

- BERNARD** Hello, I'm Bernard Gersh from the Mayo Clinic. And with me today is my friend and colleague, Dr. Scott Wright.
- GERSH:** Scott is Professor of Medicine at the Mayo Clinic, major interest in preventive cardiology. And Scott, we're going to talk a bit about evolving strategies in lipid-lowering therapy. Welcome.
- SCOTT** Thank you very much, Bernard. Pleasure to be with you.
- WRIGHT:**
- BERNARD** So what are the new strategies? I know the statins. We don't have to talk about those. Ezetimibe is currently the subject of a trial. What are some of the new agents out there on the horizon?
- GERSH:**
- SCOTT** Well, if we think about the strategies that are evolving to lower LDL further, there are two new classes of drugs that are being developed and tested in phase III clinical trials. The first is a drug called mipomersen. It's an antisense compound that inhibits the message RNA from producing lipoprotein or apoprotein B. Apoprotein B is the protein that works with LDL to form the LDL particle. So if you make less ApoB, you have less LDL.
- WRIGHT:**
- BERNARD** You've got to keep it simple, Scott, for those of us who are not lipidologists. But I follow.
- GERSH:**
- SCOTT** So it blocks LDL synthesis. And it's an interesting strategy because it's an antisense oligotide, which means that it blocks things at the message RNA level.
- WRIGHT:**
- BERNARD** Injectable?
- GERSH:**
- SCOTT** It's an injectable, and right now it's given weekly. And of course, that will be a whole new paradigm for our patients. We're going to move from preventive cardiology, perhaps, to interventional lipidology with these.
- WRIGHT:**
- The second class of therapies are a series of antibodies called PCSK9 antibodies. A PCSK9, Bernard, has been discovered I think since the turn of the century, just a few years ago. It is a protein that causes the LDL receptor to be degraded or removed. So if you have fewer LDL receptors around to take out LDL, you have higher concentrations.
- BERNARD** Now, correct this. There are certain polymorphisms in which you either have a low or a high PCSK9.
- GERSH:**
- SCOTT** That's right.
- WRIGHT:**
- BERNARD** But if you have it, you have a lifelong low LDL cholesterol level.
- GERSH:**
- SCOTT** That's right.
- WRIGHT:**
- BERNARD** And that has had-- and they don't get coronary disease, is that correct?
- GERSH:**

**SCOTT** That's right. That's correct. They get much lower levels.

**WRIGHT:**

**BERNARD** Now, are these people with high levels of PCSK9 or low?

**GERSH:**

**SCOTT** They have low levels.

**WRIGHT:**

**BERNARD** Low levels.

**GERSH:**

**SCOTT** Because we're injecting, now, antibodies to block the PCSK9 to keep it from taking away or degrading the LDL receptor. So basically this is a great magical therapy that upregulates LDL receptors and removes LDL.

**WRIGHT:**

**BERNARD** So what is the preliminary data, never mind the animal data, but preliminary clinical data?

**GERSH:**

**SCOTT** Well, the data really focuses on just lipid-lowering. We don't have outcome studies yet. Those are being planned and executed.

**WRIGHT:**

But both classes of therapy, lower LDL between 30% and 50%, it's rather dramatic.

**BERNARD** Is that on a background of statin therapy?

**GERSH:**

**SCOTT** It is. And I think there are studies without statins showing it's comparable to that. So in many respects, you can bring the LDL down with a statin, and then if you don't get the LDL to the goal, you add a second agent.

**WRIGHT:**

Now we use Ezetimibe or niacin. In the future, we may be able to add one of these injectables, which will do it even more effectively.

**BERNARD** So I'm trying to think of the clinical scenarios. Obviously, one is people don't tolerate the statin.

**GERSH:**

**SCOTT** Correct.

**WRIGHT:**

**BERNARD** Or the statin is not lowering LDL sufficiently, or they get side effects. And certainly, I think in the last year, there's been an increasing number of reports of unwanted side effects from statins.

**GERSH:**

**SCOTT** Well, that's right.

**WRIGHT:**

**BERNARD** The myopathy myositis is more common than you think.

**GERSH:**

**SCOTT** Right, and also cognitive function. And there's some concern about developing diabetes, if you're taking a potent statin, like atorvastatin, I think. But overall, I think it's safe to say for our patients that the benefits of statin generally outweigh any of these risks.

**WRIGHT:**

**BERNARD** Yeah, and I think that's really very important in regard to the diabetes message.

**GERSH:**

**SCOTT** It is.

**WRIGHT:**

**BERNARD** There is this almost hysteria statins--

**GERSH:**

**SCOTT** Yes.

**WRIGHT:**

**BERNARD** --cause diabetes. But clearly, the benefit outweighs the risks. But what about the scenario where you get the LDL

**GERSH:** down below 100 on a statin, or below 70. Do you ever see these agents now coming in to super lowest cholesterols, to super levels, LDLs of 30? And very speculative.

**SCOTT** I think so. I think clinicians have been quite aggressive at lowering LDL. You can remember that we, in our own practice, were lowering LDLs to 70 before the guidelines recommended it. And in many of our patients, who are either young with advanced atherosclerosis, or people with multiorgan atherosclerosis-- CVD, CAD, PVD-- we try to drop the LDL to 50.

To achieve that, though, you get a lot of statin intolerance. You get myalgias. You get muscle aches. People don't feel as well. So I think this will allow us to get the benefit from a statin, and then to add to that without having to fully up-titrate it.

**BERNARD** I think it's reasonable to say, or do you think it's reasonable to say, that lowering the LDL to 50, and 40, and 30?

**GERSH:** There isn't any evidence.

**SCOTT** There's no evidence.

**WRIGHT:**

**BERNARD** We know that Pygmies in the jungles of the Congo have LDLs of 38 and they don't get coronary disease. But we

**GERSH:** don't have any evidence that it's going to work clinically. That would have to be tried.

**SCOTT** We have no evidence, and we don't know in Western society if it really will work. And we also-- many, including me, believe that the statins give benefit beyond LDL lowering. They, clearly, at the molecular level upregulate expressible nitric oxide synthase, and they do other things to promote basal dilatation and suppress inflammation.

So I don't think we'll ever want to treat coronary patients without a statin. But I think there are many who can't get to goal. And so this class of therapy, these classes, will compete with this Ezetimibe to be an add-on.

Now, for the second group, where the incidence of this is really rising, statin intolerance, we only have niacin, Ezetimibe, and perhaps these injectables. And niacin has its intolerance issues. We don't know if Ezetimibe will provide a long-term outcome benefit. There's preliminary data suggesting it probably does, but we're waiting on the improve at trial to show us and tell us.

And if the improve at trial fails to show a difference, there may be skepticism about the therapy. So it will be nice to have another class. And I'm glad to see the companies are testing these now in outcome-driven studies.

**BERNARD** Why injectable? Will they become oral agents?

**GERSH:**

**SCOTT** I don't think so.

**WRIGHT:**

**BERNARD** Really?

**GERSH:**

**SCOTT** I think the inner ACEs, and other enzymes in the intestine, would probably destroy the compounds. Because one really is an antisense nucleotide, that has to be picked up in the bloodstream and delivered to the liver, where it's exerting its effects. The other has to stimulate antibodies to PCSK9. It would be nice to have an oral one.

**WRIGHT:**

What I think may happen is that somebody, some company, will likely come out with a once a month injectable. And I think that will be more palatable than a once a week injection.

**BERNARD** Yeah.

**GERSH:**

**SCOTT** I think if you look at the diabetic treatment regimens, many patients really are reluctant to go on insulin or to go on the GLP-1 agonist. And the GLP-1 agonists have wonderful data in terms of glycemic control and, perhaps, novel ways to inhibit atherosclerosis. But yet, they're expensive and people don't want to take them because of the fear of injectables.

**WRIGHT:**

I think that will be true with these. I think it's also going to be a paradigm shift for cardiologists, because you and I have been used to prescribing medications, or referring them to the Cath lab, or the EP lab for procedures. Now we're going to become almost like our rheumatology colleagues, where we're also going to be giving injectables. So that's a bit of a paradigm shift.

**BERNARD** I think there's going to be a block in uptake both from cardiologists and patients.

**GERSH:**

**SCOTT** I think so too.

**WRIGHT:**

**BERNARD** During the last year, or two, three years, probably the hottest topic in preventive cardiology was HDL elevation.

**GERSH:**

**SCOTT** Yes.

**WRIGHT:**

**BERNARD** And we've now had a few trials that are disappointing. The torcetrapib trial was stopped because it probably-- hyperaldosteronism and hypertension.

**GERSH:**

**SCOTT** Yes.

**WRIGHT:**

**BERNARD** We've had the defined trial of anacetrapib, which is promising. And now we have a very large trial--  
**GERSH:**

**SCOTT** Yes.  
**WRIGHT:**

**BERNARD** --ongoing. There's the dalcetrapib, that I know you can't comment on in detail. But we do know, since you are one  
**GERSH:** of the principal investigators, but we do know that there's been an announcement that this drug has been discontinued for--

**SCOTT** It has been.  
**WRIGHT:**

**BERNARD** --further development. So the HDL elevating hypothesis has taken a knock.  
**GERSH:**

**SCOTT** It has. It has. I think it's been very disappointing, because AIM-HIGH was negative. And the curves were--  
**WRIGHT:**

**BERNARD** And that's for the niacin trial.  
**GERSH:**

**SCOTT** That's that niacin trial. The curves were superimposed. And it's hard to argue that the study was under-powered.  
**WRIGHT:** Although I know why people are arguing that and I understand that rationale.

I think we were very excited, three, or four years ago, about the CETP class. We had three drugs beyond torcetrapib that were being tested or to be tested. A second one now has been stopped, and more will come out about that later on. And it was just simply announced publicly that because of futility it was stopped. And I think that's going to put a lot of pressure on the anacetrapib and evacetrapib studies.

**BERNARD** So it's had great expectations--  
**GERSH:**

**SCOTT** Yes.  
**WRIGHT:**

**BERNARD** --but so far unmet.  
**GERSH:**

**SCOTT** That's right. And there is one more niacin trial that Rory Collins is leading. And I'm hopeful that it will show a  
**WRIGHT:** benefit. Because, look, we all recognize that patients who have low HDLs have higher risks for cardiovascular disease, both for their first MI and recurrent MI. And we know that patients who undergo percutaneous revascularization who have low HDLs have higher recurrent risks.

I like to think that HDL is a player and a modulator. Some argue that it's simply a risk marker and we shouldn't mess with it. And I think the door is still open. It's been disappointing, but I'm holding out hope that one of the two--

**BERNARD** Yeah, I think it's premature to dispel the HDL elevating hypothesis. I suppose the key question is-- we know  
**GERSH:** epidemiologically that low levels of HDL are a very bad actor, indeed.

**SCOTT** Yes.  
**WRIGHT:**

**BERNARD** And certainly, that high HDL levels, in most populations, appear to be predictive.  
**GERSH:**

**SCOTT** Yes.  
**WRIGHT:**

**BERNARD** What we don't know is the HDL, that is elevated pharmacologically, is that the same HDL as is present  
**GERSH:** endogenously-- if I can use the term.

**SCOTT** That's right.  
**WRIGHT:**

**BERNARD** Because the functioning of them may be different.  
**GERSH:**

**SCOTT** That's correct. And we also know that prior to statins, several trials with fibrate showed some clinical benefit--  
**WRIGHT:**

**BERNARD** Yeah.  
**GERSH:**

**SCOTT** --the Helsinki Heart study and the VA HDL Intervention study. But currently, no trial, which adds a second drug on  
**WRIGHT:** top of a statin that's designed to exploit and raise HDL, and perhaps lower LDL, like niacin, or simply raise HDL, like a CETP inhibitor, has shown a benefit, a clinical benefit. So maybe the statins are doing something to HDL that we can't add upon. Maybe pharmacologically we haven't found the right class of drugs to exploited it.

And I think there's another hypothesis, and that is that LDL is a very simple, straightforward hypothesis. That delivers cholesterol and causes atherosclerosis. HDL has 100 to 1,000 functions in vivo, one of which is reverse cholesterol transport. And there are different classes of HDL.

And it may be that we are stimulating all of the classes, instead of the wrong subtype, to promote reverse cholesterol transport.

**BERNARD** So to sum up, a lot of interest in new agents for LDL lowering. Very powerful--  
**GERSH:**

**SCOTT** And very promising.  
**WRIGHT:**

**BERNARD** --in the next few years, and very promising. Unmet expectations with HDL, but the game is not over.  
**GERSH:**

**SCOTT** It's not over. And I think my bottom line to clinicians and to patients are the following. One, treat the LDL. Get it  
**WRIGHT:** to goal. And, two, work on nonpharmacologic ways to raise HDL: weight loss, better dietary management, exercise. And let's hope that one of the trials works.

**BERNARD** And, of course, drinking red wine.

**GERSH:**

**SCOTT** Of course.

**WRIGHT:**

**BERNARD** Thank you very much, Scott.

**GERSH:**

**SCOTT** Thank you, Bernard.

**WRIGHT:**

**BERNARD** Thanks.

**GERSH:**