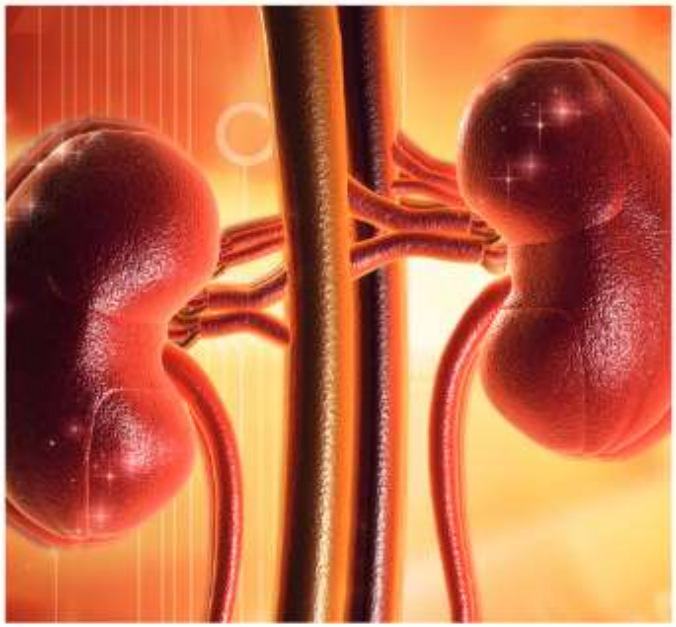


9. BRANDENBURGER NEPHROLOGIE KOLLEG

13. - 14.06.2019

Familiäres Chylomikronämie-Syndrom

Gerald Klose, Bremen

Klose.bremen@t-online.de

Endokrinologie Bremen: Dr. med. Knut W. Spieker · Dr. med. Iris van de Loo, Dr. med. Claudia Otte

Praxis für Gastroenterologie, Kardiologie und Präventionsmedizin: Dr. T. Beckenbauer und Dr. S. Maierhof

Interessenkonflikte

Vorträge, Advisory Board
Aegerion, Akcea, Amgen, BMS, BERLIN CHEMIE, MSD, OmniaMed, Sanofi, Synlab

Vorträge für Non-Profit-Organisationen:

Arzneimittelkommission der Deutschen Ärzteschaft, DGIM, DGK, NWGIM, DDG, D.A.CH, Schlichtungsstelle für Arzthaftpflichtfragen der Norddeutschen Ärztekammern

Neue Arznei in Sicht

RNA-Therapie gegen zuviel Chylomikronen

Der Ausschuss für Humanarzneimittel der EMA hat sich für die bedingte Zulassung von Waylivra® als 285 mg-Lösung zur Injektion für die Therapie bei familiärem Chylomikronämie-Syndrom (FCS) ausgesprochen.

Ärzte Zeitung-Newsletter vom Montag, 1. April 2019

AKCEA THERAPEUTICS

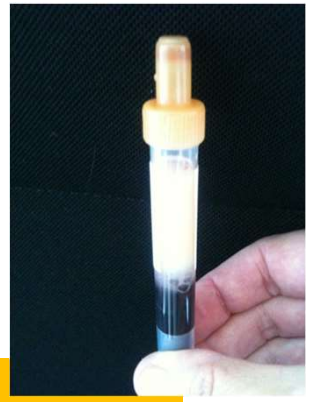
Akcea and Ionis Receive Positive EU CHMP Opinion for WAYLIVRA™ (volanesorsen)

March 1, 2019

Familiäres Chylomikronämie-Syndrom

- Differentialdiagnose
- Definition, Prävalenz
- Pathophysiologie
- Klinik/Pankreatitis
- Therapie

Manifestationsformen primärer Nüchtern-Chylomikronämien
Prävalenz: 1:600 (5 % monogen, 95 % polygen)



Monogen „early onset“	**polygenic late-onset**
Sehr selten Auftreten in Kindheit und Adoleszenz Homozygote Mutationen	Akkumulation mehrerer genetischer Abweichungen, Exazerbations-Möglichkeit durch sekundäre Faktoren wie Alkohol,Typ1 - oder Typ2- Diabetes mellitus, Schwangerschaft

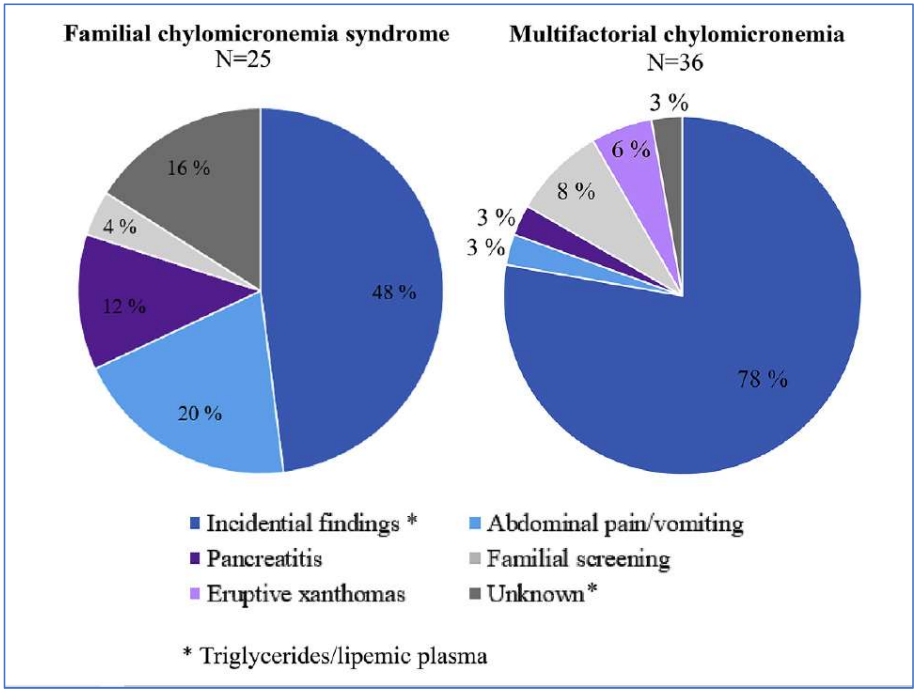
Brahm, A. J. & Hegele, R. A. Nat. Rev. Endocrinol. advance online publication 3 March 2015

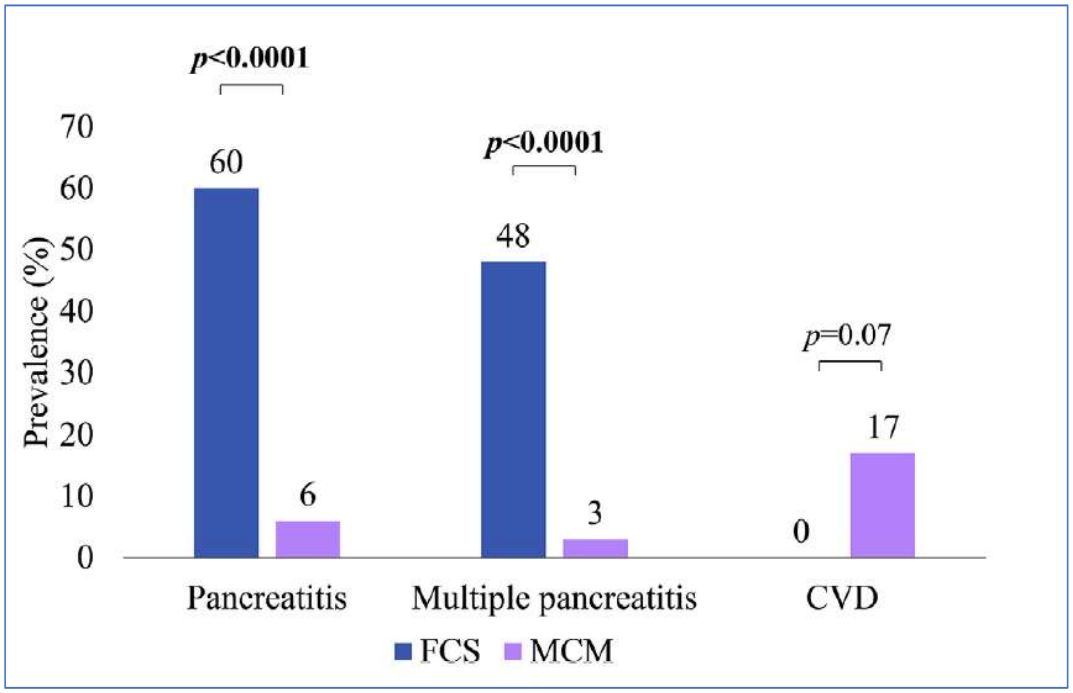
Charakteristika monogener und polygener Chylomikronämien

	Monogen	polygen
Bezeichnung	Familial chylomicronaemia Type 1 HLP	Mixed dyslipidaemia Type 5 HLP
Lipoproteine	Nur Chylos erhöht	Chylos und VLDL
Klinik	Gedeihstörungen, Nausea, eruptive Xanthome, Lipämia retinalis abdominelle Beschwerden, Pankreatitis	Nausea, abdom. Beschwerden Pankreatitis
CVD Risiko	CVD – Risiko minimal	CVD-Risiko erhöht
Vererbung	Autosomal rezessiv	Familiär möglich, kein Muster
Mutationen	Mutationen LPL, APOC2,APOA5 GPIHBP1 und LMF1	Common variants (SNP) with small effects in ~40 genes identified in genome-wide association studi
Bisherige Therapien	Ernährung, absolute Fettrestriktion, Mittelkettige TG	Ausschalten sekundärer Ursachen, Fibrate, Omega-3-FS

Chylomicronemia: Differences between familial chylomicronemia syndrome and multifactorial chylomicronemia

Martine Paquette[a], Sophie Bernard[a,b], Robert A. Hegele[c], Alexis Baass[a,d,e,*]





Atherosclerosis. 2019 Apr;283:137-142

Familiäres Chylomikronämie-Syndrom: Differentialdiagnose

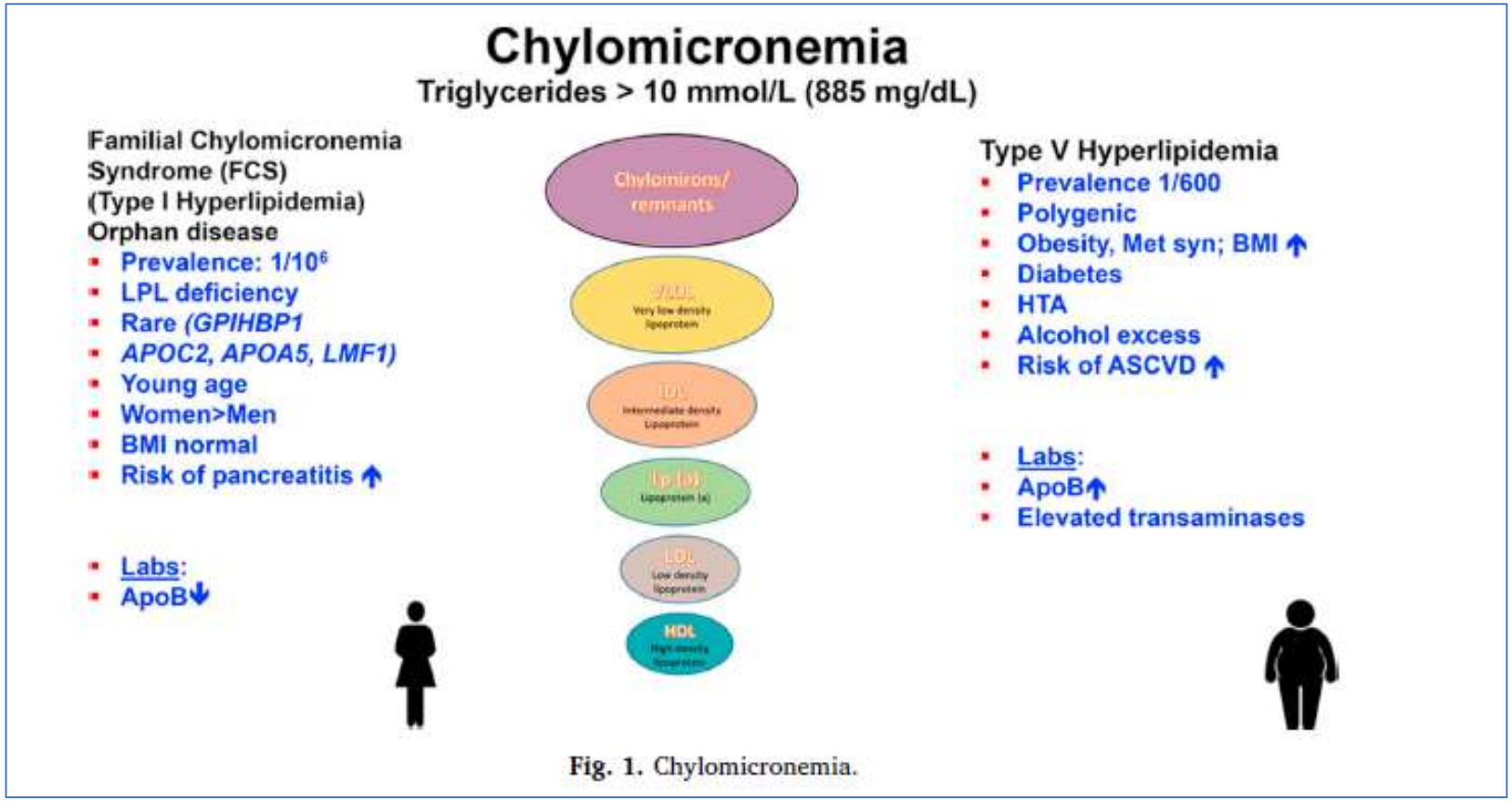


Fig. 1. Chylomicronemia.

Alothman L et al. Atherosclerosis. 2019 Apr;283:121-123.

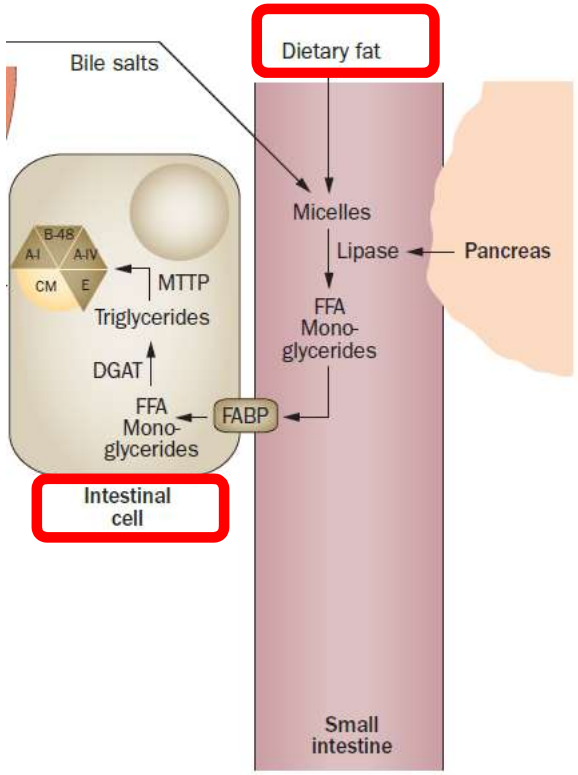
Familial chylomicronemia syndrome (FCS)

Chylomikronämie, Triglyceride > 885 mg/dl (> 10mmol/L)

- Synonym Typ I Hyperlipoproteinämie nach Fredrickson
- Orphan Disease mit Prävalenz von 1: 1 000 000
- Lipoproteinlipase (LPL) – Mangel
- Seltener GHIHBP1, Apo C2,APOA5, LMF1 Mutationen
- Junges Alter
- Frauen> Männer
- BMI normal
- Pankreatitis-Risiko

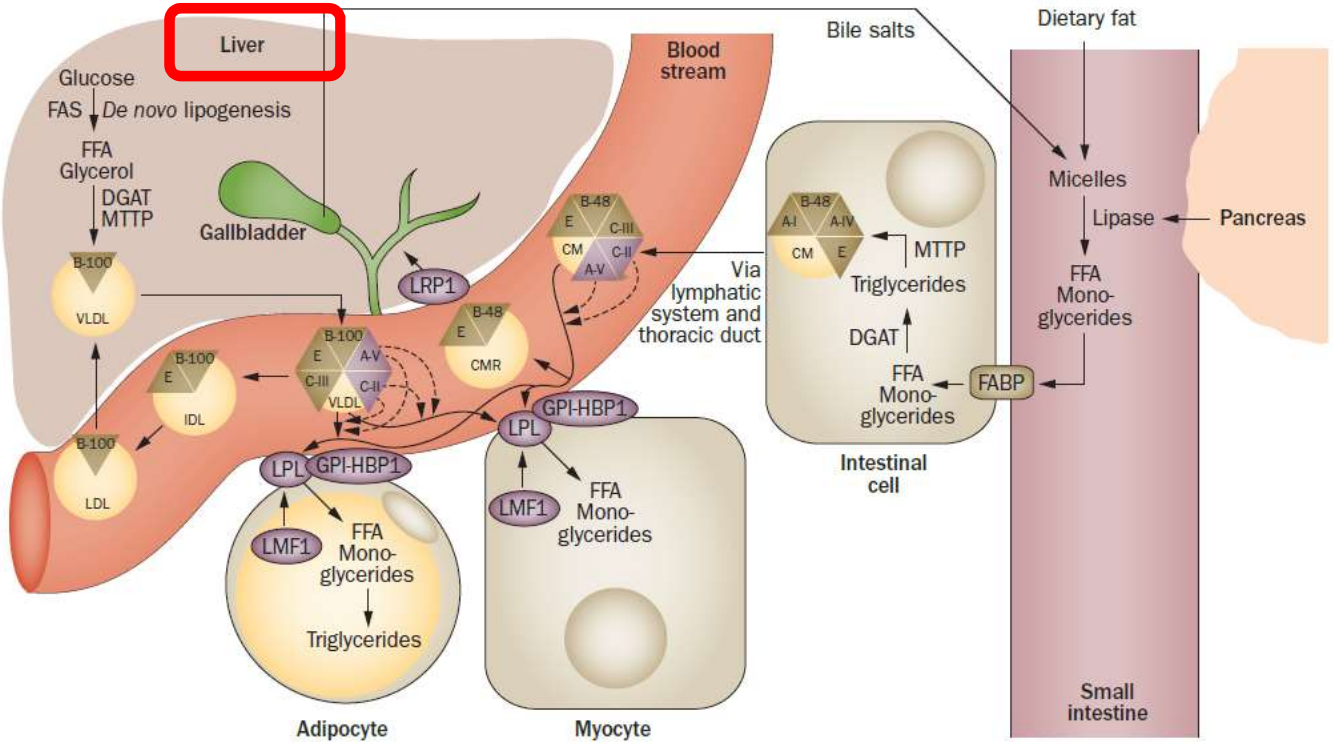
Mod. nach Parquette M et al., Ather**oscl**erosis. 2019 Apr;283:137-142

Stellenwert lipolytischer Enzyme im Triglycerid-Metabolismus



Brahm, A. J. & Hegele, R. A. Nat. Rev. Endocrinol. advance online publication 3 March 2015

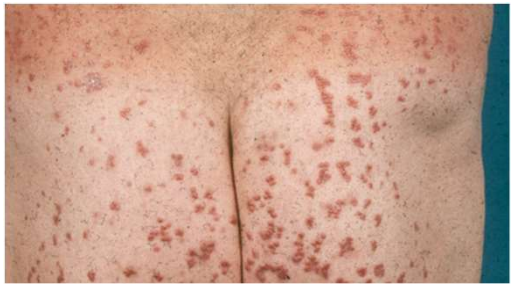
Stellenwert lipolytischer Enzyme im Triglycerid-Metabolismus

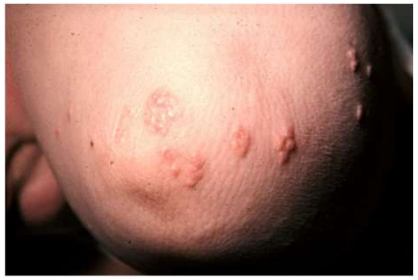


Brahm, A. J. & Hegele, R. A. Nat. Rev. Endocrinol. advance online publication 3 March 2015

FCS : Klinische Charakteristika

- Eruptive Xanthom
- Lipämia retinalis
- Pankreatitis / Hepatosplenomegalie





Reminder of important clinical lesson

CASE REPORT

Severe hypertriglyceridaemia and pancreatitis in a patient with lipoprotein lipase deficiency based on mutations in lipoprotein lipase (LPL) and apolipoprotein A5 (APOA5) genes

Charlotte Koopal[1], Remy Bemelmans[2], A David Marais[3] and Frank LJ Visseren[4]

- A 44-year-old woman was admitted with pancreatitis caused by hypertriglyceridaemia (fasting triglycerides 28 mmol/L) (**2478 mg/dl)**
- Genetic analysis revealed mutations in two genes involved in triglyceride metabolism (apolipoprotein A5 and lipoprotein lipase [LPL])
- initially treated with gemfibrozil, but this was discontinued due to side effects.
- Dietary triglyceride restriction and discontinuation of the oral contraceptives lowered the plasma triglycerides within 2 weeks to 3.4 mmol/L.
- Hypertriglyceridaemia is a risk factor for pancreatitis and cardiovascular disease, and has a broad differential diagnosis including genetic causes. Patients can achieve near-normal triglyceride values with a low-fat diet only.

BMJ Case Report 2019

26- jähriger Patient

6-7/2017 stationäre Behandlung wegen

[1]schwerer, ödematös- exsudativer Pankreatitis, massive Hypertriglyceridämie (3896 mg/dl), V. a. angeborene Fettstoffwechselstörung mit führender Hypertriglyceridämie, V. a. pankreopriven Diabetes mellitus Typ 3 c

8 x Plasmaaustausch, Beginn einer intensivierten Insulintherapie

Beginn einer Fibrattherapie (Fenofibrat 200 mg) Omega-FS 3 x 100 mg, Insulin Lantus 32 IE, Actrapid nach Schema)

[1]Angaben des Entlassungsberichtes

26 jähriger Patient mit Z.n. HTG- assoziierter Pankreatitis und pankreoprivem DM

Daten ambulanter Weiterbehandlung

Ergebnisse ***Auffälliger Befund!***

Gen	Variante	Zygotie	MAF (%)	Erbgang	ACMG-Klasse	Klinische Bewertung
LPL	c.788T>C p.(Leu263Pro)	Hetero	unbekannt	AD/AR	Klasse 3	Variante unklarer Signifikanz

Phänotyp OMIM	Variantentyp	Konsequenz	Labor-Einschätzung
144250: Combined hyperlipidemia, familial (AD) 238600: Lipoprotein lipase deficiency (Vorwiegend AR)	Missense-Variante	Austausch einer stark konservierten Aminosäure; Domäne „Lipoprotein-Lipase" betroffen	Tendenz pathogene Wirkung; Familienanalyse ist zu erwägen; evtl. weiterführende Diagnostik erwägen

Beurteilung

Bei o.g. Patienten war eine heterozygote Sequenzvariante im LPL-Gen nachweisbar, die derzeit mit unklarer klinischer Signifikanz gewertet wird (Klasse 3 Variante). Das LPL-Gen wird u.a. mit dem Vorliegen einer Lipoproteinlipase-Defizienz assoziiert und folgt vorwiegend einem autosomal rezessiven Erbgang.

Synlab

26 jähriger Patient

6/2017 ausgewähltes pathol. Labor bei Aufnahme[1]

Leuko	**11,7 (4-10)**
CRP	7,5 (0-0,05
BZ	228
Na	128 (136-145)
Ca	2,10 (2,15-2,5)
Chol	602
Triglyceride	3.896
Lipase	243 (13-60)
pH	7,28 (7,35-7,45)

[1]Angaben des Entlassungsberichtes

26 jähriger Patient mit Z.n. HTG- assoziierter Pankreatitis und pankreoprivem DM

Daten ambulanter Weiterbehandlung (Hinweis auf MCT- Fette)

	5.12.17	23.1.18	31.8.18
Cholesterin	315	327	269
Triglyceride	186	548	132
LDL	247		209
Glucose	285	134	136
HbA1c	9,1	7,0	6,4
Lipase U/L (< 60)		32	26

Hypertriglyceridämie und Pankreatitis

BERLINER

KLINISCHE WOCHENSCHRIFT.

Organ für practische Aerzte.

Mit Berücksichtigung der preussischen Medicinalverwaltung und Medicinalgesetzgebung

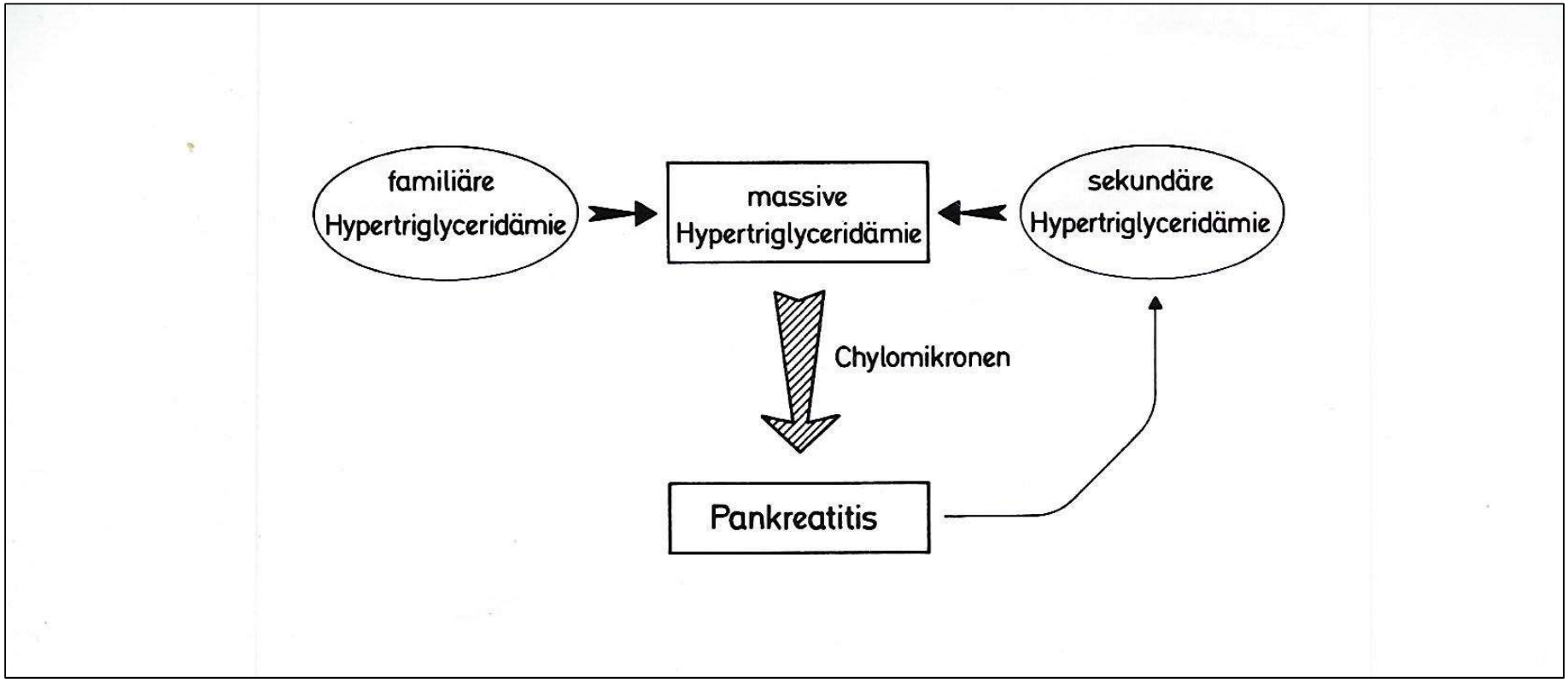
Dr. 0. J. Wijnhausen, 1921: Ueber Xanthomatose in einem Falle rezidivierender Pankreatitis, 1921

...der Patient, dessen Krankheitsgeschichte ich unterbreiten will, ist ein 35jähriger Jurist...

...Wie in allen bisher untersuchten Fällen von Xanthombildung war bei unserem Patienten der Cholesteringehalt des Blutserums stark erhöht. Indem dieser in normalen Fällen bestimmt nach der Methode Windaus durchschnittlich 1,75 g pro Liter beträgt, war der Gehalt einmal drei Tage vor einem Anfalle, als schon viele Xanthome bemerkbar waren, der Harn Spuren Zucker enthielt, und der Blutzuckergehalt 0,19 pCt. betrug, 8,6 g pro Liter, einer der höchsten Werte, welcher bis auf heute festgestellt worden ist.

...Das Blut war alsdann sehr stark lipämisch...

Pathogenese von Hypertriglyceridämien bei akuter und rezidivierender Pankreatitis



CORRESPONDENCE ARCHIVE

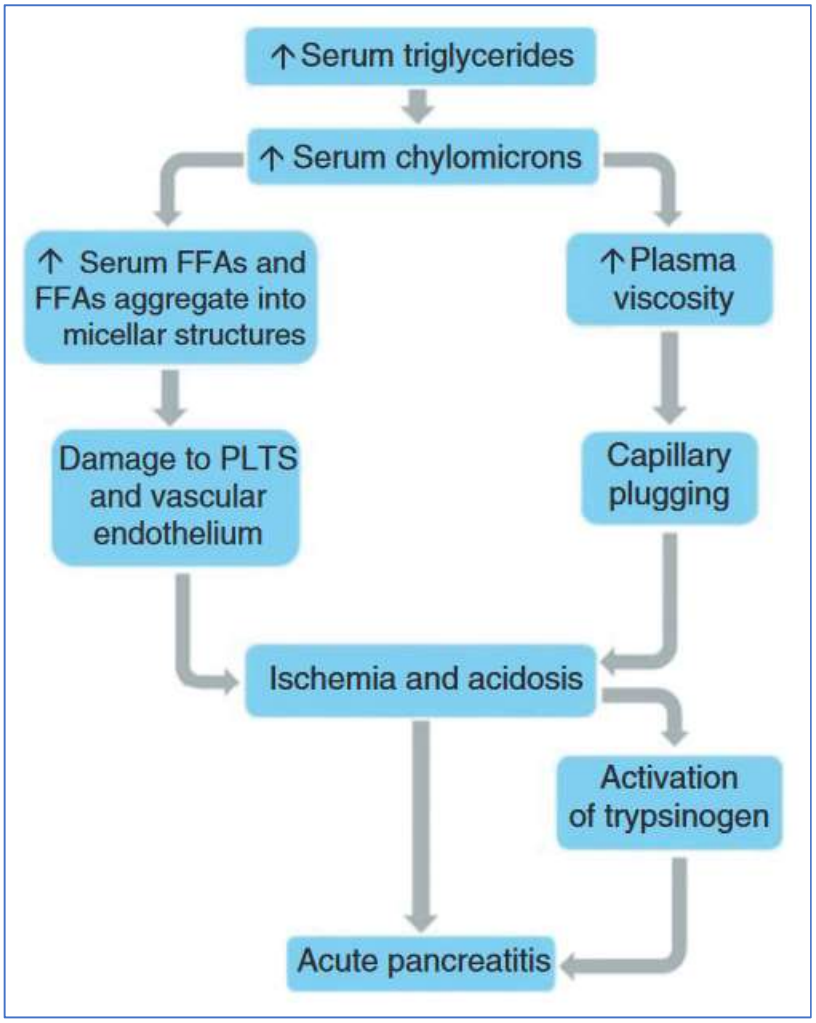
Low Hepatic Triglyceride Lipase in Pancreatitis

September 7, 1978
N Engl J Med 1978; 299:553-554
DOI: 10.1056/NEJM197809072991016

"…it may be concluded that acute or relapsing pancreatitis itself is associated not only with low lipoprotein lipase but also with low hepatic triglyceride lipase activities."

Klose G et al., N Engl J Med 1978; 299:553-554

Wodurch und wann führt eine Hypertriglyceridämien zu Pankreatitiden?



Possible mechanisms involved in the pathophysiology of hypertriglyceridemic pancreatitis

De Pretis N et al., United European Gastroenterol J. 2018 Jun;6(5):649-655

Epidemiologie der hypertriglyceridämischen Pankreatitis

- 20% incidence, retrospective study of patients with severe HTG(triglycerides>1000 mg/dl) Lloret Linares C et al., Pancreas 2008; 37: 13–2
- 10% bis 50% (Pregnancy) Ewald N et al., Current opinion in Lipidology 2009
- 6% incidence with triglyceride levels >1772 mg/dl versus 3% of those with triglyceride levels between 886 mg/dl and 1771 mg/dl Sandhu S et al., Lipids HealthDis 2011; 10: 157
- 2.3%–10% incidence of HTGP Anderson F et al., Pancreatology2009; 9: 252–257, Cavallini G et al., .Dig Liver Dis 2004;36: 205–211, Charlesworth A et al., Int J Surg 2015; 23(Pt A):23–27.

Therapie der hypertriglyceridämischen Pankreatitis 2009

Treatment modality	Limitations
Apheresis	Limited availability, invasive and expensive tool
Insulin	Only of limited efficiency
Heparin	Cave: increased LPL degradation and depletion of LPL plasma stores
Fibrates	Slow onset of TG lowering
Omega-3-FA	No limitations
Nicotinic acid	Prominent side effects such as facial flushing, slow onset of TG lowering
HMG-CoA reductase inhibitors	Higher risk of myositis or myopathy, no drug of first choice
MCT	No limitations

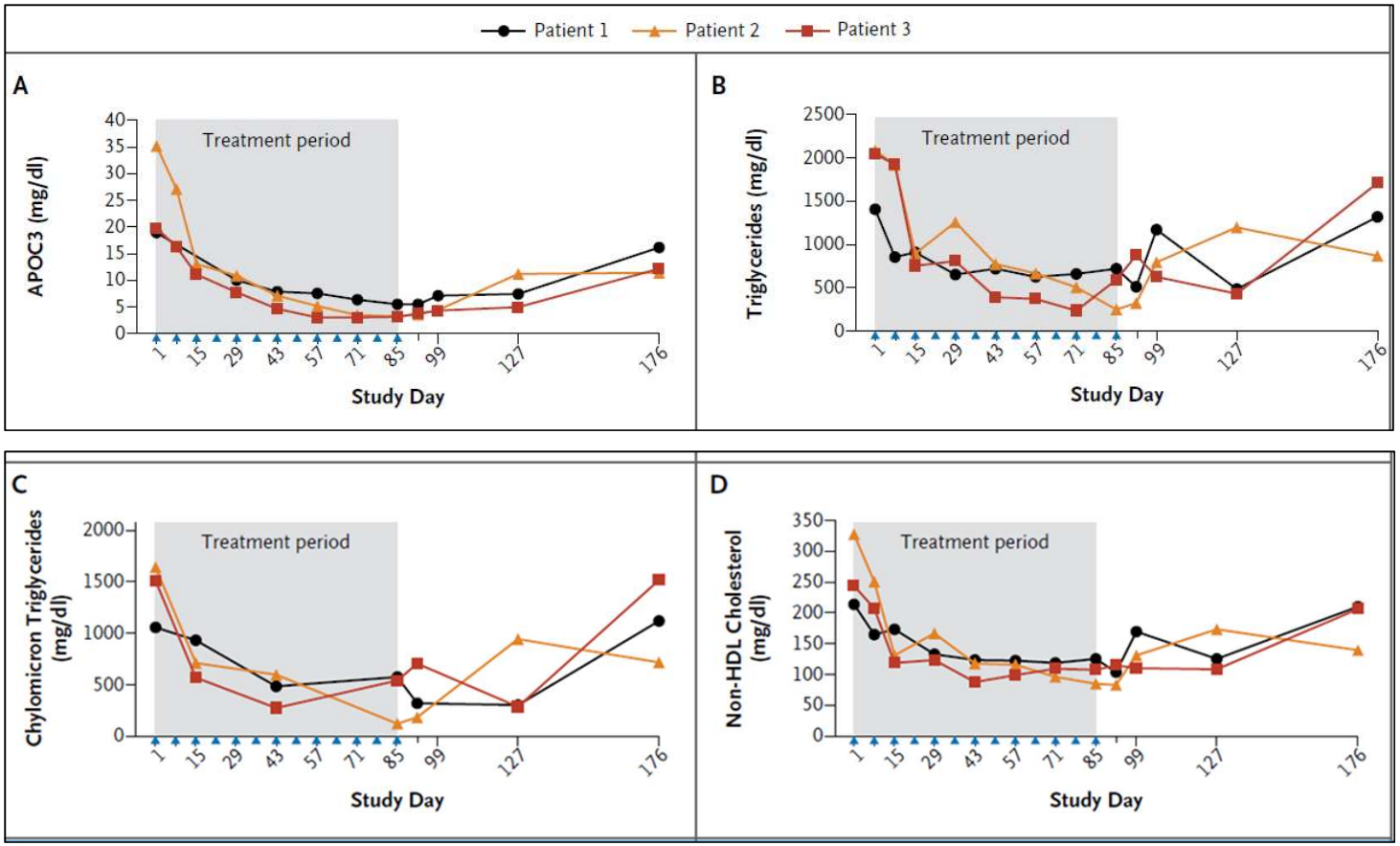
Current Opinion in Lipidology 2009,20:497–507

Neuere therapeutische Entwicklungen bei Chylomikronämie

Drug class (example)	Mechanism of action	Advantages	Disadvantages	References
MTTP inhibition (lomitapide)	Prevents triglyceride transfer to apoB-containing particles during their formation	Small molecule that can be administered orally Reduces triglyceride levels by 30–40%	Common gastrointestinal adverse effects: nausea and diarrhoea Increased levels of liver enzymes and hepatosteatosis Cost	101,104–107
LPL gene therapy (alipogene tiparvovec)	Introduces a normal *LPL* gene into tissues of LPL-deficient patients	One time intramuscular injection Possible improvement in chylomicron kinetics	No enduring triglyceride effect after 12 weeks Indicated only for patients with autosomal recessive *LPL* gene deficiency	108–110,112
DGAT1 inhibition (AZD7687, PF0460110, ABT-046 and LCQ908)	Prevents triglyceride synthesis and re-synthesis	Small molecule that can be administered orally Reduces triglyceride levels by up to 80%	Gastrointestinal adverse effects Limited long-term data and safety data available Possible cross-reactivity with DGAT2	113–119
APOB mRNA interference (mipomersen)	Prevents synthesis and secretion of apoB-containing lipoproteins	Subcutaneous administration of antisense RNA Theoretical efficacy by reducing both apoB-48 and apoC-III production	Limited efficacy data in chylomicronaemia Uncertain delivery of agent to primary site of action (intestine) Common injection site reactions and flu-like symptoms	101,121
APOC3 mRNA interference	Increases LPL activity and reduces triglyceride-rich	Genetically validated target Subcutaneous administration	Limited long-term data and safety data available	120,122,124

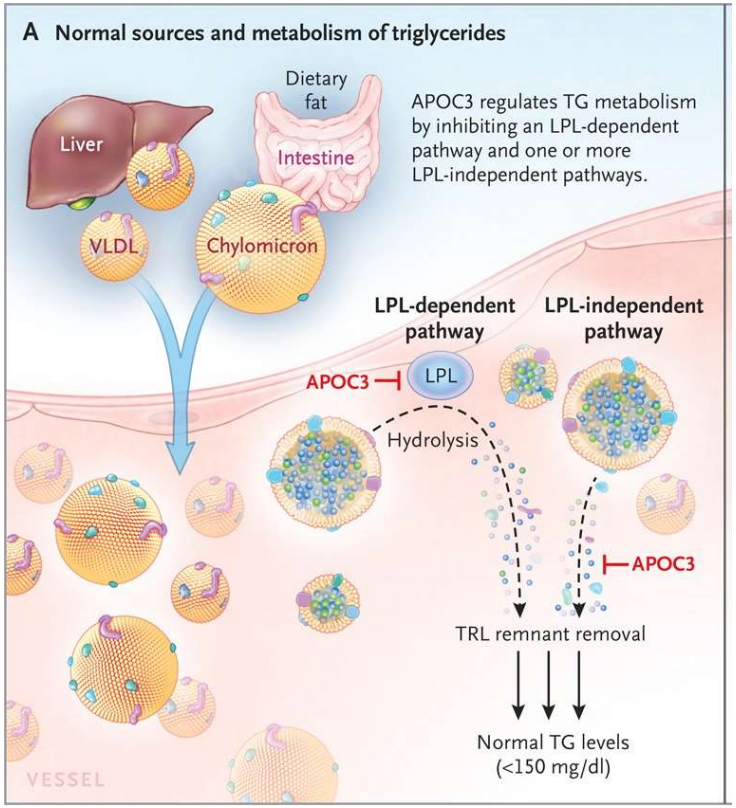
Brahm, A. J. & Hegele, R. A. Nat. Rev. Endocrinol. advance online publication 3 March 2015

Targeting APOC3 in the familial chylomicronemia syndrome



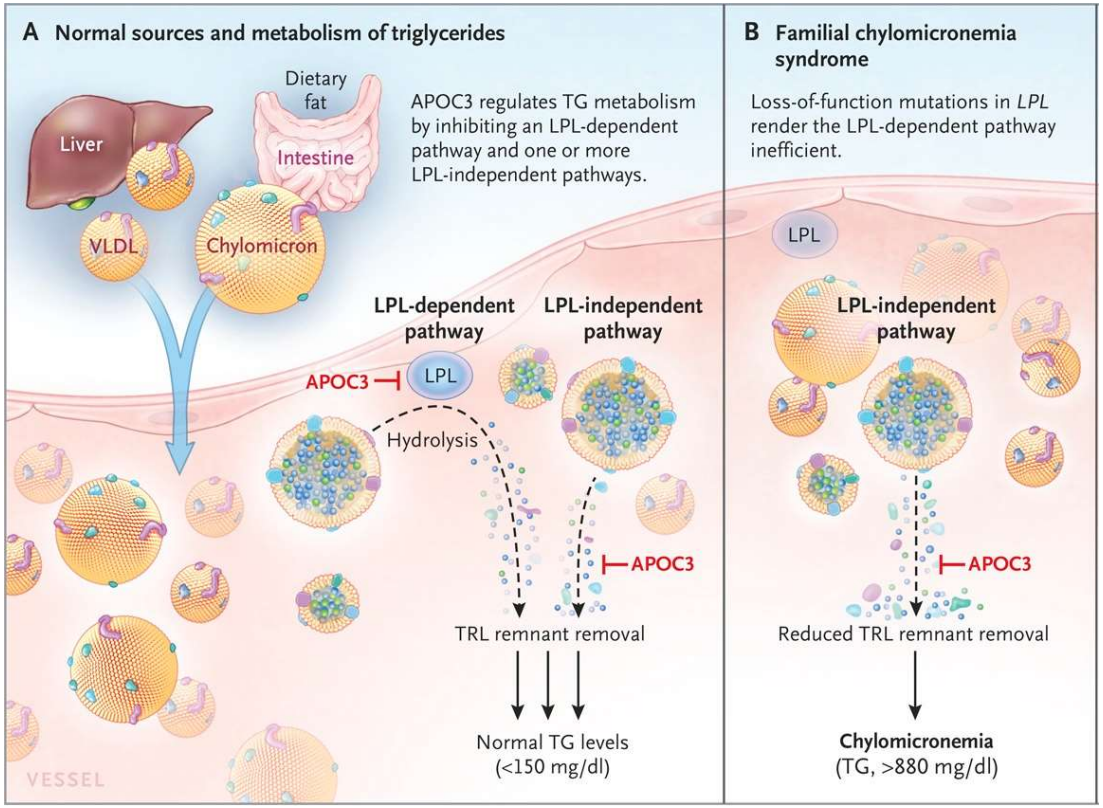
Gaudet D et al., N Engl J Med. 2014 Dec 4;371(23):2200-6

Targeting APOC3 in the Familial Chylomicronemia Syndrome



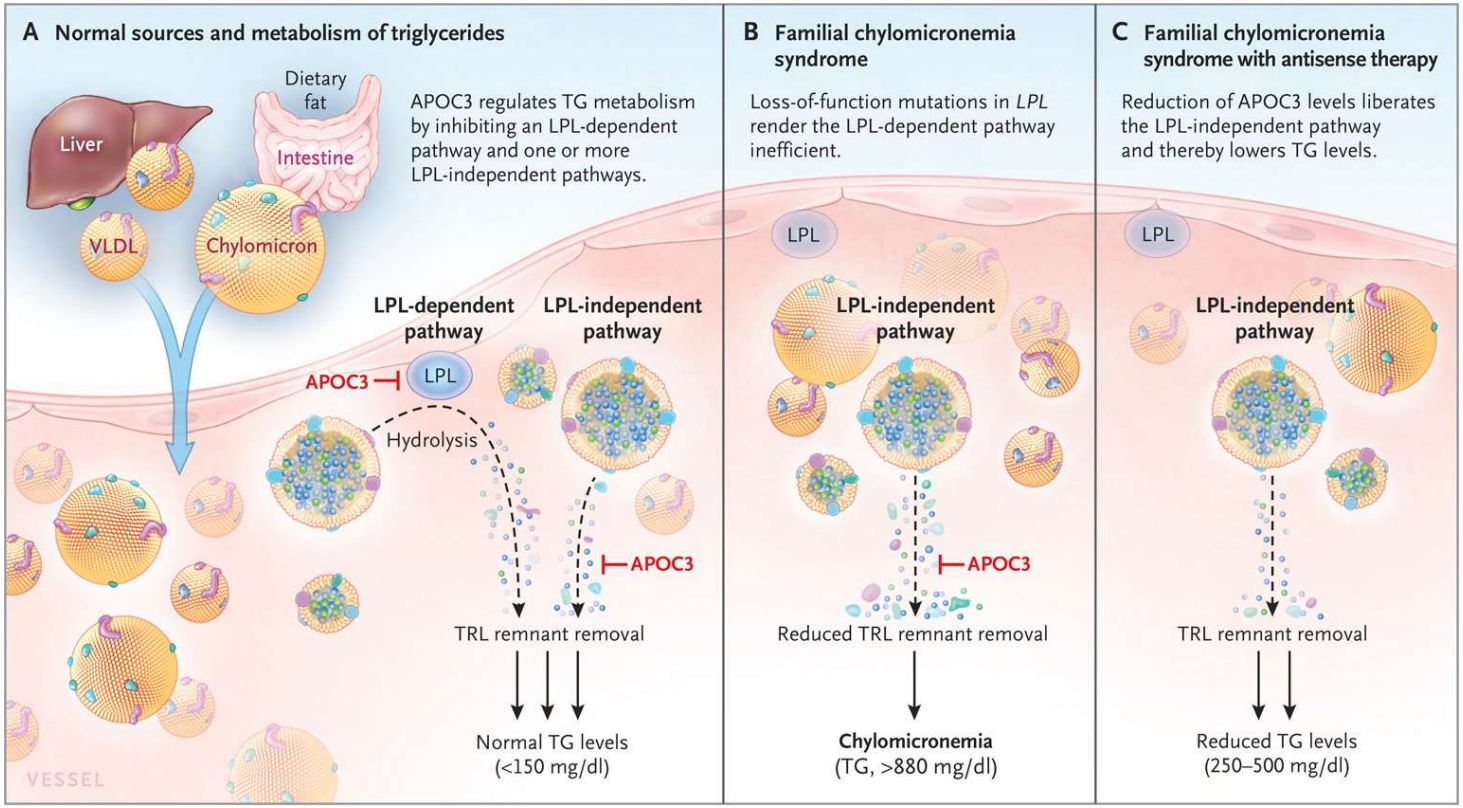
Gaudet D et al., N Engl J Med 2014;371:2200-6.

Targeting APOC3 in the Familial Chylomicronemia Syndrome



Gaudet D et al., N Engl J Med 2014;371:2200-6.

Targeting APOC3 in the Familial Chylomicronemia Syndrome

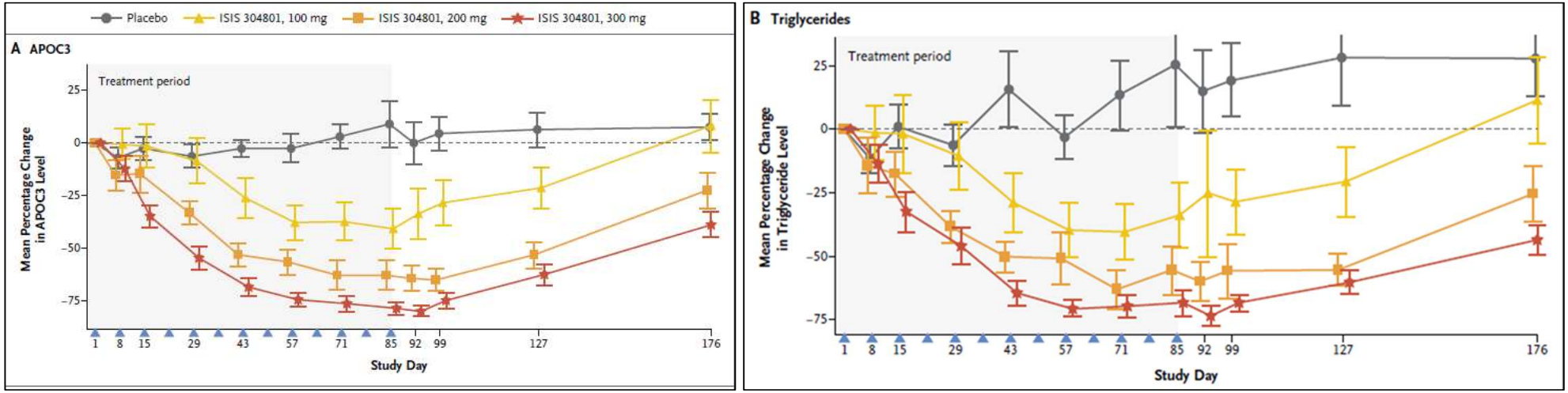


Gaudet D et al., N Engl J Med 2014;371:2200-6.

Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

Daniel Gaudet, M.D., Ph.D., Veronica J. Alexander, Ph.D., Brenda F. Baker, Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Walter Singleton, M.D., Richard S. Geary, Ph.D., Steven G. Hughes, M.B., B.S., Nicholas J. Viney, B.Sc., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., Joseph L. Witztum, M.D., John D. Brunzell, M.D.,* and John J.P. Kastelein, M.D., Ph.D.

RCT , N=57

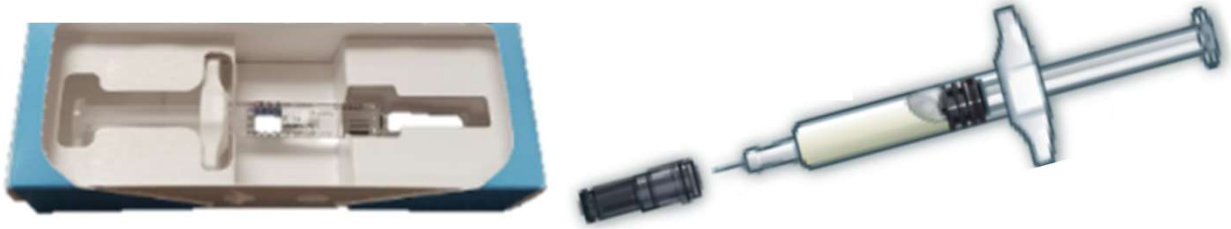


N Engl J Med. 2015 Jul 30;373(5):438-47

Volanesorsen

Overview

- Binding of volanesorsen to the cognate mRNA results in the RNase H1-mediated **degradation of *APOC3* mRNA, thus preventing production of the ApoC-III protein**[1]
- Reduction of ApoC-III levels liberates the LPL-independent pathway and thereby lowers TG levels[2]
- Volanesorsen is administered at a dose of 285 mg via subcutaneous injection (1.5 ml) once weekly for 3 months following 3 months every 2 weeks[1]
    - Self-administered, pre-filled syringe, 27 gauge, 8 mm needle



2'MOE, 2'-O-methoxyethyl

1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019.
2. Gaudet D et al. *N Engl J Med* 2014;371:2200–2206.

Waylivra® - Volanesorsen

Therapeutic indication[1]

- Waylivra® is indicated as an adjunct to diet **in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis**, in whom response to diet and triglyceride lowering therapy has been inadequate.

1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019,

Original Article

Characterizing familial chylomicronemia syndrome: Baseline data of the APPROACH study

Dirk J. Blom, MD, PhD*, Louis O'Dea, MD, Andres Digenio, MD, PhD,
Veronica J. Alexander, PhD, Ewa Karwatowska-Prokopczuk, MD, PhD,
Karren R. Williams, PhD, Linda Hemphill, MD, Ovidio Muñiz-Grijalvo, MD, PhD,
Raul D. Santos, MD, Seth Baum, MD, Joseph L. Witztum, MD

- N= 66, Durchschnittsalter 46 Jahre;
- Kausale Mutationen bei 79% (52), davon LPL Mutationen bei 62% (41).
- low-fat diet, 43% Fibrate, 27% FischÖl, 21% Statine.
- Median Nüchtern-TG: 1985 mg/dl
- 76% der Patienten ≥1 lifetime episode of acute pancreatitis; 23 Patienten 53 Pankreatitis- Ereignisse in den 5 vorausgegangenen Jahren

APPROACH: Phase 3 study[1]

Primary & secondary objectives[1,2]

Primary[1]

- To evaluate the efficacy of volanesorsen (285 mg once weekly) compared with placebo on the percent change in fasting TG at month 3 from baseline

Secondary[2]

- To evaluate the efficacy of volanesorsen (285 mg once weekly) compared with placebo on the following:

MRI, magnetic resonance imaging; TG, triglyceride

1 Blom DJ *et al. J Clin Lipidol. 2018*;12: 1234-1243

2 Akcea Therapeutics Briefing Document. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. May 10, 2018. p76
Accessible at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM606860.pdf

APPROACH: Phase 3 study

Tertiary & exploratory objectives[1,2]

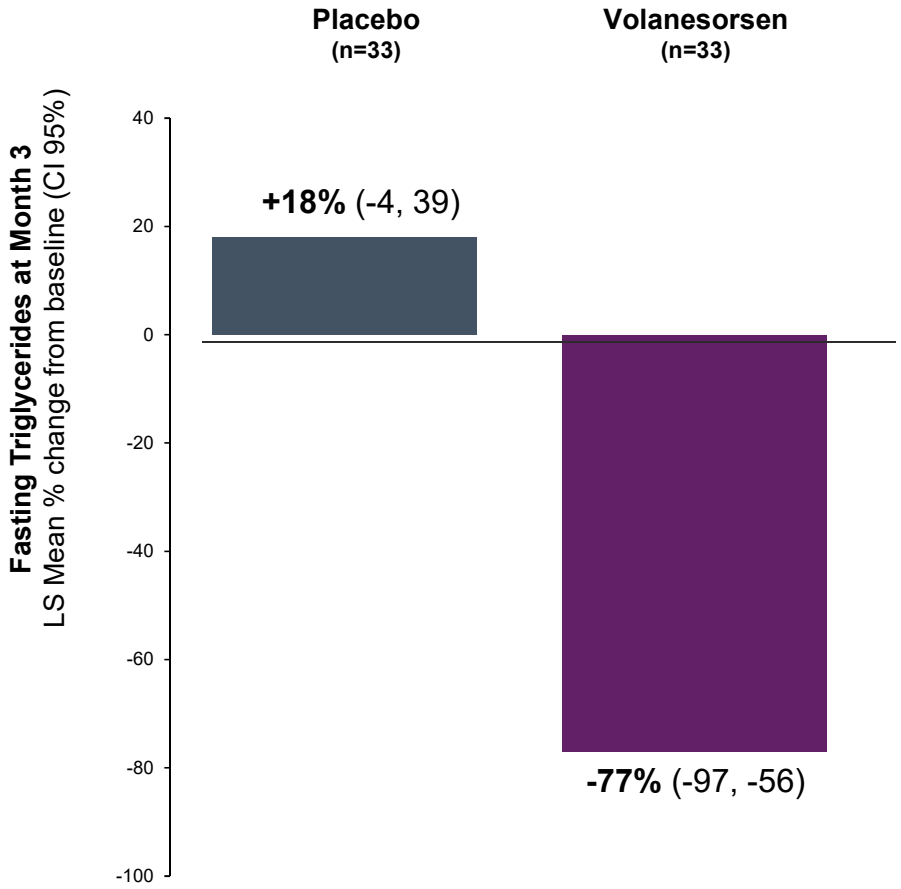
- To evaluate the effect of volanesorsen (285 mg once weekly) as compared with placebo on:
  - Exploratory endpoints included changes in other lipid/lipoprotein parameters, frequency of xanthoma, lipemia retinalis, change in post-heparin LPL mass and activity, and adjudicated acute pancreatitis event rate before and after treatment with volanesorsen

LPL lipoproteinlipase

1. Blom DJ *et al. J Clin Lipidol. 2018*;12: 1234-1243.
2. Akcea Therapeutics Briefing Document. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. May 10, 2018. p76
Accessible at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM606860.pdf

APPROACH: Phase 3 study

Primary endpoint[1]



Adapted from SmPC Waylivra May 2019[1]

Adapted from SmPC Waylivra May 2019[1]

TG, triglyceride; LS, least squares

1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019,

APPROACH: Effects of volanesorsen on lipid parameters

Mean baseline and percent change in lipid parameters from baseline to month 3[1]

	Placebo (n=33)		Volanesorsen (n=33)	
	Baseline	% Change	Baseline	% Change
Total Cholesterol (mmol/L)	7.3	+13%	7.6	-39%
HDL-C (mmol/L)	0.43	+5%	0.44	+45%
LDL-C (mmol/L)	0.72	+7%	0.73	+139%
Non-HDL-C (mmol/L)	6.9	+14%	7.1	-45%
ApoC-III (g/L)	29	+6%	31	-84%
ApoB (g/L)	69	+2%	65	+20%
ApoB-48 (g/L)	9	+16%	11	-75%
Chylomicron TG (mmol/L)	20	+38%	22	-77%

Adapted from SmPC Waylivra May 2019[1]

C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; Apo, apolipoprotein

1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019.

APPROACH: Phase 3 study

Acute pancreatitis events[1,2]

Patients experiencing pancreatitis attacks and pancreatic attack events in patients[1,2]

Placebo n=33		Volanesorsen n=33	
Patients	Events	Patients	Events
3	4	1	1
p=0.61			

Adapted from Blom et al.[2]

Pancreatitis in patients at high risk of recurrent attacks (≥2 adjudicated pancreatic events in the past 5 years)[1,2]

	Placebo n=33		Volanesorsen n=33	
	Patients	Events	Patients	Events
Patients with multiple (2 or more) adjudicated events in past 5 years* (post-hoc analysis)	4	17	7	24
Events during study	3	4	0	0
p=0.02				

Adapted from Blom et al.[2]

*Pancreatitis events were independently adjudicated by an independent, blinded, medical committee according to the Atlanta classification of acute pancreatitis and as outlined in the Pancreatitis Adjudication Charter)

1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019

2. Blom DJ et al, Treatment with Volanesorsen (VLN) Reduced Triglycerides and Pancreatitis in Patients with Familial Chylomicronemia Syndrome (FCS) and Severe Hypertriglyceridemia (sHTG) vs Placebo: Results of the APPROACH and COMPASS Studies, Poster presented at European Pancreas Club (EPC) 2018 Berlin 13-16, 2018.

Summary of adverse reactions in clinical studies in patients with FCS (N = 86)[1]

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)
General disorders and Administration site conditions	injection site erythema, injection site pain, injection site pallor, injection site swelling, injection site pruritus, injection site discolouration, injection site induration,	asthenia, fatigue, injection site haematoma, injection site reaction, injection site urticaria, injection site warmth, chills, pyrexia, injection site dryness, injection site haemorrhage, injection site hypoaesthesia, injection site vesicles, malaise, feeling hot, influenza-like illness, injection site discomfort, injection site inflammation, injection site mass, pain, Injection site paraesthesia, injection site scab, Injection site papule, oedema, Non-cardiac chest pain, vessel puncture site haemorrhage
Investigation		platelet count decreased, cell count decreased,
disorders		
Musculoskeletal and connective tissue disorders		myalgia, arthralgia, pain in extremity, arthritis, back pain, musculoskeletal pain, neck pain, muscle spasms, joint stiffness, myositis, pain in jaw, polymyalgia rheumatica
Nervous system disorders		headache, hypoaesthesia, presyncope, retinal migraine, syncope, dizziness, tremor
Blood and lymphatic system disorders	thrombocytopenia	eosinophilia, immune thrombocytopenic purpura, spontaneous haematoma, leukopenia
Gastrointestinal disorders		nausea, diarrhoea, dry mouth, gingival bleeding, mouth haemorrhage, parotid gland enlargement, vomiting, abdominal pain, abdominal distension, dyspepsia, gingival swelling
Respiratory, thoracic and mediastinal disorders		epistaxis, cough, dyspnoea, nasal congestion, pharyngeal oedema, wheezing
Vascular Disorders		haematoma, hypertension, haemorrhage, hot flush
Eye disorders		conjunctival haemorrhage, vision blurred
Injury, poisoning and procedural complications		contusion
Metabolism and nutrition disorders		diabetes mellitus
Immune system disorders		imunisation reaction, hypersensitivity, serum sickness-like reaction
Psychiatric disorders		insomnia
Renal and urinary disorders		haematuria, proteinuria

1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019,

APPROACH: Phase 3 study

Thrombocytopenia[1]

- 75% of volanesorsen-treated patients had platelet levels < 140 x 10^9/L[1]
- 24% of Placebo-treated patients had platelet levels < 140 x 10^9/L[1]
- 47% of volanesorsen-treated patients had platelet levels < 100 x 10^9/L[1]
- None of these patients had any major bleeding events and all recovered to normal platelet levels following drug discontinuation and administration of corticosteroids where medically indicated[1]

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1. Summary of Product Characteristics (SmPC) - Waylivra (Volanesorsen) Date May 2019,

APPROACH: Phase 3 study

Zusammenfassung

- a marked reduction in plasma triglycerides (-77% v +18%, p<0.0001) at 3 months
- fewer patients experiencing acute pancreatitis events (1 patient with 1 event vs. 3 patients with 4 events) over the 52 weeks study period

- In patients at high risk of recurrent acute pancreatitis (≥2 adjudicated events in the past 5 years), treatment with volanesorsen for 52 weeks significantly reduced the incidence of acute pancreatitis events compared to placebo (p=0.02)[2]
- Treatment with volanesorsen had a mostly well tolerated safety profile[2]
  - Most common adverse events were mild local injection site reactions
  - Platelet reductions occurred, but were manageable by dose pause, dose reduction and treatment with corticosteroids and IVIG

IVIG intravenous immunoglobulin

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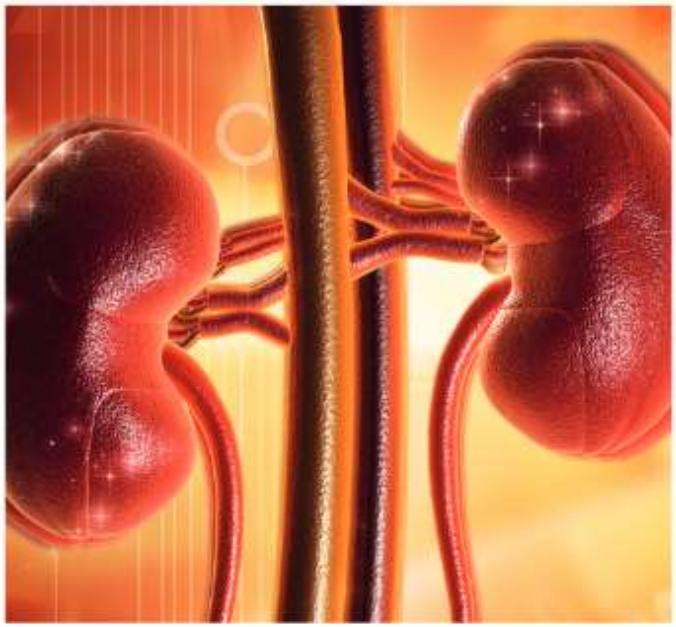
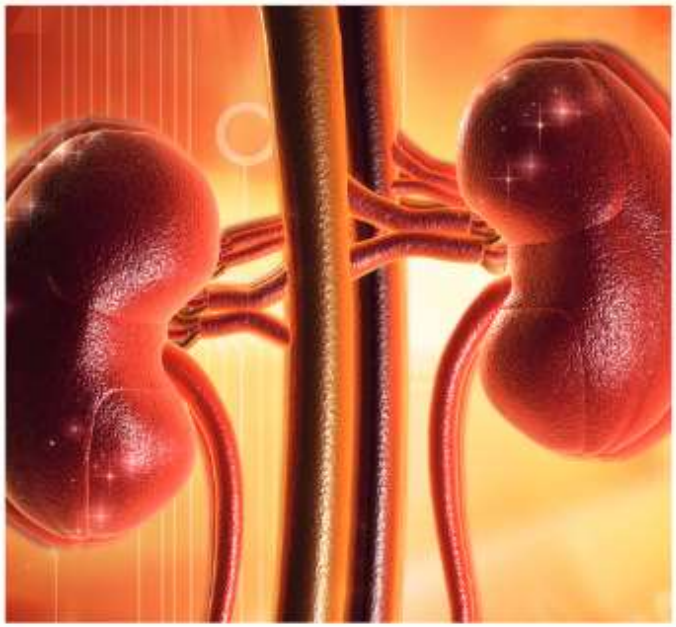
2. Blom DJ et al, Treatment with Volanesorsen (VLN) Reduced Triglycerides and Pancreatitis in Patients with Familial Chylomicronemia Syndrome (FCS) and Severe Hypertriglyceridemia (sHTG) vs Placebo: Results of the APPROACH and COMPASS Studies, Poster presented at European Pancreas Club (EPC) 2018 Berlin 13-16, 2018



9. BRANDENBURGER
NEPHROLOGIE KOLLEG
13. - 14.06.2019

Familiäres Chylomikronämie-Syndrom

Zusammenfassung



9. BRANDENBURGER NEPHROLOGIE KOLLEG

13. - 14.06.2019

Familiäres Chylomikronämie-Syndrom

Zusammenfassung

Massive monogene Hypertriglyceridämie mit sehr hohem Risiko rezidivierender Pankreatitiden

Neue Behandlungsmöglichkeit durch ApoC3 Antisense-Oligonukleotid-Therapie