Title: ACC 23 Late-Breaker Discussion: The CLEAR-Outcomes Trial
Participant: Dr Steven Nissen and Dr Harriette Van Spall
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Dr Van Spall:
I'm Harriette Van Spall, and I'm delighted, to be here at ACC 2023. And welcome Professor Steve Nissen, who is here to present the late breaking clinical trial results from the CLEAR-Outcomes trial. Welcome, Professor Nissen.

Dr Nissen:
Well, thank you so much, I'm glad to be here.

Dr Van Spall:
I wonder if you could start off by telling us the context, the problem of statin intolerance and what you were aiming to achieve with your trial.

Dr Nissen:
Well, first, let's be clear; statins are the cornerstone of LDL lowering therapy with just mounds of evidence over decades on their efficacy, not only in lowering cholesterol, but in reducing the complications of high cholesterol, such as myocardial infarction, stroke and death.
However, the literature and our own experience suggests that somewhere between 7% and 29% of people who attempt to take statins have adverse effects and in many of them, the adverse effects, typically myalgias, muscle pain, are sufficient that they cannot take the drugs.
And physicians try alternative statins, but there is a significant fraction of the population that will tell us we cannot tolerate a statin. We needed to have a therapy that we could use to treat those patients with proven benefits on adverse cardiovascular events. And along came bempedoic acid.
And bempedoic acid is an interesting drug, it's a prodrug: It works in the same pathway as statins, but upstream of statins, but it is not active when administered orally. It gets taken up by the liver, where it's converted to an active form. Since it's not active in peripheral tissues, it really doesn't cause muscle pain or any of the other adverse effects that patients on statins complain of, but all we knew until now is that bempedoic acid could lower LDL cholesterol.
So, we designed the CLEAR-Outcomes Trial, very large global trial, to determine whether or not bempedoic acid could produce the kind of benefits we saw with statins, but without the adverse effects.

Dr Van Spall:
What was your primary hypothesis?

Dr Nissen:
Well, the primary endpoint of the trial was a four-component composite of myocardial infarction, stroke, coronary revascularization, and cardiovascular death. However, we designed the trial so that we could sequentially test other endpoints, and as long as we achieve statistical significance, we could move through those endpoints.

So, the first secondary endpoint was three component MACE that didn't include coronary vascularization, just the hard events, then myocardial infarction, then coronary vascularization, and so on.
And this enabled us to test the efficacy of the drug for reduction of several different adverse cardiovascular events.

Dr Van Spall:
Okay, so a two-group parallel, individual level randomization with the primary endpoint that you mentioned, and hierarchical testing of the secondary endpoints. Really robust design. Who did you include in the trial?

Dr Nissen:
So, patients had to complain of intolerance of statin, meaning a side effect, the adverse effect that occurred when they started the drug, that went away when they stopped it.
Almost all the patients had failed at least two statins. In a few patients, they'd only failed one statin, but they were recommended by their physician not to attempt a statin.
Again, you could imagine if somebody had rhabdomyolysis from a statin, their doctor wasn't going to try another drug.
So that constituted the population. For this trial to be appropriate and ethical, we required the patients to sign a statement and their providers that they understood that statins reduced the risk of heart attack, stroke and cardiovascular death, but that they simply were unable to tolerate a statin and everybody in this trial had to sign that statement.
Obviously, it was very challenging, but we were able to do it because we had 1250 sites in 32 countries around the world that were enrolling patients. And we were successful at enrolling these patients in spite of the pandemic.

Dr Van Spall:
Would you go over the baseline characteristics of your patients with us?

Dr Nissen:
Yes. They were almost equally balanced amongst men and women. They were 48% women, which is very unusual in a trial. And I'm very pleased that we were able to do that because it gives us robust information about bempedoic acid the efficacy of acid in both genders.
They had high LDL cholesterol because they couldn't take a statin. So, the median LDL cholesterol was 139 milligrams per decilitre. There was a pretty good fraction of patients that had diabetes 45% or so and otherwise they look typical.
Now, one other nuance is that we did allow both secondary prevention patients and high-risk primary prevention patients. So, we had people that had a previous event that was about 70% of the patients. But 30% of the patients had high risk characteristics such as diabetes, smoking.
There were a variety of other factors that would allow us to enroll those patients because their risk was high enough to warrant inclusion.

Dr Van Spall:
Right, so risk enriched population that would allow for precise treatment effects. What was your primary treatment effect?
Dr Nissen:

So, first, we have a lot of endpoints: We had over 1700 primary endpoints, so very robust.
The hazard ratio for the four component MACE was 0.87, 13% reduction. For the more rigorous three component MACE was better. It was 0.85 or 15% reduction in both cases. These were highly statistically significant.
So, these were not marginal results, they were very significant results because we had a positive result with a statistically significant result. For the primary and the first secondary endpoint, we were able to move to the third endpoint, which was myocardial infarction and for myocardial infarction, the hazard ratio was 0.77, a 23% reduction.
And then we moved in the hierarchy to coronary revascularization and the hazard ratio was 0.81, a 19% reduction. And then finally, the fifth endpoint, stroke had a hazard ratio of 0.85, but it did not reach statistical significance. So that we stopped testing the hierarchy at that point.

Dr Van Spall:
And how did you split the alpha between them?

Dr Nissen:
When you do a hierarchical testing, you do not have to adjust the alpha because the way this is designed, you cannot move to the next endpoint unless you have statistical significance on the first endpoint. This is now increasingly used.
The journal statisticians were very comfortable with the approach: So you maintain the study wise alpha at 0.5, but you must stop.
So, if we had failed on the first secondary endpoint, the first key secondary endpoint, we could not have tested any further. But we ordered the endpoints what we thought was a logical way and it turned out that we got it right.

Dr Van Spall:
Okay, what about the adverse effects, uric acid, gout and other relevant adverse effects?

Dr Nissen:
There were adverse events. Let me tell you some of the things that didn't happen: Unlike statins, there was no increase in diabetes, which we obviously think is very important.
There was an increase in gout, it was about 1% compared with placebo, there was also an increase in cholelithiasis, also about 1%. Now there was a slight increase in creatinine, but we expected that because bempedoic acid reduces renal tubular excretion of creatinine, it doesn't actually worsen creatinine clearance, it simply affects the excretion of creatinine. So, we had a very, very small increase in creatinine levels. The withdrawal rate for adverse effects was the same between the bempedoic acid and placebo groups.
Myologies, which of course is how patients got in the trial, were very similar and quite uncommon in both groups.
And so the safety was good, the known safety issues like gout did come up and the new observation of cholelithiasis also will be reported in the manuscript.

Dr Van Spall:
What about co-interventions other lipid therapies? Were they equally distributed between the groups?

Dr Nissen:
They were not. The placebo group got more additional therapy than the bempedoic acid group. And so, here's what happened: At six months we had about a 22% reduction in LDL cholesterol and bempedoic acid group that gradually narrowed over the course of the trial as placebo patients. Some of them got PCSK9 inhibitors, various other therapies, and so there was a gradual reduction in the difference.
We saw this very robust reduction in cardiovascular events in spite of the convergence of the LDL curves between the two arms. But clearly the more efficacy from the bempedoic acid group compared with the placebo group was maintained at a high enough level that events were reduced.

Dr Van Spall:
And of course, you tested this intervention amongst statin intolerant patients. Trial results are often generalized beyond what the trial tested. Do you think there might be a role for bempedoic acid as add-on therapy in patients who are on statins but have elevated levels of LDL despite maximum tolerated doses?

Dr Nissen:
I think there is certainly a potential role for the drug there. Now, let me also make it clear that you could get in this trial if the most you could tolerate was a dose of statins below the lowest approved dose.
So, some of these people would be on ten milligrams of (...) statin three days a week, something like that. And you could get in the trial with these very low doses of statins. So, we had some statin use, I do think, as an add on, the drug could be used. It clearly has the most utility in statin intolerant patients. I want to say once again, however, that in high-risk patients that tolerate statins, maximal treatment with statins is the first line. But if you get the maximal treatment and you still need a little bit of additional lowering, then bempedoic acid might be a good choice. Some of those patients are going to get a PCSK9 inhibitor, but these are much more powerful drugs. They're given by injection. It's hard to get payers to pay for them.
So, I think there is a role here. But I think the real sweet spot for bempedoic acid is the patient that doesn't tolerate adequate amounts of statin to get their LDL where you want it.

Dr Van Spall:
Who would you not offer this therapy to?

Dr Nissen:
I would say that somebody that has really active gout, I'd be a little bit reluctant to treat them. Somebody that had an attack a few years ago is now on allopurinol their uric acid is down. I wouldn't worry, but somebody that's got active gut, particularly if they don't tolerate allopurinol, and there are some people like that out there, I think those would be people you wouldn't want to treat. I would not treat patients who have the ability to take adequate doses of statins. Someone that's on a low dose of statin and has not been tried on a higher dose, that would not be, in my view, a good choice here. The first choice would be to increase the statin dose.
And if they can't tolerate the increased dose, well, then obviously it will be reasonable to consider bempedoic acid.

Dr Van Spall:
Well, let me congratulate you on this practice changing trial and your presentation at ACC, as well as the publication in the New England Journal of Medicine, which we can't wait to read.
We are grateful for the generosity of your time this morning Professor Nissen. Thank you.

Dr Nissen:
I am grateful for the 14,000 patients that were willing to take a drug when they know they might have gotten a placebo and stay with us for up to five years. We all really owe a great debt of gratitude to patients who volunteer for clinical trials. And these patients were extraordinary, and they stayed with us for the trial. We had vital status on 99.4% of them, and they had full follow up in 95% of the patients. Quite extraordinary in the middle of a pandemic.

Dr Van Spall:
Absolutely, and thank you for that beautiful reminder of who is at the center of everything we do and also the folks who volunteer to make the rest of our work possible. Thank you, Professor Nissen.

Dr Nissen
Indeed. Thank you.