FONDAZIONE S.I.S.A.

Per la promozione della ricerca sulle malattie da arteriosclerosi

Advanced Course on Rare Dyslipidaemia and Atherosclerosis Importance of Personalized Medicine and Differential Diagnosis

October 19, 2018

Bassini Hospital Via M. Gorki, 50
Cinisello Balsamo – Milan

Chairman
Alberico L. Catapano

This meeting is endorsed by the European Atherosclerosis Society EAS

Genetic and phenotypic basis of familial chylomicronemia syndrome

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SAPIENZA UNIVERSITÀ DI ROMA

Disclosures

Arca has received payments for the provision of:

- Grants and consulting services: Aegerion, Akcea/Ionis, Alfasigma, Amgen, Amryt, Chiesi, Pfizer, Regeneron, Sanofi.
- Participation as a speaker at scientific meetings: Aegerion, Alfasigma, Amgen, Amryt, Pfizer, Sanofi

La definizione di ipertrigliceridemia

La definizione di ipertrigliceridemia cambia a seconda delle linee guida prese in considerazione

	Plasma triglyceride concentration (mmol/L)
2011 ESC/EAS guidelines[4,7]	
Normal	<1·7
Hypertriglyceridaemia	1·7–9·9
Severe hypertriglyceridaemia	≥10
2001 NCEP ATP III guidelines[5]	
Normal	<1·7
Hypertriglyceridaemia	
Borderline high	1·7–2·3
High	2·3–5·6
Very high	>5·6
2012 Endocrine Society guidelines[1]	
Normal	<1·7
Hypertriglyceridaemia	
Mild	1·7–2·3
Moderate	2·3–11·2
Severe hypertriglyceridaemia	
Severe	11·2–22·4
Very severe	>22·4

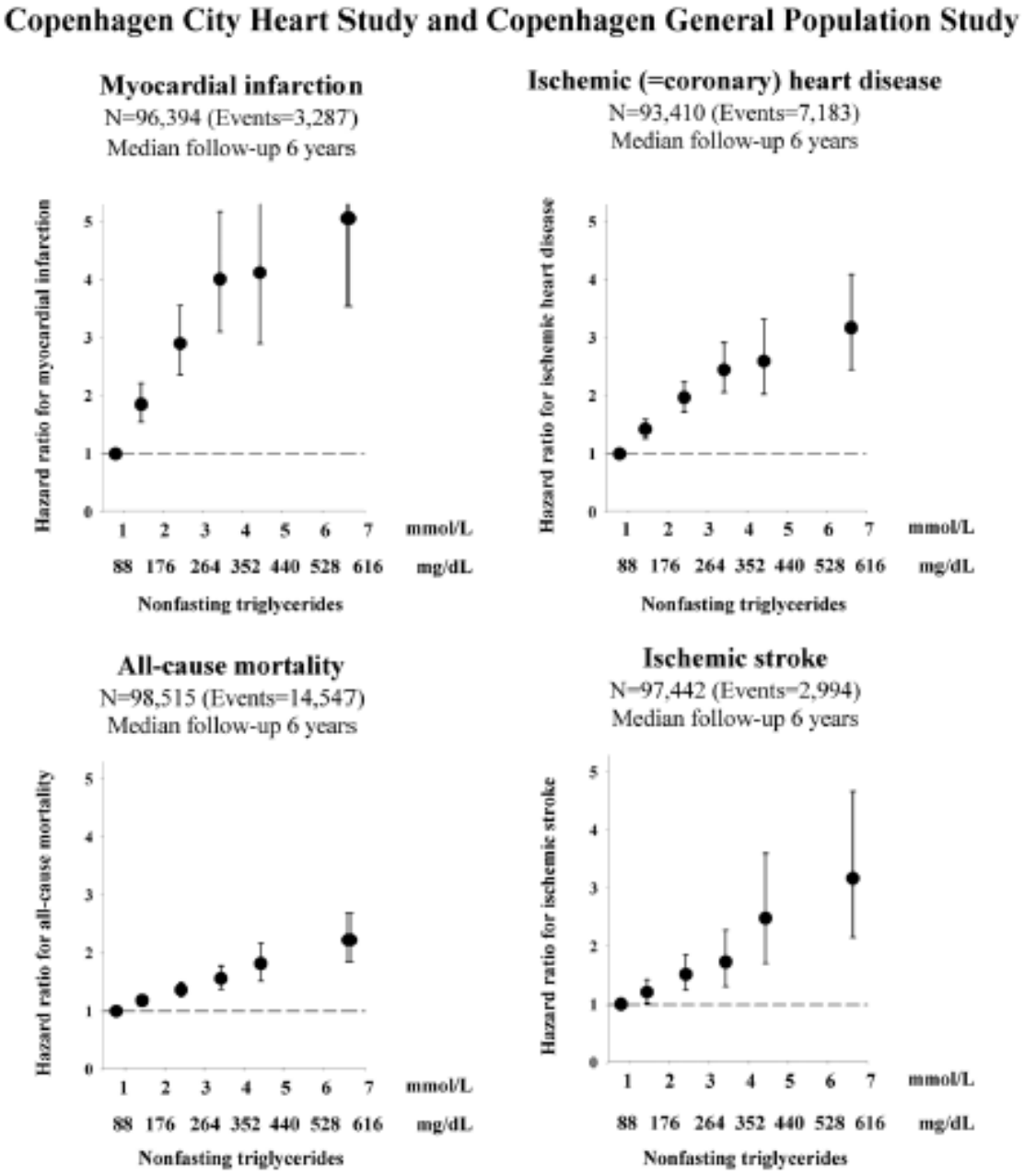
ESC=European Society of Cardiology. EAS=European Atherosclerosis Society. NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III.

Table 1: **Clinical definitions for hypertriglyceridaemia**

Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66

Perché bisogna tenere conto della severità della trigliceridemia?

Le complicanze: HTG lieve-moderata e CVD



Circ Res 2016 Feb 19;118(4):547-63.

Le complicanze: HTG severa e la pancreatite

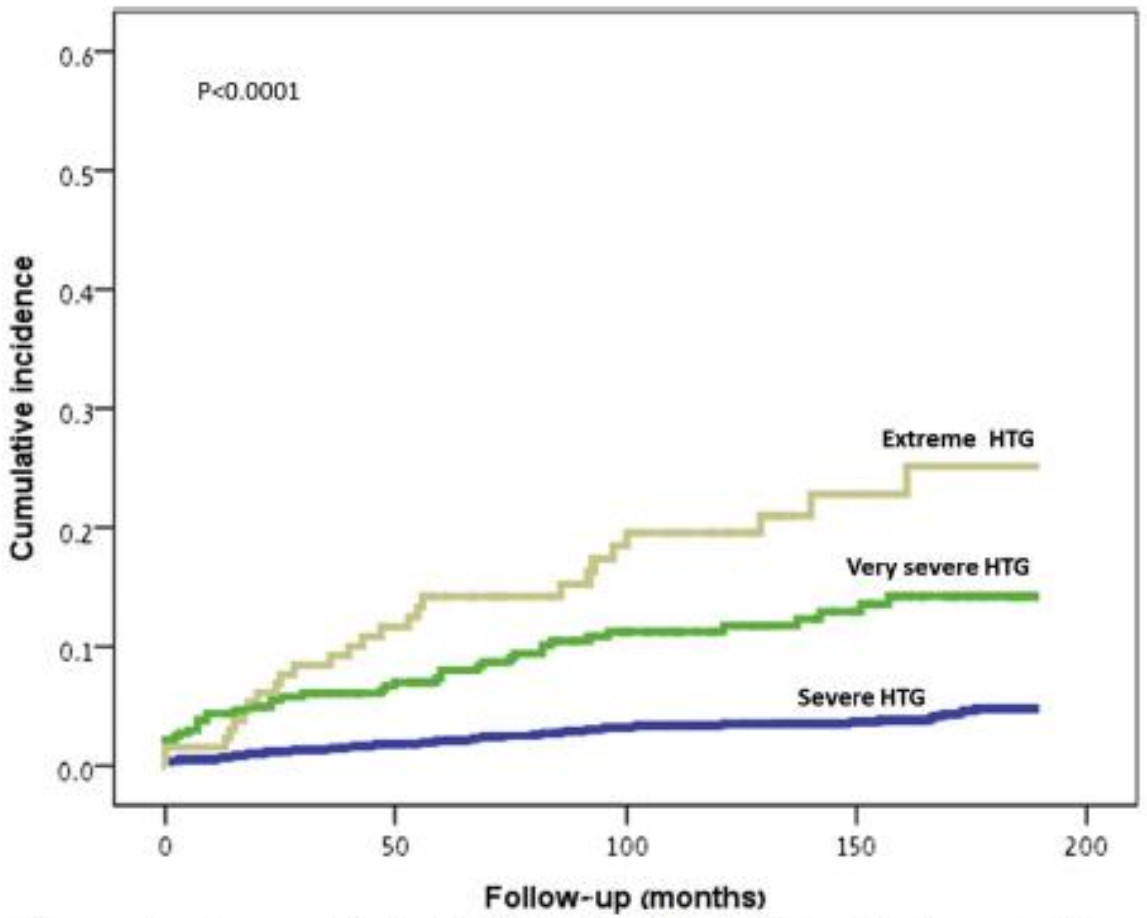


Figure 3 Cumulative incidence of acute pancreatitis stratified by grading of hypertriglyceridemia severity. Severe HTG (peak triglyceride levels 1000–1999 mg/dL); very severe HTG (peak triglyceride levels 2000–2999 mg/dL); and extreme HTG (peak triglyceride levels ≥3000 mg/dL). HTG, hypertriglyceridemia.

Atherosclerosis. 2018 Aug;275:265-272

Cosa si intende per ipertrigliceridemia familiare?

Classificazione delle ipertrigliceridemie nell'era pre-genomica

✓Per anni la parola familiare è stata usata nella definizione e classificazione delle ipertrigliceridemie creando confusione.

	WHO ICD number	Fredrickson hyper-lipoproteinaemia phenotype	OMIM number	Main lipid change	Primary lipoprotein change	Genetics
Familial hyperchylomicronaemia	E78.3	Type 1	238600	↑Triglyceride	↑Chylomicrons	Monogenic; autosomal recessive due to two mutant alleles of *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, or *GPD1*; presentation mainly paediatric or early adulthood
Familial hypercholesterolaemia	E78.0	Type 2A	143890	↑Total cholesterol	↑LDL	Monogenic; autosomal codominant; heterozygous form results from one mutant allele of *LDLR*, *APOB*, or *PCSK9*; homozygous form results from two mutant alleles of these genes or of *LDLRAP1*
Combined hyperlipoproteinaemia	E78.2, E78.4	Type 2B	144250	↑Total cholesterol, ↑triglyceride	↑VLDL, ↑LDL	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes; high GRS for LDL cholesterol
Dysbetalipoproteinaemia	E78.2	Type 3	107741	↑Total cholesterol, ↑triglyceride	↑IDL	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes; *APOE* ε2/ε2 homozygosity, or heterozygous rare mutation in *APOE*
Primary or simple hypertriglyceridaemia	E78.1	Type 4	144600 and 145750	↑Triglyceride	↑VLDL	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes
Mixed hypertriglyceridaemia	E78.3	Type 5	144650	↑Total cholesterol, ↑triglyceride	↑VLDL, ↑chylomicrons	Polygenic; high GRS for hypertriglyceridaemia; excess of rare variants in hypertriglyceridaemia-associated genes, with higher burden of risk alleles than for hyperlipoproteinaemia type 4

GRS was created by unweighted tallying of risk alleles from single nucleotide polymorphisms associated with increased plasma concentrations of triglyceride and hypertriglyceridaemia. Adapted from Hegele (2009).[33] ICD=International Classification of Diseases. OMIM=Online Mendelian Inheritance in Man database. VLDL=very low-density lipoprotein. GRS=polygenic genetic risk score. IDL=intermediate-density lipoprotiein.

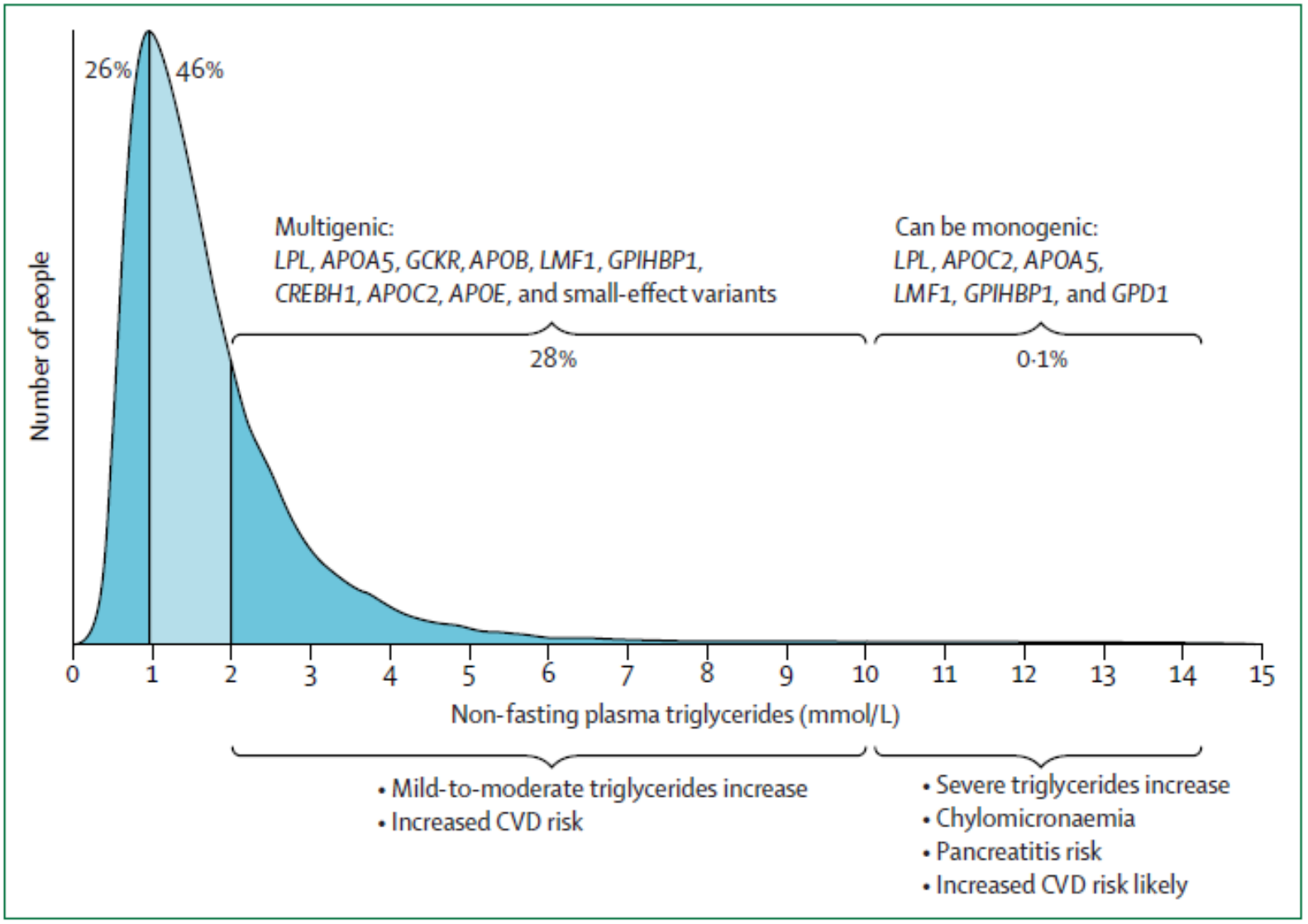
Table 2: **Summary of classic hyperlipoproteinaemia phenotypes**

Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66

✓Il termine familiare generalmente implica un problema a carico di un singolo gene.

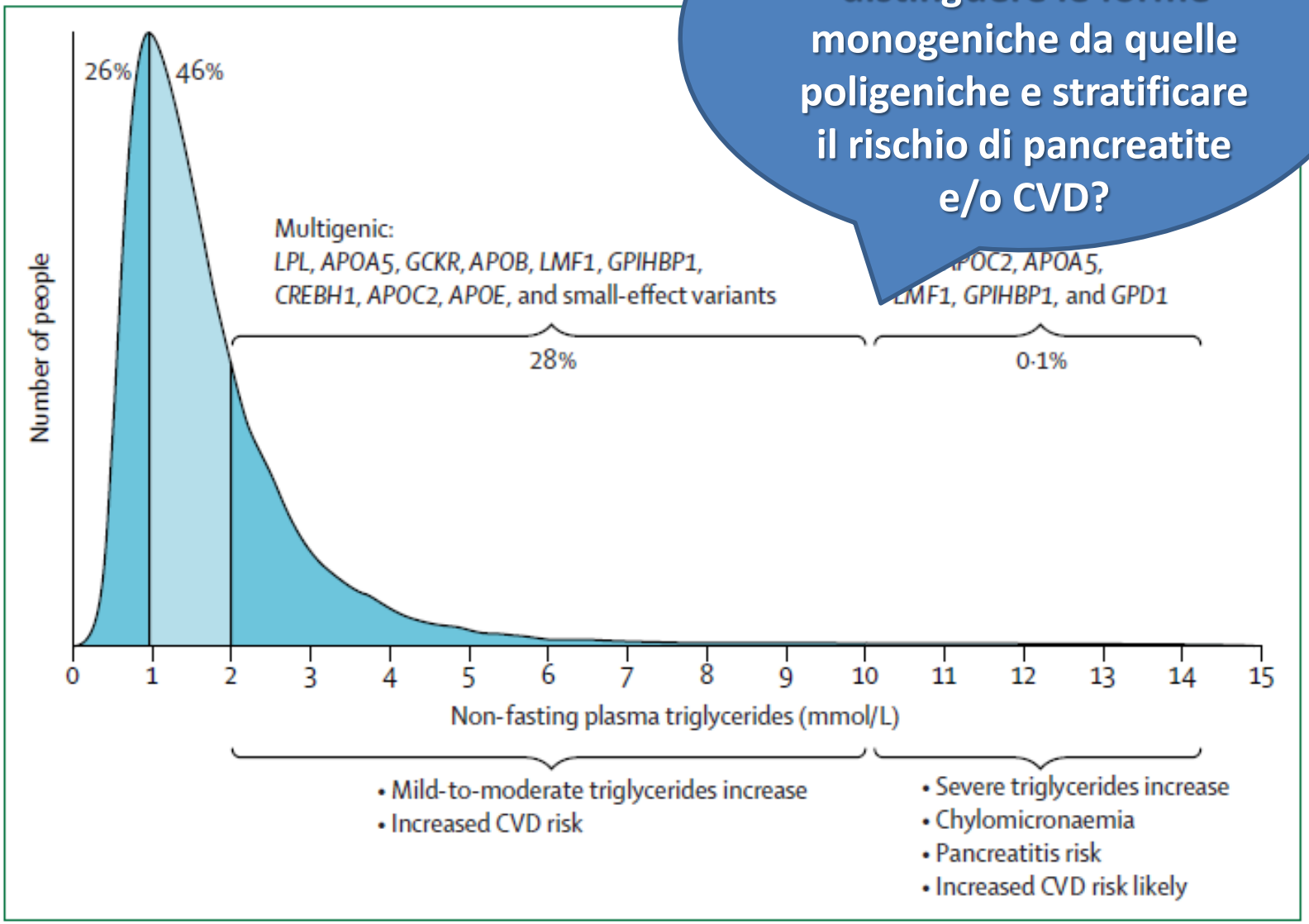
✓**Circa il 95% dei casi di ipertrigliceridemia hanno una componente di suscettibilità multigenica**.

Classificazione delle ipertrigliceridemie nell'era genomica



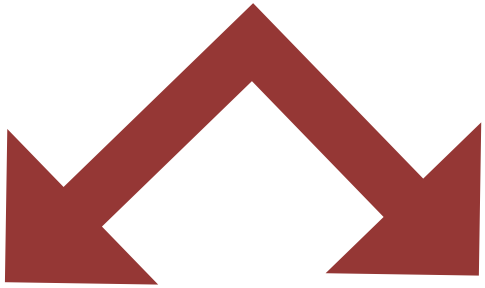
Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66

Ma basta il valore di trigliceridemia per distinguere le forme monogeniche da quelle poligeniche e stratificare il rischio di pancreatite e/o CVD?



Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66

Ipertrigliceridemia Severa (>885 mg/dl)



- **Cause primarie**
  - **Monogeniche (FCS)**
  - **Poligeniche (MCS)**

- **Cause secondarie**

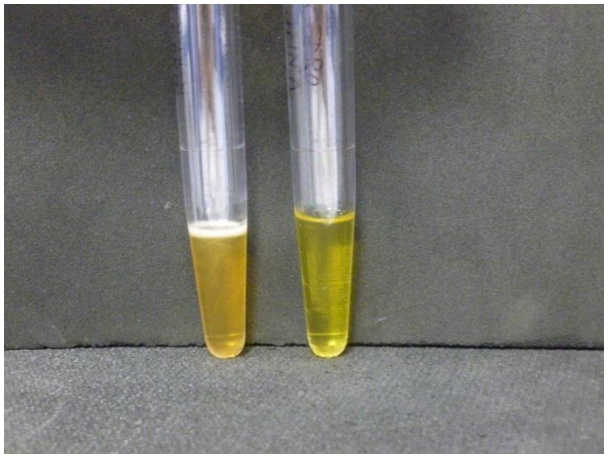
Panel 1: **Secondary causes of hypertriglyceridaemia**

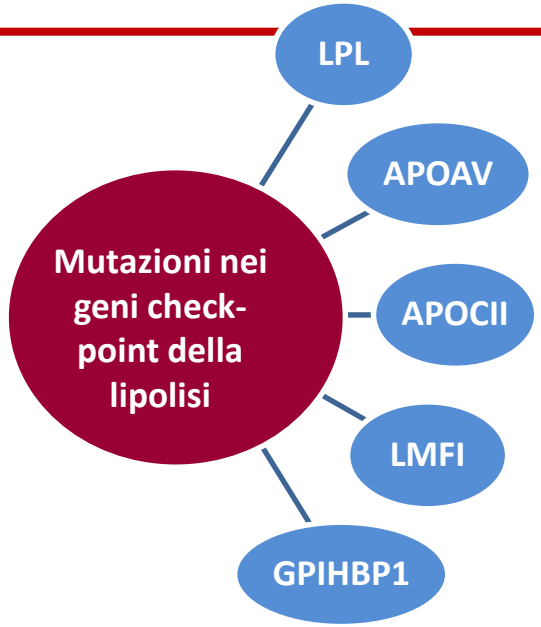
- Obesity
- Metabolic syndrome
- Diet with high positive energy-intake balance, and high fat or high glycaemic index
- Increased alcohol consumption*
- Diabetes (mainly type 2 diabetes)
- Hypothyroidism
- Renal disease (proteinuria, uraemia, or glomerulonephritis)
- Pregnancy (particularly in the third trimester)
- Paraproteinaemia
- Systemic lupus erythematosus
- Drugs including corticosteroids, oral oestrogen, tamoxifen, thiazides, non-cardioselective β blockers and bile acid sequestrants, cyclophosphamide, asparaginase, protease inhibitors, and second-generation antipsychotic drugs (eg, clozapine and olanzapine)

*Although the range is variable, clinically the risk of hypertriglyceridaemia is generally thought to increase with more than two units daily for men, and more than one unit daily for women.

Sindrome Chilomicronemica Familiare (FCS)

- Malattia monogenica a trasmissione autosomica recessiva
- Prevalenza:1/1.000.000
- Persistenza dei chilomicroni circolanti dopo oltre 12-24 ore dal pasto
- Ipertrigliceridemia severa e resistente alla terapia convenzionale
- Principale manifestazione clinica: ***pancreatite acuta***
- Diagnosi genetica (mutazioni nei geni check-point della lipolisi)



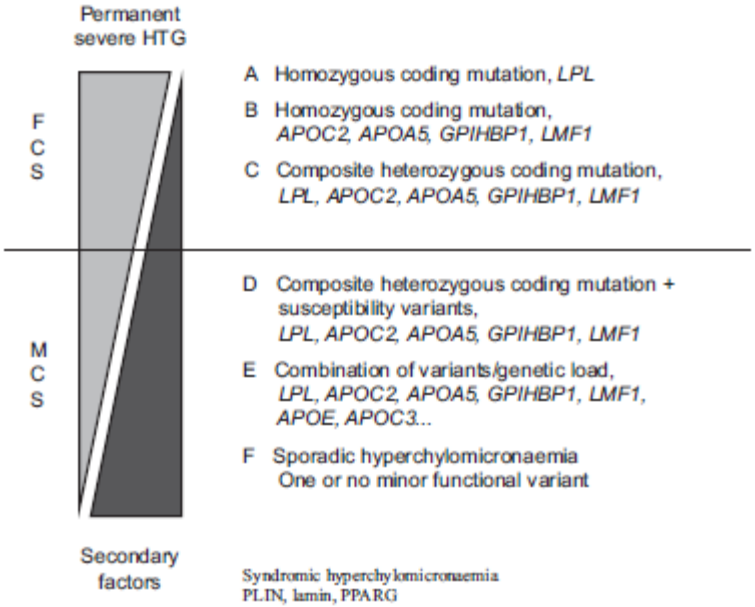


Sindrome Chilomicronemica Multifattoriale (MCS)

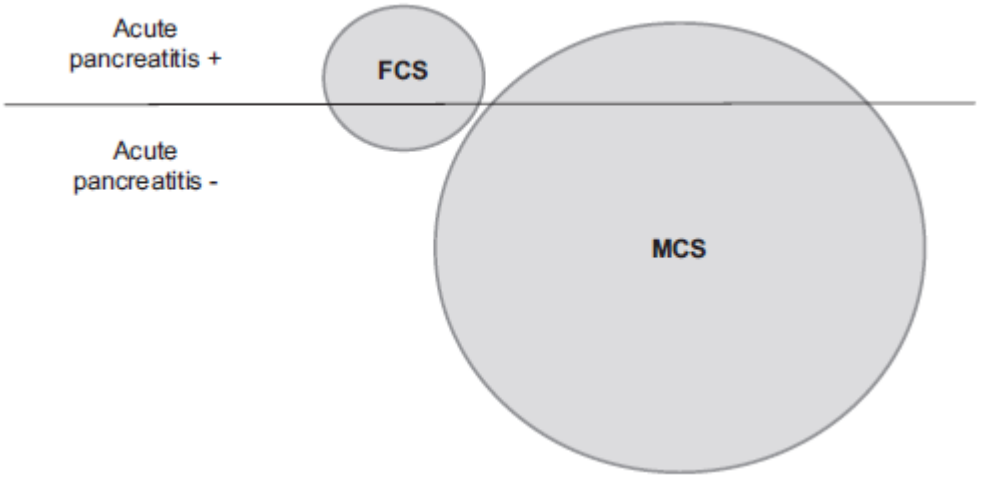
✓MCS ha una base poligenica sulla quale possono agire come trigger fattori di rischio secondari quali l'obesità.

✓Ha caratteristiche simili alla FCS che ne rendono difficile la distinzione

Carico genetico della FCS vs MCS



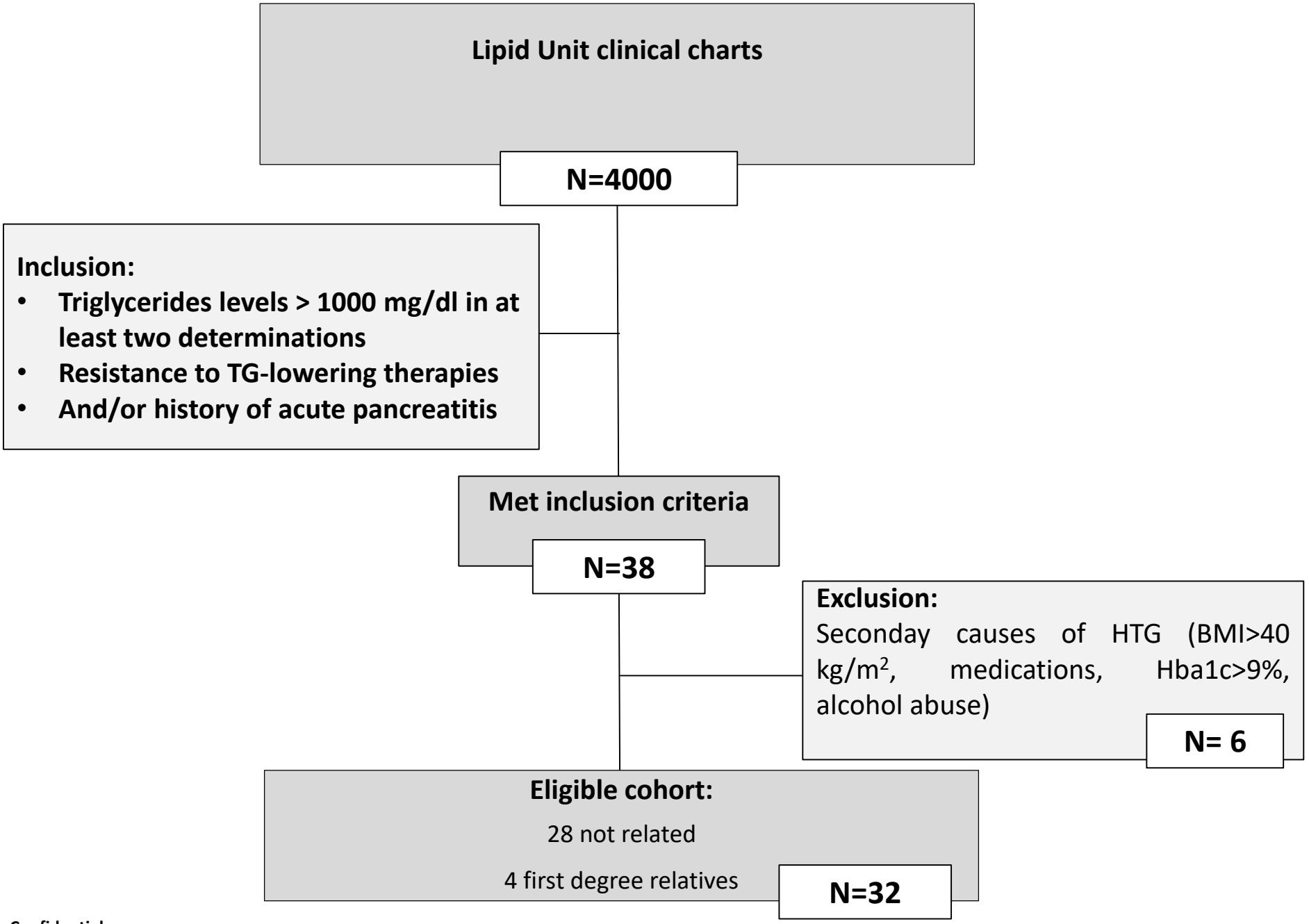
Pancreatite acuta nella FCS vs MCS



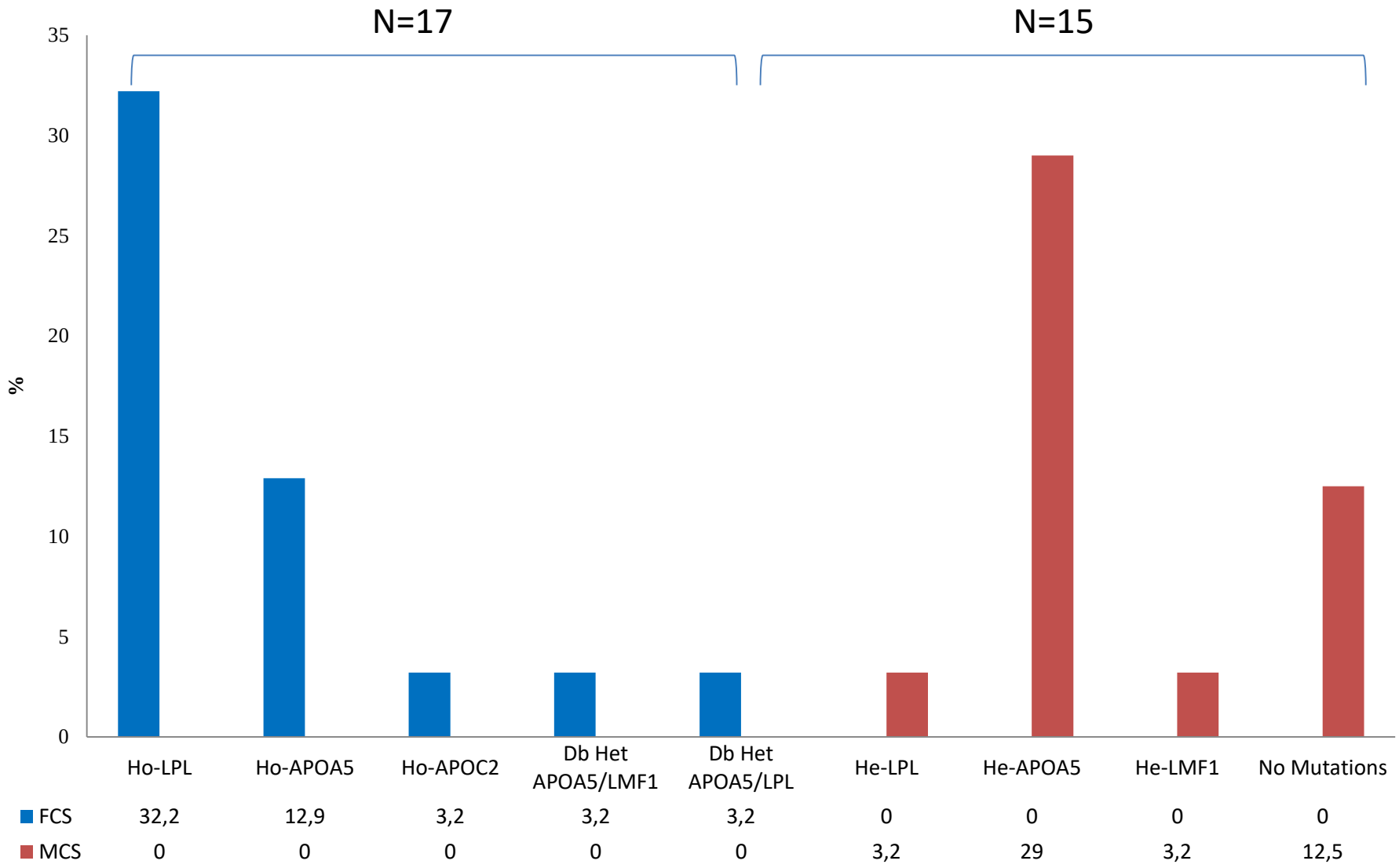
Spectrum of mutation and clinical characteristics in patient with severe hypertriglyceridemia

D'Erasmo Laura*, Di Costanzo Alessia*, Cassandra Francesca, Arca Marcello

*Equal contribution



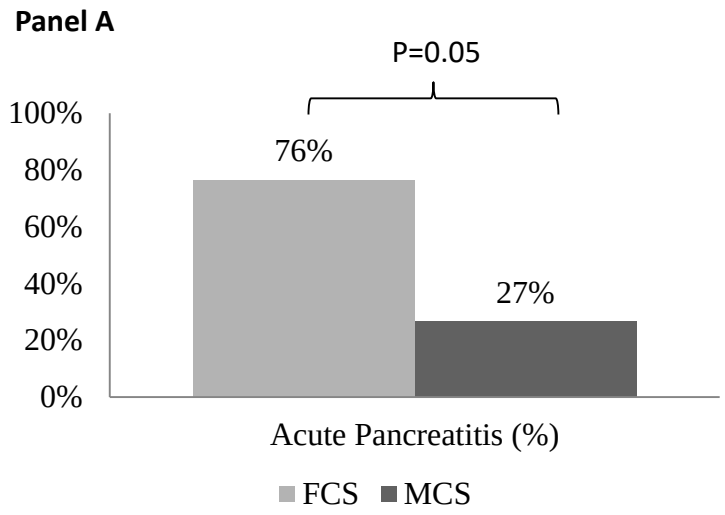
Spectrum of genotypes in candidate genes in HTG patients

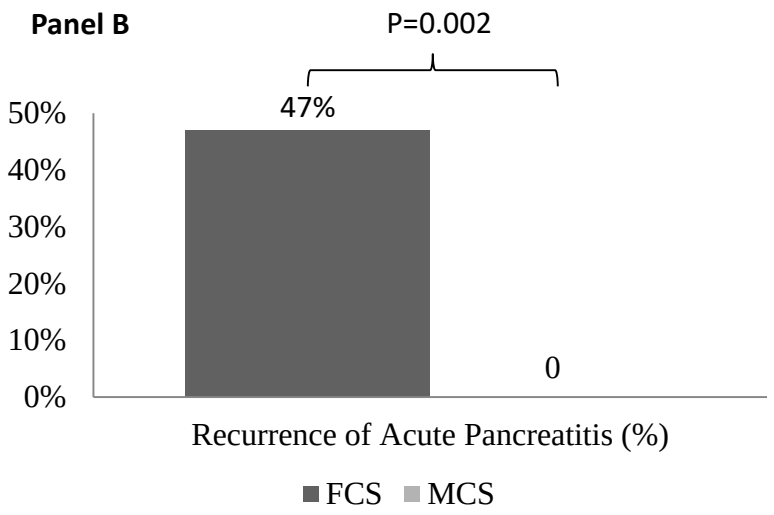


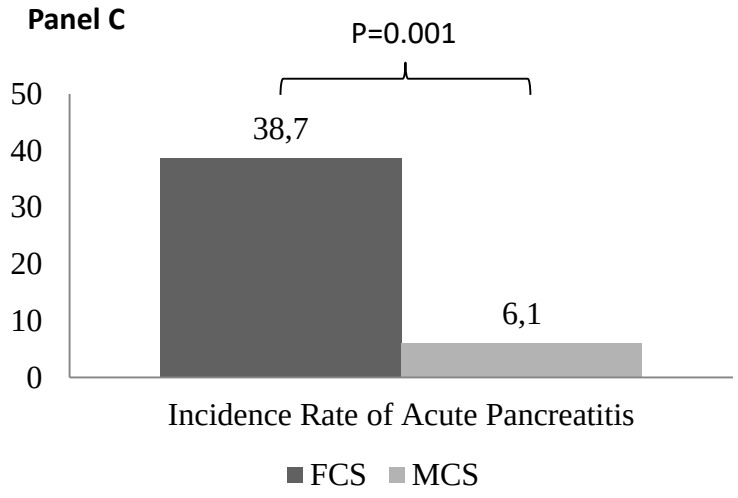
Plasma lipid changes and treatments during follow-up in HTG patients classified as FCS and MCS

	FCS (N=17)			MCS (N=15)					
	Baseline	Average value during follow-up	Best result during follow-up	Baseline	Average value during follow-up	Best result during follow-up	$P_{baseline}$	$P_{follow-up}$	$P_{Best\ Result}$
Plasma Lipids									
Total-C (mg/dl)	276.2±108.8	251.5±91.0	144.8±28.3	335.7±131.6	262.2±73.3	216.1±75.1	NS	NS	0.001
HDL-C (mg/dl)	21.4±14.5	20.0±8.8	22.5±10.9	31.0±7.9	34.5±10.0	38.7±8.3	NS	<0.001	<0.001
Triglycerides(mg/dl)	**2137.3±844.9**	**1677.7±968.5**	**628.8±393.3**	**1986.5±860.5**	**1059.0±554.9**	**370.6±396.0**	**NS**	**0.04**	**0.07**
Non HDL-C (mg/dl)	268.4±111.3	220.7±73.2	123.6±29.8	263.4±113.9	230.7±78.7	178.6±75.2	NS	NS	0.01
TG < 500 (n, %)	-	-	**8 (47.1)**	-	-	**13 (86.7)**	-	-	0.028

La pancreatite acuta

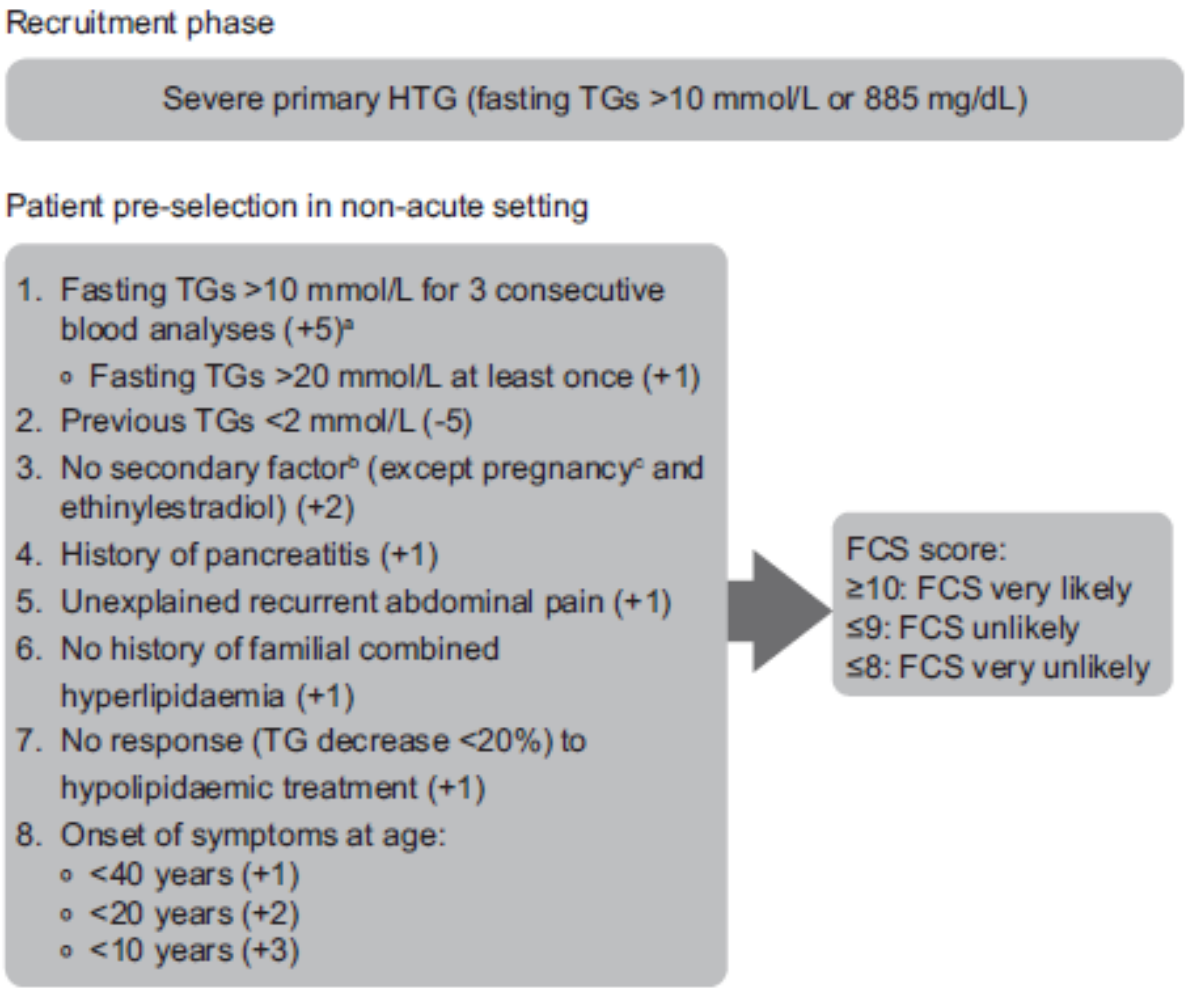






Il valore di trigliceridemia non basta per distinguere tra forme monogeniche e poligeniche e stratificare il rischio di pancreatite.

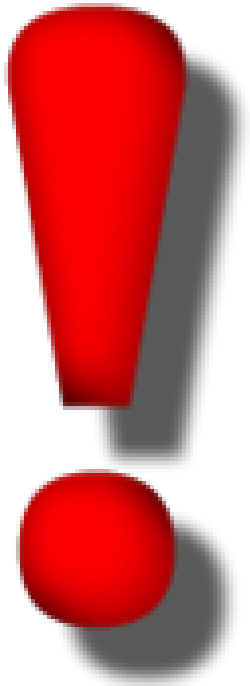
La diagnosi clinica di FCS è ancora una sfida



- **La sensibilità dello score FCS e' 88% (95% confidence interval [CI]: 0.76, 0.97)**
- **La specificità dello score FCS E' 85% (95% CI: 0.75, 0.94).**

Atherosclerosis. 2018 Aug;275:265-272

La terapia dipende dalla gravità della trigliceridemia e delle complicanze associate



	HTG lieve-moderata	HTG severa
Finalità della terapia	**Prevenzione della CVD**	**Prevenzione della pancreatite acuta**
Goal terapeutico primario	Ridurre LDL-C	Ridurre i trigliceridi idealmente <400 mg/dl
Goal terapeutico secondario	✓Non HDL-C ✓ApoB ✓Escludere e curare fattori di rischio secondari	✓Quando il rischio di pancreatite è cessato, raggiungere gli obiettivi di LDL-C e Non HDL-C ✓Escludere e curare fattori di rischio secondari
Strategie non farmacologiche	•Riduzione del peso •Riduzione dell'introito di alcool/zuccheri semplici/carboidrati •Aumento dei grassi monoinsaturi •Aumento attività fisica •Aumento acidi grassi omega3	In acuto: digiuno durante gli attacchi di pancreatite acuta + idratazione In cronico: •Dieta a basso contenuto in grassi (<20% delle calorie come grassi) •Riduzione del peso •Riduzione dell'introito di alcool/zuccheri semplici/carboidrati •Aumento dei grassi monoinsaturi •Aumento attività fisica •Aumento acidi grassi omega3
Strategie farmacologiche	Statine Statine + Fibrati Statine + Omega 3	Fibrati Omega 3

Adattata da Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66

Terapie suggerite per ipertrigliceridemia severa

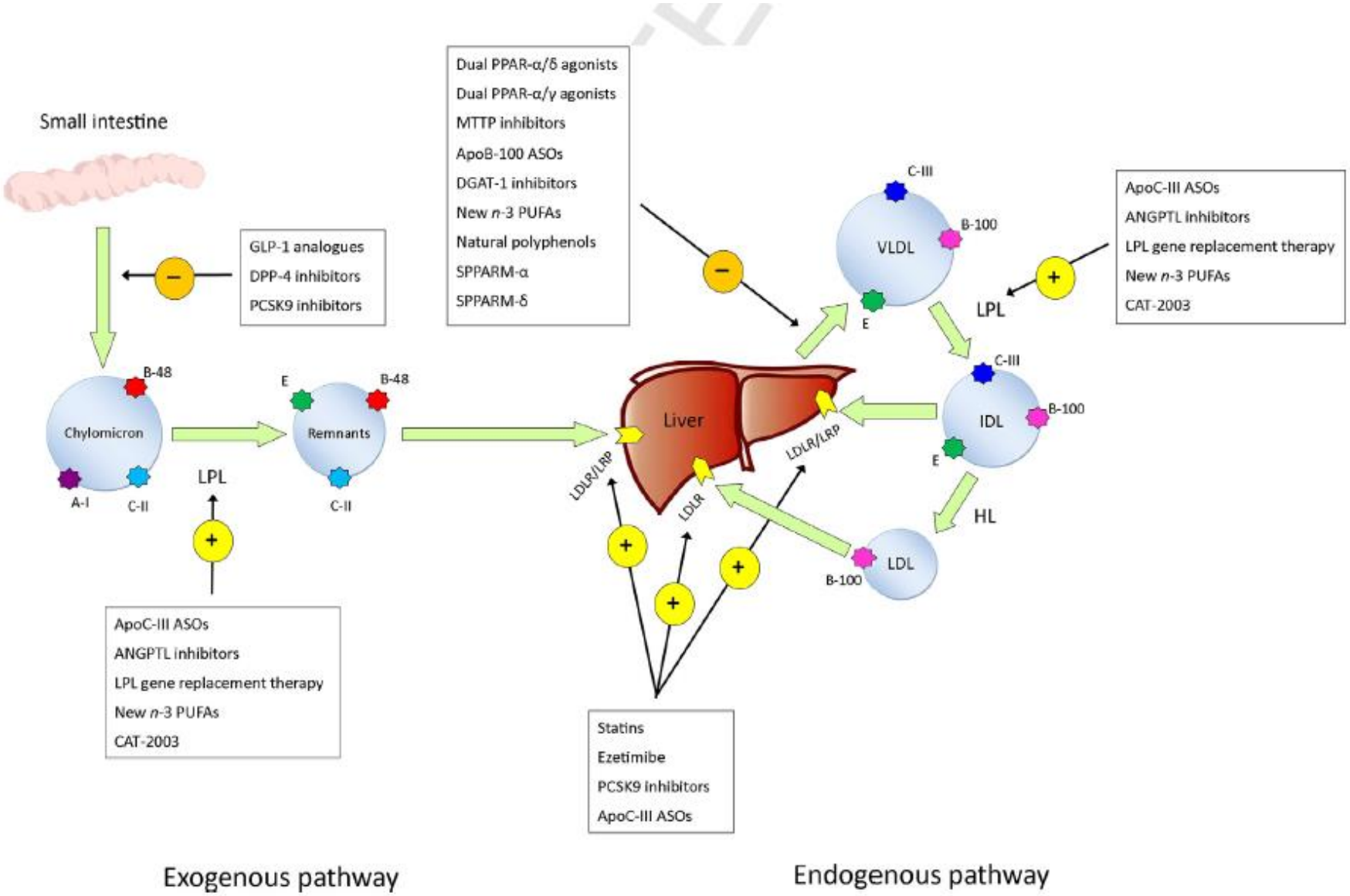
Acute treatment in severe HTG (TG > 1000 mg/dl)	Long-term treatment for the prevention of severe HTG episodes (TG levels to be reached 300–500 mg/dl)
Apheresis until plasma TG level < 1000 mg/dl	Dietary measurements
MCT and omega-3-FA in combination	< 20 g LC-FA/day, abstinence of alcohol
	Adding omega-3-FA (> 3 g EPA + DHA)
	Adding fibrates to omega-3-FA
	Adding nicotinic acid to fibrates, omega-3-FA
	Considering recurrent episodes of plasmapheresis

Note carefully that conventional treatment of any comorbidity, e.g., pancreatitis is imperative as well as screening for secondary causes of HTG and treatment of the underlying disease

HTG hypertriglyceridemia; *TG* triglycerdies; *FA* fatty acids; *MCT* medium-chain triglycerides; *LC-FA* long-chain fatty acids; *EPA* eicosapentaenoic acid; *DHA* docosahexaenoic acid

Clin Res Cardiol Suppl 2012; 7:31–35

Nuovi approcci terapeutici

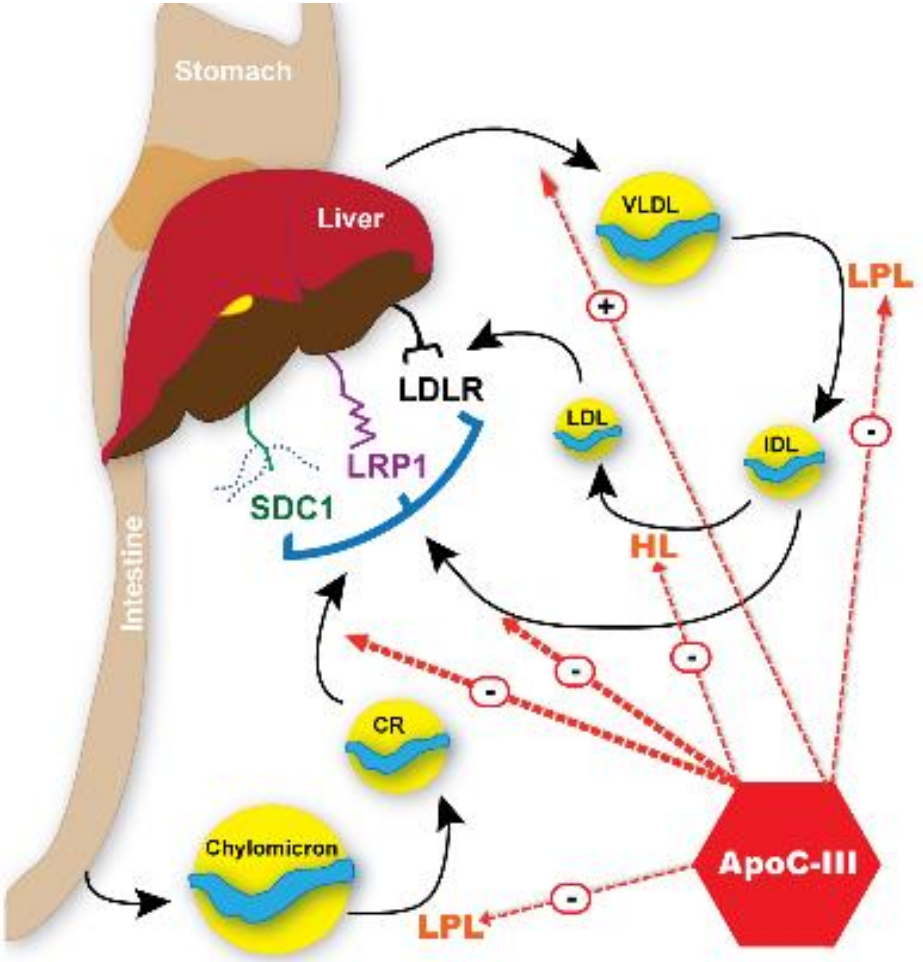


Nuovi approcci terapeutici

Terapia	Riduzione dei trigliceridi (%)		Riduzione delle pancreatiti (%)	Eventi avversi
	Ho FCS	Het FCS		
LOMITAPIDE	Dati disponibili relativamente un unico paziente affetto da FCS. Sono necessari studi su popolazione più ampia.			fibrosi epatica
ALIPOGENE TIPARVOVEC	Alipogene tiparvovec è stato autorizzato dall'EMA ma scarse prospettive commerciali + incertezze nel rimborso hanno causato il suo ritiro nel 2017			
VOLANESORSEN	In fase di valutazione per approvazione presso EMA. Valutazione del rapporto rischio-beneficio.			
EVINACUMAB	Dati non disponibili nei paziente con HTG severa o FCS. In corso studi su popolazione selezionata.			

Expert Rev Clin Pharmacol. 2018 Jun;11(6):589-598

ApoC-III as a Therapeutic Target in FCS: Role of ApoC-III in Lipid Metabolism

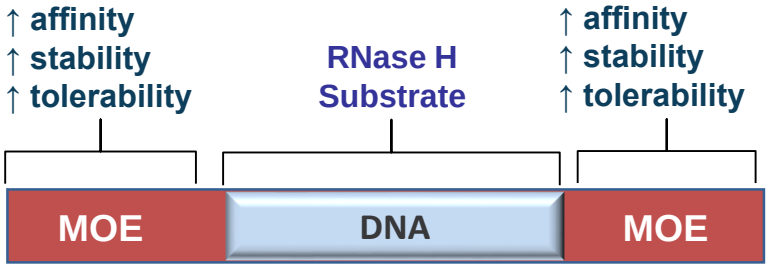


- ApoC-III is a 79-amino acid glycoprotein synthesized principally in the liver
  - Multiple apoC-III proteins on VLDL and HDL particles
- Plays key role in determining serum chylomicrons and triglyceride levels
  - Potent inhibitor of LPL
  - Inhibits hepatic uptake of Triglyceride-rich Lipoproteins (TRLs)

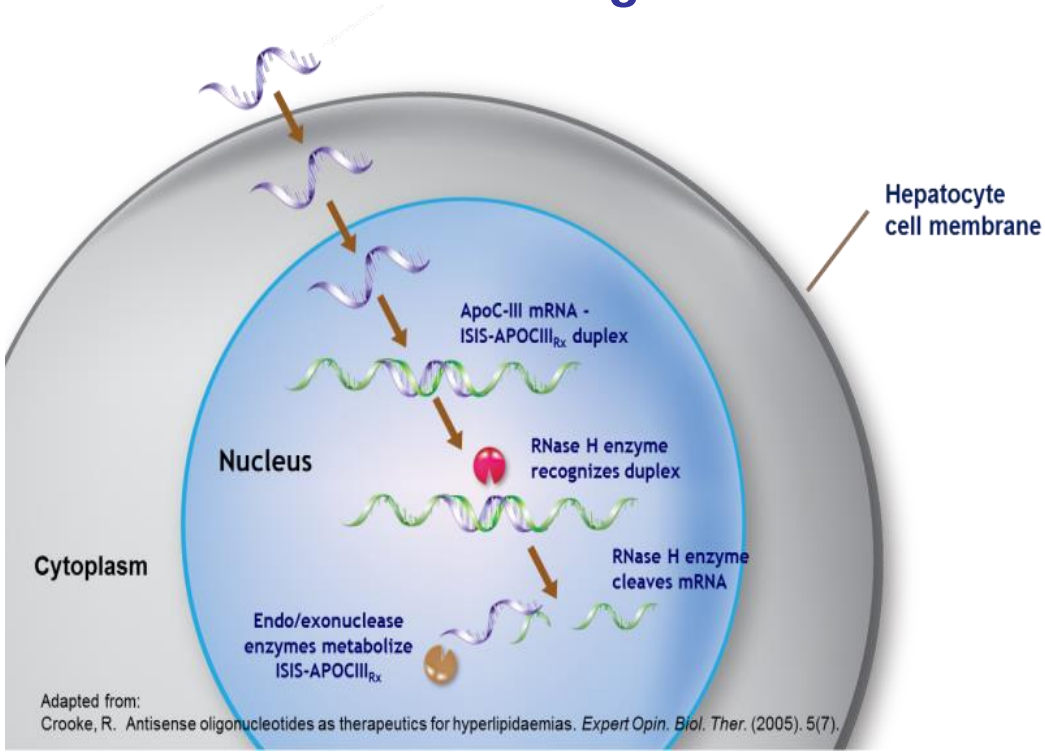
Gordts PL, et al J Clin Invest 2016

Lessons From ASO- Apo-C-III Inhibition

Chimeric RNase H ASO Design

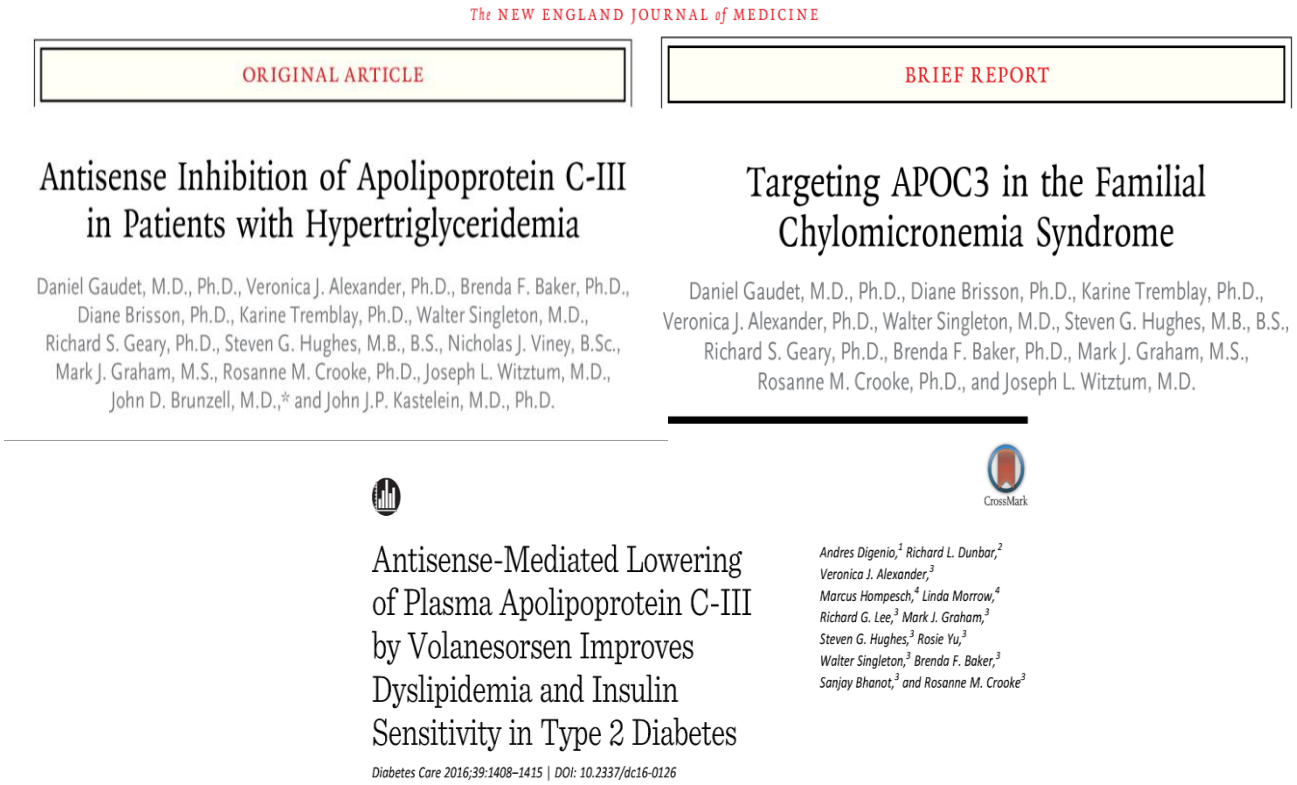


RNase H Terminating Mechanism



Volanesorsen targets ApoC-3 to lower triglycerides

In phase 2, targeted reduction of ApoC-3 by volanesorsen robustly lowered triglyceride levels in patients with a wide range of incoming triglyceride levels, including in people with type 2 diabetes



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

BRIEF REPORT

Targeting APOC3 in the Familial Chylomicronemia Syndrome

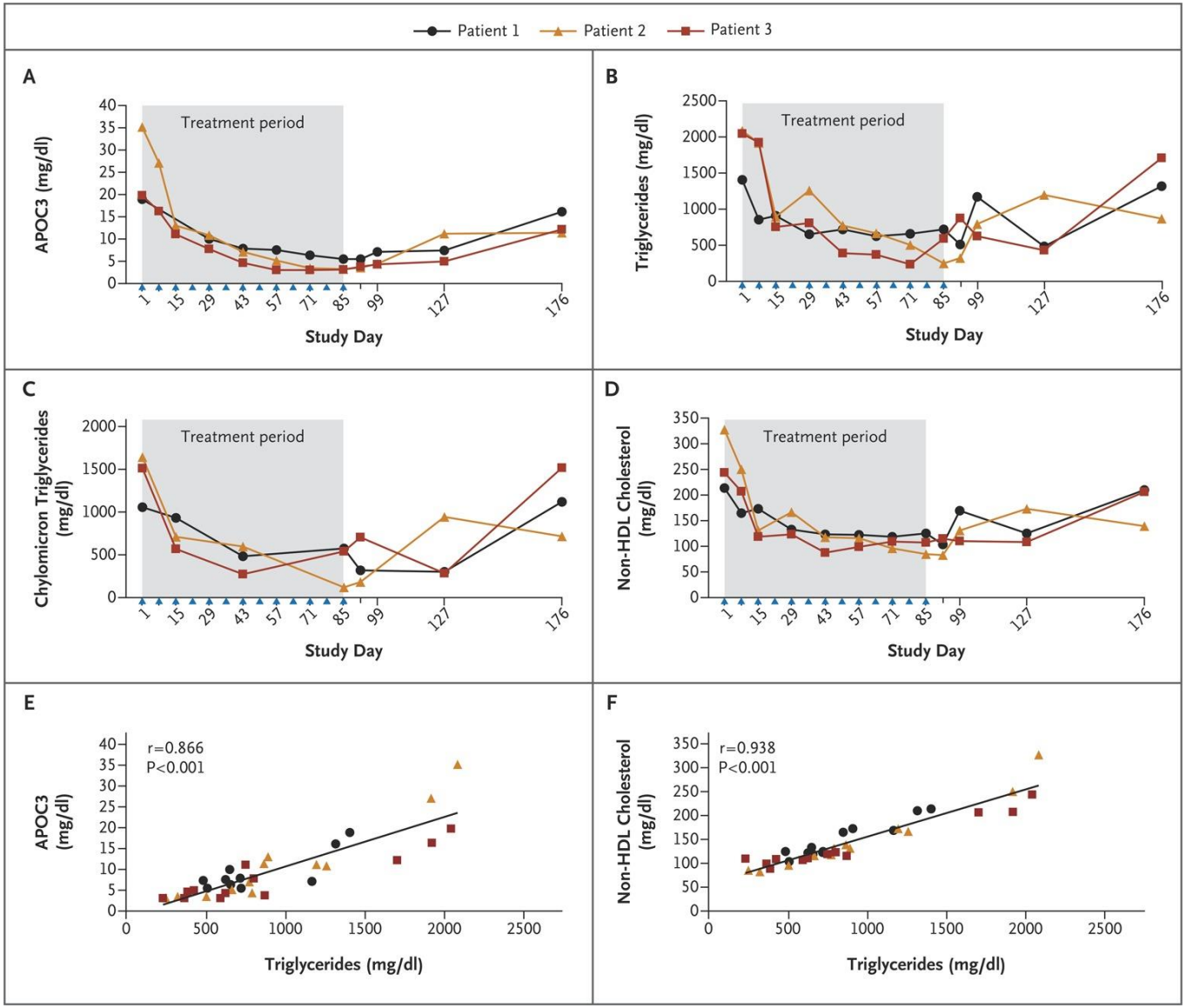
Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.

Antisense-Mediated Lowering of Plasma Apolipoprotein C-III by Volanesorsen Improves Dyslipidemia and Insulin Sensitivity in Type 2 Diabetes

Andres Digenio,[1] Richard L. Dunbar,[2] Veronica J. Alexander,[3] Marcus Hompesch,[4] Linda Morrow,[4] Richard G. Lee,[3] Mark J. Graham,[3] Steven G. Hughes,[3] Rosie Yu,[3] Walter Singleton,[3] Brenda F. Baker,[3] Sanjay Bhanot,[3] and Rosanne M. Crooke[3]

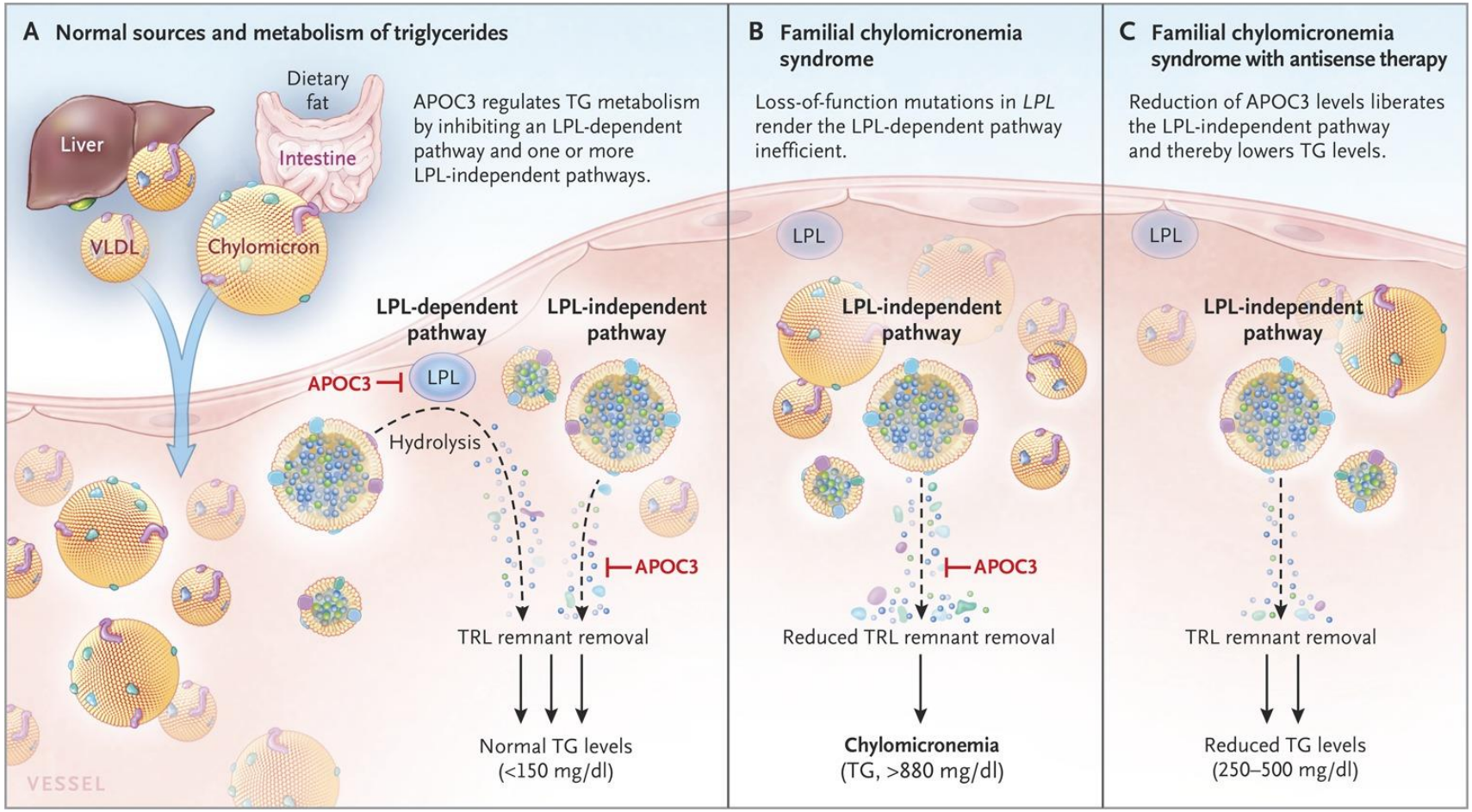
Diabetes Care 2016;39:1408–1415 | DOI: 10.2337/dc16-0126

Volanesorsen in FCS: Lessons from



Gaudet D et al. N Engl J Med 2014;371:2200-2206

Plasma Triglyceride Metabolism and the Role of APOC3

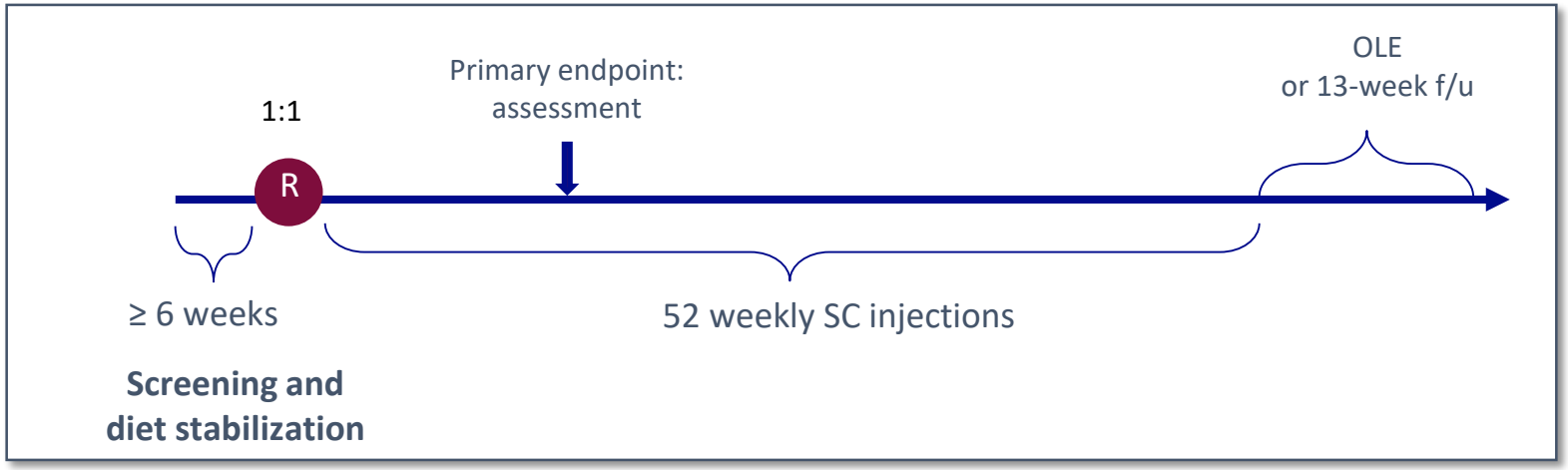


The NEW ENGLAND JOURNAL of MEDICINE

APPROACH Study Design

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

- Global study in 67* patients
- Randomized, double-blind, placebo-controlled study
  - **Primary efficacy endpoint: Percent change in fasting triglycerides from baseline after 13 weeks of dosing**



* 1 Patient noncompliant with visit schedule pretreatment, never treated with study drug

Study Population

- Adult patients with FCS
  - Genetically confirmed Type 1 Hyperlipoproteinemia (*LPL*, *APOC2*, APOA5, *GPIHBP1*, *LMF1*), OR
  - Documented LPL activity ≤ 20% of normal
- Documented history of acute pancreatitis
  - Acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis
  - Patients without a documented history of pancreatitis eligible with 28% enrollment cap
- Fasting triglyceride ≥ 8.5 mmol/L (≥ 750 mg/dL) at screening
- Willing to follow a restrictive diet comprising ≤ 20g fat per day

Patient Characteristics

	Placebo	Volanesorsen
N	33	33
Gender (M:F), n (%)	14 (42) : 19 (58)	16 (49) :17 (52)
Age (years), Mean (range)	46 (20 - 68)	47 (22 – 75)
BMI (kg/m^2), Mean (SD)	24.1 (4.7)	25.9 (6.5)
Triglycerides	24.3 mmol/L (2252 mg/dL)	25.6 mmol/L (2267 mg/dL)
Genetic Confirmation, Type 1	25 (76%)	25 (76%)
LPL Activity <=20%	18 (55%)	18 (55%)
Medical History, n(%)		
Acute pancreatitis	26 (78.8%)	24 (72.7%)
Eruptive Xanthoma	9 (27.3%)	6 (18.2%)
Lipemia Retinalis	9 (27.3%)	5 (15.2%)
Concomitant Lipid-Lowering Agents		
Statins	5 (15%)	9 (27%)
Fibrates	15 (46%)	17 (52%)
Fish Oils	9 (27%)	10 (30%)

* After 6-weeks of diet-stabilization

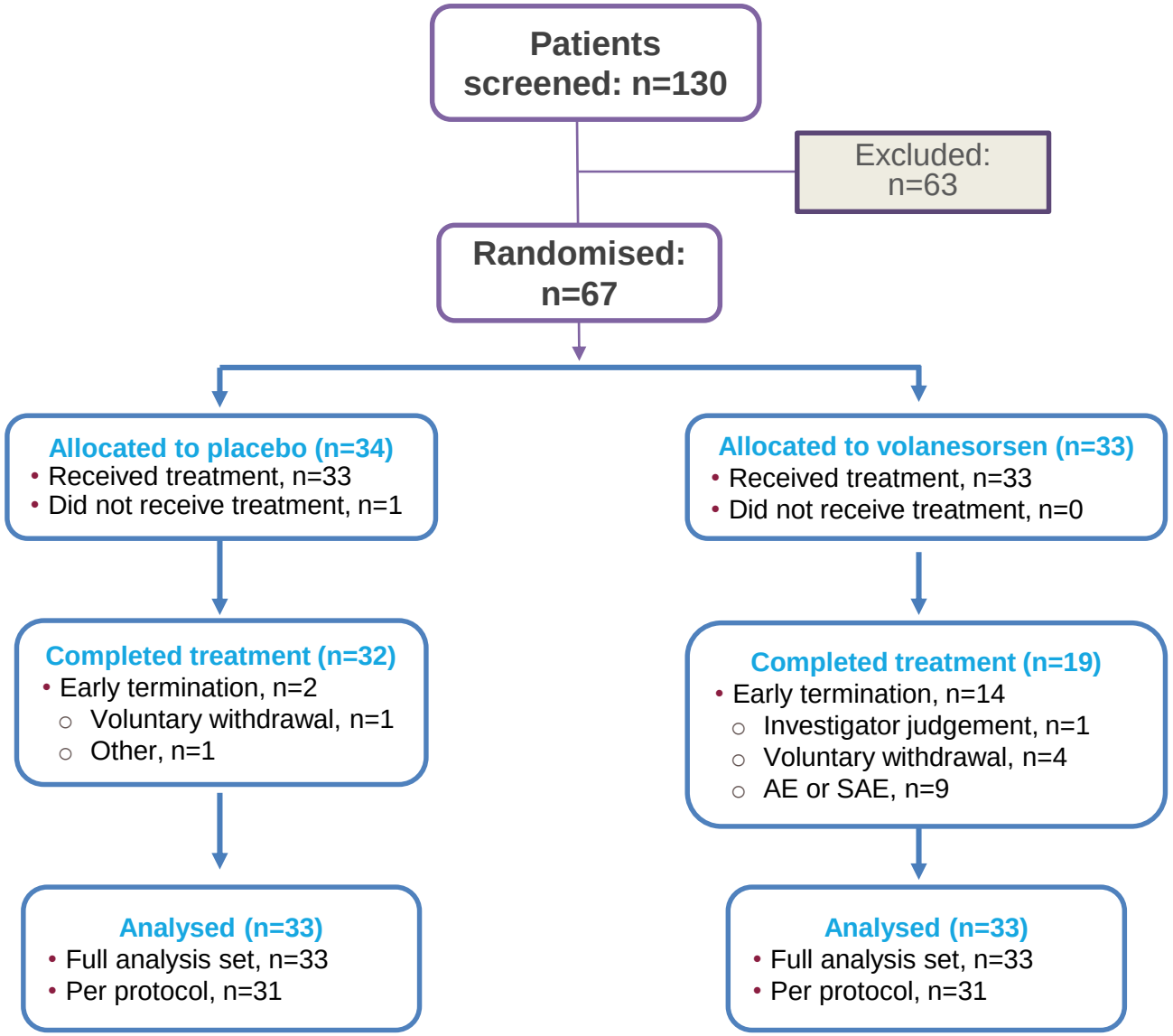
Genotypes distribution in enrolled FCS patients

Gene	Number of patients (N=66)
LPL/LPL	41
ApoA5/ApoA5	2
GPIHBP1/ GPIHBP1	5
ApoC2/ApoC2	1
LMF1/LMF1	1
LPL/LMF1	1
LPL/ApoA5	1
No mutation identified	14

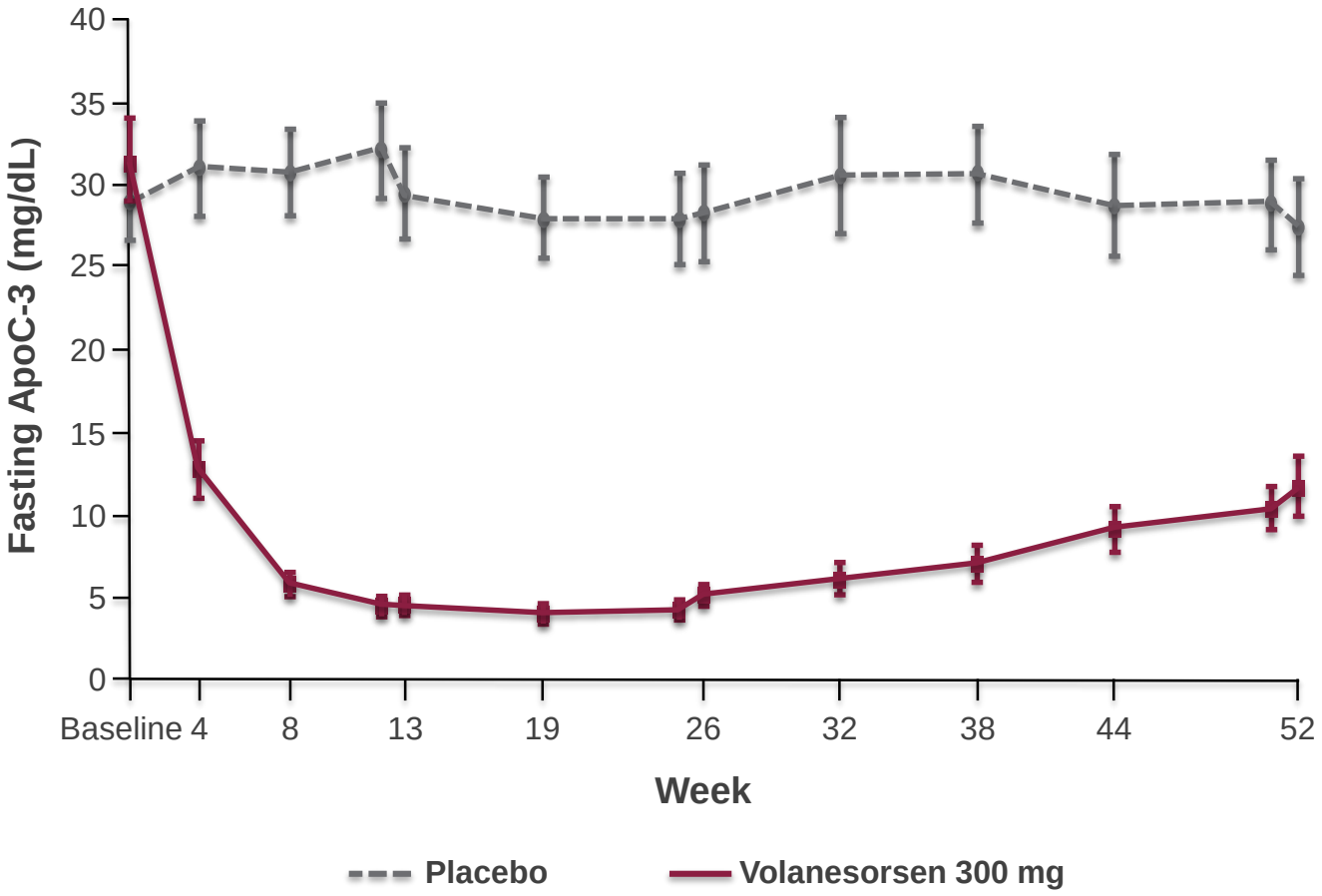
History of pancreatitis over the prior 5 years

	Placebo	Volanesorsen
No. of patients with a history of events	10	13
Total number of events	23	30
No. of patients with ≥2 events	4 (17 events in total)	7 (24 events in total)

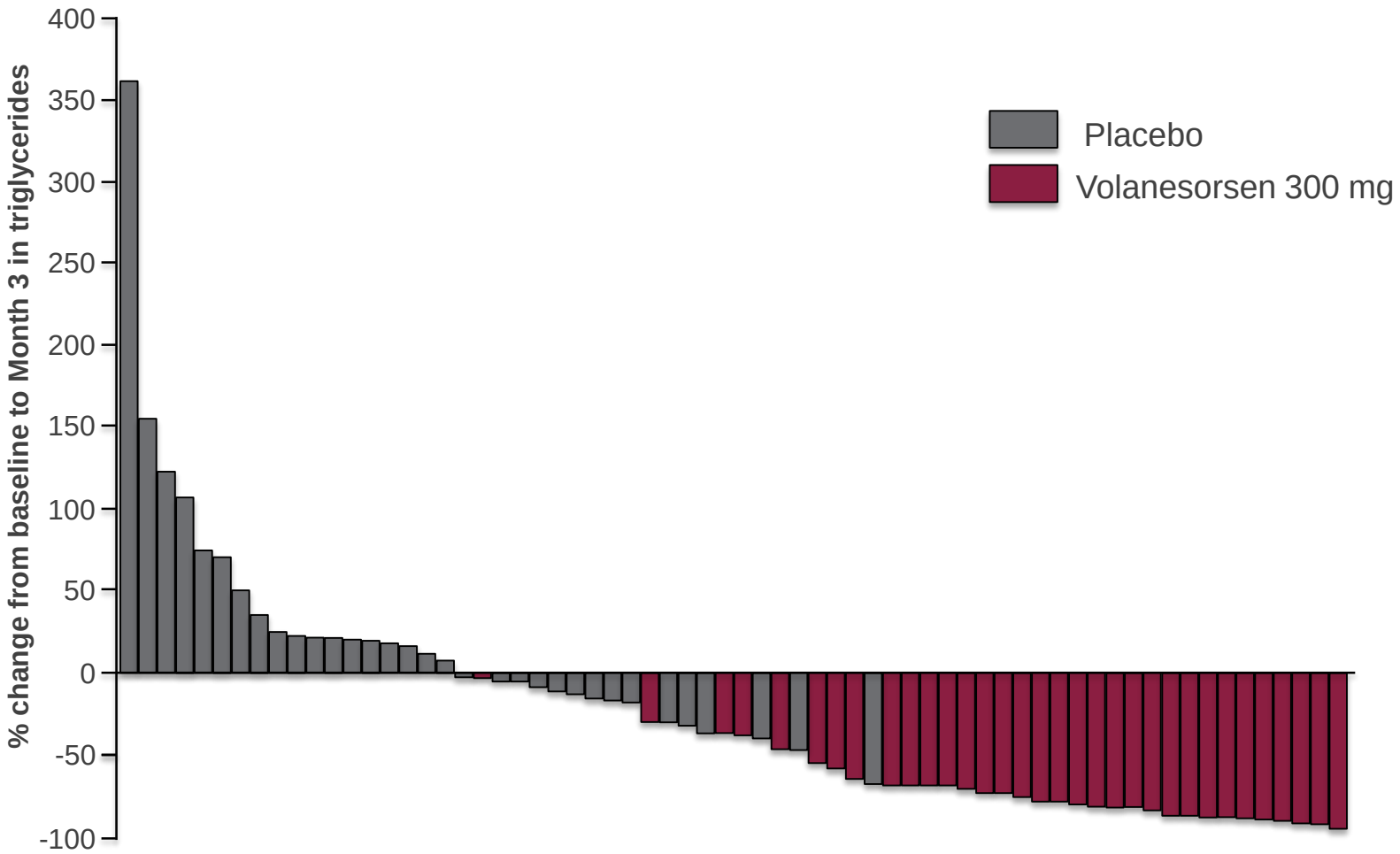
Patient disposition



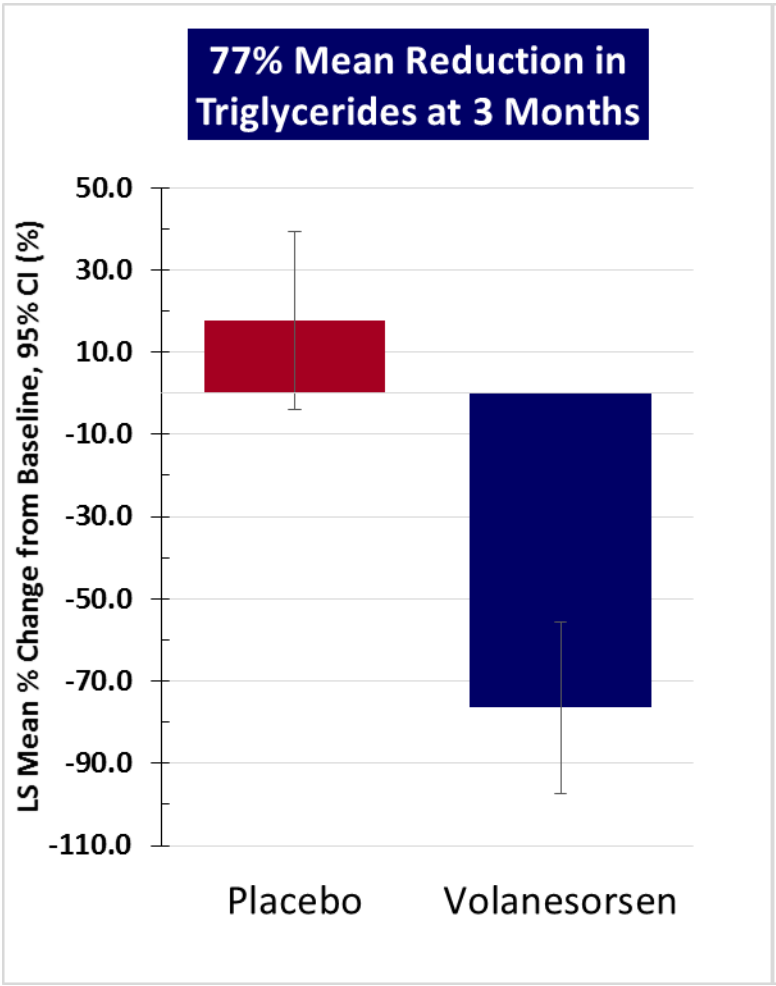
Mean change of fasting ApoC-3 over 52 weeks



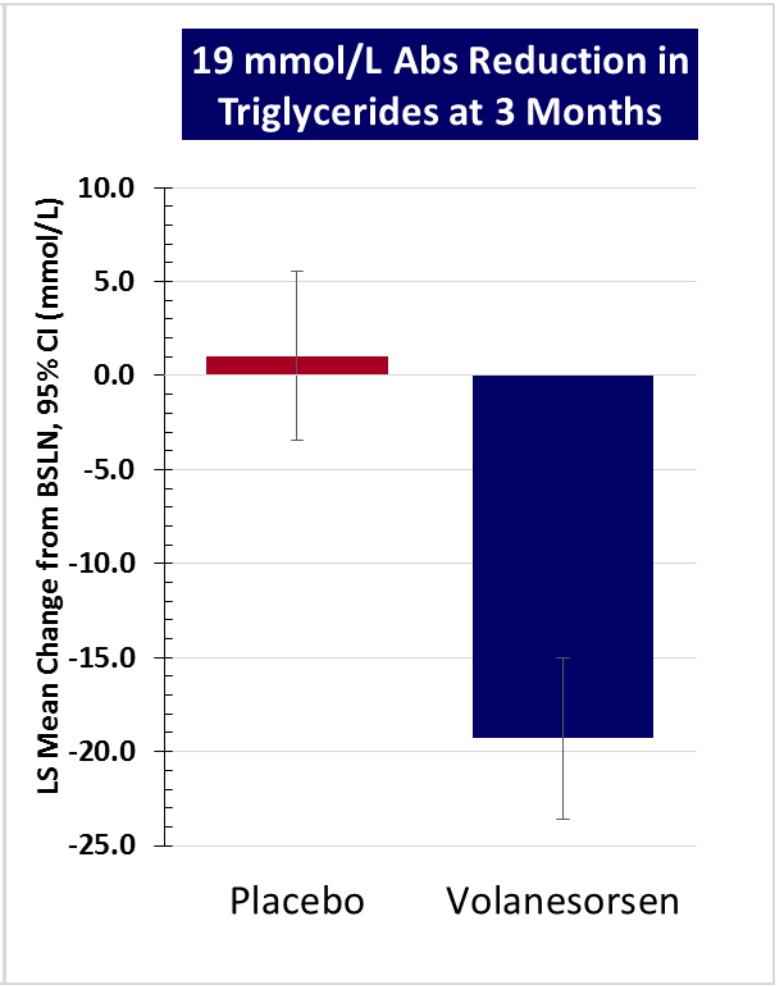
Waterfall plot of individual % TG change from baseline to 3 months of treatment



Volanesorsen Primary Endpoint & Absolute Reduction



p< 0.0001



p< 0.0001

Adverse events reported in at least 10% of patients and more common on volanesorsen than placebo*

Adverse events	Placebo (n=33)	Volanesorsen 300 mg (n=33)
	n (%)	n (%)
Platelet count decreased	1 (3.0)	10 (30.3)
Abdominal pain	7 (21.2)	9 (27.3)
Fatigue	3 (9.1)	7 (21.2)
Headache	5 (15.2)	7 (21.2)
Nausea	2 (6.1)	6 (18.2)
Asthenia	3 (9.1)	5 (15.2)
Myalgia	1 (3.0)	5 (15.2)
Diarrhoea	2 (6.1)	5 (15.2)
Epistaxis	0 (0.0)	5 (15.2)
Vomiting	3 (9.1)	5 (15.2)
Petechiae	0 (0.0)	4 (12.1)
Arthralgia	0 (0.0)	4 (12.1)
Pain in extremity	1 (3.0)	4 (12.1)
Thrombocytopenia	0 (0.0)	4 (12.1)
Diabetes mellitus	0 (0.0)	4 (12.1)

*Excludes adverse events at the injection site

Platelet reductions by level

Confirmed nadir post-baseline platelet counts for all patients

Parameter	Placebo n=33	Volanesorsen* n=33
Confirmed nadir platelet count <140,000/mm^3	9 (27%)	25 (76%)
Confirmed nadir platelet count <100,000/mm^3	0	18 (55%)
• 100,000/mm^3 to <140,000/mm^3	9 (27%)	7 (21%)
• 75,000 to <100,000/mm^3	0	6 (18%)
• 50,000 to <75,000/mm^3	0	9 (27%)
• 25,000 to <50,000/mm^3	0	1 (3%)
• 0 to < 25,000/mm^3	0 (0.0)	2 (6%)†

*None of these patients had any major bleeding events

†Both patients recovered to normal platelet count levels following drug discontinuation and administration of corticosteroids. One patient received IVIG.

Approcci terapeutici

✓**La maggior parte dei casi di deficit parziale di LPL (MCS) possono essere trattati con le terapia convenzionali mentre i casi di FCS rispondono solo parzialmente o in modo scarso.**

✓**L'aderenza alla dietoterapia è generalmente problematica.**

✓ **Lo sviluppo di nuove terapie quali il volanesorsen offrono la possibilità di ridurre la trigliceridemia ed il rischio di pancreatite a fronte della necessità di frequenti controlli ambulatoriali.**

✓**Vi sono ulteriori nuovi approcci in fase di sperimentazione (l'inibizione di ANGPLT3)**

Grazie dell’attenzione

Effects on other lipid parameters at the 3 month end point

	Placebo		Volanesorsen		Placebo	Volanesorsen	
	Baseline (mg/dL)	3 months (mg/dL)	Baseline (mg/dL)	3 months (mg/dL)	Percentage change from baseline		p-value
HDL-C	17	17	17	25	5%	45%	<0.0001
LDL-C	28	29	28	61	7%	139%	<0.0001
Non-HDL-C	267	287	276	131	14%	–45%	<0.0001
VLDL-C	41	42	40	13	9%	–65%	<0.0001
ApoB	69	70	65	76	2%	20%	0.03
Chylo TG	1,785	1,991	1,913	436	38%	–77%	<0.0001

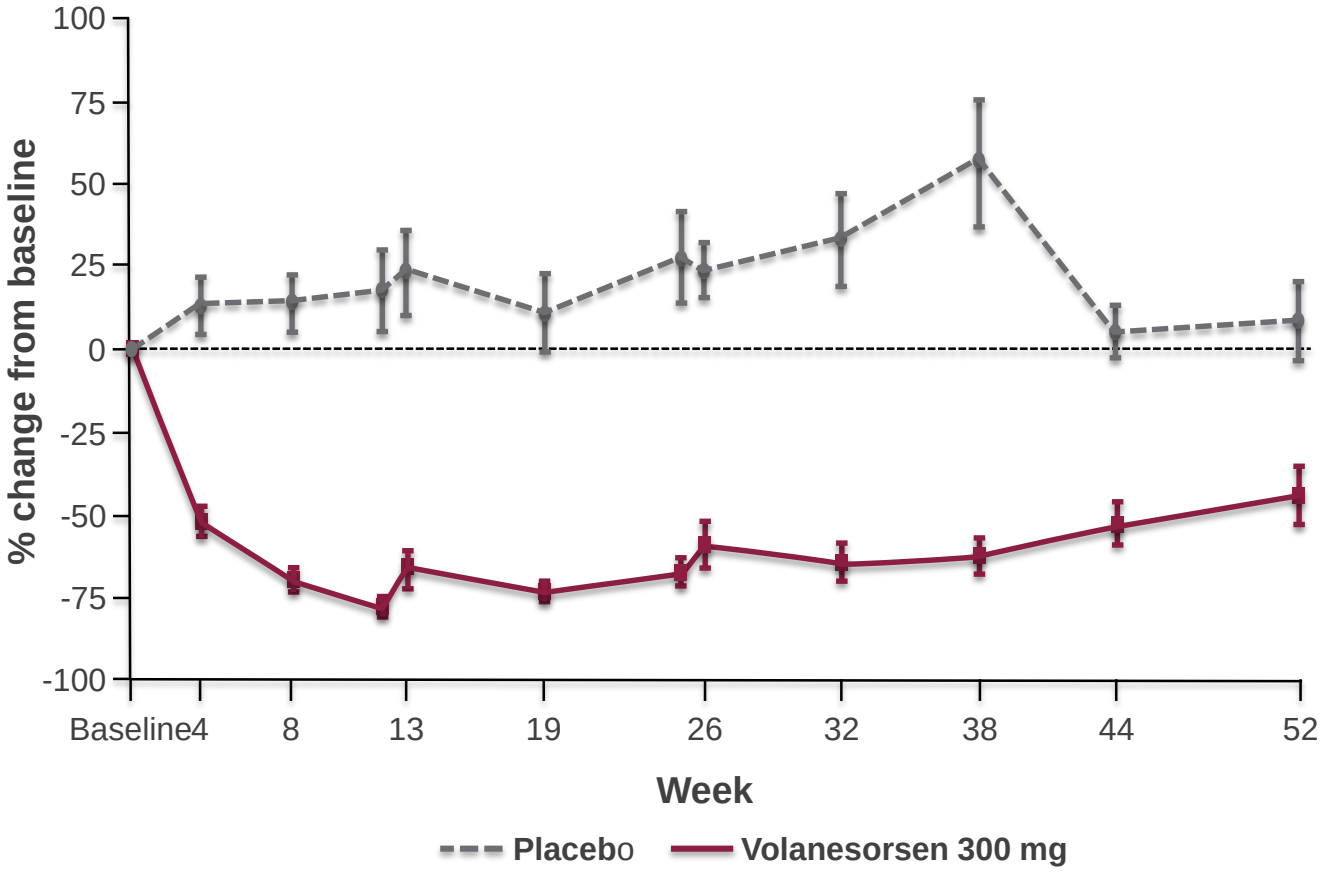
Majority of Volanesorsen-Treated Patients Achieved Fasting Triglyceride Levels Below Pancreatitis Risk Thresholds

		Placebo[1] n = 31 n (%)	Volanesorsen[1] n = 30 n (%)	P value
Threshold for chylomicronemia*	**TG <750 mg/dL (8.5 mmol/L)**	3 (9.7)	23 (76.7)	p=0.0001
Guidelines threshold for severe hypertriglyceridemia	**TG <500 mg/dL (5.7 mmol/L)**	0 (0.0)	15 (50.0)	p=0.003

Data includes all patients with triglycerides ≥ 750mg/dL at baseline

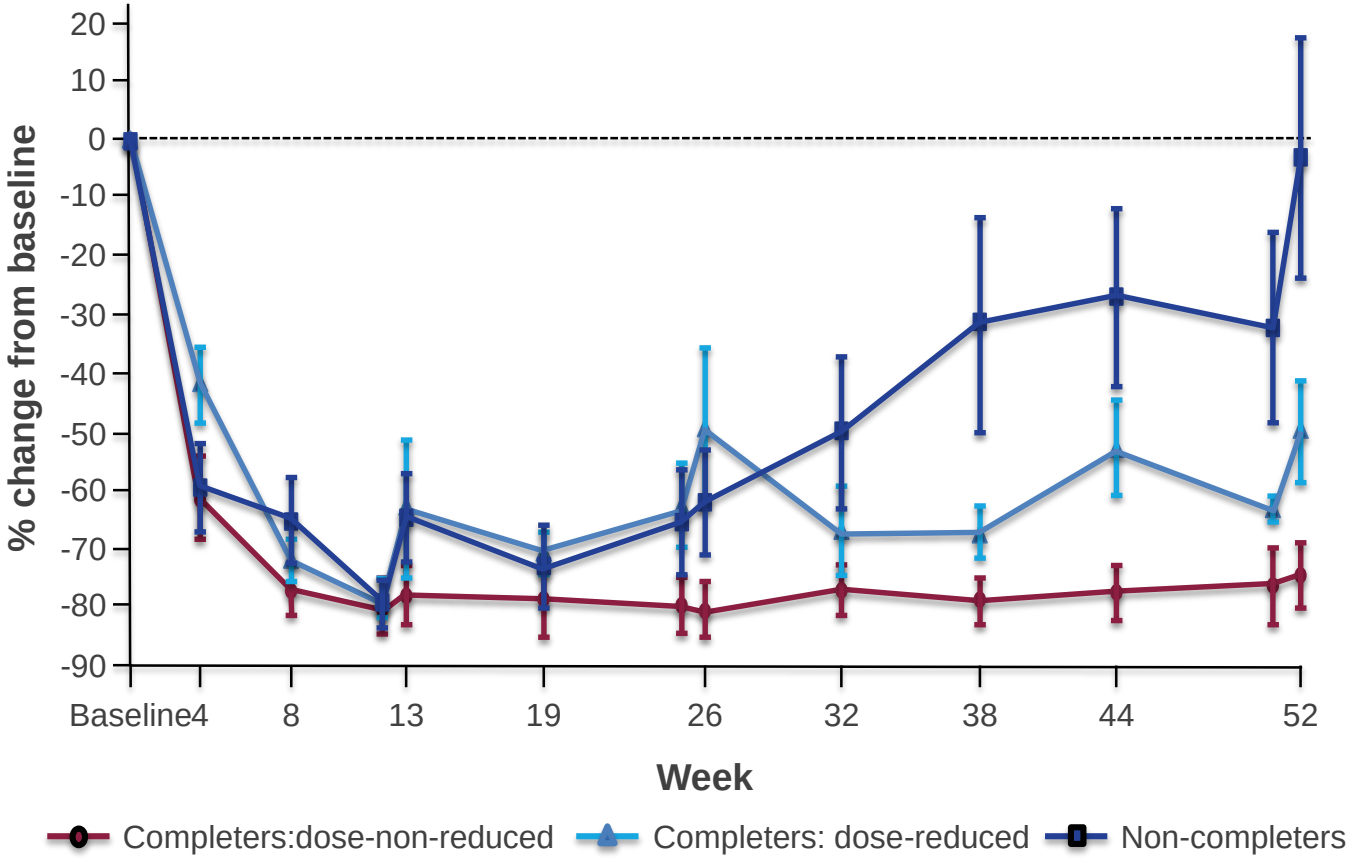
* Chylomicrons dominant over other TG-rich lipoproteins

Mean % change of TG levels during the 52 week period of treatment



Placebo	31	33	26 32	31	26 30	31	29	30	26
Volanesorsen 300 mg	30	33	28 30	28	22 27	25	24	25	24

Mean % change of TG levels during the 52 week period of treatment, with and without volanesorsen dose adjustment



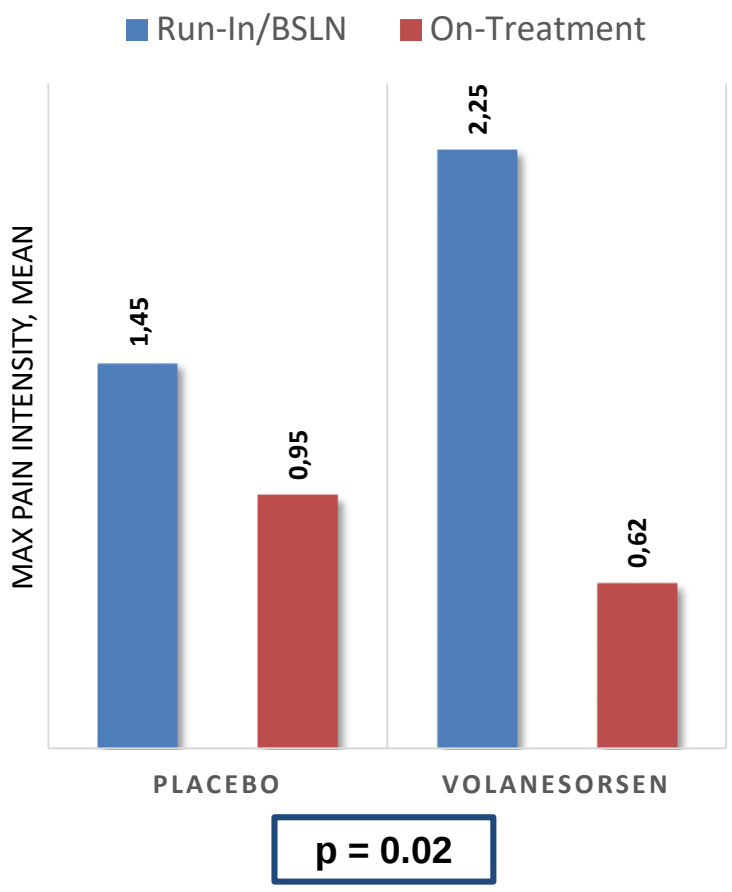
Dose-non-reduced	6	5	6	6	6	6	5	5	5	6	6	4 6
Dose-reduced	13	13	13	12	12	13	11	13	13	13	13	12 12
Non-completers	14	12	14	10	12	9	6	9	7	5	6	7 6

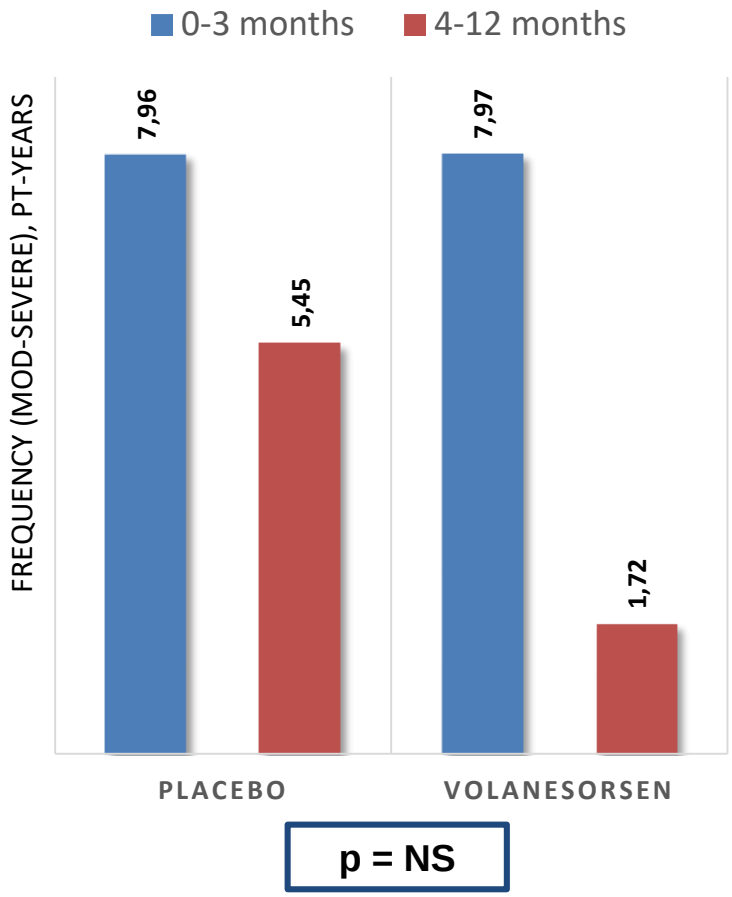
TG reductions in study completers without/with dose adjustment

	Volanesorsen n=6 without dose adjustment	Volanesorsen n=13 with dose adjustment*
Month 3		
Baseline (mg/dl)	2069	2520
Month 3 endpoint (mg/dl)	398	587
% Change from baseline	–79%	–72%
Month 6		
Month 6 endpoint (mg/dl)	413	957
% Change from baseline	–80%	–52%
Month 12		
Month 12 endpoint (mg/dl)	488	1120
% Change from baseline	–76%	–54%

*Dose adjustment = reduced frequency or dose pause

Volanesorsen Reduced Intensity and Frequency of Patient-Reported Abdominal Pain*





* Patients reporting pre-treatment pain (10 placebo; 7 volanesorsen)

APPROACH study: Patients experiencing pancreatitis attacks during treatment

Placebo n=33		**Volanesorsen n=33**	
Patients	Events	Patients	Events
3	4	1	1
	p=NS*		

Phase 3 Study Results Reflect Lower Incidence of Pancreatitis in Patients Treated with Volanesorsen: Adjudicated Pancreatitis Events During On-Treatment Period* APPROACH and COMPASS Combined

	Placebo		Volanesorsen	
	Patients n (%)	Events n	Patients n (%)	Events n
Patients with treatment emergent adjudicated event APPROACH (CS6)	3 (9%)	4	1 (3%)	1
p value	p= 0.61			
Patients with treatment emergent adjudicated event COMPASS (CS16)	3 (8%)	5	0	0
p value	p= 0.036			
Patients with treatment emergent adjudicated event CS6 + CS16	6 (8%)	9	1 (1%)	1
p value	p= 0.019			

*On treatment is last dose plus 28 days

Incidence of pancreatitis in patients treated with volanesorsen

Adjudicated pancreatitis events during on-treatment* period: APPROACH and COMPASS combined

	Placebo		Volanesorsen	
	Patients n (%)	Events n	Patients n (%)	Events n
Patients with treatment-emergent adjudicated event APPROACH CS6	3 (9%)	4	1 (3%)	1
p-value	p=0.61			
Patients with treatment-emergent adjudicated event COMPASS CS16	3 (8%)	5	0	0
p-value	p=0.036			
Patients with treatment-emergent adjudicated event CS6 + CS16	6 (8%)	9	1 (1%)	1
p-value	p=0.019			

*On-treatment is last dose plus 28 days

Pancreatitis in patients at high risk of recurrent attacks

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

*Pancreatitis events were independently adjudicated by an independent medical committee (SOCAR)

Secondary endpoint – MRI analysis

		Placebo N=33		Volanesorsen N=33
Hepatic fat fraction (%)	Baseline	5.7		8.6
	12 months	5.8		5.9
	Change	+0.1		–1.7
Normal <6.4%	p-value		0.09	
Liver volume (cc)	Baseline	1959		2063
	12 months	1965		2186
Normal 1504 ± 407 cc	Change	–25		+113
	p-value		0.12	
Spleen volume (cc)	Baseline	454		508
	12 months	488		621
Normal 147 ± 81 cc	Change	+32		+107
	p-value		0.0001	

Platelets at baseline*

- A systematic review of medical records for FCS patients found >55% incidence of thrombocytopenia**
- Variability was seen in the APPROACH study

Parameter	Placebo n=33	Volanesorsen n=33
Mean (SD)	228 (72)	215 (60)
Median	214	200
IQ range	181- 252	169- 251
Min-Max	135-471	135-366
>200,000 – N (%)	21 (63.6)	16 (48.5)
>300,000 – N (%)	4 (12.1)	3 (9.1)
≤ 140 – N (%)	1 (3.7%)	1 (3.8%)

*Baseline is calculated as an average of all pre-dose values

**SMASH Initiative presented at European Atherosclerosis Society Congress June 1, 2016 by Dr. Daniel Gaudet

Volanesorsen Safety and Tolerability

- No treatment-related liver safety signals
  - No increase in liver fat
- No treatment-related renal or cardiac safety signals
- Most common AEs were injection site reactions
- Declines in platelet counts below the LLN observed in many FCS patients
  - These declines were generally well-managed with dose adjustment and monitoring
  - 5 early terminations due to declines in platelet counts
    - **3 patients (2 in APPROACH, 1 in OLE) experienced a serious platelet event (grade 4 thrombocytopenia); all patients recovered with cessation of dosing**
- Other AEs contributing to discontinuation in 4 patients:
  - Injection site reaction (1), fatigue (1), chills and sweating (1), generalized erythema (1)

- 14 treatment-emergent SAEs (8 volanesorsen, 6 placebo):
  - 12 were unrelated to study drug
  - 2 considered related or possibly related to study drug were serious platelet events (grade 4 thrombocytopenia), which resolved without complication after cessation of dosing

FCS Platelet Variability

- **Platelet variability appears to be a manifestation of FCS***
  - **Systematic review of medical records for FCS patients found >55% incidence of thrombocytopenia**
- **Variability was seen in the APPROACH study**
- **3 patients (2 in APPROACH, 1 in OLE) experienced a serious platelet event (grade 4 thrombocytopenia);**
- **All patients recovered with cessation of dosing**

*Tremblay K., Brisson D. , Gaudet D., natural History and Gene expression Signature of Platelet Count in Lipoprotein Lipase deficiency (ePoster), EAS 2017, Prague; *Atheroscl suppl;* Gaudet et al.. Natural History of Platelet Values and Associated Risk of Acute Pancreatitis in a Sample of 87 Adults with Familial Chylomicronemia due to Lipoprotein Lipase Deficiency. Submitted, 2017; Gaudet et al. The 84th EAS Congres, Innsbruck, Austria, 2016.;

Conclusions

Volanesorsen-Treated FCS Patients Achieved Clinical Benefits

- Primary endpoint met: 77% mean reduction in triglycerides from baseline vs. 18% mean increase with placebo ($p<0.0001$)
- 19 mmol/L mean absolute reduction in triglycerides
- 77% of patients achieved triglycerides <8.5 mmol/L, and 50% <5.6 mmol/L
- Significant decrease in the incidence of pancreatitis attacks and reduced frequency and intensity of abdominal pain

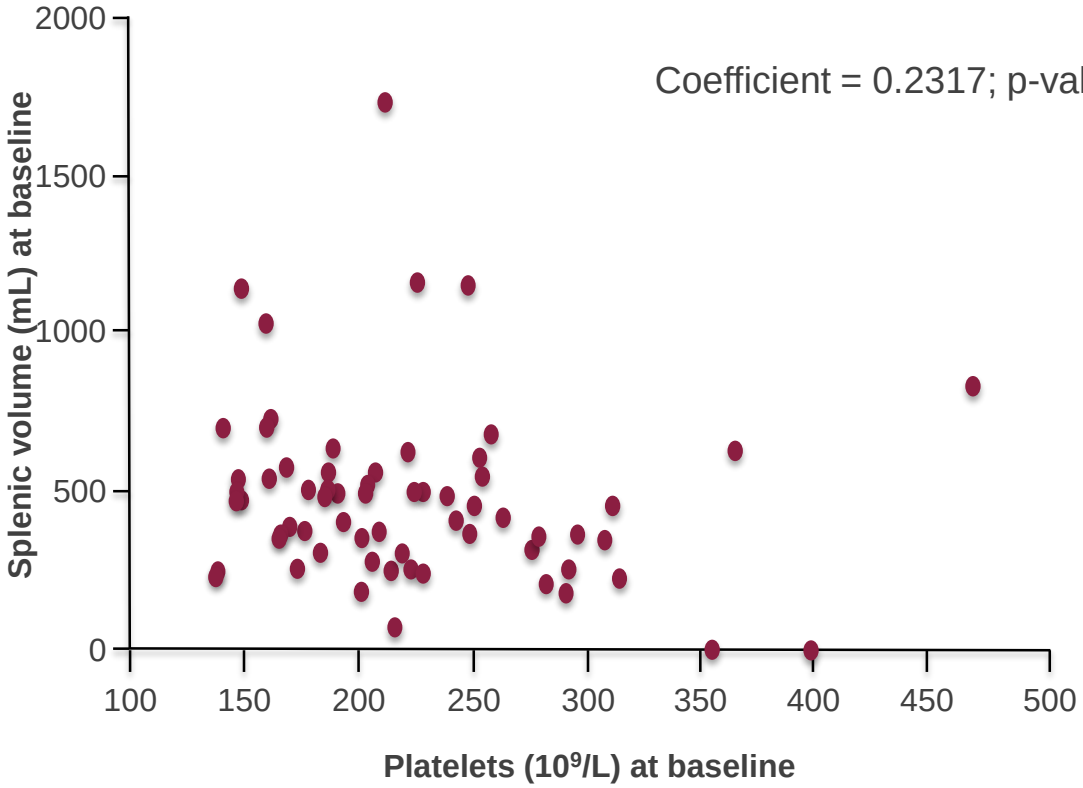
Volanesorsen Safety Profile Has Been Well Characterized

- Declines in platelet levels observed in many FCS patients
  - Generally well-managed with monitoring and dose adjustment
- 5 early terminations due to declines in platelet counts
- Other AE's were related to local tolerability

Splenic volume and platelets

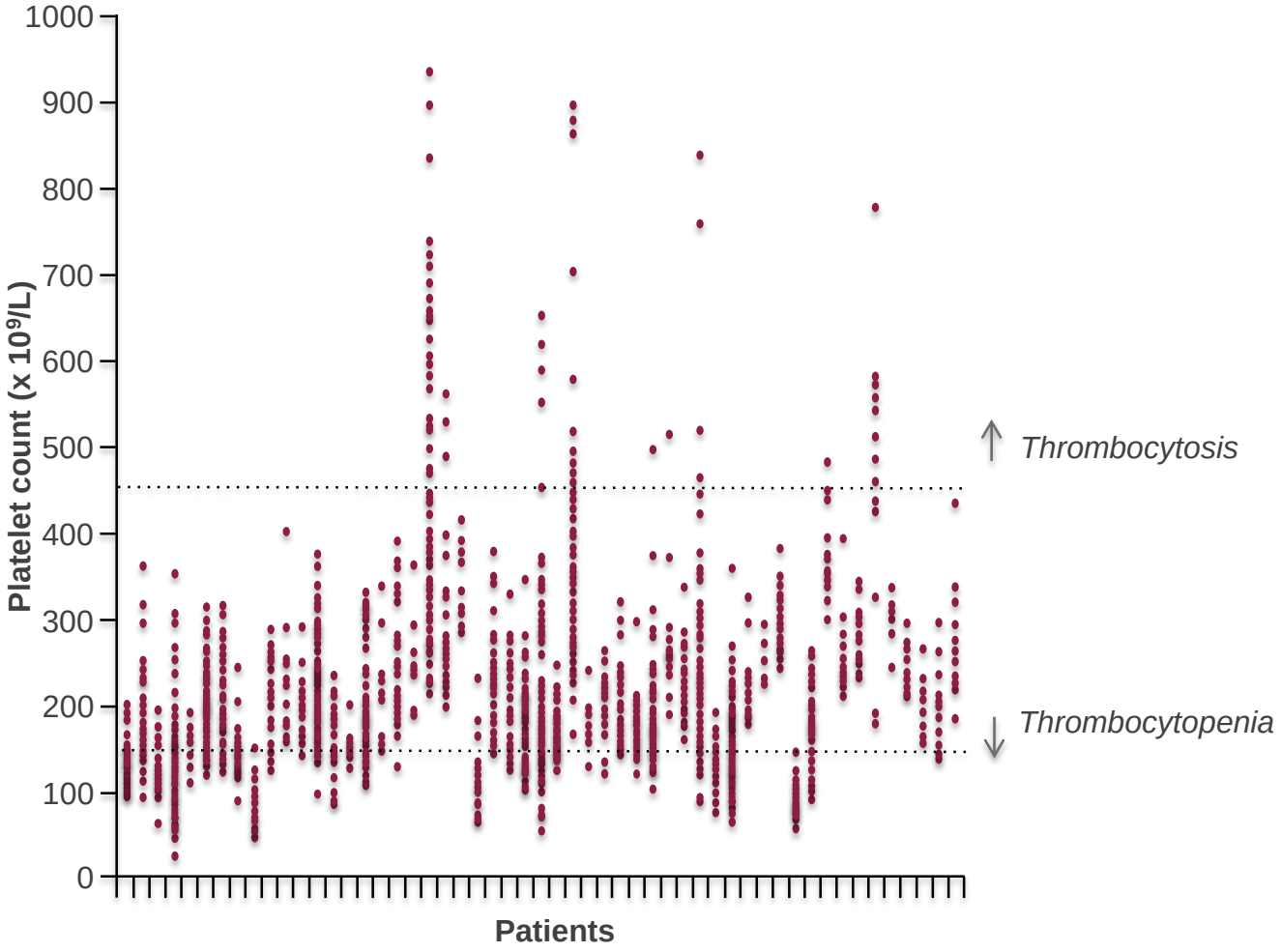
Scatter plot with Spearman correlation coefficient and *p*-value for baseline spleen volume vs. baseline platelets

Full analysis set (N=66)



The baseline for spleen volume is defined as the last non-missing assessment prior to the first dose of study drug
The baseline for platelets is defined as the average of all pre-dose values

Fluctuations of platelet values in patients with FCS (SMASH registry)



Safety and tolerability: General

- No treatment-related liver safety signals
  - No increase in liver fat
- No treatment-related renal or cardiac safety signals
- Most common AEs were injection-site reactions, mostly mild
- Other AEs contributing to discontinuation in 4 patients:
  - Injection-site reaction (1), fatigue (1), chills and sweating (1), generalised erythema (1)
- 14 treatment-emergent SAEs (8 volanesorsen, 6 placebo):
  - 12 were unrelated to study drug
  - 2 considered related or possibly related to study drug were serious platelet events (grade 4 thrombocytopenia), which resolved without complication after cessation of volanesoresen treatment and administration of corticosteroids, one patient also received IVIG.

Safety and tolerability: Platelet reductions

- Declines in platelet counts below the LLN observed in many FCS patients
  - These declines were generally well managed with dose adjustment and monitoring
  - 5 early terminations due to declines in platelet counts
    - 4 patients (2 in APPROACH, in OLE) experienced a serious platelet event (grade 4 thrombocytopenia); all patients recovered with cessation of volanesorsen treatment and administration of corticosteroids. One patient in APPROACH also received IVIG.
- No terminations in the last 6 months of the study after platelet monitoring fully implemented

Additional safety

- Most common AEs were injection-site reactions
- 14 treatment-emergent SAEs (8 volanesorsen, 6 placebo):
  - 12 were unrelated to study drug
  - 2 considered related or possibly related to study drug were serious platelet events (grade 4 thrombocytopenia), which resolved (platelet counts recovered to normal) without complication after cessation of volanesorsen and administration of corticosteriods. One patient also received IVIG.
- No treatment-related liver safety signals
- No treatment-related renal or cardiac safety signals

Conclusions

Volanesorsen-treated FCS patients achieved clinical benefits

- Primary endpoint met: 77% mean reduction in triglycerides from baseline vs. 18% mean increase with placebo ($p<0.0001$)
- 19 mmol/L mean absolute reduction in triglycerides
- 77% of patients achieved triglycerides <8.5 mmol/L, and 50% <5.6 mmol/L
- Significant decrease in the incidence of pancreatitis attacks and reduced frequency and intensity of abdominal pain

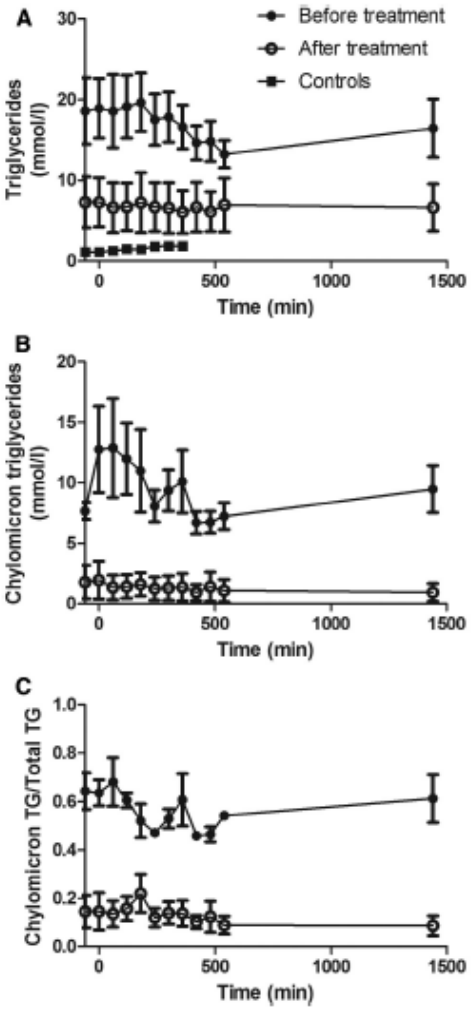
Volanesorsen safety profile has been well characterised

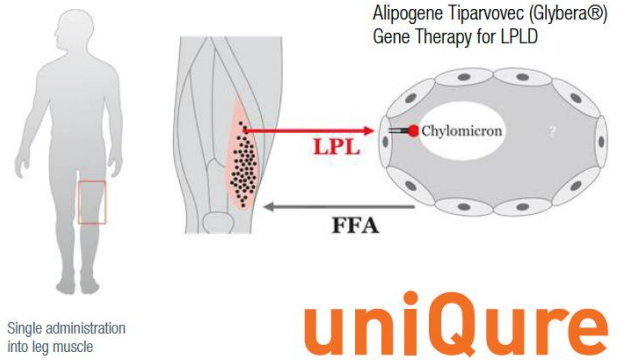
- Declines in platelet levels observed in many FCS patients
- Generally well managed with monitoring and dose adjustment
- 5 early terminations due to declines in platelet counts
- Other AEs were related to local tolerability and were mostly mild

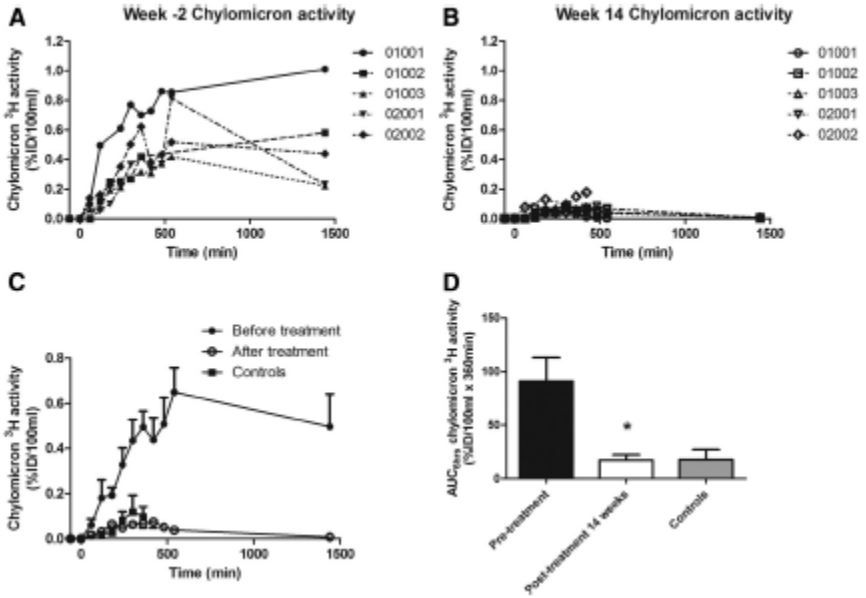
Nuove terapie: terapia genica

- Vettore virale adeno-associato (AAV1) per l'espressione di LPLS^{447X} (gain of function mutations)

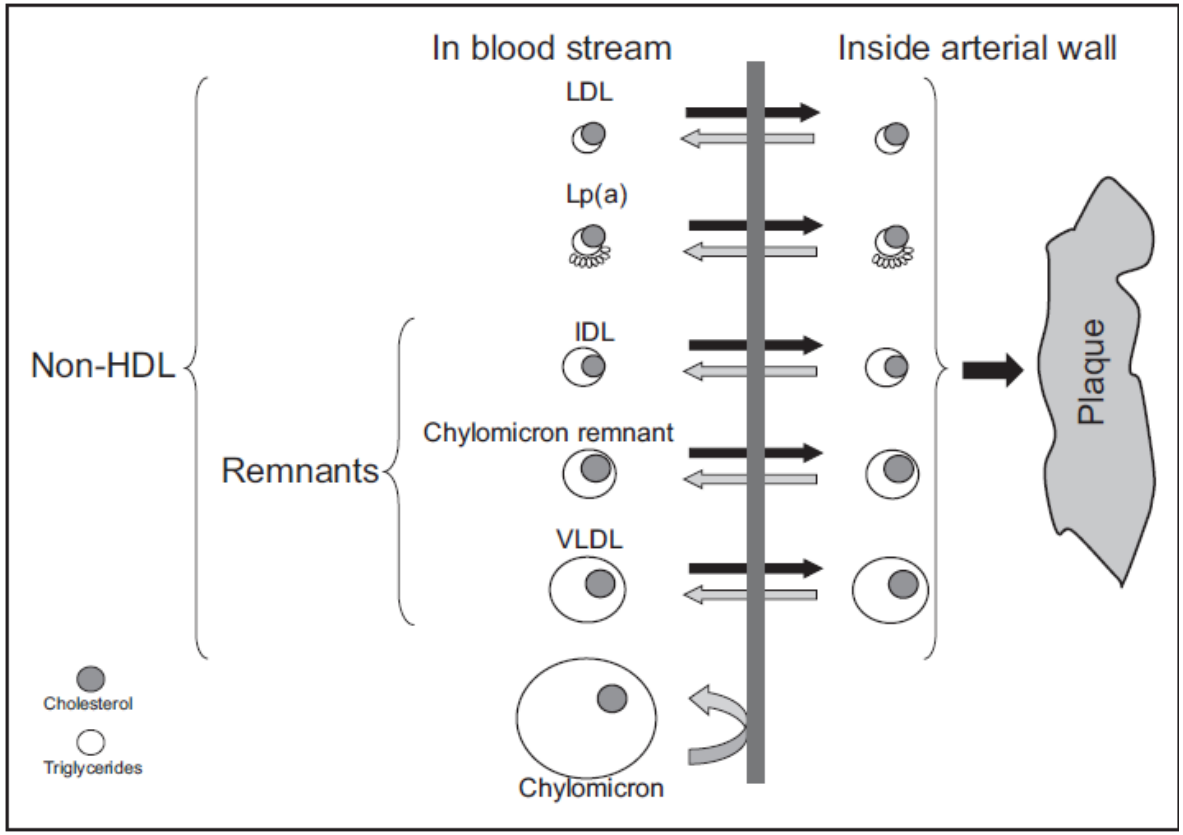
  Alipogene tiparvovec AAV1-LPLS447X (Chiesi)







Le complicanze: HTG lieve-moderata e CVD



✓Le particelle *remnants* passano attraverso la parete arteriosa dove sono captate dai macrofagi e dalle cellule muscolari lisce.

✓Le particelle remnants sono più grandi e trasportano ≤40 volte colesterolo per particella. Questo le rende più aterogene dell'LDL.

✓Le particelle remnants causano aterosclerosi attraverso una componente infiammatoria

Arterioscler Thromb Vasc Biol. 2016 Nov;36(11):2133-2135.

Baseline characteristics of patients with severe HTG

	Severe HTG (N=32)	
Age, yrs	42.2 ± 13.4	18.0 – 66.0
Male,n (%)	21 (65.6)	-
Pregnancies, n (%)	9 (81.8)	-
BMI (kg/h^2)	27.2 ± 4.9	19.7 – 40.0
Age of onset of HTG, (yrs)	**26.1 ± 14.3**	**1 - 66**
AP, n (%)	**17 (51.3)**	**-**
Age of onset of AP (yrs)	**28.9 ± 13.3**	**10.0 – 58.0**
Patients with recurrent AP, n (%)	8 (25.0)	-
Risk Factors and Cormobilities		
SBP (mmHg)	126.7 ± 15.3	90.0 – 168.0
SDP (mmHg)	82.9 ± 9.9	60.0 –102.0
Smoking,n (%)	8 (25.0)	-
Obesity,n(%)	9 (28.1)	-
Diabetes,n (%)	10 (31.3)	-
Hypertension, n (%)	11 (34.4)	-
CHD, n (%)	4 (12.5)	-
Plasma Lipids		
Total-C (mg/dl)	305.9 ± 122.3	153.0 – 565.0
HDL-C (mg/dl)	25.7 ± 12.7	9.0 – 60.0
Triglycerides (mg/dl)	**2066.6 ± 841.8**	**1019.0 – 4480.0**
Non HDL-C (mg/dl)	266.1 ± 109.5	141.0 – 519.0
Medications		
MCT oil,n (%)	5 (17.9)	-
Fish oil,n (%)	12 (42.9)	-
Fibrates,n (%)	13 (46.4)	-
Statins, n (%)	2 (7.1)	-
Glucose Lowering Therapies, n (%)	2 (6.25)	
Metformin	1 (3.6)	-
Sulphonylurea	1 (3.6)	-
Insulin	1 (3.6)	-

Plasma lipid changes and treatments during follow-up in HTG patients classified as FCS and MCS

	FCS (N=17)			MCS (N=15)					
	Baseline	Average value during follow-up	Best result during follow-up	Baseline	Average value during follow-up	Best result during follow-up	$P_{baseline}$	$P_{follow-up}$	$P_{Best\ Result}$
Plasma Lipids									
Total-C (mg/dl)	276.2±108.8	251.5±91.0	144.8±28.3	335.7±131.6	262.2±73.3	216.1±75.1	NS	NS	0.001
HDL-C (mg/dl)	21.4±14.5	20.0±8.8	22.5±10.9	31.0±7.9	34.5±10.0	38.7±8.3	NS	<0.001	<0.001
Triglycerides(mg/dl)	2137.3±844.9	1677.7±968.5	628.8±393.3	1986.5±860.5	1059.0±554.9	370.6±396.0	NS	0.04	0.07
Non HDL-C (mg/dl)	268.4±111.3	220.7±73.2	123.6±29.8	263.4±113.9	230.7±78.7	178.6±75.2	NS	NS	0.01
TG < 500 (n, %)	-	-	8 (47.1)	-	-	13 (86.7)	-	-	0.028
Medications									
MCT oil, n (%)	5 (29.4)	-	8 (47.0)	1 (6.7)	-	1 (6.7)	0.04	-	0.01
Fish oil, n (%)	11 (64.7)	-	11 (64.7)	5 (33.3)	-	5 (33.3)	<0.001	-	0.06
Fibrates, n (%)	10 (58.8)	-	14 (82.3)	7 (46.7)	-	7 (46.7)	0.02	-	0.01
Statins, n (%)	-	-	6 (35.3)	4 (26.7)	-	4 (26.7)	NS	-	NS
Glucose Lowering Therapies, n (%)			6 (35.3)						
Metformin	1 (5.9)	-	6 (35.3)	0	-	0	NS	-	0.02
Sulphonylurea	1 (5.9)	-	1 (5.9)	0	-	0	NS	-	NS
Insulin	1 (5.9)	-	3 (17.6)	0	-	0	NS	-	NS