

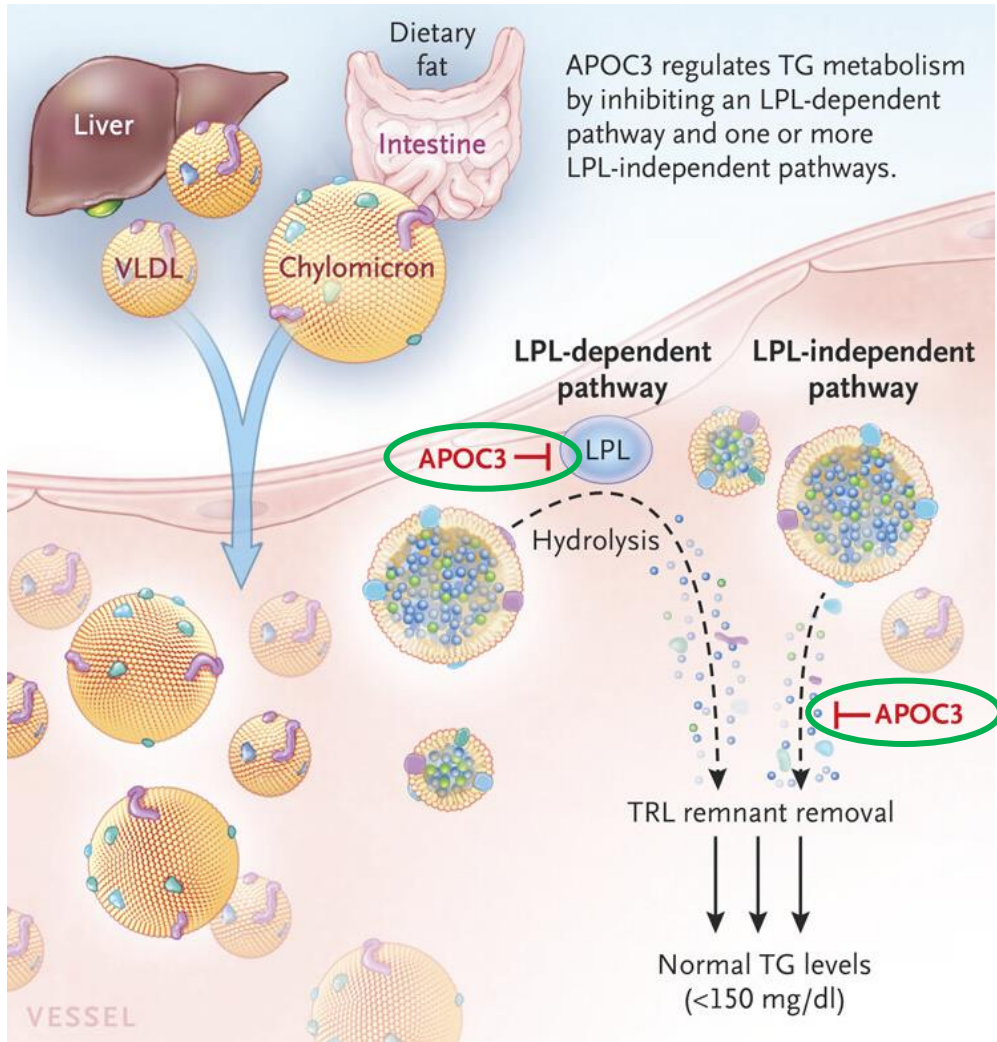
# APOLIPOPROTEIN C-III (APOC3) INHIBITION FOR SEVERE HYPERTRIGLYCERIDEMIA IN PATIENTS WITH VERSUS WITHOUT BASELINE FIBRATE USE

A PRE-SPECIFIED SECONDARY ANALYSIS OF THE CORE-TIMI 72A AND CORE2-TIMI 72B TRIALS

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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<sub>3</sub>-conjugated antisense oligonucleotide targeting APOC3 mRNA

- Reduced TGs in dose-dependent manner up to 72% in CORE and CORE2 RCTs

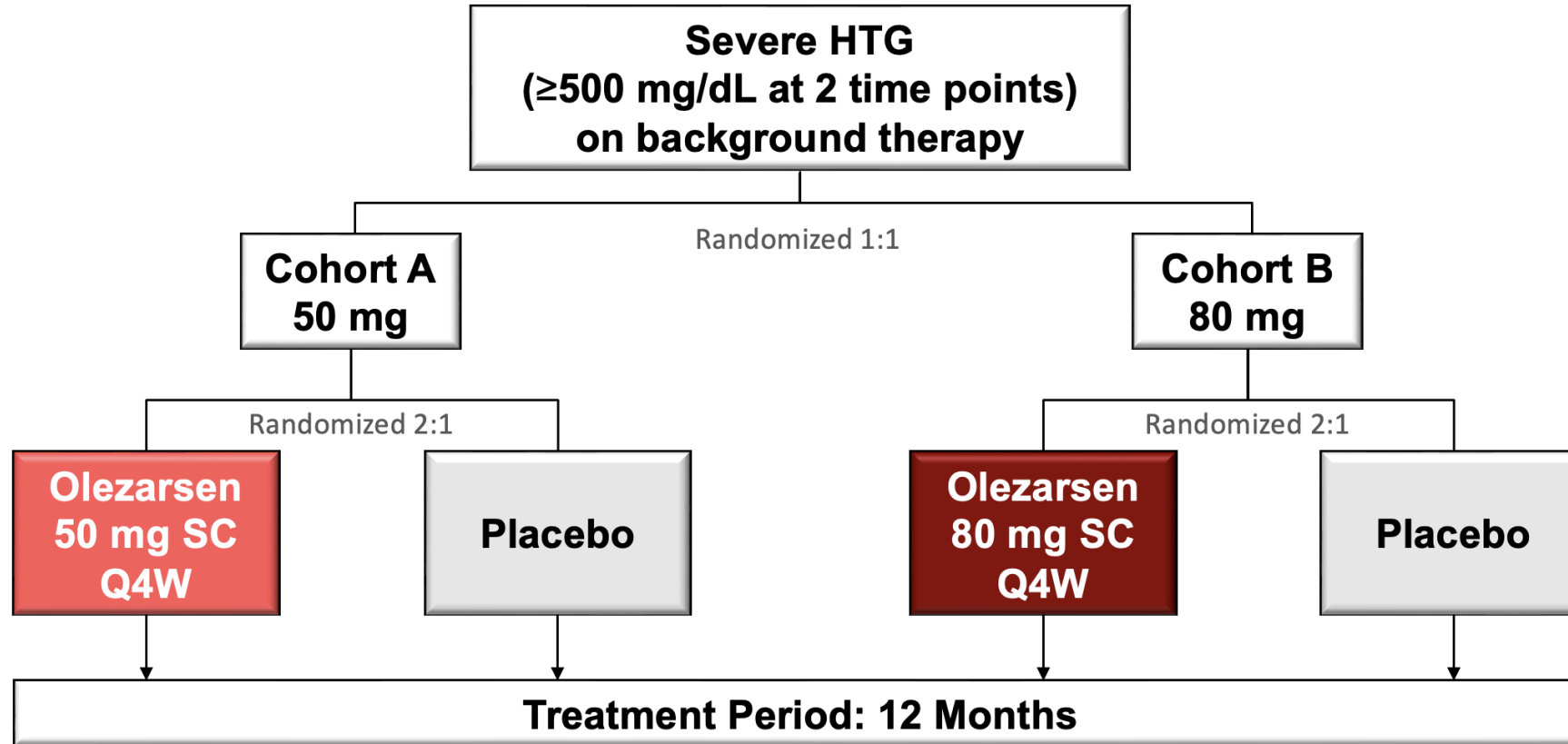
## Fibrates

- Upregulate LPL activity and downregulate APOC3 via PPAR $\alpha$

# 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 severe hypertriglyceridemia ( $\geq 500$  mg/dL).

# CORE-TIMI 72A AND CORE2-TIMI 72B TRIAL DESIGN



**Primary Endpoint (Each Trial): Pbo-adj %  $\Delta$  in triglycerides from baseline to 6 months**

**Secondary Endpoints (Each Trial): %  $\Delta$  in TG at 12 mos; %  $\Delta$  in apoC-III, Rem-C, non-HDL-C at 6 & 12mo**

# METHODS

- Pre-specified secondary analysis of the CORE-TIMI 72a and CORE2-TIMI 72b trials
- Patients with severe hypertriglyceridemia ( $\geq 500$  mg/dL)
- 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

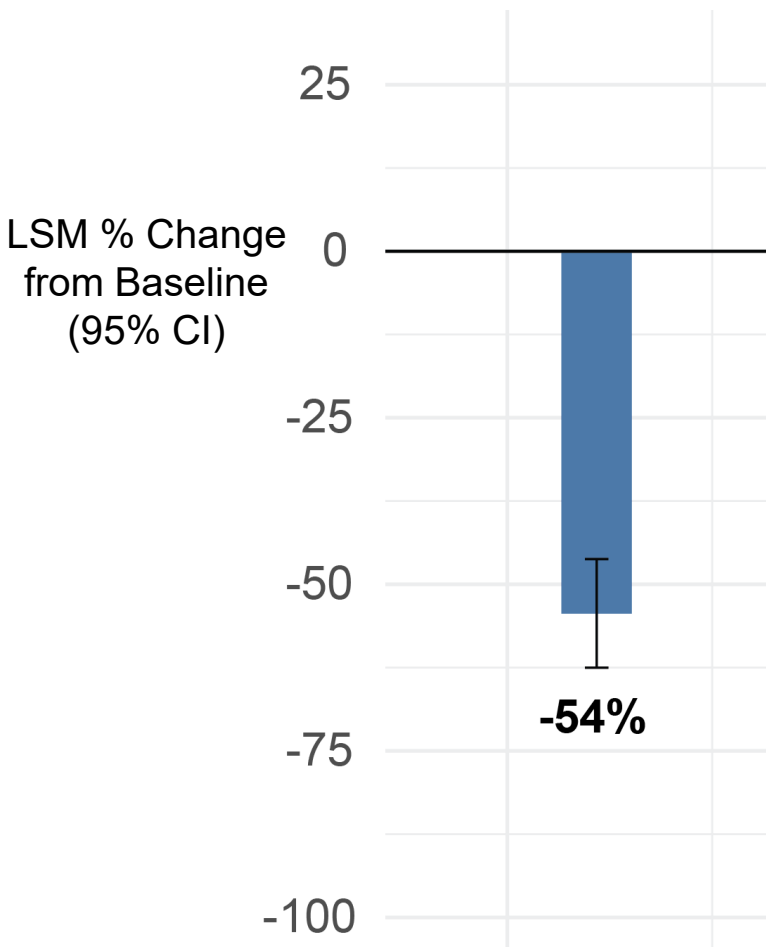
# BASELINE CHARACTERISTICS

<b>Characteristic</b>	<b>No Fibrate Use N = 387</b>	<b>Fibrate Use N = 674</b>
Age, median yrs [IQR]	56 [47-62]	53 [45-61]
Female sex, %	25	23
Diabetes mellitus, %	58	67
BMI, median kg/m <sup>2</sup> [IQR]	32 [28-35]	31 [28-35]
<b>Lipid parameters, median mg/dL [IQR]</b>		
Triglycerides	706 [557-1034]	863 [622-1427]
Apolipoprotein C-III	32 [25-40]	36 [28-48]
VLDL cholesterol	113 [91-157]	122 [89-177]
Remnant cholesterol	124 [81-173]	134 [89-187]
Apolipoprotein B	106 [90-128]	103 [84-122]
LDL cholesterol	67 [46-97]	56 [38-79]
HDL cholesterol	29 [24-34]	24 [19-29]

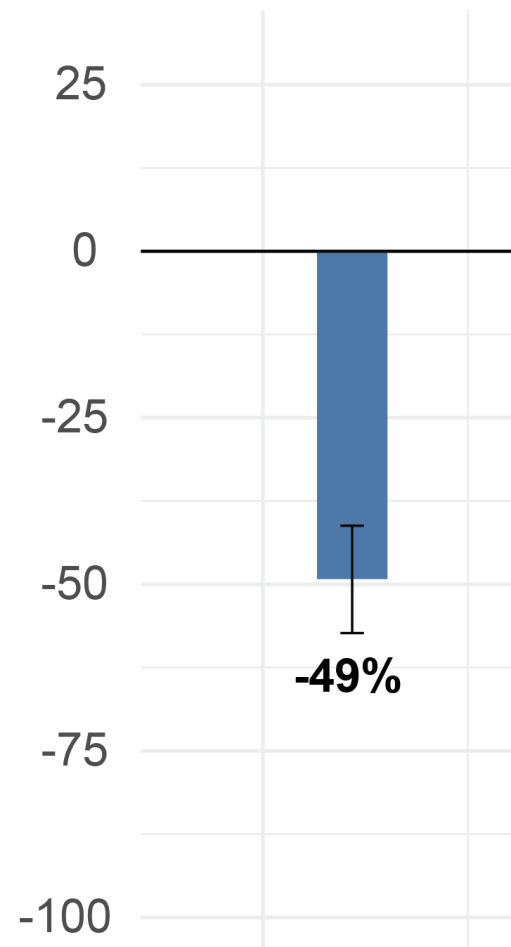
# PLACEBO-ADJUSTED TRIGLYCERIDE REDUCTIONS BY FIBRATE USE

Pooled Olezarsen Doses

### A. 6-Month Changes



### B. 12-Month Changes



■ Not on Background Fibrate (N=387)

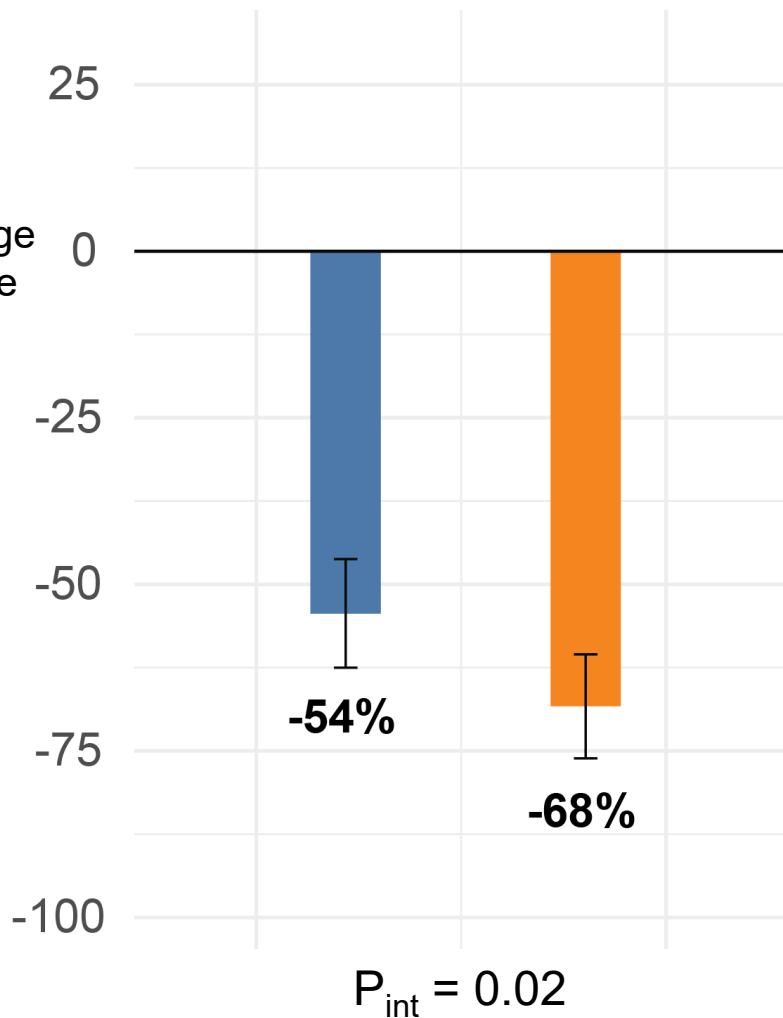


# PLACEBO-ADJUSTED TRIGLYCERIDE REDUCTIONS BY FIBRATE USE

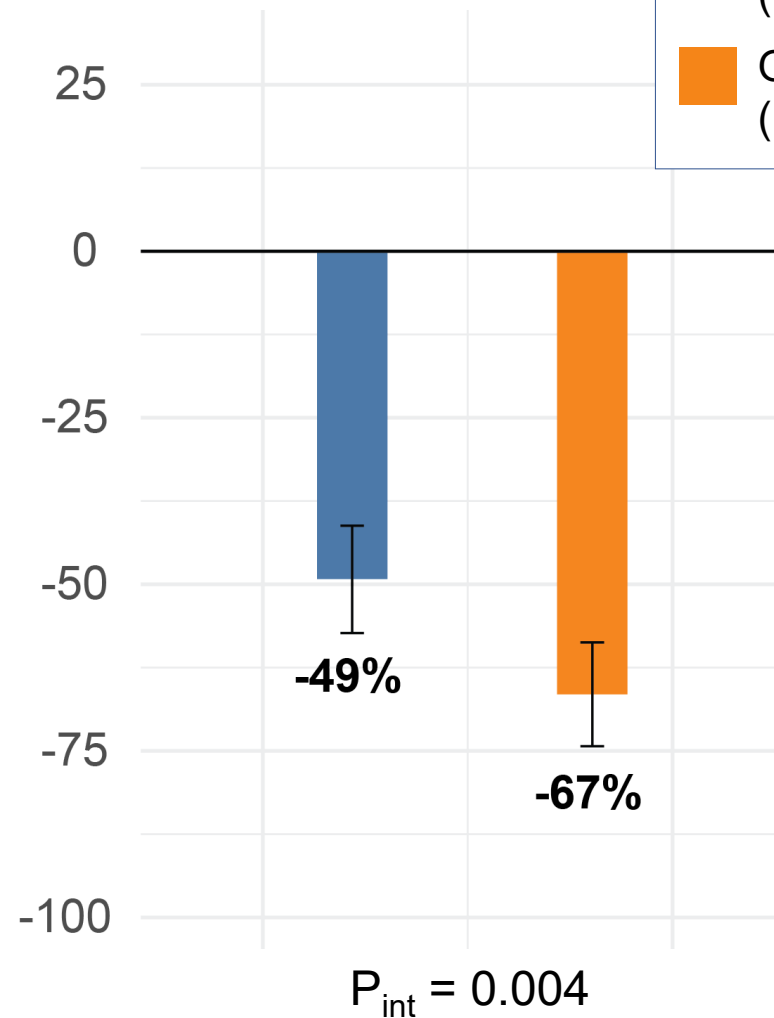
Pooled Olezarsen Doses

## A. 6-Month Changes

LSM % Change  
from Baseline  
(95% CI)



## B. 12-Month Changes

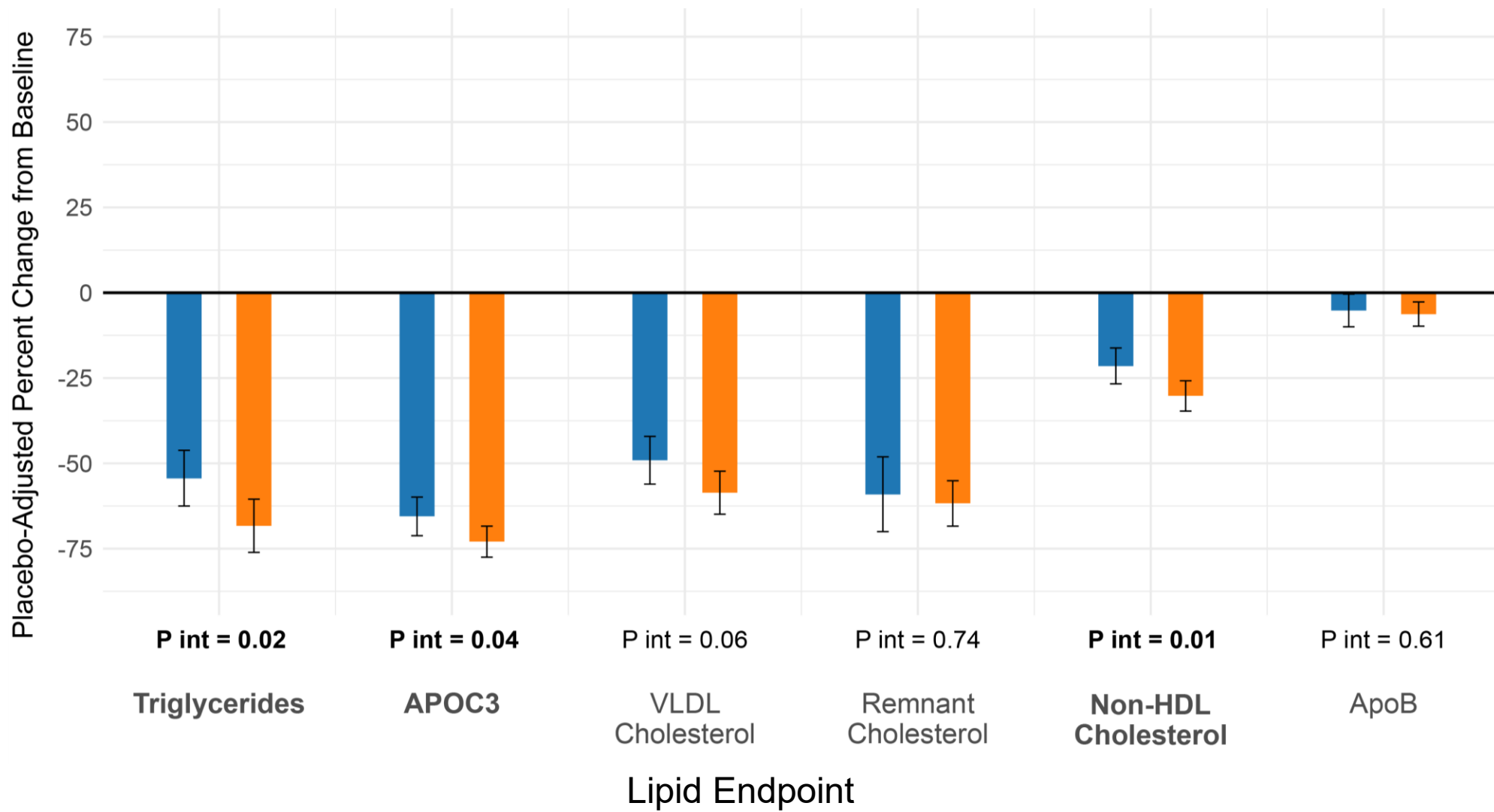


■ Not on Background Fibrate (N=387)  
■ On Background Fibrate (N=674)



# 6-MONTH PLACEBO-ADJUSTED LIPID EFFECTS BY FIBRATE USE

■ Not on Background Fibrate (N=387)  
■ On Background Fibrate (N=674)



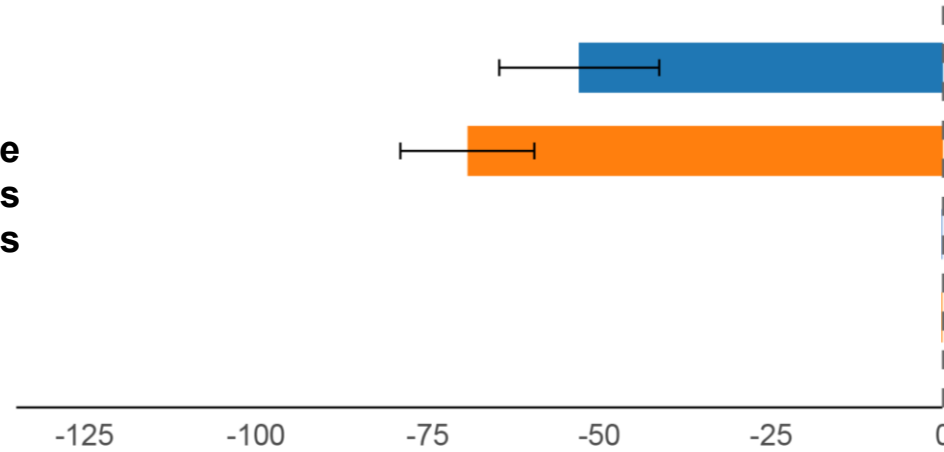
# SUBGROUP ANALYSIS: DIABETES STATUS

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

**Legend**

- Diabetes, No Fibrate (N=225)
- Diabetes, Fibrate (N=448)

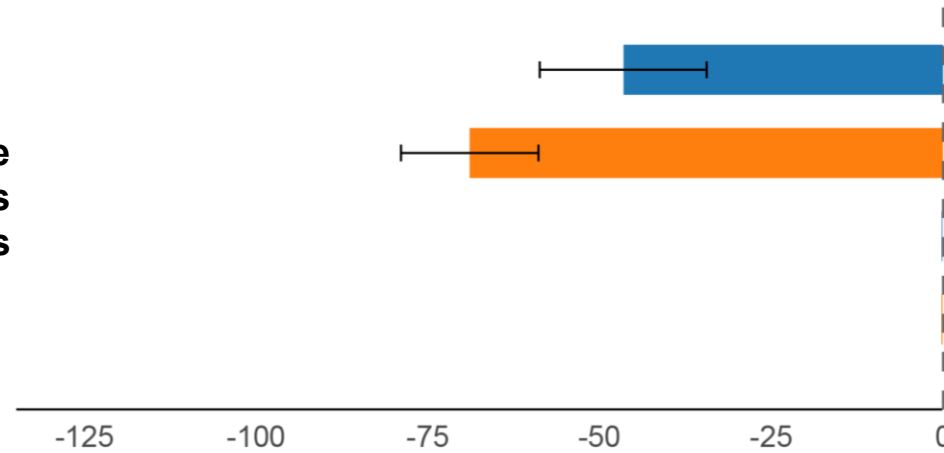
Triglyceride Changes At 6 Months



**Patients with DM**

- -52% vs. -69%
- $P_{int} = 0.04$

Triglyceride Changes At 12 Months



**Patients with DM**

- -46% vs. -69%
- $P_{int} = 0.01$

Placebo-Adjusted LSM % Change (95% CI)

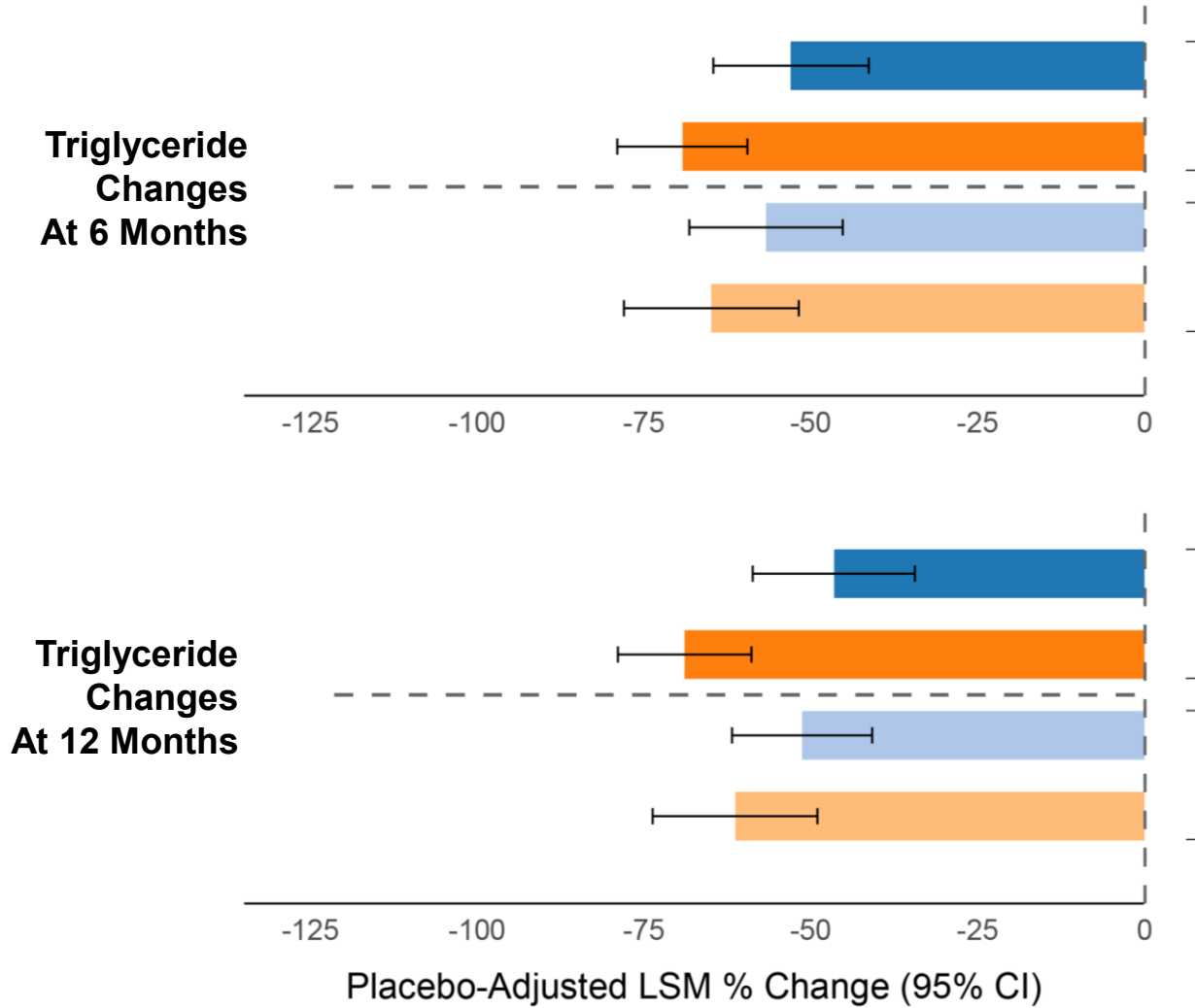


# SUBGROUP ANALYSIS: DIABETES STATUS

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

**Legend**

- Diabetes, No Fibrate (N=225)
- Diabetes, Fibrate (N=448)
- No Diabetes, No Fibrate (N=162)
- No Diabetes, Fibrate (N=226)



**Patients with DM**

- -52% vs. -69%
- $P_{int} = 0.04$

**Patients without DM**

- -57% vs. -66%
- $P_{int} = 0.25$

**Patients with DM**

- -46% vs. -69%
- $P_{int} = 0.01$

**Patients without DM**

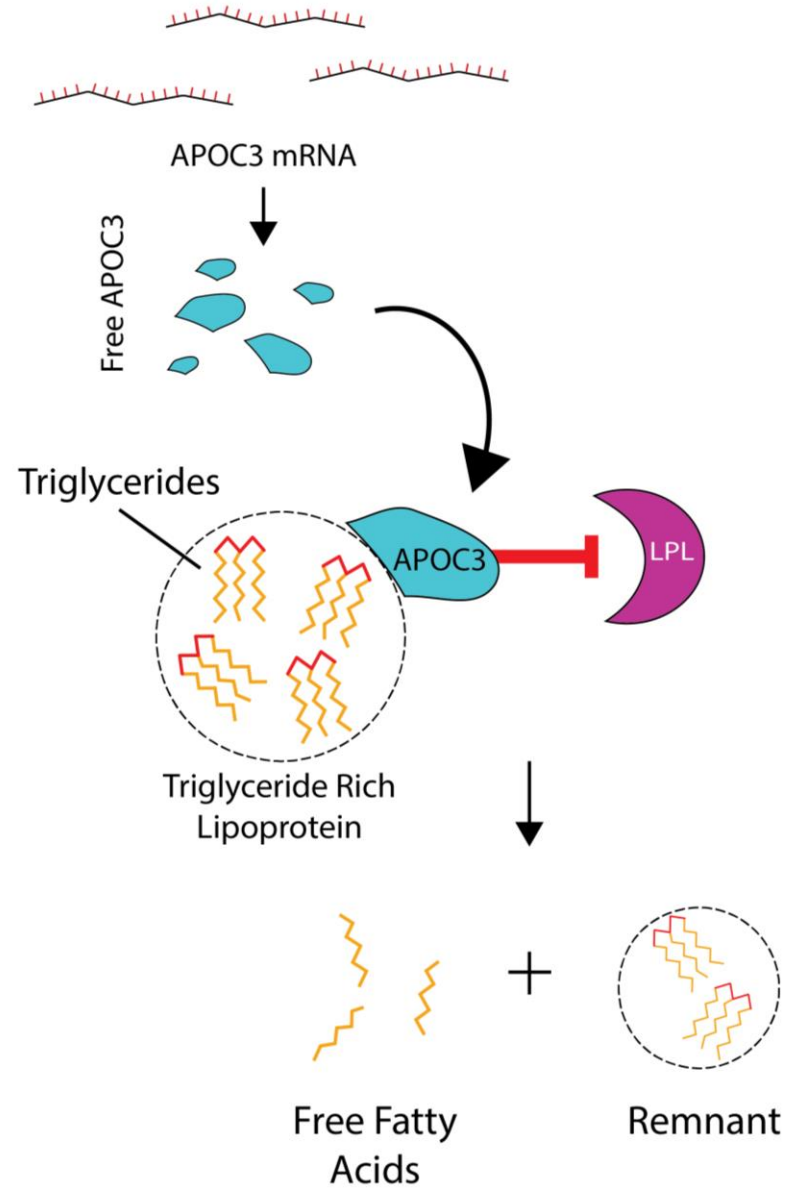
- -51% vs. -62%
- $P_{int} = 0.23$



# LIMITATIONS

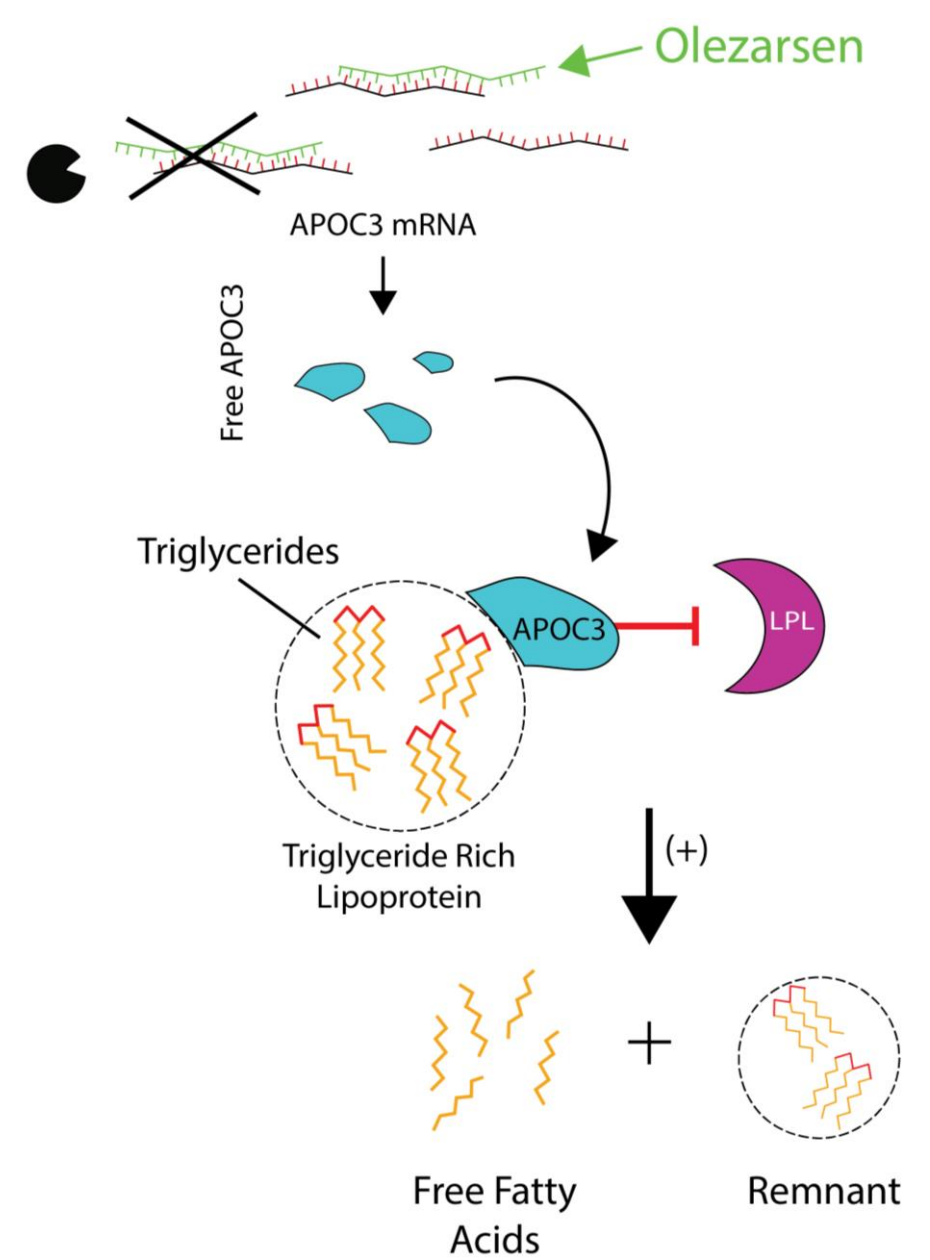
- Fibrate use was not randomized; however, analyses focused on randomized olezarsen effects stratified by fibrate use at baseline
- Cannot exclude that the greater apparent olezarsen effect with fibrates could reflect aliasing for a different underlying factor
- Study was not powered for analyses in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

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



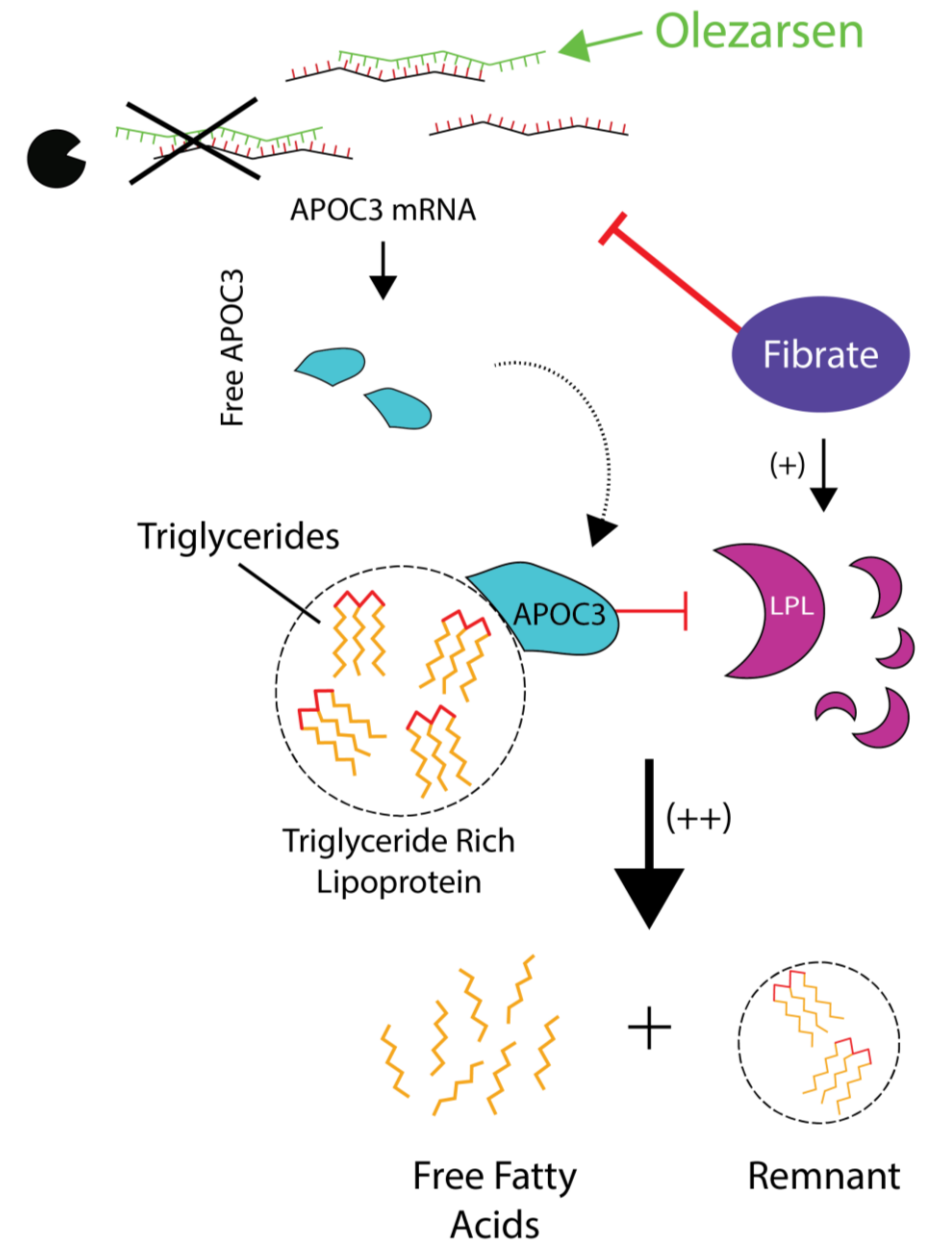
Fibrates and olezarsen (APOC3 inhibition) act on complementary pathways.

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 CORE-TIMI 72a and CORE2-TIMI 72b, olezarsen, an antisense oligonucleotide targeting *APOC3*, produced large and durable triglyceride reductions for patients with severe hypertriglyceridemia.
- Olezarsen's triglyceride lowering effects appeared greater in patients on background fibrate therapy.
- Findings support further study of concomitant fibrate and olezarsen therapy.