PROMINENT

Pemafibrate to Reduce cardiovascu triglycerides IN patiENts with diabeT

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Study Investigators and Study**

CENTER FOR CARDIOVASCULAR DISEASE PREVENTION
BRIGHAM AND WOMEN'S HOSPITAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

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ABSTRACT

BACKGROUND

High triglyceride levels are associated with increased cardiovascular risk, but whether reductions in these levels would lower the incidence of cardiovascular events is uncertain. Pemafibrate, a selective peroxisome proliferator–activated receptor α modulator, reduces triglyceride levels and improves other lipid levels.

METHODS

In a multinational, double-blind, randomized, controlled trial, we assigned patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia (triglyceride level, 200 to 499 mg per deciliter), and high-density lipoprotein (HDL) cholesterol levels of 40 mg per deciliter or lower to receive pemafibrate (0.2-mg tablets twice daily) or matching placebo. Eligible patients were receiving guideline-directed lipid-lowering therapy or could not receive statin therapy without adverse effects and had low-density lipoprotein (LDL) cholesterol levels of 100 mg per deciliter or lower. The primary efficacy end point was a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes.

RESULTS

Among 10,497 patients (66.9% with previous cardiovascular disease), the median baseline fasting triglyceride level was 271 mg per deciliter, HDL cholesterol level 33 mg per deciliter, and LDL cholesterol level 78 mg per deciliter. The median follow-up was 3.4 years. As compared with placebo, the effects of pemafibrate on lipid levels at 4 months were −26.2% for triglycerides, −25.8% for very-low-density lipoprotein (VLDL) cholesterol, −25.6% for remnant cholesterol (cholesterol transported in triglyceride-rich lipoproteins after lipolysis and lipoprotein remodeling), −27.6% for apolipoprotein C-III, and 4.8% for apolipoprotein B. A primary end-point event occurred in 572 patients in the pemafibrate group and in 560 of those in the placebo group (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15), with no apparent effect modification in any prespecified subgroup. 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 venous thromboembolism and a lower incidence of nonalcoholic fatty liver disease.

CONCLUSIONS

Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels. (Funded by the Kowa Research Institute; PROMINENT ClinicalTrials.gov number, NCT03071692.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Das Pradhan can be contacted at apradhan@bwh.harvard.edu and Dr. Ridker can be contacted at pridker@bwh.harvard.edu or at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Ave., Boston, MA 02215.

*A complete list of the PROMINENT investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 5, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2210645
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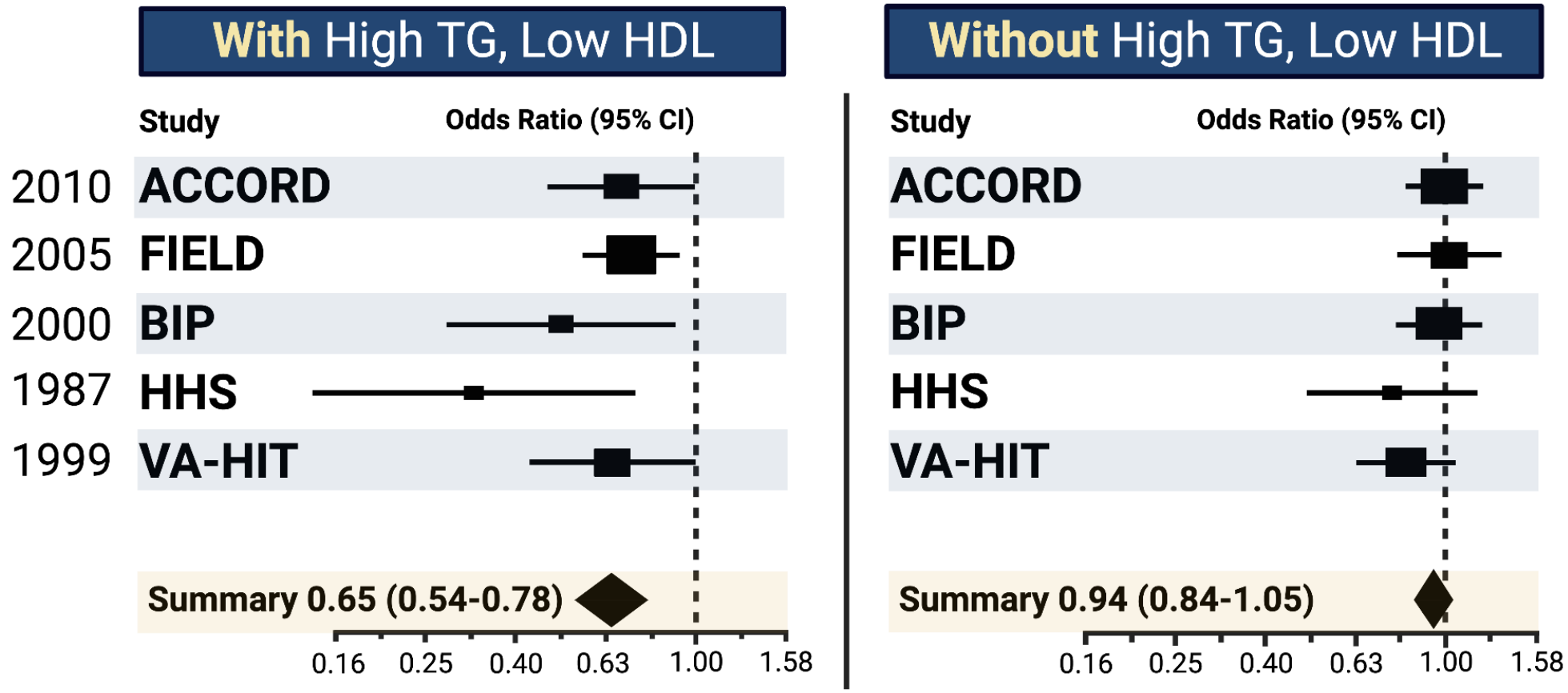
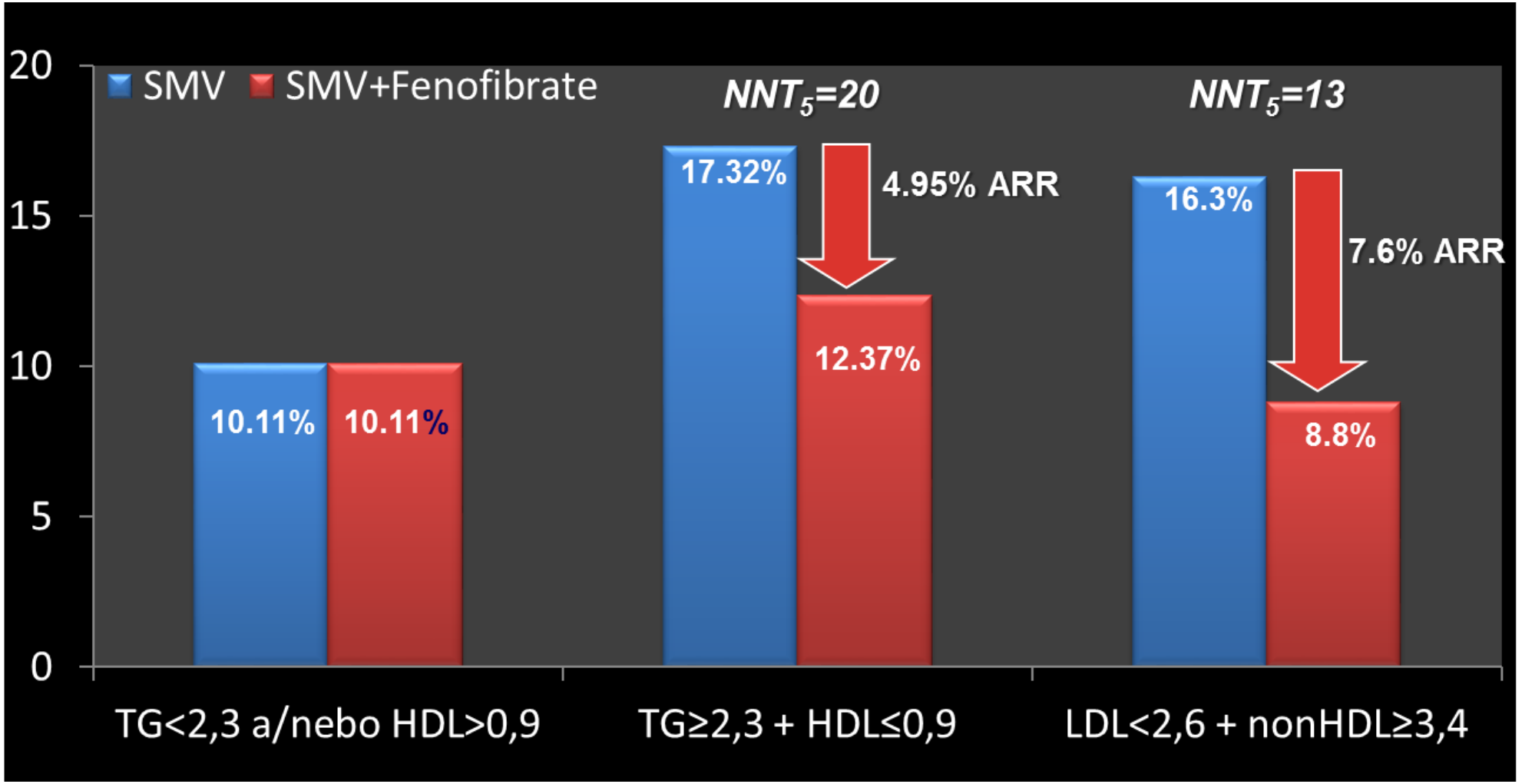
Proč PROMINENT ?
Podskupinové analýzy fibrátových studií



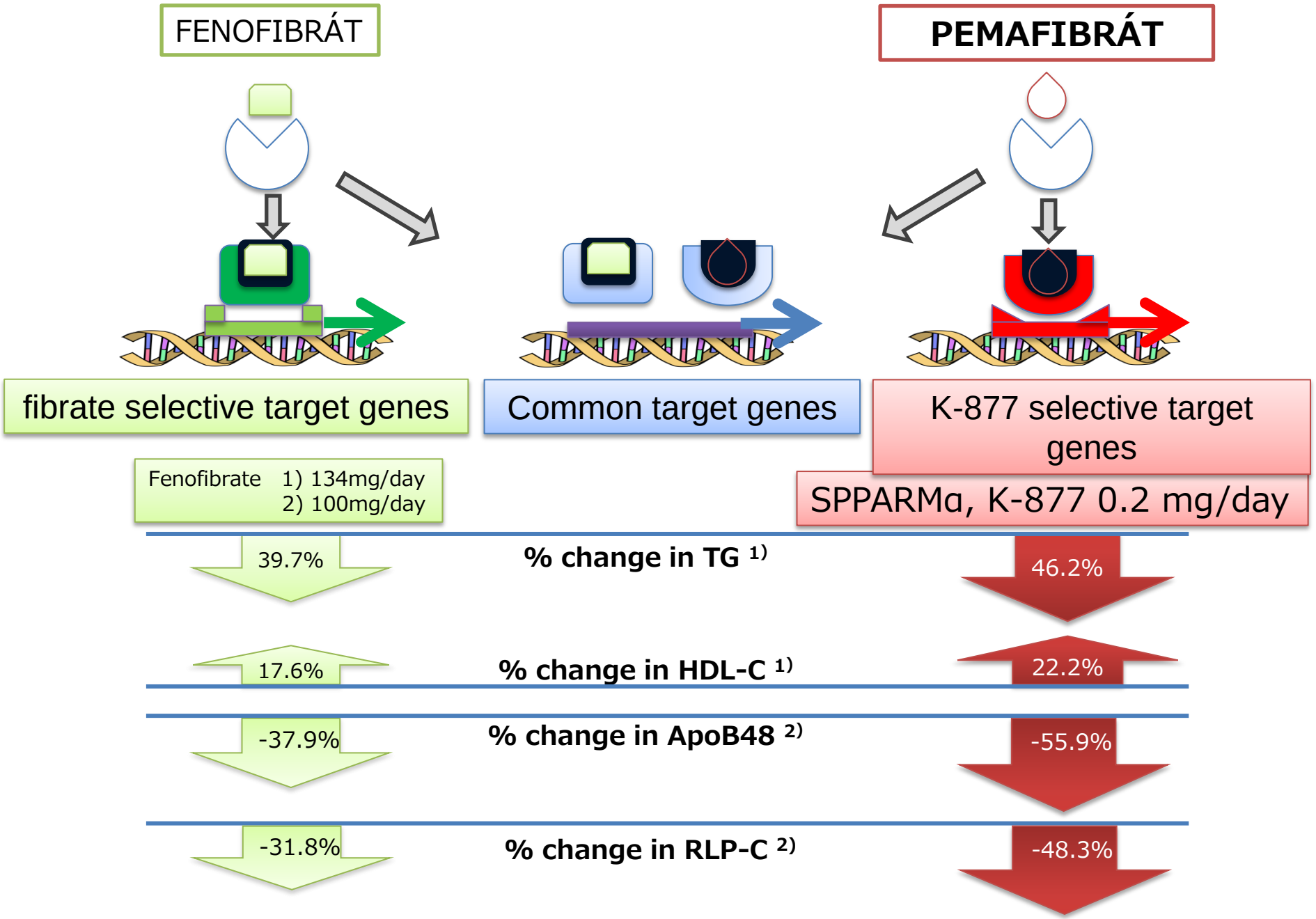
Sacks FM et al, NEJM 2010;7:692-3

Proč PROMINENT ? Protože ACCORD

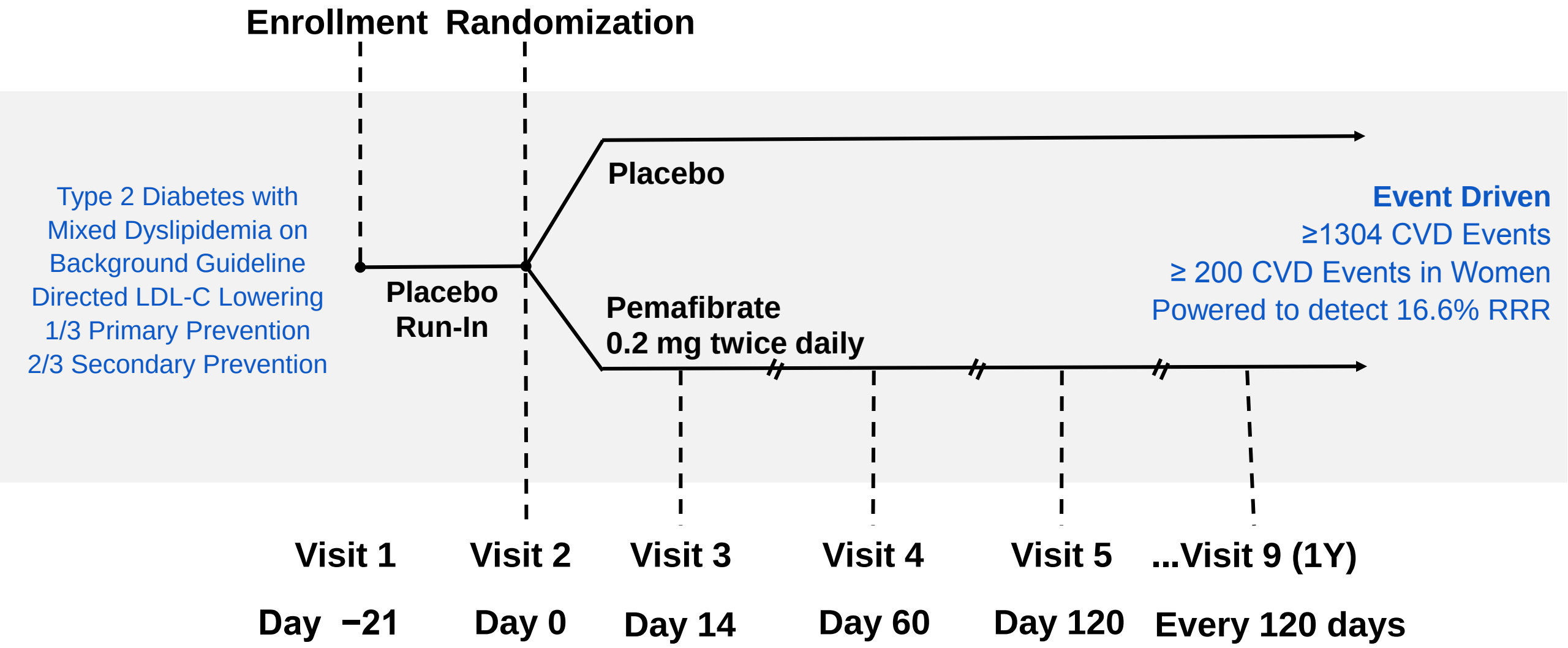


△ apoB ???

ACCORD Study Group. *N Engl J Med* **2010**; 362: 1563


FENOFIBRÁT
PEMAFIBRÁT
fibrate selective target genes
Common target genes
K-877 selective target genes
Fenofibrate 1) 134mg/day
2) 100mg/day
SPPARMα, K-877 0.2 mg/day
39.7%
% change in TG 1)
46.2%
17.6%
% change in HDL-C 1)
22.2%
-37.9%
% change in ApoB48 2)
-55.9%
-31.8%
% change in RLP-C 2)
-48.3%

PROMINENT Design



PROMINENT: Entry Criteria

Key Inclusion Criteria

Type 2 Diabetes

TG 2,6 – 5,3 mmol/l a HDL-C ≤ 1 mmol/l

Established ASCVD (CAD, CeVD, or PAD)
or age ≥ 50 (M), ≥ 55 (F) years

Statin treatment
- Qualifying moderate or high intensity statin
- Other LLT with LDL ≤ 70 mg/dl
- Statin intolerance with LDL ≤ 100 mg/dl

Key Exclusion Criteria

Type 1 Diabetes

Uncontrolled diabetes/thyroid disease/HTN

Liver disease (LFTs > 3XULN)

Renal disease (eGFR <30)

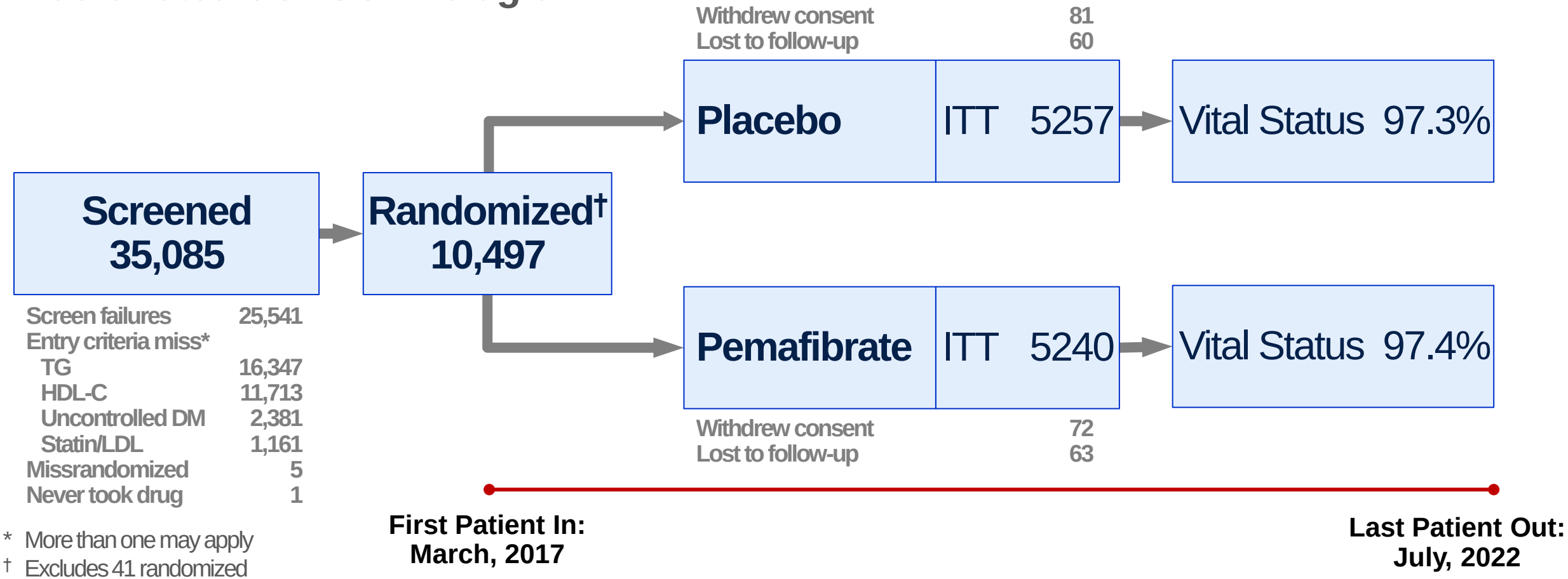
NYHA class IV HF

MACE 8 weeks before randomization

Other severe concomitant non-CV disease

PROMINENT: vysoké % pacientů dokončilo celé sledování

Abbreviated CONSORT diagram



* More than one may apply

† Excludes 41 randomized participants with GCP violations

PROMINENT:
Charakteristika pacientů

Patient characteristic	Placebo N = 5257		Pemafibrate N = 5240	
Age median (IQR) - years	64	(58, 70)	64	(58, 69)
Body mass index median (IQR) - kg/m^2	32	(29, 36)	32	(29, 36)
Type 2 Diabetes	5257	(100%)	5240	(100%)
Diabetes duration > 10 years	2403	(46%)	2430	(46%)
Female sex	1448	(28%)	1443	(28%)
White race	4542	(86%)	4477	(85%)
Hispanic ethnicity	1007	(19%)	1014	(19%)
Hypertension	4817	(92%)	4788	(91%)
Current smoking	891	(17%)	854	(16%)
HbA1c median (IQR) - %	7.3	(7, 8)	7.3	(7, 8)

PROMINENT:
Léčba a lipidové hladiny na vstupu do studie

Patient characteristic	Placebo N = 5257		Pemafibrate N = 5240	
ACE inhibitor or ARB	4216	(80%)	4194	(80%)
Any Statin	5032	(96%)	5018	(96%)
High Intensity Statin*	3610	(69%)	3621	(69%)
Icosapent Ethyl	36	(1%)	48	(1%)
GLP-1 Analogue	479	(9%)	499	(10%)
SGLT2-Inhibitor	858	(17%)	881	(17%)
TG median – mmol/l	3,0		3,1	
HDL-C median– mmol/l	0,85		0,85	
LDL-C median – mmol/l	2.0		2,0	

*Atorvastatin ≥ 40 mg/d or Rosuvastatin ≥ 20 mg/d

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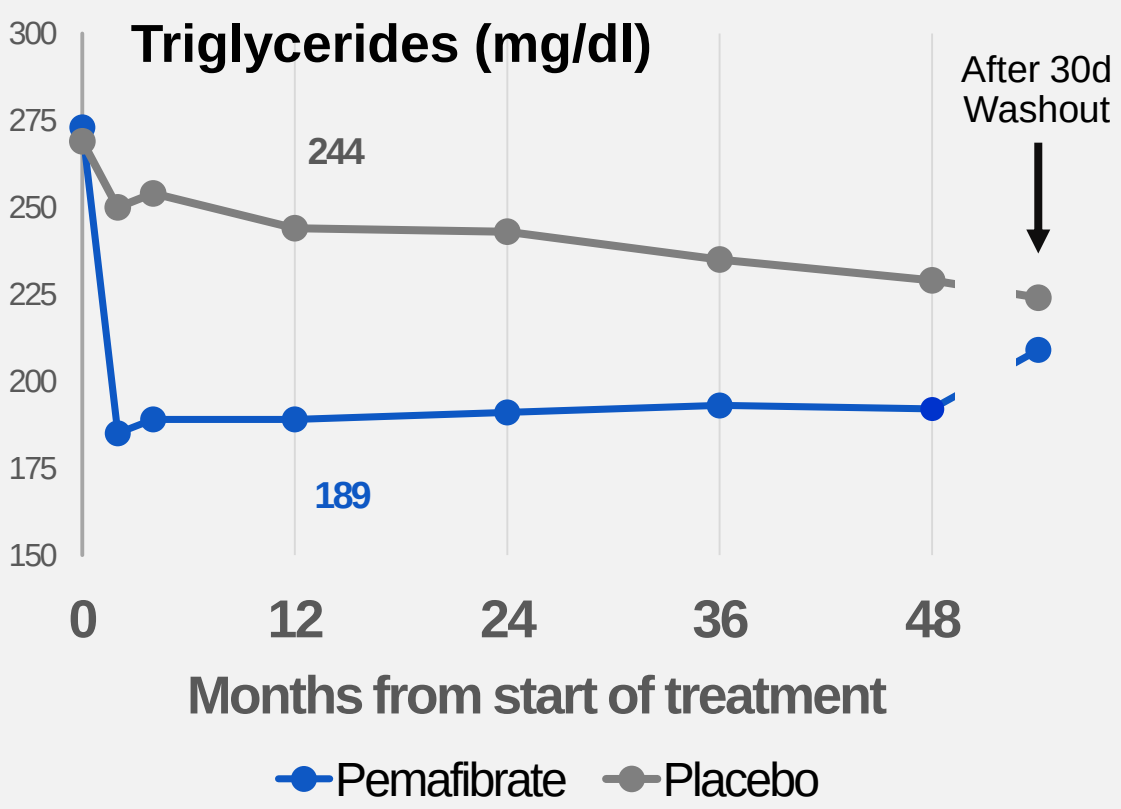
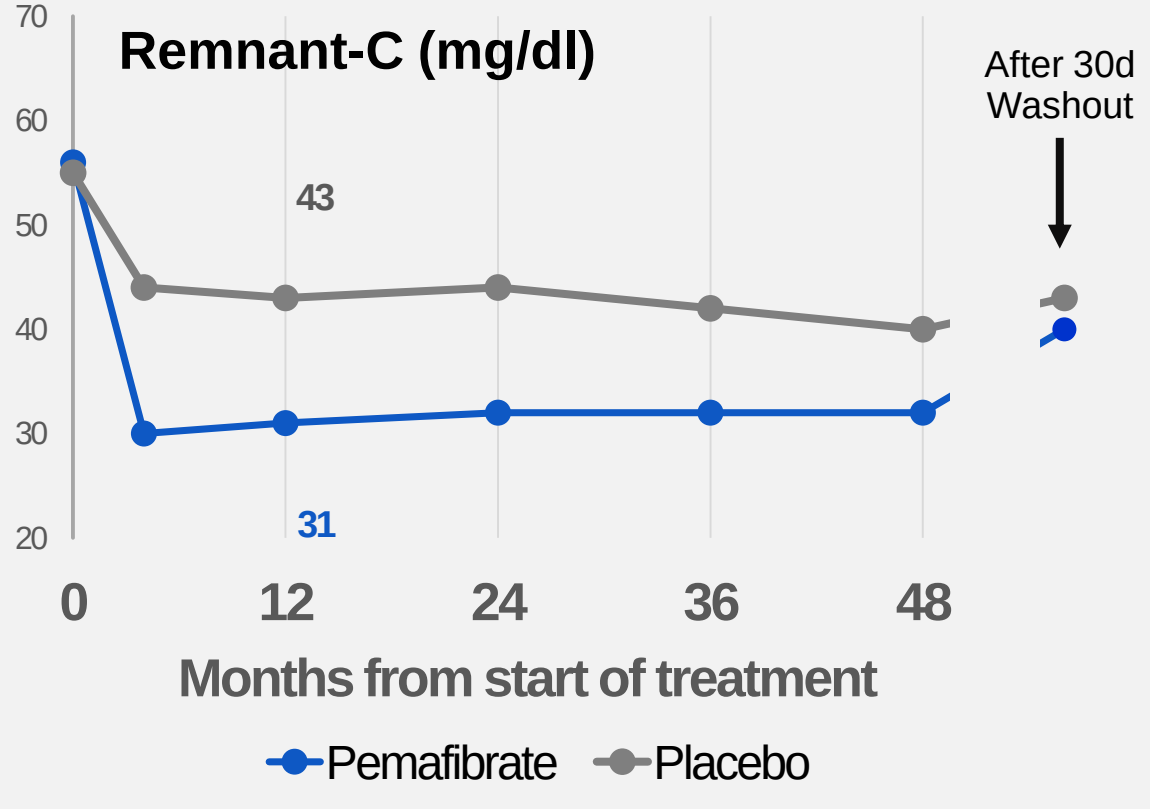
Výsledky hodnocení účinnosti

Hypolipidemická léčba

Stabilita lipidových hladin v čase





Hypolipidemická léčba
% změna ostatních lipidových ukazatelů ve 4. měsíci sledování

Treatment group	TC	HDL-C	LDL-C	Apo B
Placebo ($\%_{median}$)	-1.2	3.1	2.9	-1.6
Pemafibrate ($\%_{median}$)	-0.5	8.3	14.0	3.2
Treatment Effect ($\%_{mean}$)	**0.8**	**5.1**	**12.3**	**4.8**
95% CI	**-0.1, 1.6**	**4.2, 6.1**	**10.7, 14.0**	**3.8, 5.8**

PROMINENT účinnost

Primární sledovaný cíl, průměrná doba sledování 3, 4 let

Primary Endpoint
myocardial infarction, ischemic stroke, coronary revascularization or CVD death

Placebo
Pemafibrate

HR 1.03 (95% CI: 0.91-1.15); p=0.67

Total Mortality

Placebo
Pemafibrate

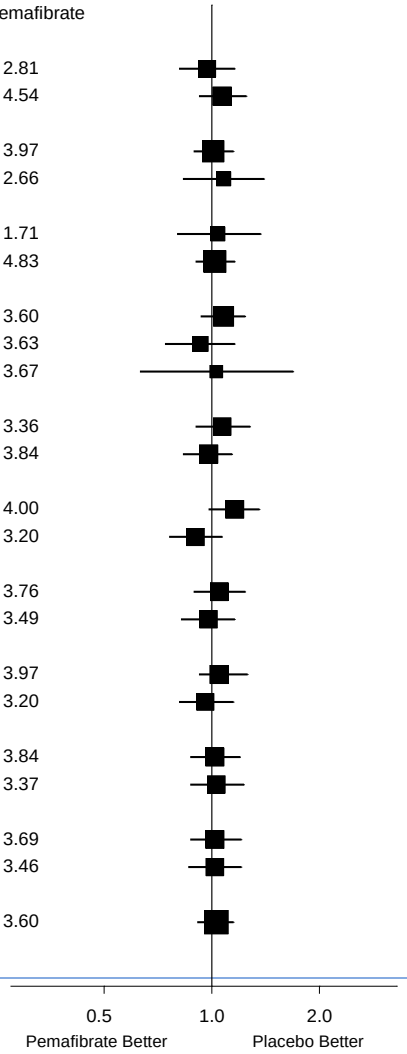
HR 1.04 (95% CI: 0.91-1.20)

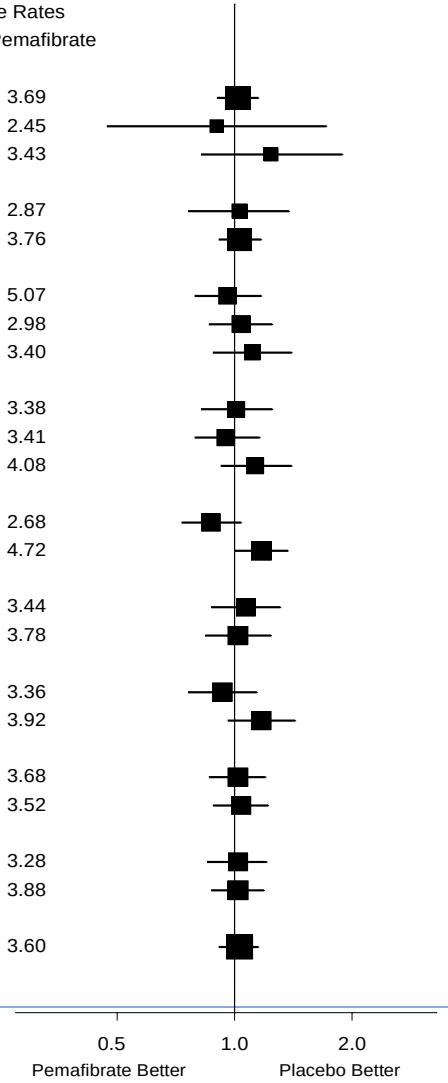
Upon review of the 75% efficacy and futility analysis, the trial's DSMB recommended early termination of the study on the basis of futility.
Final Confirmed Endpoints: 1132 primary events, 228 in women

PROMINENT primární sledované ukazatele v podskupinách

	N	# of Events	Incidence Rates Placebo	Pemafibrate
Age				
<65	5,543	489	2.92	2.81
≥65	4,954	643	4.17	4.54
Sex				
Men	7,606	904	3.92	3.97
Women	2,891	228	2.46	2.66
Prior Cardiovascular Disease				
Primary Prevention	3,471	210	1.64	1.71
Secondary Prevention	7,026	922	4.73	4.83
Statin Intensity				
High	7,231	755	3.36	3.60
Moderate	2,636	308	3.93	3.63
Intolerant, Low, None	577	63	3.35	3.67
HbA1c(%)				
≤7.2	5,178	514	3.12	3.36
>7.2	5,261	613	3.93	3.84
Triglycerides(mg/dL)				
≤271	5,247	598	3.51	4.00
>271	5,218	531	3.52	3.20
Remnant Cholesterol(mg/dL)				
≤55.6	4,994	557	3.58	3.76
>55.6	4,990	521	3.58	3.49
HDL Cholesterol(mg/dL)				
≤33	5,443	634	3.74	3.97
>33	5,023	495	3.27	3.20
LDL Cholesterol (mg/dL)				
≤78	5,229	602	3.76	3.84
>78	5,196	524	3.27	3.37
ApoB(mg/dL)				
≤89.5	5,180	577	3.61	3.69
>89.5	5,185	539	3.43	3.46
All Participants	10,497	1132	3.51	3.60

	N	# of Events	Incidence Rates Placebo	Pemafibrate
Race				
White	9,019	1007	3.63	3.69
Asian	542	37	2.53	2.45
Other	936	88	2.85	3.43
Ethnicity				
Hispanic/Latino	2,021	175	2.90	2.87
Not Hispanic/Latino	8,400	943	3.62	3.76
Region				
US/Canada	2,592	400	5.27	5.07
Europe	5,050	456	2.87	2.98
Other	2,855	276	3.08	3.40
BMI(kg/m^2)				
<30	3,530	351	3.30	3.38
30-34	3,894	416	3.57	3.41
≥34	2,981	354	3.67	4.08
Diabetes duration				
<10 yrs	5,662	504	3.09	2.68
≥10 yrs	4,833	628	4.04	4.72
Non-fasting TG(mg/dL)				
≤283	3,744	371	3.22	3.44
>283	3,740	418	3.68	3.78
Non-fasting Remnant-C(mg/dL)				
≤44.2	3,585	373	3.59	3.36
>44.2	3,595	380	3.35	3.92
nonHDL-C(mg/dL)				
≤127	5,183	577	3.60	3.68
>127	5,283	552	3.43	3.52
hsCRP(mg/L)				
≤2.3	5,198	514	3.20	3.28
>2.3	5,187	605	3.86	3.88
All Participants	10,497	1132	3.51	3.60





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Bezpečnost

PROMINENT bezpečnost

Adverse Event	Placebo	Pemafibrate	HR	95% CI
Any Serious Adverse Event	**1914**	**1970**	**1.04**	**0.98-1.11**
Infection Adverse Events	**2877**	**2797**	**0.97**	**0.92-1.02**
- COVID-19 infection	621	646	1.05	0.94-1.17
- COVID-19 death	106	101	0.96	0.72-1.27
Musculoskeletal Adverse Events	**1693**	**1605**	**0.94**	**0.88-1.01**
- Myopathy	35	22	0.63	0.35-1.11
Renal Adverse Events	**1347**	**1463**	**1.12**	**1.04-1.20**
- Chronic kidney disease	117	180	1.56	1.23-1.99
- Acute kidney injury	106	160	1.53	1.19-1.97
- Proteinuria	101	110	1.10	0.83-1.45
Venous Thromboembolism	**35**	**71**	**2.05**	**1.35-3.17**

PROMINENT: závěry a možný význam

- Tato data zdůrazňují složitost lipidových mediátorů reziduálního rizika u pacientů s inzulínovou rezistencí léčených statiny.
- Je možné, že kromě účinků na remodelaci lipoproteinů bohatých na triglyceridy je k neutralizaci reziduálního rizika u hypertriglyceridemie také zapotřebí zvýšená clearance lipoproteinů odvozených z katabolismu remnantních částic.
- Tyto údaje nemohou vyloučit možnost, že pozorované zvýšení LDL-C a ApoB negovalo jakýkoli přínos snížení triglyceridů.
- Probíhající studie látek, které využívají alternativní cesty ke snížení triglyceridů a remnantního cholesterolu, včetně inhibice ApoCIII a angiopoetinu-like protein 3 (ANGPTL3), mohou pomoci objasnit tato pozorování.

PROMINENT: Acknowledgements

Contributions from 24 Countries

Country	No. Rands	Country	No. Rands	Country	No. Rands
Argentina	398	**Germany**	268	**Romania**	149
Brazil	1033	**Hungary**	468	**Russia**	593
Bulgaria	395	**India**	130	**Slovakia**	232
Canada	521	**Israel**	204	**South Africa**	344
Colombia	157	**Japan**	305	**Spain**	126
Czech Republic	282	**Mexico**	285	**Ukraine**	1083
Denmark	208	**Netherlands**	223	**United Kingdom**	412
France	23	**Poland**	587	**USA**	2071

Simultaneous Publication

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ClinicalTrials.gov Identifier: NCT03071692