411 on PCSK9 Inhibitors
How effective are they at lowering cholesterol?

Dr. Andrew Perry: PCSK9 inhibitors are a relatively recent addition to armamentarium for cholesterol-lowering medications. They were first approved by the FDA in 2015, and they work really well. They reduce your LDL levels by upwards of 50%. But the uptake in clinical practice for these drugs has been modest, and that's being generous. A lot of these issues stem from its cost. I wanted to learn more about how these drugs fit best into clinical practice, so I visited with Dr. Tom Maddox.

My question about PCSK9 inhibitors spawned a discussion about the greater topic of how to reduce a population's overall cardiovascular risk. Dr. Maddox has a lot of interesting, innovative, and cool ideas around this subject. I really enjoyed talking with him and I think you'll enjoy this episode.

Dr. Andrew Perry: Thanks for meeting with me today. I really appreciate it. Could you first, just describe how the first concept of PCSK9 inhibitors came about, where that was discovered or where that first idea came from?

Dr. Tom Maddox: PCSK9 is an enzyme that the body manufactures, and it's involved in LDL metabolism. The idea is that, in just sort of its natural state, it's involved in the destruction of LDL as it's metabolized by the liver, and it also involves destruction of the LDL receptors. The problem with that is that if you have less LDL receptors expressed by the liver, then less of the circulating LDL is taken out of circulation. As a result, you have higher levels of LDL in the bloodstream, and then it can be oxidized and deposited in the coronary arteries or other vascular beds. Elevated levels of PCSK9 were noted to have that correlation to increased LDL.

Dr. Andrew Perry: I want to just give a quick side note about some of the history behind PCSK9 and the drug development because it's really fascinating and just is an example of how modern science really contributes to modern medicine. After the cholesterol pathways were identified in basic science labs, then the gene for PCSK9 was identified first — I think, in a French cohort — and a gain of function of the PCSK9
led to familial hypercholesterolemia in this French cohort.

Similarly, in a Dallas cohort of African Americans, it was noted that a loss of function mutation in the PCSK9 gene led to lower levels of LDL and correspondingly lower risk for cardiovascular disease. This is what then spawned the further drug development. Although, in the first clinical trials with them initially showed fairly substantial reductions in LDL, like 50%, 60% of those.

Dr. Tom Maddox: Right.

Dr. Andrew Perry: But none of those were really targeted for mortality or heart outcome.

Dr. Tom Maddox: Those were Phase 1/Phase 2 studies where you basically want to understand is the mechanism we believe to be true true? And is there any sort of early signs of a safety problem or any other unintended consequences that would torpedo any good effect of a particular end function? You're right. There's been a variety of Phase 1/Phase 2. On average, we were seeing a drop of 50% to 60%, which is really pretty impressive. This was even true in the background of statin therapy. It appeared to be additive, one of the more novel and pretty promising frontiers in cholesterol metabolism.

Dr. Andrew Perry: Then was FOURIER the first large clinical trial, like a large Phase 3 clinical trial, or were there others prior to that?

Dr. Tom Maddox: There was SPIRE 1 and 2. That came out about a year before FOURIER. Then there's a third trial that will probably come out I think later or in late 2018. I think it's right. That's ODYSSEY. These are different formulations, different patient populations of PCSK9s, but all of them are PCSK9s, all of them are Phase 3-type trials, and they're looking primarily at cardiovascular efficacy.

Dr. Andrew Perry: Okay. What are the patient populations that those are looking at? You mentioned there are some differences between the three. Are they primarily looking at secondary prevention of coronary disease and patients with familial hypercholesterolemia? Is it these two groups? I ask specifically that because I think that's what the indications from the FDA are for those two populations.

Dr. Tom Maddox: Exactly.

Dr. Andrew Perry: I presume those are probably the populations that have been studied in SPIRE and FOURIER.

Dr. Tom Maddox: That's right. SPIRE had both populations, so did FOURIER. They defined them a little bit differently. But by and large, it was firm coronary disease and an inability to get — what we believed at this time to be — optimal LDL levels on background statin therapy. Typically, we're looking for folks to get an LDL below 70 on a maximum or maximum-tolerated dose of statin.

These are folks that couldn't get it below 70. In some cases, there was a subset of SPIRE that couldn't even get below 100, just based on that individual's responses to statins. Background risk was high, the inability to modify, at least their cholesterol profile, was somewhat impaired by that patient's relative lack of response to statin therapy.

We looked at those folks, and then there was the familial hypercholesterolemia. That was defined somewhat variably. Largely it was just very high endogenous levels of
LDL. There was a little bit of genetic testing, but not all of them had it confirmed, genetic mutations that we know are associated with that condition.

Dr. Andrew Perry: What have been overall results, at least, from SPIRE and FOURIER?

Dr. Tom Maddox: The overall SPIRE was actually a little neutral. It didn't show as much of a benefit except in a second part of the trial called SPIRE-2, where they looked at folks with even a little bit higher risk. This was the group, confirmed coronary disease, and I believe they could not get their LDL levels below 100 on background statin therapy. They showed a little bit of a benefit there.

That was an early and sort of promising suggestion that there may be some actually hard outcome benefit for these particular medications. There were some issues. Part of the issue is that PCSK9s are a monoclonal antibody, and so we're sort of interacting with a patient's immune system. We actually, in SPIRE, had a little bit of an issue where there was this substantial amount of immune response to the antibody, so it started to inactivate the implication, so there needed to be some rethinking about the formulation. [00:10:11] With that said, both trials — SPIRE-1, FOURIER — and hopefully ODYSSEY are all showing an impact, even with that play, and they're seeing a benefit after a couple years of follow up. It still seems somewhat beneficial.

Dr. Andrew Perry: Good, and FOURIER, its results from what I read, looking at the trial just again last night, overall, no difference in mortality. Their composite outcome of death or of MACE outcomes was significant. It looks like it was primarily driven from reductions in myocardial infarctions.

Dr. Tom Maddox: That's right.

Dr. Andrew Perry: But overall, no difference in mortality and cardiovascular death.

Dr. Tom Maddox: Right.

Dr. Andrew Perry: This is something that I wanted to just take a minute and spend on is that it's a bit odd to me that we have these large trials not showing a difference in mortality when we know from prior studies on statins that a reduction in your LDL is beneficial in terms of your mortality.

Dr. Tom Maddox: Yeah.

Dr. Andrew Perry: Additionally, that's part of what the cholesterol guidelines were changed in 2013 reflected that to then even have a lower target goal for those and broader indications for statin therapy. It's odd to me that now we're getting to the point where additional targeted statin-reducing therapies didn't result in a reduction in mortality and cardiovascular death.

Dr. Tom Maddox: Right.

Dr. Andrew Perry: Your thoughts about that.

Dr. Tom Maddox: One thing. A way I would think about it — and the way that I think it's important to think about all trials and their various outcomes — is if we don't see a signal, is the answer it doesn't happen? Or we don't know yet? I think, in this particular case, we do not know anything, and there's a couple reasons I say that. One is the rates of death were quite small in the trial. As a result, you're generally underpowered to understand what exactly was going on with the mortality signal because, frankly, not enough people have died to be able to see a difference between the two arms.

Dr. Andrew Perry: Meaning that you can have a lot of people in your trial. But if they're
not having enough events, that's really what's driving your power, maybe not so much how many people you've enrolled, but it's your event rate.

**Dr. Tom Maddox:** That's exactly right. The ability to distinguish between groups is dependent on the number of outcomes that a group has. Now that correlates, of course, with the size of the study, just simple math.

**Dr. Andrew Perry:** Yes.

**Dr. Tom Maddox:** The more people you have, the more events you're going to have. That's why — particularly in cardiology, now that we have such good background therapy — we need to enroll thousands, sometimes over ten thousand patients. Because now we're looking at effects that are relatively small and somewhat prolonged, particularly in these type of prevention trials where it takes time for these kind of events and any benefit that would follow from a medicine to accrue.

I think at this particular point... and it's another reason why we do these combined endpoint studies, too, because we're looking for any signal. It's good to impact any of these outcomes. You don't want to have another MI. You don't want to die. What were the other ones? You don't want to have a stroke. You don't want to an emergent PCI. We put them all together saying, "Hey, avoiding any of these is good, so do we have any signal that any of this is being impacted?" That's why that's the primary endpoint and that's what the headline results always are of the trial.

But then you unpack the individual endpoints, and now we're getting into much smaller numbers. You're always at a risk for underpower. I think the other thing, too, is the median follow-up time for FOURIER is 2.2 years. That's not enough... that's pretty short and just given the baseline death rates in these populations, not a lot of people are going to die in that relatively short timeframe.

What'll happen — and this has happened in all our statin trials — is these study investigators continuing to follow the cohort, and they'll report out results in three years on the five-year data, and again, down the road, they'll report 10-year data on all this stuff. We'll continue to track this. Do we see a late mortality signal show up? If that's true, obviously, we need to know that and be able to counsel our patients on the benefit we're providing. But I think because A) it's a small event rate and B) it's a short follow-up time, but which, of course, are related, I think the answer right now is we don't know the impact of PCSK9s on mortality.

**Dr. Andrew Perry:** Okay.

**Dr. Tom Maddox:** If we postulate, to your point, that lower LDL does ultimately result in decreased cardiac death, then I would expect the mortality signal, but we don't have that data yet.

**Dr. Andrew Perry:** One of the big things that gets a lot of news about is cost. I think that's what most of the articles that I see popping up on it is how PCSK9 inhibitor, their adjustment on a quality adjusted life year or qualities and policy indications, economic indications for that. How much do these cost?

**Dr. Tom Maddox:** Annually, they are going to cost whoever is paying, which is obviously primarily an insurer, they're going to cost around $14,500.

**Dr. Andrew Perry:** For a year.

**Dr. Tom Maddox:** For a year's worth of therapy, which typically is injections every two weeks.
Dr. Andrew Perry: Okay. I guess why, first off, do they cost so much?

Dr. Tom Maddox: Because, to be honest, the drug company thinks the market will bear the price.

Dr. Andrew Perry: Okay.

Dr. Tom Maddox: They go through extensive market surveys and economic modeling and whatnot to set that price. Their rationale, and a lot of times I think a lot is made of adversarial relationships between the public or maybe the physician community and pharma, and I think it’s a little overblown. But, at the end of the day, they have invested huge amounts of R&D dollar cost into developing this, and there’s carcasses of ideas littered throughout their R&D labs that they invested a ton of money in and it went nowhere. I think they view that when they do have a drug that shows benefit, that they want to bake into that cost a bit of the R&D expense that it took to get that to market and available.

The breakdown of how much should be in there, how much does that really end up being $14,000? Is that really true? I don't know. I don't have that kind of detail. I think there's been some debate around that, but nonetheless, that's what the companies have believed to be the value of the medicine on the market.

Dr. Andrew Perry: Are there any moves on making it more affordable or to lower that price in some way?

Dr. Tom Maddox: The pharmaceutical market is a bizarre one. If you study sort of classic market economics... I remember when I was an undergrad economics major the professors would get up and show us all these models and say, "Hey, you have this whole list of assumptions about what makes an effective market work, and it's things like transparency of information between the buyer and the seller, and the mobility of the buyer to move around and if I don't like the price you're offering me, then I can go next door and get this price," etc.

Almost all of those assumptions are violated in healthcare. The ability to expect sort of the market to deliver in an effective fashion is probably not a good operating principle or not a realistic principle. To that end, patients, of course, and even smaller physician practices don't have much bargaining power. There's nobody else selling the med. They can't go anywhere else, so they're basically facing a monopoly situation.

There's been some movement to band together and negotiate saying that we'll come to the table with a large number of patients and practices that we represent, and we are going to collectively buy from you if you give us the price that we think is more fair or more... just a better price.

Dr. Andrew Perry: Interesting, okay.

Dr. Tom Maddox: One of the ways that that's been done are these pharmacy benefit managers. Here, in St. Louis, actually, we're home to the biggest one in the country and that's Express Scripts. They will band together with different practices and health plans and insurers, and it's an amalgamation of folks. All of them have an interest in getting this medicine. They'll say, "Hey," to Amgen or Sanofi, or whomever is selling the medicine of interest, "Hey, we represent X thousands and thousands of patients who potentially would buy this medicine, but we do not accept the $14,000 price tag. We need a discount."

When you look at the discounts across the country and average them together,
right now it's roughly a 30% discount that a lot of those PBMs and other entities are getting, so now we're down to around $10,000 or so. That's kind of where we are. Even at that level, we are still seeing that the value in the qualities, as you said, the quality-adjusted life year is still far north of what the generally accepted cost-effectiveness ratio is. Is it helpful to have a background on how that works?

Dr. Andrew Perry: Yes, it would be.

Dr. Tom Maddox: In sort of health economics, there’s been sort of a standard developed of saying, "Well, at the end of the day, healthcare costs money." For us to say something is free is just sort of fantasyland. We've got to recognize that we do need to pay for things that are valuable. But how much is it valued? How much is it worth?

[00:20:02] There's a lot of debate and work around how do we value a life and what does that mean? Is just being alive enough? Is it different if you're running around and playing with your kids versus alive on a ventilator in a long-term acute-care facility or something?

All that was part of the nature of the debate. We ended up with this quality-adjusted life years. It matters that you're alive, and it matters that you have good quality of life. Then with that, they said, "Well, how much should any intervention that delivers more of a quality be worth? How much should we pay for that that makes sense?" We've settled on roughly a number of $50,000 to $100,000 per quality-adjusted life. It came to be somewhat historically that's actually how Medicare set the pricing for dialysis back in the 60s.

They basically said, "We're going to pay this much, roughly around $50,000 per quality-adjusted life year of this dialysis intervention, and we think that seems to make sense."

Then, that's kind of been the operating mantra for the decades following. There are people that said, "Well, maybe $50,000 is a little restrictive. Maybe we can go up to $100,000." But I think once you get north of $100,000, I think most people are starting to say, "Mmm, this might be a little bit more than it's worth." To the patient, to society, it's obviously a very complex sort of conversation and discussion. There are a lot of very valid opinions around it, but nonetheless, that's kind of what we're operating with. When we did the cost-effectiveness studies for PCSK9s, they were coming in somewhere between $350,000 and $650,000 for quality-adjusted life year.

Dr. Andrew Perry: Wow!

Dr. Tom Maddox: Even with that 30% reduction, we're not even close to that $100,000 line.

Dr. Andrew Perry: How far would the price, then, have to drop in order to hit that benchmark?

Dr. Tom Maddox: For us to hit the $100,000 threshold, the PCSK price should be $4,536.

Dr. Andrew Perry: Okay.

Dr. Tom Maddox: Yeah, almost $10,000 less than what we're currently seeing.

Dr. Andrew Perry: Okay. I want to spend a minute and think about other statin-reducing therapies or other therapies to reduce cardiovascular risk or other behavior modifications. For example, the addition of ezetimibe to statins, maybe how that changes this picture. Then also taking somebody who's a smoker, knowing that
they are at high risk and may be one of these patients who benefits the most from an expensive medication to reduce their risk. However, also getting them to quit smoking would also be a major reduction for their risk.

**Dr. Tom Maddox:** Mm-hmm, absolutely.

**Dr. Andrew Perry:** Then, now I guess that's kind of getting us into the picture of how this plays out into clinical practice of which patients we then start selecting for and which patients you're looking at your clinic and saying, "I'm probably going to get more bang for my buck in helping you quit smoking versus prescribing this medication." Or this is the right patient who benefit from that PCSK9.

**Dr. Tom Maddox:** Yeah.

**Dr. Andrew Perry:** I guess let's first tackle smoking cessation, that one.

**Dr. Tom Maddox:** Okay. Well, you're making my public health geek heart just smile with all these sort of considerations. That's exactly the right way to think about it as we look at our patient population, and we look at the various contributors, both things that are increasing their risk and the things we can do to reduce that risk, I think being thoughtful about what is really driving their risk and what can they do not just pharmacologically, but globally to make the most impact.

All of us have limited time. All of us have limited resources. If we can, in pretty rigorous fashion, determine that for this patient they're going to get the biggest bang for their buck, maybe not even from an additional medicine, but from smoking cessation or dietary changes, weight loss, etc., then really deploy resources to go after that. These lifestyle things are super hard. One of the reasons that sometimes clinicians are like, "Oh, yeah, yeah, yeah, lifestyle," and they kind of dismiss them is it's just such a tough nut to crack, particularly in the context of the way our healthcare system is designed where it's I see you every three months or every six, or every 12 months for 15 minutes. It's everything I can do to kind of get the information of what's happened and prescribe the right meds and get you out the door. Hardly enough time to sit down and go, "Let's talk about your diet. Let's talk about smoking cessation. Let's talk about these things you need to do every day in your life that I don't have a ton of insight into to make a difference." With that preamble, I think there's some interesting work going on around the contributors to cardiovascular risk and incenting practices to invest their time and resources into those things with the most impact.

The most clear example we have is an ongoing trial called the Million Hearts Project. It's being run out of CMMI, so the Centers for Medicare & Medicaid Innovation Center. This was a center that was funded out of the ACA back in 2010, and it was a group of folks connected to CMS who were charged with the task of let's be innovative about how we pay for healthcare for our Medicare and Medicaid patients in a way that would incent providers and insurers, and everybody else involved in this to provide more value and higher outcomes, and the way to do it, as opposed to sort of our traditional fee-for-service, where it sort of didn't really matter what the outcome is of what you did. Just do some stuff that you can bill for and us generate the revenue.

The group that worked on this particular project said, "Okay, we know that there's benefit in certain meds and cardiovascular disease, aspirin or statins. We also know there's benefit to tobacco cessation, etc." All of that goes into cardiac risk. Right now, we use a 10-year pooled-risk calculator to sort of say, "You, with your risk factors today,
your risk for a cardiac event over the next 10 years is X."

**Dr. Andrew Perry:** The ASCVD risk score.

**Dr. Tom Maddox:** The ASCVD risk score, exactly, and it was developed for that and they used that. Then they said, "We're going to give you your risk score for your patient population." Let's say you have a thousand patients. We're going to take each of those individual risk scores, all thousand, and aggregate them together. Then, let's say that the average risk is 15%. That's a pretty high-risk population, but some of your patients are going to be 5%. Some of your patients are going to be 30%. You have this mixture. They said, "We're going to calculate your baseline risk, and then for the next year, we're going to pay you based on how much you can get that aggregate risk down." What are you going to do? What I'm going to do, what I would do and what anybody would do is you say, "Okay. How am I going to move that needle? Let me go find my high-risk guys." You start slicing and dicing the data and drill down to your patients who are at the 30%-risk level. Why? Then they're going to start to say, "Okay. Well, I have identified of the thousand, a hundred are my really risky guys and they're driving that average really up."

In that hundred, what's going on? A third, they're heavy smokers. A third are not taking effective cholesterol therapies, and then a third have really elevated blood pressure. Now I'm going to invest my clinic resources into what I believe to be effective smoking cessation programs for that population. Even if it's a heavy smoker who maybe has a blood pressure a little bit over the guidelines, that slight elevation of blood pressure isn't going to change their risk as much as quitting smoking. I may even say, "You know what? It's not optimal, but just keep doing what you're doing on the blood pressure side. But man, go to the smoking cessation clinics. Let me do everything I can to get you off the cigarettes." We know that if they do that their risk goes from 30% to, say, 15% over the course of that year, and then they contribute back to that overall average that I'm getting paid on and start to drop that average.

It basically is just it's not the end-all-be-all solution. I'm not trying to imply that that's the case, but it is making us think with the motivator of pay, which is important, to say, "Where's the biggest bang for my buck?" For that population of smokers, sure, they're really high risk and maybe if you were saying, "Well, I want to give my PCSK9s to my highest-risk patients," you might be tempted to say, "Well, give it to them," but I would argue... I haven't run this head-to-head comparison, but I suspect that the benefit that they would derive from getting off cigarettes far exceeds anything that they could get from a PCSK9. To my end, put aside this whole idea of getting them on that med and focus really on getting them off cigarettes.

**Dr. Andrew Perry:** That would be a interesting, new approach, at least from what I see and how I approach my patients in clinic.

**Dr. Tom Maddox:** That's right.

**Dr. Andrew Perry:** Because I frequently see them and the things that I can change are the prescriptions, and so that's where I end up focusing my time on is, "Oh, your A1C is too high, so I'm going to fix that."

**Dr. Tom Maddox:** That's right.

**Dr. Andrew Perry:** "I'm going to change your insulin. Your blood pressure is too high. I can change that."
Dr. Tom Maddox: That's right.
Dr. Andrew Perry: "But really, you're still smoking, so maybe your A1C being 8 is okay, not a goal. Your blood pressure at now 145 over 100 is maybe not a goal, but you're still smoking a pack a day." [00:30:00]
Dr. Tom Maddox: Right.
Dr. Andrew Perry: Maybe my 15 minutes with you is better spent formulating a plan and getting smoking cessation.
Dr. Tom Maddox: I'm with you halfway.
Dr. Andrew Perry: Okay.
Dr. Tom Maddox: But you're actually illustrating my point about incentives. At the end of the day, if there's one sort of thing that I've learned at least to date in my career, is incentives are so important. They push us to organize our mindsets and our work in ways sometimes we're not even conscious of. Let me just unpack what you said a little bit. You said, "All right, what can I control in 15 minutes?" Why the hell is it 15 minutes? You know why it's 15 minutes? It's because your preceptors in your internal medicine clinic know that they have to churn through enough... X number of patients that meet their margins to keep the medical center going.
Dr. Andrew Perry: Yeah.
Dr. Tom Maddox: It's not even a profit thing. It's literally keep the lights on.
Dr. Andrew Perry: For our resident clinic? Yeah, that's totally the case.
Dr. Tom Maddox: Yeah. Keep the lights on, pay you not an awesome amount of money, but enough to be respectful of the training and talent that you provide. Similarly, pay the MAs and the nurses and ancillary staff that do excellent work. Anyway, the point is that that is, at the core, they know they're going to get paid if you churn through those patients. In reality, would it be better if you had an hour? Absolutely, but you would have to shut the lights off. You'd be out of job in a year because you wouldn't be able to make that.

It illustrates that the governing payment model that we have is shaping how we put care together, and it's totally ineffective to have that kind of structure if we run a counsel and follow up on to support a patient through these really hard, complicated lifestyle changes like smoking cessation, etc.

If we change the payment model — and this Million Hearts project I talked about is an example — if we change that to where you're now paid for the outcomes you're delivering to your patients, and I talked about you're delivering a risk outcome. You could also model it on do they stay out of the hospital? Do they report good health? Are they dying less? That's obviously a straightforward one. But you provide this sort of set of metrics.

Then how would we reorganize care to try and deliver, particularly if we're getting paid for it? At least, we're not having the perverse incentive. That's what I mean of just being paid for churning people through in a volume basis. If we're paid to deliver these outcomes and let's take that smoking cessation example, I would argue you're probably not the right person to be working with that patient.
Dr. Andrew Perry: Yeah, I have no training.
Dr. Tom Maddox: You're not trained and maybe you could get trained. That's a path. Maybe we need better training on our physicians. Fine. Alternatively, we could expand
our care team and get somebody who is trained in that. The psychology in smoking cessation, we know from our substance abuse communities that often when you get groups of patients together that are struggling through things like Alcoholics Anonymous, that provides a ton of support to have that community. Often, they're led by prior alcoholics or maybe prior smokers or somebody who can give sort of the blow-by-blow firsthand experience, which often can be super effective for folks struggling with this.

There are things we know to do, but we don't necessarily have them integrated into our care team. Maybe the better approach is we take those of us who are trained in medicine, that what are we good at? We're good at diagnosing. We're good at organizing some of these care processes and their relative contributions to health. But once we set that plan up, maybe our job is to then hand it off to a very trained, comprehensive care team that has within it various skillsets around the psychology, the counseling, the community support, all the other things that I'm not necessarily that familiar with, but that are out there. They're known things that can get folks to the place they need to be for optimal health.

I mentioned it early on that one of my other roles is Director of the Health Systems Innovation Lab. That's part of the charge of innovation labs both here in Wash. U. and then around the country. How do we think differently about care delivery that gets us to outcomes that are important for our patients?

Dr. Andrew Perry: Interesting stuff. I'm realizing that I probably came to you with the wrong question. There's probably a lot more interesting discussion that I'm now discovering with this. That's great stuff.

Dr. Tom Maddox: Anyway, I didn't mean to get totally off tangent on PCSK9s, but I think it is part of the overall conversation.

Dr. Andrew Perry: No, it totally is and that's the whole reason to have a PCSK9 inhibitor is reducing your risk of death or cardiovascular disease and improving your quality of life, not having a heart attack or etc.

Dr. Tom Maddox: Right.

Dr. Andrew Perry: All this plays into that.

Dr. Tom Maddox: Sometimes I think in addition to all the data we traffic in everyday, I think the stories are important, too. I'm relatively new to Wash. U. and for the last 10 years, I was in Colorado working at the VA hospital out there. PCSK9s were approved in the VA system for select patients some time in the last year or two. I remember I had a patient, a really great guy, sort of a... he was a farmer who lived outside of Denver, Colorado and 67. I just can't remember his age, but he just had terrible coronary disease, and he had had a bypass about 10 years ago, a couple of PCIs since, four MIs.

He was doing his level best. He and his wife were obviously petrified that he would have another heart attack. He had fortunately recovered well, so he was still working on the farm and enjoying a quality of life. But very worried about a subsequent event, particularly one that would rob him of his ability to live the life he wanted to. They were sort of standard Colorado farmers. They had a meat and potatoes kind of lifestyle. His wife totally... they didn't go vegan. That's a little hard for a Colorado farmer to do, but they did at least make serious lifestyle changes.
I can't remember if he used to be a smoker, but he certainly had no exposure to tobacco now. He did everything he could from a lifestyle point of view to be able to optimize his cardiac health, yet, he continued to have cholesterol values north of 200, LDLs north of 200, and he was one of these guys who had a legitimate statin intolerance. A statin could look at him and he would sort of ball up in muscular pain.

Sometimes people, I think, mistake joint pain or other arthritic pain for statin myopathy. This guy, not at all. He was a super stoic guy. He would have powered through anything. He was totally debilitated, could not do any of his chores on the farm with any dose of statin, even once a week. Now, he’s trucking along, can't get the therapy we know works, doing everything he can from a lifestyle point of view, cholesterol numbers still around low 200s. This is the guy who needs a PCSK9.

But the VA has got a pretty streamlined process for this, actually. But even with that, it took a fair amount of advocacy of me and my staff to try and get him on it, and in the meantime, he had another heart attack. In the meantime, he actually had another bypass. We had him on Zetia, and we did everything we could. But just with that kind of genetic profile for the LDL, this is where PCSK9s could really help.

Finally, we got him on it and true to form. He went from, I think it was 210, and the last LDL I saw in him before I left Colorado was probably 105. He had a huge drop, 50% drop in his LDL. I haven't talked to him recently, but I know that'll help alter the trajectory of heart disease that he has.

I don't want to walk away saying, "Oh, there's no role for PCSK9s. We're totally misguided about pushing these sorts of things." They're really important, but they're really important for a small group of people. I think it's incumbent upon us as providers to think about our populations and say, "Okay, we have some great options in our pharmacologic arsenal. We have the product of super-smart scientists from the pharma companies working in conjunction with our academic centers." That's an outstanding resource that we have, and I wouldn't, in any way, want to try and impede that. I mean that's how we’ve made all the improvements we’ve made over the last 50 years.

But I think if we don't bring similar work and talent and expertise to serve our public health, where we're sort of viewing on a population level how best we allocate the various interventions we know to do: pharmacologic, procedural, lifestyle, public-health stuff like public-health interventions, public policy, what do we think about our built-in environment? What do we think about our food supply and the amount of sugar in our food? What do we think about these various things, where people living their day-to-day lives, if they have no options for healthy food, if they have no options for a healthy lifestyle? Do we have a role in the public health today and the public infrastructure today, and trying to change that to provide those options to all our patients? I think we do. If we go through the process of what kind of impact would we expect from that, I think we can have a much more nuanced and targeted view of all the things we can provide to the patients.

**Dr. Andrew Perry:** Yeah, those sound like great closing words.
**Dr. Tom Maddox:** I'm sure I've worn you out, but...
**Dr. Andrew Perry:** We've covered all the main points that I wanted to.
**Dr. Tom Maddox:** Super.
**Dr. Andrew Perry:** I really appreciate your time.
Dr. Tom Maddox: Yeah. Thanks for letting me get on the bully pulpit or the soapbox or whatever, but it's obviously something that I really like and I'm passionate about and I think it's an exciting time. [00:40:00]

END OF TRANSCRIPT [00:40:46]