

BroadcastMed | Statin Intolerance and Diabetes Risk: What Do We Know?

DR. THOMAS ALLISON: Greeting. I'm Dr. Thomas Allison. I'm Director of Exercise Testing and Sports Cardiology at Mayo. But I've also worked for many years in the Preventive Cardiology Clinic. I'm joined today by my colleagues, Dr. Francisco Lopez-Jimenez, who's the Director of Preventive Cardiology at Mayo and Dr. Vinaya Simha, who's an endocrinologist and specialist in Lipidology. Welcome, guys.

DR. VINAYA SIMHA: Thank you.

DR. THOMAS ALLISON: So we're gonna talk today about statin intolerance. And first of all is a lot of patients complain of this. We see patients all the time. Is this real? And if so how common is it?

DR. FRANCISCO LOPEZ-JIMENEZ: Well, that's a very good point. It seems to be real. There are so many patients complaining of it every day. And even though the idea has been controversial in the medical community, it is so frequent that there seems to be something going on there.

It is reported to be about 5% of patients taking the statins might develop some symptoms that can be attributed to the statins. But I think the problem is that we don't really know how bad the problem is. Because most clinical trials actually have these run in period, where they gave the medication to patients and only those who came back would enroll in the trials.

So unfortunately, we don't really have good--

DR. THOMAS ALLISON: They've weeded out. They've weeded out the-- and on the other side of the coin, how many times do you recommend that the patient increase physical activity and start an exercise program at the same time you prescribe statin?

DR. FRANCISCO LOPEZ-JIMENEZ: Very, very frequently. So I suspect that the problem is real, it exists. But unfortunately, many patients, especially when patients have this preconceived notion that statins might be harmful, they might be more aware of any little things or pains. But the other hand, we're probably dealing with something real that happens to some patients. And the problem is how to identify the real.

DR. THOMAS ALLISON: Right. And have we yet found a simple test, other than talking with the patient? Is there any lab test? Or is there anything we can do to distinguish between the patient who's just complaining and somebody that really is reacting to the statin?

DR. VINAYA SIMHA: Well, I mean, we have traditionally been using the CK levels. And clearly, we have realized that you can have statin-induced myalgias and even myositis in the absence of biochemical evidence of muscle damage. So I guess the short answer is no. There will be people where you cannot biochemically establish that there is statin induced muscle damage.

But now, in the research studies, we have set a very high bar, in the sense-- unless somebody has over a 10 time elevation and CK levels. We don't label them as having statin-induced myositis. I think in clinical practice, that's probably a very high bar. And I would never be comfortable. If my patient has a three time, five time elevation in CK level, that would certainly make me nervous.

DR. FRANCISCO And I think it's a clinical diagnosis. Essentially, if the symptoms start soon after the patient starts taking the medicine, if they go away when the patient stops the medication, and they recur when we try another one, I think we can confidently make the diagnosis, whereas real or the patient has a lot of, maybe some bias or something, it's hard to know. But I think it's a clinical diagnosis.

DR. THOMAS Now, another current concern about statins is diabetes. And so we've got somebody that's recommending a lot of statins. And we've got somebody who's treating some diabetic patients. So do statins cause diabetes? Is this real?

DR. VINAYA I think it's real. The statins cause new onset diabetes. I think it is true. But it is a very small effect. Just to speak numbers, so the most recent large meta analysis of about 17 trials had over 100,000 patients. And again, it is a class effect. But then, it's not all statins cause the same degree of glucose tolerance.

So perhaps like with pravastatin, which is perhaps the least glucotoxic of all the statins, the odds ratio is about 1.07. So there's about a 7% increase, as opposed to say something like rosuvastatin and 20 milligrams causes a 25% increase. So overall, yes, the use of statins, even when compared to a placebo or a high dose compared to a low dose, is associated with a small but definite increase in the risk of diabetes.

DR. THOMAS Now, so my BMIs may be 25 or 26 I go to the gym, exercise every day. I try to eat healthy. If Francisco puts me on a statin, am I likely to get diabetes? Is that the profile? Who's likely to get diabetes with the statin?

DR. VINAYA I'm not sure if Francisco will put you on a statin. But then, if he does, I think you can breathe more easily. Your risk is much lesser than somebody who is already predisposed to get diabetes. So this would be things like somebody who is already-- though interestingly, the BMI did not play out in all the meta analysis. But that could just be because it was diluted.

But it is a common clinical practice that fasting plasma glucose itself, of course, predicts. So people who already have impaired fasting glucose, people have impaired glucose tolerance these are at the highest risk. And they have also noticed that polymorphisms in certain genes, which impact beta cell function, so if you have that deleterious polymorphism, you're more likely to get statin induced new onset diabetes.

DR. FRANCISCO It seems to be real. But I think it's important to put things in perspective. If statins increase the fasting glucose level this much and that moves some patients from being pre-diabetic to diabetic, I think the clinical relevance of that is minimal. Will be equivalent in the opposite or in the inverse point of view, that if a medicine decreased the glucose level by 5 units and moving you from being diabetic to just pre-diabetic, that that will be an amazing drug. And we know that would not be true.

DR. THOMAS So here's a question. The new guideline, if you sort of do the calculation, if you're a male and you get to be about 62 or 63 years old, you're gonna reach that 7.5% and be a candidate for statin therapy. If you're younger and maybe have a little high blood pressure, you're gonna reach that an even younger age, which means we're gonna put a lot of patients on statin therapy.

Is it worth the benefit? I mean, the risk benefit of treating large numbers of patients in their 60s and 70s with statin drugs, even though they don't at this point have a diagnosis of coronary disease? Is it worth the risk with the diabetes and the myalgias?

DR. VINAYA So just looking at the-- now, it's a very loaded question. The way you ask about-- I mean, if it's a straight question, is it worth treating statins for primary prevention? Absolutely. We have had many trials. But then, **SIMHA:** people who are over 60, 65 we don't really know that. I mean, there are just very few trials like Proper and so on which have looked at the older people.

With respect to diabetes, it's like this. So based at the CTT meta analysis, so if you have like about 250 people you treat with statins for four years, there will be one new case of diabetes. And during the same period, you will have prevented a composite vascular event of nine. So you would probably benefit nine people and cause diabetes in one.

So on balance it still appears--

DR. THOMAS So benefit nine, risk one? Sounds like a very favorable equation.

ALLISON:

DR. VINAYA Yes, but this did not include just people who are 65. And the meta analysis included both primary and secondary **SIMHA:** prevention.

DR. FRANCISCO Now, if the concern is that statins cause diabetes, because statins might increase the glucose level, but we know **LOPEZ-** that in patients with diabetes, statins actually give a pretty strong benefit, I think that's a very good point to not **JIMENEZ:** be too concerned about this increasing the sugar, when the benefit is gonna be that much.

DR. THOMAS This is a complex topic. But I want a quick summary. The patient comes to you with statin intolerance. What's **ALLISON:** your approach?

DR. FRANCISCO Well, first of all, I will try to verify that that is real intolerance. I will ask a few questions to the patient. And if I **LOPEZ-** confirm that it indeed sounds like intolerance, I will give the patient-- I will first try a very low dose of the statins, **JIMENEZ:** like 5 milligrams or rosuvostatin, perhaps 10 milligrams of atorvastatin every other day and see if the patient tolerates that dose.

If the patient has been on different statins and refuses to try that, I will then focus on very strict dietary recommendations and lifestyle changes.

DR. THOMAS Any role for intestinal acting agents in this population?

ALLISON:

DR. FRANCISCO That's a good point. If the patient has a high LDL cholesterol, I will certainly try other medications to lower **LOPEZ-** cholesterol. But if the LDL is not high, I will then focus on noncholesterol drugs. **JIMENEZ:**

DR. VINAYA Yes. So I won't do the z-word, but then the other [INAUDIBLE].

SIMHA:

So we as endocrinologists have a lot of interest in this, because the bile acid binding resins, they also lower glucose. So if I have somebody who-- and as it is, we are worried about increasing the risk for diabetes. So using a bile acid binding resin in a statin intolerant patient would probably help lower both glucose and LDL cholesterol. So we do use that quite often.

DR. THOMAS ALLISON: The healthiest people in the US are the Seventh Day Adventists, who follow a plant-based diet. Do either of you recommend a plant-based diet to your patients with hyperlipidemia that don't want to take statins or can't take statins?

DR. VINAYA SIMHA: Yes, I think that goes without saying. I mean, whatever we do in terms of statin, any pharmacotherapy, is an adjunct to lifestyle changes. And yes, not a vegan, but at least a plant-based diet with a lot of phytosterols, sterol esters, I think, would be very beneficial. And I strongly emphasize that.

DR. FRANCISCO LOPEZ- JIMENEZ: And the other thing is that it's important to keep in mind-- and this is in the prevent side-- is to avoid high intensity statin treatment in the elderly and also being very careful with patients with chronic kidney disease and particularly in patients who have some history of muscle problems or patients with rheumatology conditions, where they may be more sensitive to high dose of statins and might develop either symptoms or actual myositis.

DR. THOMAS ALLISON: Last quick question. Polypill trials are going on around the world. Polypills are advocated, particularly in developing countries that may have limited resources for traditional office-based medicine and a lot of laboratory work and checking risk factors. Do you think that these concerns about myalgias and diabetes should derail the polypill approach? Or is this a still valid approach?

DR. VINAYA SIMHA: I believe it is still a valid approach. The polypill, generally, implies a lower dose, generic statins. And we have oversimplified things by calling statins as diabetogenic. There's actually an ongoing trial of pitavastatin called J Predict in Japan, which is trying to see whether pitavastatin reduces the incidence of diabetes. So I don't think that all statins are bad and a small does in a polypill.

DR. THOMAS ALLISON: And it was kind of surprising. Because didn't one of the first statin trials, the West of Scotland trial--

DR. VINAYA SIMHA: Right.

DR. THOMAS ALLISON: Show the opposite effect, that there was a reduced risk of diabetes with this 40 milligrams of pravastatin in this population?

DR. VINAYA SIMHA: Exactly.

DR. THOMAS ALLISON: So it kind of caught us by surprise, didn't it?

DR. VINAYA SIMHA: Yes. The WOSCOPS actually showed that though of course the definition of diabetes in WOSCOPS was an increase in glucose by 2 million moles. But nonetheless, yes, it's not that all statins cause hyperglycemia.

DR. THOMAS ALLISON: Francisco, Vinaya, I'd like to thank both of you for your contributions and insights on this interesting, timely, and controversial topic. And thanks also to all of our viewers. We hope you'll continue to follow our roundtable review series at theheart.org on Medscape.