

ApoC-III inhibition: Entering a new era in
managing risks of **severe**
hypertriglyceridemia (sHTG)



Welcome

Prof. Ulrich Laufs
Leipzig University Hospital
Leipzig, Germany

Disclaimer & important information

This presentation serves **educational purposes** and is intended to provide information and **stimulate discussion on** familial chylomicronemia and severe hypertriglyceridemia.

The symposium contains information about Sobi products.

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No identifiable patient-specific information is included.

Introductions



Prof. Ulrich Laufs

Leipzig University Hospital
Leipzig, Germany



Prof. Sybil Charrière

Lyon University Hospital
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Prof. Thomas Stulnig

Karl Landsteiner Institute for
Metabolic Diseases & Nephrology
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Vienna, Austria

ApoC-III inhibition: Entering a new era in managing risks of severe hypertriglyceridemia (sHTG)

Agenda

Welcome

Prof. Ulrich Laufs
(Chair)

**Triglycerides: A cardiologists' concern
– What are the risks?**

Prof. Ulrich Laufs

**ApoC-III targeting: A new era in
triglyceride management**

Prof. Sybil Charrière

How I manage my patients with sHTG

Prof. Thomas Stulnig

Q&A, panel discussion and closing remarks

All (Moderated by Chair)



Please remember to
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your feedback contributes to
improving future events





Triglycerides: A Cardiologists' Concern - What are the risks?

Ulrich Laufs



Klinik und Poliklinik für Kardiologie



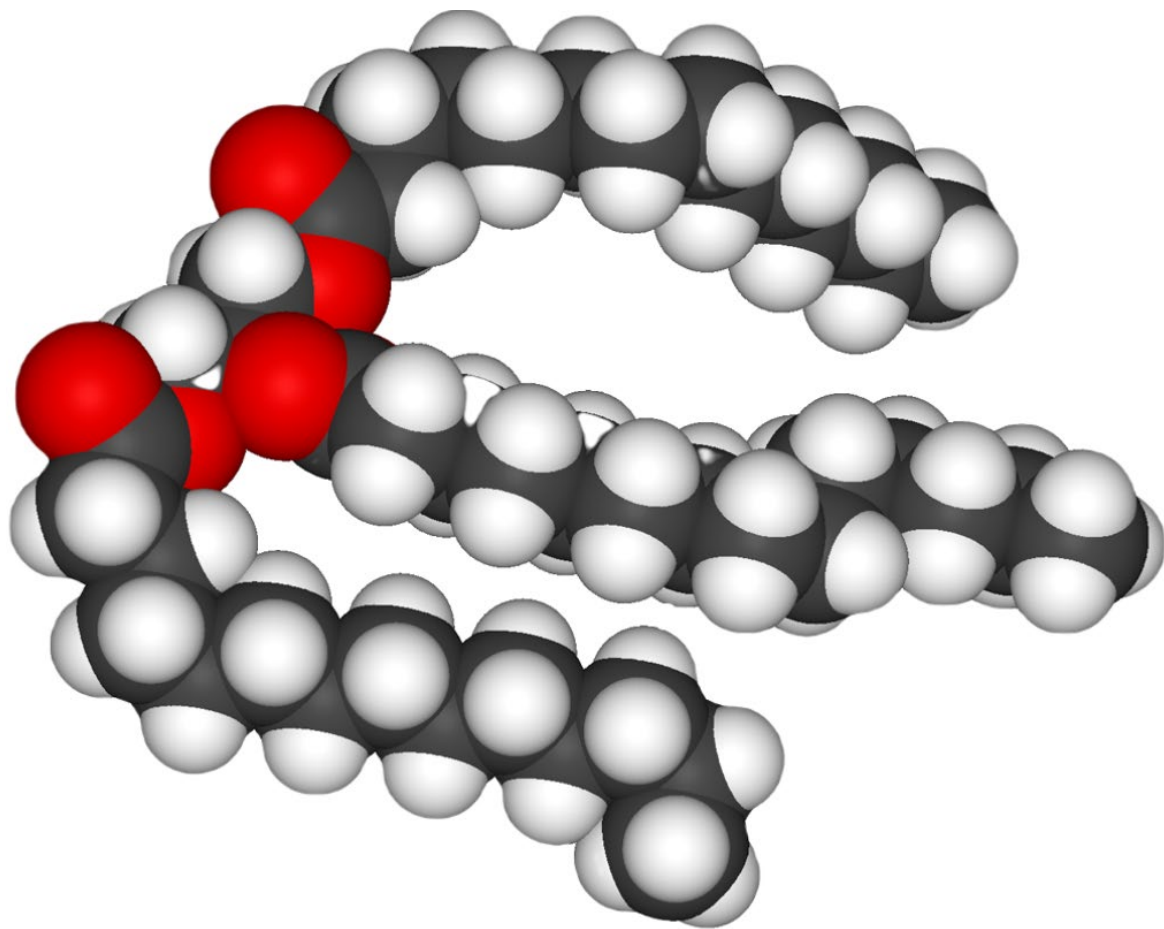
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im Herzen Leipzigs

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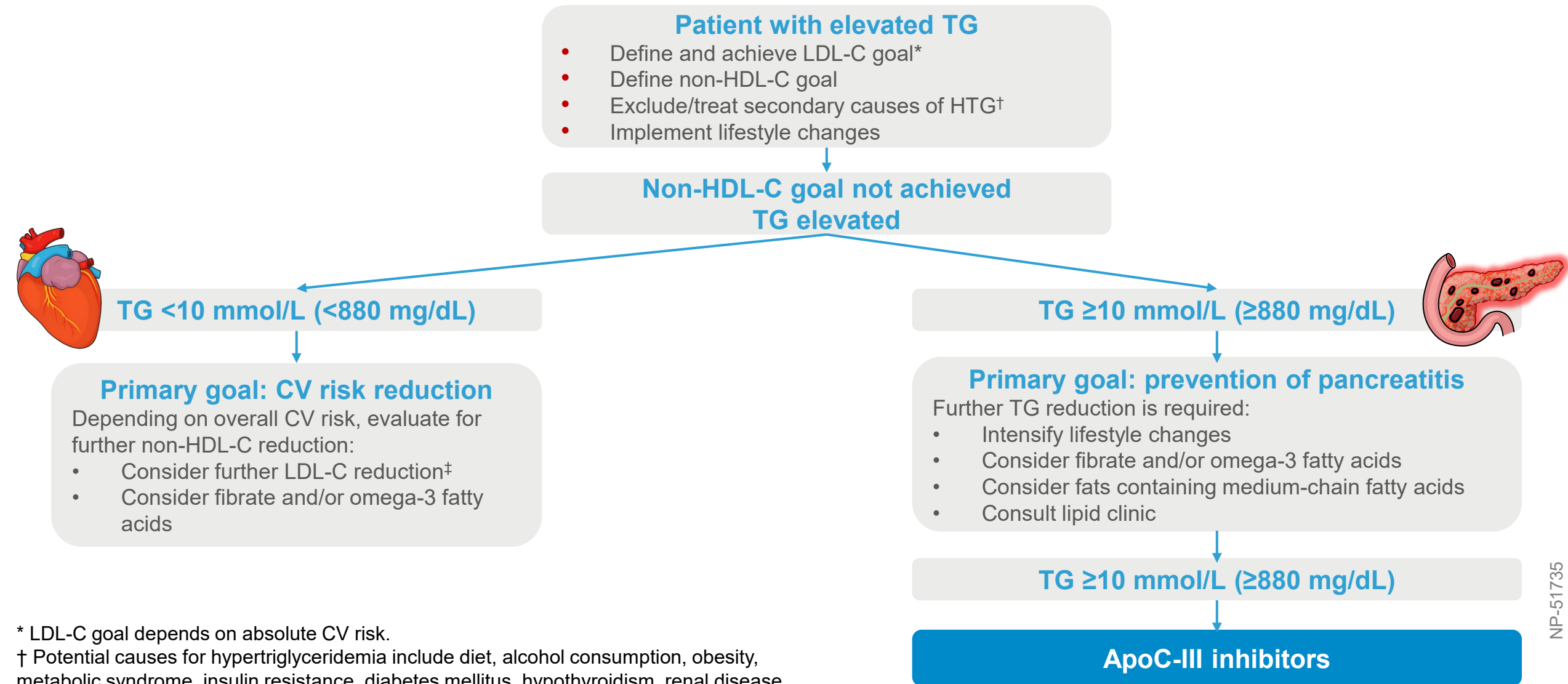
<https://commons.wikimedia.org/wiki/File:Trimyristin-3D-vdW.png#/media/File:Trimyristin-3D-vdW.png>

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Tünnemann-Tarr et al. *Medicine* 2021;100(42):e27573

Elevated triglycerides



* LDL-C goal depends on absolute CV risk.

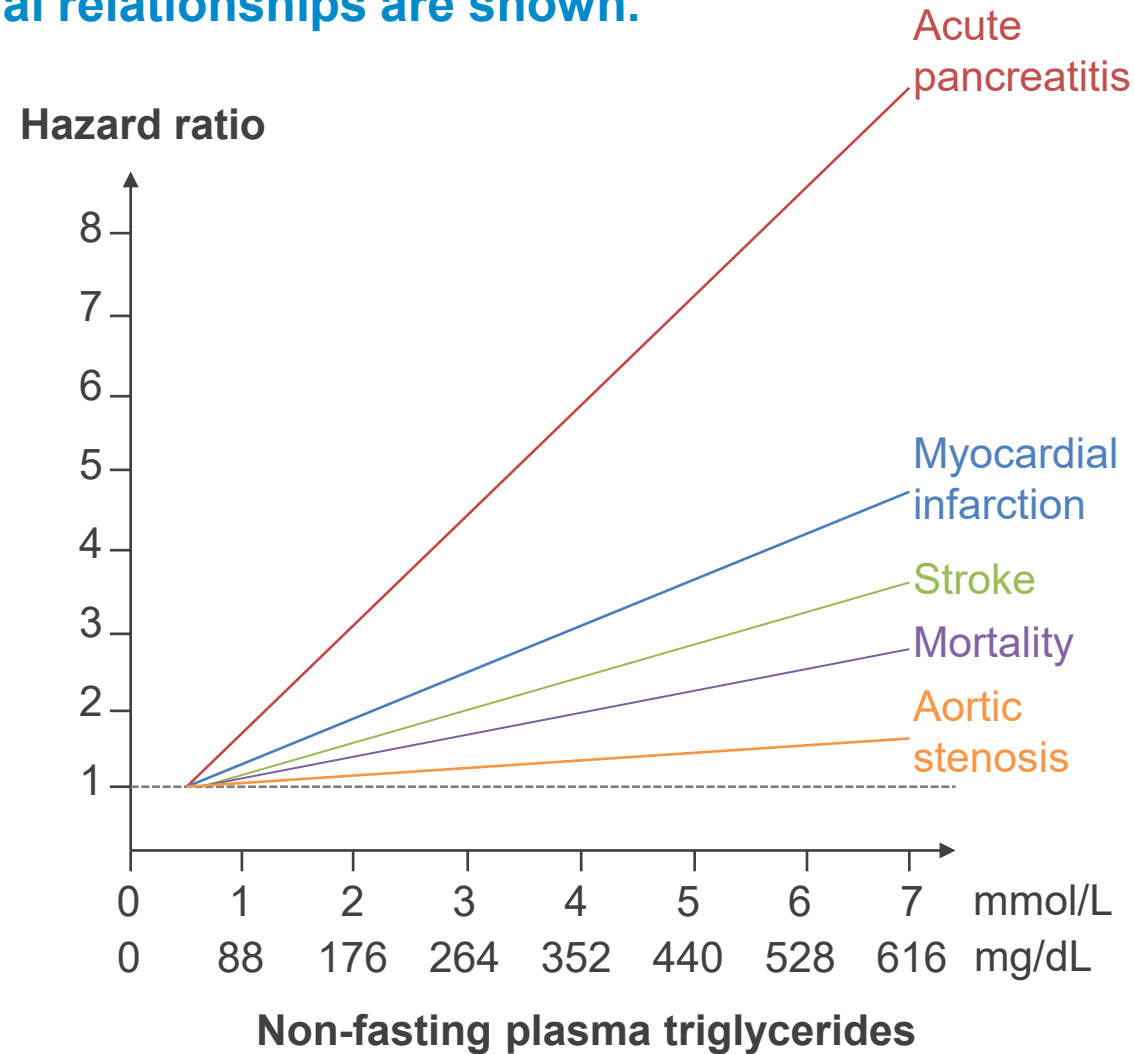
† Potential causes for hypertriglyceridemia include diet, alcohol consumption, obesity, metabolic syndrome, insulin resistance, diabetes mellitus, hypothyroidism, renal disease, pregnancy, paraproteinemia, systemic lupus erythematosus and certain medications.

‡ Further LDL-C reduction will also help in achieving non-HDL-C goals.

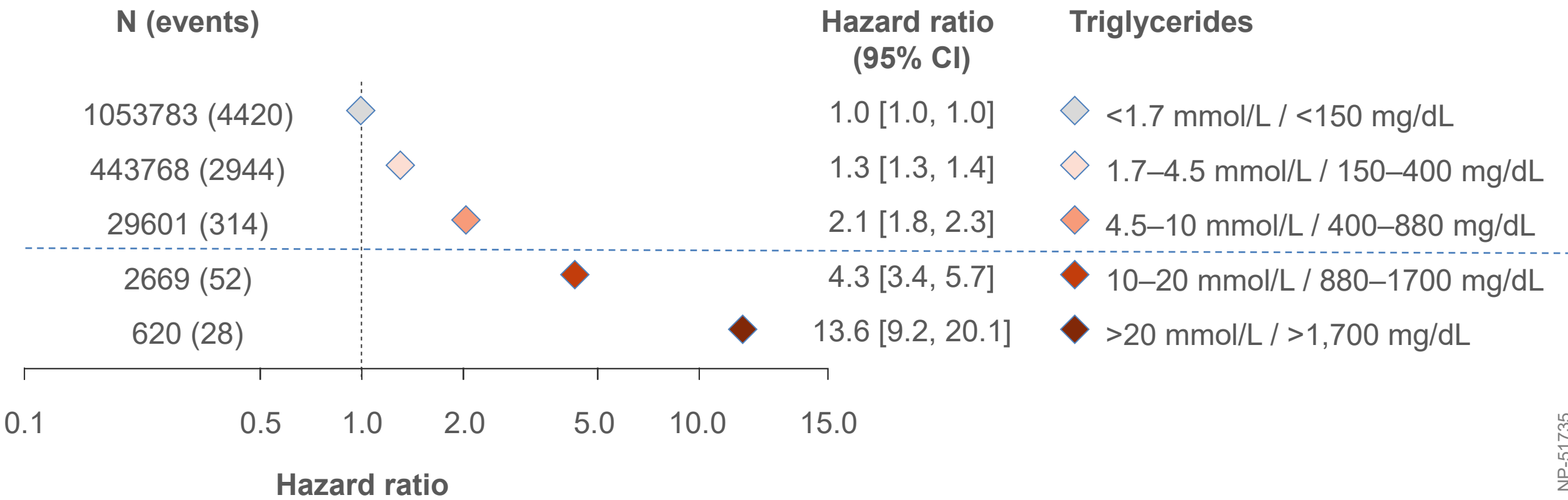
Laufs et al. EHJ 2020;41(1):99-109
Mach et al. EHJ 2025;46(42):4359-4378

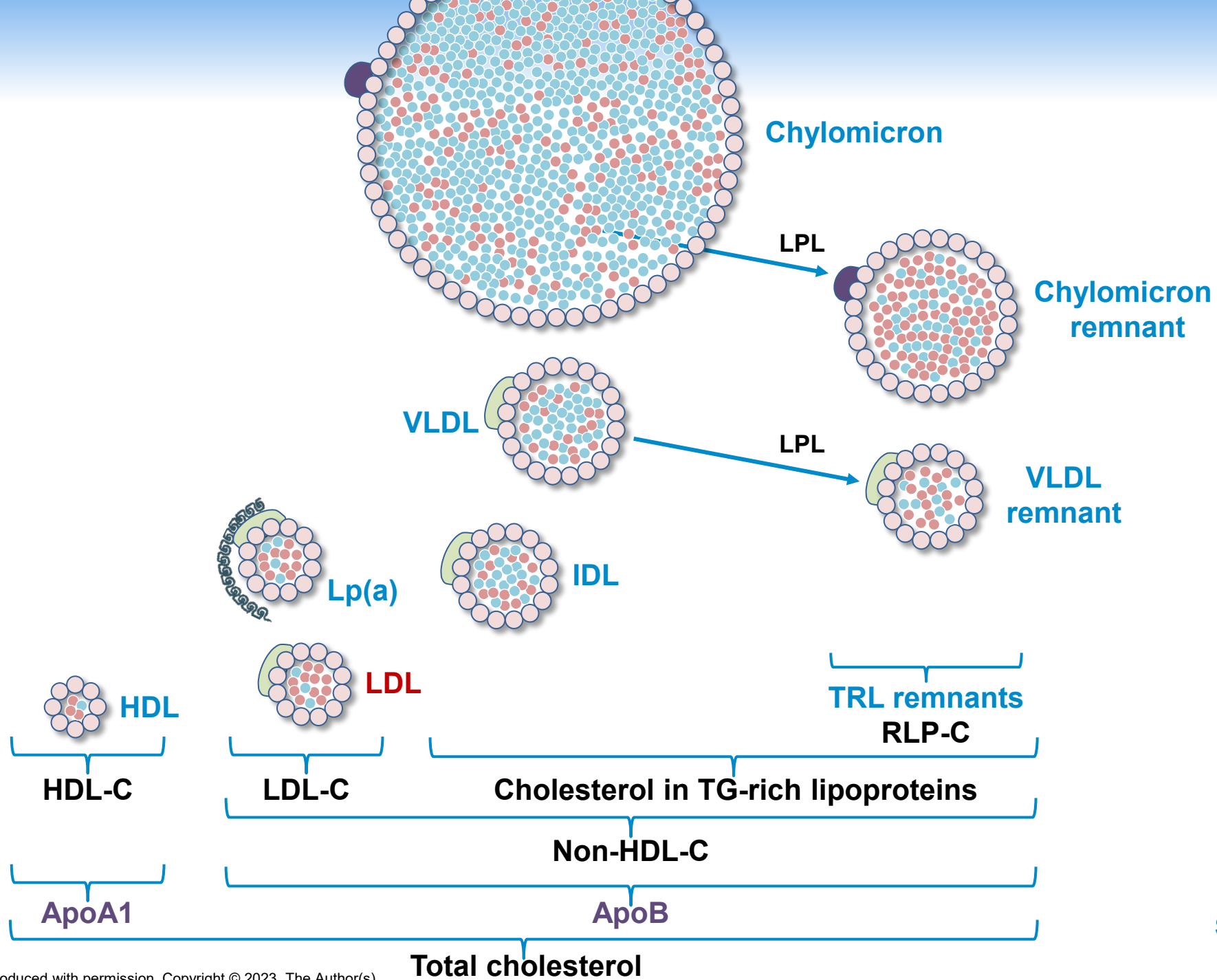
Hypertriglyceridemia and associated risks

Figure based on ~100,000 individuals participating in the Copenhagen General Population and City Heart Study. Observational relationships are shown.



Triglycerides increase risk for acute pancreatitis



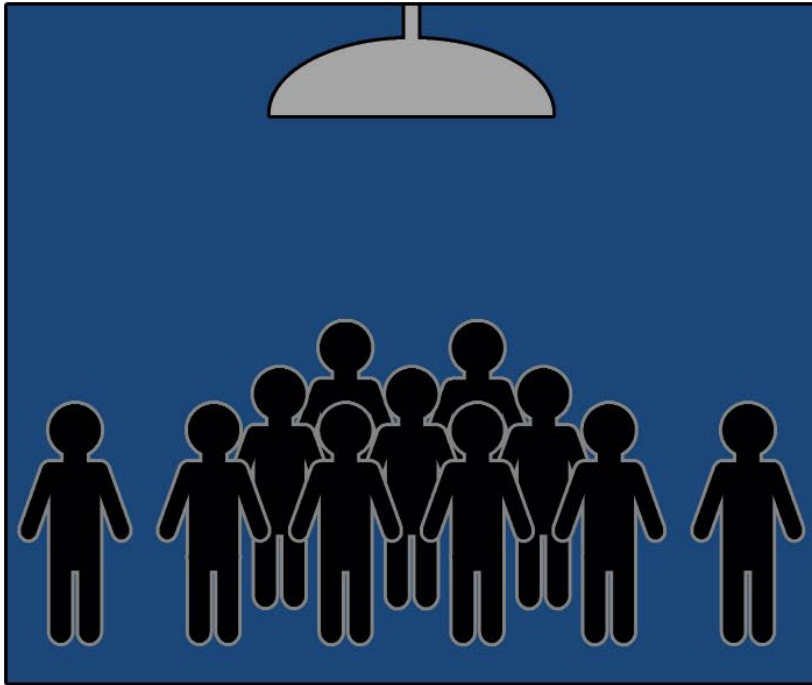


- Cholesterol
- Triglycerides
- ApoB-48
- ApoB-100

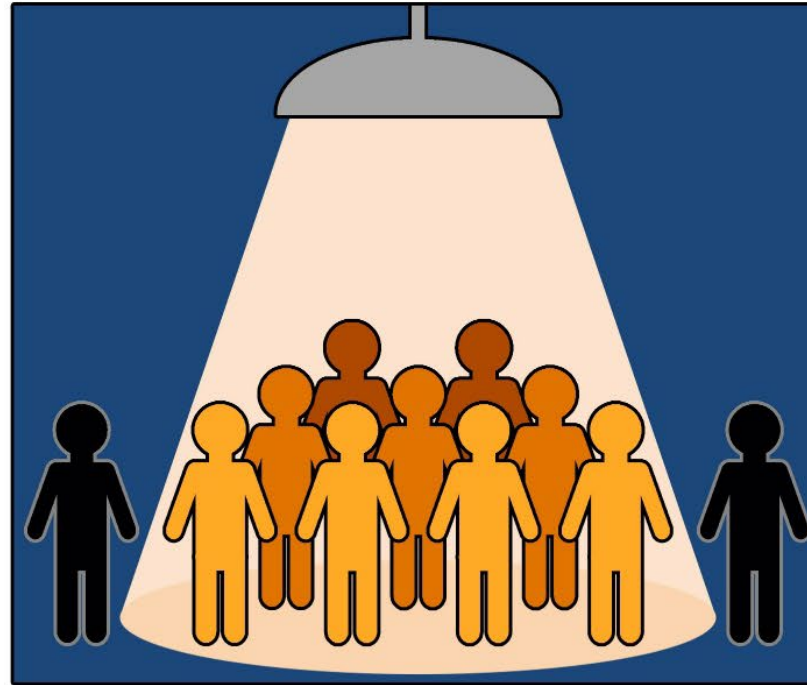
Stürzebecher, Katzmann, Laufs
EHJ 2023;44(16):1446-1448.

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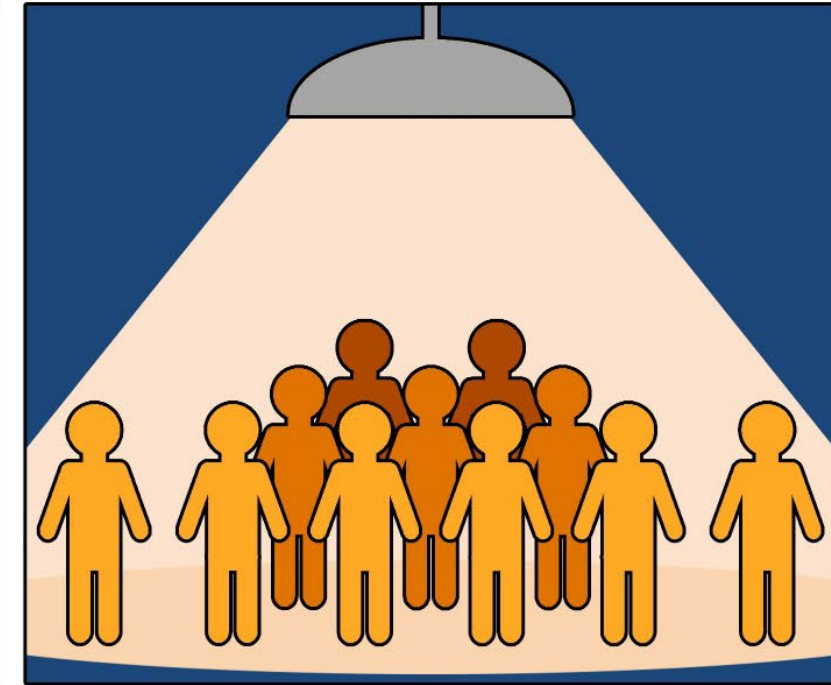
Apolipoprotein B for the refinement of cardiovascular risk assessment



No lipid testing



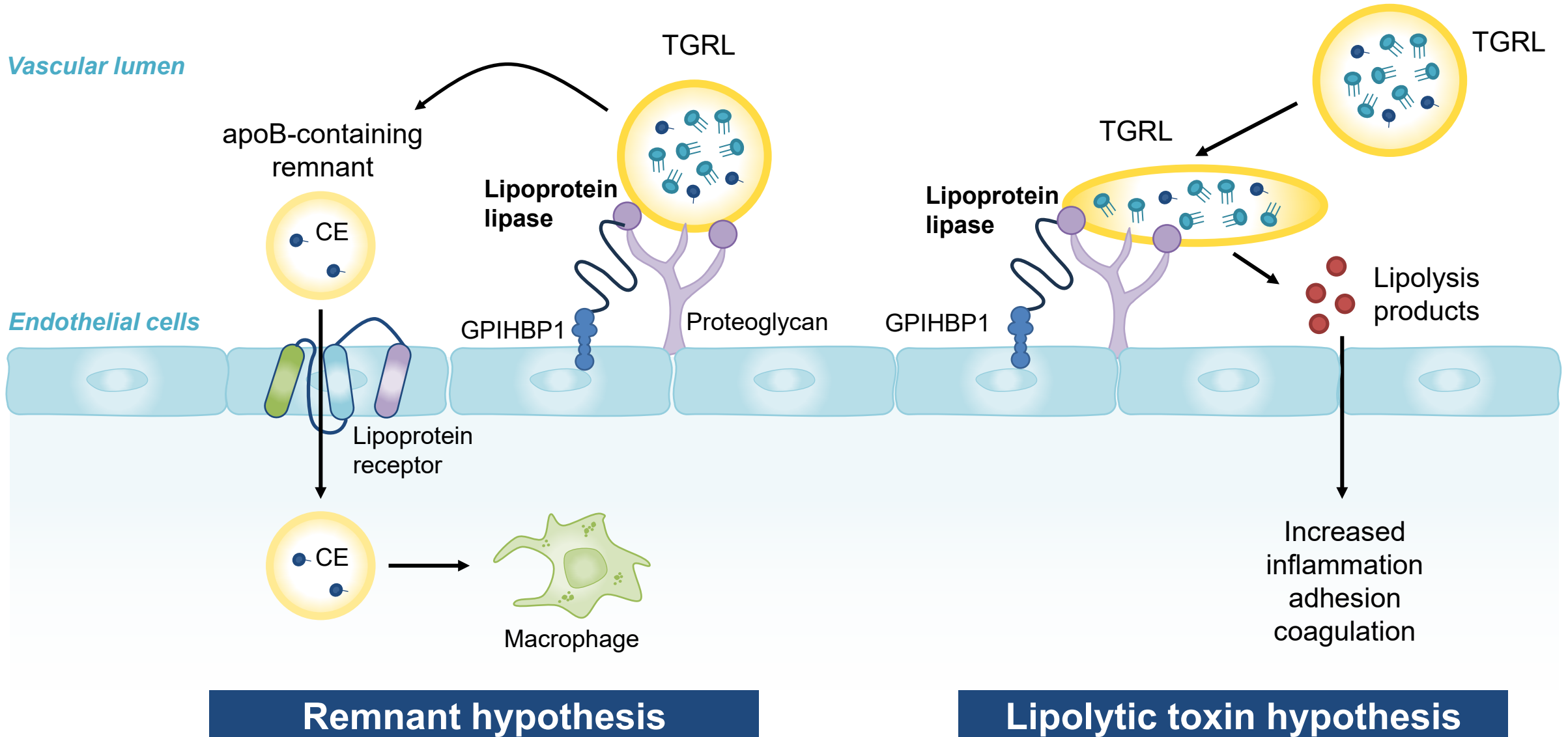
**Lipid testing
with conventional
lipid panel**



**Lipid testing
with ApoB**

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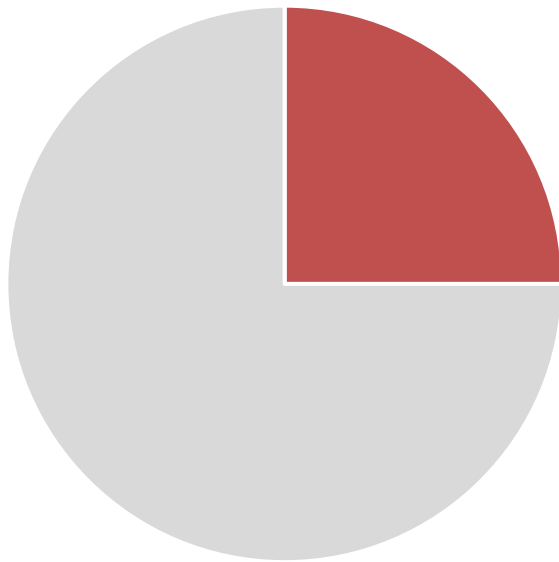
Atherogenicity of TG-rich lipoproteins (TGRL)



Among patients with ASCVD, hypertriglyceridemia is common and associated with higher risk

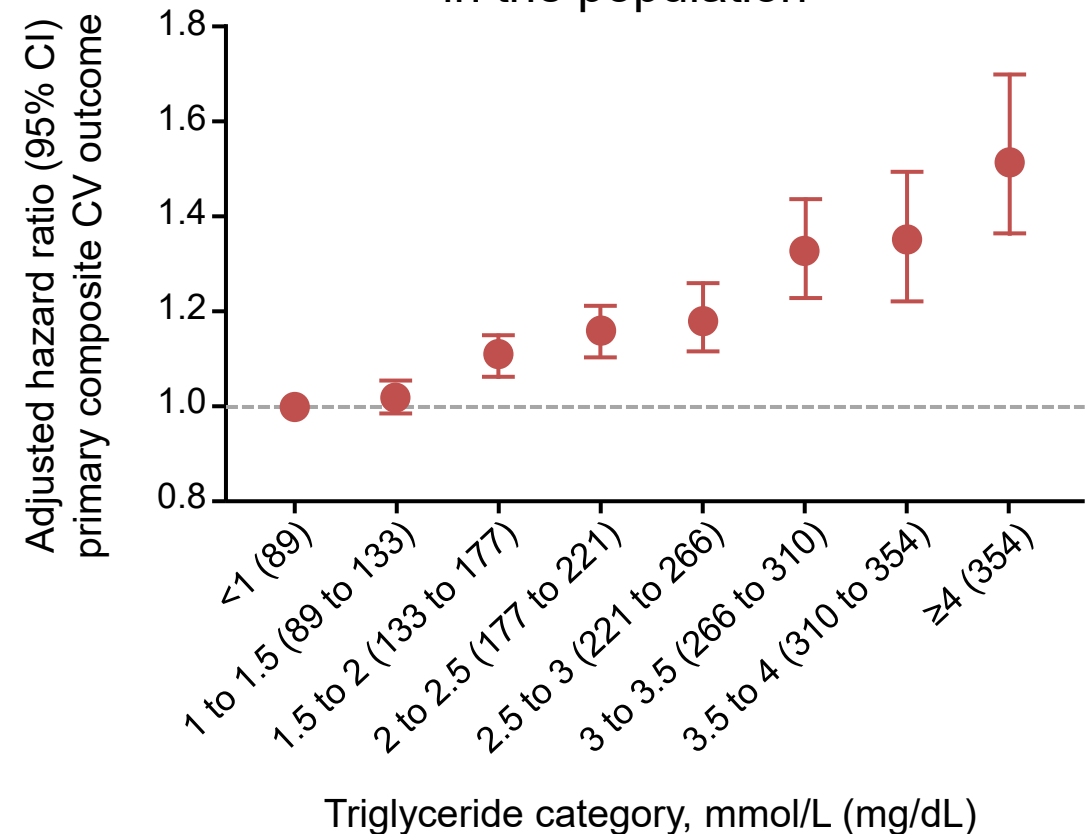
Data from 2,424,865 adults with lipid panels in the Ontario population

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDL-C*



* Defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDL-C 1.06-2.59 mmol/L (41-100 mg/dL)

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



Figures adapted from Lawler et al. EHJ 2020;41:86–94

Statin non-eligible individuals with TG ≥ 3.0 mmol/L (264 mg/dL) show ASCVD risk similar to statin eligible individuals

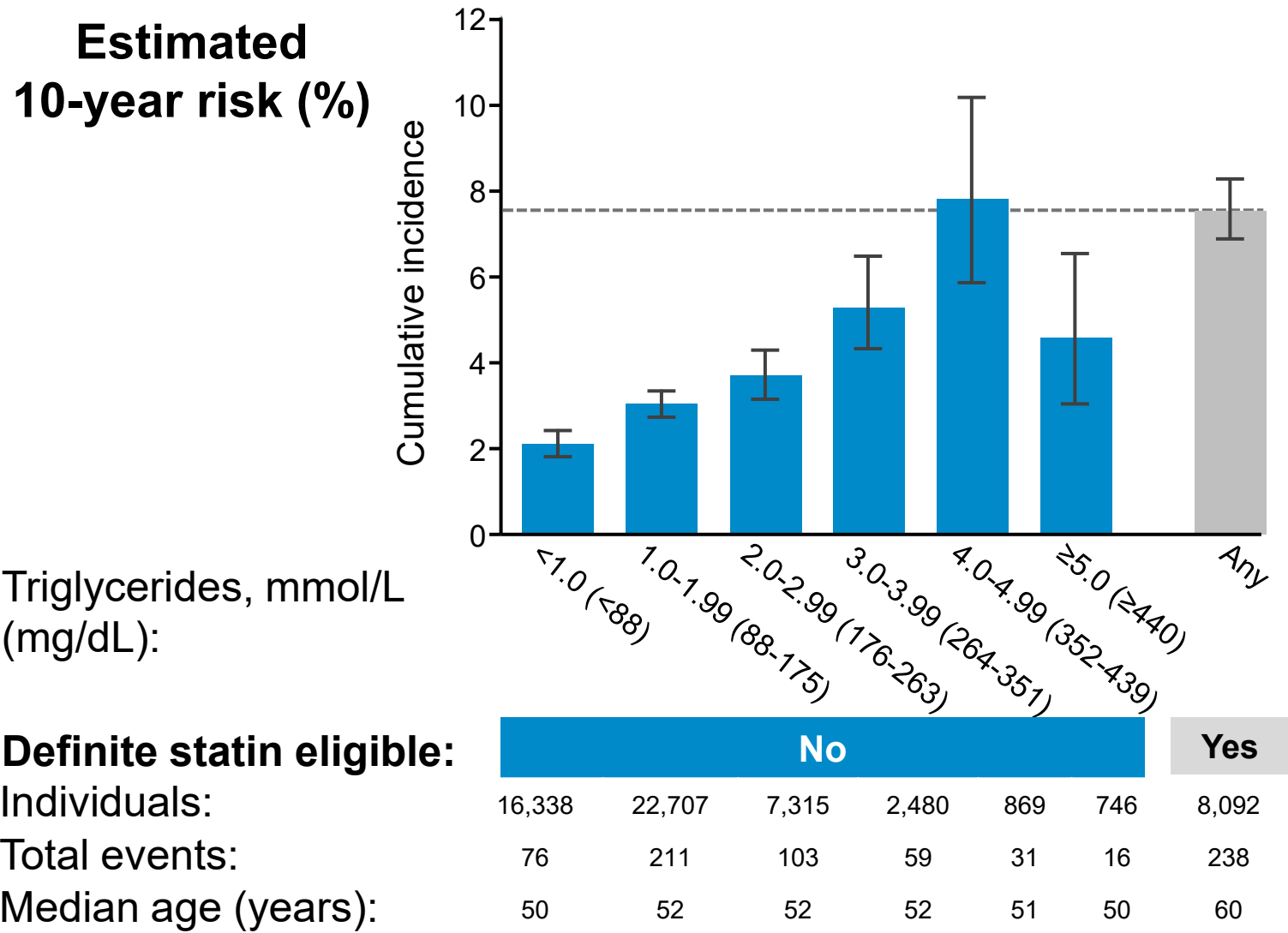
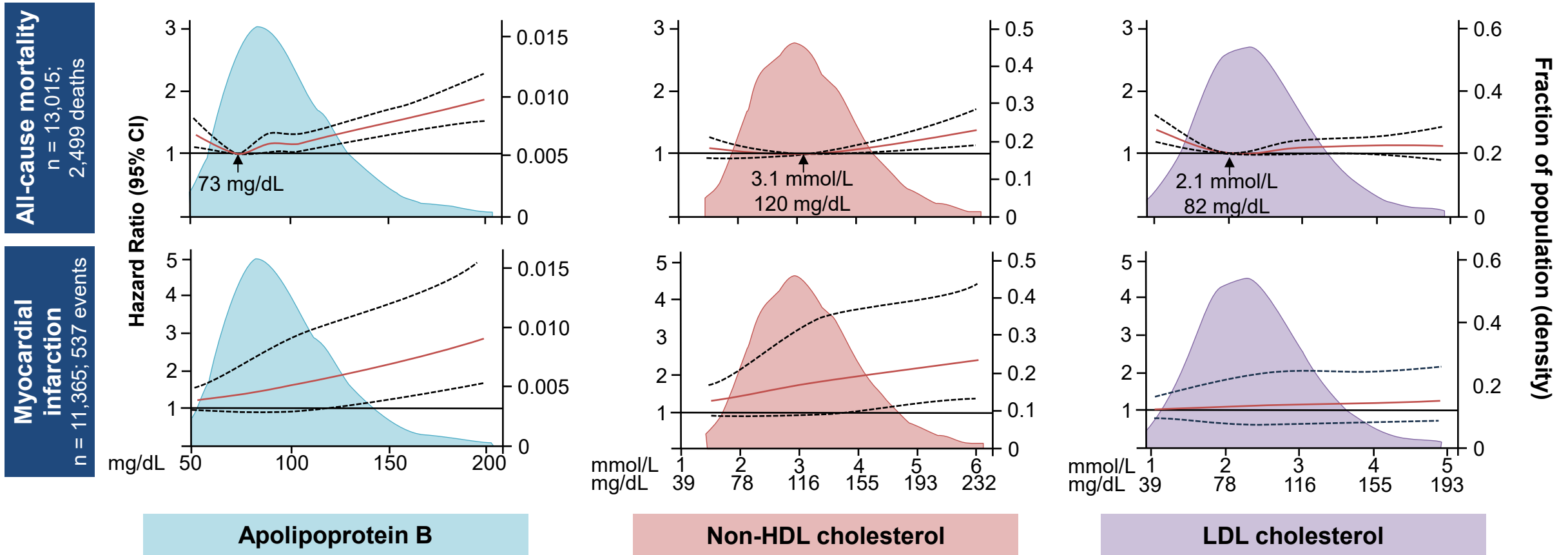


Figure adapted from Madsen et al., EHJ 2018; 39:610-9

In statin-treated patients, apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol

13,015 individuals from the Copenhagen General Population Study with 8-year follow-up

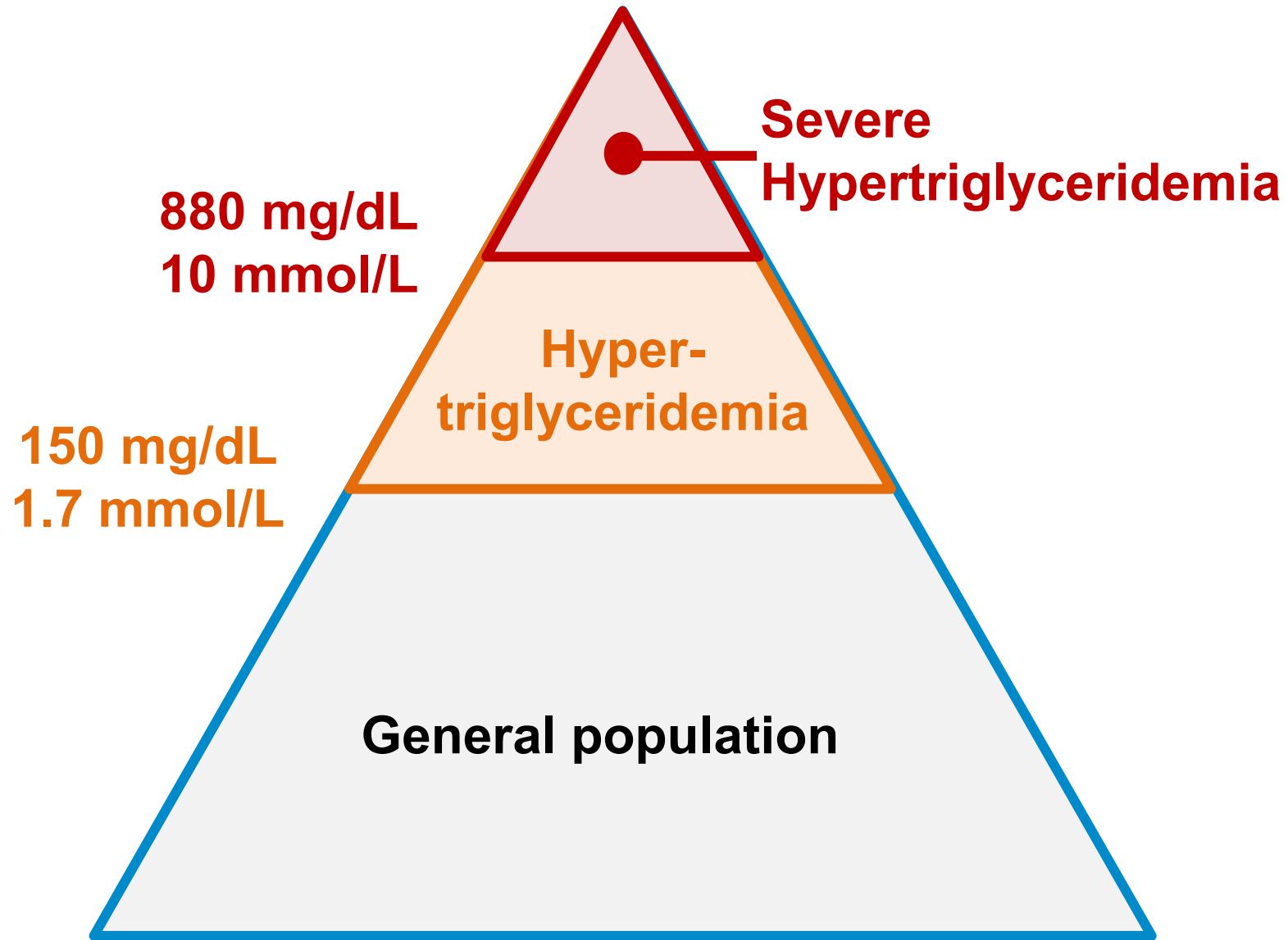


NP-51735

* Based on restricted cubic spline regressions.

† No association HR 1.0.

Figures adapted from Johannesen et al. *JACC* 2021;77(11):1439-50.



Monogenic HTG
(e.g. FCS)
Polygenic HTG

Step 1

Exclude secondary causes of hypertriglyceridemia

Lifestyle



- High energy diet
- Increased alcohol consumption

Comorbidities & medical conditions



- Hypothyroidism
- Renal disease
- Paraproteinemia
- Systemic lupus erythematosus
- Obesity
- Metabolic syndrome
- Insulin resistance
- Diabetes mellitus
- Pregnancy

Medications



Examples: corticosteroids, oestrogen, tamoxifen, thiazides, cyclophosphamide, protease inhibitors, antipsychotic agents

Step 2

Lifestyle

Approximate effect size of lifestyle changes on serum triglycerides

Intervention	Lowering of triglycerides	PMID
Alcohol abstinence	Variable response Up to 80% in subjects with high TG and excess intake	6736783 4359737
Weight loss	Approximately 8 mg/dL (0.1 mM/L) per kg weight loss	27324830 1386186
Aerobic exercise	10–20%	17533202
n3-PUFA (e.g. fish, flaxseed)	10–15%	16287956

PMID is the PubMed identifier of the respective literature.

Step 3

**Drugs that lower LDL-C and ASCVD risk
without large effects on serum triglycerides**

**Statins, Ezetimibe, Bempedoic-Acid,
PCSK9 Inhibitors**

Effects on serum triglycerides

Therapy	TG Lowering
Lifestyle changes	Variable; up to 70%
Weight reduction	Variable; up to 70%
Diabetes control	Variable; up to 70%
Fibrates	20-50% but RCT neutral
Omega-3 fatty acid mix	20-50% but RCT neutral
Eicosapentaenoic acid (EPA) 4g	18.3% positive RCT
MCT-Fat	Variable no RCT
Statins	10-20%
Ezetimibe	5-10%
PCSK9-Inhibitors	10-20%

Niacin does not reduce ASCVD risk

HPS2-THRIVE: No Effect of ER-Niacin+Laropiprant

ER niacin + laropiprant vs placebo

screened n=51,698; randomized n=25,673

patients with pre-existing cardiovascular disease treated with statin/ezetimibe

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Please refer to the original cited publication for the complete figure.

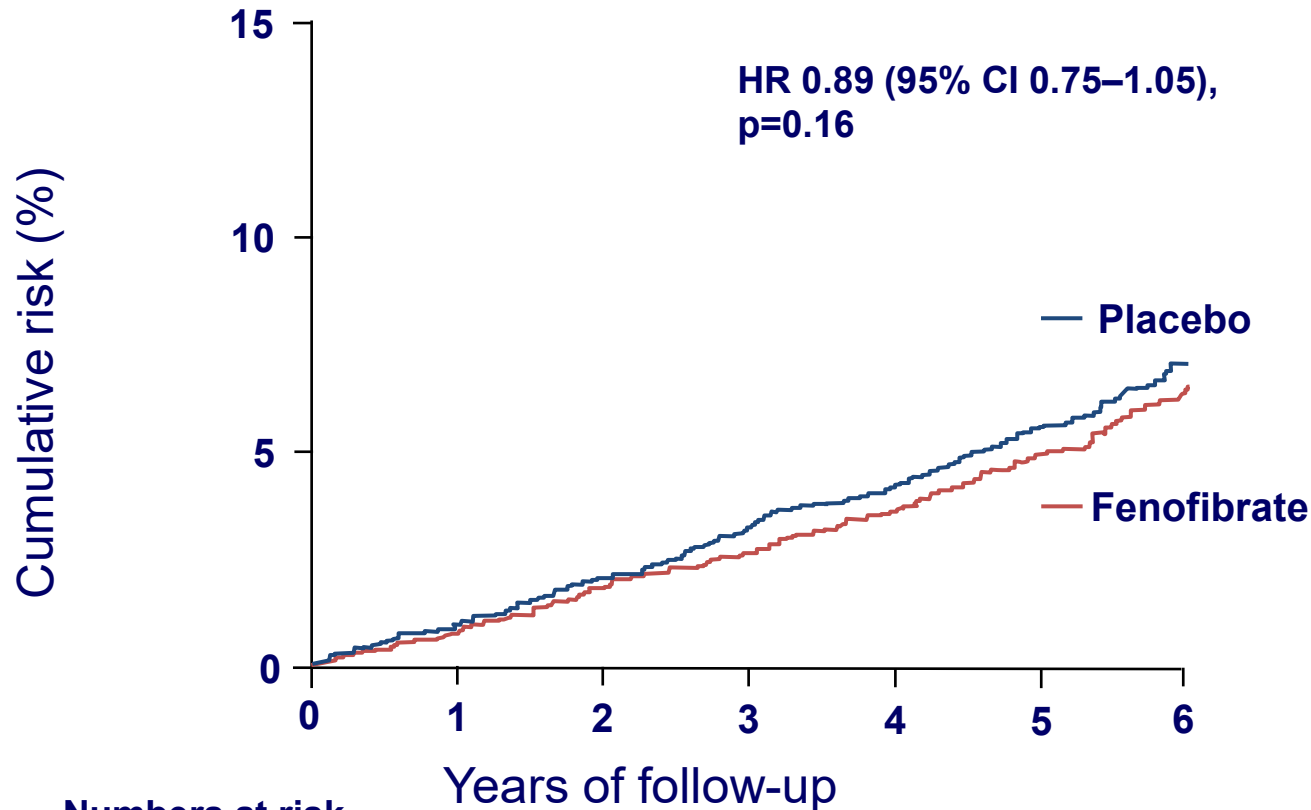
- Patients suffering MACE event over 4 years of follow-up:
14.5% with ER-niacin + laropiprant vs 15.0% with placebo
- Risk ratio 0.96 (95% CI 0.90 – 1.03), logrank P=0.29

no effects in low HDL / high TG subgroups

Fenofibrate does not reduce cardiovascular events

FIELD; n=9795 with DMT2, not taking statin therapy at study entry, 5 years follow-up

CHD events (non-fatal MI & CHD death)



Numbers at risk

Placebo	4900	4835	4741	4646	4547	2541	837
Fenofibrate	4895	4837	4745	4664	4555	2553	850

Effect on serum lipids:

LDL-C - 5.8%

HDL-C + 1.2 %

TG - 21.9 %

Increase in pancreatitis:

0.5% vs 0.8%, p=0.031

FIELD. Lancet 2005; 366: 1849–61

Pemafibrate does not reduce ASCVD risk

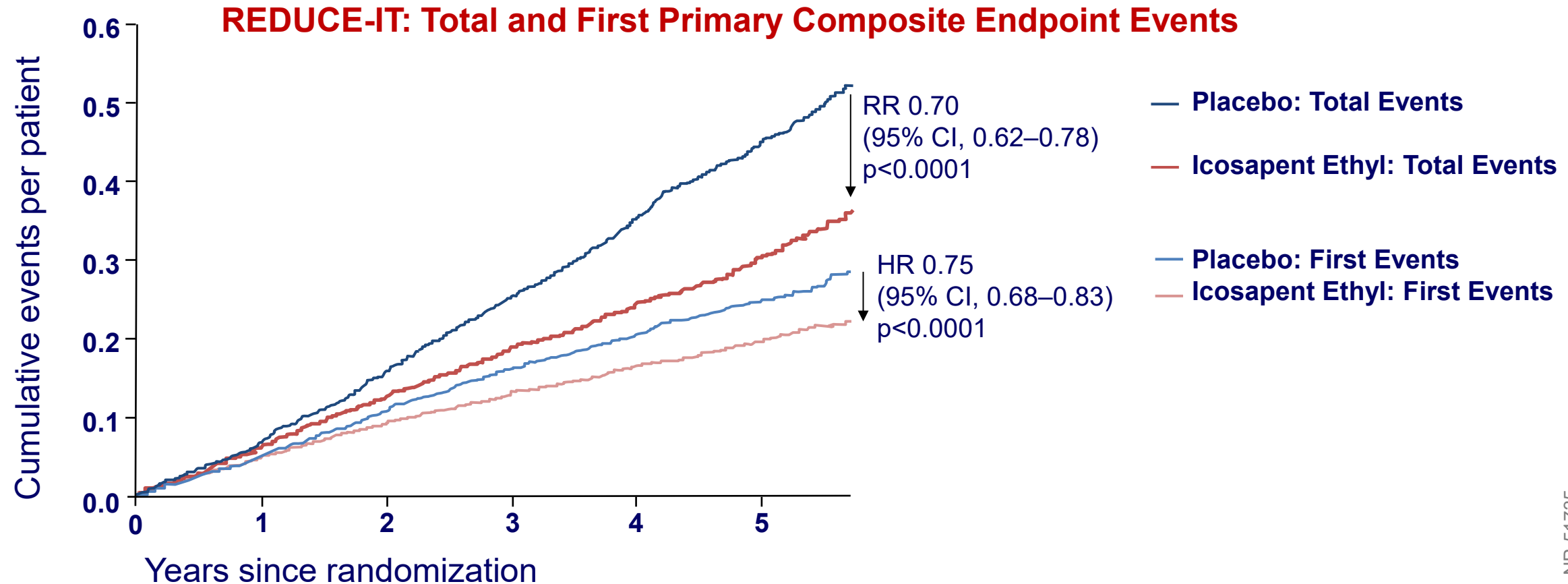
PROMINENT: n= 10,497 with diabetes T2 and triglycerides 200-500 mg/dL and HDL-C ≤40 mg/dL; 66.9% with ASCVD; Pemafibrate 0.2 mg BID vs placebo; 3.4 years follow up

*For copyright reasons, this figure has been removed from the recording.
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- **Endpoint: MI, ischemic stroke, coronary revascularisation or CV death**
 - **Hazard ratio 1.03 (95% CI, 0.91–1.15), p=0.67 over 3.4 years of follow-up**

Eicosapentaenoic acid (EPA) reduces ASCVD Risk

High risk patients with TG >150 mg/dL; n= 8179; baseline: TG 216 mg/dL, LDL 75 mg/dL
4 g icosapent ethyl 2x 2g daily or placebo (mineral oil); FU 4.9 y; TG – 19.7%; LDL-C -6.6%

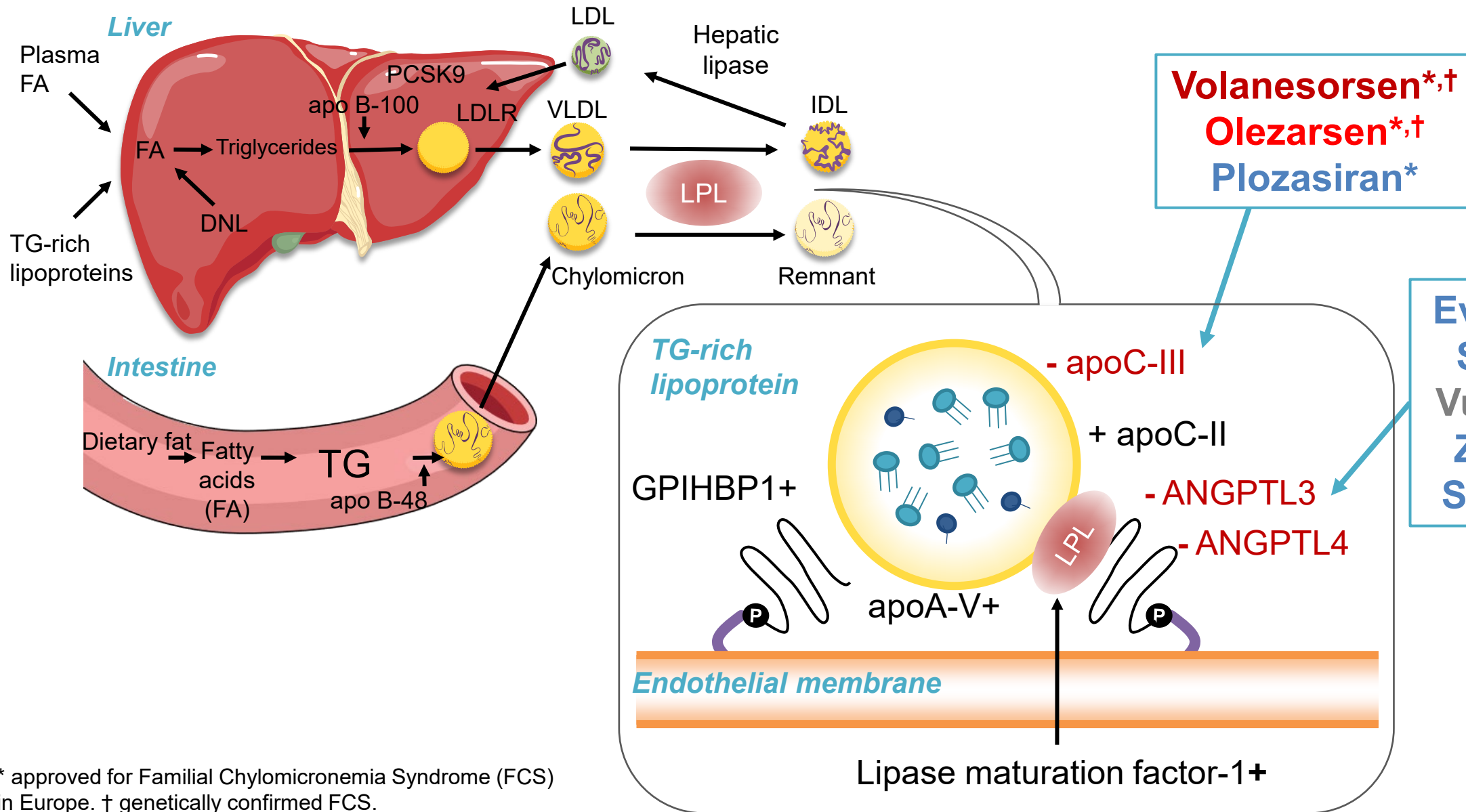


Numbers at risk

Placebo	4090	3914	3674	3236	2788	1653
Icosapent Ethyl	4089	3933	3701	3276	2861	1692

Bhatt et al., NEJM 2019; 380(1):11-22
Bhatt et al., JACC 2019; 73(22):2791-802

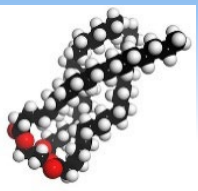
Drugs targeting TG-rich lipoproteins



* approved for Familial Chylomicronemia Syndrome (FCS) in Europe. † genetically confirmed FCS.

‡ Not approved for FCS or Hypertriglyceridemia in Europe.

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Triglycerides: A cardiologists' concern

Fasting TG >1.7 mmol/L (150 mg/dL): **risk marker for atherosclerosis and pancreatitis^{1,2}**

Therapy: **Lifestyle measures are the primary focus → stop alcohol, weight normalization, healthy diet, physical activity^{3,4}**

Medications: **Neutral data for fibrates and niacin; EPA 4g available but not reimbursed in all countries; statins / LLT used for risk reduction without major effect on TG³⁻⁵**

Unmet therapeutic need: **Targeted treatments such as apoC-III inhibitors needed to effectively control TG-associated risks^{6,7}**

1. Patel et al. *Cardiovasc Diabetol* 2022;21:102; 2. Lawler et al. *EHJ* 2020;41:86–94;
3. Parhofer & Laufs. *Deutsches Ärzteblatt* 2019 (116), 49; 4. Laufs et al. *EHJ* 2020;41(1):99-109; 5. Vascepa US Prescribing Information 2026;
6. Marston et al. *NEJM* 2025;394(5):429-441; 7. Stroes et al. *NEJM* 2024;390:781-1792



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Abbreviations

- ANGPTL3 – angiopoietin-like protein 3
- ANGPTL4 – angiopoietin-like protein 4
- ApoA1 – apolipoprotein A1
- ApoB – apolipoprotein B
- ApoC-III – apolipoprotein C-III
- ASCVD – atherosclerotic cardiovascular disease
- CE – cholesteryl ester
- CHD – coronary heart disease
- CI – confidence interval
- CM – chylomicron
- CMR – chylomicron remnant
- CV – cardiovascular
- DMT2 – type 2 diabetes mellitus
- DNL – de novo lipogenesis
- EPA – eicosapentaenoic acid
- ERN/LRPT – extended release (ER) niacin + laropiprant
- Eze – ezetimibe
- FCS – familial chylomicronemia syndrome
- FU – follow-up
- GPIHBP1 – glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
- HDL – high-density lipoprotein
- HDL-C – high-density lipoprotein cholesterol
- HR – hazard ratio
- HTG – hypertriglyceridemia
- IDL – intermediate-density lipoprotein
- LDL – low-density lipoprotein
- LDL-C – low-density lipoprotein cholesterol
- LDLR – low-density lipoprotein receptor
- LLT – lipid-lowering therapies
- Lp(a) – lipoprotein (a)
- LPL – lipoprotein lipase
- MACE – major adverse cardiovascular event
- MCT – medium-chain triglyceride
- MI – myocardial infarction
- PCSK9 – proprotein convertase subtilisin/kexin type 9
- PUFA – polyunsaturated fatty acid
- RCT – randomised controlled trial
- RLP-C – remnant-like particle cholesterol
- RR – risk ratio
- T2(DM) – type 2 (diabetes mellitus)
- TG – triglyceride
- TRL – triglyceride-rich lipoprotein
- VLDL – very-low-density lipoprotein



ApoC-III Targeting: A New Era in Triglyceride Management

Prof. Sybil Charrière

Lyon University Hospital,
Lyon, France

Disclosures

Honoraria for clinical trials, scientific work, consulting, lectures or symposia:

Amgen, Astra Zeneca, Boehringer Ingelheim, Ionis, Lilly, MSD, Novartis, Novo Nordisk, Organon, Pfizer, PTC, Sanofi, Sobi

ApoC-III is an important regulator of triglyceride metabolism¹

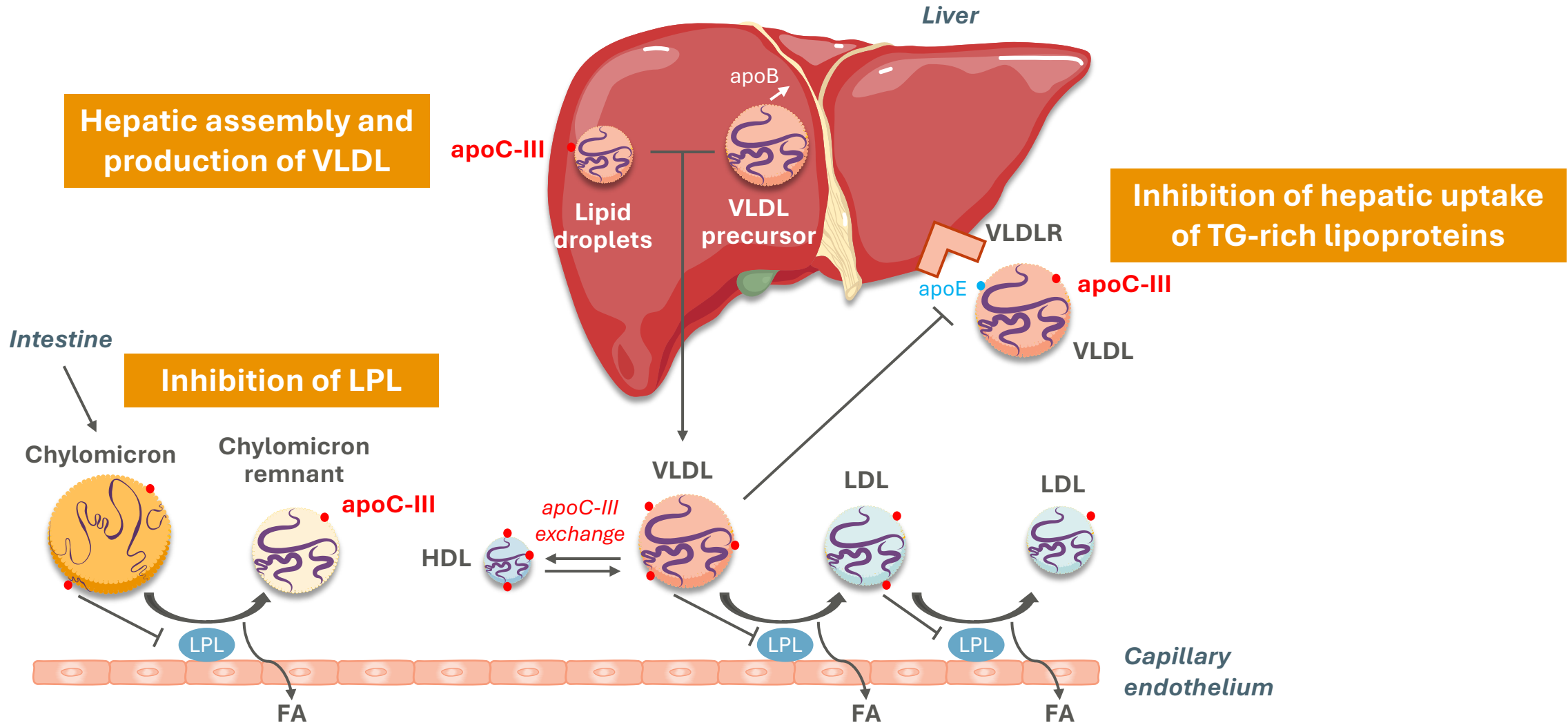


Illustration made with MindTheGraph using published data¹

ApoB, apolipoprotein B; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; FA, fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very low-density lipoprotein; VLDLR, very low-density lipoprotein receptor.

Figure adapted from Norata et al. *Trends Pharmacol Sci* 2013; 34:198-205.

Targeting apoC-III reduces TG levels and the risk of acute pancreatitis^{1,2}

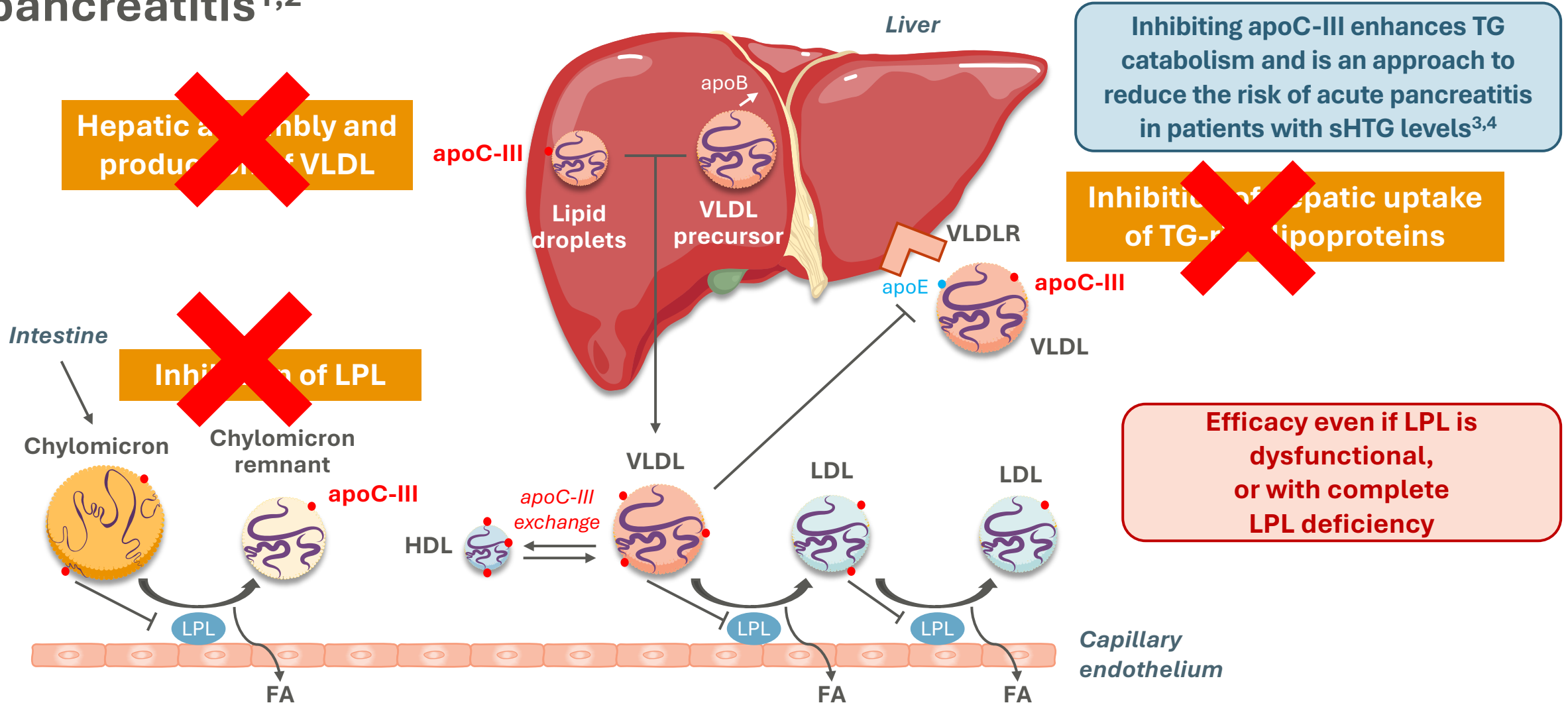


Illustration made with MindTheGraph using published data¹

ApoB, apolipoprotein B; apoC-III, apolipoprotein C-III; apoE, apolipoprotein E; FA, fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very low-density lipoprotein; VLDLR, very low-density lipoprotein receptor. Figure adapted from Norata et al. *Trends Pharmacol Sci* 2013.

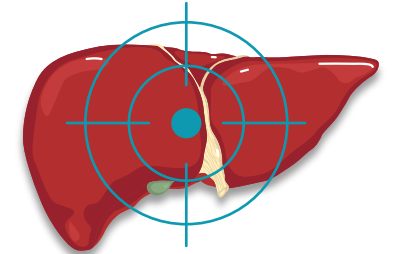
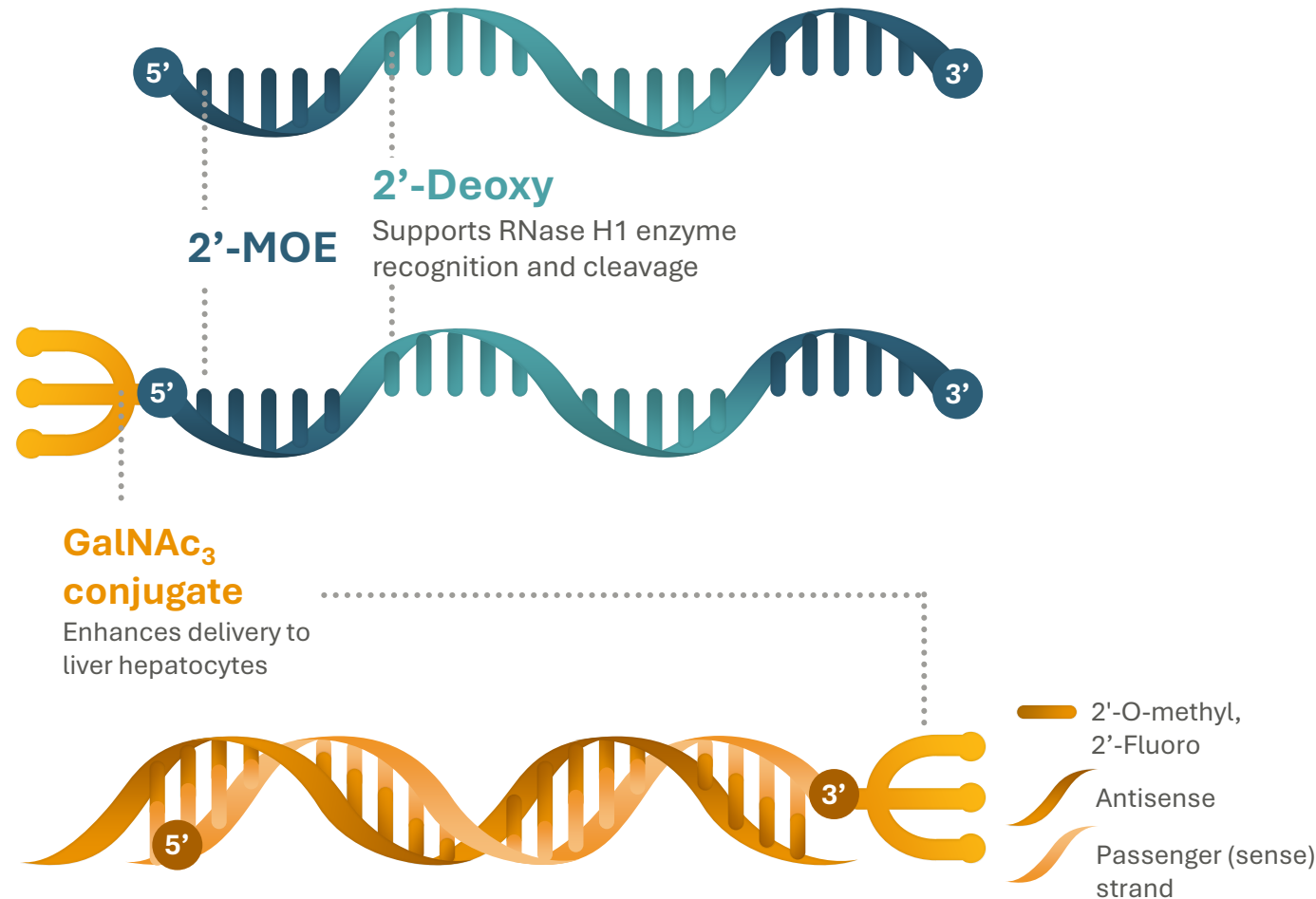
1. Norata GD, et al. *Trends Pharmacol Sci* 2013;34:198-205 2. Stroes ESG, et al. *N Engl J Med* 2024;390:1781-92 3. Gaudet D, et al. *New Engl J Med* 2014;371:2200-6 4. Mach F, et al. *Eur Heart J* 2025;46:4359-78.

RNA targeting strategies to reduce apoC-III

ASO (volanesorsen)
Approved for FCS

ASO-GalNAc₃ (olezarsen)
Approved for FCS

siRNA-GalNAc₃ (plozasiran)
Approved for FCS



The aim of directing the ASO/siRNA to hepatocytes by **GalNAc₃ conjugation** is:

- To achieve **efficacy at lower and less frequent doses**^{1,2}
- To **limit the systemic exposure** in order to **reduce off-target side effects**²

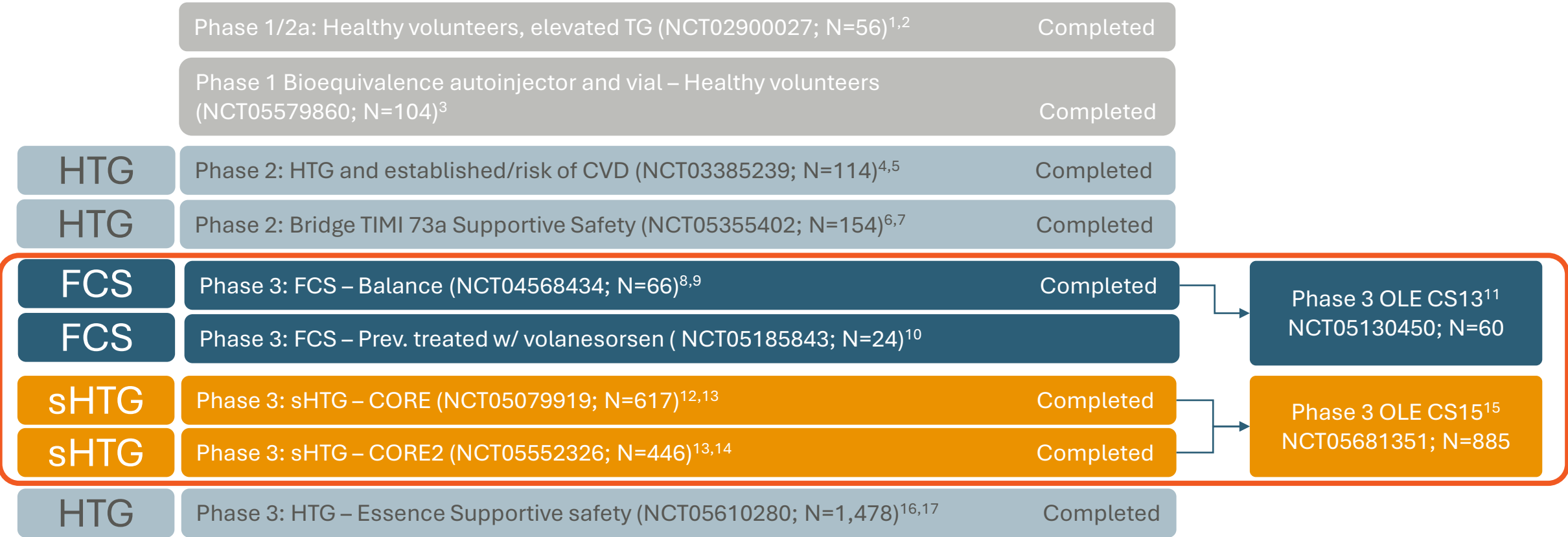
2'-MOE, 2'-methoxyethyl; apoC-III, apolipoprotein C-III; ASO, antisense oligonucleotide; GalNAc₃, triantennary *N*-acetylgalactosamine; FCS, familial chylomicronemia; siRNA, small interfering RNA. ASO figure adapted from European Medicines Agency. Assessment report Waylivra. 28 February 2019. Available from: https://www.ema.europa.eu/en/documents/assessment-report/waylivra-epar-public-assessment-report_en.pdf (Accessed 21 July 2025). ASO-GalNAc₃ figure adapted from IONIS protocol ISIS 678354-CS3, 02 August 2023. Available at: https://cdn.clinicaltrials.gov/large-docs/34/NCT04568434/Prot_SAP_000.pdf (Accessed 23 July 2025). siRNAs are usually made up of patterns of alternating of 2'-O-methyl and 2'-O-fluoro nucleotides. siRNA figure adapted from BACHEM website. Available at: <https://www.bachem.com/articles/oligonucleotides/galnac-delivery-service-liver/> (Accessed 28 August 2025).

1. Crooke ST, et al. *Nucleic Acid Ther* 2019;29:16-32 2. Brinton EA, et al. *Atherosclerosis* 2025;403:119114.

Olezarsen: Extensive clinical development programme in FCS and sHTG¹⁻²⁰



Approved: **US¹⁸, EU^{19*}, UK^{20*}** **Approved: US^{18,21}**



Ionis Pharmaceuticals Inc. is the sponsor of all clinical studies shown on this slide, except for CS2 (NCT03385239), which was sponsored by Akcea Therapeutics (with Ionis Therapeutics as a collaborator).
*genetically confirmed FCS. CVD, cardiovascular disease; FCS, familial chylomicronemia syndrome; (s)HTG, (severe) hypertriglyceridemia; OLE, open-label extension; TG, triglyceride.
1. clinicaltrials.gov NCT02900027 2. Alexander VJ, et al. *Eur Heart J* 2019;40:2785-96 3. clinicaltrials.gov NCT05579860 4. clinicaltrials.gov NCT03385239 5. Tardif JC, et al. *Eur Heart J* 2022;43:1401-12
6. clinicaltrials.gov NCT05355402 7. Bergmark BA, et al. *N Engl J Med* 2024;390:1770-80 8. clinicaltrials.gov NCT04568434 9. Stroes ESG, et al. *N Engl J Med* 2024;390:1781-92 10. clinicaltrials.gov NCT05185843 11. clinicaltrials.gov NCT05130450 12. clinicaltrials.gov NCT05079919 13. Marston et al. *N Engl J Med* 2026;394:429-41 14. clinicaltrials.gov NCT05552326 15. clinicaltrials.gov NCT05681351
16. clinicaltrials.gov NCT05610280 17. Bergmark BA et al. *N Engl J Med* 2025;393:1279-91 18. Tryngolza (olezarsen) US FPI, Update 06 -2026 19. Tryngolza (Olezarsen) European SmPC, 17 OCT 2025
20. UK Prescribing information MHRA Products | Product results 21. FDA press release, 24 June 2026. **Olezarsen – Discovered by Ionis Pharmaceuticals Inc.**

Balance study with olezarsen in FCS: Study design¹

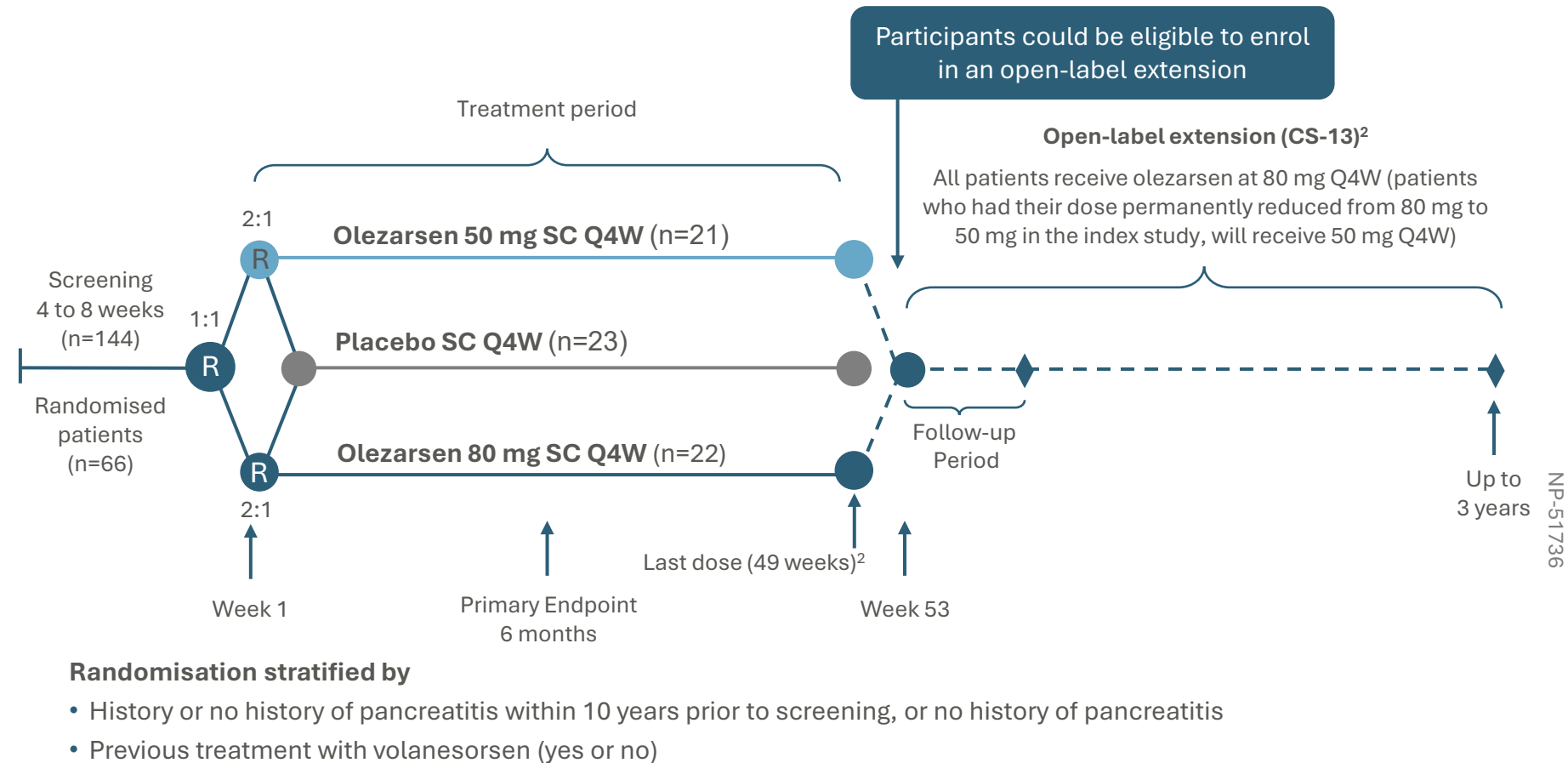
Randomised, double-blind, placebo-controlled Phase 3 trial in **66 adults** with genetically confirmed FCS and fasting TG ≥ 880 mg/dL (≥ 10 mmol/L)

STUDY POPULATION

- Age ≥ 18 years
- genetically confirmed FCS*
- Fasting TG ≥ 880 mg/dL (≥ 10 mmol/L) at screening
- History of pancreatitis ≤ 10 years prior to screening in $\geq 65\%$ of patients[†]
- Diet ≤ 20 g fat/day during the study

PRIMARY ENDPOINT:

- **Percent change in fasting TG from baseline at 6 months** (mean of weeks 23, 25 and 27)
- 1. Primary endpoint 1: for 80 mg olezarsen
- 2. Primary endpoint 2: for 50 mg olezarsen



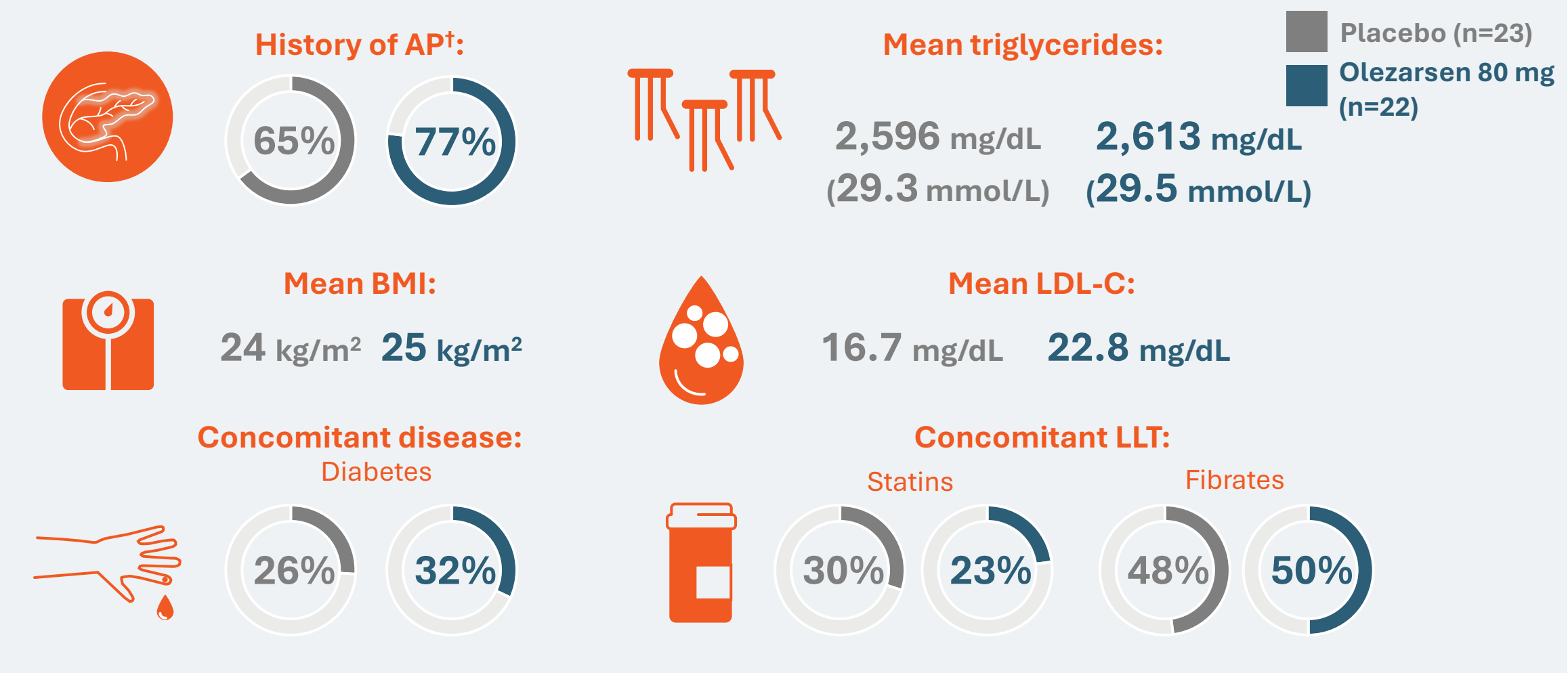
* Ho, compound / double He loss of function mutation in genes such as LPL, GPIHBP1, APOA5, APOC2 or LMF1. † Patients with no history of pancreatitis capped at 35% of enrolment.

FCS, familial chylomicronemia syndrome; Ho, homozygous; He, heterozygous; Q4W, every 4 weeks; SC, subcutaneous; TG, triglyceride.

1. Stroes ESG, et al. *N Engl J Med* 2024; 390:1781-92 (supplement) 2. Stroes ESG, et al. *N Engl J Med* 2024; 390:1781-92.

Balance study in FCS: Key baseline characteristics

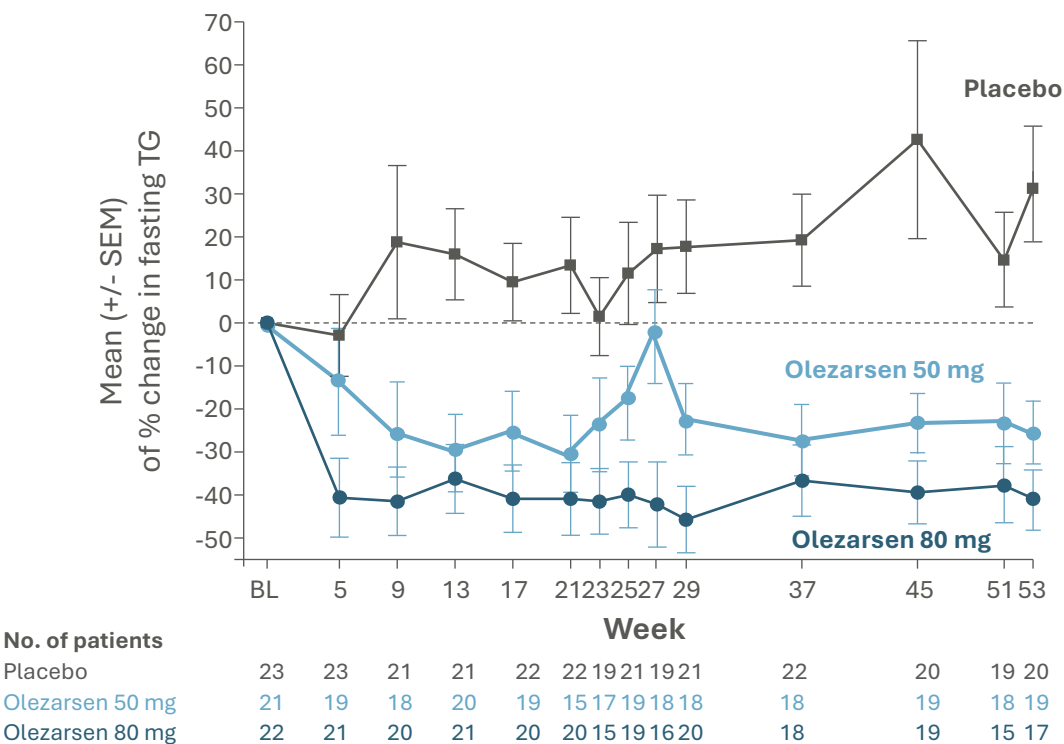
Placebo and Olezarsen 80 mg group^{1,*}



* Approved dose by EMA.
† The numbers of previous episodes of pancreatitis were obtained from the medical records; episodes were not adjudicated for patients older than 5 years of age.
AP, acute pancreatitis; BMI, body mass index; FCS, familial chylomicronemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.
1. Stroes ESG, et al. *N Engl J Med*. 2024;390:1781-92.

Balance study in FCS: Up to 59.4% reduction in triglycerides vs. placebo at month 12 in olezarsen 80 mg* treated patients^{1,2}

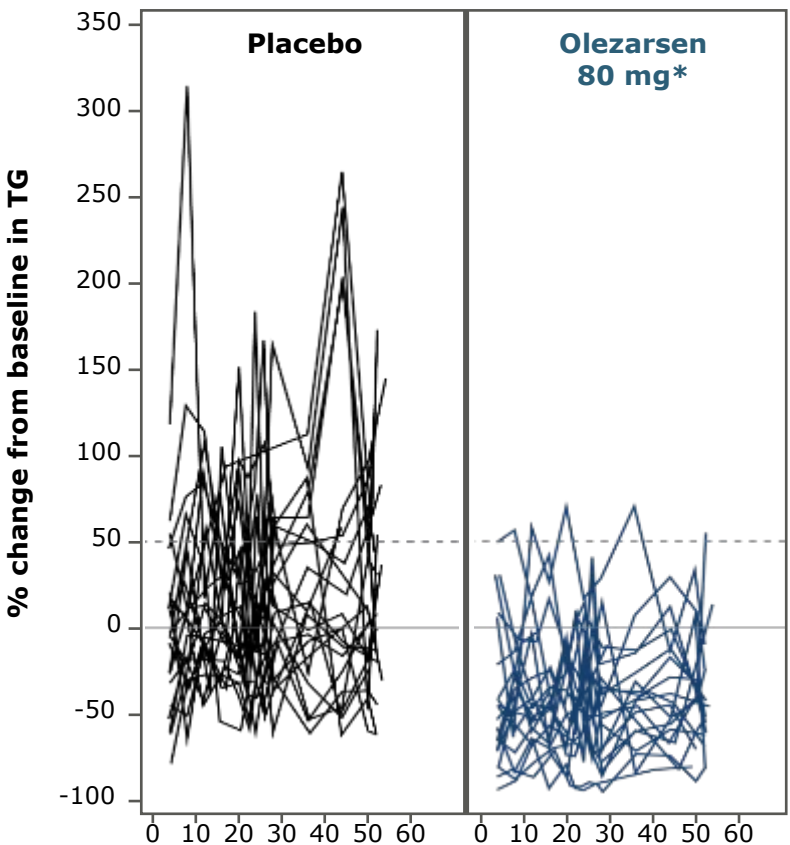
Rapid and persistent change in fasting plasma TG levels¹



LSMD vs. Placebo
6 Months
(primary endpoint)
Olezarsen 80 mg*
-43.5%
(95% CI: -69.1, -17.9), p<0.001

LSMD vs. Placebo
12 Months:
Olezarsen 80 mg*
-59.4%
(95% CI: -90.7, -28.1)

Reduced TG-fluctuations over time in individual patients (compared to placebo)²

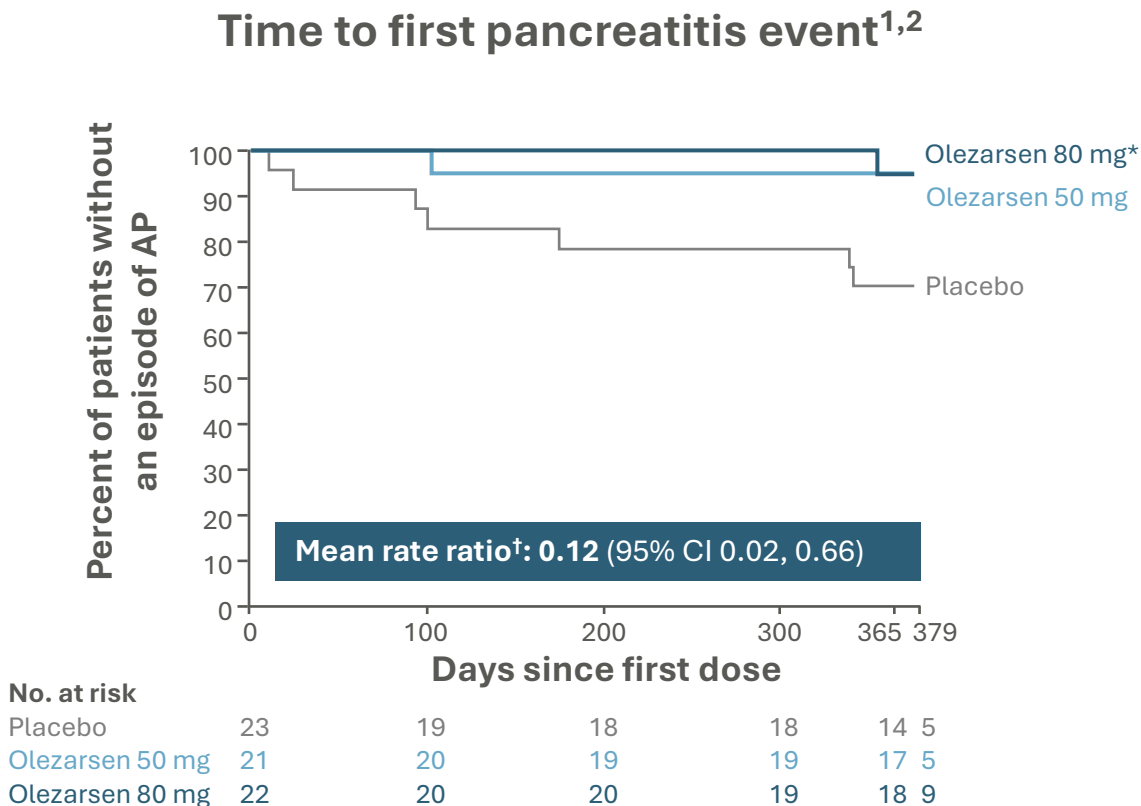


* Approved dose by EMA.

BL, baseline; CI, confidence interval; FCS, familial chylomicronemia; LSMD, least squares mean difference; SEM, standard error of the mean; TG, triglycerides.

Figures adapted from Stroes ESG, et al. *N Engl J Med* 2024. 1. Stroes ESG, et al. *N Engl J Med* 2024; 390:1781-92 2. Stroes ESG, et al. *N Engl J Med* 2024; 390:1781-92 (supplement).

Balance study in FCS: 88% reduction of pancreatitis events in olezarsen-treated patients within 12 months¹



Patients with pancreatitis events

	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg* (n=22)
Patients with events, n (%)	7 (30%)	1 (5%)	1 (5%)
Pancreatitis events, n	11	1	1
First pancreatitis event, study day	9	102	357

Fewer and ‘delayed’ pancreatitis events in olezarsen-treated patients compared to placebo

* Approved dose by EMA. † Pooled olezarsen vs placebo; exposure-adjusted event rate in the treatment group divided by the exposure-adjusted event rate in the placebo group; a ratio of 1 would indicate no difference. AP, acute pancreatitis; CI, confidence interval; FCS, familial chylomicronemia; PY, patient-year.
Figure adapted from Stroes ESG, et al. *N Engl J Med* 2024. 1. Stroes ESG, et al. *N Engl J Med* 2024; 390:1781-92.

Balance study in FCS: Favourable safety and tolerability profile^{1,2}

AEs, n (%)	Placebo (n = 23)	Olezarsen 50 mg (n = 21)	Olezarsen 80 mg* (n = 22)
Any	22 (95.7)	18 (85.7)	19 (86.4)
Related to study drug	5 (21.7)	6 (28.6)	7 (31.8)
Mild	3 (13.0)	6 (28.6)	3 (13.6)
Moderate	0	0	4 (18.2)
Severe	2 (8.7)	0	0
Leading to treatment discontinuation	0	1 (4.8)	2 (9.1) [†]
Leading to death	0	1 (4.8) [‡]	0
Any serious	9 (39.1)	4 (19.0)	3 (13.6)
Serious related to study drug	0	0	0
Adverse event of interest			
Reduction in platelet count [§]	0	0	0
≥1 Injection-site reaction in a patient	2 (9)	3 (14)	3 (14)
≥1 Influenza-like illness in a patient [#]	0	1 (5)	1 (5)
≥1 Hypersensitivity AE in a patient	3 (13)	1 (5)	0
Narrow FMQ for anaphylactic reaction	0	0	0
Narrow FMQ for hepatic failure	0	0	0

- A greater proportion of placebo-treated patients experienced SAEs
- No drug-related SAEs
- No clinically meaningful changes in platelet count or in measures of hepatic and renal function

* Approved dose by EMA. † AEs in the 80 mg group leading to treatment discontinuation were diarrhoea, vomiting, flushing, and chest discomfort in 1 patient and chills, myalgia, and trismus in the other patient.

‡ AE leading to death in the 50 mg group was considered unrelated to study treatment by the investigator. § A reduction in platelet count was defined as a reduction to levels <50,000/mm³ accompanied by a major bleeding event or clinically relevant nonmajor bleeding event or a reduction in platelet count to levels <25,000/mm³, irrespective of bleeding status. # AEs with preferred terms in MedDRA, version 26.0, include influenza-like illness, pyrexia, feeling hot, body temperature increased, chills, myalgia, or arthralgia, starting on the day of injection or the next day. AE, adverse event; FCS, familial chylomicronemia; FMQ, Food and Drug Administration medical query; SAE, serious adverse event. 1. Stroes ESG, et al. *N Engl J Med* 2024; 390:1781-92.

CORE/CORE2 studies in sHTG

Subgroup analysis ≥ 880 mg/dL (≥ 10 mmol/L) presented at EAS 2026

Two randomised, double-blind, placebo-controlled Phase 3 trials in **1,061 adults** with **fasting TG ≥ 500 mg/dL (5.6 mmol/L)** and identical design

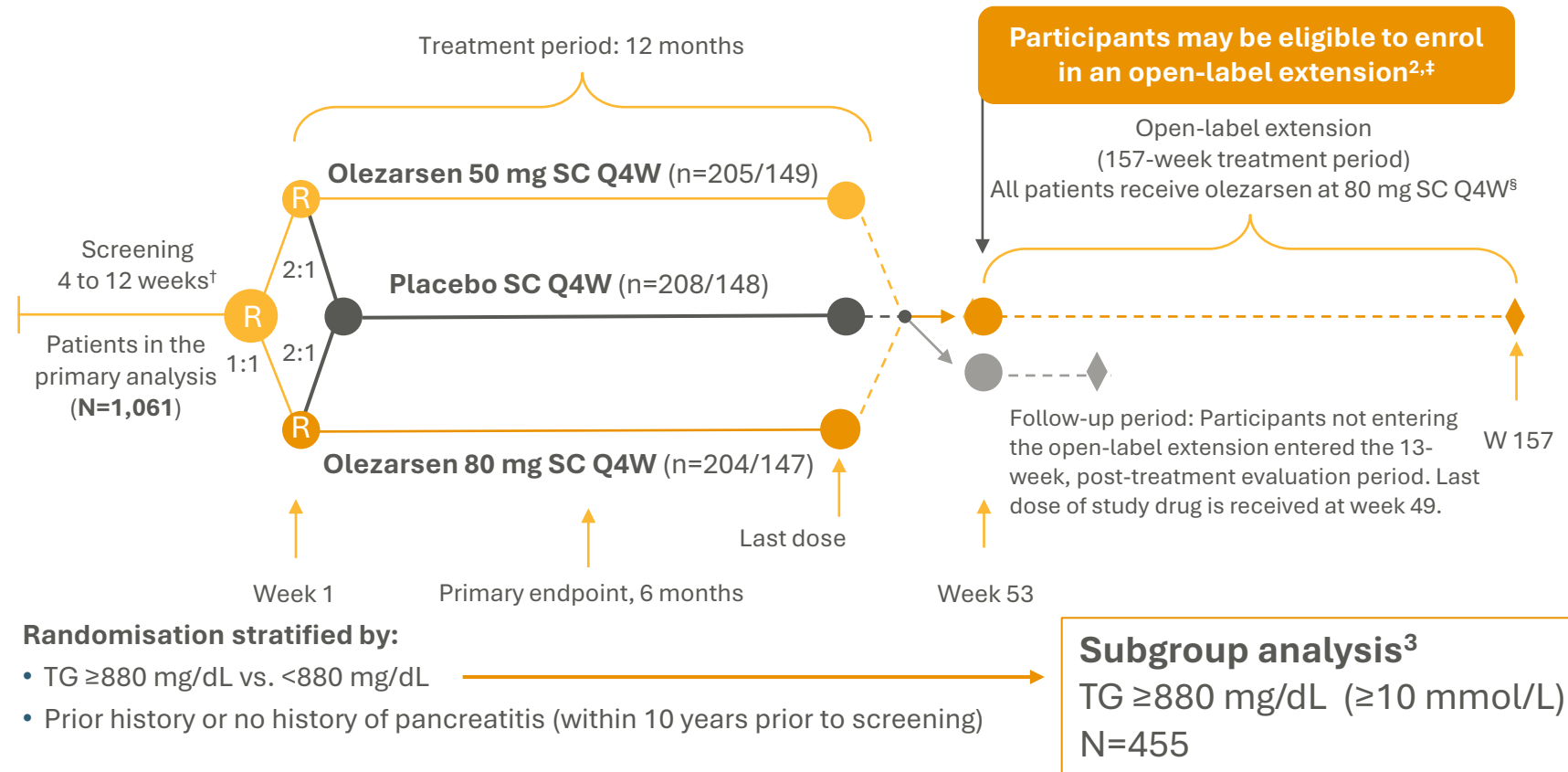
STUDY POPULATION

CORE (N=617)/CORE2 (N=444)

- Aged ≥ 18 years
- **Fasting TG ≥ 500 mg/dL (≥ 5.6 mmol/L)** at screening & qualification
- Must be on lipid-lowering therapy that should adhere to SoC per local guidelines*

PRIMARY ENDPOINT:

- Percent change from baseline in fasting TG at 6 months



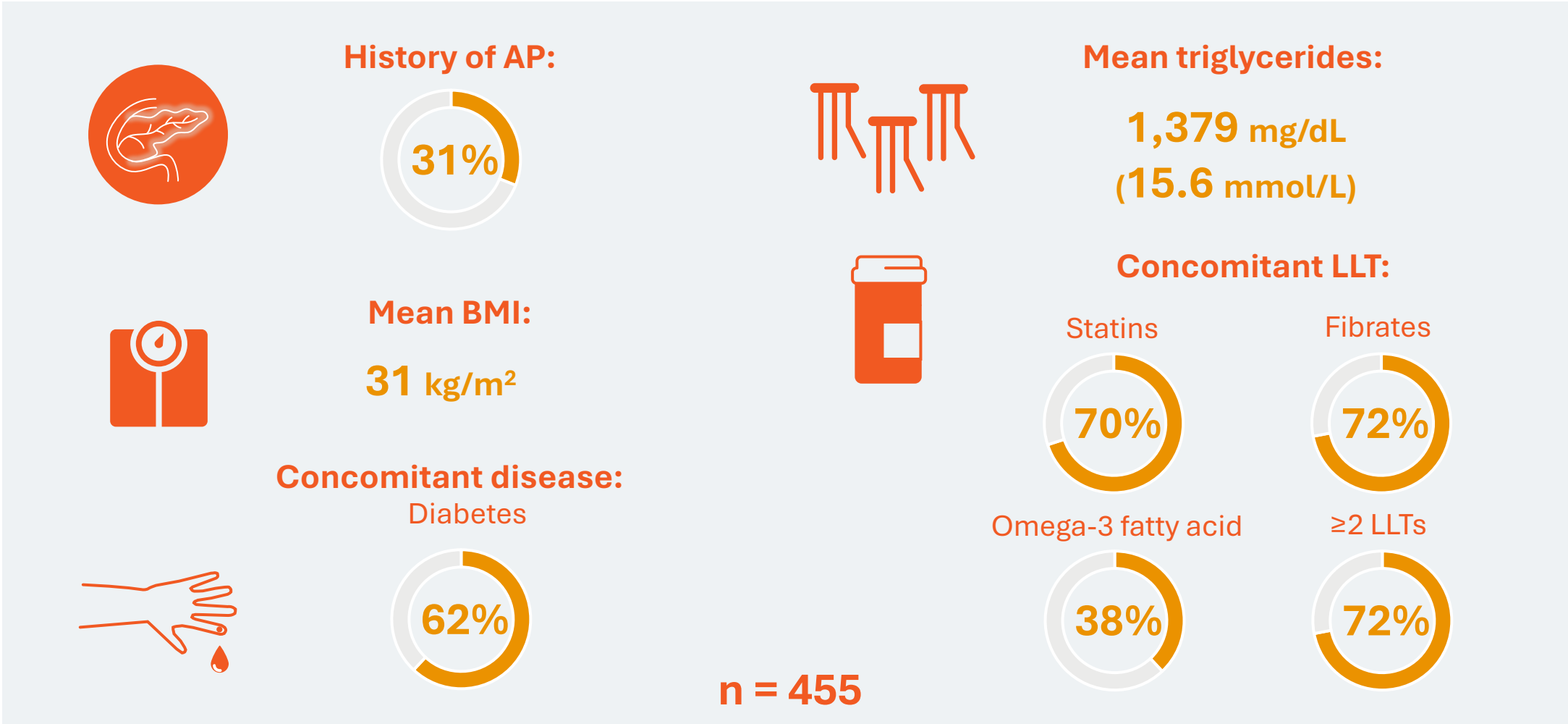
Disclaimer: Olezarsen is not an approved treatment of sHTG. Submission to EMA for label extension to sHTG ≥ 880 mg/dL (≥ 10 mmol/L) in March 2026.

* Lipid lowering therapy should be optimised and stabilised at least 4 weeks prior to screening. [†] Screening period of approximately 4 to 12 weeks including a 2-week diet and lifestyle stabilisation, followed by a 2 to 4-week qualification period. [‡] Participants not entering the open-label extension will enter the 13-week post-treatment safety evaluation period. [§] The open-label extension study is ongoing with an estimated completion in 2027.³ Patients who had their dose permanently reduced from 80 mg to 50 mg in the index study, will receive 50 mg Q4W.

MRI, magnetic resonance imaging; Q4W, every 4 weeks; SC, subcutaneous; sHTG, severe hypertriglyceridemia; SoC, standard of care; TG, triglyceride.

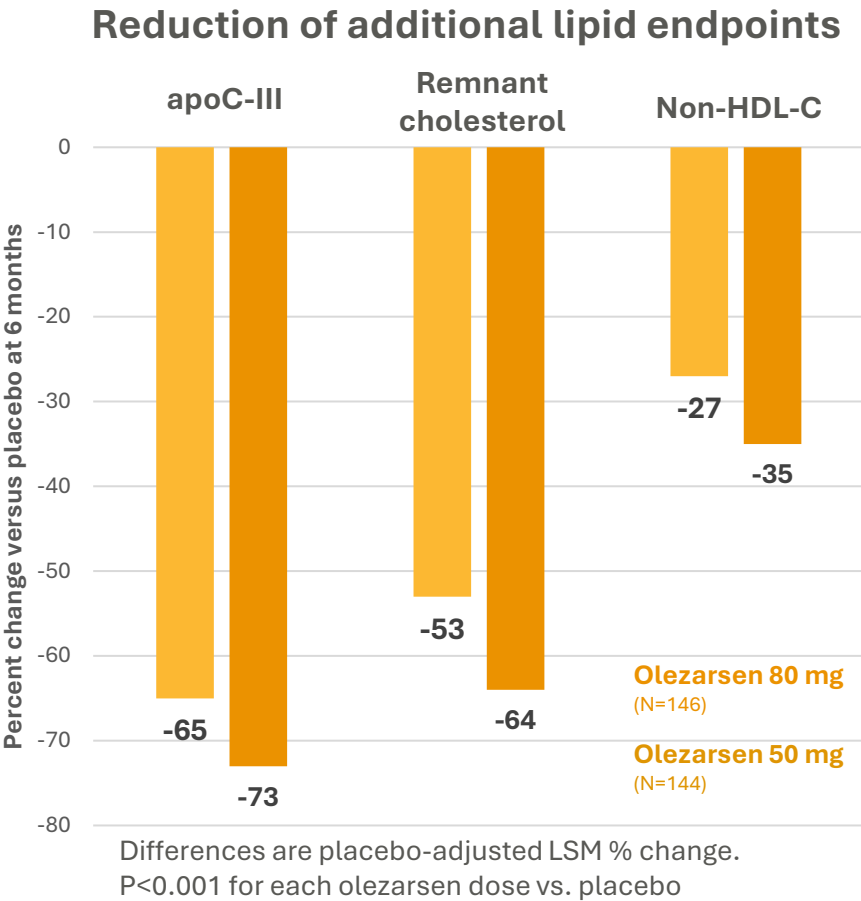
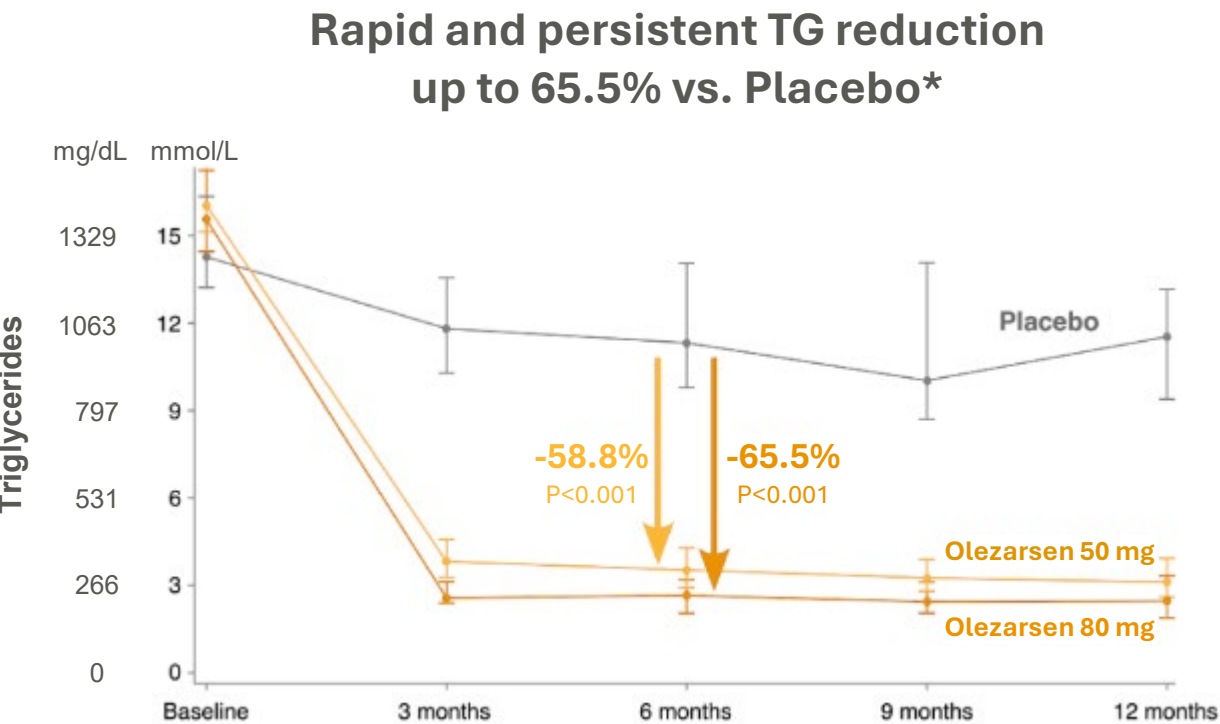
1. Marston NA, et al. *N Engl J Med* 2025;394:429-41 2. Clinicaltrials.gov NCT05681 3. Zimmerman A, et al. Presentation at EAS 2026;ID1635.

CORE/CORE2 in sHTG ≥ 880 mg/dL (≥ 10 mmol/L): Baseline characteristics reveal high comorbidity burden and concomitant LLT¹



Disclaimer: Olezarsen is not an approved treatment of sHTG. Submission to EMA for label extension to sHTG ≥ 880 mg/dL (≥ 10 mmol/L) in March 2026.
AP, acute pancreatitis; BMI, body mass index; LLT, lipid-lowering therapy; sHTG, severe hypertriglyceridemia.
1. Zimmerman A, et al. Presentation at EAS 2026;ID1635.

CORE/CORE2 in sHTG ≥ 880 mg/dL (≥ 10 mmol/L): Significant reduction of TG, apoC-III, remnant cholesterol and non-HDL-C¹



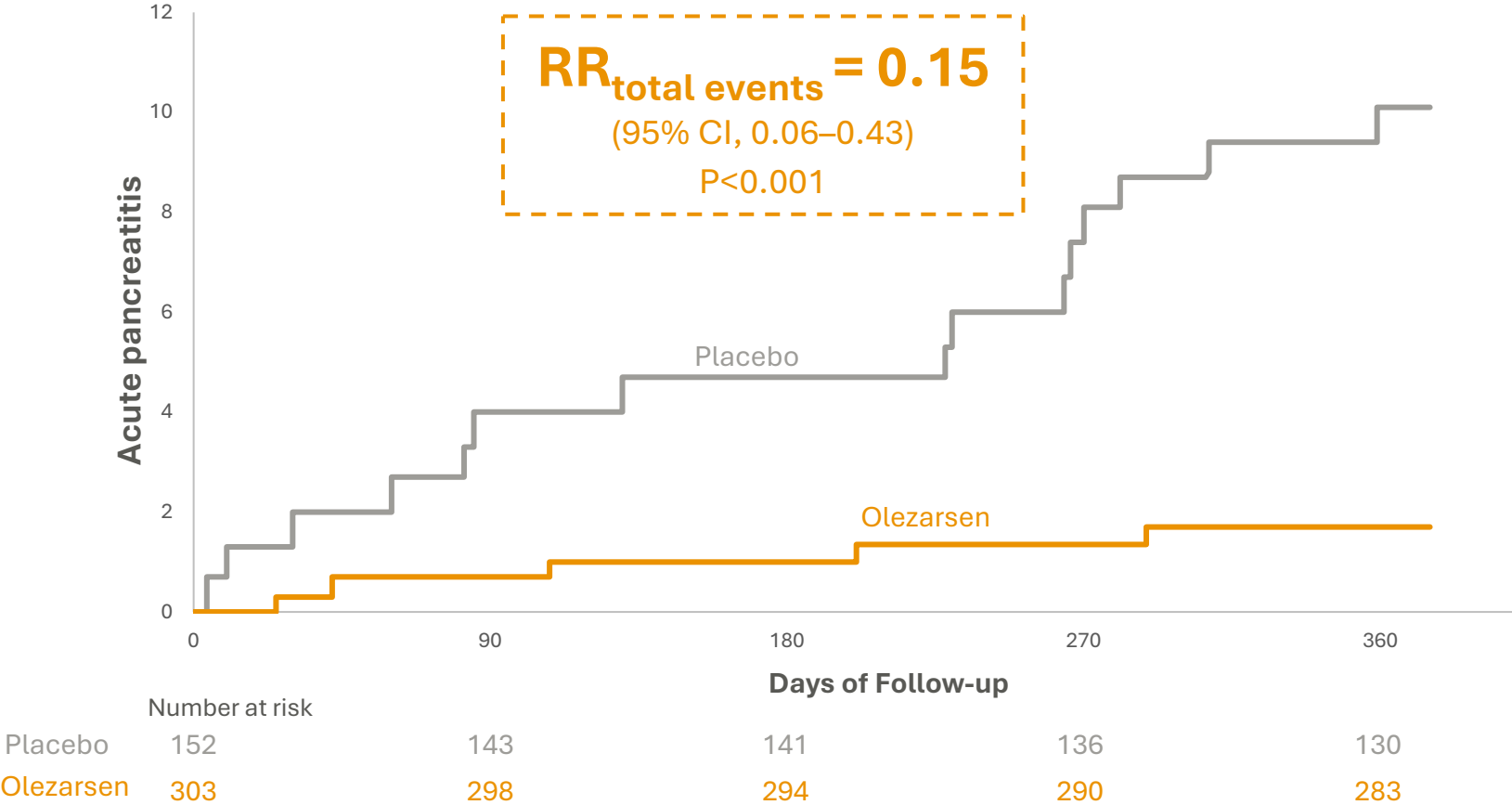
Disclaimer: Olezarsen is not an approved treatment of sHTG. Submission to EMA for label extension to sHTG ≥ 880 mg/dL (≥ 10 mmol/L) in March 2026.

* Points indicate median values; bands indicate 95% CI of the mean. Differences are placebo-adjusted least-squares mean change in TG levels at month 6. Data are pooled from CORE-TIMI 72a and CORE2-TIMI 72b and include patients with baseline TGs ≥ 880 mg/dL (≥ 10 mmol/L).

apoC-III, apolipoprotein C-III; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LSM, least squares mean; RR, relative risk; sHTG, severe hypertriglyceridemia; TG, triglycerides.

Figures adapted from Zimmerman A, et al. Presentation at EAS 2026;ID1635.

CORE/CORE2 in sHTG ≥ 880 mg/dL (≥ 10 mmol/L): 85% reduction of pancreatitis events within 12 months¹



Olezarsen reduced the rate of acute pancreatitis by 85%

	NNT over 1 year
Pooled olezarsen patients with TG ≥ 500 mg/dL (≥ 5.6 mmol/L) ² (n=705)	20
Patients with TG ≥ 880 mg/dL (≥ 10 mmol/L) ¹ (placebo n=152, pooled olezarsen n=303)	9
Patients with TG ≥ 880 mg/dL (≥ 10 mmol/L) + prior pancreatitis ² (placebo n=49, pooled olezarsen n=92)	4

Disclaimer: Olezarsen is not an approved treatment of sHTG. Submission to EMA for label extension to sHTG ≥ 880 mg/dL (≥ 10 mmol/L) in March 2026.
Time to first acute pancreatitis in the pooled olezarsen groups vs. placebo in patients with baseline TGs ≥ 880 mg/dL (≥ 10 mmol/L). The rate ratio and NNT were based on total pancreatitis events.
CI, confidence interval; NNT, number needed to treat; RR, rate ratio; sHTG, severe hypertriglyceridemia; TG, triglyceride.
Figure adapted from Zimerman A, et al. Presentation at EAS 2026;ID1635. **1.** Zimerman A, et al. Presentation at EAS 2026;ID1635 **2.** Marston NA, et al. *N Engl J Med* 2025;394:429-41, incl. supplement.

ApoC-III Targeting: A New Era in Triglyceride Management Conclusion

Pivotal studies have shown that targeting apoC-III can significantly reduce triglycerides and acute pancreatitis in patients with FCS and sHTG¹⁻³

Familial chylomicronemia syndrome (FCS) and multifactorial sHTG have different CV risk profiles

In patients with TG levels ≥ 880 mg/dL (≥ 10 mmol/L) primary prevention of acute pancreatitis events is the predominant therapeutic goal in FCS and sHTG

GalNAc₃-conjugated apoC-III antisense oligonucleotides (ASOs) have shown consistent results in FCS and sHTG (≥ 880 mg/dL [≥ 10 mmol/L]):^{1,4}

- **Reduction of TGs of up to 59–66% (vs. placebo)**
- **Reduction in acute pancreatitis events of 85–88%**
- **A favourable safety profile based on studies in >700 patients^{1,5}**

ApoC-III, apolipoprotein C-III; CV, cardiovascular; FCS, familial chylomicronemia syndrome; GalNAc₃, triantennary N-acetyl galactosamine; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. Stroes ESG, et al. *N Engl J Med* 2024;390:1781-92 2. Watts GF, et al. *N Engl J Med* 2025;392:127-37 3. Witztum JL, et al. *N Engl J Med* 2019;381:531-42 4. Zimmerman A, et al. Presentation at EAS 2026;ID1635

5. Marston NA, et al. *N Engl J Med* 2025;394:429-41.

How I Manage my Patients with sHTG

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Wiener Gesundheitsverbund
Klinik Hietzing



Für die
Stadt Wien

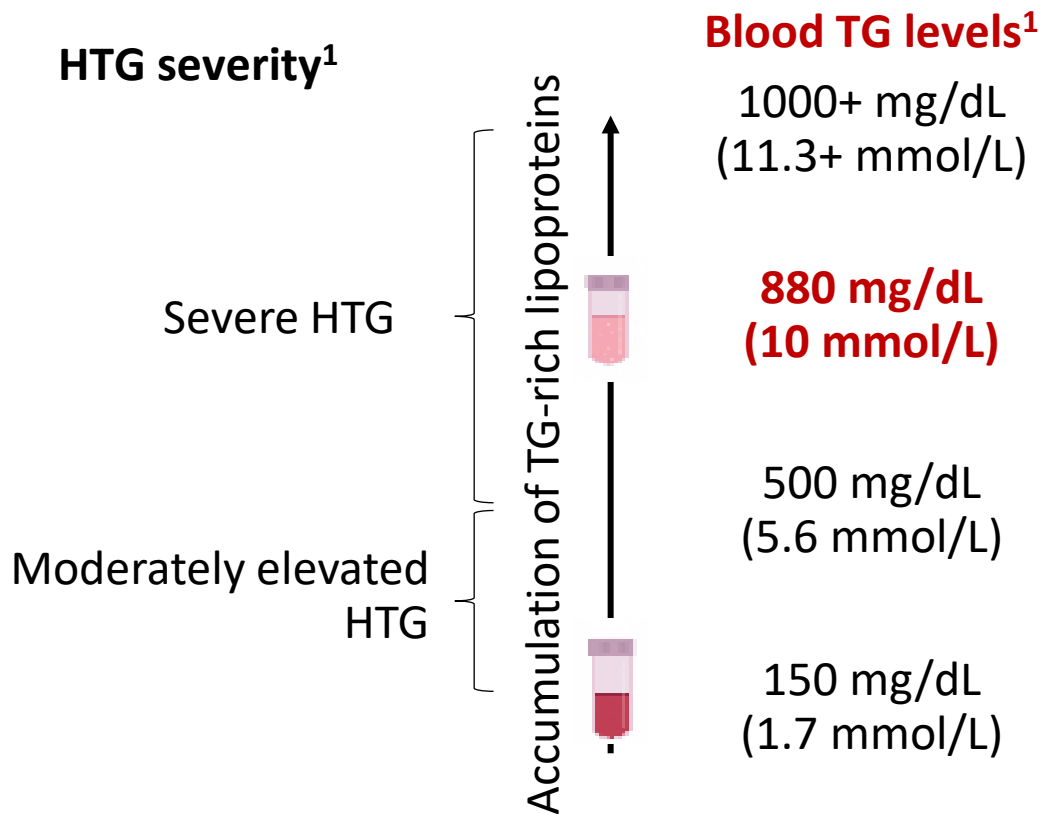


NP-51737

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- This presentation is supported by Sobi

Guidelines mandate actions to prevent acute pancreatitis for TG ≥ 880 mg/dL (≥ 10 mmol/L)



Cut-off points used to define HTG categories vary across published guidelines and consensus statements

According to the 2019 ESC/EAS Guidelines for the management of dyslipidemias²: The risk of pancreatitis is clinically significant if triglycerides are ≥ 880 mg/dL (≥ 10 mmol/L), and actions to prevent acute pancreatitis are mandatory

Triglyceride levels should be determined in all cases of acute pancreatitis, as severe hypertriglyceridemia may contribute even when the primary cause is obvious³

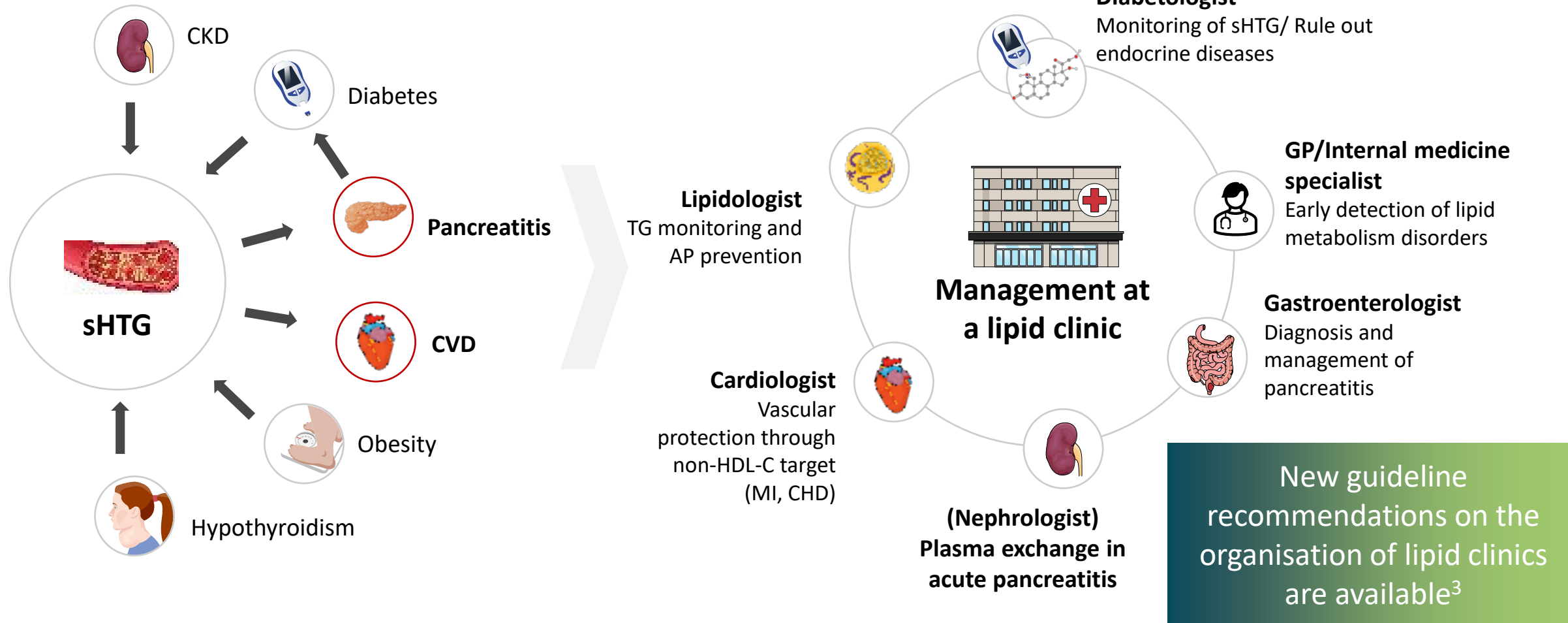


Normal TG <150 mg/dL (<1.7 mmol/L)



sHTG: TG ≥ 880 mg/dL (≥ 10 mmol/L)

Patients with sHTG face serious health issues that require multidisciplinary care^{1,2}



Clinical laboratory workup for sHTG^{1,2}

Standard lipid panel

Fasting TG, total cholesterol, LDL-C, HDL-C

Non-fasting samples are acceptable for initial screening;
fasting sample needed if TG markedly elevated

ApoB and non-HDL-C

Recommended in patients with high TG, DM, obesity, or very low LDL-C

ApoB levels combined with TG/cholesterol ratio distinguish FCS from multifactorial sHTG³

ApoB provides the most accurate estimate of total atherogenic particle burden

Lp(a) measurement

All adults at least once in a lifetime

Metabolic assessment and exclusion of secondary causes

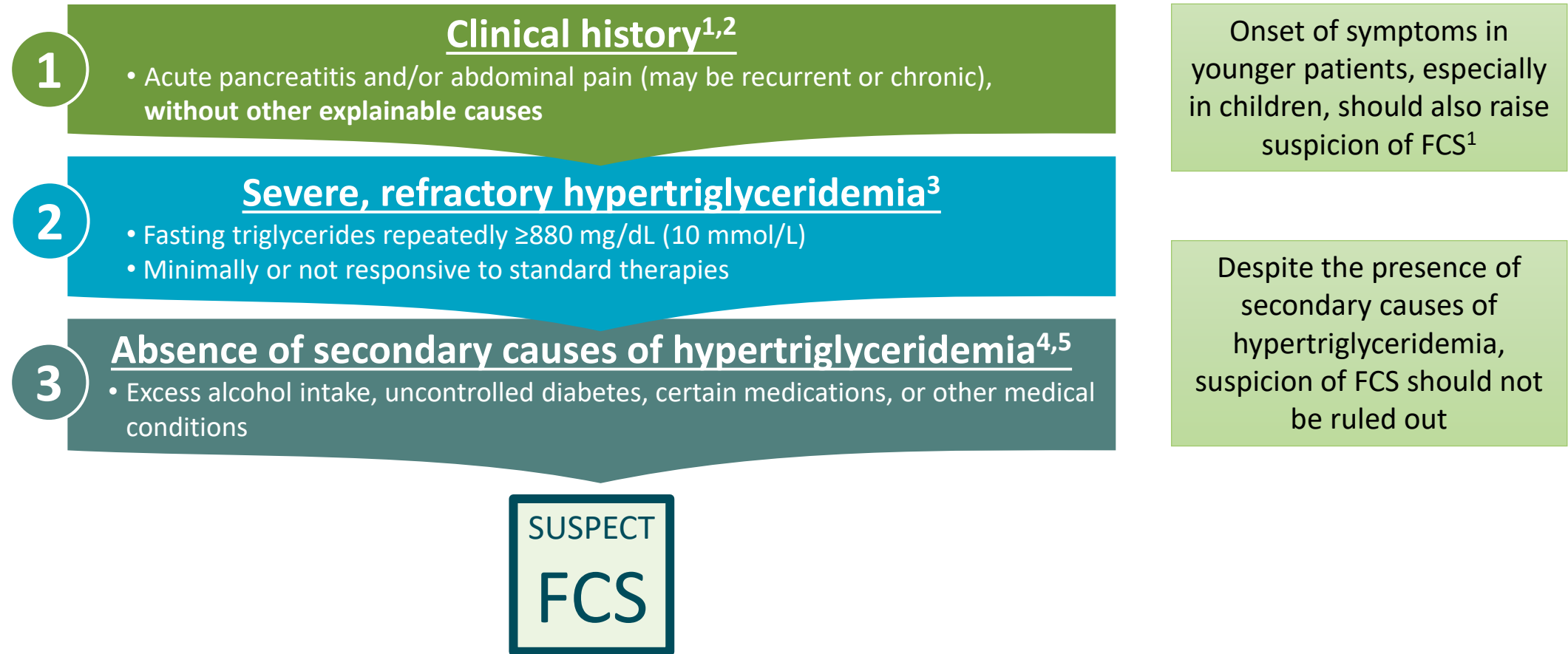
HbA1c/fasting glucose, TSH, liver and renal function, urinalysis for nephrotic syndrome^{1,2,4}

Visual inspection / Refrigerator test

Lipemic plasma appearance and lipaemia index to detect chylomicron presence

Identifying potential FCS in the clinical setting

Clinical findings that assist HCPs in identifying patients with FCS



FCS–Score: a helpful tool to assess potential FCS

In patients with triglycerides > 10 mmol/L (880 mg/dL), scoring is based on:

Triglyceride levels:

- Fasting TG >10 mmol/L (>880 mg/dL) 3 consecutive times*(+5)
- Fasting TG at least once >20 mmol/L (> 1,800 mg/dL)(+1)
- Previous TG <2 mmol/L (<180 mg/dL)(-5)

Medical history:

- History of pancreatitis.....(+1)
- Unexplained recurrent abdominal pain(+1)
- No history of familial combined hyperlipidemia.....(+1)

Differential diagnosis:

- No secondary factors[†] (except pregnancy[‡]/OO)(+2)
- No response (<20%) to hypolipidemic treatment(+1)

Age at onset of symptoms:

- <40 years(+1)
- <20 years.....(+2)
- <10 years.....(+3)

FCS-Score:

≥10:	FCS very likely
≤9:	FCS unlikely
≤8:	FCS very unlikely

Genetic work-up to diagnose FCS¹⁻⁴

Genetic factors

Secondary factors

Mono-causal genetic

- LPL-deficiency
- ApoC2 deficiency
- ApoA5 deficiency
- LMF1 deficiency
- GPIHBP1 deficiency
- Additional:^{5,6} GPD-1, CREB3L3, GCKR

Multifactorial

Genetic predisposition +

- **Comorbidities** (diabetes, obesity, metabolic syndrome, kidney disease, etc.) and/or
- **Medications** and/or
- **Lifestyle** (alcohol, high-fat/high-glycaemic index diet)

Mono-causal secondary

- Very rare
 - Lymphomas
 - Autoantibodies⁷

**Familial
chylomicronemia
syndrome (FCS)**

Severe hypertriglyceridemia (sHTG)

ApoC2, apolipoprotein C2; ApoA-5, apolipoprotein A-5; CREB3L3, CAMP responsive element binding protein-3-like-3; GCKR, glucokinase regulatory protein; GPD-1, glycerol-3-phosphate dehydrogenase 1; GPIHBP1, glycosyl-phosphatidyl-inositol anchored high density lipoprotein binding protein 1; LMF-1, lipase maturation factor 1; LPL, lipoprotein lipase.

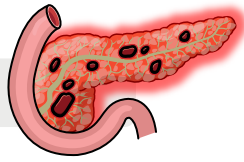
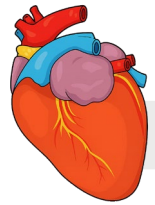
1. Karanchi H, et al. Hypertriglyceridemia *StatPearls* 2023 2. Hegele FA, et al. *Lancet Diabetes Endocrinol* 2014;2:655-66 3. Ginsberg HN. *Eur Heart J* 2021;42:4791-806

4. Laufs U, et al. *Eur Heart J* 2020;41:99-109 5. Bashir B, et al. *Metabolites* 2023;13:621

6. D'Erasmus L, et al. *Arterioscler Thromb Vasc Biol* 2019;39:2531-41

7. Berglund L, et al. *J Clin Endocrinol Metab* 2012;97:2969-89.

How to manage sHTG patients¹



Patient with elevated TG

- Define and achieve LDL-C goal*
- Define non-HDL-C goal
- Exclude/treat secondary causes of HTG[†]
- Implement lifestyle changes

Non-HDL-C goal not achieved TG elevated

TG <10 mmol/L (<880 mg/dL)

Primary goal: CV risk reduction

Depending on overall CV risk, evaluate for further non-HDL-C reduction:

- Consider further LDL-C reduction[‡]
- Consider fibrate and/or omega-3 fatty acids

TG ≥10 mmol/L (≥880 mg/dL)

Primary goal: prevention of pancreatitis

Further TG reduction is required:

- Intensify lifestyle changes
- Consider fibrate and/or omega-3 fatty acids
- Consider fats containing medium-chain fatty acids
- Consult lipid clinic

TG ≥10 mmol/L (≥880 mg/dL)

ApoC-III inhibitors²

* LDL-C goal depends on absolute CV risk. † Potential causes for hypertriglyceridemia include diet, alcohol consumption, obesity, metabolic syndrome, insulin resistance, diabetes mellitus, hypothyroidism, renal disease, pregnancy, paraproteinemia, systemic lupus erythematosus and certain medications. ‡ Further LDL-C reduction will also help in achieving non-HDL-C goals.

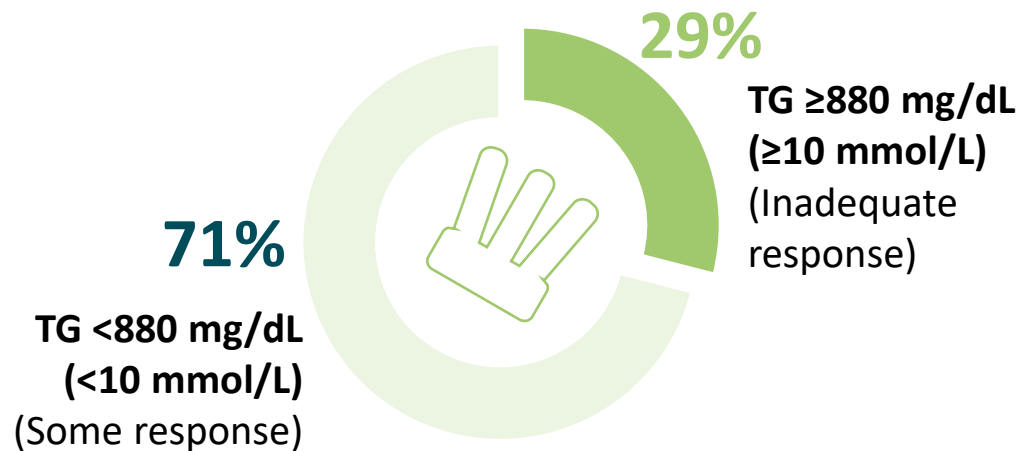
ApoC-III, apolipoprotein C-III; CV, cardiovascular; HDL-C, high-density lipoprotein-cholesterol; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein-cholesterol; sHTG, severe hypertriglyceridemia; TG, triglycerides.

Figure adapted & reproduced with permission under CC BY-NC 4.0. Copyright © 2019, The Author(s).

1. Laufs U, et al. *Eur Heart J* 2020;41:99–109 2. Mach F, et al. *Eur Heart J* 2025;46:4359–78.

Challenges in the management of sHTG

Very few patients achieve normal TG levels (<150 mg/dL/<1.7 mmol/L) with conventional lipid-lowering therapies¹



Persistently high risk for acute pancreatitis²

There are no convincing data that current lipid-lowering treatments for sHTG prevent acute pancreatitis³ and the lifelong treatment and lifestyle modifications required for managing sHTG can be challenging for patients⁴

Patient case



Patient history

66-year-old male

168 cm, 72 kg

- Family hx: Father T2DM, CHD
- Numerous recurrent abdominal pain since adolescence (*gastritis suspected*)
- **Hyperlipoproteinemia type I** (first detected at 25 years old): suspected LPL deficiency
- Recurrent **pancreatitis attacks** recorded
- **TG levels of 2,000-4,000 mg/dL (23-45 mmol/L)** despite dietary adherence

Patient case



Initial assessment

24/08/2004 (49-years-old)

- **TG: 1,894 mg/dL (21.4 mmol/L)**, cholesterol: 332 mg/dL,
- T2DM: glucose: 146 mg/dL (8.10 mmol/L), HbA1c: 7.8%
- Strict Diet initiated: low-fat, carbohydrate-reduced, no alcohol
- Tx: Fibrates, metformin

Genetic findings:* Biallelic LPL loss-of-function variants

- **LPL gene:** Exon 3 c.292G>A (rs145657341, p.Ala98Tyr) het (*probably pathogenic*)
- **LPL gene:** Intron 6 c.1019-3C>A het (*definitely pathogenic*)

Genetically confirmed familial chylomicronemia syndrome (FCS)

- **Comorbidities:** T2DM (age 49), CKD (age 52), symptomatic CHD, PCI (age 62)

Patient case

Volanesorsen

Volanesorsen start

13/03/2020



- HbA1c reduced to <6.5%
- **TG remaining around 1,300 mg/dL (14.7 mmol/L)**
- No impact of fibrates, nicotinic acid or omega-3 on TG levels
- Ongoing attacks of abdominal pain (despite maximally available therapy)
- Recurrent abdominal pain managed by patient by strict avoidance of food

Patient case

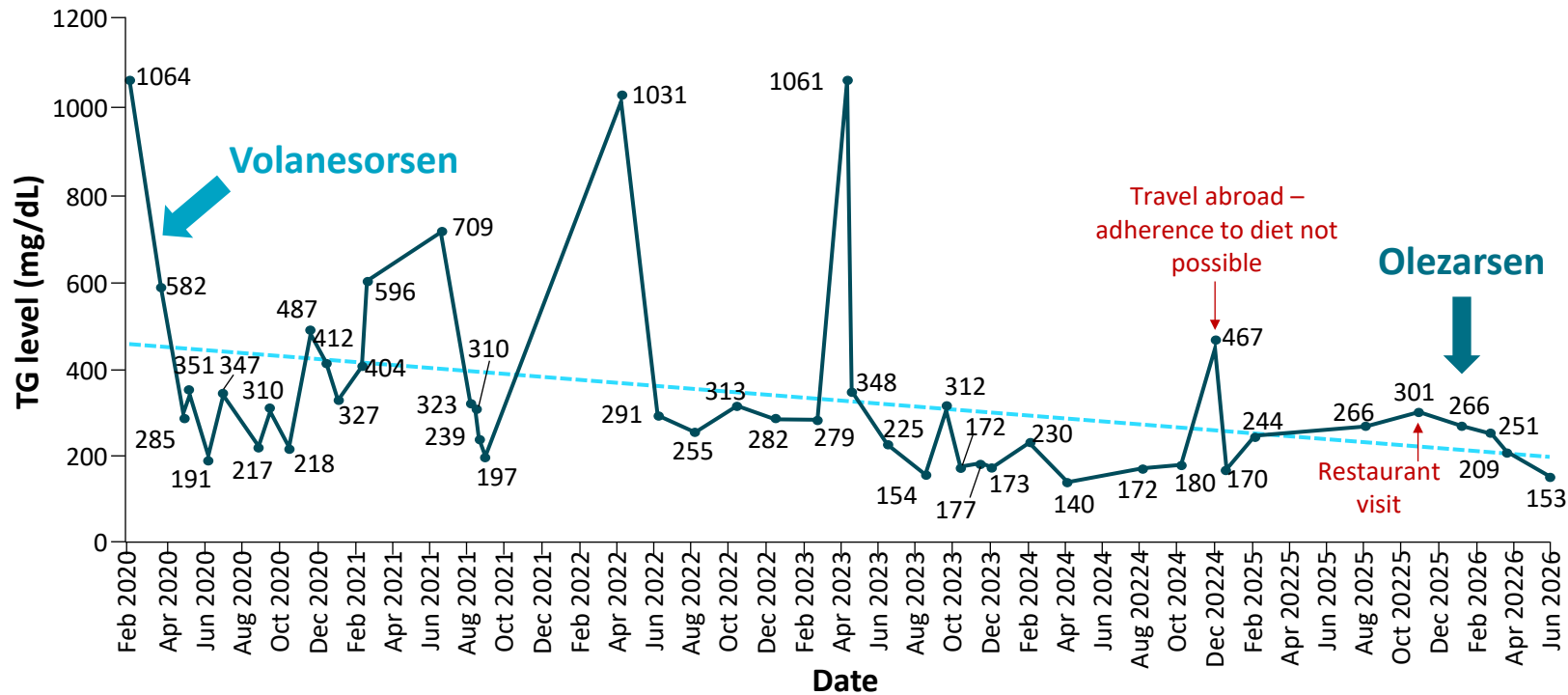


Volanesorsen
Volanesorsen start

Olezarsen
Olezarsen start

March 2020

January 2026



- Immediate TG response upon **volanesorsen** start
- Few elevated TG-levels due to dietary non-adherence
- Thrombocytes at 140 G/L
- Further TG reduction with **olezarsen** (*once monthly injections via autoinjector*)

Olezarsen vs volanesorsen: Practical aspects

Volanesorsen¹

Indication: Adjunct to diet in adult patients with **genetically confirmed FCS** and at high risk for pancreatitis, with inadequate response to diet and TG lowering therapy

Recommended dose:
285 mg SC **once weekly***

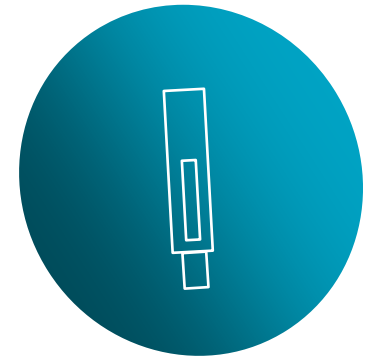


- **Platelet monitoring** every 2 weeks
- Quarterly **monitoring of liver and renal function**
- Contraindicated in patients with **thrombocytopenia**[†]

Olezarsen²

Indication: Adjunct to diet in adult patients for the treatment of **genetically confirmed FCS**

Recommended dose:
80 mg SC **once monthly**
(single-dose **pre-filled pen for auto-injection**)



- **No need to monitor** platelet count, renal or liver function
- **No contraindications** for patients with a low platelet count

* Once weekly for 3 months, following dose frequency reduction to 285 mg every 2 weeks.

† Patients with platelet count $<140 \times 10^9/L$.

FCS, familial chylomicronemia syndrome; SC, subcutaneous; TG, triglyceride.

1. Waylivra (volanesorsen) SmPC 2025 2. Tryngolza (olezarsen) SmPC 2025.

Conclusions

- sHTG is associated with a **distinct risk and comorbidity, requiring a multidisciplinary approach** to optimal diagnosis and management¹⁻³
- **Identification and management of secondary contributing factors** should always be the first step^{4,5}
- The **Clinical FCS Score** supports selection of patients for genetic testing⁶
- **ApoC-III inhibition** represents an **effective therapeutic option for FCS**, with potential applicability across broader severe hypertriglyceridemia populations⁵
- **GalNAc₃-conjugated apoC-III targeting therapies** have reduced treatment and monitoring burden while improving safety^{7,8}
- **Lifestyle modification**, particularly strict dietary fat restriction, **remains the basis of management**⁹

Thank you!



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Klinik Hietzing



Für die
Stadt Wien





Closing remarks

Prof. Ulrich Laufs

Key takeaways

- High triglycerides are an independent risk factor for cardiovascular disease and acute pancreatitis
- As of triglycerides ≥ 880 mg/dL (≥ 10 mmol/L) the risk of pancreatitis is clinically significant and actions to prevent acute pancreatitis are mandatory
- ApoC-III inhibition is transforming the treatment landscape for patients with elevated triglycerides
- Therapeutic apoC-III therapies complement, but do not replace lifestyle management

The symposium recording
will be **available on-**
demand on the ESC Online
Platform after the congress



**Thank you
for joining us**



ApoC-III inhibition: Entering a new era in
managing risks of **severe**
hypertriglyceridemia (sHTG)