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Essence TIMI-73b

TIMI

Apolipoprotein C-III (APOC3) Inhibition in Patients With Versus Without Baseline Fibrate Use

A Pre-Specified Secondary Analysis of the Essence TIMI-73b Trial

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AMERICAN COLLEGE of CARDIOLOGY

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Disclosures

- Speaker (AZW): None
- The Essence-TIMI 73b trial was sponsored by Ionis Pharmaceuticals

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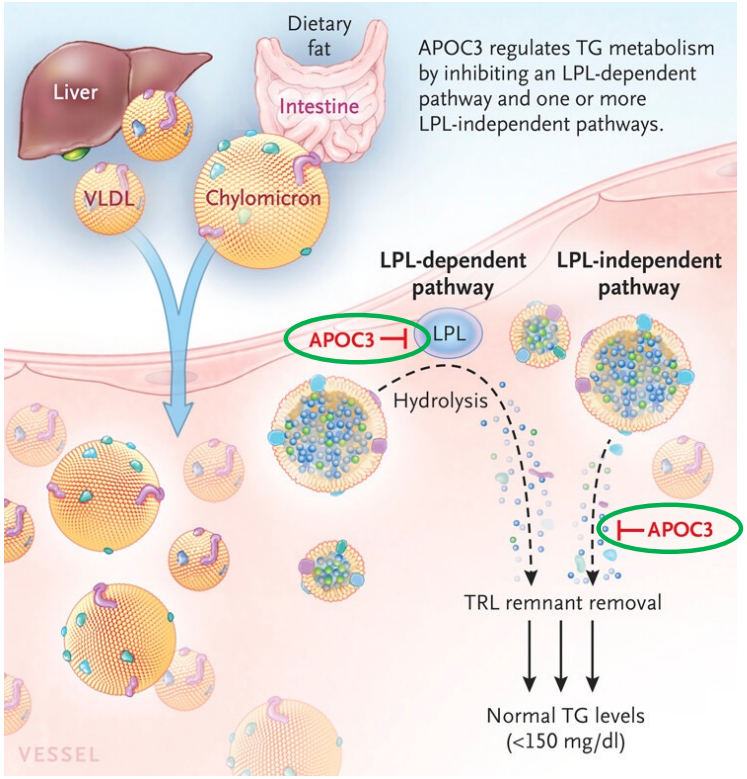
Background

- Hypertriglyceridemia is associated with ASCVD and pancreatitis risk
- Highly-effective therapies for reducing triglycerides across the full spectrum of hypertriglyceridemia are lacking



Lipoprotein Lipase (LPL)

- Hydrolyzes triglycerides
- Facilitates clearance of triglyceride-rich lipoproteins (TRLs)

Apolipoprotein C-III (APOC3)

- Inhibits LPL
- ↑ Triglyceride levels

Olezarsen is a $GalNAc_3$-conjugated antisense oligonucleotide targeting *APOC3* mRNA

- Reduced TGs by ~60% in Essence

Fibrates

- Upregulate LPL activity and downregulate APOC3 via PPARα

Gaudet D. *N Engl J Med*. 2014;371:2200-6
Bergmark BA, et al. *N Engl J Med*. 2025;393:1279-91

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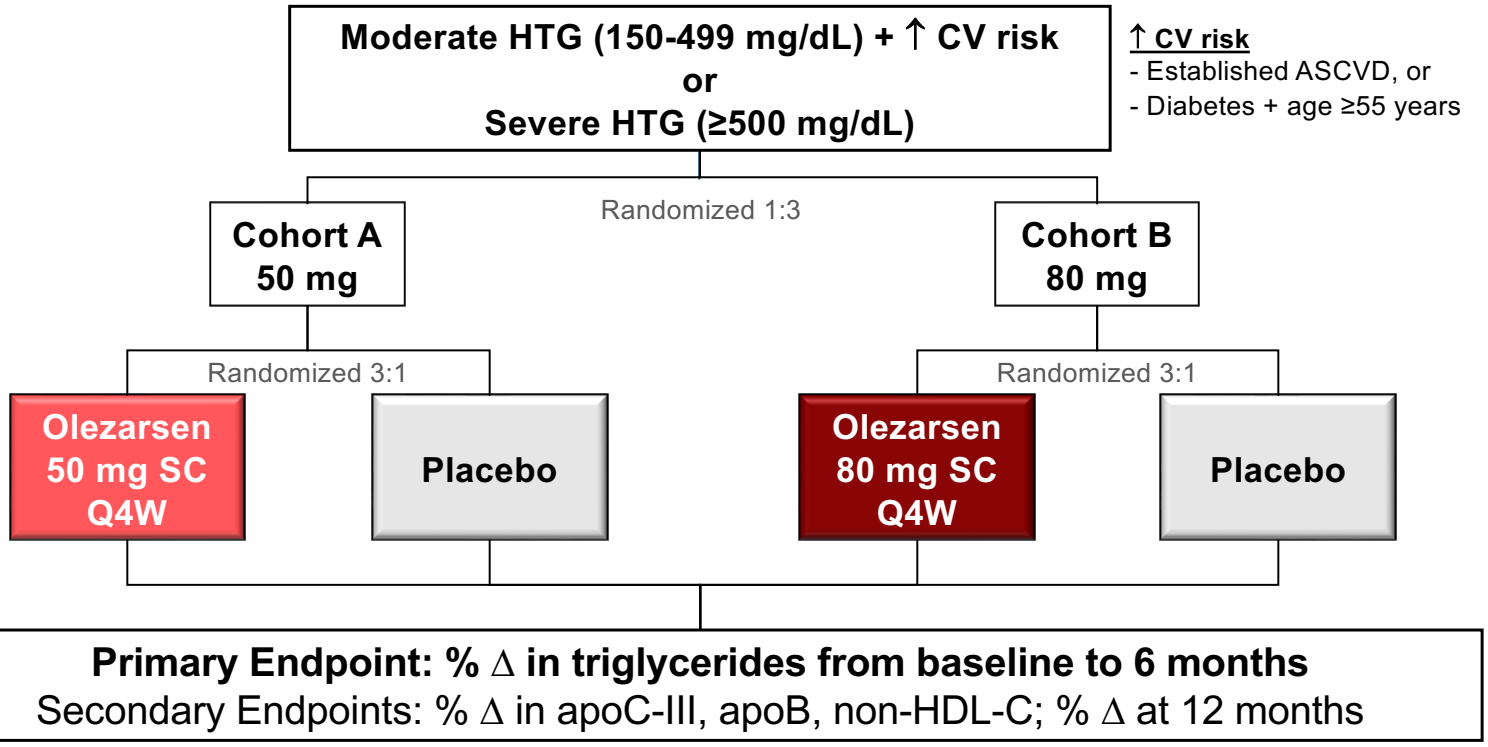
Study Objective

To evaluate the **association between baseline fibrate use and the magnitude of olezarsen's effects** on triglycerides and atherogenic lipoproteins in patients with moderate hypertriglyceridemia (150-499 mg/dL) plus elevated CV risk

Essence TIMI-73b Trial Design



NCT 05610280; Trial funded by Ionis.

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Methods

- Patients with moderate hypertriglyceridemia (150-499 mg/dL) plus elevated CV risk
- Baseline fibrate use defined at time of randomization
- Changes in background therapy discouraged during treatment period
- ANCOVA models comparing pooled olezarsen doses with placebo, adjusted for baseline lipids and clinical covariates
- Interaction tested between olezarsen effect and fibrate use

Baseline Characteristics

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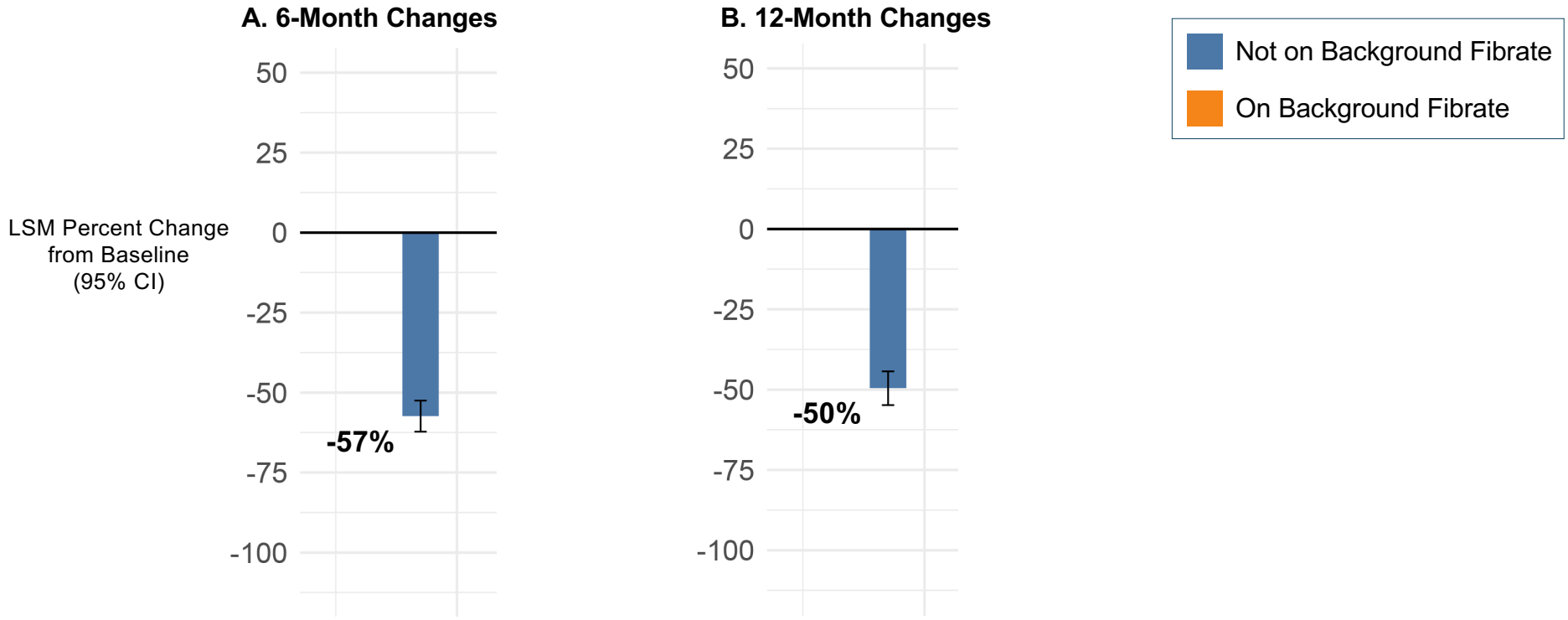
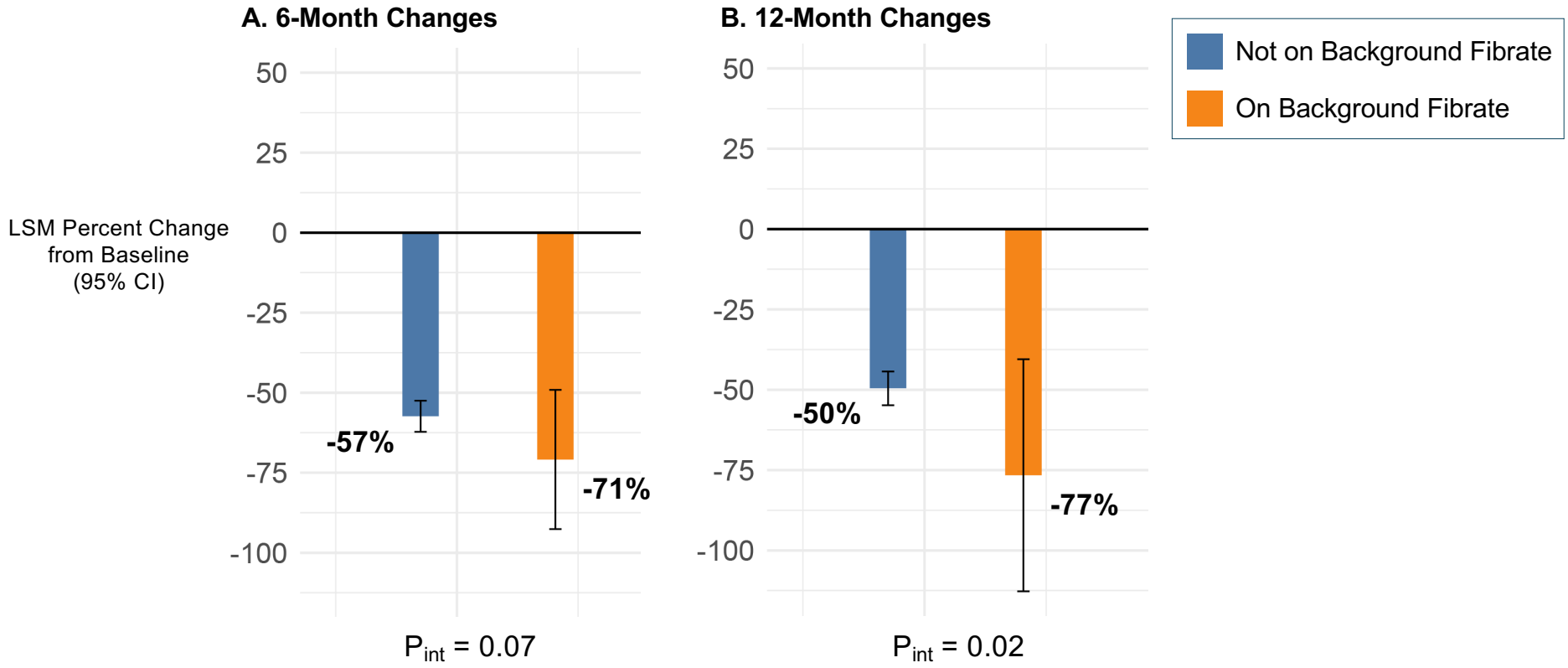
Characteristic	No Fibrate Use N = 1,040	Fibrate Use N = 309
Age, median yrs [IQR]	64 [57-70]	61 [55-68]
Female sex, %	42	35
Diabetes mellitus, %	57	70
BMI, median kg/m^2 [IQR]	32 [28-36]	31 [28-35]
Lipid parameters, median mg/dL [IQR]		
Triglycerides	234 [189-300]	257 [199-333]
Apolipoprotein C-III	15 [13-18]	16 [13-19]
VLDL cholesterol	41 [32-52]	45 [34-56]
Remnant cholesterol	50 [36-70]	49 [36-73]
Apolipoprotein B	90 [73-110]	96 [80-116]
LDL cholesterol	81 [60-110]	87 [66-112]
HDL cholesterol	39 [33-47]	36 [29-43]

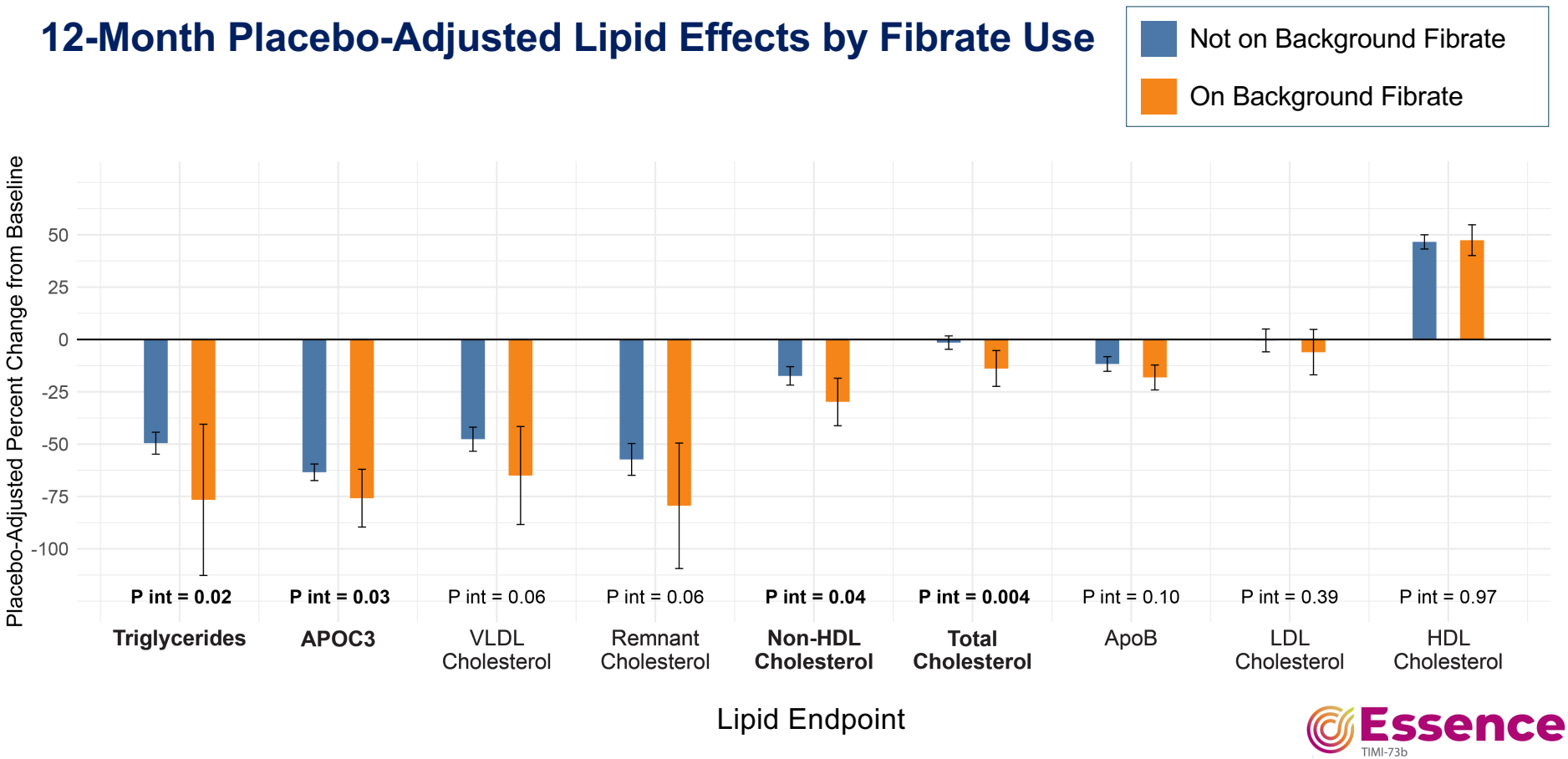
Placebo-Adjusted Triglyceride Reductions by Fibrate Use



Placebo-Adjusted Triglyceride Reductions by Fibrate Use



12-Month Placebo-Adjusted Lipid Effects by Fibrate Use



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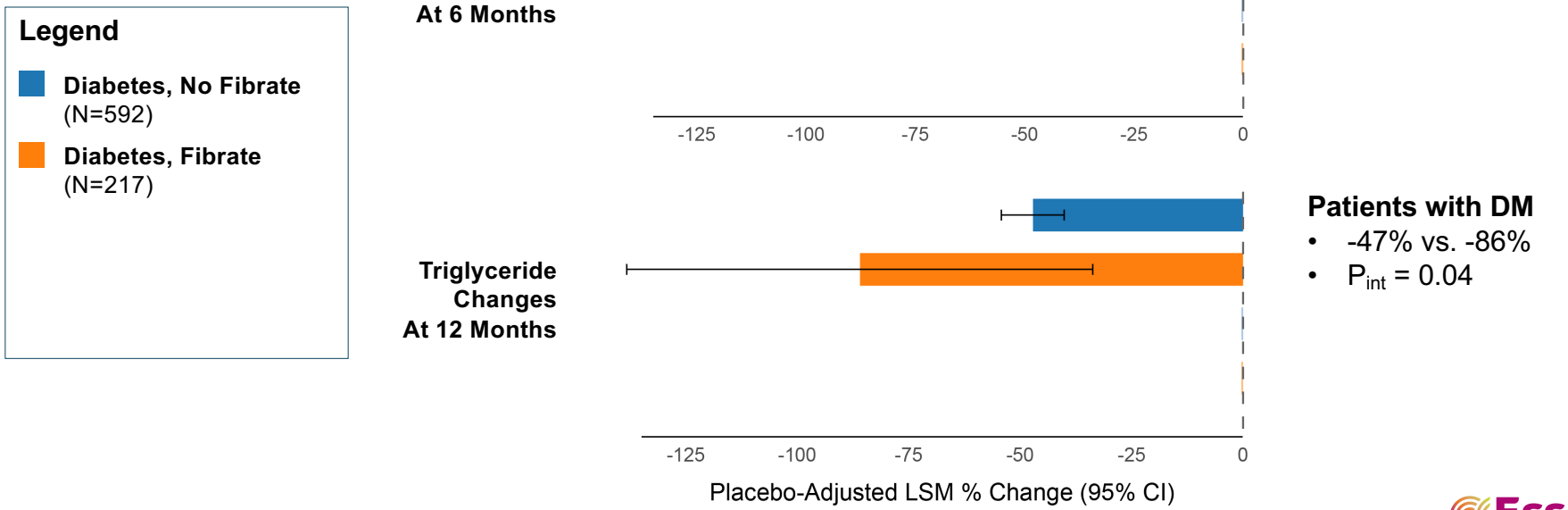
Subgroup Analysis: Diabetes Status

Placebo-Adjusted TG Reductions
Non-Users vs. Fibrate Users:



Patients with DM
- -51% vs. -73%
- P_{int} = 0.03

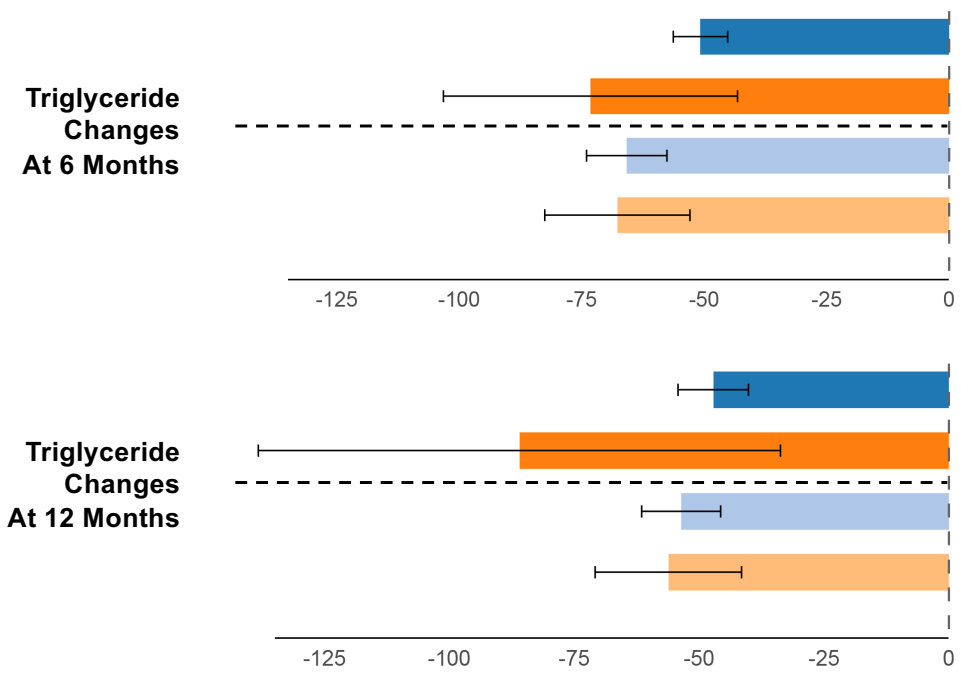
Patients with DM
- -47% vs. -86%
- P_{int} = 0.04

Subgroup Analysis: Diabetes Status

Placebo-Adjusted TG Reductions
Non-Users vs. Fibrate Users:

Legend

- **Diabetes, No Fibrate** (N=592)
- **Diabetes, Fibrate** (N=217)
- **No Diabetes, No Fibrate** (N=448)
- **No Diabetes, Fibrate** (N=92)



Patients with DM
- -51% vs. -73%
- P_{int} = 0.03

Patients without DM
- -66% vs. -68%
- P_{int} = 0.96

Patients with DM
- -47% vs. -86%
- P_{int} = 0.04

Patients without DM
- -54% vs. -56%
- P_{int} = 0.86

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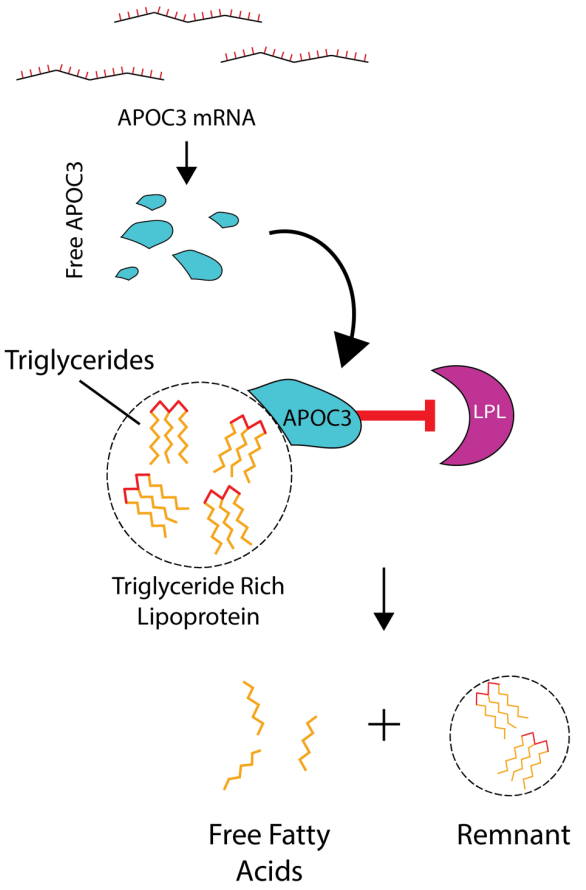
Limitations

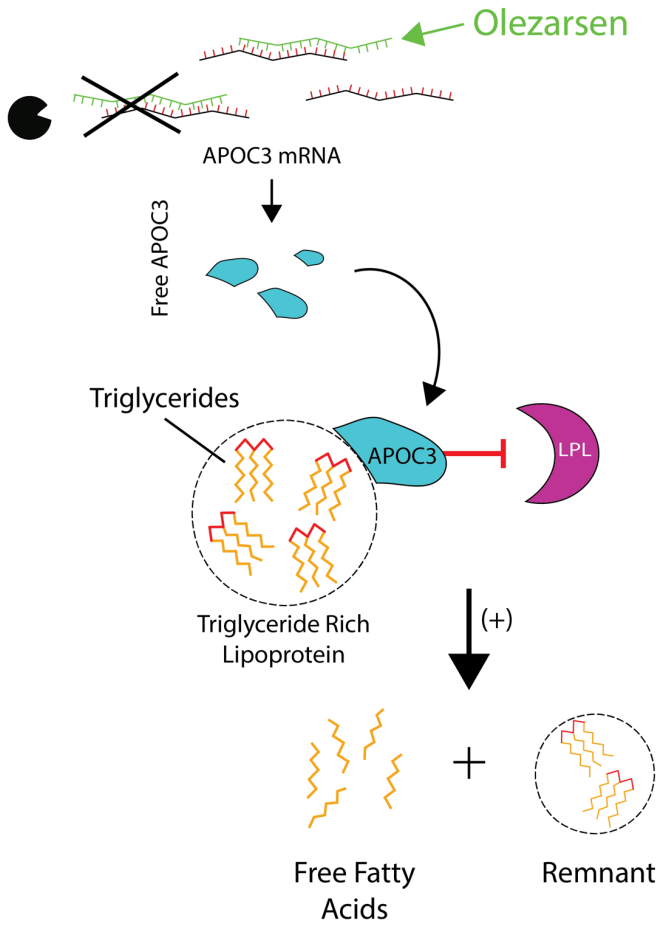
- Fibrate use was not randomized; however, analyses focused on randomized olezarsen effects stratified by fibrate use at baseline
- Cannot exclude that the greater apparent olezarsen effect with fibrates could reflect aliasing for a different underlying factor
- Study was not powered for analyses in smaller subgroups

Fibrates and olezarsen (APOC3 inhibition) act on complementary pathways.



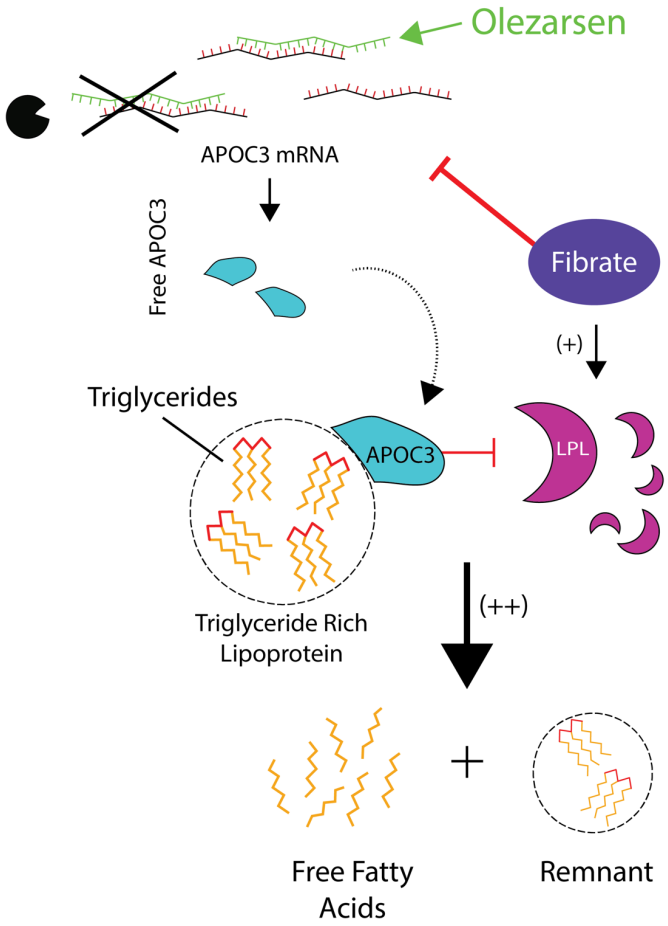
Fibrates and olezarsen (APOC3 inhibition) act on complementary pathways.

Reduced APOC3 (by **olezarsen**)



Fibrates and olezarsen (APOC3 inhibition) act on complementary pathways.

Reduced APOC3 (by **olezarsen**) in the setting of LPL upregulation and reduced APOC3 (by **fibrates**) may enhance TG clearance.



Conclusions

- In Essence-TIMI 73b, olezarsen, an antisense oligonucleotide targeting *APOC3*, produced large and durable triglyceride reductions.
- Olezarsen's triglyceride lowering effects appeared greater in patients on background fibrate therapy.
- Findings support further study of concomitant fibrate and olezarsen therapy to reduce residual cardiometabolic risk.