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<https://reachmd.com/programs/cme/pemafibrate-to-reduce-cardiovascular-outcomes-by-reducing-triglycerides-in-patients-with-diabetes-prominent/14368/>

Released: 11/23/2022

Valid until: 11/23/2023

Time needed to complete: 1h 08m

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Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes - PROMINENT

Announcer:

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Dr. Watson:

Hi, I'm Karol Watson. I am a cardiologist at UCLA. I'm co-director of the program in Preventive Cardiology at UCLA and director of the Women's Cardiovascular Center. I'd like to give you my thoughts, about the PROMINENT clinical trial that was just presented as a late-breaking clinical trial at the AHA. We've known for some time that high triglycerides are a risk factor for cardiovascular disease, and recent data suggests that they're an independent risk factor. Unfortunately, though, the data on lowering triglycerides and preventing cardiovascular events is very mixed. The three predominant pharmacotherapies for triglyceride lowering are niacin fibrates, and omega-3 fatty acids. And of those, only the EPA-only omega-3 fatty acids have actually shown benefit, in terms of reduction in cardiovascular events. But for the other agents, some post hoc analyses have suggested that there are certain clinical characteristics, that are associated with more benefit from triglyceride lowering. Those are diabetes, the dyslipidemia combination of high triglycerides and low HDL cholesterol, or high cardiovascular risk. So, in order to evaluate potential risk reduction, cardiovascular risk reduction, with the fibrate, pemafibrate, the PROMINENT study was performed in the above population. So, when you look at who was enrolled, they enrolled precisely the patients you think would have the most benefit. Those with type 2 diabetes, mixed dyslipidemia, or high cardiovascular risk. And they made sure that all participants were on background LDL-lowering therapy, and they had good LDL control with both groups having a mean median LDL of about 78. The primary efficacy outcome was a composite of myocardial infarction, ischemic stroke, coronary revascularization, or cardiovascular death.

So, the results. Well, pemafibrate was effective at lowering triglycerides, lowering it more than 25%. Despite this, pemafibrate did not reduce cardiovascular events. And in fact, there were some worrisome adverse events, including an increased risk of venous thromboembolism and renal adverse events. But the investigators did note that there were some possible beneficial reduction, in nonalcoholic fatty liver disease. Those were an exploratory analyses, however, so clearly not definitive.

So, what do these results mean? What do they mean for the strategy? Triglyceride lowering? What do they mean for the drug, pemafibrate? And what do they mean for the drug class? Well, triglyceride lowering has been tested with another drug, icosapent ethyl, and did show benefit. And this trial really did tell us about pemafibrate, and only pemafibrate. So, this trial was specific, for that agent. So, there will be no effect on our thinking about the overall strategy of triglyceride lowering, because of this trap. What about the drug? Well, as you know, fibrates are PPAR alpha agonist, and there was some hope for pemafibrate to be even more potent and selective, because it really has very high potency for PPAR alpha agonism and high selectivity. But, as you know, that wasn't the case, and this trial was prematurely discontinued for futility. At the same time as the investigators gave us this information, they also told us that there were some other potential benefits that they were going to continue to investigate. So, they said they were going to continue to pursue the potential of pemafibrate in new therapeutic areas, including nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

So, as for the drug, we saw that it was effective in lowering triglycerides. And for some of our patients, predominantly those at risk for pancreatitis, triglyceride lowering is the primary goal. But for most of our patients, who are at higher cardiovascular risk, cardiovascular risk reduction is the goal. And there was no cardiovascular risk reduction in this trial, using the drug pemafibrate. And there were also some worrisome, adverse outcomes. But as you heard, the developers may pursue other beneficial effects which they saw in exploratory analyses.

So, what do we know about fibrates? Well, there have been a number of randomized controlled trials of fibrates, looking at cardiovascular risk reduction, beginning over 30 years ago with the Helsinki Heart Study. The Helsinki Heart Study studied men with dyslipidemia. They were randomized to the fibrate gemfibrozil, versus placebo, and they saw a significant reduction in their primary outcome, which was nonfatal MI or coronary heart disease death. So that looked good. Then about 20 years ago, the VA-HIT trial was published. This study looked at a coronary heart disease patient population. Again, treated with the fibrate gemfibrozil. And again they saw a reduction in nonfatal MI or coronary heart disease death. But, that was the last positive fibrate trial we had. For the last 20 years, we've seen a number of other fibrate trials. Using different fibrates, different patient populations, different composite cardiovascular outcomes, but none of them have shown a reduction in cardiovascular events. Now, what was different about all of those trials in the last 20 years is that they were all performed during the statin era. So, many of the participants were on statins. So, in the era of statins, with good LDL control, we have not seen cardiovascular risk reduction in multiple fibrate trials. So, it's not clear that there's benefit.

So, what do I take home from this study? Well, fibrates, we know are some of the most widely-prescribed medications for triglyceride lowering, but recent trials have not shown cardiovascular benefit for stat, for fibrates in the statin era. So, in the statin era, currently tested fibrates do not appear to lower cardiovascular risk. And in the PROMINENT trial, despite enrolling a population that you would have predicted to have the most benefit from lowering triglycerides with a fibrate, pemafibrate did not lower events and had some worrisome adverse effects. Now, when I think about this, where do I put this? Well, we've asked this question of fibrates before in at least five randomized controlled clinical trials during the statin era. And we've gotten similar answers: no cardiovascular risk reduction. So, I think we can definitively say in the statin era, with good LDL control, currently available fibrates do not lower cardiovascular risk. We need to prioritize agents that do have documented, demonstrated risk reduction and rethink those that don't.

Announcer:

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