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Forget Fibrates for Cardiovascular Risk Reduction: Commentary on the Failure and Implications of the PROMINENT Trial

International Study Shows No Benefit of Pemafibrate on Cardiovascular Events

The international, randomized controlled Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes (PROMINENT) trial was terminated early in April 2022 after a median follow-up of 3.4 years for treatment futility after the data safety and monitoring board concluded that the primary endpoint was unlikely to be met during a planned interim analysis.[1,2] After 1132 total events, the primary composite endpoint in the pemafibrate group was 10.92% compared with 10.65% in the placebo group (HR 1.03 [95% CI: 0.91–1.15]; *P*=0.67; **Figure**).[1]

Risk of Cardiovascular Disease in Patients Treated With Statin Therapy and With Elevated Triglyceride Levels

Patients with elevated triglyceride (TG) levels have substantially increased cardiovascular (CV) risk despite well-controlled low-density lipoprotein cholesterol (LDL-C).[3] However, therapies that reduce TG levels have not been shown to lower the incidence of CV events.[4-7] Although overall results have suggested no benefit from lowering TG levels on CV events, a subgroup analysis from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial suggested that patients with type 2 diabetes and both high TG and low high-density lipoprotein cholesterol (HDL-C) levels may benefit from fenofibrate.[5] Based on these data, the PROMINENT trial selected this specific population to study.

PROMINENT Trial

The PROMINENT trial included 10,497 patients with type 2 diabetes who were receiving moderate- or high-intensity statin therapy, had mild to moderate hypertriglyceridemia (200–499 mg/dL), and low HDL-C levels (≤40 mg/dL).[1] The trial included adults with or without previous CV disease (CVD). The primary efficacy endpoint of PROMINENT was the composite of nonfatal myocardial infarction (MI), nonfatal ischemic stroke, coronary revascularization, and CV death. Secondary and tertiary endpoints included a composite of MI, ischemic stroke, hospitalization for unstable angina warranting unplanned coronary revascularization, or death from CV causes; composite of MI, ischemic stroke, or death from CV causes; composite of the primary endpoint or hospitalization for heart failure; composite of the primary endpoint or death from any cause; individual components of the primary endpoint; and the endpoint of new or worsening peripheral artery disease, biomarkers, and quality of life.[1,8]

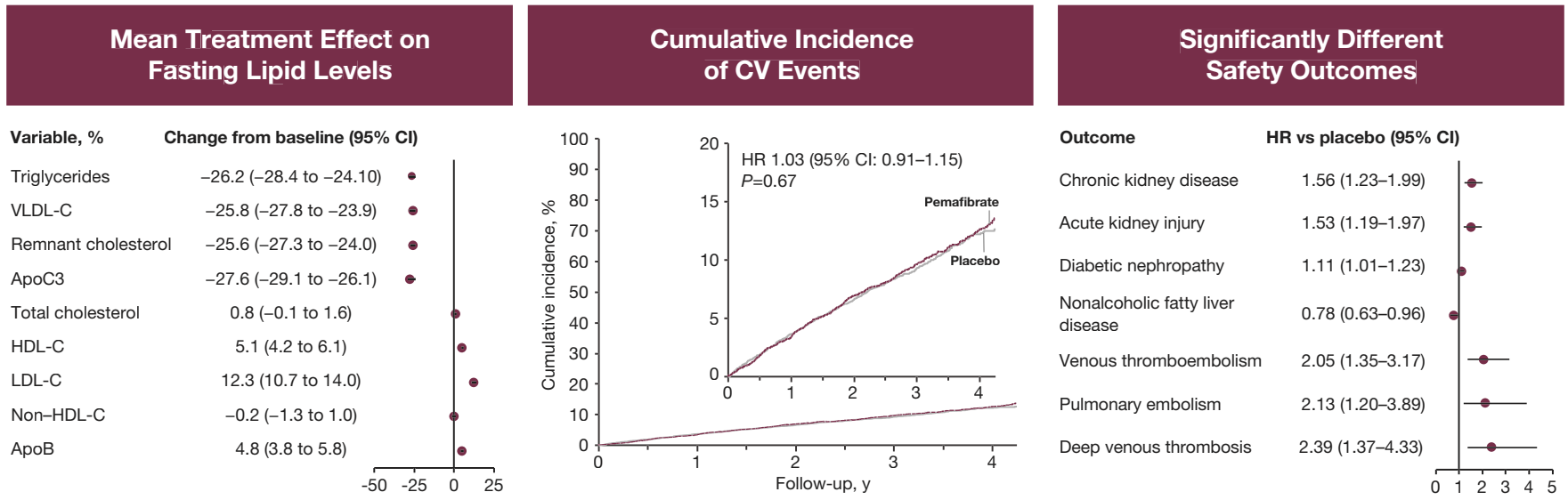
Patients meeting eligibility criteria were randomized to receive either pemafibrate 0.2 mg twice daily (n=5240) or matching placebo (n=5257).[1] Nearly three-quarters of the study cohort were men, and more than 85% were White. More than 95% of participants received statin therapy, and high-intensity statin treatment was used in 69% of both groups. Median baseline lipoprotein levels for the pemafibrate and placebo groups were well controlled, well balanced, and were, respectively: LDL-C (79 and 78 mg/dL), TG (273 and 269 mg/dL), non–HDL-C (both 128 mg/dL), and apolipoprotein (Apo) B (90 and 89 mg/dL).

Compared with placebo, pemafibrate led to reductions in TG levels, very-low-density lipoprotein cholesterol (VLDL-C), remnant cholesterol, and Apo C-III (ApoC3), whereas total cholesterol, HDL-C, LDL-C, and ApoB levels slightly increased (**Figure**).[1] Despite changes in lipid parameters, the risk for the primary composite endpoint over a median of 3.4 years in the pemafibrate group was no different from placebo, and none of the secondary composite endpoints or the individual components of the endpoints trended significantly. Pemafibrate was not more effective than placebo for the primary outcome, regardless of age, sex, or prior CVD. Importantly, pemafibrate demonstrated a significant increase in venous thromboembolism, pulmonary embolism, and deep venous thrombosis. A significant increase in renal-related adverse events was also observed in the pemafibrate group (**Figure**).[1]

Treatment Futility of PROMINENT Study Results Confirms Failure of Previous Fibrate-Class Cardiovascular Outcome Trials in the Statin Era

The null finding of the PROMINENT study with a signal instead for adverse events with fibrates in this highly selected population marks the latest in a series of randomized clinical trials, following Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)[4] and ACCORD Lipid,[5] in which fenofibrate and the broader class of fibrates have not demonstrated a CV benefit when added to statin therapy for patients at high risk of CVD. Failure of pemafibrate to reduce CV events provides further evidence that TG lowering in and of itself does not directly correlate with CV risk reduction. For this reason, the US Food and Drug Administration revoked the approved indication of fenofibrates to manage CV risk in 2016 after concluding that no incremental benefit of fenofibrate on CV morbidity and mortality exists when added to statin treatment.[9] The adverse events of fenofibrates include hepatotoxicity and increases in serum creatinine.[10] However, many US physicians

Figure. Effects of pemafibrate on fasting lipid levels, CV events, and adverse events[1]



ApoC3, apolipoprotein CIII; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol.

continue to extensively prescribe fibrate, with an estimated 13 million prescriptions dispensed and more than 2 million Americans treated each year.[11,12]

The results from PROMINENT confirm that fibrates are not useful for reducing CV risk in patients treated with statins with well-controlled LDL-C, even in the presence of diabetes.

Conclusion

What do the findings of PROMINENT mean for clinical practice? The results from PROMINENT definitively underscore that fibrates are not useful for reducing CV risk in patients treated with statins with well-controlled LDL-C, even in the presence of diabetes.[1,13] Fibrates are commonly prescribed in the primary care setting with the intention of reducing CV risk, but they should not be used for this indication. Fibrates may continue to have a role in the treatment of severe hypertriglyceridemia to reduce the risk of pancreatitis. The findings of PROMINENT also highlight that adjunct treatments to statins in patients at high risk for CVD must have established reductions in major adverse CV events beyond changes to lipid profiles. In short, when it comes to TG levels, treating the number does not treat the risk. This requires a definitive paradigm shift in how clinicians approach the treatment of hypertriglyceridemia in patients with or at risk for CVD. Consistent with guidelines from the American Heart Association/ American College of Cardiology,[14,15] icosapent ethyl is a treatment option that should be considered for lowering persistent CV risk in patients treated with statins who have elevated TG levels with high persistent risk of CV events.

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Conflict of interest disclosure

CV is a consultant for Johnson & Johnson, GlaxoSmithKline, and Boehringer Ingelheim. **PK** is on the speakers' bureau for Novo Nordisk, Janssen, Lilly, Boehringer Ingelheim, Bayer, GlaxoSmithKline, AstraZeneca, and Idorsia. She is a consultant for Novo Nordisk, Janssen, Lilly/Boehringer Ingelheim, Bayer, GlaxoSmithKline, AstraZeneca, Bausch, Intuity Medical, Phathom Pharmaceuticals, Abbott Laboratories, and KOWA Pharmaceuticals America.