30. You look at the mammals, the non-human mammals. There's no non-human mammal that has an LDL below about 30.

What else is LDL used for? Well, remember, it is the transport. It's not the bad cholesterol. It's the transport cholesterol around the body. So the lipoprotein, you wrap the fat in the protein so it can get around our water-based transport system called the blood. And what's it used for? Well, testosterone, estrogen, cortisone, many of our thyroid or hormones need to have that ring. Every cell in our body has to have it.

So there is evidence if you get below about 25 to 30, you start to get into troubles with stress tests, meaning provocative ACTH stimulation tests and things like that in animal models. We haven't seen that much in the testing in humans.

But remember, we did the same thing with statins 20 years ago. No, there's no side effects to statins. Take them all you want. You're fine. Oh, those side effects you're feeling, Mrs. Smith, that isn't real. And now the patients don't trust us.

You know what the number one question I have, Dr. Wright, when a patient I say we have these new nine month drugs coming out? They say, oh, my God, you mean I'm going to hurt for nine months if I take that drug? I mean, we have to deal with this, and we have to accept it. The patients may not want to take these drugs.

SCOTT WRIGHT: Yeah, I think that's real. But I think the tradeoff is this. The risks about an impaired stress response to a fight or flight reaction is theoretical in humans. It's not been proven, but the anti-anthropogenic and the cardiovascular event reduction data are compelling.

And data from a very large PCSK9 trial called Fourier using Dr. Kopecky's favorite monoclonal antibody, evolocumab, showed that taking patients LDLs to 10 resulted in the lowest clinical event rates for two subsequent years of any group in that entire trial with no serious outcome issues, OK?

Now I grant all of the caveats that that's a clinical trial population. They are likely different than the general population. They're watched more carefully. They're more compliant and more highly motivated. I get that. But that data is compelling.

And while I try not to be a carpenter who hammers every nail that he sees, this is one nail that I keep pounding back in because we don't have any other therapy short of exercise and lifestyle that reduces events as effectively as taking your LDL so low. So on this issue, I say it's never too low to go too low.

DARRYL CHUTKA: All right.

STEPHEN KOPECKY: Well, Scott, do you think that 22 months is long enough to find all the side effects, first off, that we see from these drugs? And it may not be long enough because it's a lifelong commitment to a very low LDL.

SCOTT WRIGHT: You have a good point there, and especially in the patients who seemed to come into your office, they do have a lot of late side effects, I agree.

STEPHEN KOPECKY: Well, that's our population. And most of them just quit the drug and don't tell us.

SCOTT WRIGHT: They do.

DARRYL CHUTKA: So we have to be aware of that.

SCOTT WRIGHT: Yeah, no, and I think one needs long-term follow up on any therapy-- statins, aspirin. Look at aspirin. We've learned a lot about aspirin side effects five, 10 years out. And I think that's true of any therapy. So no, I don't disregard the side effect risks, but I do think, in the short run, there is certainly a lot of benefit with regard to cardiovascular risk reduction.

STEPHEN KOPECKY: Well, remember, too, it took us 20 years to find that statins cause diabetes. So in those--

SCOTT WRIGHT: It's only a 1% absolute increase in those who were likely to develop it anyway.

STEPHEN KOPECKY: Well, but tell that to your patients. They need to understand this. And we need to know that upfront and tell them, not to say, oh, here, let me give it to you. We're not sure about taking these drugs and the side effects.

SCOTT WRIGHT: I certainly do that, but I think they get diabetes three years after they start the statin, instead of 4 and 1/2 years, without taking the statin. And they have lower cardiovascular risks on the statin, despite having developed diabetes 18 months sooner.

STEPHEN KOPECKY: No, I'm not saying that's not true. And the only thing that's not true about that it's actually three months earlier on the statin than not on the statin.

SCOTT WRIGHT: OK. Thank you.

STEPHEN KOPECKY: But the point is that we need to tell our patients about the risks. And we need to admit that there may be risks we don't yet know of. Because I have so many patients. There are three types of statin intolerant patients. One is the one that takes a statin, gets these horrible muscle aches, proximal, stops it, gets better, go back on it, they get it back. We all agree that's a statin intolerant patient.

The second one is the patient gets the left thumb that hurts when they're playing tennis. And that's not statin intolerance. But the third statin intolerant group, which is the biggest group and the most worrisome group for me, is the ones that don't want to become statin intolerant. They will never go on a statin, and we all see these patients every day. Doctor, can I do it my way? Can I try something different? Can you have a natural option? Those are the ones we need to really start paying attention to.

DARRYL CHUTKA: Yeah, and you watch their LDL climb every year, despite the fact that they're reluctant to take the statin.

SCOTT WRIGHT: Yeah. And then after their first myocardial infarction, they're still reluctant.

DARRYL CHUTKA: Yeah.

SCOTT WRIGHT: They want to go on flaxseed or something else.

DARRYL CHUTKA: Well, let's finish up by talking about the REDUCE-IT trial.

STEPHEN KOPECKY: Oh, yeah.

DARRYL CHUTKA: Steve.

STEPHEN KOPECKY: Yeah. So REDUCE-IT was a fascinating trial, the first official trial that really showed significant benefit since we had the France-- the Lyon study, or one of those earlier studies. But this showed that they gave fish oil, 4 grams a day of EPA-- icosapent ethyl, a specific EPA-- to patients that had their LDLs well controlled, had triglycerides over about 200 that changed during the study, but went from 175 to 200.

But if they took it and their triglycerides lowered, they did much better. The question is was it the icosapent ethyl? Was it the dose of 4 grams a day? Or was it the patients they chose, the ones with high triglycerides? And I think it's really the latter two, that they picked the ones that had high triglycerides. They gave a high enough dose that made a difference to lower the triglycerides. I'm not convinced that it was the specific agent that they gave.

DARRYL CHUTKA: Because we've seen conflicting reports about how effective fish oil is in treating cardiovascular disease, preventing it.

SCOTT WRIGHT: Yeah, that's the challenge. I mean, the REDUCE-IT trial is one of the few studies with actual absolute risk reductions of 4% to 5%, so a number needed to treat a 22 to 26. One or two caveats about REDUCE-IT that are worth pointing out, one, patients who have had a prior history of atrial fibrillation are more likely to have it recur with treatment. We don't know why.

Secondly, there was an absolute increase of 1% in serious bleeding, and serious bleeding is serious bleeding, meaning hospitalization or other, requiring blood transfusions. So I'm cautious in my patients who are on triple anticoagulant therapy-- Clopidogrel, aspirin, and a DOAC or warfarin-- to really push them to take this type of therapy because I don't want to turn them into a serious bleeding situation and then have them stop everything. And then we've lost the whole battle of preventing stroke and recurrent coronary events.

I think the jury is still out about whether it's icosapent ethyl or whether it's just fish oil. I think today it's hard to say that it's any fish oil. My personal bias is that it's likely to be supported by other trials showing the same benefit. I certainly hope so. But it's more than lowering triglycerides, really.

I wrote an editorial with Joe Murphy. Steve, I don't remember if you were part of it as well. But it's entitled "A Statin a Day May Not Keep the Doctor Away" and that it's important to see patients who have elevated triglycerides. In this trial, it was 125 or above, and even at 150, where there is a tremendous benefit from being randomized to the fish oil versus placebo.

So there's something going on, and I happen to think it's altering lipoprotein class and altering lipid size, particle size, inside the body that's playing a major role here, in addition to triglyceride lowering.

DARRYL CHUTKA: Yeah. Well, I think fish oil is kind of like estrogen. I've been around long enough to know. When I first started practice, all women should have been taking estrogen. And then nobody should be taking it. And then everybody should be taking it again. And now only those who need it for this.

It goes back and forth, and our patients get confused, especially when we keep telling them to do the opposite every time we see them. We'll have to wait and see what happens with fish oil.

SCOTT WRIGHT: I think it's tough to tolerate fish oil, too. I think many patients just have GI side effects, eructation, a bad taste. Let's be frank about it. It's not the best tolerated class of therapy anyway.

STEPHEN KOPECKY: One point I think we need to make to our patients every day instead is we do not have a pill that replaces lifestyle. And just like fish oil, taking a fish oil tablet a day, we've shown that doesn't work.

The second thing is-- we haven't brought it up and I want to mention it-- is that the data clearly shows if you're on a statin and you don't eat healthy, meaning a Mediterranean plant-based diet, you lower your LDL, but you do not get the full benefit reduction of cardiac events. And that's something we need to tell our patients every day, too. This isn't taking a pill, instead of a lifestyle.

SCOTT WRIGHT: I think you need to repeat that because most of my patients believe if they take a high dose of Lipitor or atorvastatin now, they can go to Ruth Chris and eat what they want. And what you're saying is that the statin does not replace eating a low fat diet.

STEPHEN KOPECKY: Well, I'm not saying that at all. I'm not saying a low fat diet. Because that does not been shown to reduce mortality. The American heart low fat diet has never been shown to reduce mortality. What's been shown to reduce mortality is the DASH diet and the Mediterranean diet, more plant-based, less salt, less sodium. That's what's been shown to be beneficial.

SCOTT WRIGHT: Well, I admire Dr. Kopecky's courage. Not only has he attacked the American Heart Association, he's attacked the other diets, too, so at least you're equal opportunity there, Steve.

STEPHEN KOPECKY: OK.

DARRYL CHUTKA: We've been discussing hyperlipidemia therapy, specifically the pros and cons of the PCSK9 inhibitors with Dr. Scott Wright and Dr. Setphen Kopecky, both cardiologists at the Mayo Clinic. Scott, Stephen, thank you so much for this interesting debate.

STEPHEN KOPECKY: Thank you, Darryl.

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