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### Examining LDL Cholesterol and Our Growing Therapy Options in Primary Prevention

Dr. Nicholls:

Atherosclerosis is one of the leading factors responsible for coronary heart disease, and cholesterol-lowering agents that target low-density lipoprotein, or LDL-C, along with statins have proven effective for reducing cardiovascular outcomes. Now we're in 2020, and the lipid field has never been more promising with the availability of multiple therapies that lower LDL cholesterol via different pathways. While statins are first-line, we now have other effective therapies – some approved, some likely to be approved in future years – providing more treatment options. The question now becomes – as clinicians, how do we prioritize and approach LDL cholesterol lowering with all these different therapy choices? This is a Medtelligence editorial program on ReachMD. I'm Steve Nicholls, Professor of Medicine, Director of MonashHeart in Melbourne, Australia, and joining me today to discuss the current lipid landscape and treatment strategies is my colleague and good friend, Professor Kausik Ray, Director of the Imperial Centre for Cardiovascular Disease Prevention. Welcome, Kosh.

Dr. Ray:

Hi, Steve. Pleasure to be here.

Dr. Nicholls:

So, let's talk about the risk of cardiovascular disease, or CVD, and its use in primary prevention. What's your approach to how we best assess CVD risk currently in the clinic?

Dr. Ray:

So, thank you, Steve. So, I think we've moved away from looking at single risk factors in isolation unless they are extremely elevated – so extreme elevations of blood pressure, of LDL cholesterol – but for the vast majority, their risk is going to be determined by small combinations of lots of different things. So, we move towards using global risk, and we tend to use risk calculators that predict ten-year risk of both fatal and nonfatal events. In Europe, for example, they'll use a ten-year risk calculator looking at fatal events, so there are some differences, but in general that's what we try to do, and then there is also the question about people who are close to that threshold because one of the limitations is – in younger people and in women – you'll often tend to underestimate risk, and so there may be risk enhancers, particularly imaging like coronary artery calcium scoring or biomarkers such as lipoprotein a, Lp(a), that may change your decision-making by pushing people into this high threshold for treatment, and I suspect that's probably very similar to what you're doing in Australia.

Dr. Nicholls:

So, in the high-risk patient, lipid management becomes pretty important. LDL is still the first target for risk reduction, and now we have several agents that can reduce LDL cholesterol by multiple pathways. So, what is your current approach to lowering LDL cholesterol in these patients?

Dr. Ray:

So, largely based on the amount of data that we've got with statins and also their cost (they're generic in every part of the world), we will start with statins, and one of the things that we've moved away from, and, again, I think it's all been cost-driven that – because we've now got the more potent statins now available as generics – we tend to start with what would've been an intermediate dose range. So, 20 mg of atorvastatin or 10 mg of rosuvastatin are your first starting doses, and the rationale was that it kind of avoids people being on the low dose statins and suboptimal reduction as to population level for a while, and then you might titrate that up to achieve the level of LDL reduction for level of risk in that particular individual, and if somebody can't tolerate either your starting dose or can't tolerate the

increasing dose, you might think about the addition of ezetimibe, which is also now generic, as an add-on or as an alternative if they really can't tolerate it.

Dr. Nicholls:

Do you see a lot of adherence issues with the first line lipid-lowering agents? Are there any tips in how to best manage that in the clinic?

Dr. Ray:

So, I think that's a really good, good question, and, and I think that I have probably moved increasingly towards actually spending a lot of time, and I think this is largely related to things like adverse publicity around some of these medications. So what I would probably do is now spend a lot more time explaining to patients, trying to provide reassurance that if they get side effects, if there are any issues, which are really fairly low, in general in trials, that we can do things around that and try to maintain their confidence. So, with that, I think that one true tolerability appears to be a little bit better than, for example, five years ago getting people prescriptions without that additional information. Adherence is really difficult, I think, unless you measure LDL, if you, you know, if this is the whole principle of measuring a lipid parameter is in part largely to look for adherence. In general, I think with good explanation, it tends to be good, but the problem I think is that often people will have blood, will have checks done just before they come and see you, and what they're doing during the rest of the year, we do know that there is a sort of an attrition a little bit whereby people might space out their prescriptions, they don't necessarily understand about the importance, so at a population level, I think we all probably, individually, I think we all do a good job, but I think when you look at populations, we know that adherence is an issue.

Dr. Nicholls:

Yeah, and, and you really raise an important point. We saw a major change to the US lipid guidelines a number of years ago with the concept that you could just prescribe a statin and, and not necessarily have to monitor lipid profiles, the kind of so-called "fire and forget..."

Dr. Ray:

Yeah.

Dr. Nicholls:

...strategy, and you've just highlighted a really important problem with that strategy where we're going to miss the patients who aren't adhering with their daily statin therapy, and you're going to have a lot of patients who are potentially ignoring your goal.

Dr. Ray:

Yes, and I think there is a lot of interest in things like shared decision-making obviously, and we tend to see that people that have access to multidisciplinary clinics whereby you've got additional healthcare professionals, nurses, dietitians, pharmacists, for example – every opportunity to reinforce adherence is really important because the problem is, you know, you don't feel any better with a higher or a lower cholesterol, and yet if you leave somebody like that with suboptimal levels, then it's going to progress, and that's the real challenge with these non-communicable diseases, isn't it?

Dr. Nicholls:

It is, and the complications can be catastrophic. For those just tuning in, you're listening to a Medtelligence editorial program on ReachMD. I'm Steve Nicholls, and joining me today to discuss the current lipid landscape and treatment strategies is Professor Kausick Ray, Director of the Imperial Centre for Cardiovascular Disease Prevention. So, what about these monoclonal antibodies that we hear about to lower LDL. We're kind of targeting this new factor PCSK9. How effective are they at lowering LDL, and can they be used in primary prevention?

Dr. Ray:

So, great question, and, and I think for the audience, it's probably worth mentioning what PCSK9 is. This is a protein that's produced by the liver. It binds to the cholesterol at the LDL receptor, and it helps to break down the LDL receptor, so that when we give people statins, or ezetimibe, we produce more of these LDL receptors, but if there's a lot of PCSK9 around, many more of these receptors will be, will be destroyed. So, you're getting suboptimal, benefits in some ways, and the monoclonal antibodies bind to PCSK9, and they stop it binding to the LDL receptor, thereby increasing the survival time. We know that the PCSK9 inhibitors have been shown to be beneficial in established cardiovascular disease. Trials are ongoing looking at cardiovascular outcomes in primary prevention. We know they lower LDL cholesterol by exactly the same amount in primary and secondary prevention, and because we know the benefits are related to the magnitude of LDL lowering, there is no reason to believe that these treatments would not be beneficial in this patient group. So, that's kind of where we are, and what has really limited the uptake has been cost. So, they are approved, for example, and reimbursed in many countries, but primary prevention in heterozygous familial hypercholesterolemia and obviously homozygous FH as well primary prevention – in those groups and, and largely I think in other groups like diabetes or primary prevention per se – it's

probably just cost that's limited their uptake or approval unless somebody's, for example, paying for it themselves.

Dr. Nicholls:

Alright. So, so we've already talked about adherence to statin therapy and, and the impact of adverse events that patients experience, as being one of the factors that causes them to either lower the dose of their statin or to stop taking statin altogether, but I guess, Kosh, the other important factor to think about is where patients receive their information from, and we know that they read a lot about statins in the media, and that coverage tends to be more negative than positive, and that does have an influence in terms of patients continuing to adhere with statin therapy. I get the sense that is something that you deal with a fair bit in the UK. Is, is that right?

Dr. Ray:

Yeah, I think we've – anybody managing cardiovascular disease and, with an interest in lipid modification anywhere in the world, it's a source of frustration. I think we're seeing this everywhere. I think the fact that, also, that opinions can be put easily on blogs and online and you have individual n=1 – for example, personal experiences, that are shared – everybody's, a conspiracy theorist, that this is Big Pharma driving uptake of these medications. So, there are a number of challenges and also confusing that is there are a whole bunch of people that will, I tend to refer to them as citizen scientists who mean well but essentially are not qualified to interpret some of the data – and there's a mixing up of different things as well, so dietary information, for example, dietary trials, which are incredibly difficult to do. When you change one thing in your diet, you replace it with another, so you don't know whether actually reducing saturated fats is a good or a bad thing cause you haven't just taken one thing out. So, there are a number of challenges there, and I think people sometimes point to the lack of mortality benefits in primary prevention, and without considering actually the risk of dying, all-cause mortality, is really low in a short-term trial, and the importance is to try and change these factors over a much longer period of time, and that's been a real challenge. So, you know, practically for us, what it means is we have to spend a lot more time – it's not just a case of "take the medications" but actually explaining the percentage of people that might get side effects, what you can do about it should they, and walk them through, you know, empower the patient – something I have to do now, and I'm sure you do, just really because of trying to mitigate against this problem.

Dr. Nicholls:

So, if we kind of look into the future with all these new therapies, are there going to be different approaches to the way that we try and predict risk and tailor the use of therapies in our patients moving forward?

Dr. Ray:

Yeah, I think that's really where the future is going to change so much in terms of our daily clinical practice. The challenge that we've had with primary prevention is this whole thing about short-term risk, and what that means is we delay treatment. So, if you think about being able to predict risk earlier, we all tend to think about trajectories and lifetime risk, and that means that if there was a way of predicting those individuals early on, for example, and the most promising of these seems to be genetics and looking at global polygenic scores, and what we now know is, for example, that these may well be able to predict long-term risk much better than existing algorithms, and if you can do that, then potentially these people you can intervene with diet and lifestyle first of all but maybe pharmacological interventions earlier. Then the question becomes – well, if I can predict risk, then what do I do about it? One of the challenges will be telling younger people, for example, in particular, to take medication daily, and I think this is where various new approaches like, which will involve injectables, probably the first of these will be injectables that can be taken once a year like sRNA-based approaches, and there's a new promising therapy called inclisiran that might be the first of these, and there's a convenience factor here for the patient where, "Okay, my risk is high. I probably wouldn't adhere to the next 30 years of taking 365 pills a year for the next 30 years, but a once-a-year injection might be acceptable," and beyond that, if you like, if you had people with sufficient risk and treatments were safe, you might even think about gene editing, for example, that lowered your lifetime exposure to LDL cholesterol. So, I think those are some of the more promising approaches that tend to tackle things like the long-term adherence or non-adherence, compliance with medication. They need to be shown to be safe obviously, and I think the biggest change is this ability to manage risk earlier.

Dr. Nicholls:

You know, I think it ultimately comes back to we're really moving towards a point where we're going to be able to get the right therapy for the right patient at the right time in the life course of the disease that we're trying to manage, and so if we can find markers to identify patients who would benefit very early from new treatments, then I think we're going to be in a position to do that, and that will ultimately be good in terms of our way to personalize prevention of cardiovascular disease. Well, I'm afraid we're all out of time. This has been a great discussion. I want to thank Professor Kausik Ray for such a stimulating and important examination of LDL cholesterol and our therapy options. Professor Ray, it was great having you with us today.

Dr. Ray:

Thank you, Steve. Pleasure.

Dr. Nicholls:

I'm Steve Nicholls. Thanks for listening. This is a Medtelligence editorial program on ReachMD.