EDITORIALS

The Fibrates Story — A Tepid End to a PROMINENT Drug

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Pemafibrate is a selective peroxisome proliferator–activated receptor α modulator that has putative greater triglyceride-lowering and high-density lipoprotein (HDL) cholesterol–raising properties than other fibrates.[1] Now in the *Journal*, Das Pradhan et al.[2] describe the results of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial. In this trial, 10,497 patients with type 2 diabetes, a triglyceride level between 200 and 499 mg per deciliter, and an HDL cholesterol level of 40 mg per deciliter or less were randomly assigned to receive 0.2-mg tablets of pemafibrate twice daily or placebo.

In the PROMINENT trial, two cohorts of patients with diabetes underwent randomization. The primary-prevention cohort (patients who did not have atherosclerotic cardiovascular disease) constituted one third of the trial population, and the secondary-prevention cohort (those who did have atherosclerotic cardiovascular disease) constituted two thirds. A total of 96% of the patients were receiving statins, and more than two thirds were receiving high-intensity statins. The median glycated hemoglobin level was 7.3%.

Although, as compared with placebo, pemafibrate lowered triglyceride levels by 26.2% and increased HDL cholesterol levels by 5.1%, it did not reduce the incidence of events that made up the primary efficacy end point (a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes). Patients who received pemafibrate had a higher incidence of renal events and venous thromboembolism and a lower incidence of nonalcoholic fatty liver disease than those who received placebo. So, what can be learned from this trial?

First, this trial targeted the correct patient population — patients with a high fasting triglyceride level (median, 271 mg per deciliter at baseline) and a low HDL cholesterol level (median, 33 mg per deciliter). I think that the lack of efficacy despite triglyceride lowering may be largely due to a lack of an overall decrease in the apolipoprotein B level. Despite decreases in levels of remnant cholesterol, non-HDL cholesterol levels did not change significantly, whereas, as compared with placebo, the percentage change in the apolipoprotein B level was 4.8%. Although some of these findings would be expected given an increase in the low-density lipoprotein (LDL) cholesterol level with pemafibrate, they support the observation that in order for lipid-lowering therapies to show an effect, a net reduction in apolipoprotein B–containing lipoprotein levels is vital.[3] It is likely that the apolipoprotein B–lowering effects of fibrates are negated in the presence of moderate-to-high-intensity statins, as seen in this trial. This phenomenon was also noted in early phase 2 trials of pemafibrate.[4] Moderate-to-high-intensity statin therapy is considered to be the standard of care, so the bar is set much higher now than with earlier trials of triglyceride lowering.

Second, as the authors note, by stimulating the activity of lipoprotein lipase, pemafibrate may have led to increased efficiency in the conversion of remnant lipoproteins to LDL. Thus, levels of remnant cholesterol were decreased, but at the cost of increasing levels of plasma LDL cholesterol and apolipoprotein B, with no overall change in non-HDL cholesterol levels. The effects of high triglyceride levels on atherosclerotic disease are in fact mediated by the cholesterol content of remnant particles. Consequently, in order for therapies that lower triglyceride levels to be ef-

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fective, they probably have to have mechanisms to increase clearance of triglyceride-rich remnant lipoprotein cholesterol particles rather than just converting remnant lipoproteins to LDL. A net reduction in apolipoprotein B levels would therefore be an important early surrogate to follow in such cases.

Two recently concluded trials of triglyceride lowering provide further support for this notion. In the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT),[5] apolipoprotein B levels were 9.7 percentage points lower and the incidence of primary endpoint events was significantly lower in the icosapent ethyl group than in the placebo group. In contrast, the Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH)[6] did not show a significant decrease in apolipoprotein B levels or a decrease in the incidence of cardiovascular events among patients who received Epanova, an eicosapentaenoic acid–docosahexaenoic acid combination. Furthermore, in REDUCE-IT, the decrease in the risk of atherosclerotic cardiovascular disease was not explained by triglyceride-lowering effects of icosapent ethyl. These results highlight the importance of net lowering of atherogenic lipoprotein levels rather than lowering of triglyceride levels per se. The extent to which these discrepant results in REDUCE-IT and STRENGTH are explained by the increase in LDL cholesterol levels (and consequently apolipoprotein B levels) from the use of mineral-oil placebo in REDUCE-IT remains debatable.[7] Finally, women constituted 27.5% and Black persons constituted 2.6% of the participants in the PROMINENT trial. Future trials should aim for a broader representation with respect to sex and race.

The PROMINENT trial provides a teachable moment for the clinical trial community. Post hoc or secondary analyses of fibrate trials have suggested that patients with high triglyceride levels and low HDL cholesterol levels benefited from fibrate therapy even when the overall trial results were neutral.[8] The PROMINENT trial precisely picked this patient population and still did not show a benefit; these findings highlight the importance of rigorously confirming post hoc findings before implementing them in clinical practice.

What do these findings mean for the future of fibrates and other therapies that primarily target triglycerides? First, fibrates should not be used to reduce the risk of atherosclerotic cardiovascular disease among statin-treated patients, although they may still have a role to play in decreasing the risk of pancreatitis associated with severe hypertriglyceridemia and perhaps nonalcoholic fatty liver disease. Alternatively, triglyceride lowering without decreases in the apolipoprotein B level will probably not suffice if therapies in development[8] are to produce meaningful decreases in the risk of atherosclerotic cardiovascular disease.

The opinions expressed are those of the author and not necessarily those of the Department of Veterans Affairs or the U.S. government.

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