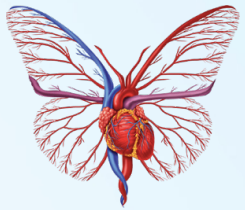
# 3 concetti chiave nella diagnosi e terapia di:

# Ipercolesterolemia Familiare Omozigote

**Arturo Cesaro**

Università della Campania «Luigi Vanvitelli»

AORN Sant'Anna e San Sebastiano, Caserta



AORN CASERTA

Università degli Studi della Campania *Luigi Vanvitelli*

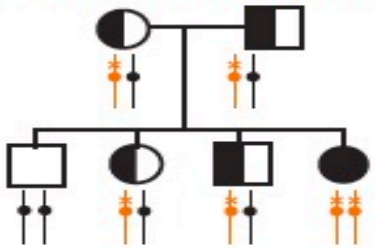
# Homozygous familial hypercholesterolaemia

## Biochemistry

Extremely elevated LDL-C↑↑↑

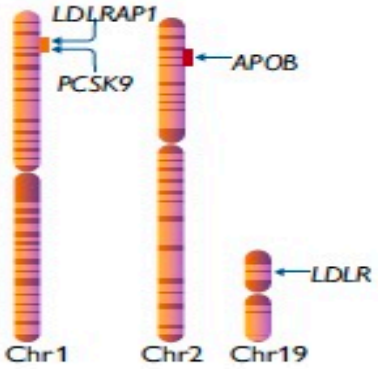
## Clinical genetics

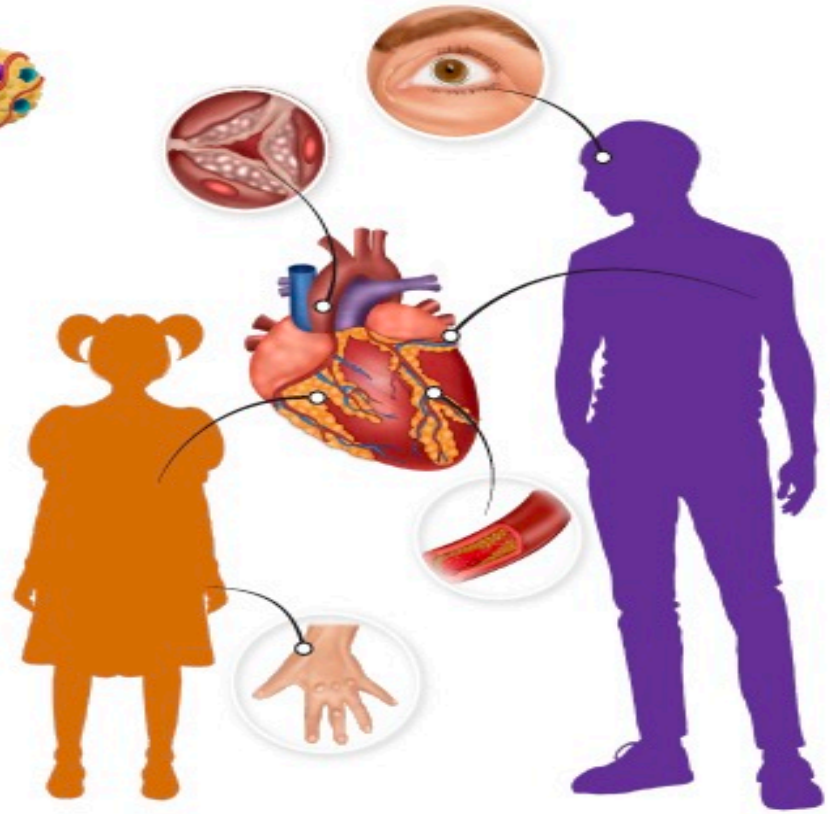
Semi-dominant inheritance



## Molecular genetics

Numerous genes and variants



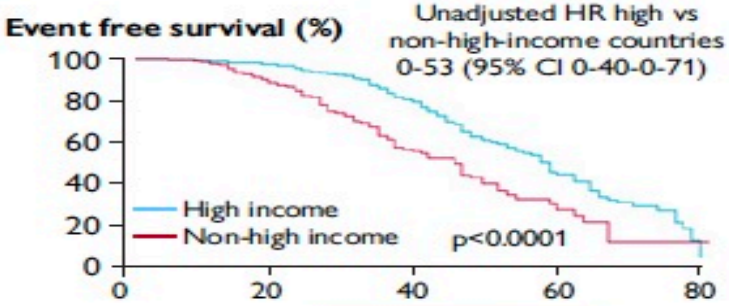
- Screening program creation for early detection
- Use of multi-prong lipid lowering therapy starting at diagnosis
- Management by multidisciplinary team
- Family planning

## Clinical features

- Xanthomatosis
- Premature atherosclerosis
- Aortic disease

## Early mortality

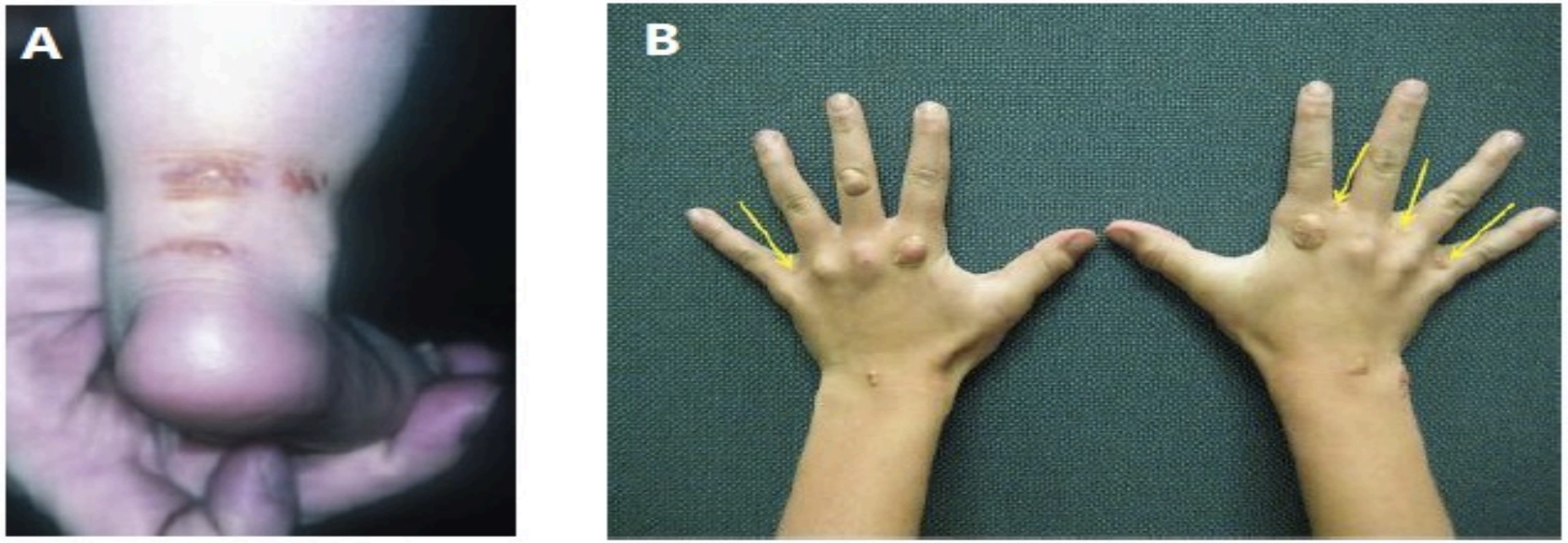
- Worse in non-high-income countries
- Worse at higher LDL-C levels




## Treatments

- Apheresis
- Oral agents
- Biologic therapies

# Xanthomas in HoFH




Cutaneous and tuberous xanthomas in HoFH.

Interdigital xanthomas (see B, yellow arrows) in children are highly suggestive of HoFH diagnosis.

*Photograph (A) kindly provided by Prof. Eric Bruckert.*
*Photograph (B) kindly supplied by Prof. Frederick Raal.*





Cuchel M, Bruckert E, Ginsberg H et al. *Eur Heart Journal* 2014

# Cardiovascular complication of HoFH

**Box 2 Cardiovascular complications of homozygous familial hypercholesterolaemia**

- HoFH is characterized by accelerated atherosclerosis, typically affecting the aortic root, although other vascular territories may also be affected.
- The first major cardiovascular events often occur during adolescence, possibly younger when patients are *LDLR*-negative and/or untreated.
- In young children, early symptoms and signs are often linked to aortic stenosis and regurgitation, due to massive accumulation of cholesterol at the valvular levels.
- As aortic and supra-valvular aortic valve diseases may progress even when cholesterol levels are reduced, regular screening for subclinical aortic, carotid, and coronary heart disease is indicated.

**Late referral of HoFH patients to specialised center increases the severity of CVD complications**





Cuchel M, Bruckert E, Ginsberg H et al. *Eur Heart Journal* 2014

# Box 2 Updated criteria for the diagnosis of homozygous familial hypercholesterolaemia

Clinical criteria

- LDL-C criteria:
  Untreated LDL-C >10 mmol/L (>~400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis.
- Additional criteria:
  Cutaneous or tendon xanthomas before age of 10 years and/or
  untreated elevated LDL-C levels consistent with heterozygous FH in both parents*
  *In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.

Genetic criteria

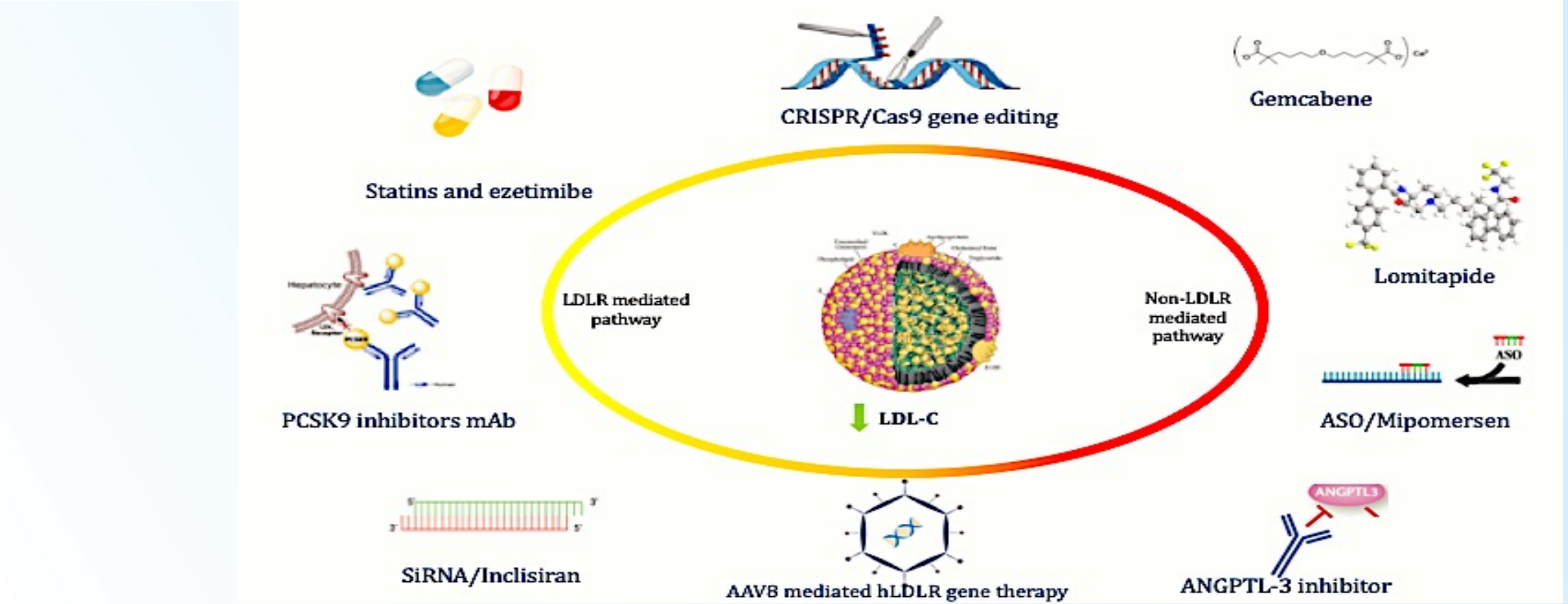
- Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes or ≥2 such variants at different loci (*Box 3*); for abbreviations for genetic nomenclature see below.

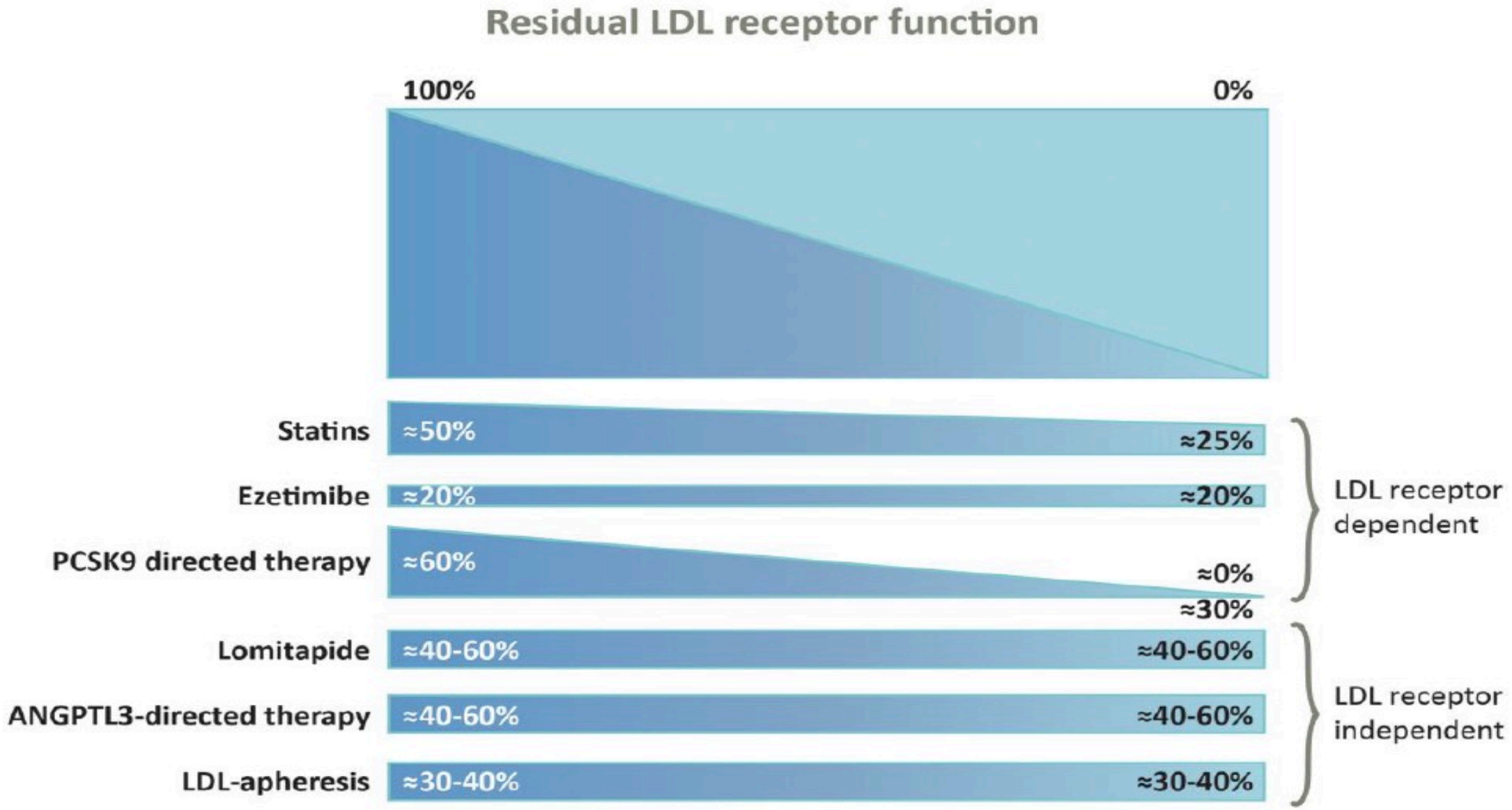
*ABCG5*, *ABCG8*: Genes encoding ATP-binding cassette subfamily G members 5 and 8
*APOB*: Gene encoding apolipoprotein B
*LDLR*: Gene encoding the low-density lipoprotein receptor
*LDLRAP1*: Gene encoding low-density lipoprotein receptor adaptor protein 1
*LIPA*: Gene encoding lysosomal acid lipase
*PCSK9*: Gene encoding proprotein convertase subtilisin/kexin type 9 protein (PCSK9)

# New Frontiers in the Treatment of Homozygous Familial Hypercholesterolemia



Arturo Cesaro, MD[a,b], Fabio Fimiani, BSc[c], Felice Gragnano, MD[a,b], Elisabetta Moscarella, MD[a,b], Alessandra Schiavo, MD[a,b], Andrea Vergara, MD[a,b], Leo Akioyamen, MD[d], Laura D'Erasmo, MD, PhD[e], Maurizio Averna, MD[f], Marcello Arca, MD[e], Paolo Calabrò, MD, PhD[a,b,*]




Residual LDL receptor function
100%
0%
Statins
≈50%
≈25%
Ezetimibe
≈20%
≈20%
PCSK9 directed therapy
≈60%
≈0%
≈30%
Lomitapide
≈40-60%
≈40-60%
ANGPTL3-directed therapy
≈40-60%
≈40-60%
LDL-apheresis
≈30-40%
≈30-40%
LDL receptor dependent
LDL receptor independent

# New Frontiers in the Treatment of Homozygous Familial Hypercholesterolemia

Arturo Cesaro, MD[a,b], Fabio Fimiani, BSc[c], Felice Gragnano, MD[a,b], Elisabetta Moscarella, MD[a,b], Alessandra Schiavo, MD[a,b], Andrea Vergara, MD[a,b], Leo Akioyamen, MD[d], Laura D'Erasmo, MD, PhD[e], Maurizio Averna, MD[f], Marcello Arca, MD[e], Paolo Calabrò, MD, PhD[a,b,*]



**Table 1**
**Major medications in the treatment of HoFH and their effect in reducing LDL-C**

| Drug Name | Mechanism of Action | Administration Route and Dosage | Efficacy in HoFH Patients | Adverse Events |
|---|---|---|---|---|
| PCSK9 Inhibitors | Inhibition of PCSK9 by mAb | *Subcutaneous*<br>Evolocumab 420 mg monthly/every 2 wk<br>Alirocumab 150 mg every 2 wk | LDL-C reduction (20%-30%) | Injection site reactions and Flu-like symptoms |
| Inclisiran | Inhibition of PCSK9 by siRNA | *Subcutaneous*<br>300 mg (every 3 mo) | LDL-C reduction (12%-37%) | Injection site reactions |
| Lomitapide | Reduced secretion of ApoB-containing lipoproteins by the liver via inhibition of MTP | *Oral*<br>5–60 mg daily | Reduction in:<br>LDL-C (50%)<br>ApoB (49%)<br>TG (45%) | • Hepatic steatosis<br>• Gastrointestinal disorders<br>• Impaired liver function |
| Mipomersen | Inhibition of ApoB synthesis | *Subcutaneous*<br>200 mg – weekly (160 mg in subjects < 50 kg [110 lbs]) | Reduction in:<br>LDL-C (20%-50%)<br>Lp(a) (30%) | • Injection site reactions<br>• Flu-like symptoms<br>• Impaired liver function<br>• Liver steatosis |
| Evinacumab | Inhibition of ANGPTL-3 | *Intravenous*<br>15 mg/kg every 4 wk | Reduction in:<br>LDL-C (~47%)<br>TG (~50%) | Flu-like symptoms |

*Abbreviations:* ANGPTL-3, angiopoietin-like protein 3; ApoB, apolipoprotein B; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); mAb, monoclonal antibody; MTP, microsomal triglyceride transport protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SiRNA, small interfering RNA; TG, triglycerides.

# Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial



| | Placebo group (n=16) | Evolocumab group (n=33) | All patients (n=49) |
|---|---|---|---|
| Age (years) | 32 (14) | 30 (12) | 31 (13) |
| Age range (years) | 14–57 | 13–51 | 13–57 |
| Female sex | 8 (50%) | 16 (48%) | 24 (49%) |
| Ethnicity* | | | |
| White | 15 (94%) | 29 (88%) | 44 (90%) |
| Asian | 1 (6%) | 1 (3%) | 2 (4%) |
| Clinically evident coronary artery disease | 6 (38%) | 15 (46%) | 21 (43%) |
| Previous coronary artery bypass surgery | 4 (25%) | 8 (24%) | 12 (25%) |
| Aortic valve replacement | 3 (19%) | 4 (12%) | 7 (14%) |
| Lipid parameters | | | |
| LDL cholesterol, ultracentrifugation (mmol/L) | 8·7 (3·8) | 9·2 (3·5) | 9·0 (3·5) |
| LDL cholesterol, calculated (mmol/L) | 8·7 (3·7) | 9·2 (3·5) | 9·0 (3·6) |
| Apolipoprotein B (g/L) | 2·1 (0·8) | 2·1 (0·7) | 2·1 (0·7) |
| Lipoprotein(a) (nmol/L) | 128 (80–201) | 76 (26–145) | 101 (31–146) |
| Apolipoprotein A1 (g/L) | 1·1 (0·4) | 1·1 (0·2) | 1·1 (0·3) |
| HDL cholesterol (mmol/L) | 1·0 (0·4) | 1·0 (0·3) | 1·0 (0·3) |
| Triglycerides (mmol/L) | 1·3 (0·7) | 1·2 (0·6) | 1·2 (0·6) |
| Free PCSK9 (nmol/L) | 9·4 (2·5) | 8·9 (2·9) | 9·0 (2·7) |
| Lipid-lowering therapy | | | |
| Statin | 16 (100%) | 33 (100%) | 49 (100%) |
| Atorvastatin | 10 (63%) | 22 (67%) | 32 (65%) |
| Atorvastatin ≥40 mg/day | 10 (63%) | 21 (64%) | 31 (63%) |
| Rosuvastatin | 6 (38%) | 11 (33%) | 17 (35%) |
| Rosuvastatin ≥20 mg/day | 5 (31%) | 10 (30%) | 15 (31%) |
| Ezetimibe | 15 (94%) | 30 (91%) | 45 (92%) |
| Genotype | | | |
| LDL receptor mutations | 14 (88%) | 31 (94%) | 45 (92%) |
| True homozygous | 7 (44%) | 15 (45%) | 22 (45%) |
| Compound heterozygous | 7 (44%) | 16 (48%) | 23 (47%) |
| Heterozygous | 0 | 1 (3%) | 1 (2%) |
| Apolipoprotein B | 2 (13%) | 0 | 2 (4%) |
| Autosomal recessive hypercholesterolaemia | 0 | 1 (3%) | 1 (2%) |

Data are mean (SD), range, n (%), or median (IQR). PCSK9=proprotein convertase subtilisin/kexin type 9. *Ethnicity was self-reported and some patients did not answer this question.

*Table 1:* Baseline characteristics

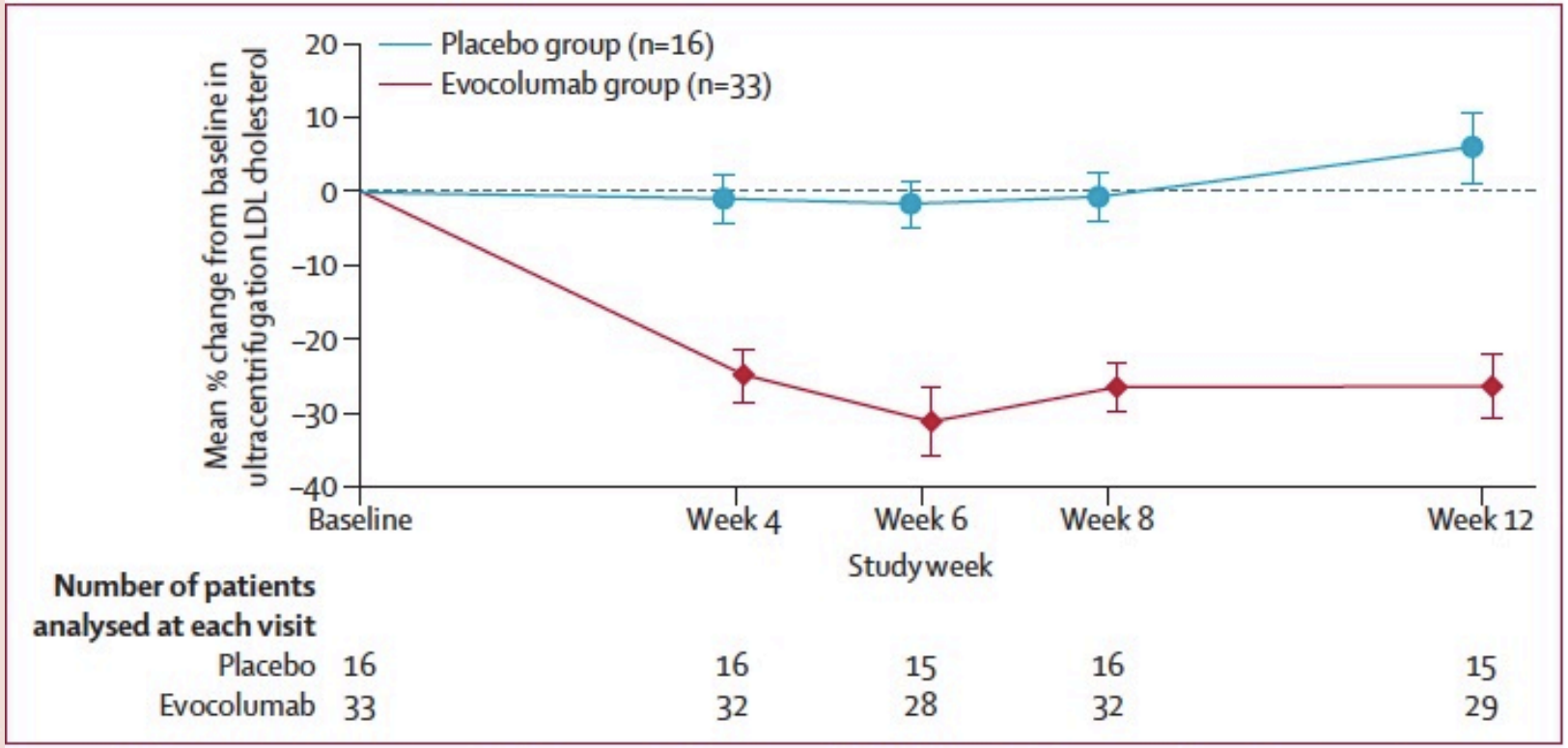



*Figure 2:* Mean percentage change in ultracentrifugation LDL cholesterol concentration from baseline to week 12



*Lancet 2015; 385: 341–50*

# Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study



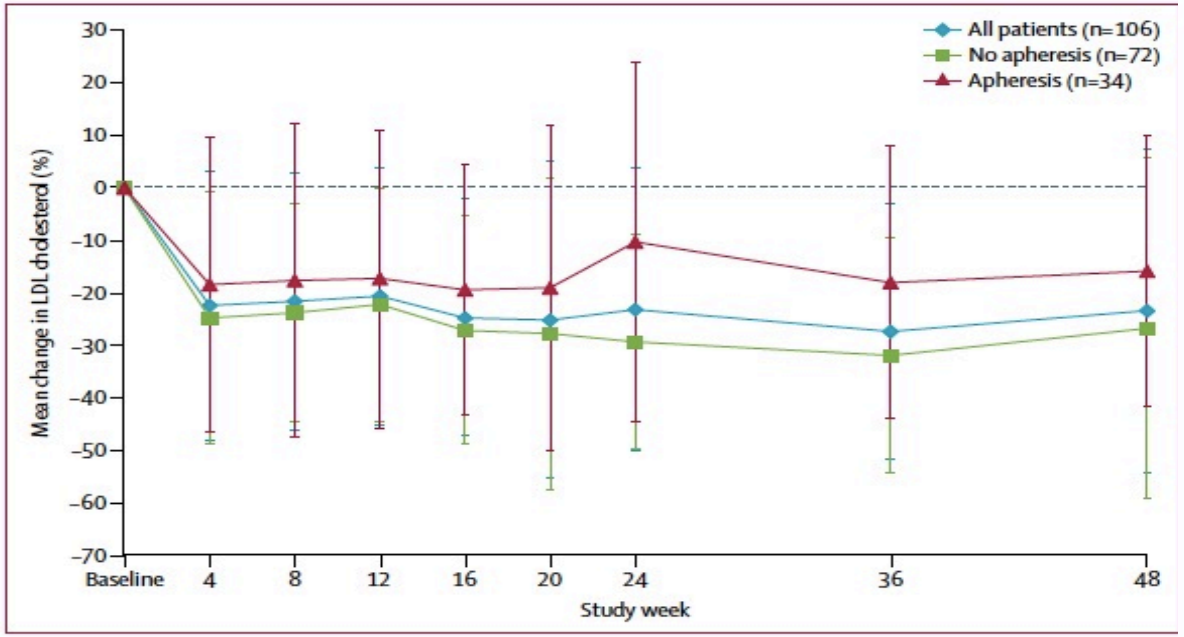



***Figure 1:*** **LDL cholesterol change between baseline and 48 weeks**
Figure shows data for 106 patients with homozygous familial hypercholesterolaemia treated with evolocumab, all together and by apheresis status at study entry. Data are mean and error bars show SD.

| | After ≥12 weeks of 420 mg evolocumab every month | After 12 weeks of 420 mg evolocumab every 2 weeks |
|---|---|---|
| Value at baseline, mmol/L | 9·35 (3·35) | 9·35 (3·35) |
| Change from baseline, mmol/L | −1·77 (2·05) | −2·57 (2·14) |
| Percentage change from baseline | −20·1% (21·7) | −28·3%(21·1) |

Data are mean (SD). Data are for 47 patients who were not on apheresis who increased their dosing to every 2 weeks. p=0·0001 for difference between groups in change from baseline.

***Table 3:*** **Effect of evolocumab uptitration on LDL cholesterol**

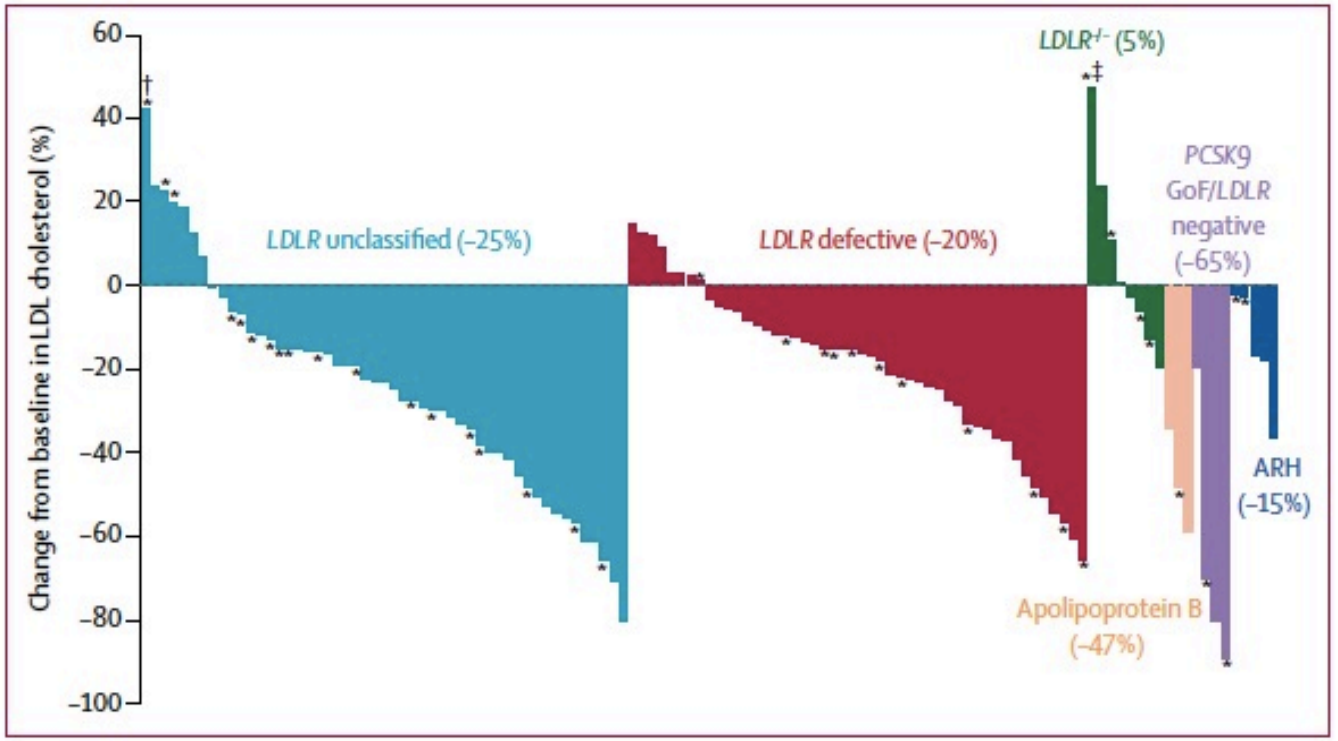



***Figure 2:*** **LDL cholesterol change from baseline to week 12, by underlying genetic abnormality**
Mean change in LDL cholesterol is shown in parentheses after each genetic abnormality category. GoF=gain of function. *Apheresis patient. †Patient missed apheresis before week 12 blood draw due to snowstorm. ‡Week 12 immediately after vacation; dietary indiscretion suspected. ARH=autosomal recessive hypercholesterolaemia.



*Lancet Diabetes Endocrinol* 2017; 5: 280–90

# Long-Term Evolocumab in Patients With Familial Hypercholesterolemia

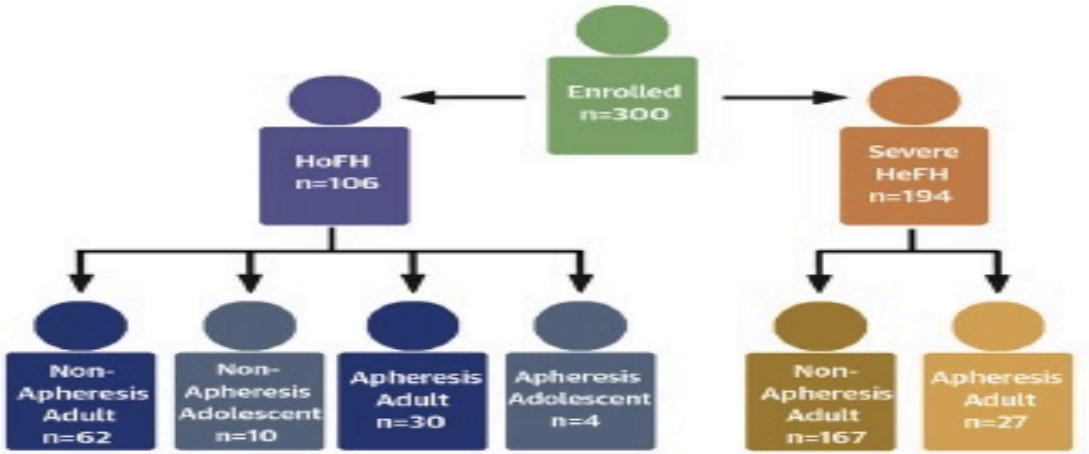
**CENTRAL ILLUSTRATION** Long-Term Evolocumab Treatment in Patients With Familial Hypercholesterolemia

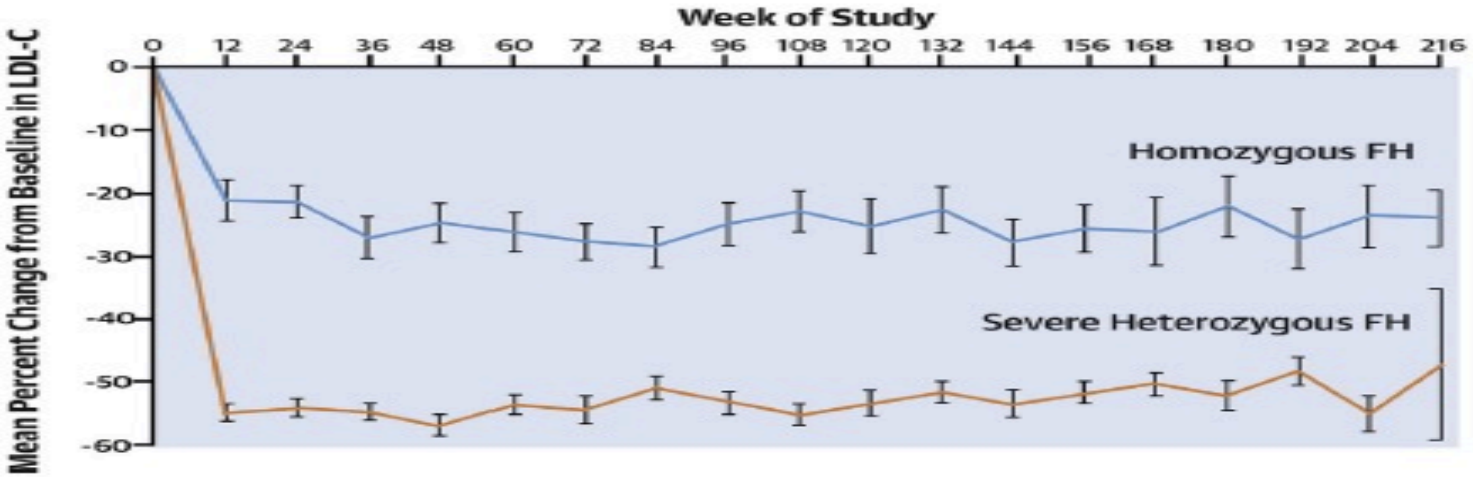
**TAUSSIG Trial**
Open-label, single-arm study

**300**
Patients with homozygous and severe heterozygous FH

**4.1**
Year duration (median)

**Objective:** To provide long-term safety and efficacy data for evolocumab in FH




Evolocumab was well-tolerated

26% Stopped apheresis

2.7 per year CV event rate

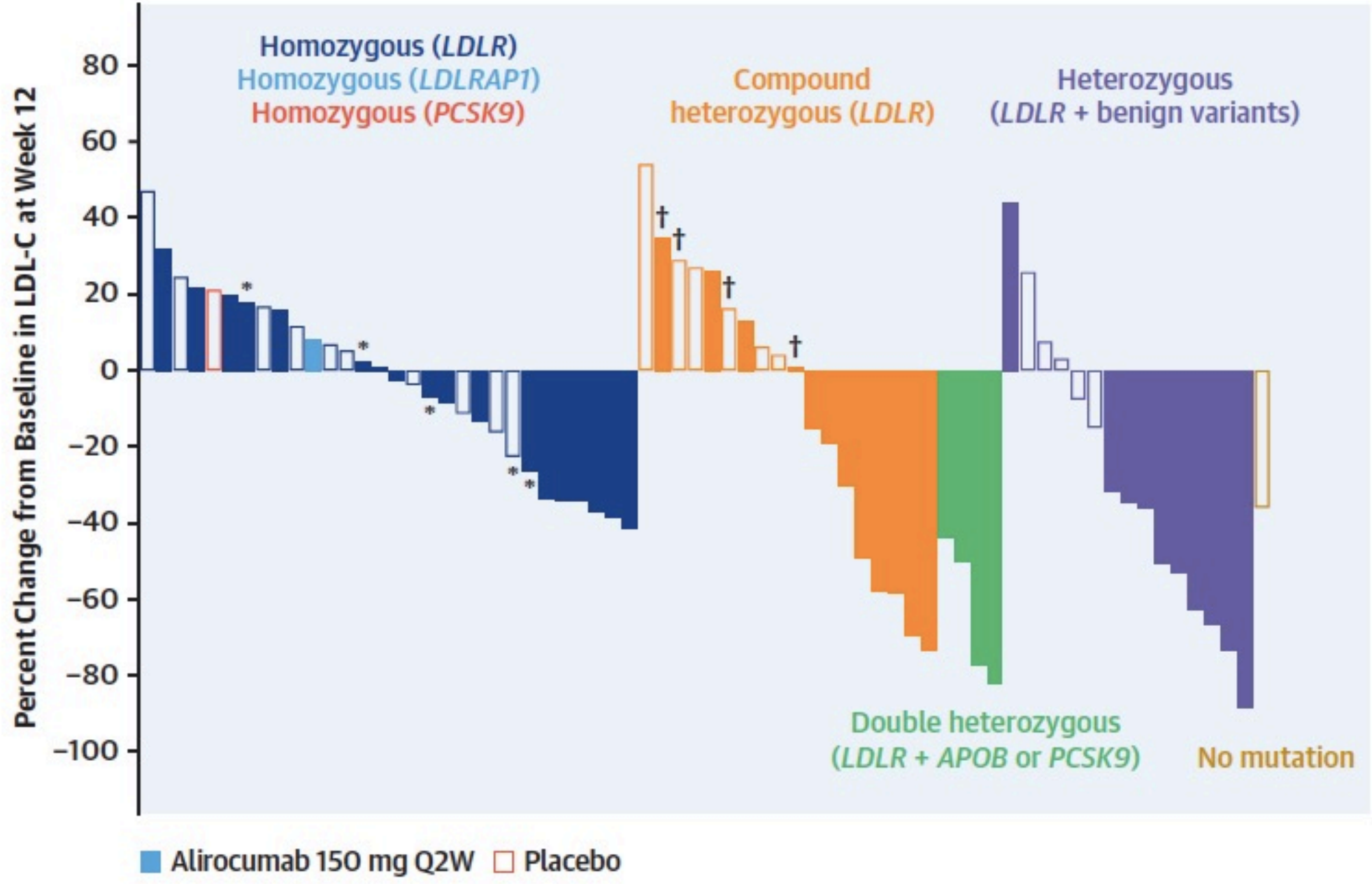
LDL-C levels were effectively reduced

Santos, R.D. et al. J Am Coll Cardiol. 2020;75(6):565-74.

Effica
in Ac
Fami
The OD

le 2024

**FIGURE 3** Percent Change From Baseline in LDL-C at Week 12 According to Genotyping Results



# New Frontiers in the Treatment of Homozygous Familial Hypercholesterolemia

Arturo Cesaro, MD[a,b], Fabio Fimiani, BSc[c], Felice Gragnano, MD[a,b], Elisabetta Moscarella, MD[a,b], Alessandra Schiavo, MD[a,b], Andrea Vergara, MD[a,b], Leo Akioyamen, MD[d], Laura D'Erasmo, MD, PhD[e], Maurizio Averna, MD[f], Marcello Arca, MD[e], Paolo Calabrò, MD, PhD[a,b,*]

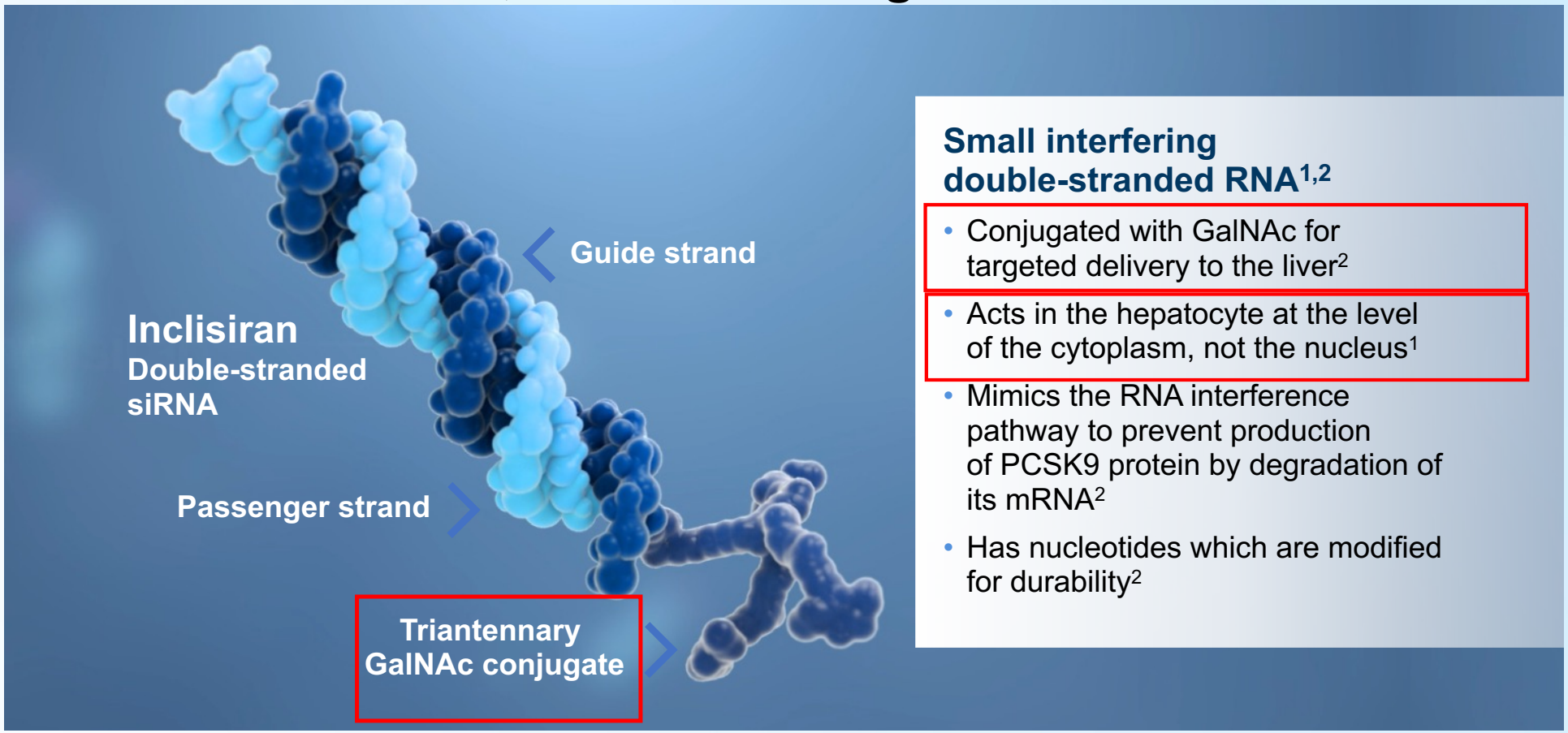
V: Napoli, 5-6 aprile 2024

**Table 1**
**Major medications in the treatment of HoFH and their effect in reducing LDL-C**

| Drug Name | Mechanism of Action | Administration Route and Dosage | Efficacy in HoFH Patients | Adverse Events |
|---|---|---|---|---|
| PCSK9 Inhibitors | Inhibition of PCSK9 by mAb | *Subcutaneous*<br>Evolocumab 420 mg monthly/every 2 wk<br>Alirocumab 150 mg every 2 wk | LDL-C reduction (20%-30%) | Injection site reactions and Flu-like symptoms |
| Inclisiran | Inhibition of PCSK9 by siRNA | *Subcutaneous*<br>300 mg (every 3 mo) | LDL-C reduction (12%-37%) | Injection site reactions |
| Lomitapide | Reduced secretion of ApoB-containing lipoproteins by the liver via inhibition of MTP | *Oral*<br>5–60 mg daily | Reduction in:<br>LDL-C (50%)<br>ApoB (49%)<br>TG (45%) | • Hepatic steatosis<br>• Gastrointestinal disorders<br>• Impaired liver function |
| Mipomersen | Inhibition of ApoB synthesis | *Subcutaneous*<br>200 mg – weekly (160 mg in subjects < 50 kg [110 lbs]) | Reduction in:<br>LDL-C (20%-50%)<br>Lp(a) (30%) | • Injection site reactions<br>• Flu-like symptoms<br>• Impaired liver function<br>• Liver steatosis |
| Evinacumab | Inhibition of ANGPTL-3 | *Intravenous*<br>15 mg/kg every 4 wk | Reduction in:<br>LDL-C (~47%)<br>TG (~50%) | Flu-like symptoms |

*Abbreviations:* ANGPTL-3, angiopoietin-like protein 3; ApoB, apolipoprotein B; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); mAb, monoclonal antibody; MTP, microsomal triglyceride transport protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SiRNA, small interfering RNA; TG, triglycerides.

# Inclisiran is a siRNA that mimics the body's process of RNA interference, thus increasing LDLRs on the liver



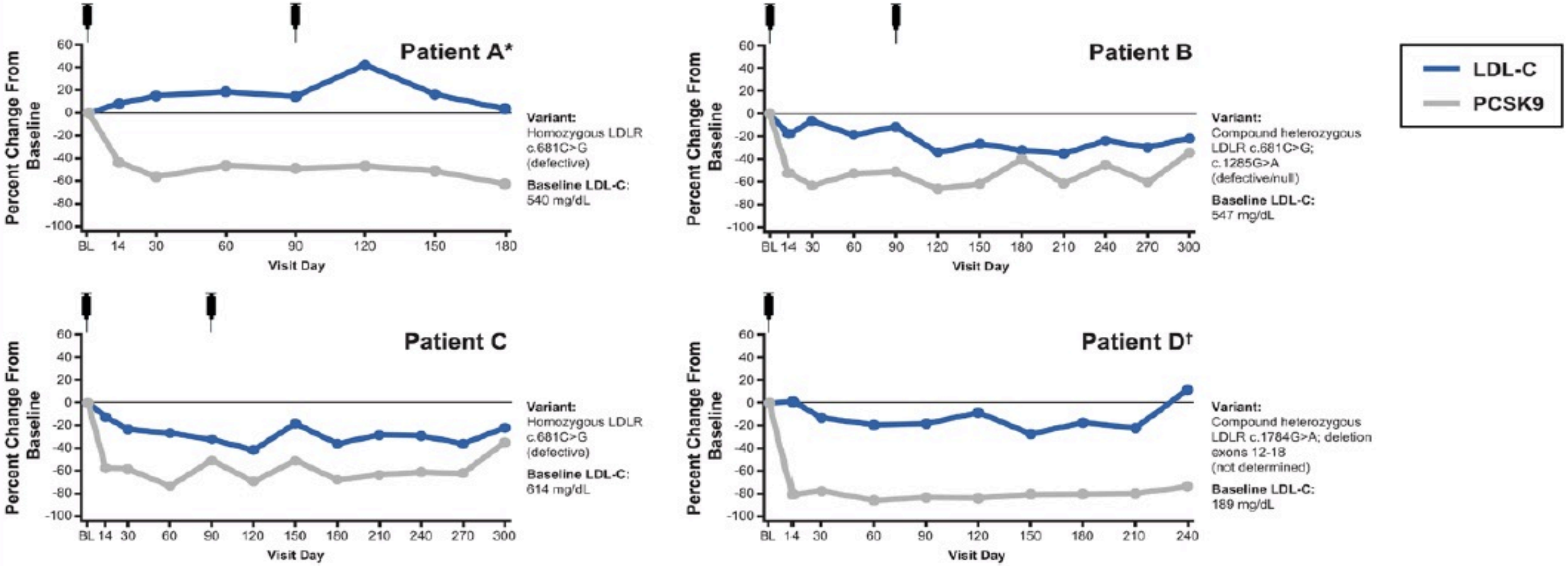

## Small interfering double-stranded RNA[1,2]

- Conjugated with GalNAc for targeted delivery to the liver[2]
- Acts in the hepatocyte at the level of the cytoplasm, not the nucleus[1]
- Mimics the RNA interference pathway to prevent production of PCSK9 protein by degradation of its mRNA[2]
- Has nucleotides which are modified for durability[2]

1. Khvorova A, et al. *N Engl J Med*. 2017;376:4-7.
2. Fitzgerald K, et al. *N Engl J Med*. 2017;376:41-51.

# Inclisiran Durably Lowers Low-Density Lipoprotein Cholesterol and Proprotein Convertase Subtilisin/Kexin Type 9 Expression in Homozygous Familial Hypercholesterolemia

## The ORION-2 Pilot Study



# New Frontiers in the Treatment of Homozygous Familial Hypercholesterolemia

Arturo Cesaro, MD[a,b], Fabio Fimiani, BSc[c], Felice Gragnano, MD[a,b], Elisabetta Moscarella, MD[a,b], Alessandra Schiavo, MD[a,b], Andrea Vergara, MD[a,b], Leo Akioyamen, MD[d], Laura D'Erasmo, MD, PhD[e], Maurizio Averna, MD[f], Marcello Arca, MD[e], Paolo Calabrò, MD, PhD[a,b,*]

V: Napoli, 5-6 aprile 2024

**Table 1**
**Major medications in the treatment of HoFH and their effect in reducing LDL-C**

| Drug Name | Mechanism of Action | Administration Route and Dosage | Efficacy in HoFH Patients | Adverse Events |
|---|---|---|---|---|
| PCSK9 Inhibitors | Inhibition of PCSK9 by mAb | *Subcutaneous*<br>Evolocumab 420 mg monthly/every 2 wk<br>Alirocumab 150 mg every 2 wk | LDL-C reduction (20%-30%) | Injection site reactions and Flu-like symptoms |
| Inclisiran | Inhibition of PCSK9 by siRNA | *Subcutaneous*<br>300 mg (every 3 mo) | LDL-C reduction (12%-37%) | Injection site reactions |
| Lomitapide | Reduced secretion of ApoB-containing lipoproteins by the liver via inhibition of MTP | *Oral*<br>5–60 mg daily | Reduction in:<br>LDL-C (50%)<br>ApoB (49%)<br>TG (45%) | • Hepatic steatosis<br>• Gastrointestinal disorders<br>• Impaired liver function |
| Mipomersen | Inhibition of ApoB synthesis | *Subcutaneous*<br>200 mg – weekly (160 mg in subjects < 50 kg [110 lbs]) | Reduction in:<br>LDL-C (20%-50%)<br>Lp(a) (30%) | • Injection site reactions<br>• Flu-like symptoms<br>• Impaired liver function<br>• Liver steatosis |
| Evinacumab | Inhibition of ANGPTL-3 | *Intravenous*<br>15 mg/kg every 4 wk | Reduction in:<br>LDL-C (~47%)<br>TG (~50%) | Flu-like symptoms |

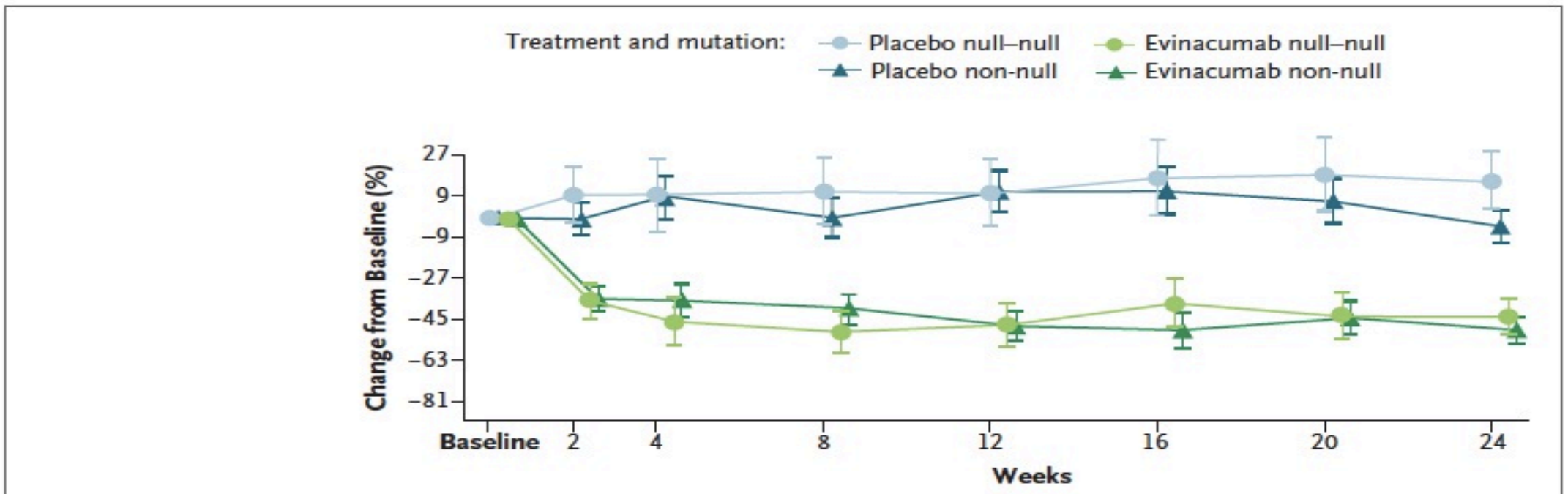
*Abbreviations:* ANGPTL-3, angiopoietin-like protein 3; ApoB, apolipoprotein B; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); mAb, monoclonal antibody; MTP, microsomal triglyceride transport protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SiRNA, small interfering RNA; TG, triglycerides.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2020 VOL. 383 NO. 8

# Evinacumab for Homozygous Familial Hypercholesterolemia

A Percent




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo null–null | 6 | 4 | 6 | 6 | 6 | 6 | 6 | 6 |
| Placebo non-null | 16 | 15 | 14 | 15 | 14 | 14 | 14 | 15 |
| Evinacumab null–null | 15 | 14 | 15 | 15 | 14 | 15 | 15 | 15 |
| Evinacumab non-null | 28 | 24 | 28 | 27 | 28 | 25 | 28 | 28 |

No. at Risk
Placebo
Evinacuma

0 24

0 21
3 43

# New Frontiers in the Treatment of Homozygous Familial Hypercholesterolemia

Arturo Cesaro, MD[a,b], Fabio Fimiani, BSc[c], Felice Gragnano, MD[a,b], Elisabetta Moscarella, MD[a,b], Alessandra Schiavo, MD[a,b], Andrea Vergara, MD[a,b], Leo Akioyamen, MD[d], Laura D'Erasmo, MD, PhD[e], Maurizio Averna, MD[f], Marcello Arca, MD[e], Paolo Calabrò, MD, PhD[a,b,*]

V: Napoli, 5-6 aprile 2024

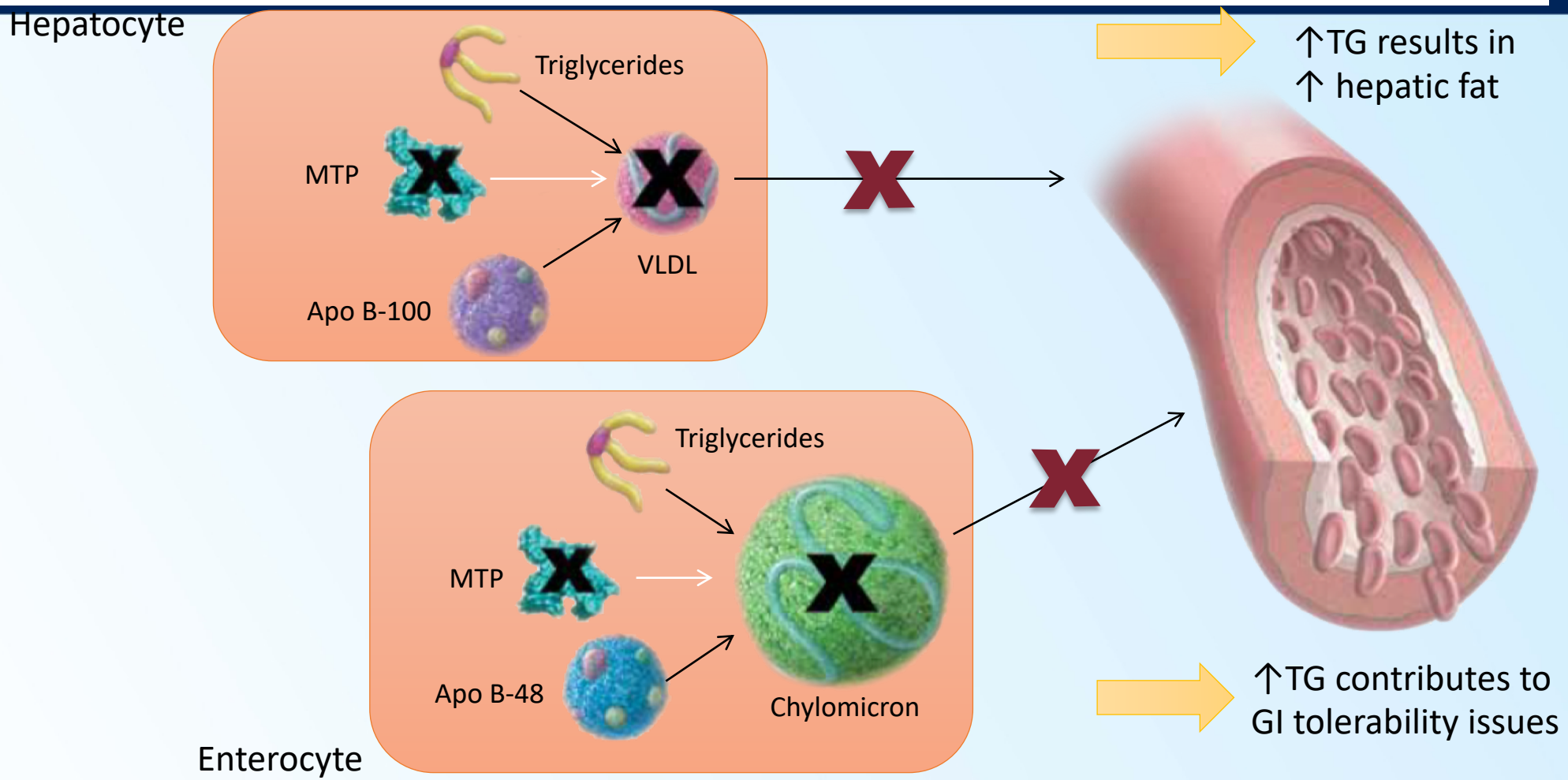
**Table 1**
**Major medications in the treatment of HoFH and their effect in reducing LDL-C**

| Drug Name | Mechanism of Action | Administration Route and Dosage | Efficacy in HoFH Patients | Adverse Events |
|---|---|---|---|---|
| PCSK9 Inhibitors | Inhibition of PCSK9 by mAb | *Subcutaneous*<br>Evolocumab 420 mg monthly/every 2 wk<br>Alirocumab 150 mg every 2 wk | LDL-C reduction (20%-30%) | Injection site reactions and Flu-like symptoms |
| Inclisiran | Inhibition of PCSK9 by siRNA | *Subcutaneous*<br>300 mg (every 3 mo) | LDL-C reduction (12%-37%) | Injection site reactions |
| Lomitapide | Reduced secretion of ApoB-containing lipoproteins by the liver via inhibition of MTP | *Oral*<br>5–60 mg daily | Reduction in:<br>LDL-C (50%)<br>ApoB (49%)<br>TG (45%) | • Hepatic steatosis<br>• Gastrointestinal disorders<br>• Impaired liver function |
| Mipomersen | Inhibition of ApoB synthesis | *Subcutaneous*<br>200 mg – weekly (160 mg in subjects < 50 kg [110 lbs]) | Reduction in:<br>LDL-C (20%-50%)<br>Lp(a) (30%) | • Injection site reactions<br>• Flu-like symptoms<br>• Impaired liver function<br>• Liver steatosis |
| Evinacumab | Inhibition of ANGPTL-3 | *Intravenous*<br>15 mg/kg every 4 wk | Reduction in:<br>LDL-C (~47%)<br>TG (~50%) | Flu-like symptoms |

*Abbreviations:* ANGPTL-3, angiopoietin-like protein 3; ApoB, apolipoprotein B; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); mAb, monoclonal antibody; MTP, microsomal triglyceride transport protein; PCSK9, proprotein convertase subtilisin/kexin type 9; SiRNA, small interfering RNA; TG, triglycerides.

# Lomitapide is an MTP inhibitor






Lipoprotein B; MTP, microsomal triglyceride transfer protein TG, triglycerides; GI, gastrointestinal; LDL, low-density lipoprotein

Cuchel M, Rader DJ. Curr Opin Lipidol 2013;24:246-50

# Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study



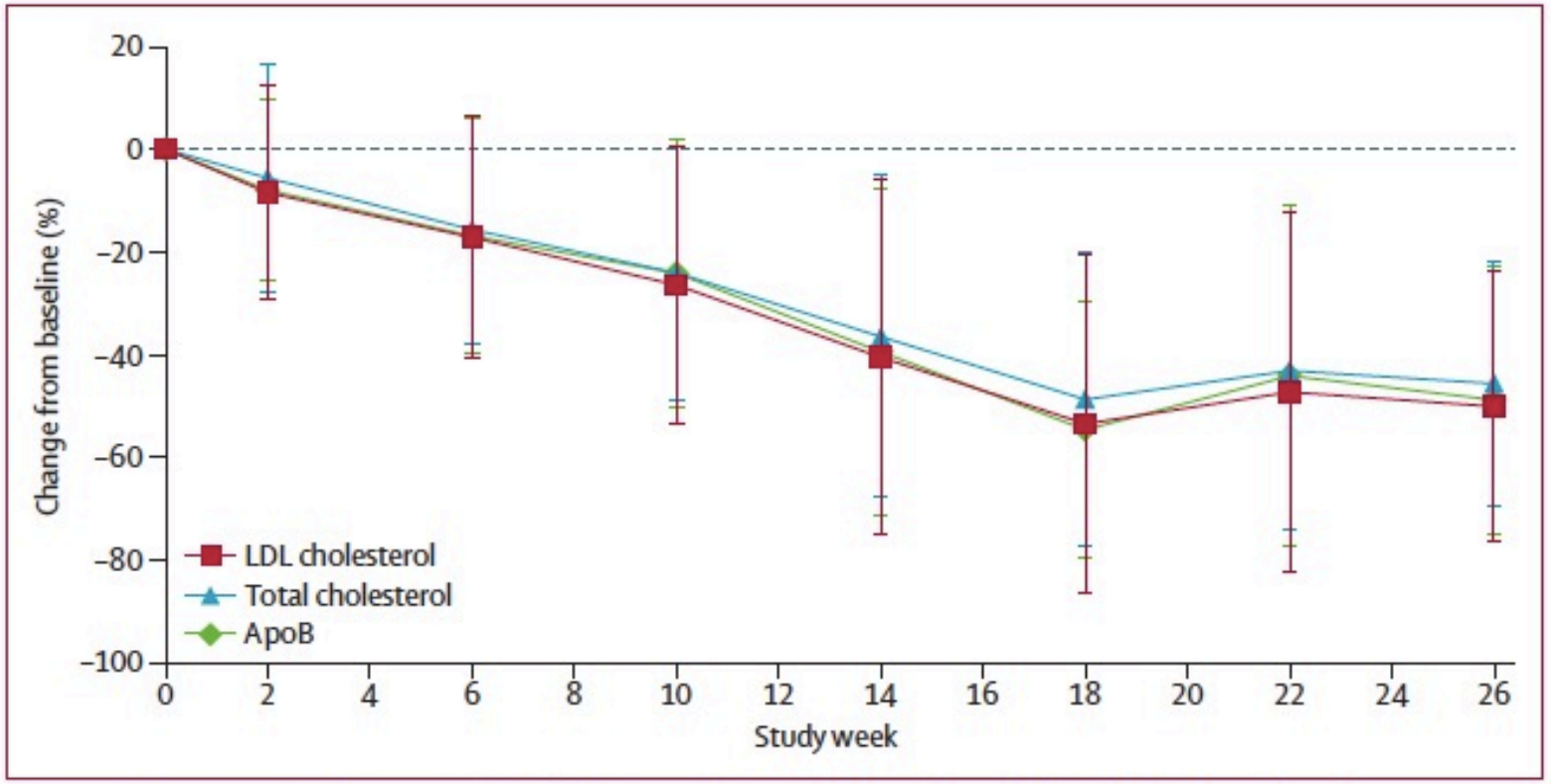
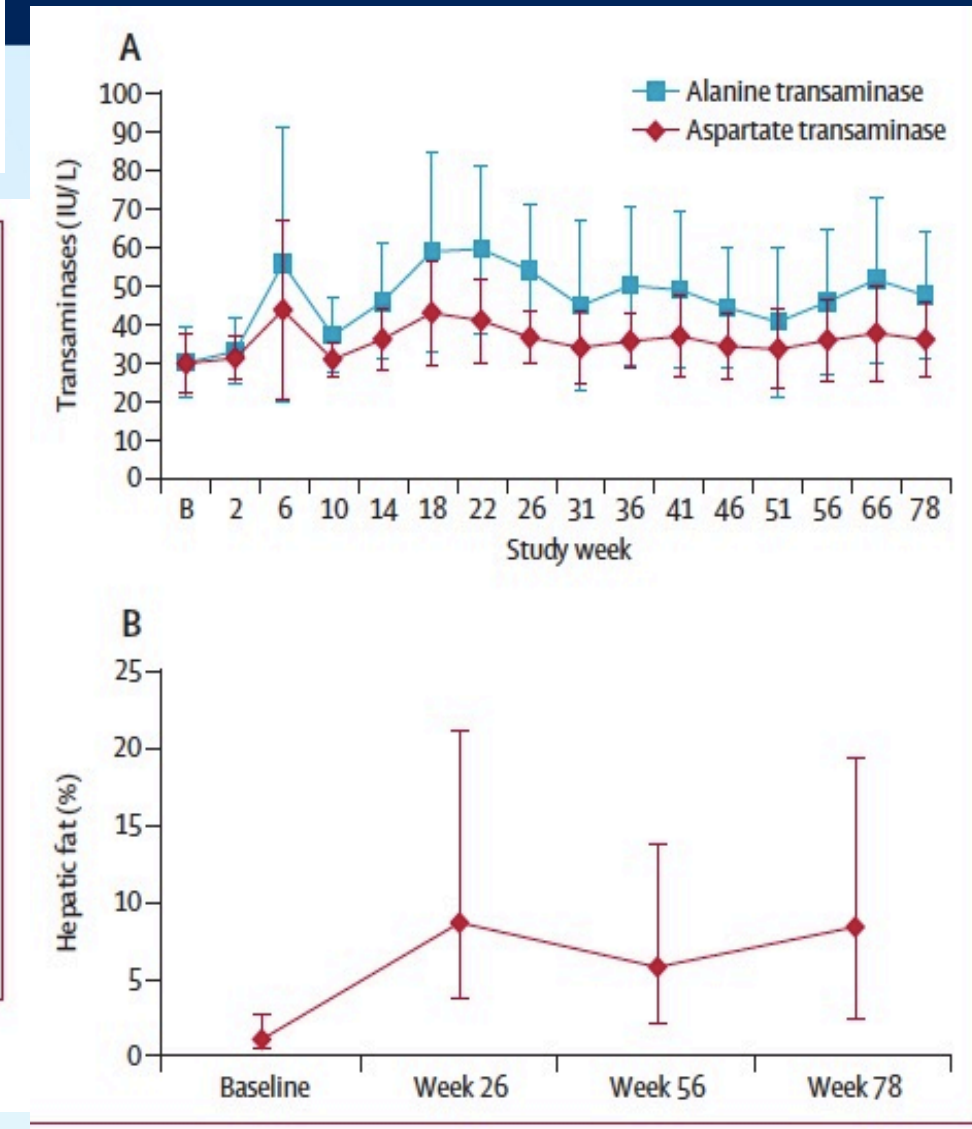
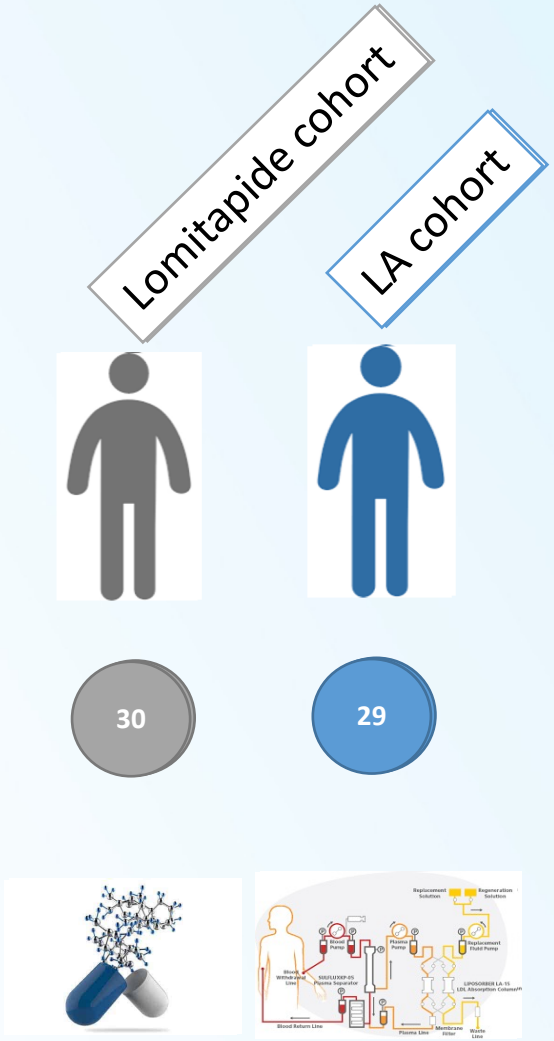
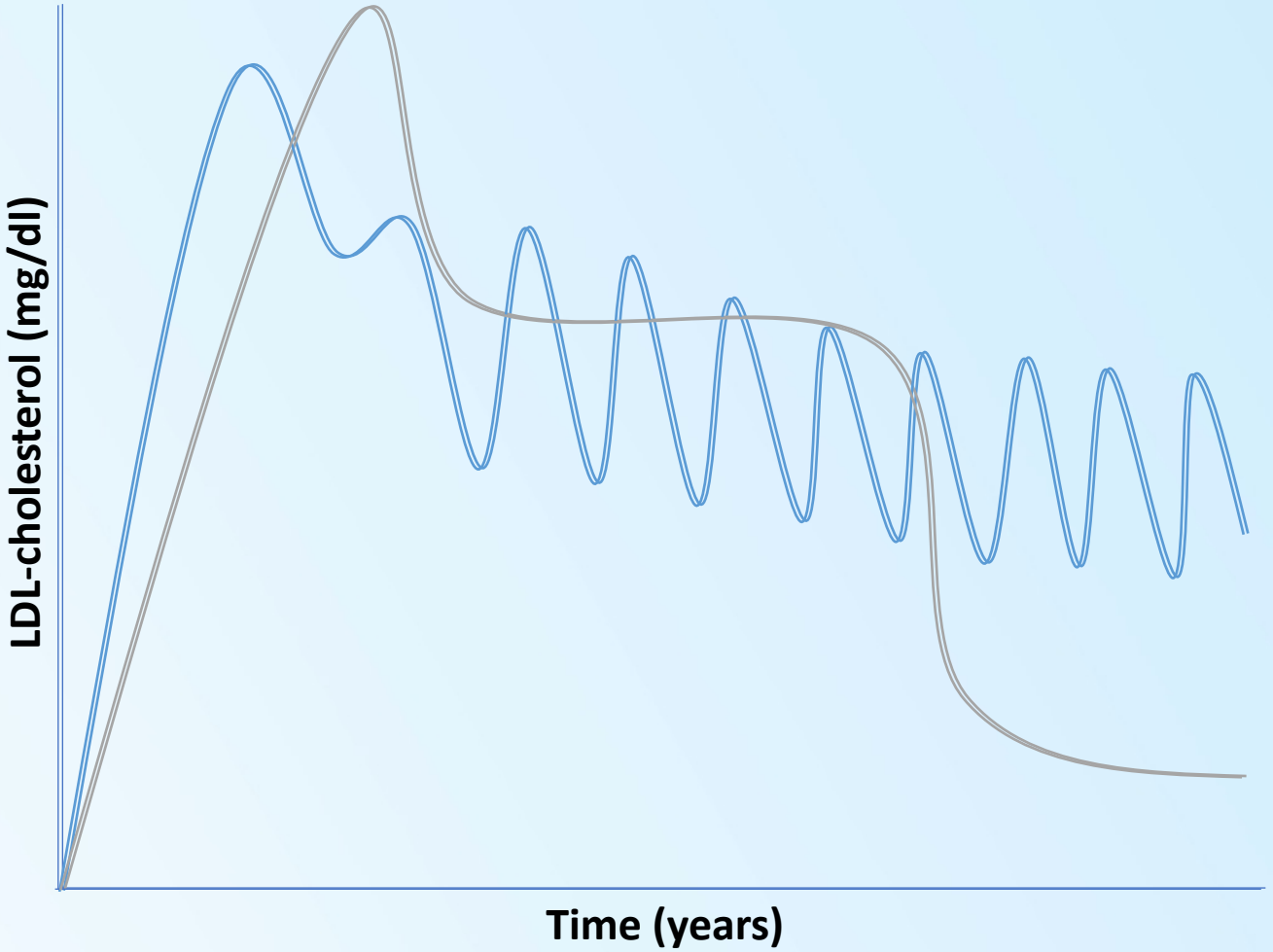



*Figure 1:* **Mean percent changes in LDL cholesterol, total cholesterol, and ApoB levels from baseline to week 26 (end of efficacy phase)**



# LDL-C APHERESIS AND LOMITAPIDE IN THE TREATMENT OF HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH): A CROSS-NATIONAL RETROSPECTIVE STUDY



Percorso Diagnostico Terapeutico Assistenziale

# Ipercolesterolemia Familiare Omozigote

**Malattia Rara**

**CODICE**
***RCG070***



# Thank you

-

@arturocesaro

arturo.cesaro@unicampania.it