**Title: ACC 23: Effect of Evolocumab on Coronary Plaque Morphology: The YELLOW III Study**

**Participants:**

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" - So I'm Dr. Annapoorna Kini I'm the director of the Cardiac Cath Lab at Mount Sinai Medical Centre in New York City.

What prompted the YELLOW studies?

- So we actually did YELLOW I, YELLOW II in the past essentially to understand what happens to the plaque morphology. So in YELLOW I, we had this hypothesis that if you have obstructive coronary lesion so we made sure it is obstructive by doing physiology testing FFR. If that FFR was positive then we confirmed that the lesion had some plaque by doing IVUS and NIRS, which was a chemogram. Then we randomised patients to standard statin versus aggressive statin which was a Rosuvastatin 40 milligramme. The patients were followed for six to eight weeks and then we saw that patients with aggressive therapy were on Rosuvastatin 40, had a decrease in the lipid plaque as you see it in LCBI. FFR was no different. IVUS was not different because our follow-up was only six to eight weeks. So I think it was very soon to see any other difference with the plaque. Now why we included FFR? One, to include it was obstructive lesion. Two, if the lesion actually regressed, then we've thought that FFR, which is a physiology test, would improve so that you will only continue on the medication and you don't need to stent these patients. Then we went to YELLOW two to really understand what happens how does that cholesterol in the plaque comes out. So there is a theory where we know the good cholesterol HDL actually does what is called Efflux. It removes the cholesterol from the plaque takes it out and deep dive. We wanted to see the genetic changes transcriptomic changes that happens in this patient. So in YELLOW II we only gave Rosuvastatin because we knew that was a treatment now. There's no need to go to a lower statin dose. And then we did cholesterol eflux as well as when we are doing YELLOW II, we changed our imaging modality. We include newer imaging modality called OCT Optical Currents Tomography, where we can understand how the plaque is cowed which is called as a fibrous cap. So we checked that. Then we also did the NIRS to understand how much cholesterol is in the body. So what we found that patient who fibrous cap thickness improved the efflux was better as well as their CRP, which means an inflammatory marker had improved. And in the genetic makeup of this patient, most of the genes that were upregulated means the genes that were important for plaque- plaque to change was one was a gene that was part of a cholesterol metabolism. The gene that was involved in smooth muscle cell and also the gene that was involved in cholesterol efflux everything was coming into to make a nice story. So that was YELLOW II. Now, newer medication came into the market. So we got to- and the guidelines were changing that lower is better. So initially used to be 100 of LDL than it went down to 70. Now they've gone down to 55 just with statin. Not every group of patient we can bring the LDL very low. So we had to introduce the new medication, the PCSK9 and we used Evolocumab. So we took the patient this time we took a nonobstructive patient because we had to make sure the patients were on this medication for a longer time, which is a 26 weeks. You cannot do it on obstructive lesions. So we did the non-obstructive lesion, we did OCT we did the NIRS, which also continue has IVUS. And then we did the blood test for these patients at the baseline and at follow up to check their genetic profile. And when they came back at follow up and I will tell you the findings that we saw the cap thickened which means the plaque is becoming stable. The cholesterol in the blood LDL decreased LVADs in the plaque also decreased. And the IVUS also showed that the plaque, what we say the plaque volumes improve.

What are the baseline characteristics of the patients in YELLOW III?

So the baseline patients were all high risk population. Average age was 65. Most of them were, had prior PCI diabetes. 50% of them were diabetic. And you know, so these were a high risk population where everybody sees this in their daily practice. And these patients had to be on statins for at least four weeks to make sure their LDL was at least lower not naive patients. And then most of them had coronary artery disease, about 15 patients. So we took a total of 137 patients. Of that 110, were able to come back for follow up. A couple of them we know there will be dropouts they will not come back for follow up. So a total of 110 patients came back for a follow up. So when I would say about 15 patients were nonobstructive disease, means they had like a 30% or a lesion less than 50%.

What are the key findings?

The key findings are we only presented our imaging data today. So in OCT we found that was a primary endpoint. The fibrous cap thickness significantly improved. So the so-called vulnerable plaque or TCFA patients who have thin cap, they were about 48%. At baseline they decreased to 13% or 35% reduction, which is significant. And NIRS also decreased. That means the YELLOW lipid in the patients at baseline and they came back also decreased. And overall LDL also decreased in these patients. There was no change in CRP in these patients.

What is the potential impact on patient care?

So this is an interesting question that first of its kind that we did it in stable patients. Most of the other studies were in non STEMI and acute MI patients where we know this kind of high risk efflux are higher and patient's cholesterol level is higher. In stable patients, they're already on statin your cholesterol level is lower. The question for the cardiologist and other people are that, Do we give this aggressive medication right now? How do we say who should get what? So our genetic analysis will be presented in the next, you know, meetings. That time we will understand who are those patients that who should go directly to this PCSK9 versus somebody that can just stay on statin. But there is also financial constraint for the healthcare that if you put everybody on this currently expensive medication. So I guess until we have more data on the, of this thing that we still go with what the current guidelines are that everybody goes on statin. There are few patients who will not tolerate statin will not respond to statin. Those patients are the ones could be the ones that should get the PCSK9. But if the guidelines become, lower is better and they're going that LDL should be lower than 55 then that number of patients who need this PCSK9 may increase.