

Reducing acute pancreatitis Through apoC-III inhibition in people with **severe hypertriglyceridemia**





Welcome

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Disclaimer & important information



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The symposium contains information about Sobi products.

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No identifiable patient-specific information is included.

Introductions



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Disclosures

	Prof. Raffaella Buzzetti	Prof. Laura D'Erasmus	Prof. Stefano Romeo
Research support/PI	AstraZeneca	Ionis, Novartis	AstraZeneca, Novo Nordisk
Employee			
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Reducing acute pancreatitis through apoC-III inhibition in people with severe hypertriglyceridemia



Agenda

Welcome

Prof. Raffaella Buzzetti
(Chair)

Does diabetes cause severe
hypertriglyceridemia?

Prof. Raffaella Buzzetti

Protecting the pancreas in people with
severe hypertriglyceridemia

Prof. Laura d'Erasmus

ApoC-III inhibition for acute pancreatitis prevention

Prof. Stefano Romeo

Panel discussion and conclusion

All (Moderated by Chair)



Does diabetes cause severe hypertriglyceridemia?



UMBERTO I
POLICLINICO DI ROMA



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AGENDA

1



Setting the Stage

Background

2



The Metabolic Origins of Hypertriglyceridemia

3



Is the Relationship Bidirectional?

4



From Severe Hypertriglyceridemia to Acute Pancreatitis and Diabetes

5



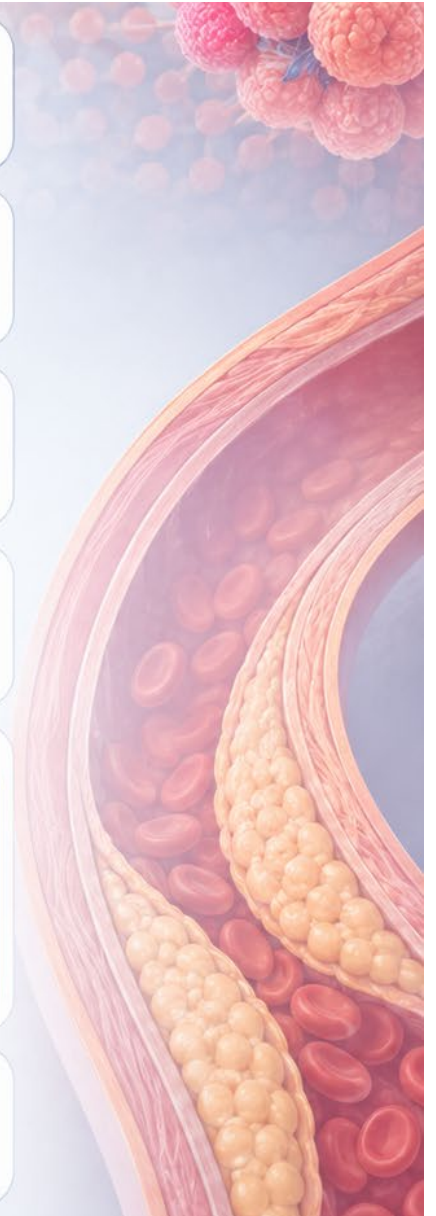
The Clinical Impact of Severe Hypertriglyceridemia

- Atherosclerosis
- Residual risk
- Neuropathy
- Association or Causation: T2D

6



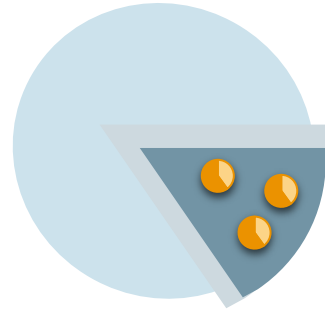
Conclusions



1 The Dyslipidemia Triad in Diabetes:

Increased LDL-C^{1,2}

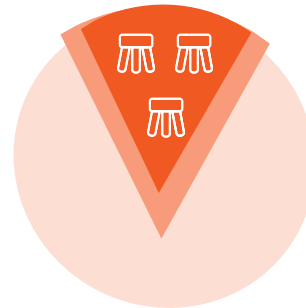
The canonical therapeutic target¹,
yet only ~1 in 4 T2DM patients
with very high cardiovascular risk
reach the LDL-C goal^{2,*}

 $2-4x$

excess in **ASCVD risk** vs
people without
diabetes¹

Decreased HDL-C³

Low and dysfunctional in people with T2DM; mean HDL-C falls from 52 to 34 mg/dL as triglycerides rise



Increased triglycerides³

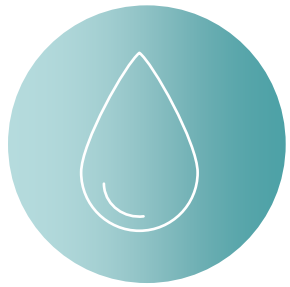
in 39% of people with T2DM³

* LDL-c < 55 mg/dL².

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

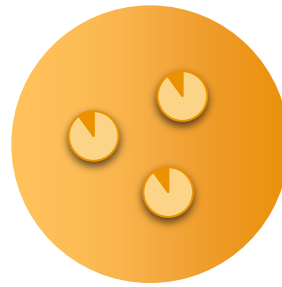
1. Federici et al. *Cardiovasc Diabetol* 2026 2. Rossi et al. *Cardiovasc Diabetol* 2025 3. Echegoyen et al. *J Diabetes Complications* 2023.

1 Pathophysiological mechanisms linking **insulin resistance** to Hypertriglyceridemia:



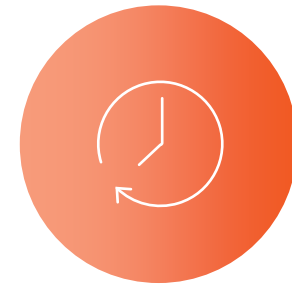
Substrate overload

Insulin no longer restrains lipolysis: increased free fatty-acid flux to the liver adding to liver fat and hyperglycemia^{1,2}



Hepatic VLDL overproduction

Pathway-selective insulin resistance drives *de novo* lipogenesis and overproduction of large, triglyceride-rich VLDL, with increased apoC-III^{1,3}

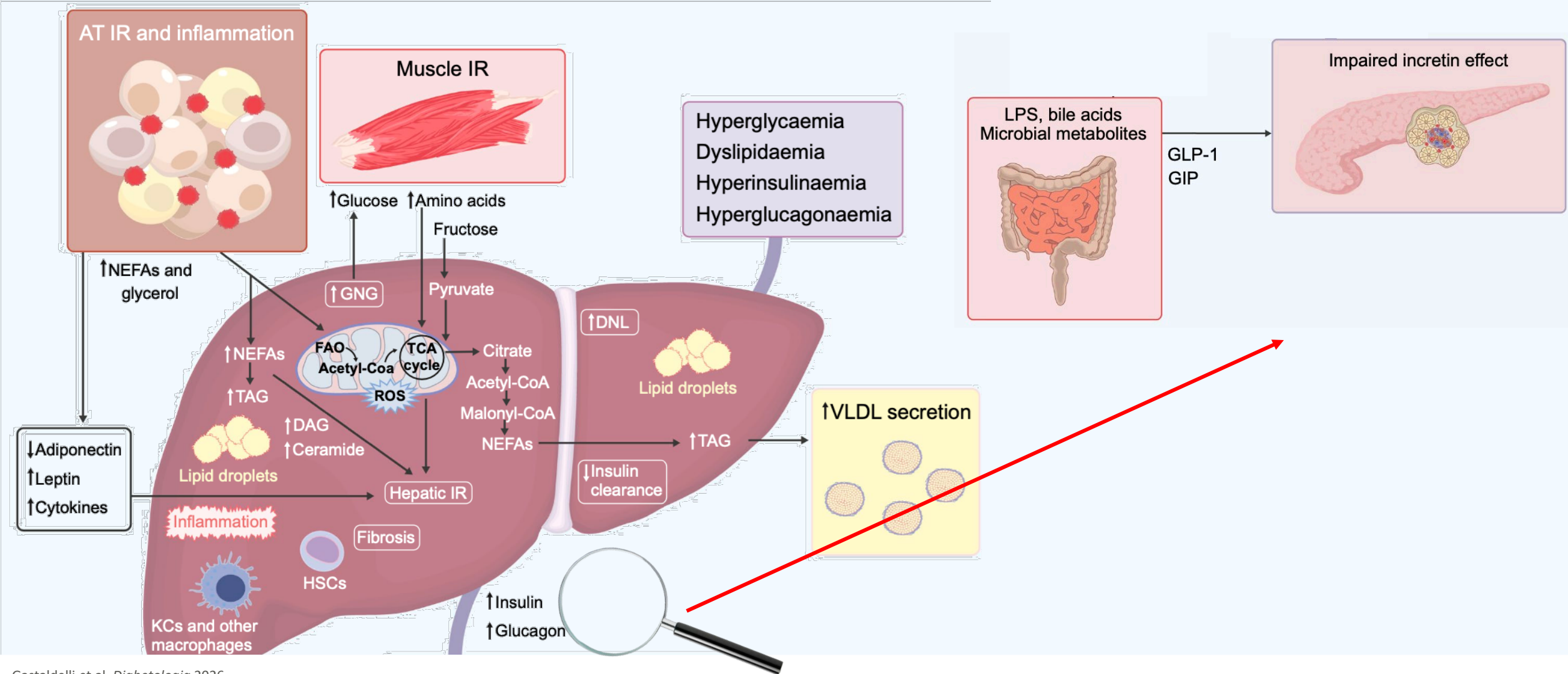


Impaired clearance

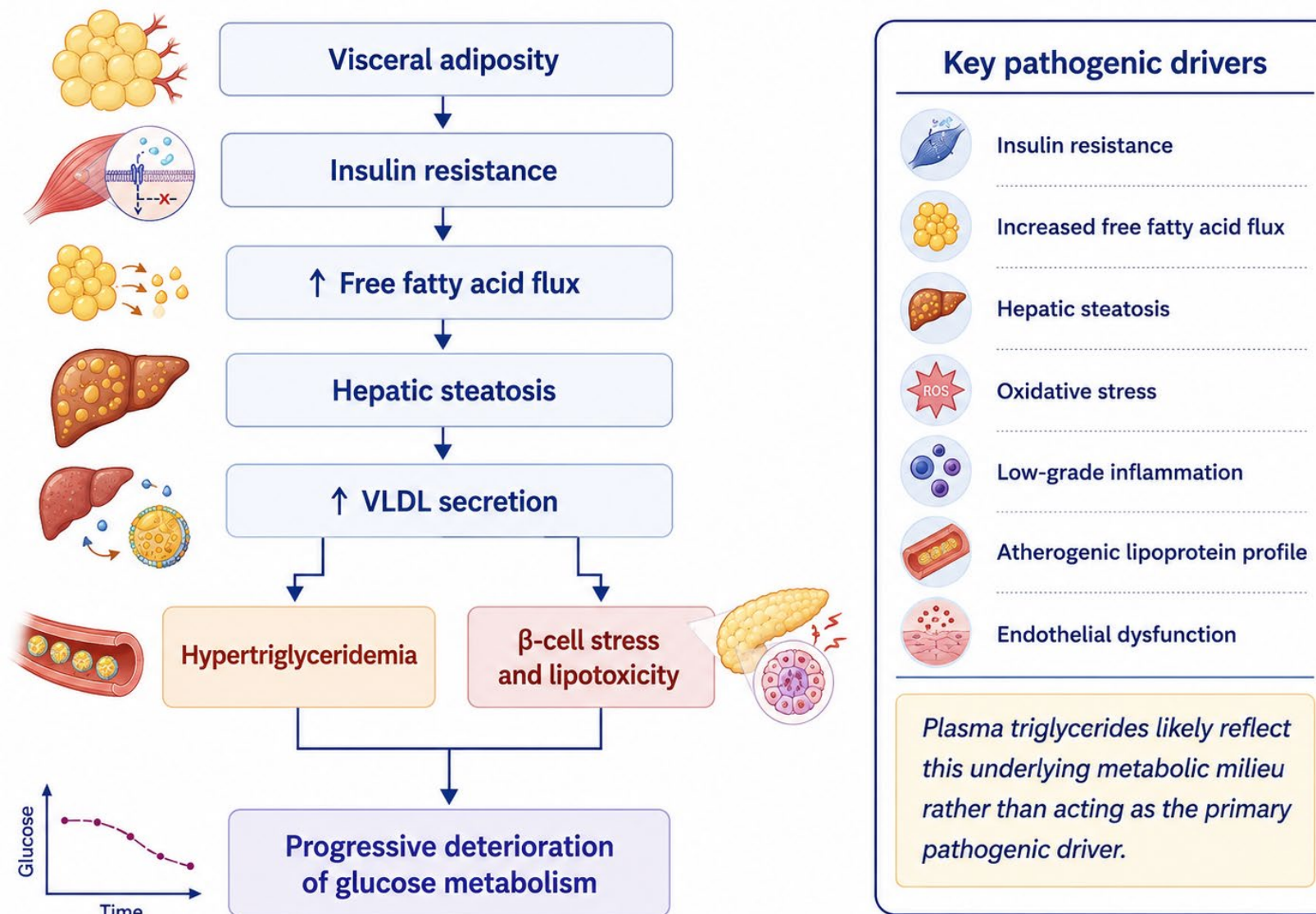
Higher apoC-III and lower lipoprotein lipase activity, with impaired remnant uptake, prolong TG-rich lipoprotein residence¹

Triglyceride-rich VLDL particles and their atherogenic remnants accumulate and drive hypertriglyceridemia in diabetes¹

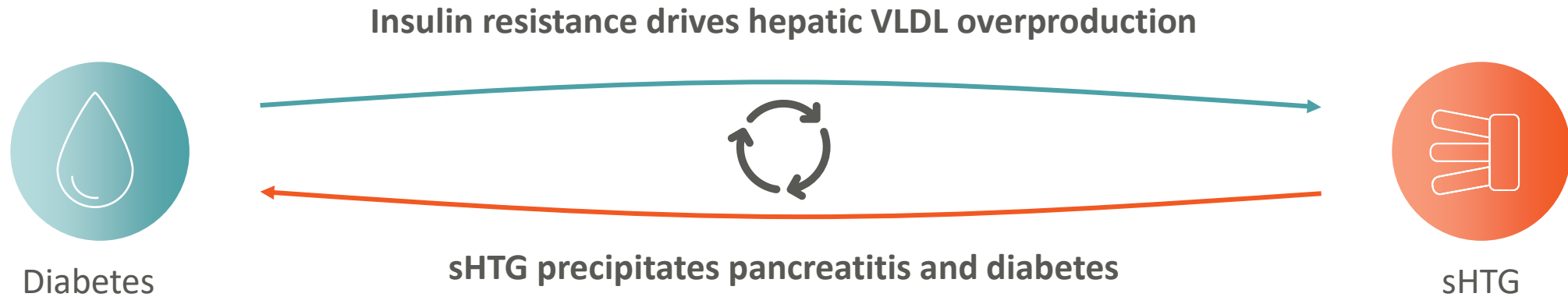
2 The Hepatic Mechanisms Driving Hypertriglyceridemia:



2 Hypertriglyceridemia: A Marker and Mediator of Metabolic Dysfunction



3 Is the relationship between diabetes and severe hypertriglyceridemia *bidirectional*?



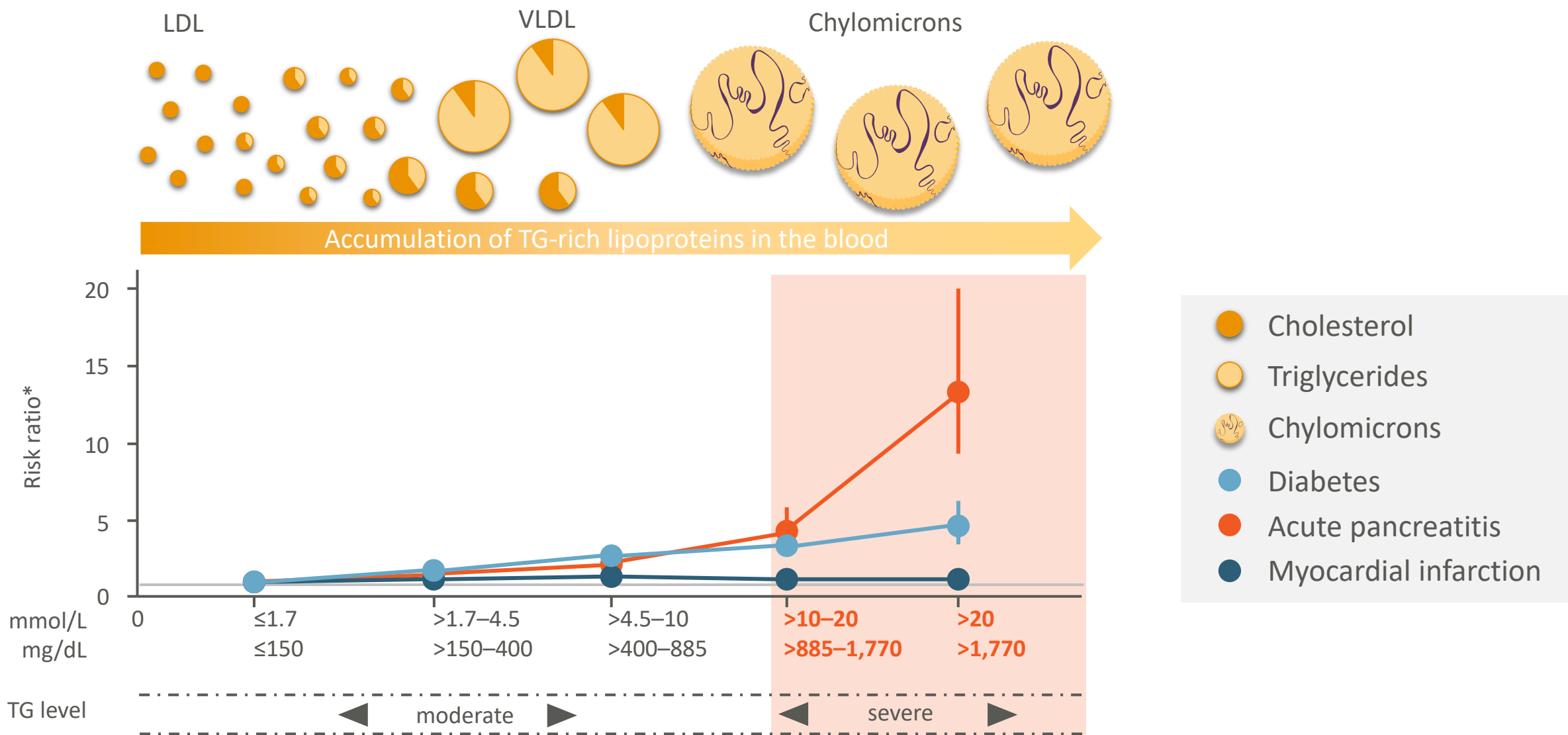
How diabetes leads to sHTG

- T2DM and obesity are the leading secondary causes of HTG¹
- The net effect is accumulation of triglyceride-rich VLDL and their atherogenic remnants¹
- Poorly controlled T2DM is a major contributor to HTG,² but even people with HbA1c <8% may still have persistently elevated TG levels³

How sHTG can lead to diabetes

- sHTG is itself a risk for T2DM by inducing insulin resistance and beta-cell dysfunction⁴
- Severe HTG can lead to recurrent acute pancreatitis¹
- Recurrent episodes progress to chronic pancreatitis with exocrine insufficiency and pancreatogenic (type 3c) diabetes¹

4 Risk of AP and other complications increase as TG levels rise:

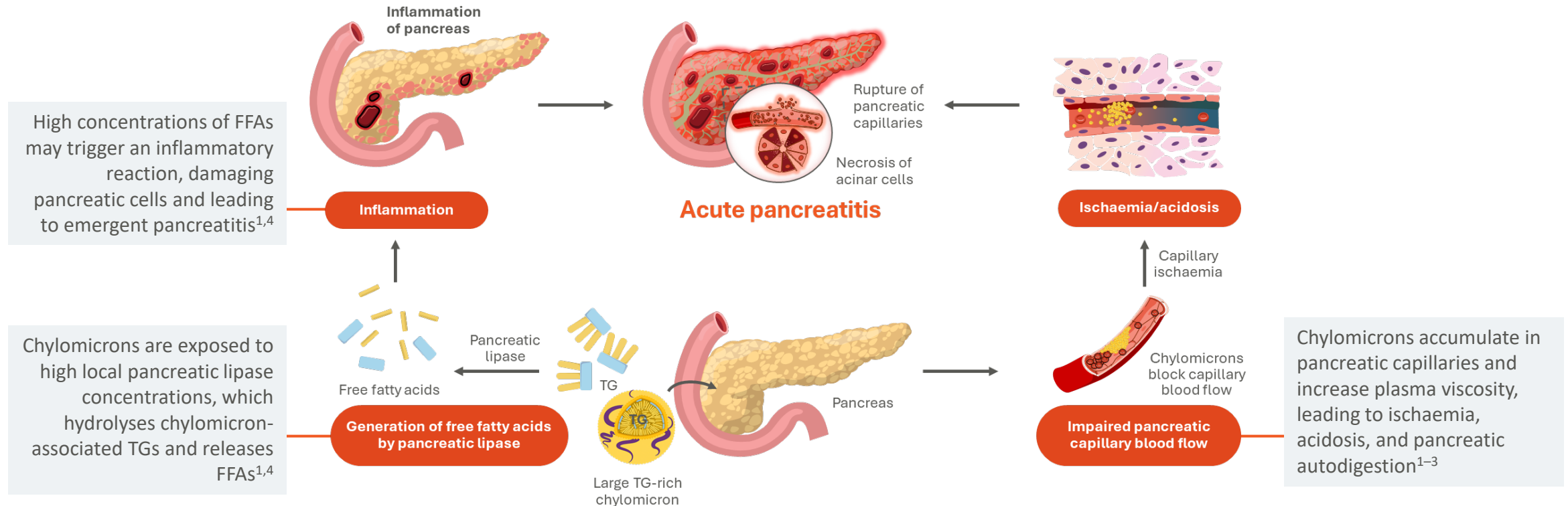


Adapted from Patel et al. *Cardiovasc Diabetol* 2022.

In people without statin treatment. LDL, low-density lipoprotein; TG, triglycerides; VLDL, very-low-density lipoprotein. 1. Patel et al. *Cardiovasc Diabetol* 2022.

4 The mechanisms by which sHTG leads to pancreatitis have not been completely elucidated:

Potential mechanisms of pancreatitis caused by sHTG¹

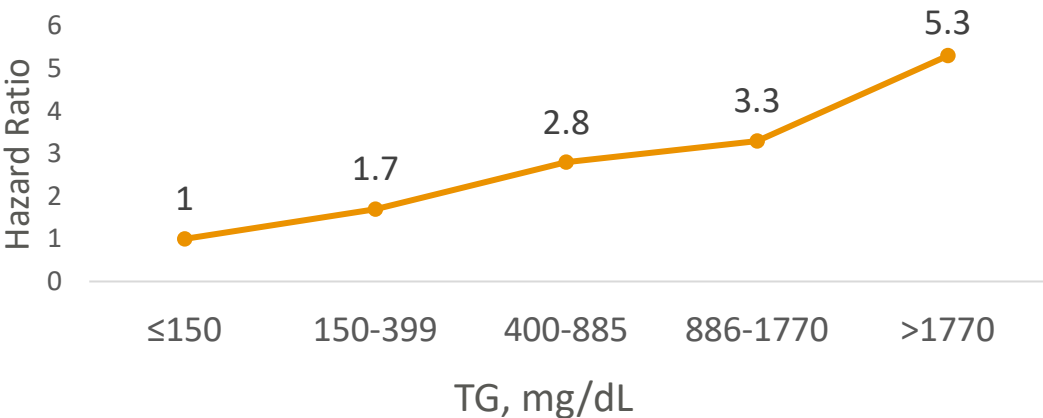


NP-51714

Illustration made with MindTheGraph using published data.¹⁻⁴
FFA, free fatty acids; sHTG, severe hypertriglyceridemia; TG, triglyceride.
1. Chyzyk & Brown. *Trends Cardiovasc Med* 2020 2. Valdivielso et al. *Eur J Intern Med* 2014 3. Javed et al. *J Clin Lipidol* 2025 4. Berglund et al. *J Clin Endocrinol Metab* 2012.

4 Occurrence of acute pancreatitis increase the risk of new onset diabetes:

New onset of diabetes



10–15%

Will develop **new onset diabetes** within **1 year** after AP of any aetiology³

40%

Will develop **new onset diabetes** within **5 years** after AP episode³

~40%

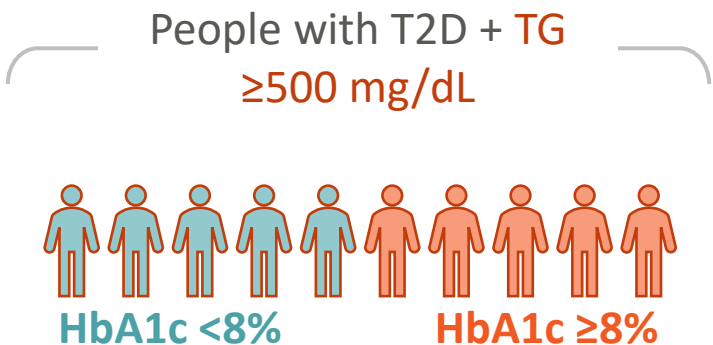
Will develop **new onset diabetes** within **3 years** after **HTG-AP** (TG ≥ 500 mg/dL)³

There is a significant, progressive increase in the incidence of newly diagnosed diabetes with increased TG levels^{1,2}

AP event increases the risk of developing diabetes and chronic pancreatitis³

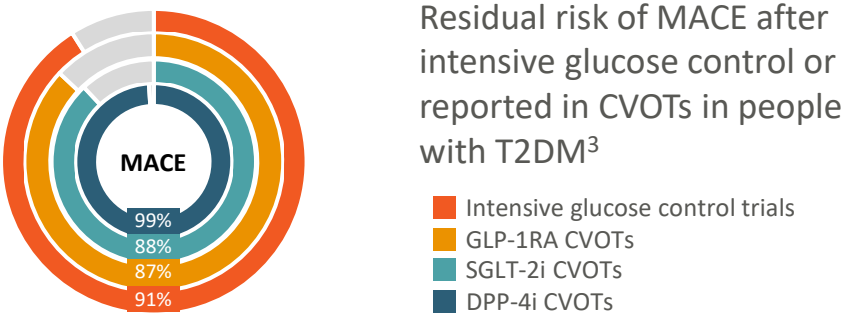
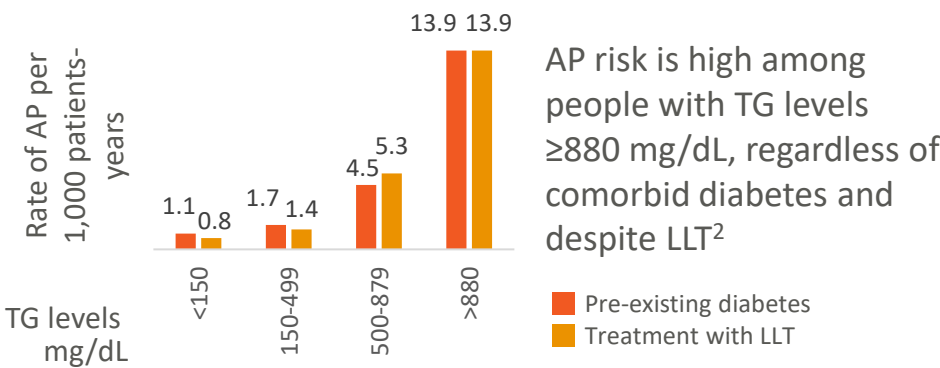
AP, acute pancreatitis; HTG, hypertriglyceridemia; TG, triglyceride.
Figure on the left adapted from Patel et al. *Cardiovasc Diabetol* 2022.
1. Arca et al. *J Am Heart Assoc* 2020 2. Zhang et al. *HPB (Oxford)* 2019 3. Subramanian et al. *Eur J Intern Med* 2026.

5 There is a residual risk of sHTG and complications in people with diabetes despite metabolic control:



Half of people with T2DM and TG levels ≥500 mg/dl were found to have HbA1c <8%¹

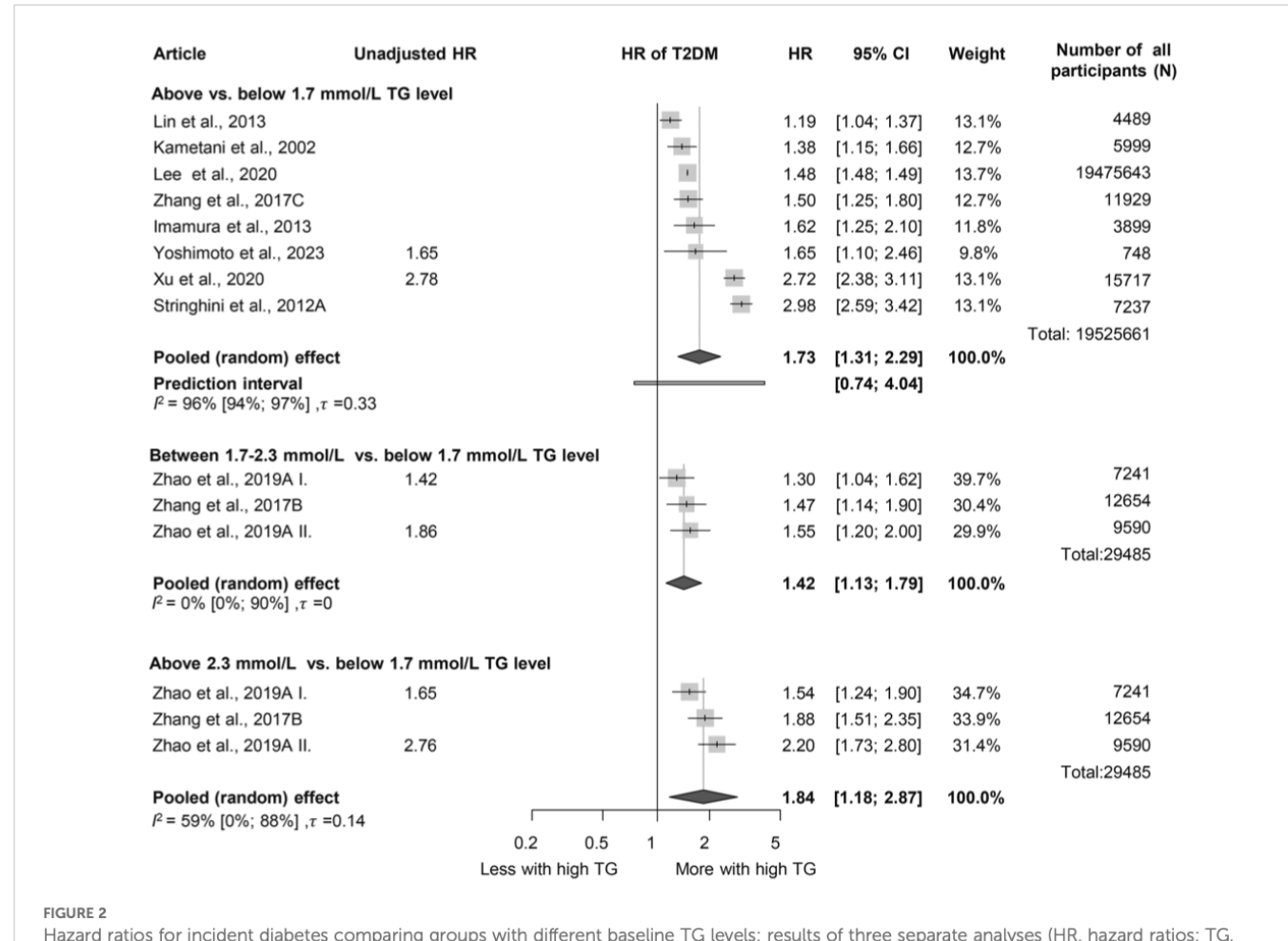
TG can remain high in people with type 2 diabetes and appropriate glycaemic control¹



People with T2D and metabolic diseases have a high risk of complications despite optimal treatment^{2,3}

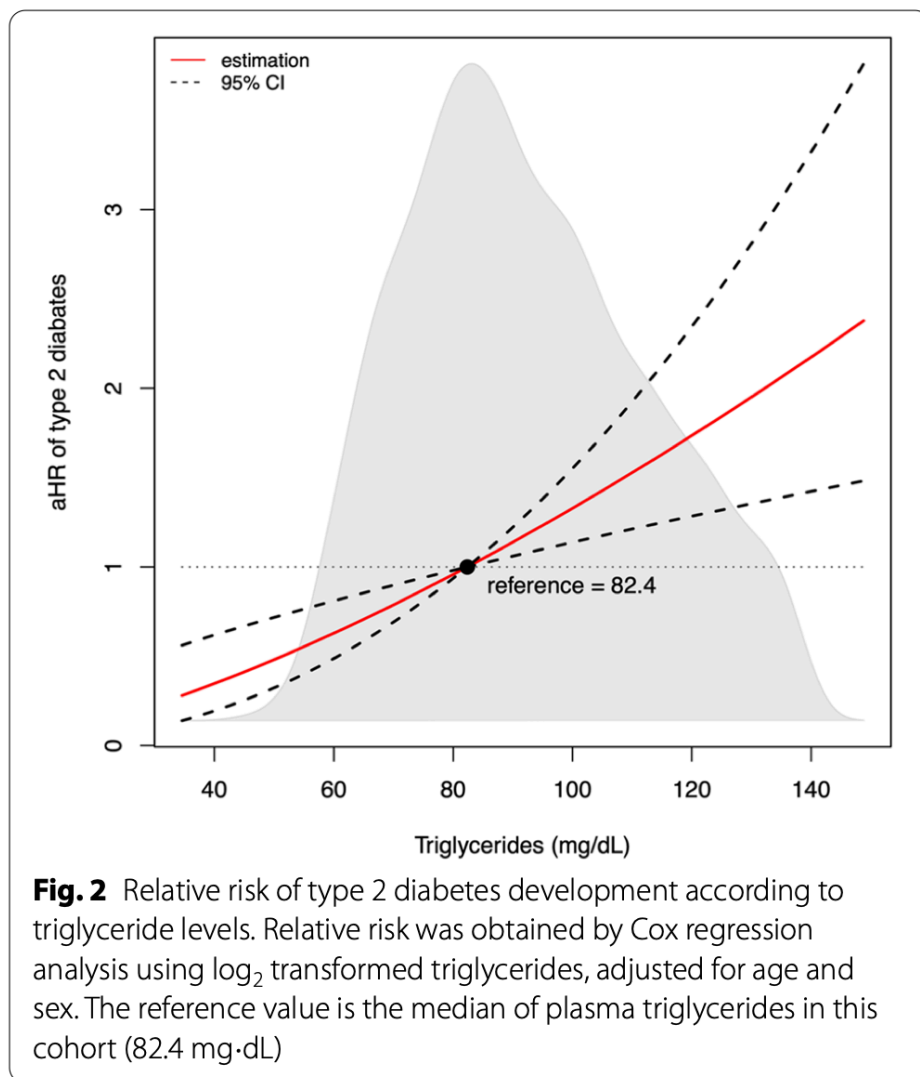
AP, acute pancreatitis; CVOT, cardiovascular outcome trial; LLT, lipid-lowering therapy; MACE, major adverse cardiovascular events; sHTG, severe hypertriglyceridemia; T2DM, type 2 diabetes mellitus; TG, triglycerides.
1. Echegoyen et al. *J Diabetes Complications* 2023 2. Kessler et al. *Lipids Health Dis* 2025 3. Giugliano et al. *Cardiovasc Diabetol* 2021.

5 Hypertriglyceridemia Is Associated with Incident T2D:



Take-home message: Higher triglyceride levels are associated with an increased risk of type 2 diabetes in a dose-dependent manner, with central adiposity (high waist circumference) showing an even stronger association.

5 Triglycerides: An Early Marker of Metabolic Dysfunction?



Higher-normal triglycerides are independently associated with markers of metabolic dysfunction



↑ Insulin

$p < 0.001$



↑ HOMA-IR

$p < 0.001$



↓ HDL cholesterol

$p < 0.001$



↑ Waist circumference

$p = 0.023$



↑ Systolic blood pressure

$p < 0.001$



Glucose

$p = 0.102$ (NS)



Metabolic abnormalities precede fasting hyperglycaemia

Figure on the left from, and table on the right adapted from: Szili-Torok et al. *Cardiovasc Diabetol* 2022.

THE TRIGLYCERIDE-ASSOCIATED PATHWAY

A linear chain, not the full picture



Elevated Triglycerides



Acute Pancreatitis



**Diabetes
(type 3c)**



**Oxidative stress,
 β -cell dysfunction,
Worse glycemic control**

Triglycerides are both
a **marker** of metabolic
dysfunction and a
potential contributor
to disease progression.

Both roads
converge on:

**Pancreatic lipotoxicity,
inflammation, β -cell dysfunction
and diabetes**

THE BROADER METABOLIC CONTEXT.

The road that leads to disease



Insulin resistance
drives metabolic dysfunction



Visceral & hepatic fat
fuel excess lipid production



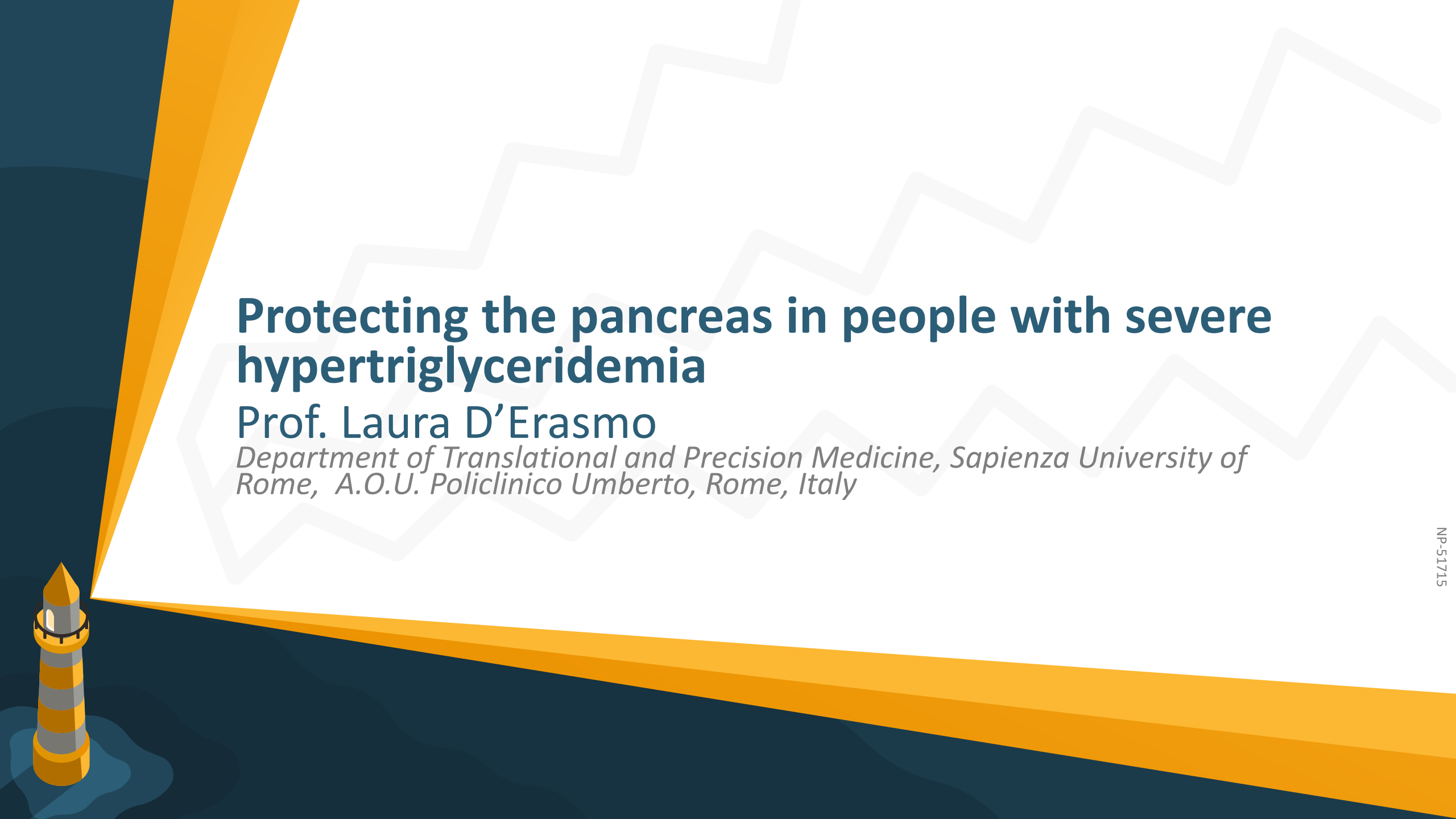
Free fatty acid flux
increases substrate delivery to the liver



TG-rich lipoproteins
(VLDL, Chylomicrons)
overproduction



Impaired lipoprotein clearance
leads to accumulation of remnant lipoproteins



Protecting the pancreas in people with severe hypertriglyceridemia

Prof. Laura D'Erasmus

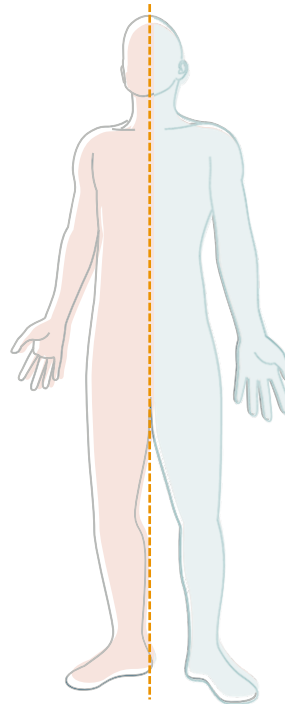
Department of Translational and Precision Medicine, Sapienza University of Rome, A.O.U. Policlinico Umberto, Rome, Italy

Consequences and comorbid conditions of FCS and sHTG

FCS, a rare genetic subset of sHTG

Prevalence of:

- **Pancreatitis¹:**
 - Acute pancreatitis in 60–88% of people
 - Recurrent pancreatitis in 17–48% of people
- **Diabetes mellitus²:** 26% of people
- **Atherosclerotic cardiovascular disease complications²:** 3% of people
- **Chronic kidney disease³:** Proteinuria in 42% of people

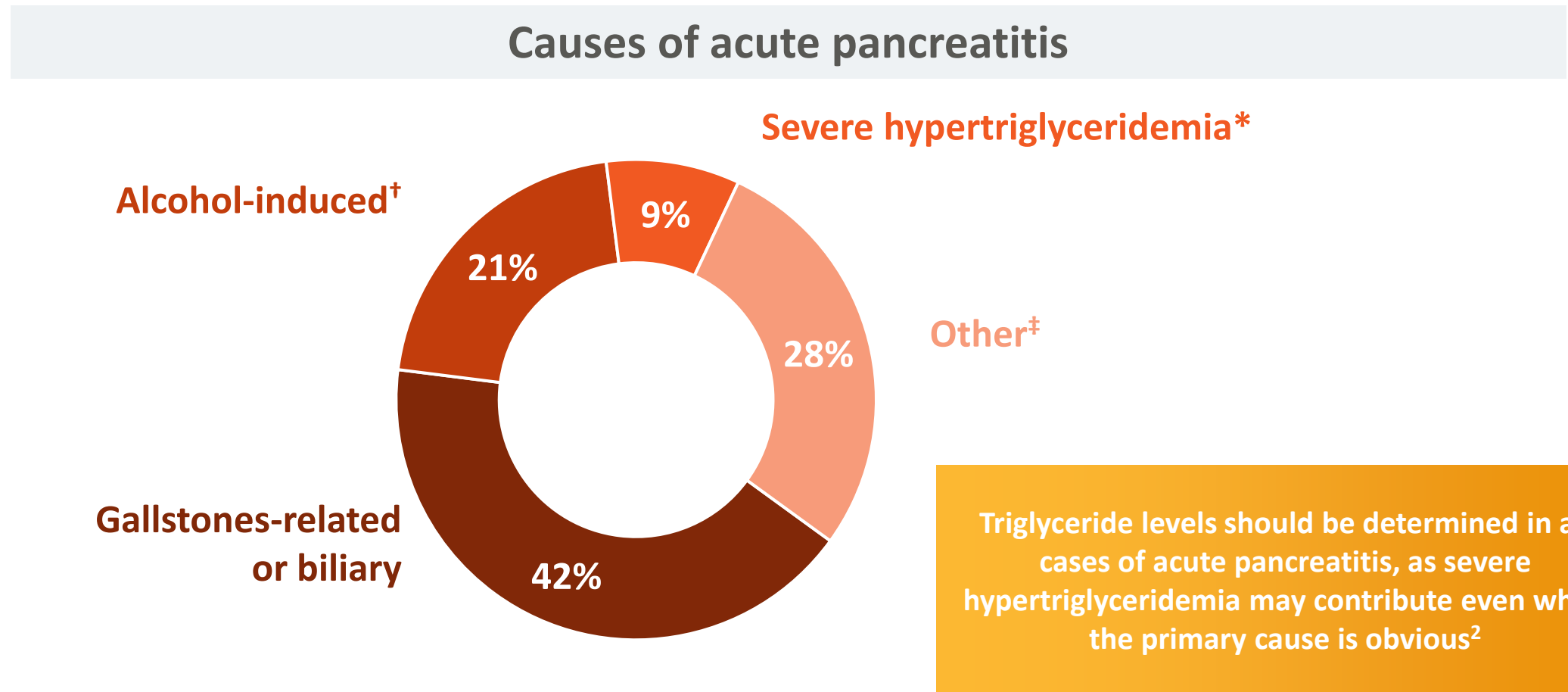


sHTG

Prevalence of:

- **Pancreatitis⁴:**
 - Acute pancreatitis in 6–37% of people
 - Recurrent pancreatitis in 3–16% of people
- **Diabetes mellitus⁵:** 25–76% of people
- **Atherosclerotic cardiovascular disease complications²:** 11% of people
- **Chronic kidney disease⁵:** Unknown; ~5–10% of people with sHTG or HTG-AP had chronic renal failure

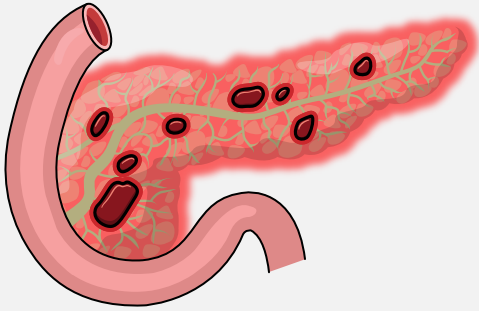
sHTG is the third most commonly identified cause of acute pancreatitis¹



* Defined as serum triglyceride concentrations above 1,000 mg/dL. † Derived from the 2:1 biliary-to-alcohol ratio reported by Bálint et al.¹ ‡ "Other" represents all causes excluding gallstones, alcohol and sHTG. (e.g., endoscopic retrograde cholangiopancreatography, hypercalcaemia, pancreas divisum, tumours, genetic polymorphisms, drugs).

1. Bálint et al. *Sci Rep* 2020 2. Laufs et al. *Eur Heart J* 2020.

sHTG-associated AP has high morbidity and mortality and is a medical emergency requiring hospitalisation¹⁻³



Pancreatic necrosis

45% of people develop pancreatic and/or peripancreatic necrosis over the disease course¹

Chronic pancreatitis

~9% of people develop new-onset chronic pancreatitis post-AP¹

New onset diabetes

~40% of people during an average 3 years follow-up²

Significant symptoms

Abdominal pain, nausea, vomiting, back pain, fatigue³

Persistent organ failure

~33% of people³

ICU admission

~45% of people¹

Death

5–8% of people³

Mortality in those who develop **pancreatic necrosis, infected abscesses, or multiple organ system failure** can reach⁴:



sHTG-associated acute pancreatitis can be fatal and people who recover may develop diabetes, organ failure, recurrent acute pancreatitis, and chronic pancreatitis

The risk of acute pancreatitis increases with increasing TG level^{1,2}

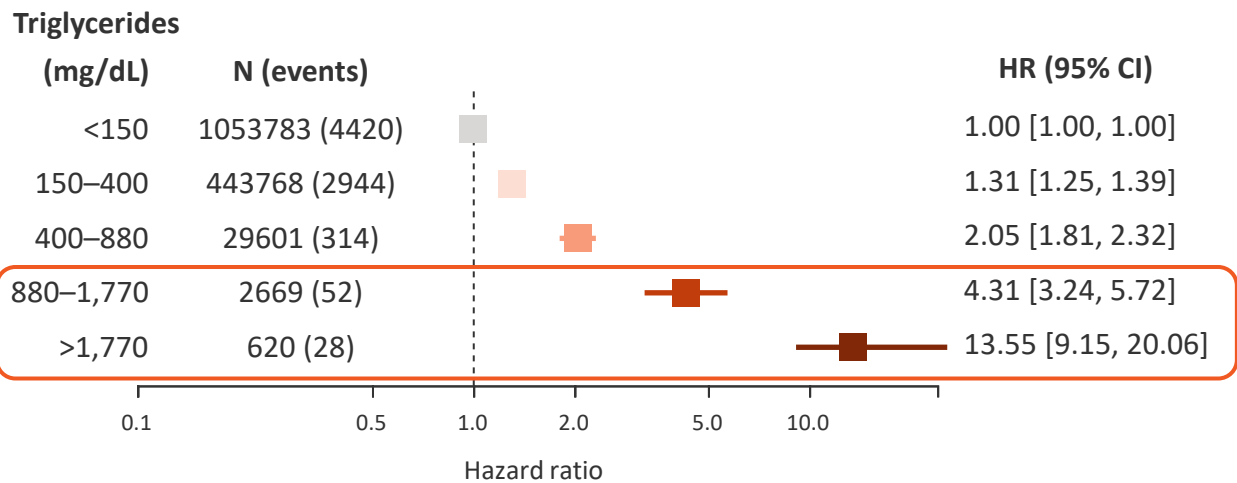


UK data

CALIBER study: Retrospective cohort study of ~1.5 million people using linked data in primary and secondary care in England (1997–2016)

Retrospective of 67,269 people using data from a Medicines Monitoring Unit in Scotland, UK (1993–2007)²

Multivariable adjusted risk of acute pancreatitis



4% increase in risk of acute pancreatitis with every 100 mg/dL increase in TG levels*

The relative risk of acute pancreatitis increases exponentially with increasing TG levels based on UK data

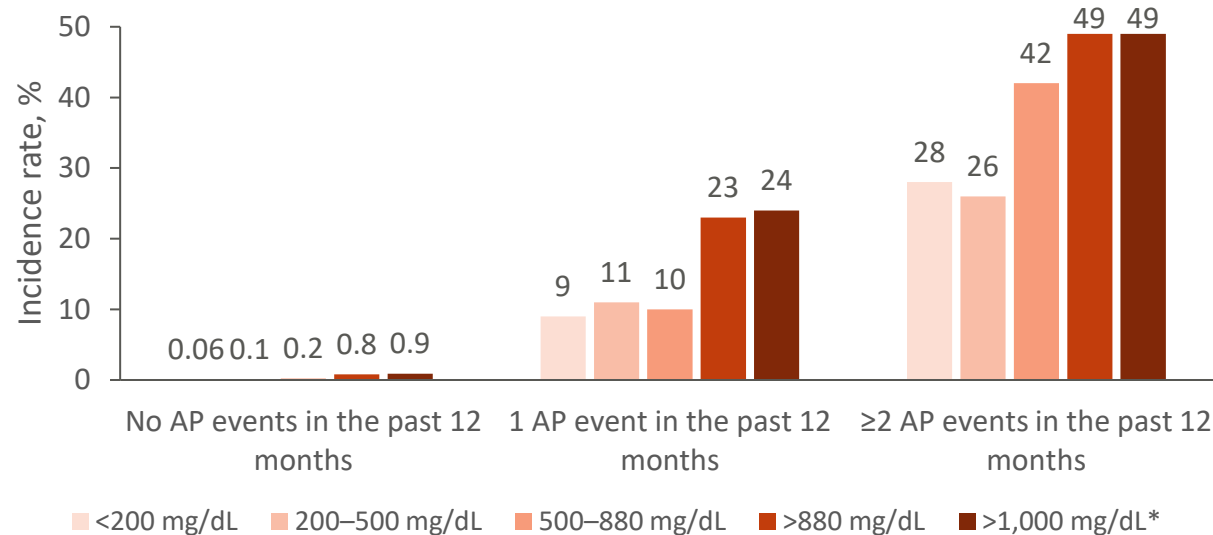
* After adjustment for covariates and exclusion hospitalisation for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure and other biliary disorders.
CI, confidence interval; HR, hazard ratio; HTG, hypertriglyceridemia; TG, triglyceride.
1. Patel et al. *Cardiovasc Diabetol* 2022 2. Murphy et al. *JAMA Intern Med* 2013.

People with sHTG and a history of AP are at greater risk for AP recurrence and chronic pancreatitis^{1,2}

Retrospective cohort study of ~7 million people using data from a US EMR database (2006–2020)¹

Meta-analysis including 119 articles (1992–2023)²

Incidence rate of AP by TG concentration and prior AP



8.58 per 100 person-years

Incidence rate of **recurrent AP** after first AP event in HTG-induced AP (95% CI 6.86–10.72)

1.38 per 100 person-years

Incidence rate of **chronic pancreatitis** after **first** AP event (95% CI 0.97–1.96)

4.31 per 100 person-years

Incidence rate of **chronic pancreatitis** after **recurrent** AP (95% CI 3.10–5.99)

3-fold increase with recurrent AP

Preventing an initial episode of AP in people with sHTG is crucial, as experiencing even one AP event increases the risk of recurrent episodes and of developing chronic pancreatitis

* The group of >880 mg/dL includes people with triglycerides >1,000 mg/dL. AP, acute pancreatitis; EMR, electronic medical records; sHTG, severe hypertriglyceridemia.

1. Sanchez et al. *Lipids Health Dis* 2021 2. Gagyí et al. *Ther Adv Gastroenterol* 2024.

Preventing the first HTG-associated AP is crucial to prevent AP recurrence associated with long-term complications

A single HTG-associated AP event can trigger a cascade leading to chronic pancreatitis, permanent organ failure with high morbidity and mortality¹⁻⁵

19.5x

Higher rate of recurrent AP in people with history of AP vs. overall sHTG population⁶

~10x

Higher risk of severe and very severe HTG-AP vs. normal TG⁷



High economic burden due ED visits, ICU admissions, and hospitalisations^{7-10,*}

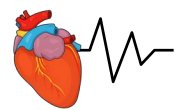
Long-term complications after HTG-AP can include



Organ failure



Diabetes



Death

People with sHTG⁺-AP compared to people with no or mild HTG have:¹

~3x

increase of **persistent organ failure**

~5x

increase of newly diagnosed **diabetes mellitus**

~4x

increase of **mortality**

* On average 10–12 inpatient days per AP episode.^{9,10} † With TG ≥1000 mg/dL. AP, acute pancreatitis; ED, emergency department; ICU, intensive care unit; (s)HTG, (severe) hypertriglyceridemia; TG, triglyceride.

1. Zhang et al. *HPB* 2019 2. Gagyí et al. *Therap Adv Gastroenterol* 2024 3. Hajibandeh et al. *J Gastroenterol Hepatol* 2023 4. Li et al. *Eur J Intern Med* 2023 5. de Rijk et al. *J Gastroenterol Hepatol* 2024

6. Kessler et al. *Lipids Health Dis* 2025 7. Pothoulakis et al. *Digestion* 2021 8. Broder et al. *J Clin Lipidol* 2025 9. Gaudet et al. *J Med Econ* 2013 10. Fan et al. *Sci China Life Sci* 2025.

Guidelines mandate action in FCS to prevent acute pancreatitis

In FCS, European and American guidelines recommend TG-lowering to prevent AP^{1,2}

The risk of pancreatitis is clinically significant if TGs are >880 mg/dL (10 mmol/L)^{1,*}

Dietary restrictions & lifestyle modifications	Conventional LLTs [†]	Considerations	Additional therapies
- Extremely restrictive low-fat diet³ - Limit carbohydrates and simple sugars³ - Avoid alcohol³	- Statins^{3,4} - Fibrates^{3,4,‡} - Omega-3 fatty acids^{3,4}	- Monitoring and supplementation for fat-soluble vitamins^{3,4} - Adjust calories for weight management^{3,4} - Plasmapheresis to rapidly lower TG (acute setting)¹	- Volanesorsen in FCS with TG >750 mg/dL^{5,§} - Olezarsen in FCS with fasting TG ≥1,000 mg/dL^{2,} - Lomitapide[¶] is available in Italy for FCS under Law 648/96^{6–8}

Effective management through diet, lifestyle modifications and therapy is critical to prevent acute pancreatitis

* TG ≥500 mg/dL (5.7 mmol/L) used as threshold in American guidelines.² † Minimal TG-lowering efficacy in FCS.³ ‡ Fenofibrate, bezafibrate. § 2025 ESC/EAS focused update. || 2026 ACC/AHA multisociety guideline. ¶ Lomitapide is authorised in the EU for HoFH only; in Italy it is reimbursed for FCS under Law 648/96 (AIFA Determina n. 27277, 1 March 2023). ACC/AHA, American College of Cardiology/American Heart Association; AIFA, Italian Medicines Agency; AP, acute pancreatitis; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FCS, familial chylomicronemia syndrome; HoFH, homozygous familial hypercholesterolaemia; LLT, lipid-lowering therapy; TG, triglyceride. 1. Mach et al. *Eur Heart J* 2020 2. Blumenthal et al. *J Am Coll Cardiol* 2026 3. Javed et al. *J Clin Lipidol* 2025 4. Bashir et al. *Metabolites* 2023 5. Mach et al. *Eur Heart J* 2025 6. Giammanco et al. *J Clin Lipidol* 2026 7. AIFA, 1 March 2023 8. Lojuxta SmPC.

Guidelines mandate action in sHTG to prevent acute pancreatitis

In sHTG, European and American guidelines recommend TG-lowering to prevent AP^{1,2}

The risk of pancreatitis is clinically significant if TGs are >880 mg/dL (10 mmol/L)^{1,*}

Dietary restrictions & lifestyle modifications	Conventional LLTs	Considerations
• Low fat diet¹ • Limit carbohydrates and simple sugars³ • Avoid alcohol¹ • Weight loss¹	• Statins^{1,4} • Fibrates^{1,4,†} • Omega-3 fatty acids¹	• Manage secondary causes, including diabetes and obesity¹ • Plasmapheresis to rapidly lower TG (acute setting)¹

Effective management through diet, lifestyle modifications and therapy is critical to prevent acute pancreatitis

* TG ≥500 mg/dL (5.7 mmol/L) used as threshold in American guidelines.² † Fenofibrate, bezafibrate.

AP, acute pancreatitis; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. Mach et al. *Eur Heart J* 2020 2. Blumenthal et al. *J Am Coll Cardiol* 2026 3. Javed et al. *J Clin Lipidol* 2025 4. Bashir et al. *Metabolites* 2023 5. Mach et al. *Eur Heart J* 2025.

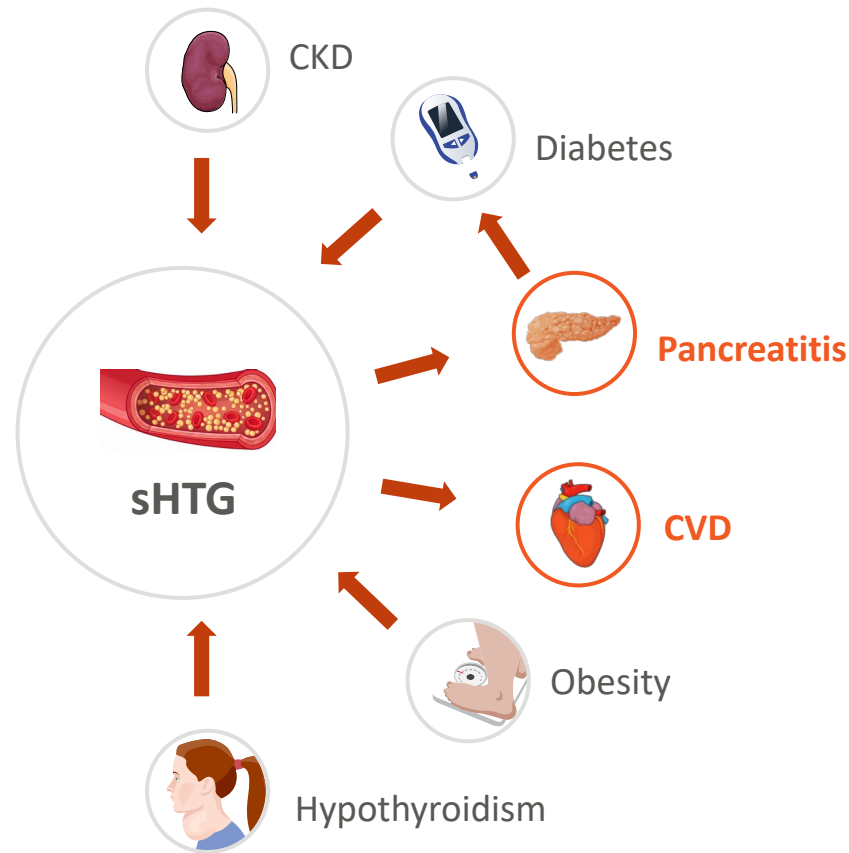
From treatment recommendations...

...to coordinated patient management

Implementing guideline-directed care requires multidisciplinary collaboration



People with sHTG face multiple health issues^{1,2}



Common goal across specialties: Manage lifestyle and diet modifications, and elevate the awareness of AP risk associated with sHTG (TG >880 mg/dL / 10 mmol/L)

A new consensus statement on working together with lipid clinics has recently been published¹

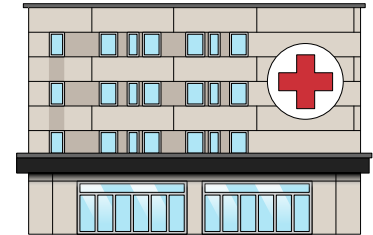
Refer to a specialist lipid clinic if:

- sHTG (>880 mg/dL / 10 mmol/L) or suspected HTG-induced pancreatitis
- Persistent triglycerides ≥ 500 mg/dL (5.7 mmol/L) **despite** lifestyle intervention & management of secondary causes
- Suspected genetic/inherited lipid disorder or complex dyslipidaemia

Common causes of secondary hyperlipidemia (e.g., dysregulated diabetes mellitus) should be **evaluated before referral**

The Lipid Clinic:

A specialised healthcare unit for diagnosing and managing people with lipid disorders



Tiered care model:



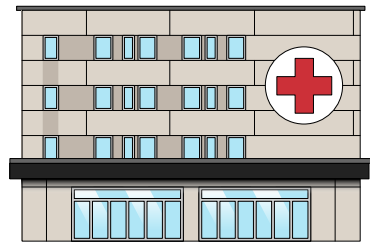
Collaboration with specialist lipid clinics is essential for optimal, multidisciplinary management of severe lipid disorders

* Dependent on country-level income.

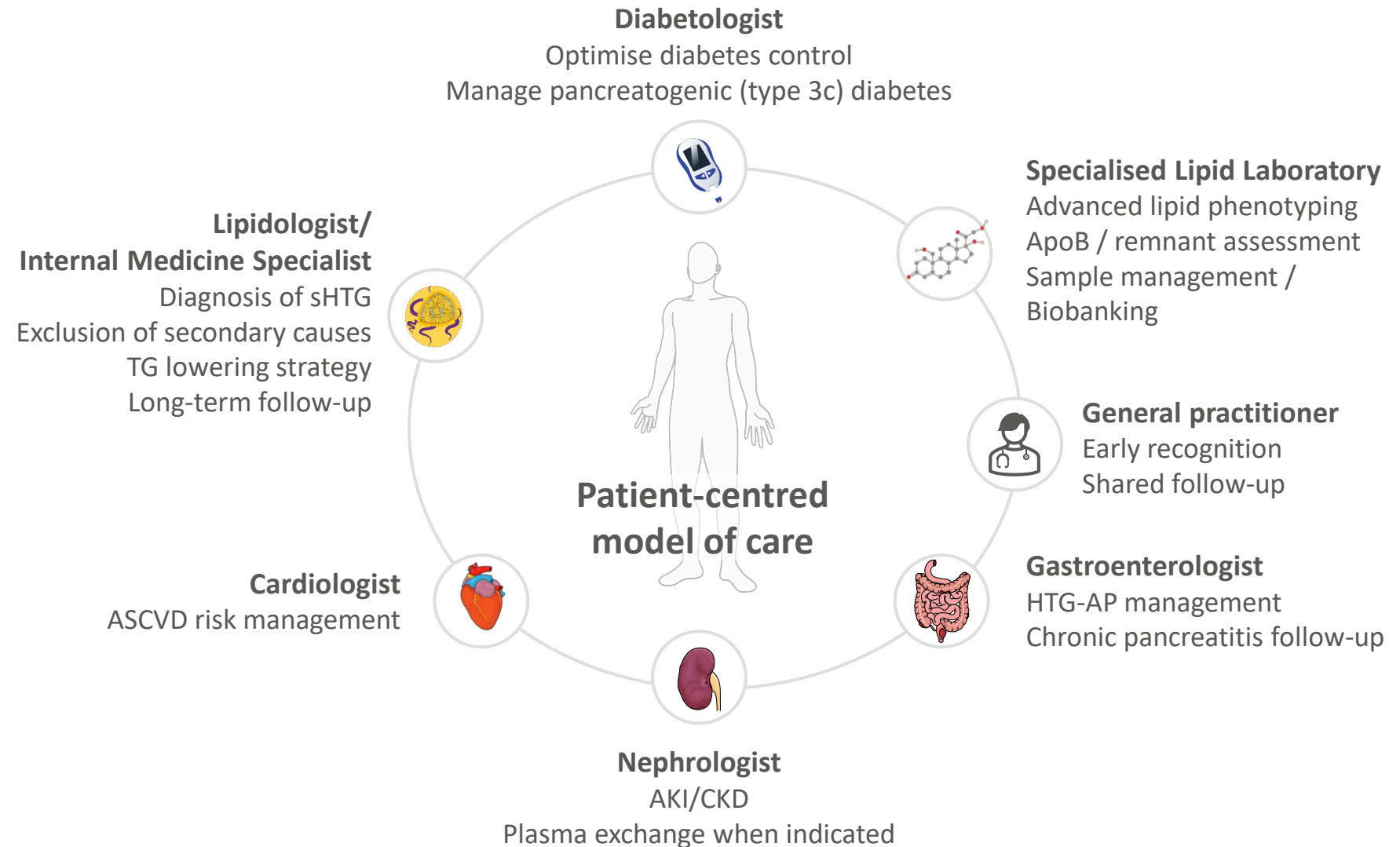
HTG, hypertriglyceridemia; sHTG, severe hypertriglyceridemia.

1. Bork et al. *Atherosclerosis* 2026:120757.

My experience: The local care model



**Lipid clinic/
Internal medicine**



My experience: National level

The LIPIGEN Network¹



Referral, shared expertise, genetic support,
data and research collaboration



Key takeaways

- sHTG-associated pancreatitis has high morbidity and mortality and is a medical emergency requiring hospitalisation^{1–3}
- sHTG-associated pancreatitis may be prevented by lowering TG levels^{2,3}
- ESC/EAS guidelines state that it is mandatory to take actions to prevent acute pancreatitis for people with sHTG (TG levels >880 mg/dL / 10 mmol/L)⁴
- People with sHTG face multiple, often inter-linked health issues, including diabetes, that require multidisciplinary care^{5,6}
- Guidelines now exist to improve treatment collaboration with specialist lipid clinics for optimal, multidisciplinary management of severe lipid disorders⁷

TG monitoring and multi-disciplinary care are vital for optimal care of people with diabetes

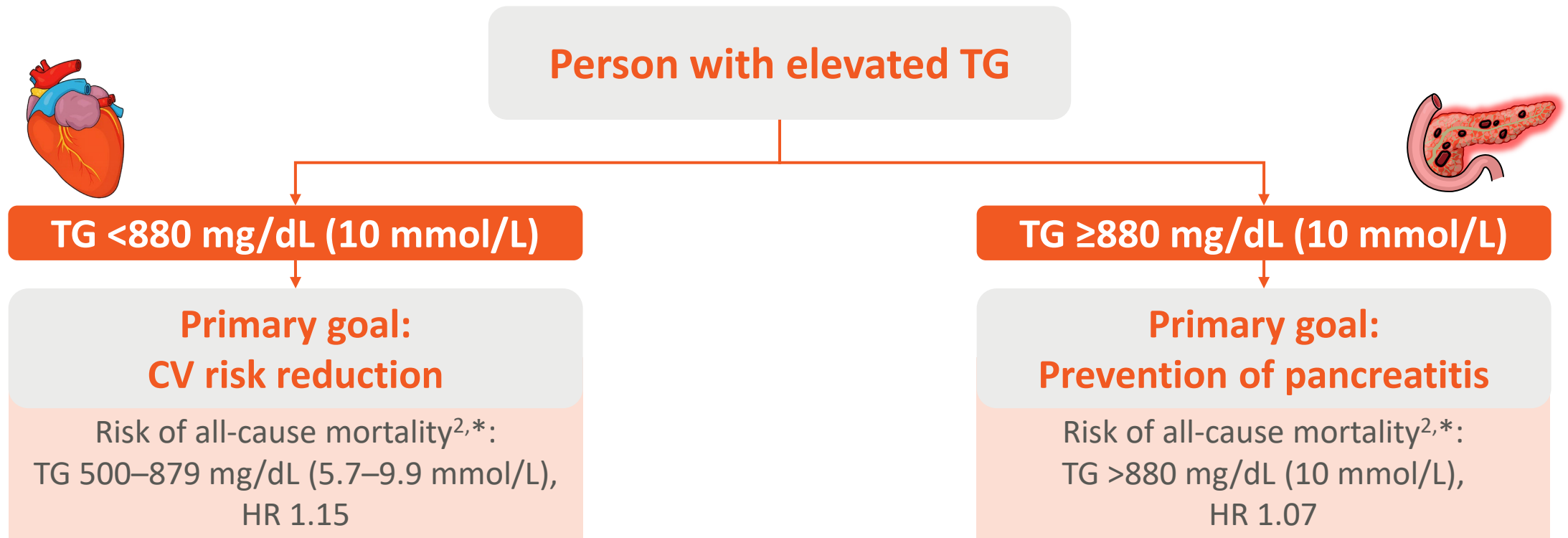


ApoC-III inhibition for acute pancreatitis prevention

Prof. Stefano Romeo

Karolinska Institute
Sweden

Severe hypertriglyceridemia (sHTG) management: Triglyceride threshold and associated risk¹



Illustrations made with MindTheGraph.

* Adjusted for age, sex, type 2 diabetes mellitus, glomerular filtration <60 mL/min/1.73m², current tobacco consumption, alcohol consumption, cholestasis, MEDEA deprivation index, body mass index, and history of previous pancreatitis. Based on an analysis of 2,256–261 individuals in a Spanish healthcare database (SIDIAP).

CV, cardiovascular; HR, hazard ratio; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. Laufs et al. *Eur Heart J* 2020 2. Vlachos et al. *J Clin Lipidol* 2025.

Typical presentation of persons with elevated TGs^{1,2}



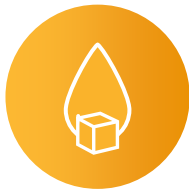
**Cardiovascular
disease**



**Liver
steatosis**



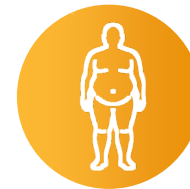
**Chronic kidney
disease**



**Type 2
diabetes**

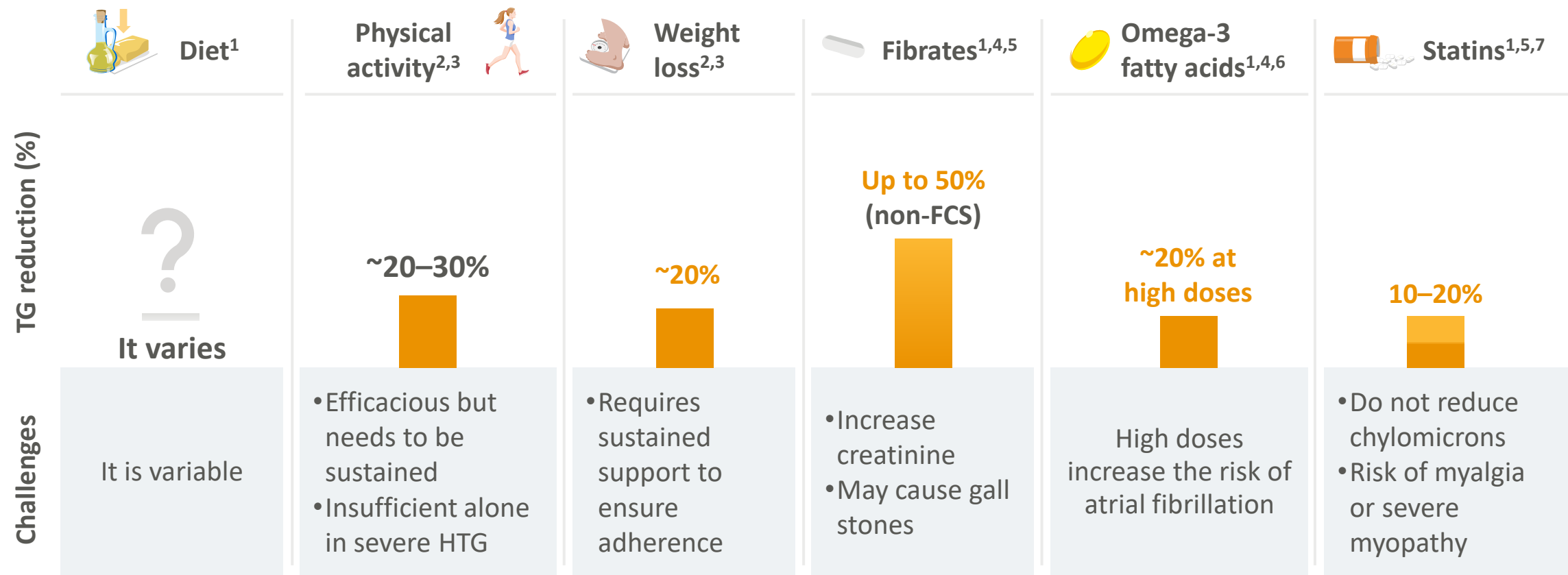


Hypertension



Obesity

Treatment of hypertriglyceridemia



Effective management of severe hypertriglyceridemia through diet, lifestyle modifications and therapy is critical to prevent acute pancreatitis

Illustrations made with MindTheGraph. FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; TG, triglyceride.
1. Gouni-Berthold et al. *Curr Atheroscler Rep* 2023 2. Miller et al. *Circulation* 2011 3. Berglund et al. *J Clin Endocrinol Metab* 2012 4. Wierzbicki et al. *J Clin Pathol* 2022 5. Canfora & Pierno. *Int J Mol Sci* 2024
6. Bhatt et al. *N Engl J Med* 2019 7. Shamsudeen & Hegele. *Expert Rev Clin Pharmacol* 2022.

Challenges in the management of FCS

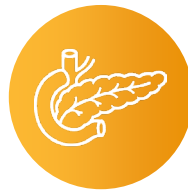
Burden of dietary management¹

Difficulty managing dietary fat intake

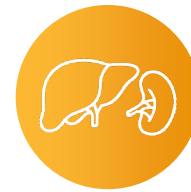


53% experience symptoms despite adherence to diet

Clinical complexity^{2,3} (multisystem burden)



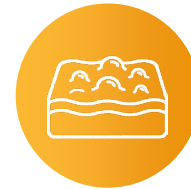
Pancreatitis



Hepatosplenomegaly



Chronic abdominal pain



Eruptive xanthomas

Therapeutic limitations² (minimal LLT response)

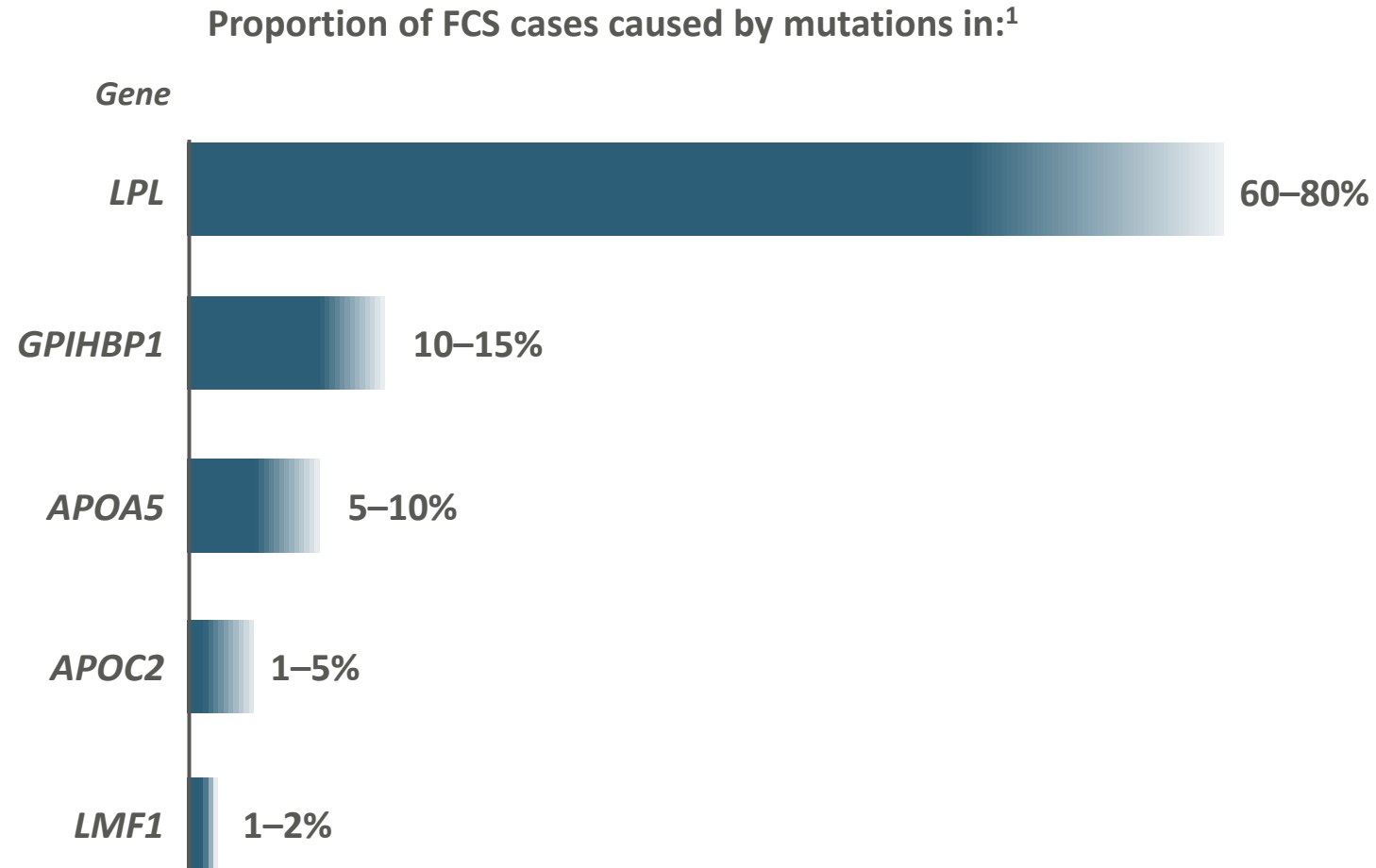
Statins, fibrates, niacin and omega-3 fatty acids are ineffective at TG lowering in FCS



Pancreatitis risk remains inadequately addressed

Conventional lipid-lowering therapies are ineffective in FCS², and the lifelong extreme fat restriction needed to reduce TGs is burdensome and difficult to sustain¹

Five genes make up the group referred to as the ‘canonical’ genes causing FCS^{1–3}



ApoA-V, apolipoprotein AV; apoC-II, apolipoprotein C-II; FCS, familial chylomicronemia syndrome; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein-1; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase.

1. Javed et al. *J Clin Lipidol* 2025 2. Bashir et al. *Metabolites* 2023 3. Hegele et al. *J Clin Lipidol* 2025.

Management of FCS, a rare genetic subset of severe HTG



Main goal¹



**Lower TG levels to
reduce the risk of
pancreatitis**



Management approach¹

Dietary restrictions



Extremely low-fat diet*



Limit carbohydrates & simple sugars



Avoid alcohol

Treatment¹⁻³

apoC-III inhibitor: *olezarsen*, *volanesorsen*[†]

LLT: omega-3 fatty acids, statins, fibrates

Monitoring and supplementation

Vitamins A, D, E and K



Challenges

- Limited FCS treatment options¹
- Response to conventional triglyceride- and lipid-lowering therapies[‡] is minimal¹
- Dietary restrictions are burdensome and challenging⁵:
 - **>90%** of people report difficulty managing fat intake
 - **~50%** experience symptoms despite adherence to diet
- Does not adequately address burden of pancreatitis risk

* Less than 20 g of fat per day. † Recommended by the 2025 ESC/EAS guidelines in people with severe HTG (>750 mg/dL or >8.5 mmol/L) due to FCS, to lower TG levels and reduce the risk of pancreatitis⁴. The Guidelines were updated based on evidence up to 31 March 2025, i.e. before Tryngolza (olezarsen) received a positive CHMP opinion in July 2025. ‡ Fibrates, niacin, omega-3 unsaturated fatty acids, statins. ApoC-III, apolipoprotein C-III; CHMP, Committee for Medicinal Products for Human Use; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; LLT, lipid-lowering therapies; TG, triglyceride.

1. Javed et al. *J Clin Lipidol* 2025 2. Waylivra (volanesorsen) SmPC July 2025 3. Bashir et al. *Metabolites* 2023 4. Mach et al. *Eur Heart J* 2025 5. Davidson et al. *J Clin Lipidol* 2018.

People with FCS require an extremely restrictive, low-fat diet



Dietary requirements:

- Restrict fat:
 - Less than 15–20g of fat per day¹, including daily intake of α -linolenic acid and linoleic acid^{1,2}
- People with FCS are recommended to distribute fat and other nutrient intake throughout the day¹
- Medium chain triglyceride (MCT) oil may be used as a supplement to increase dietary fat and calorie intake, and adjust macronutrient composition of the diet^{1,3}
- Fat-free or low-fat protein should be included with each meal and snack¹

ApoC-III is an important regulator of triglyceride metabolism¹⁻⁷

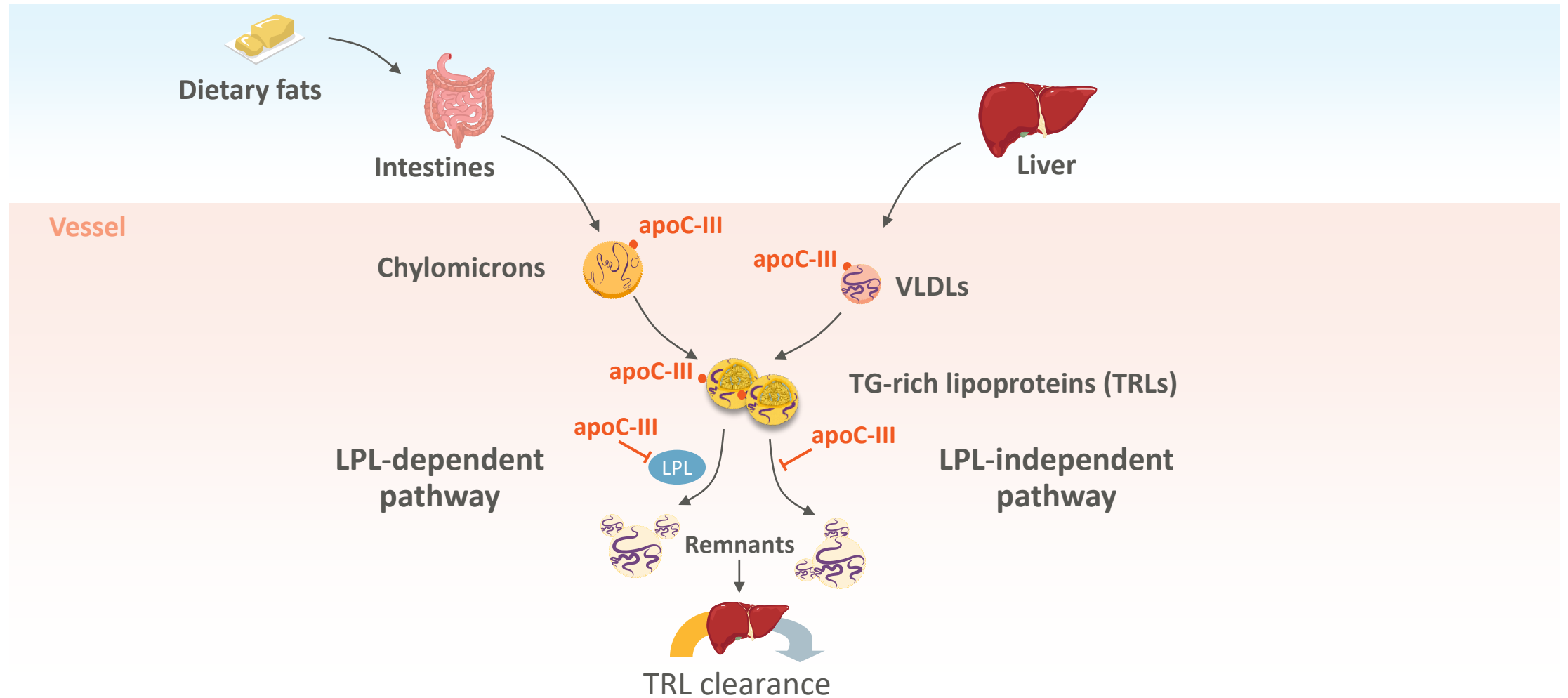


Illustration made with MindTheGraph using published data.¹⁻⁷ apoC-III, apolipoprotein C-III; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; TRL, triglyceride-rich lipoprotein; VLDL, very low-density lipoprotein. 1. Giammanco et al. *Curr Atheroscler Rep* 2023 2. Brinton et al. *Atherosclerosis* 2025 3. Gaudet et al. *N Engl J Med* 2014 4. Bashir et al. *Arterioscler Thromb Vasc Biol* 2024 5. IONIS protocol ISIS 678354-CS3, 02 August 2023 6. Stroes et al. *N Engl J Med* 2024 7. Ginsberg et al. *Eur Heart J* 2021.

Targeting apoC-III reduces TG levels and the risk of acute pancreatitis¹⁻⁹

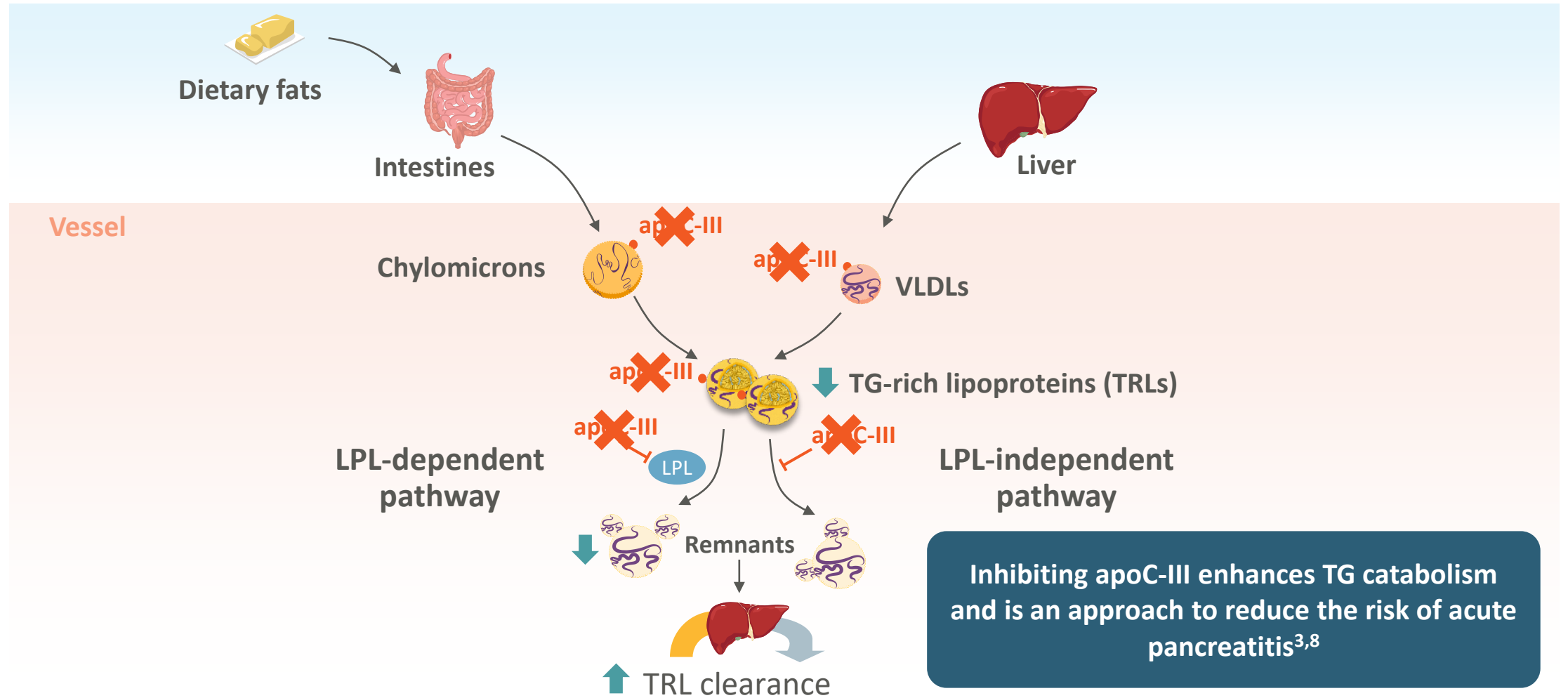


Illustration made with MindTheGraph using published data.¹⁻⁷

apoC-III, apolipoprotein C-III; LPL, lipoprotein lipase; sHTG, severe hypertriglyceridemia; TG, triglyceride; TRL, triglyceride-rich lipoprotein; VLDL, very low-density lipoprotein.

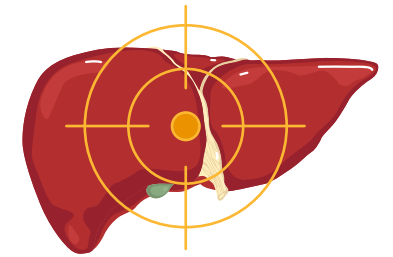
1. Giammanco et al. *Curr Atheroscler Rep* 2023 2. Bashir et al. *Arterioscler Thromb Vasc Biol* 2024 3. Gaudet et al. *N Engl J Med* 2014 4. IONIS protocol ISIS 678354-CS3, 02 August 2023 5. Brinton et al. *Atherosclerosis* 2025 6. Stroes et al. *N Engl J Med* 2024 7. Ginsberg et al. *Eur Heart J* 2021 8. Mach et al. *Eur Heart J* 2025 9. Laufs et al. *Eur Heart J* 2019.

RNA targeting strategies to reduce apoC-III

ASO
(volanesorsen, 285 mg)
*Approved for FCS as
an adjunct to diet¹*

ASO-GalNAc₃
(olezarsen, 80 mg)
*Approved for FCS as
an adjunct to diet²*

siRNA-GalNAc₃
(plozasiran)
*Approved for FCS as an
adjunct to diet⁵*



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 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). 2'-MOE, 2'-O-methoxyethyl; apoC-III, apolipoprotein C-III; ASO, antisense oligonucleotide; FCS, familial chylomicronemia syndrome; GalNAc₃, triantennary *N*-acetylgalactosamine; RNase H1, ribonuclease H1; siRNA, small interfering RNA.

1. Witztum et al. *N Engl J Med* 2019 2. Stroes et al. *N Engl J Med* 2024 3. Crooke et al. *Nucleic Acid Ther* 2019 4. Brinton et al. *Atherosclerosis* 2025 5. Watts et al. *N Engl J Med* 2025.

The rationale for inhibiting apoC-III: Olezarsen's mechanism of action

Apolipoprotein C-III (**apoC-III**) is found mainly in the liver. It is a **key inhibitor** of TG metabolism and **causes TGs to accumulate in the bloodstream**^{1,2}

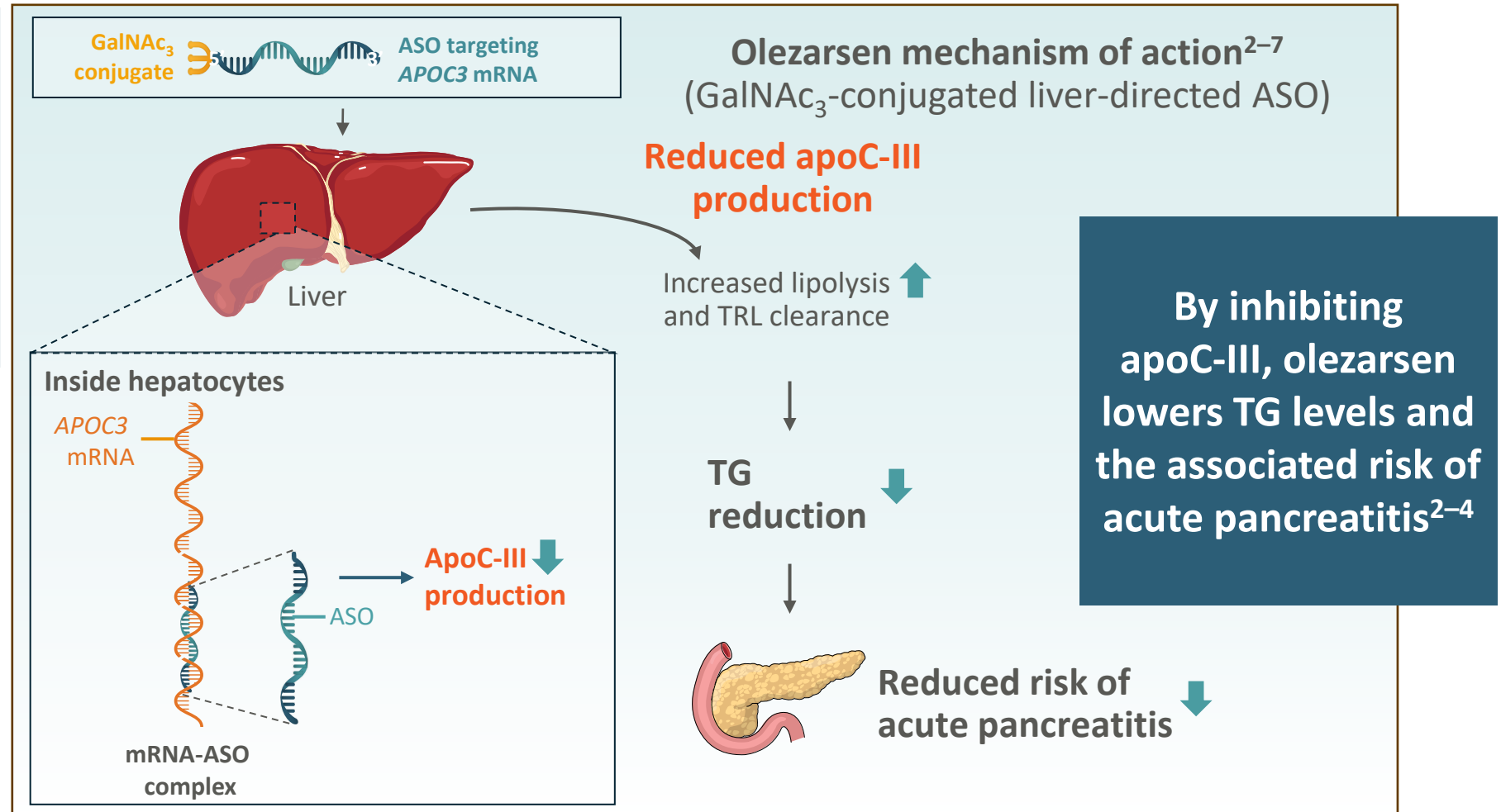
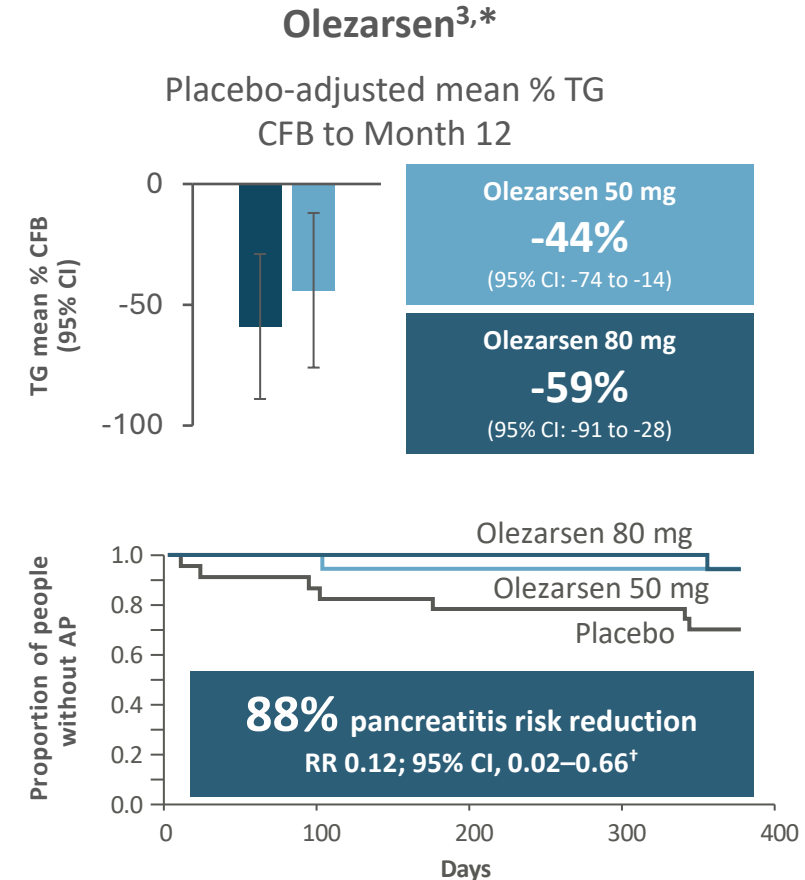
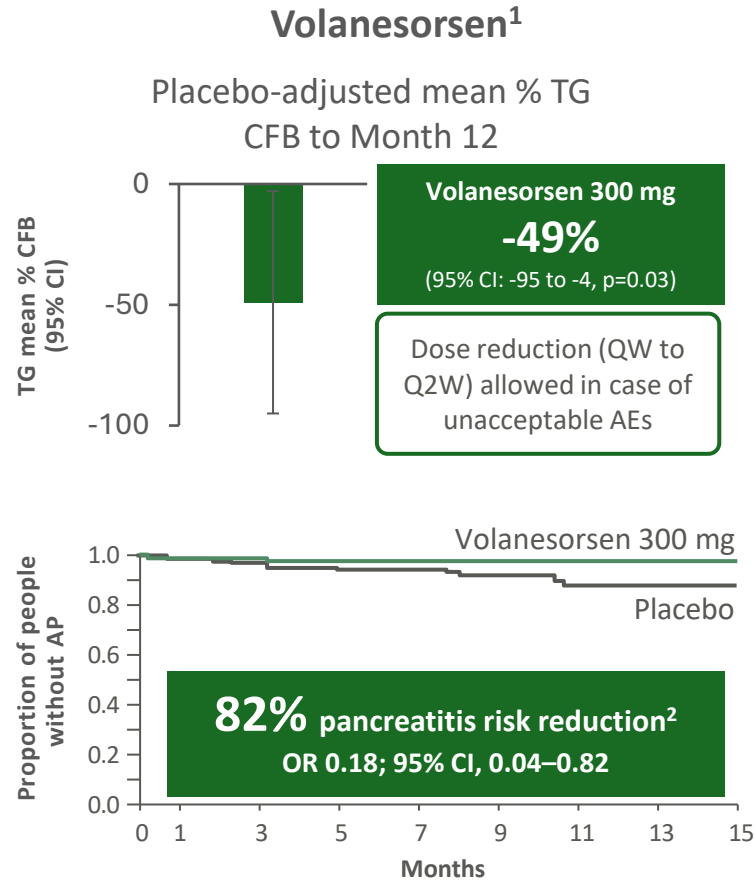


Illustration made with MindTheGraph using data from cited references.²⁻⁷ apoC-III, apolipoprotein C-III; ASO, antisense oligonucleotide; GalNAc₃, triantennary N-acetylgalactosamine; mRNA, messenger ribonucleic acid; TG, triglyceride; TRL, triglyceride-rich lipoprotein. 1. Giammanco et al. *Curr Atheroscler Rep* 2023 2. Gordts et al. *J Clin Invest* 2016 3. Marston et al. *N Engl J Med* 2026 4. Tryngolza (olezarsen) SmPC 2025 5. Gaudet et al. *N Engl J Med* 2014 6. Witztum et al. *N Engl J Med* 2019 7. Stroes et al. *N Engl J Med* 2024.

ApoC-III targeting effectively reduced triglyceride levels and pancreatitis events in FCS at 12 months



Disclaimer: Direct comparisons between studies may be misleading due to differences in study design, population, and methodology. The results presented should be interpreted cautiously and in the context of the individual studies. * Primary and secondary efficacy endpoints were tested hierarchically. As the second primary endpoint with the 50 mg olezarsen dose was not statistically significant, the secondary end points are presented as LSM changes with the 95% CI. The 95% CI for the secondary end points were not adjusted for multiplicity, and the results should not be interpreted as hypothesis tests.

[†] Pooled olezarsen vs placebo. Pancreatitis figure adapted from Tsimikas S. *Curr Atheroscler Rep* 2025. AE, adverse event; AP, acute pancreatitis; apoC-III, apolipoprotein C-III; CFB, change from baseline; CI, confidence interval; FCS, familial chylomicronemia syndrome; LSM, least-squares mean; OR, odds ratio; RR, risk ratio; TG, triglyceride; QW, weekly; Q2W, every other week.

1. Witztum et al. *N Engl J Med* 2019 2. Tsimikas. *Curr Atheroscler Rep* 2025 3. Stroes et al. *N Engl J Med* 2024.

Balance study with olezarsen in FCS: Study design¹

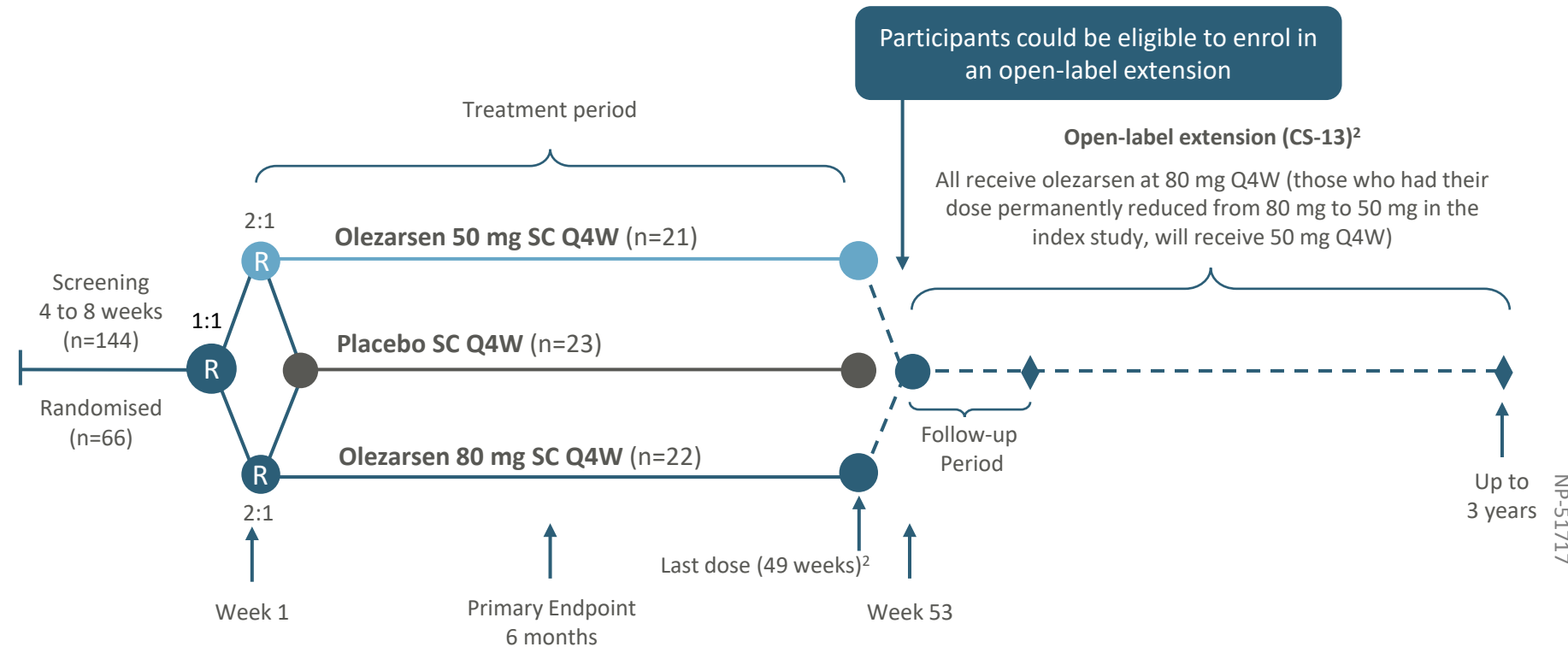
Randomised, double-blind, placebo-controlled Phase 3 trial in adults with genetically confirmed FCS and fasting TG ≥ 880 mg/dL

STUDY POPULATION

- Age ≥ 18 years
- genetically confirmed FCS*
- Fasting TG ≥ 880 mg/dL at screening
- History of pancreatitis ≤ 10 years prior to screening in $\geq 65\%$ of people enrolled[†]
- 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



Randomisation stratified by

- History or no history of pancreatitis within 10 years prior to screening, or no history of pancreatitis
- Previous treatment with volanesorsen (yes or no)

* Ho, compound / double He loss of function mutation in genes such as LPL, GPIHBP1, APOA5, APOC2 or LMF1. † People with no history of pancreatitis capped at 35% of enrolment. FCS, familial chylomicronemia syndrome; Ho, homozygous; He, heterozygous; Q4W, every 4 weeks; R, randomisation; SC, subcutaneous; TG, triglyceride.

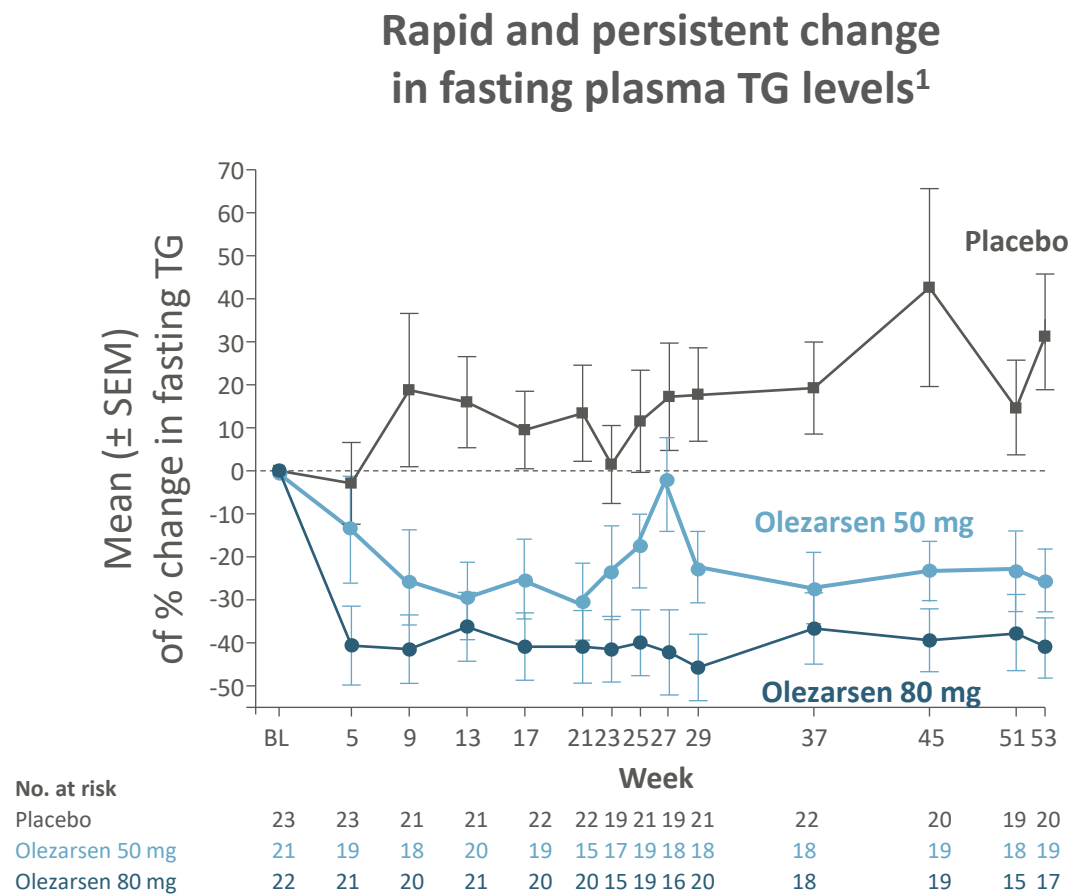
1. Stroes et al. *N Engl J Med* 2024 (supplement) 2. Stroes et al. *N Engl J Med* 2024.

Balance study in FCS: Key baseline characteristics¹

	Placebo n=23	Olezarsen 50 mg n=21	Olezarsen 80 mg n=22
BMI, kg/m ² , mean (SD)	24.2 (4.1)	22.4 (3.5)	25.1 (6.0)
History of AP in prior 10 years, n (%)	15 (65)	15 (71)	17 (77)
Diabetes mellitus, n (%)	6 (26)	3 (14)	7 (32)
Triglycerides, mg/dL, mean (SD)	2,596 (1,256)	2,684 (1,235)	2,613 (1,499)
LDL-C, mg/dL, mean (SD)	16.7 (8.4)	17.6 (8.5)	22.8 (14.1)
Concomitant medications, n (%)			
Statin	7 (30.4)	4 (19.0)	5 (22.7)
Fibrate	11 (47.8)	8 (38.1)	11 (50.0)

AP, acute pancreatitis; BMI, body mass index; FCS, familial chylomicronemia syndrome; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.
1. Stroes et al. *N Engl J Med* 2024.

Balance study in FCS: 59.4% reduction in triglycerides vs placebo at Month 12 with olezarsen 80 mg^{1,*}

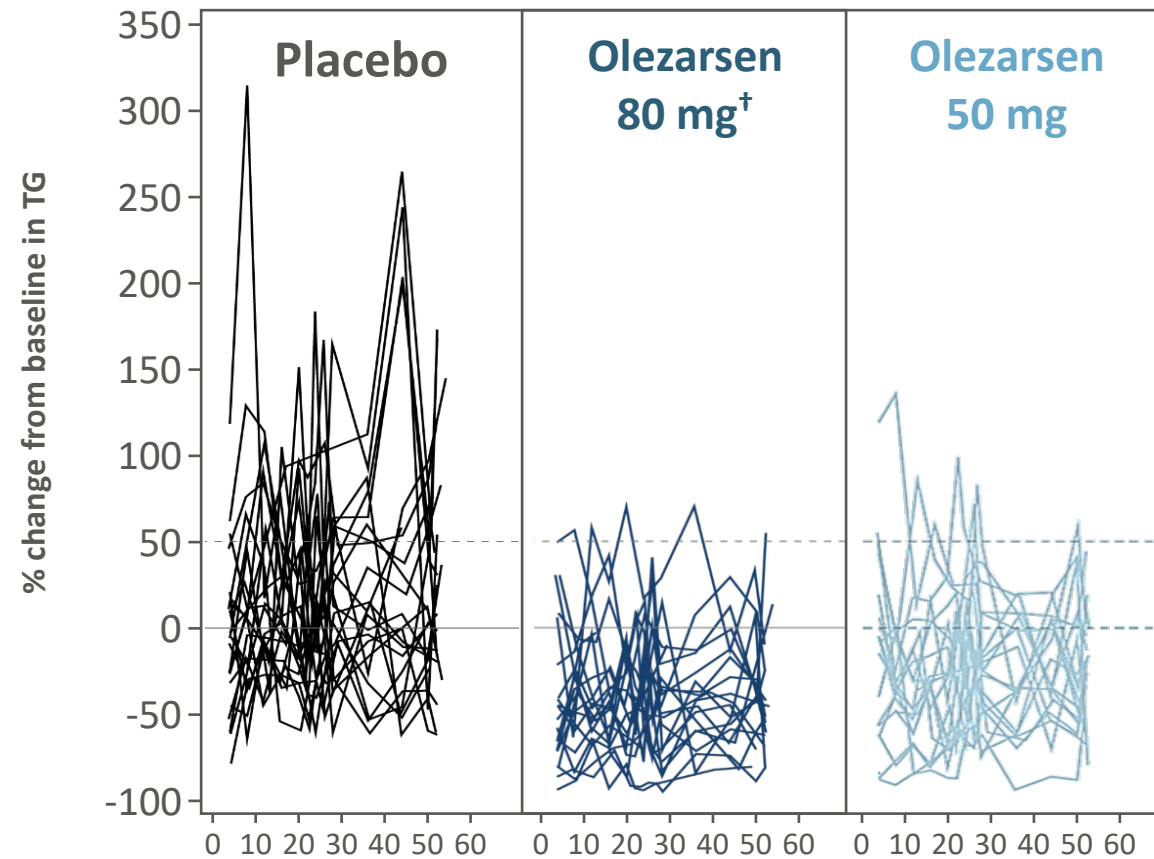


LSMD vs Placebo
6 months (primary endpoint)
Olezarsen 80 mg*
- 43.5%
(95% CI: -69.1 to -17.9), p<0.001

LSMD vs Placebo
12 months:
Olezarsen 80 mg*
- 59.4%
(95% CI: -90.7 to -28.1)

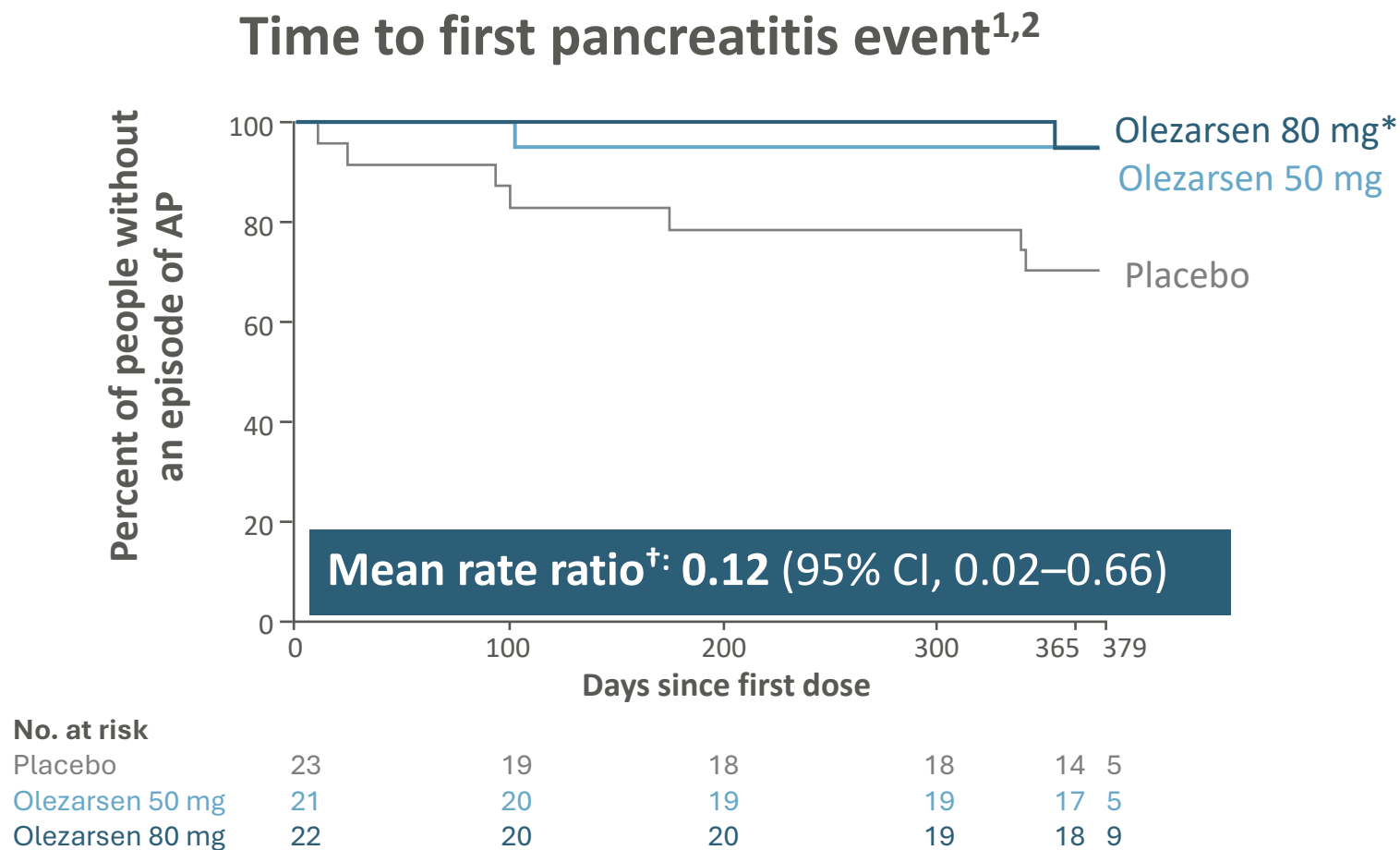
* Approved dose by European Medicines Agency.
BL, baseline; CI, confidence interval; FCS, familial chylomicronemia syndrome; LSMD, least squares mean difference; SEM, standard error of the mean; TG, triglyceride.
1. Stroes et al. *N Engl J Med* 2024.

Balance study in FCS: Reduced TG fluctuations* over time with olezarsen 80 mg^{1,†}



* Reduction in TG fluctuations compared to placebo. † Approved dose by European Medicines Agency.
CI, confidence interval; FCS, familial chylomicronemia syndrome; TG, triglyceride.
1. Stroes et al. *N Engl J Med* 2024 (supplement).

Balance study in FCS: 88% reduction in pancreatitis events within 12 months for people receiving olezarsen¹



* Approved dose by European Medicines Agency. † 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 syndrome. 1. Stroes et al. *N Engl J Med* 2024.

Balance study in FCS: Longer time to a first pancreatitis event for people receiving olezarsen¹

Pancreatitis events

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

* Approved dose by European Medicines Agency.
AP, acute pancreatitis; CI, confidence interval; FCS, familial chylomicronemia syndrome.
1. Stroes et al. *N Engl J Med* 2024.

Balance study in FCS: Safety and tolerability profile¹

	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
AEs, n (%)			
Any	22 (96)	18 (86)	19 (86)
Related to study drug	5 (22)	6 (29)	7 (32)
Mild	3 (13)	6 (29)	3 (14)
Moderate	0	0	4 (18)
Severe	2 (9)	0	0
Leading to treatment discontinuation	0	1 (5)	2 (9)*
Leading to death	0	1 (5) [†]	0
Any serious	9 (39)	4 (19)	3 (14)
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 person	2 (9)	3 (14)	3 (14)
≥1 Influenza-like illness in a person [§]	0	1 (5)	1 (5)
≥1 Hypersensitivity AE in a person	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 people experienced SAEs
- No drug-related SAEs
- No clinically meaningful changes in platelet count or in measures of hepatic and renal function
- No clinically meaningful increases in HbA1c in any treatment group

* AEs in the 80 mg group leading to treatment discontinuation were diarrhoea, vomiting, flushing, and chest discomfort in 1 person and chills, myalgia, and trismus in the other person. † 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 syndrome; FMQ, Food and Drug Administration medical query; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event. 1. Stroes et al. *N Engl J Med* 2024.

Key takeaways



FCS is a disease with refractory high TG levels and extremely high risk of acute pancreatitis^{1,2}



apoC-III is a key regulator of triglyceride metabolism^{3,4}



In people with FCS, apoC-III inhibition effectively reduces triglyceride levels and acute pancreatitis^{4–6}

**Q&A and
panel discussion**
All faculty

Q&A and panel discussion

All faculty

Please use the available
microphones to ask your
question



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using the **EASD app**





Closing remarks

Prof. Raffaella Buzzetti



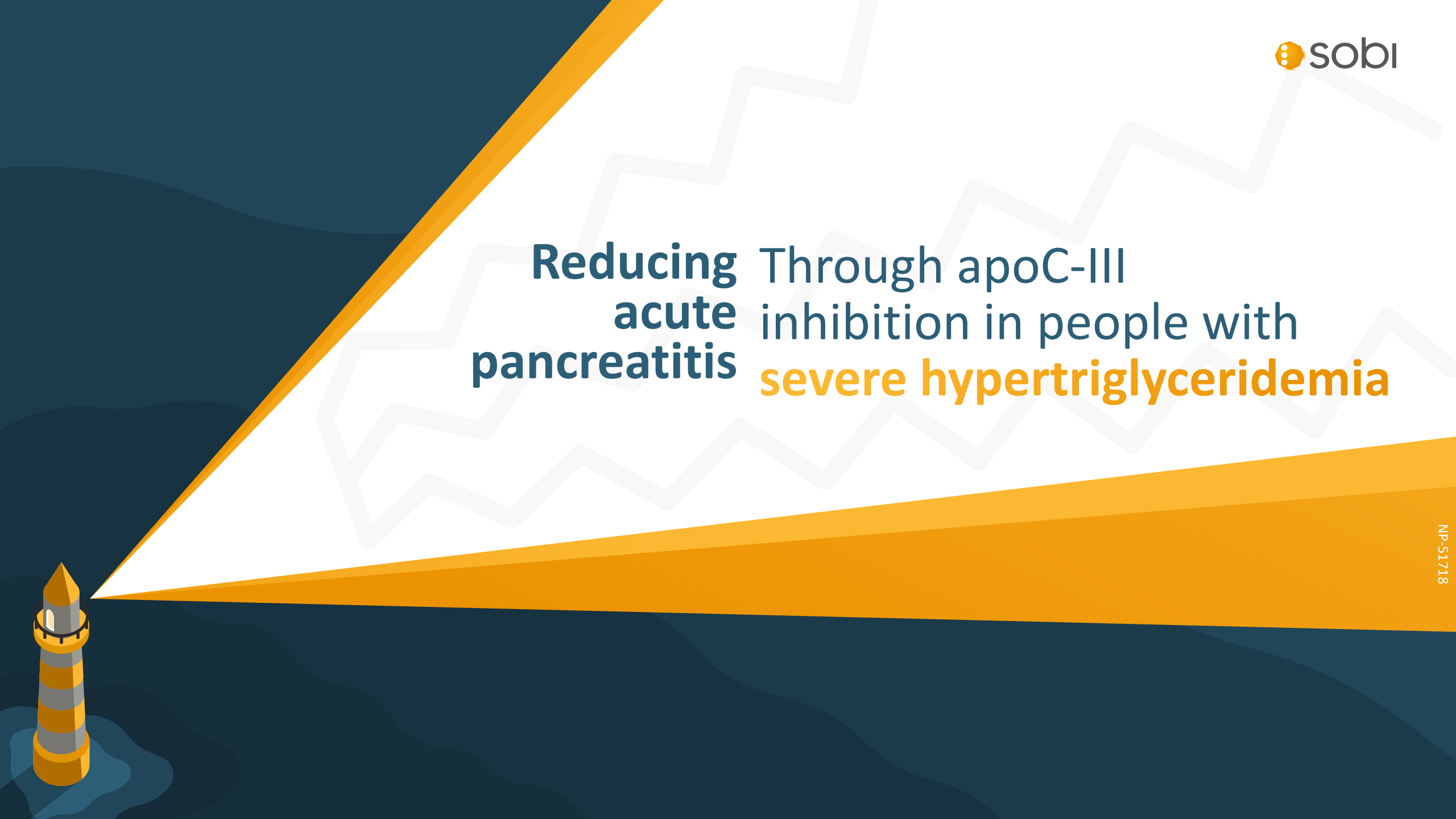
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improving future events



Thank you
for joining us





**Reducing acute
pancreatitis** Through apoC-III
inhibition in people with
severe hypertriglyceridemia