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Investigating the Impact of Bempedoic Acid on Cardiovascular Outcomes in Statin-Intolerant Patients

Dr. Buse:
In patients with statin intolerance, bempedoic acid can reduce low-density, or LDL, cholesterol levels. But what do we know about its impact on cardiovascular outcomes? Today we're joined by an expert in the field who will share with us critical issues relevant to that discussion.

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to take a look at the impact of bempedoic acid on cardiovascular outcomes in statin-intolerant patients is Dr. Steven Nissen. Dr. Nissen is the Chief Academic Officer at the Heart and Vascular Institute in Cleveland, Ohio.

Steve, thank you so much for joining us today.

Dr. Nissen:
Oh, it's a pleasure, John, to be with you.

Dr. Buse:
Can you tell us about bempedoic acid, an ATP citrate lyase inhibitor? What do we know about this cholesterol-lowering drug and its mechanisms?

Dr. Nissen:
Well, it's really a quite interesting drug. It works along the same pathway as statins. As I think most listeners know, statins work by inhibiting HMG-CoA reductase, a critical step in the synthesis of cholesterol and hepatocytes. Bempedoic acid works upstream of HMG-CoA reductase, and it works on ATP citrate lyase. Now, the reason that's interesting is that bempedoic acid itself is inactive. It has to actually be activated in the hepatocytes. And what that means is that the drug in peripheral tissues, particularly in muscle but also in other tissues, is inactive, and so this is why the drug was developed as an alternative treatment for people that have muscle problems when taking statins.

Dr. Buse:
So you published a paper in *The New England Journal*. It's a placebo-controlled study of bempedoic acid among statin-intolerant patients. Can you tell us about the key design elements of the study?

Dr. Nissen:
Well first of all, we had to make certain that we were studying statin-intolerant patients because, as everyone knows, statins are the cornerstone of cholesterol-lowering therapies in contemporary medical practice, so patients had to sign a statement that they understood that statins could reduce their risk of heart attack, stroke, or death but that they were unable to take statins, and that they tried several statins and simply couldn't tolerate them. Providers were also required to sign a statement that they deem the patient to be statin-intolerant. So that was important for ethical reasons. But if they met those criteria and they had an LDL cholesterol of over 100 mg/dL, they were either secondary prevention patients who had had a previously cardiovascular event or primary prevention patients with multiple risk factors. They were randomized to bempedoic acid 180 mg daily or placebo, and this was typical of modern cardiovascular trials. It was event-driven, so the trial was to run until 1,600 4-component MACE events had occurred. That's death, stroke, MI, and coronary revascularization. We also required at least 24 months of follow-up and at least 810 hard MACE events. That's MI, stroke, or death.

Dr. Buse:

So to learn about the results, let's just start with the lipid levels. What did bempedoic acid do for that?

Dr. Nissen:
Bempedoic acid modestly reduced LDL cholesterol. We specified in the statistical analysis plan that we would measure at six months when adherence was likely high and retention was high. There was a 21.7 percent reduction in LDL cholesterol after six months from a baseline of 139 mg/dL, but importantly, high-sensitivity C-reactive protein was also reduced, in this case 22.2 percent, so bempedoic acid had both cholesterol-lowering effects and anti-inflammatory effects, and those anti-inflammatory effects we think play a role in the benefits that patients accrue from taking statins.

Dr. Buse:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm joined by Dr. Steven Nissen, who is sharing clinical data from a recent study on bempedoic acid for statin-intolerant patients.

So, Steve, let's take a deeper dive into the results. What were the cardiovascular findings?

Dr. Nissen:
Like many contemporary trials, there was a hierarchical procedure for testing the endpoints, and we were able to continue to test as long as they were significant, and when we reached lack of significance, then we had to stop testing at that point. For 4-component MACE, the hazard ratio was .87, a 13 percent reduction, with a P value of 005, an absolute risk reduction of 1.6 percent and a number needed to treat of 63 patients. The next in line was 3-component MACE, and there the hazard ratio was actually a little bit better. It was 0.85. That's a P value of 006. And we then could proceed and test for nonfatal and fatal MI, and this was where the biggest effect was. The hazard ratio was 0.77. That's a 23 percent reduction in myocardial infarction, P=002. We then tested coronary revascularization, and the hazard ratio was 0.81 with a P value of 001, so that's a 19 percent reduction in coronary revascularization. And then the next endpoint was fatal and nonfatal stroke. And although the hazard ratio was 0.85, the upper confidence limit was greater than 1. It was 1.07. It was, therefore, not significant, and we had to stop testing at that point.

Dr. Buse:
You know, that's a very interesting result. Do you think this different or this lowest hazard ratio for fatal and nonfatal MI is meaningful, or is that just noise in a moderately effective cardiovascular risk-reducing effect?

Dr. Nissen:
You know, that's a great question. First of all, I don't think it's spurious. We had so many events here that it's pretty hard for this not to be very close to the true result, so I do think that happened. In this case, I think the effect on stroke was a little bit less robust. And if you look at 4-component and 3-component MACE, you have stroke there, and the effect on cardiovascular death and all-cause mortality was neutral. So when you look at the composite endpoints, you get modest hazard ratios, good benefits but not as big, but if you look at what it's really doing, it's reducing myocardial infarction, and that's really what a good LDL-lowering and anti-inflammatory drug should do.

Dr. Buse:
How about safety? Were there any concerns raised regarding safety or tolerability?

Dr. Nissen:
There are safety issues. There was a 1 percent absolute increase in the risk of gout. Bempedoic acid reduces renal tubular excretion of uric acid. There was a 1 percent absolute increase in the risk of cholelithiasis, something we've seen in some of the other lipid-lowering drugs. What the drug didn't do is increase the risk of new-onset diabetes. There was a 16.1 percent risk of new-onset diabetes with bempedoic acid and a 17.1 percent risk with placebo. Now that difference wasn't statistically significant, but as you know, the statins do increase the risk of diabetes, and we expected that bempedoic acid would not have that adverse effect, and it did not have that effect.

Dr. Buse:
Great. And any things in the subgroup analyses?

Dr. Nissen:
Yeah, there was at least a signal, and the signal was a very big reduction in MACE 4-component adverse outcomes. Primary prevention had a hazard ratio of 0.68. That's compared with 0.87 for the pool population. That was pretty striking, and there was a statistically significant interaction. Accordingly, I will be presenting at the ADA meeting and hopefully publishing simultaneously the results in the primary prevention subgroup: 30 percent of the patients, 4,200 patients, and a pretty striking result for those high-risk primary prevention patients. It reminds me a little bit of what Paul Ridker saw in the JUPITER trial many years ago.

Dr. Buse:

Finally, to bring this all together, when should clinicians be using bempedoic acid for their statin-intolerant patients?

Dr. Nissen:
Let me be absolutely clear. We should try a statin. We should try another statin. We should keep trying as long as the patient is willing to try different drugs. Some patients will tolerate one statin and not another. If we really can't get the patient to take a statin, then bempedoic acid is a very reasonable alternative. Now, please understand that bempedoic acid is available both as monotherapy and in combination with ezetimibe. The combination of bempedoic acid with ezetimibe can lower LDL cholesterol 35–40 percent. That's very similar to 40 mg of simvastatin. So we can get the effects of a moderate-intensity statin with this combination pill and have very low incidence of adverse muscle-related effects that will limit these patients from taking a statin.

Dr. Buse:
Well with those recommendations in mind, I'd like to thank my guest, Dr. Steven Nissen, for sharing his insights on bempedoic acid and cardiovascular outcomes in statin-intolerant patients.

Steve, thank you so much for joining us.

Dr. Nissen:
And thank you, John, for having me.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse, where you can Be Part of the Knowledge. Thanks for listening.