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# Current and future management of hyperlipidaemia and atherosclerosis: From statins to combination therapy

## Transcript from a touchPANEL DISCUSSION

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# THE EXPERTS

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# INTRODUCTION

Watch renowned clinical specialists in atherosclerosis discuss the impact of a range of cholesterol-lowering regimens on hyperlipidaemia and the risk for atherosclerosis with our touchPANEL DISCUSSION.

Prof. Alberico Catapano chairs a discussion with Dr Jacques Genest and Prof. Kausik Ray on recent data and issues surrounding the use of statin monotherapy and combination therapy in the management of hyperlipidaemia and atherosclerosis.

This activity is intended for cardiologists, endocrinologists and healthcare professionals globally.

This touchPANEL DISCUSSION was recorded in October 2020.

## LEARNING OBJECTIVES

**After accessing the touchPANEL DISCUSSION activity, you should be able to:**

- Recall the current standard of care for cholesterol-lowering therapy and the potential limitations of statin monotherapy
- Discuss the clinical considerations which guide the choice of second-line or add-on therapy when statin monotherapy is ineffective or not tolerated
- Summarize the most recent data on the effect of dual lipid-lowering therapy on hyperlipidaemia and the risk for atherosclerosis

## TOPICS DISCUSSED

**The expert panel will discuss:**

- What is the impact of statins on lipidaemia and what are their limitations?
- When is monotherapy with statins no longer sufficient?
- What are the advantages of combination therapy and when should it be considered?

## CURRENT AND FUTURE MANAGEMENT OF HYPERLIPIDAEMIA AND ATHEROSCLEROSIS: FROM STATINS TO COMBINATION THERAPY

**Alberico Catapano:** Hello everyone, my name is Alberico Catapano and I'm Professor of Pharmacology at the University of Milan, Italy.

Today it is my pleasure to welcome you to this discussion on current and future management of hyperlipidaemia and atherosclerosis, from statins to combination therapy. I'm here with two distinguished colleagues and friends who are Dr Jacques Genest, Professor of Medicine and McGill/Novartis Chair in Medicine at McGill University and Director of the Center for Innovative Medicine at McGill University Health Center in Montreal, Canada; and Professor Kausik Ray, Professor of Public Health, Deputy Director of Imperial Clinical Trials Unit and Head of Commercial Trials within the Department of Primary Care and Public Health at Imperial College in London.

With these two colleagues today we are going to go through this agenda that has three main questions: What is the impact of statins on lipidaemia and what are their limitations? The second will be: When is monotherapy with statins no longer sufficient to achieve goals? And: What are the advantages of a combination therapy and when should such a combination be considered?

## WHAT IS THE IMPACT OF STATINS ON LIPIDAEMIA AND WHAT ARE THEIR LIMITATIONS?

**Alberico Catapano:** So, let's address the first question: What is the impact of statins on lipidaemia and what are their limitations? Just to recapitulate briefly how statins are currently classified, you have heard over and over this concept of high intensity, moderate intensity and low intensity statins, and this intensity is related to the capability of lowering the LDL cholesterol, going from above 50%, such as a high dose of atorvastatin and rosuvastatin, as well as moderating the intensity like atorvastatin 10 milligrams up to 20, rosuvastatin, simvastatin 20-40 milligrams, and low intensity simvastatin 10 milligrams. Other statins are recapitulated in these lines as well between the moderate and low intensity, as you may see here.


Now here come the questions for the panel. The first one is: Are all statins the same or do they have a varying effect on different lipoproteins? I would like Dr Genest to answer this question first.

**Jacques Genest:** Thanks very much Dr Catapano. As you mentioned before, statins differ in potency and as a general rule their potency is related to their effect on not just LDL cholesterol but also on all cholesterol-carrying lipoproteins, which include the triglyceride-rich lipoproteins. Their effect on HDL is quite neutral, and we stopped worrying about HDL in our risk calculation. So, in my view, the more potent the statin the better effect on all the lipoprotein cholesterol concentrations.

**Alberico Catapano:** Professor Ray, would you like to add something on this statement by Jacques?

**Kausik Ray:** Thank you Professor Catapano. I'd completely agree. The one thing that I would add is that with respect to the atherogenic lipoproteins, the one that statins don't really have any effect on – and if anything, there's probably a non-clinically relevant but small increase – is lipoprotein(a). So, we see reductions in LDL, we see reductions in non-HDL, we see reductions in ApoB, and more modest reductions in triglyceride in a dose-dependent fashion, and little or no change in lipoprotein(a).

**Alberico Catapano:** Along with this question, the second one: What is the impact that statins have on the risk of atherosclerotic cardiovascular disease? In other words, do they differ, and if they differ, why? Professor Ray, please.

**Kausik Ray:** Thank you Professor Catapano. I think the first thing to say is that we now benefit from the CTC, Cholesterol Treatment Trialists, which essentially were able to standardize the assessment of benefiting clinical trials per unit change in LDL cholesterol. So, although some statins are more or less potent than others, if you standardize what is achievable for a 1 mmol/L lowering (or 39 mg/dL) you get exactly the same benefit, about 22%. The second thing is, the benefit is greater from Year 2 onwards. So, in Year 1 you get about 10 or 11% benefit, but from Year 2 onwards, it's greater, it's more like 22% per 1 mmol/L.

**Alberico Catapano:** Professor Genest, anything you would like to add on top of these considerations?

**Jacques Genest:** I agree entirely with what Professor Ray added, except that we tend to forget that we've had statins now for 33 years, and in my view no other intervention has been as potent pharmacologically as statin therapy in reducing cardiovascular risk. Perhaps the only other one is smoking cessation. So, statins since their inception in 1987 have had a major, major impact on the primary and secondary prevention of cardiovascular disease.

**Alberico Catapano:** Yes, this is an important observation, because I was recently reviewing the data of the global burden of diseases about cholesterol, and in the countries where statins are widely used you can see a decrease in LDL cholesterol in these nations. The United States is one of them, for instance.

Now a third question for this part of the discussion relates to your clinical experience, and that's very important because it relates to the common side effects that limit the use of statins: Which are the ones that most impinge on your clinical experience? Professor Ray, please.

**Kausik Ray:** Thank you. I think today the commonest things that I would see would be people complaining of muscle-related symptoms and these would be muscle aches, generally reproducible after stopping and starting, if it was attributable to the statins. And often in many of these individuals with no measurable abnormalities in muscle enzymes, for example, that is by far the commonest reason that people complain about statins.

**Alberico Catapano:** Professor Genest?

**Jacques Genest:** Thank you. What we've noticed in three decades of use is lipotoxicity is quite rare and quite unusual, so the main goal-inhibiting statin tolerance effect is muscle-related symptoms. And in clinical trials these were very, very low because we screened these patients out of the study, but in registry data it's probably as high as 15, maybe 20%. And unfortunately for myalgia we have no biomarkers, such as elevated creatine kinase, to guide us, so we need to trust the patients' symptoms. And we have defined statin intolerance as intolerable muscle side effects on at least two different statins with one being at the lowest dose.

**Alberico Catapano:** The last question for this part of the discussion is: Under what circumstances might statin treatment fail or provide sub-optimal outcomes? Professor Ray, please.

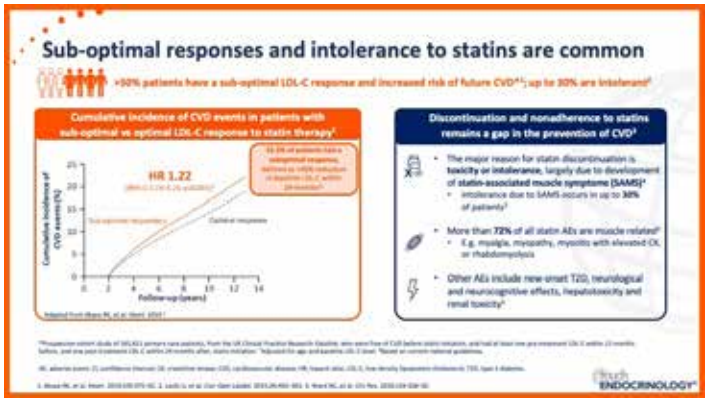
**Kausik Ray:** Thank you Professor Catapano. There are several scenarios when statin treatment may fail. The first is probably patient non-adherence, so if a patient does not take the medications regularly as prescribed, these are small molecules that need to be taken daily, and therefore you may get a sub-optimal response. The second would be when a patient cannot tolerate effective doses, so perhaps they're on only low-intensity statins because that is the highest dose that they can tolerate. And then the other reasons are the inability to get sufficient reduction in LDL cholesterol initially in percentage terms and then afterwards goals, because either the person's level of risk is so high you need a very low goal, or occasionally people need, because they start so far away from goal, more than one therapy, so they might need combination therapy. And these would be the main reasons.

**Alberico Catapano:** Professor Genest?

**Jacques Genest:** Well, there are really two major ones. One is lack of efficacy, in other words the patient's cholesterol is so high that even maximally tolerated statin therapy does not allow the patient to reach the treatment goal threshold. And the second, of course, is intolerable muscle side effects that limit using a higher dose of statin.

## WHEN IS MONOTHERAPY WITH STATINS NO LONGER SUFFICIENT?

**Alberico Catapano:** So, the second key question is: When is monotherapy with statins no longer sufficient? And just a slide to set the stage, sub-optimal responses and intolerance to statins are quite common, as we have also heard.




The left-hand panel of this slide depicts for you the cumulative incidence of CVD events in patients with sub-optimal versus optimal responses. As you can see here this line depicts the sub-optimal versus the optimal therapy, and it's quite clear that there is a benefit; the hazard ratio is 1.22, so 22% better in the ones who have optimal LDL response.

And then discontinuation and non-adherence to therapy remains a gap in the prevention of cardiovascular disease because several data have indicated if you are not adherent to therapy then the outcomes, both in cardiovascular, and I must say also in total mortality, are worse. So, that's very important to bear in mind for our discussion.

And here we have the questions for the panel. Let me start with the first one: What are the guidelines in your region on who to treat and what are the lipid levels that should be achieved with statin monotherapy? I would like to start with Professor Ray, please.

**Kausik Ray:** Thank you, so statins are first-line treatment in my country and in most regions of the world, and the aim is to try and identify those groups at highest risk of atherosclerotic cardiovascular disease. And so, there are broadly four groups: there are those who have established cardiovascular disease; then there are those people with diabetes who will have an elevated lifetime risk; and there are people then with genetic dyslipidaemia, so they're born with elevated LDL cholesterol and a high lifetime exposure. And if you fail to fall into these three groups then we use in primary prevention 'global risk', where we count different risk factors and we use an equation that is validated – ideally in the patient population in which it's being applied – and to estimate 10-year risk and then offer people lipid-lowering therapy. And in general, most guidelines advocate a certain percentage reduction, although there is some vagueness about potentially adding in second and third drugs. So, for example in my country at the moment we don't routinely advocate a particular goal, yet we will have specific LDL recommendations for the introduction of PCSK9 inhibitors. And we expect these to be updated very soon, so it takes into account ezetimibe as well in the middle.

**Alberico Catapano:** Professor Genest, would you like to elaborate further on that?

**Jacques Genest:** I agree completely with Professor Ray. The guidelines across the world are remarkably well harmonized, whether they're in Europe, in America, in Canada or elsewhere. We all have the same strategy of statin-indicated therapy according to cardiovascular risk. And while we may differ on the risk algorithm or risk engine used, the principle is the same; high-risk individuals benefit more from statin therapy. The main issue raised by the Americans has been whether we should have a target level or a threshold, which I think we'll discuss further.

**Alberico Catapano:** So, let's now move to the second question to the panel that is: Do you consider other factors aside from LDL levels, such as ApoB or triglyceride, to define therapeutic targets? Professor Genest, please.

**Jacques Genest:** We should keep in mind that all the clinical trials targeted LDL cholesterol with statins, but we've now come to appreciate that non-HDL cholesterol, also reflected by total ApoB, is probably a better marker of atherosclerotic cardiovascular disease. Similarly, high triglyceride is probably a marker of poor cardiovascular health and a reason to intensify therapy. Although LDL cholesterol remains the main target, I believe that non-HDL cholesterol or ApoB will probably be better biomarkers to achieve.

**Alberico Catapano:** So, moving to Professor Ray, I would like to address a slightly different point in this question, that is, European guidelines do actually target ApoB and non-HDL cholesterol and the specific circumstances as a secondary goal. Would you like to comment on that in addition to what has been said?

**Kausik Ray:** Sure, so in general most of our cholesterol is carried in LDL particles. Now where LDL, non-HDL and ApoB diverge is when we have insulin resistance states like diabetes, obesity, and here we often have additional ApoB-containing lipoproteins, which are triglyceride rich. So, we recognize them by the presence of an elevated triglyceride. These particles also contain cholesterol, so if we only use LDL in those people we'll be underestimating risk if we're using LDL for a goal, for example. This is why in those individuals with diabetes, obesity, high triglyceride, the ESC recommendations also have a non-HDL and ApoB target in those individuals. You could argue in the future why not simply go to non-HDL and ApoB? And that would be a very good reason, because then you could take out that step of 'which patient do I choose LDL in and which patient do I need to go to those additional targets in?'

**Alberico Catapano:** Thank you very much. Okay, let's now move to the third question, that is: What factors help you to determine whether or not statin therapy has been successful and the need for a second-line therapy emerges? Professor Ray, would you like to answer first?

**Kausik Ray:** Thank you. So, we always start with risk assessment, because if I have a low-risk patient then the LDL goal, or my aim in that patient will be less conservative, shall we say. And where we have a much higher-risk patient, we will tend to aim for much lower LDL-cholesterol goals. So, we tend to start by thinking about a percentage reduction, particularly in those people at high- or very-high risk, and the aim of that is to try and get us to optimize particularly the dose of statins. Having done that we try to match the goal or LDL threshold for that level of risk, and if the patient – despite a significant or sufficient percentage reduction – is above that goal or threshold, at that point we need to think about adding in non-statin lipid modification therapy, because otherwise they have a high residual risk that we could easily reduce with add-on treatment.

**Alberico Catapano:** Professor Genest, would you like to add some facts on this point?

**Jacques Genest:** I agree entirely with Professor Ray. Our initial goal is to reach an LDL cholesterol according to current guidelines. If the patient has a residual lipid risk, as demonstrated by a high non-HDL cholesterol, a high apolipoprotein B, or a high triglyceride, these are reasons we believe to intensify statin therapy.

**Alberico Catapano:** Okay, now the last question, which is quite nice if you will, is: Will you describe a memorable patient case where statin monotherapy failed and the steps you took to address this? And Professor Genest, you may start.

**Jacques Genest:** My clinic deals with a lot of statin intolerance and my approach is to wash the patient out of the statin, then put the patient on rosuvastatin 5 milligrams three times a week, often with ezetimibe. If that fails then I switch to a PCSK9 inhibitor. But there are many patients in my clinic, both with atherosclerotic cardiovascular disease and, in my case, familial hypercholesterolaemia, in whom statin therapy has been totally insufficient, either because of intolerance or because of not reaching the appropriate targeted threshold, in which intensification of therapy with another agent was necessary.

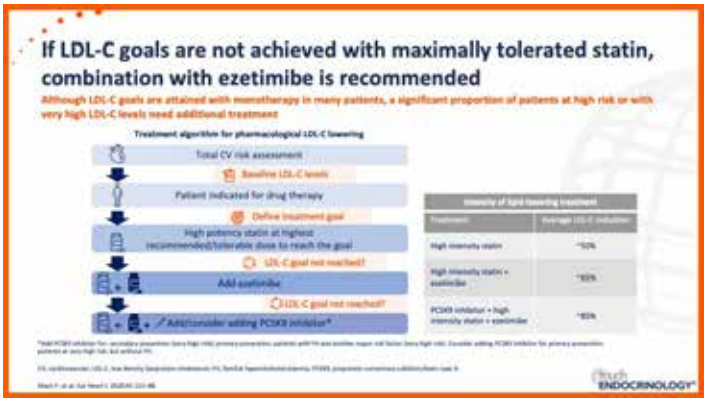
**Alberico Catapano:** Professor Ray, would you like to add to that?

**Kausik Ray:** Sure, so one of my cases that gave me an awful lot of pleasure in being successful was with somebody in his twenties who has familial hypercholesterolaemia. And he was diagnosed in another European country, he probably wasn't very compliant with his medication, initially he didn't appreciate the importance of compliance with daily dosing, and he probably started with LDL-cholesterol levels above 300 or so. And when he came to my clinic I changed the intensity of statin. He was only taking simvastatin, moved into one of the more potent statins, rosuvastatin, and then that was clearly not going to be enough. And then with the addition of ezetimibe and then, because he didn't qualify for a PCSK9 inhibitor because he was below the threshold for FH monotherapy, I added in colesevelam. And the three together brought his LDL down to about 68 and he actually said, "I have never in my entire life had LDL cholesterols like this before." So, that gave me an enormous amount of pleasure.

**Alberico Catapano:** Thank you very much. And probably an enormous benefit to the patient as well.

## WHAT ARE THE ADVANTAGES OF COMBINATION THERAPY AND WHEN SHOULD IT BE CONSIDERED?

**Alberico Catapano:** Let's move on now to the third part that relates to this question: What are the advantages of combination therapy and when should it be considered? This slide just depicts for you what is usually said on the guidelines, this is for example what we say in the European Guidelines. If the LDL goals are not achieved with maximum tolerated statin a combination with ezetimibe is recommended. So, the point is start with the statin, maximum possible dose that the patient can tolerate and then look what happens. Here, just to refresh your memory, high-intensity statins on average will give you slightly above 50% reduction. When you combine that with ezetimibe you can get up to 65% as an average, some respond more, some less. And then on top of that if you add PCSK9 inhibitors with triple therapy, you can get down to 85%.




Having said that let's now move to the questions to the panel. What are the guidelines in your region on initiating and selecting combination therapy when statin monotherapy has failed? Professor Ray, please.

**Kausik Ray:** Thank you. There's a disconnect in our guidelines at the moment. Our guidelines talk about, for those people at highest risk, achieving at least a 40% reduction in non-HDL, so the equivalent of 50% reduction in LDL cholesterol. If you do not get sufficient reduction in non-HDL then consider add-on therapy, but those guidelines don't currently have a goal. We have for initiation of PCSK9 inhibitors essentially two groups: primary prevention FH where LDLs are above 5, then we have those with very-high-risk cardiovascular disease with LDLs above 3.5, so these are people with progression 2 territories recurrent events or any vascular disease, which is an LDL above 4.

**Alberico Catapano:** Professor Genest, would you like to comment from the part of the world you are living in?

**Jacques Genest:** Yes, our healthcare system is very similar to that of Europe and therefore our health agencies and Ministry of Health recommends that we use ezetimibe as second-line therapy before going onto PCSK9 inhibitors. We consider maximally tolerated statin therapy as the dose that the patient will tolerate, and that dose can be zero. And in a retrospective analysis of over a thousand patients with familial hypercholesterolaemia, we noted that the addition of ezetimibe decreased LDL cholesterol by 26%, which is higher than what we expected in a normal population. So, in that group of patients with genetically determined LDL, we found the combination of statin and ezetimibe to be particularly useful.

**Alberico Catapano:** Now, let's move to the next question: Is there recent evidence to show clinical benefit with ezetimibe combined with a statin? And I would ask Professor Genest to comment first.

**Jacques Genest:** So far the clinical evidence we have comes from the IMPROVE-IT trial, which tested the hypothesis that ezetimibe added onto simvastatin reduced cardiovascular risk. It did, but the level of cholesterol lowering was not the one we see in clinical practice. So, in my view the use of ezetimibe with at least a 20% reduction certainly has clinical benefits beyond that shown in the IMPROVE-IT trial.

**Alberico Catapano:** Professor Ray, would you like to clarify further what has been commented by Professor Genest?

**Kausik Ray:** Sure, I think that there are some people that look at the IMPROVE-IT trial and they say well, there's a much more modest benefit, and what they forget is that relative benefit depends upon the absolute reduction in LDL. So, if you start with a relatively low LDL cholesterol, 20-25% further percentage reduction in LDL will give you a small absolute change in LDL. The benefit was exactly what you would have predicted for the starting level of LDL and for the efficacy of the drug. The second thing I would say is there's also now the 'treating stroke to target secondary prevention of stroke' trial, where ezetimibe was added in, and we've seen that, and we've seen in an older patient population in Japan, ezetimibe as monotherapy reducing major cardiovascular events. So, the way to think about this, I guess, is that when considering risk reduction, risk reduction is absolutely agnostic to how you lower LDL cholesterol. What counts is how much and how long you maintain that reduction.

**Alberico Catapano:** Is there any recent evidence to show that when combining a PCSK9 inhibitor with a statin there is a further cardiovascular benefit? Professor Ray, if you may start first.

**Kausik Ray:** Yes, we've got now two cardiovascular outcome trials with two different agents in two different populations, both considered to be high risk because they have established cardiovascular disease. And what we've seen, basically, is a further reduction in clinical events that's proportional to the absolute reduction and the duration of therapy.

**Alberico Catapano:** Professor Genest, would you like to elaborate further on that?

**Jacques Genest:** I agree entirely. We have the FOURIER and ODYSSEY outcomes trials, which showed that on top of standard medical therapy, and these patients were very well treated indeed, there was a 15-20% relative risk reduction in the primary outcomes. So, there is good and solid evidence for PCSK9 inhibition in high-risk individuals.

**Alberico Catapano:** Allow me to add just one consideration on top of that, that is, both trials did not last 5 years. So, you had to discount in the relative risk reduction the effect of the first year that shows a lower benefit; a range of 10% is mentioned earlier. And that's why some people got confused with a benefit that was coming out from those trials. But if you plot them according to the time of the trials, they go exactly where you would have expected them to be in terms of relative risk reduction.

Let's now move to the fourth question for this session, and that goes to Professor Genest first: Can you summarize the key side effects of combination therapies?

**Jacques Genest:** We already talked about statin intolerance. I've been personally, as a clinician, very impressed on how remarkably safe ezetimibe is. I have very few patients who say they cannot tolerate it, but the symptoms have not been very consistent: gastrointestinal, myalgia symptoms, maybe more related to the patient's perception of harm than true harm. For PCSK9s, these agents are extremely well tolerated, and we cannot find a lot of side effects with them. So, the main limitation of combination therapy is due to the statin therapy.

**Alberico Catapano:** Professor Ray, would you like to add from your clinical experience as well as from literature?

**Kausik Ray:** I completely agree with the statement that Professor Genest has just made about ezetimibe, incredibly well tolerated, you don't really see anything. What would I warn my patients about? They might see a change in bowel habit, and very few actually do if you think about the mechanism of action of the drug. For PCSK9 inhibitors, it's very specific drugs; the commonest thing that you might think about in about 1% is a small excess of injection-site reactions, which might mean somebody says "Ow, the injection hurt," or there's a tiny bit of redness there. But in the real world we really don't see that as a complaint

because these are people with huge unmet needs, and they don't really describe any of those.

**Alberico Catapano:** Again, allow me to add a bit to this discussion that doesn't relate to the side effects themselves but the fact that people are worried that side effects may pop up as you go very low with the LDL; now we must reassure those people. Because now we have unprecedented capability of lowering LDL, we can go as low as 40, 30, 20 and all the trials have consistently shown from the IMPROVE-IT to the ODYSSEY and the FOURIER that if you stay for up to 7 years in IMPROVE-IT with an LDL below 30 mg/dL, the incidence of side effects has not changed. That's not to say there are no side effects, but that to say that there is no pop-up of any specific side effect as you go low with the LDL. So, the safety of the drug remains the same independent of the LDL you have achieved. Would you agree, both of you, with that?

**Kausik Ray:** Absolutely.

**Jacques Genest:** Fully agree.

**Alberico Catapano:** Thank you. So, let's now move to the last question: Based on clinical experience, what are the advantages of each type of combination therapy according to patient profile? So, in other words, what will you choose according to the patient? And Jacques, Professor Genest, may you start first?

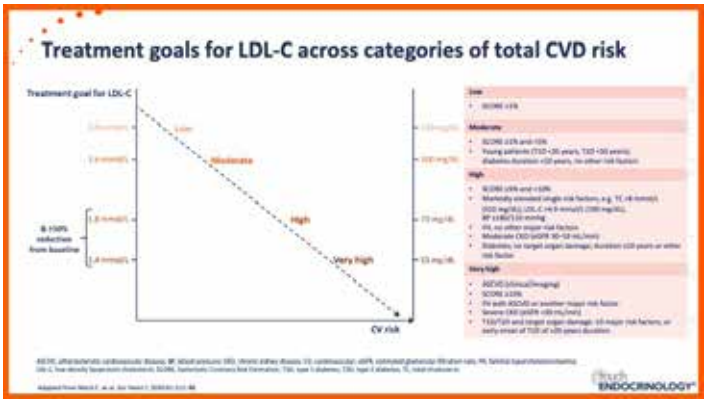
**Jacques Genest:** Let me take the extreme of familial hypercholesterolaemia. The world-wide prevalence is about 1 in 311, so it's much more frequent than people believe; those patients benefit from high-intensity statin plus ezetimibe. I would say 95% of my own patients are on that combination therapy and many of them have to also go on PCSK9 because of the severity of their mutation. So, in those patients I find that they tend to tolerate these medications very well because they understand the severity of their disease.

In patients with established atherosclerotic cardiovascular disease, high-dose, high-intensity statin is my first choice, ezetimibe will be the second one, and if we can go through the regulatory approval, then PCSK9. The most difficult question, I think, is in the primary prevention setting of a patient who is not at what we think should be the goal or threshold, and there we initiate a discussion with the patient on the risks and benefits of the medication, and we really take into account the patients' values and preferences. There is no straight answer to that question but the elephant in the room, I think, is the primary prevention patient who is not at goal yet.

**Alberico Catapano:** Professor Ray, would you concur?

**Kausik Ray:** Absolutely. I think that those are all really key points. I think another issue that we find is different treatments may not be available in certain regions of the world, and also the cost of those treatments and what the local reimbursement guidelines are. Of course one of the advantages of combination therapy, and we've not maybe talked about this as much, but for oral daily medications there are some patients that will not get enough reduction in LDL with a statin alone, and I think increasingly we are seeing the emergence of fixed-dose combinations where the pill burden is reduced from two to one and that may be convenient. Now obviously if you're using a monoclonal in conjunction with a statin you can't combine them into one. One is a daily pill, the other one is an injection every 2 weeks. So, they may be additional considerations.

**Alberico Catapano:** Thank you very much. Now let's move to the closing remarks which I will make very briefly. And I will take this figure from our ESC/EAS Guidelines just to reiterate this concept here.




We have been talking mainly about high- and very high-risk people and as you may see here, this is the area where you have more demanding goals. For the high-risk people, the goal is 70 mg/dL, that is 1.8 mmol/L; or, for the very high-risk the goal is even lower, 55 mg/dL or below, that is 1.4 mmol/L. However, we also have a second goal that is at least a 50% reduction. This has always been in our guidelines since 2016, and part of this, the 50%, is in many, many older guidelines, so there is a concurrent point under these circumstances. And this is to say that at least 50% of the people on statins, high-intensity statins, highest tolerable dose, will not be at goal by this definition. So, the room for a combination therapy is certainly there.

We have just proven now and discussed how safe this therapy is; addition of ezetimibe and also PCSK9 inhibitors doesn't really change the safety profile of the treatment. We all agree that there are some side effects, adverse events that are linked to statins, some of them probably related to patients' perceptions, not really objective, and can't be really

measured by the physician, but that's life, that's the way it is. But now we have the possibility and the weapons to be able to bring many of the patients we are treating to these goals, and for their benefit to dramatically reduce their cardiovascular risk.

Thank you very much for your attention. Thank you very much to all of you who have followed us. I hope you enjoyed the discussion, as I did, and a special thanks to Professor Genest and Professor Ray who were enlightening us about this key question in lipid lowering therapy and combination therapy. Thank you very much again.

**Jacques Genest:** Thank you.

**Kausik Ray:** Thank you.