ORIGINAL ARTICLE

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

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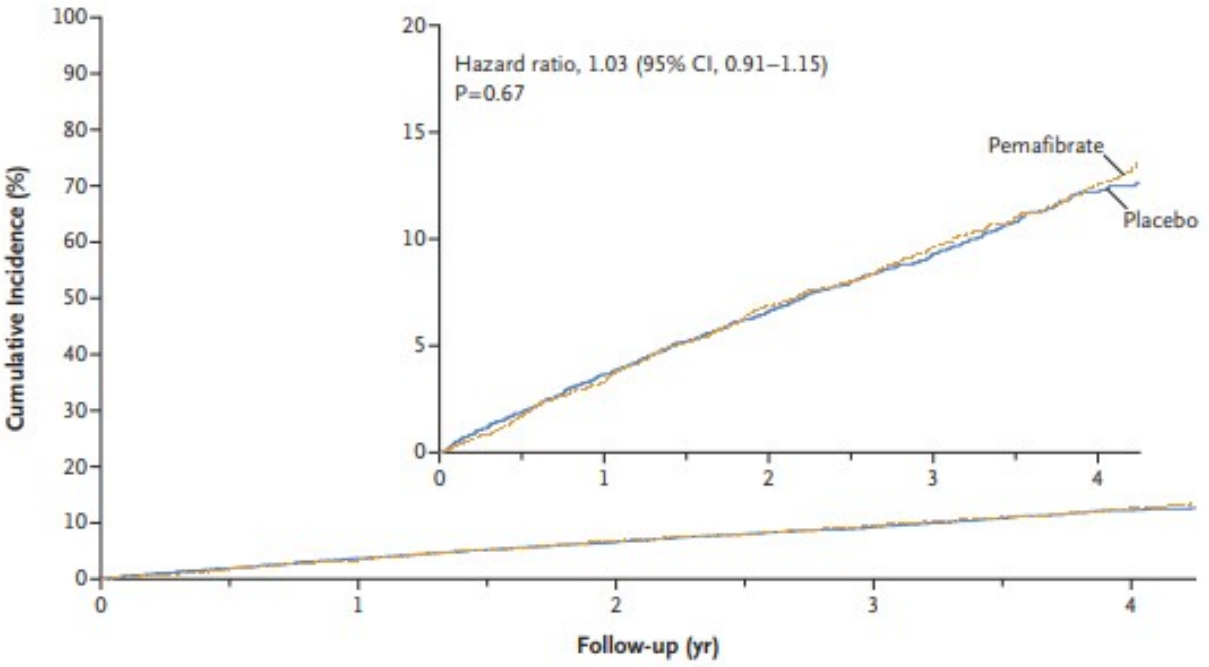
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pemafibrate (N = 5240)	Placebo (N = 5257)
Median age (IQR) — yr	64.0 (58.0–69.0)	64.0 (58.0–70.0)
Female sex — no. (%)	1443 (27.5)	1448 (27.5)
Geographic region — no. (%)		
United States and Canada	1278 (24.4)	1314 (25.0)
Europe	2519 (48.1)	2531 (48.1)
Latin America, South Africa, Japan, Israel, and India	1443 (27.5)	1412 (26.9)
Race — no. (%)†		
White	4477 (85.4)	4542 (86.4)
Black	133 (2.5)	136 (2.6)
Asian	291 (5.6)	251 (4.8)
Other	339 (6.5)	328 (6.2)
Hispanic or Latinx ethnic group — no./total no. (%)†	1014/5201 (19.5)	1007/5220 (19.3)
Median body-mass index (IQR)‡	32.0 (28.7–35.7)	32.0 (28.8–35.6)
Hypertension — no./total no. (%)	4788/5238 (91.4)	4817/5257 (91.6)
Current smoking — no./total no. (%)	854/5188 (16.5)	891/5175 (17.2)
Duration of diabetes ≥10 yr — no./total no. (%)	2430/5238 (46.4)	2403/5257 (45.7)
Primary-prevention cohort — no. (%)§	1732 (33.1)	1739 (33.1)
Secondary-prevention cohort — no. (%)¶	3508 (66.9)	3518 (66.9)
Concomitant medications — no./total no. (%)		
ACE inhibitor or ARB	4194/5240 (80.0)	4216/5257 (80.2)
Any statin	5018/5240 (95.8)	5032/5257 (95.7)
High-intensity statin‖	3621/5214 (69.4)	3610/5230 (69.0)
Glucagon-like peptide-1 analogue	499/5240 (9.5)	479/5257 (9.1)
SGLT2 inhibitor	897/5240 (17.1)	868/5257 (16.5)
Median glycated hemoglobin level (IQR) — %**	7.3 (6.5–8.1)	7.3 (6.5–8.1)

Table 2. Effects of Pemafibrate on Fasting Lipid Levels at 4 Months.*

Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)	269 (226 to 338)	
4 Mo — mg/dl	189 (143 to 253)	254 (193 to 341)	
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
VLDL cholesterol level, calculated — mg/dl‡			
Baseline — mg/dl	49 (39 to 63)	49 (39 to 62)	
4 Mo — mg/dl	31 (23 to 42)	43 (32 to 59)	
Median change from baseline — %	−35.0 (−54.1 to −11.5)	−10.5 (−33.3 to 17.4)	−25.8 (−27.8 to −23.9)
Remnant cholesterol level, calculated§			
Baseline — mg/dl	47 (38 to 60)	47 (37 to 59)	
4 Mo — mg/dl	32 (24 to 42)	39 (29 to 52)	
Median change from baseline — %	−31.3 (−49.1 to −8.2)	−15.6 (−36.8 to 10.8)	−18.2 (−20.3 to −16.1)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (43 to 73)	56 (43 to 72)	
4 Mo — mg/dl	30 (23 to 41)	44 (32 to 61)	
Median change from baseline — %	−43.6 (−57.8 to −24.1)	−20.2 (−38.3 to 3.8)	−25.6 (−27.3 to −24.0)
Apolipoprotein C-III level, measured			
Baseline — mg/dl	15 (13 to 19)	15 (13 to 18)	
4 Mo — mg/dl	11 (9 to 14)	15 (12 to 19)	
Median change from baseline — %	−27.8 (−43.8 to −9.1)	0.0 (−18.8 to 18.8)	−27.6 (−29.1 to −26.1)
Other lipid biomarkers			
Total cholesterol level, measured			
Baseline — mg/dl	161 (139 to 193)	161 (137 to 191)	
4 mo — mg/dl	162 (138 to 190)	158 (134 to 190)	
Median change from baseline — %	−0.5 (−12.2 to 13.2)	−1.2 (−12.1 to 11.0)	0.8 (−0.1 to 1.6)
HDL cholesterol level, measured			
Baseline — mg/dl	33 (29 to 37)	33 (29 to 37)	
4 Mo — mg/dl	36 (30 to 42)	34 (30 to 39)	
Median change from baseline — %	8.3 (−5.3 to 25.0)	3.1 (−7.4 to 15.6)	5.1 (4.2 to 6.1)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)	78 (59 to 102)	
4 Mo — mg/dl	91 (71 to 115)	80 (62 to 105)	
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)
Non-HDL cholesterol level, calculated§			
Baseline — mg/dl	128 (106 to 159)	128 (104 to 157)	
4 Mo — mg/dl	125 (102 to 153)	122 (100 to 154)	
Median change from baseline — %	−2.4 (−18.0 to 15.0)	−2.5 (−16.3 to 13.0)	−0.2 (−1.3 to 1.0)



No. at Risk

Pemafibrate	5240	5060	4901	4742	4552	3627	2820	2067	1147
Placebo	5257	5082	4925	4762	4596	3651	2838	2063	1130

Figure 1. Cumulative Incidence of Cardiovascular Events.

Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

PROMINENT: Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes

Purpose: To evaluate if lowering triglyceride levels and improving other lipid levels with pemafibrate would reduce the elevated risk of CVD in patients with type 2 diabetes who were on statins.

Trial Design: Multinational, double blind RCT (N=10,497). All patients (with type 2 diabetes, mild to moderate hypertriglyceridemia, and with HDL ≤ 40 mg/dl) received standard of care management of CV risk factors, including treatment with high-intensity statins. In addition, patients received either pemafibrate (0.2mg twice daily) or placebo.

Primary Endpoints: Composite of nonfatal MI, ischemic stroke, coronary revascularization, or CV death.

Key Takeaways for the Clinician:

- In patients with diabetes, mild to moderate hypertriglyceridemia and low levels of HDL, lowering triglycerides with pemafibrate did not lower rates of cardiovascular disease.
- The study results calls into question whether TG lowering should be used at all in patients with diabetes who are already on statins.

	Placebo (N= 5257)	Pemafibrate (N= 5240)	HR (95%CI)	P value
Primary Composite Endpoint	560	572	1.03 (0.91-1.15)	0.67
Components				
Nonfatal MI	178	205	1.16 (0.95-1.42)	-
Nonfatal Ischemic Stroke	104	95	0.92 (0.69-1.21)	-
Coronary revascularization	344	334	0.98 (0.84-1.13)	-
Death from CV causes	133	133	1.00 (0.79-1.28)	-

Results:

- Although levels of TG, VLDL cholesterol, Apo C-III and remnant cholesterol were 26-28% lower in the pemafibrate group, the incidence of CV events was not lower compared to the placebo group.
- The overall incidence of serious adverse events did not differ significantly between the groups, but pemafibrate was associated with a higher incidence of adverse renal events and VTE and lower incidence of NAFLD.

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Results reflect the data available at the time of presentation.