



OLD HOUSE DETAIL
ΙΟΑΝΝΙΝΑ

ΘΕΡΑΠΕΥΤΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ
ΕΤΕΡΟΖΥΓΗΣ ΚΑΙ ΟΜΟΖΥΓΗΣ
ΟΙΚΟΓΕΝΟΥΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑΣ:
ΠΑΡΟΝ ΚΑΙ ΜΕΛΛΟΝ

ΜΩΥΣΗΣ ΕΛΙΣΑΦ, ΚΑΘΗΓΗΤΗΣ
ΠΑΘΟΛΟΓΙΑΣ ΙΑΤΡΙΚΗΣ ΣΧΟΛΗΣ
ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΙΩΑΝΝΙΝΩΝ

LDL-C Clinical targets

- There are no current European guidelines for the management of HoFH
- ESC/EAS Guideline recommendations for LDL-C clinical targets in patients with HeFH¹

Recommendations	Class of evidence	Level of evidence
Treatment is aimed as reaching the LDL-C goals for high risk subjects (<2.5 mmol/L, less than 100mg/dL) or in the presence of CVD of very high risk subjects (1.8 mmol/L less than 70mg/dL). If targets cannot be reached, maximal reduction in LDL-C should be considered using appropriate drug combinations in tolerated doses	IIa	C

In patients receiving apheresis these “levels will only postpone rather than prevent CV disease but advances in adjuvant therapy such as microsomal triglyceride transfer protein and anti-sense apoB may enable more radical reductions in LDL-C in the future”²

ΣΤΟΧΟΙ ΥΠΟΛΙΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ FH

ΣΤΟΧΟΣ LDL CHOL <135 mg/dl σε παιδιά

ΣΤΟΧΟΣ LDL CHOL <100mg/dl

ΜΟΝΟΘΕΡΑΠΕΙΑ Ή ΣΥΝΔΥΑΣΜΟΙ (+ΕΖΕΤΙΜΙΒΕ-
COLESEVELAM)

ΣΤΟΧΟΣ LDL CHOL <70mg/dl ΣΕ ΑΤΟΜΑ ΜΕ
ΕΓΚΑΤΕΣΤΗΜΕΝΗ ΑΓΓΕΙΑΚΗ ΝΟΣΟ

Consensus Statement of the European
Atherosclerosis Society, 2013

ΒΑΣΙΚΕΣ ΑΡΧΕΣ ΑΓΩΓΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ FH

Διακοπή καπνίσματος

Δίαιτα (+ ΦΥΤΙΚΕΣ ΣΤΕΡΟΛΕΣ)

Άσκηση

ΦΑΡΜΑΚΑ

Στατίνες^{+,++} (μέγιστες ανεκτές δόσεις)

Ezetimibe

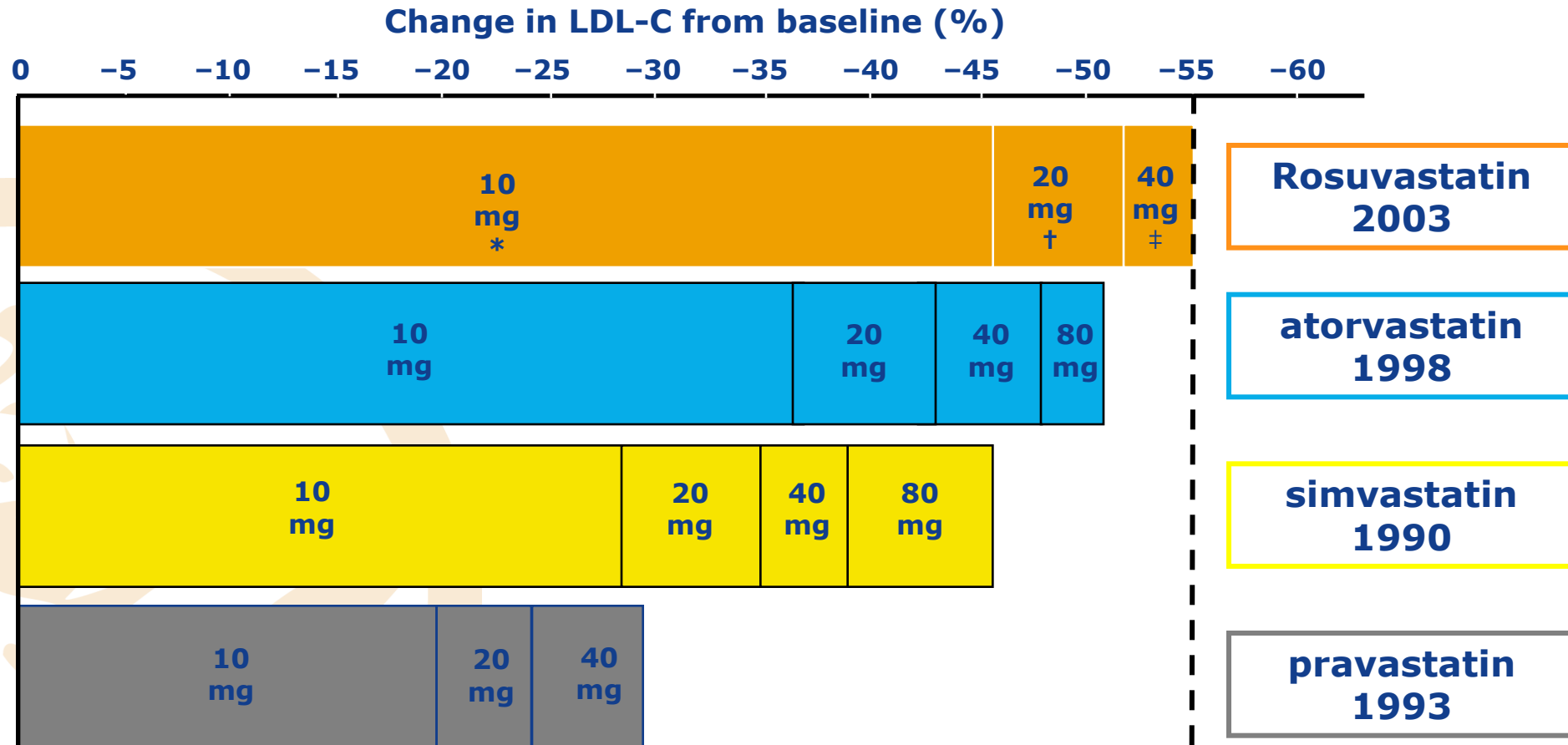
Colesevelam

+ Atorva 80mg/d, Rosuva 40mg/d, Pita 4mg/d

++ >8-10 έτη

LIPID APHERESIS

Statin development: Evolution towards more powerful molecules



*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
 †p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
 ‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

ΠΕΡΙΟΡΙΣΜΟΙ ΤΗΣ ΜΟΝΟΘΕΡΑΠΕΙΑΣ ΜΕ ΣΤΑΤΙΝΕΣ

ROSUVA 40mg/d: ↓ LDL CHOL ΚΑΤΑ 51-55%

ATORVA 80mg/d: ↓ LDL CHOL ΚΑΤΑ 51-55%

ΕΤΟΙΜΟΣ ΣΤΑΘΕΡΟΣ ΣΥΝΔΥΑΣΜΟΣ

INEGY (10+40mg/d): ↓ LDL CHOL ΚΑΤΑ 55%

Genetic and environmental factors affecting the response to statin therapy in patients with molecularly defined familial hypercholesterolemia

MATERIAL

- ❑ 49 unrelated patients with heterozygous FH in whom the genetic defect of LDLR gene was previously detected
 - ❑ 28 patients carried the G1646A and C858A mutations, which are class II mutations
 - ❑ 21 patients were heterozygous for the G1775A mutation, which is a class V mutation
- Administration of atorvastatin 20mg/d

RESULTS

Parameters	Baseline Values	Values after treatment	% decrement	p
LDL CHOL (mg/dl)	287±70	178±38	37±11	0.001
Apo B (mg/dl)	191±58	132±28	36±22	0.001

Genetic and environmental factors affecting the response to statin therapy (atorvastatin 20mg/day) in patients with molecularly defined familial hypercholesterolaemia

Type of the LDLR mutation	n	-LDL-C% mean±SD	Covariate baseline LDL-C	p [*]
II	28	34±9	297	0.001
V	21	49±9	254	

* by ancova

Miltiadous G. et al: Pharmacogenetics and Genomics 2005;15:219-225

Factors affecting the statin LDL-C lowering effect in patients with heterozygous FH

PARAMETER	beta	P-value*
CLASS OF THE LDLR GENE MUTATION II vs V	0.60	0.00
APOE POLYMORPHISM	0.07	0.60
CETP POLYMORPHISM	-0.15	0.41
SEX	0.00	0.98
AGE	0.06	0.66
TOBACCO	0.16	0.30
BMI	0.27	0.09
BASELINE LDL-C LEVELS	0.69	0.001

*multiple regression analysis (n=49)

EZETIMIBE ADDED TO ONGOING STATIN THERAPY (META-ANALYSIS)

EZETIMIBE / STATIN VS PLACEBO/STATIN

LDL CHOL: **-23.6%**, $p < 0.0001$

HDL CHOL: **+1.7%**, $p < 0.0001$

ROSUVASTATIN 40mg + EZETIMIBE 10mg

  **LDL CHOL** κατά **69,8%**

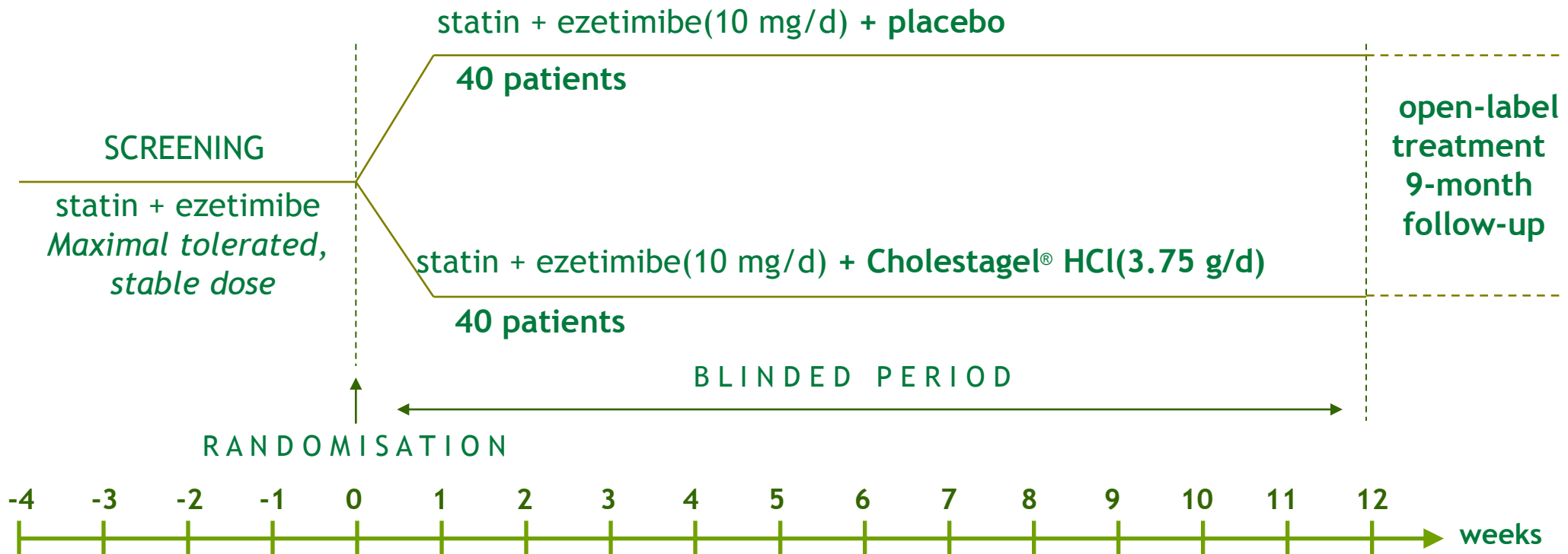
 **TRG** κατά **35%**

 **HDL CHOL** κατά **11%**

EXPLORER STUDY: Am J Cardiol 2007;99:673-680

Triple Design

- Phase 4 randomised, double-blind, placebo-controlled, parallel-group, multicentre study of Cholestagel[®] as add-on therapy in patients with FH with LDL-C > 100mg/dL (2.5 mmol/l)



ΤΡΙΠΛΗ ΥΠΟΛΙΠΙΔΑΙΜΙΚΗ ΑΓΩΓΗ ΣΕ ΕΝΗΛΙΚΑ ΑΤΟΜΑ

Ασθενείς με FH υπό αγωγή με ΣΤΑΤΙΝΗ +
ΕΖΕΤΙΜΙΒΕ

Τυχαιοποίηση σε COLESEVELAM (3.8g/d) vs
placebo

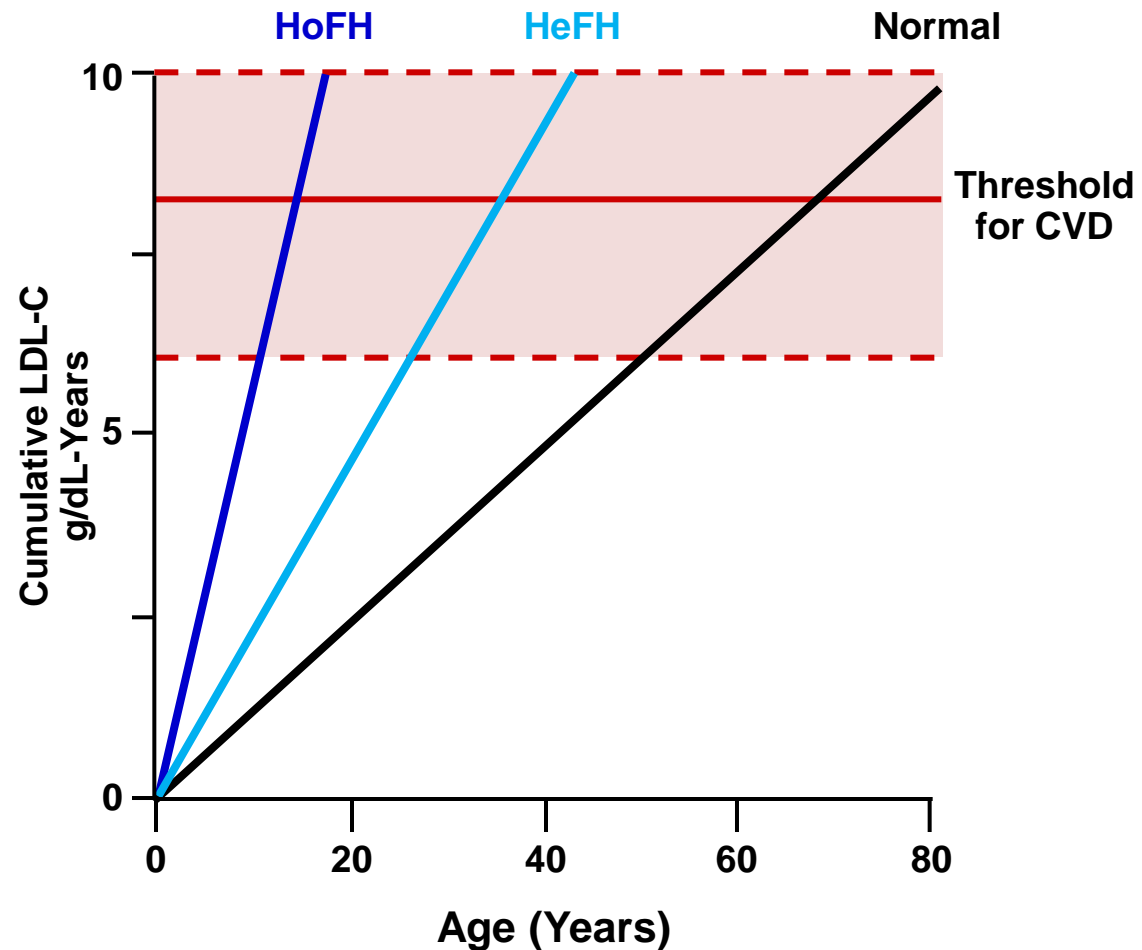
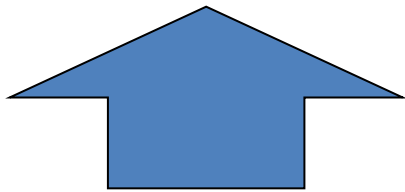
Δ LDL CHOL: -18.5%, 6 εβδομάδες
-12%, 12 εβδομάδες

Δ HDL CHOL: +3.3%, 12 εβδομάδες

Δ ApoB/ApoA₁: -12.2%, 12 εβδομάδες

Elevated LDL-C is the cause of cardiovascular disease in **HoFH**

- LDL-C is a causal factor in the development of CVD
- Patients with HoFH typically develop cardiovascular disease before the age of 20 years¹
- Even with currently existing therapies, the mean age of death is 33 years²



1. Goldstein, J. L., H. H. Hobbs, et al. (2001). *The Metabolic and Molecular Basis of Inherited Disease*.

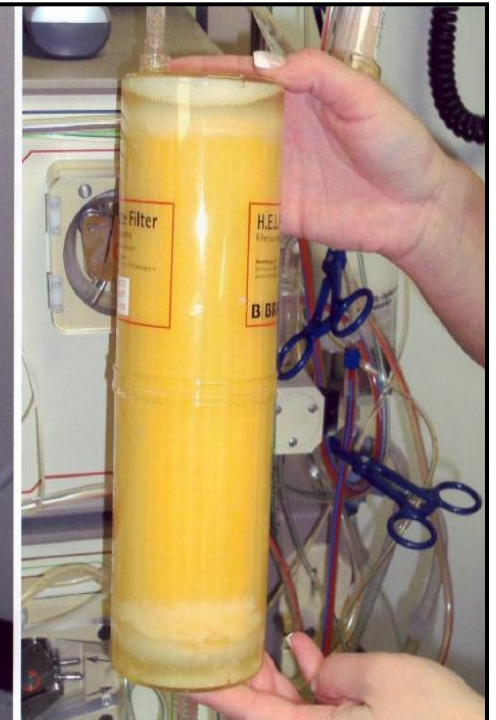
2. Raal J, et al. *Circulation*. (2011).

3. Adapted from Horton et al. *J Lipid Res*. 2009;50:S172-S177

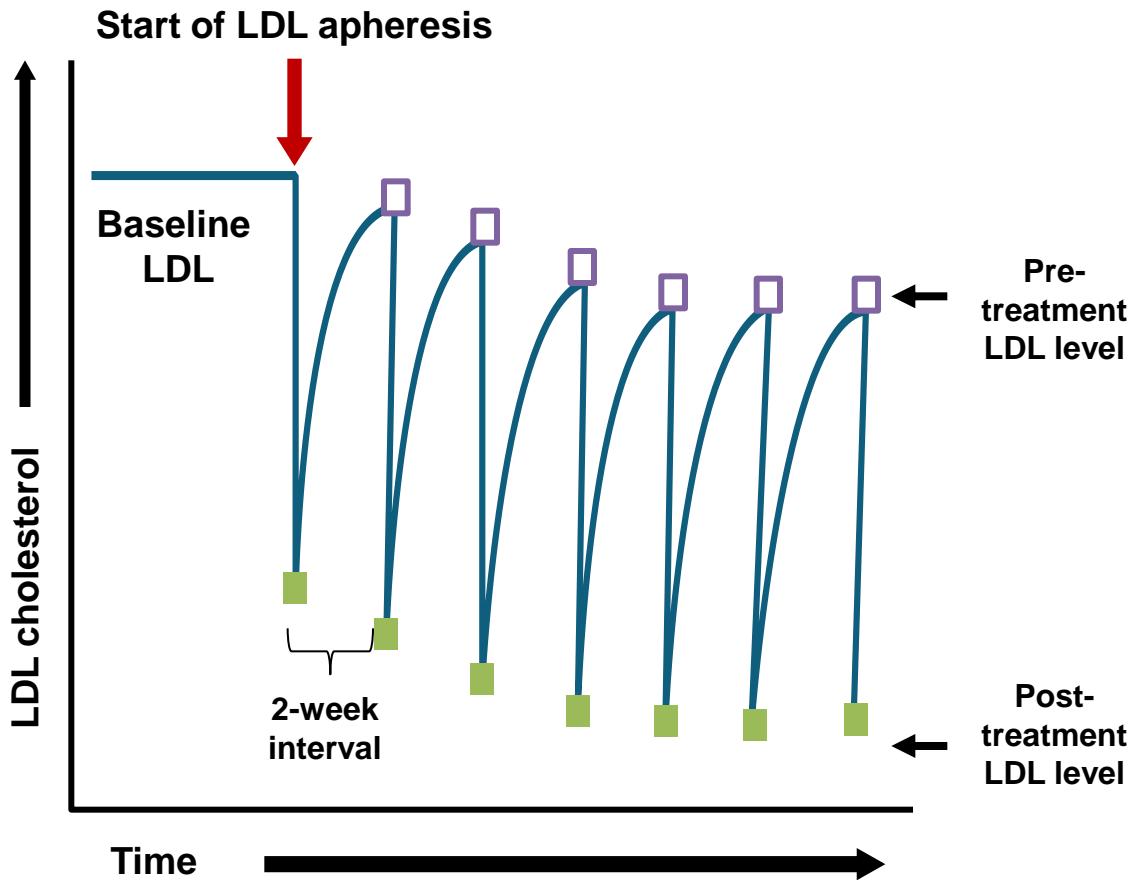
Current cholesterol lowering drugs are insufficient in HoFH

Class	Major Effect	Typical LDL-C-Lowering Response
Statins (e.g. atorvastatin, rosuvastatin)	↑ LDLR activity	<10 to 25%
Bile acid sequestrants (e.g. cholestyramine, colestipol)	↑ LDLR activity	<10%
Cholesterol absorption inhibitors (e.g. ezetimibe)	↑ LDLR activity	<10%
Nicotinic acid (i.e. niacin)	Unknown	<10%

LDL apheresis is current standard of care for HoFH

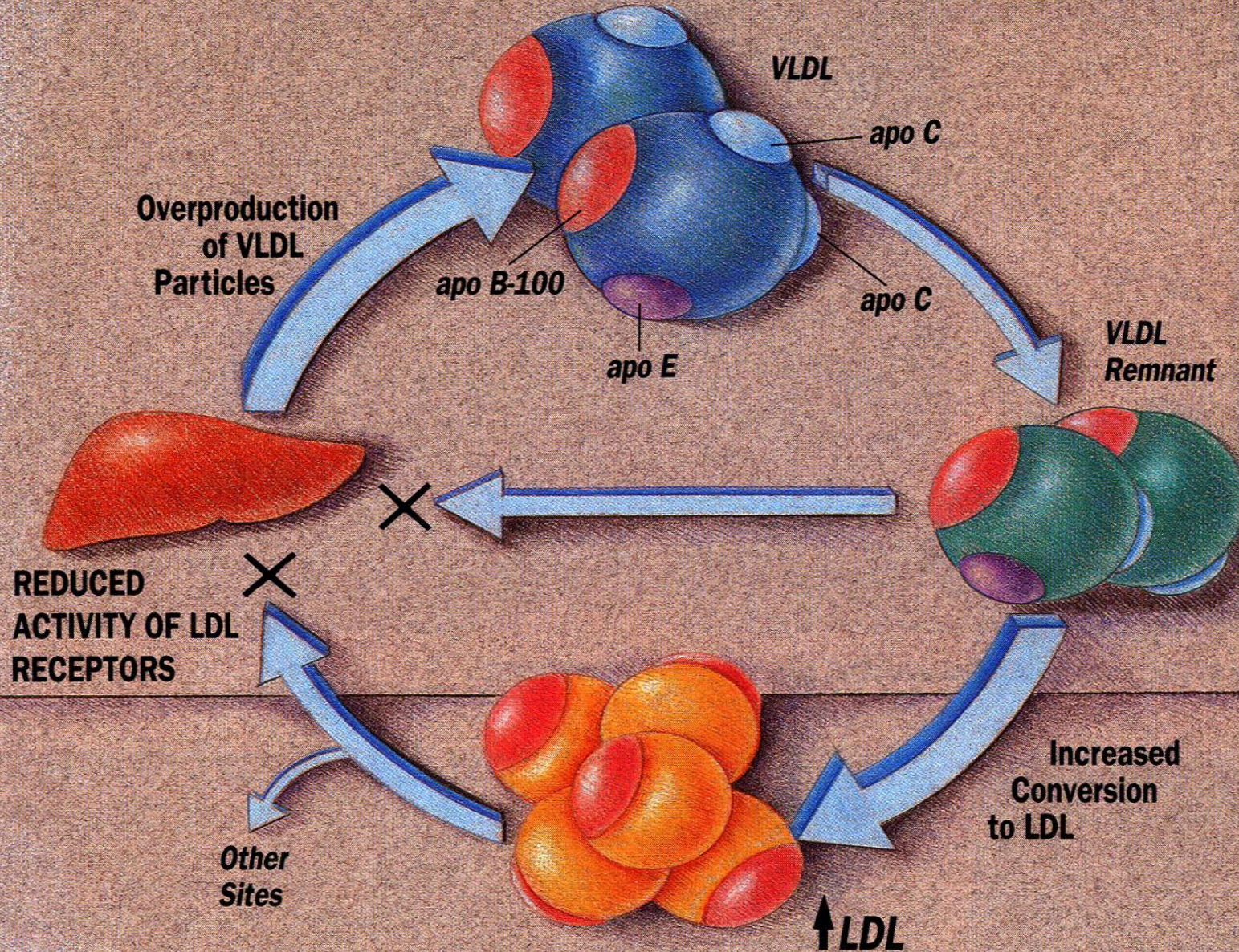


LDL-C Levels acutely decrease and then rebound following apheresis

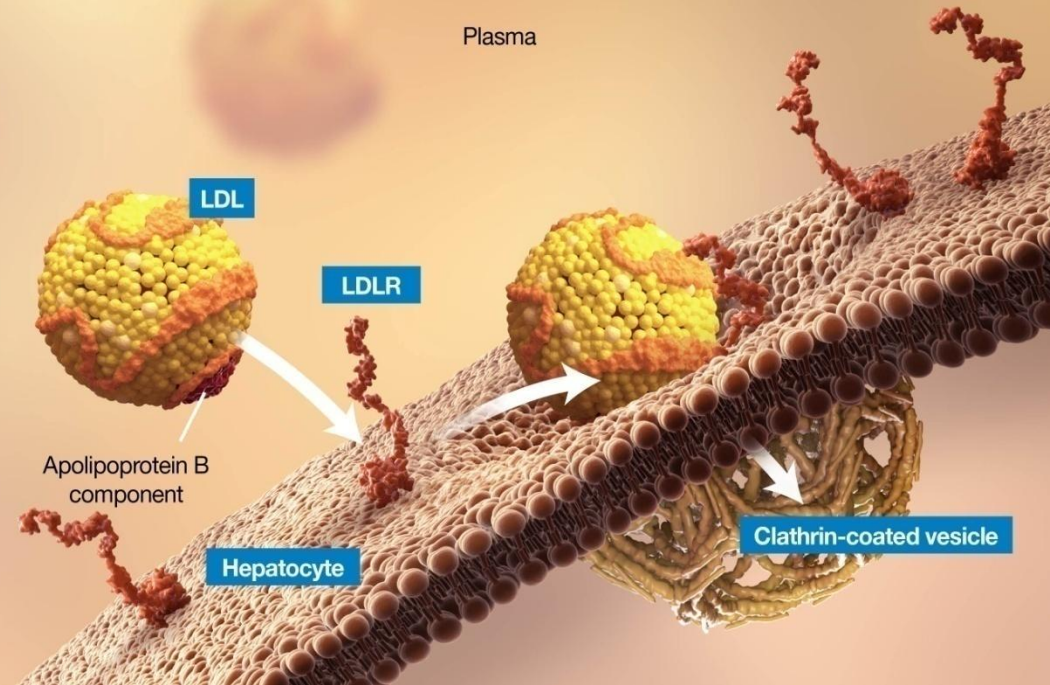


- In a cohort of 7 patients with HoFH, lipid lowering therapies and once weekly apheresis reduced LDL-C to
 - Pre-apheresis - 5.1 mmol/l
 - Post apheresis - 2.2 mmol/l
 - Mean interval - 4.2 mmol/l

HYPERCHOLESTEROLEMIA

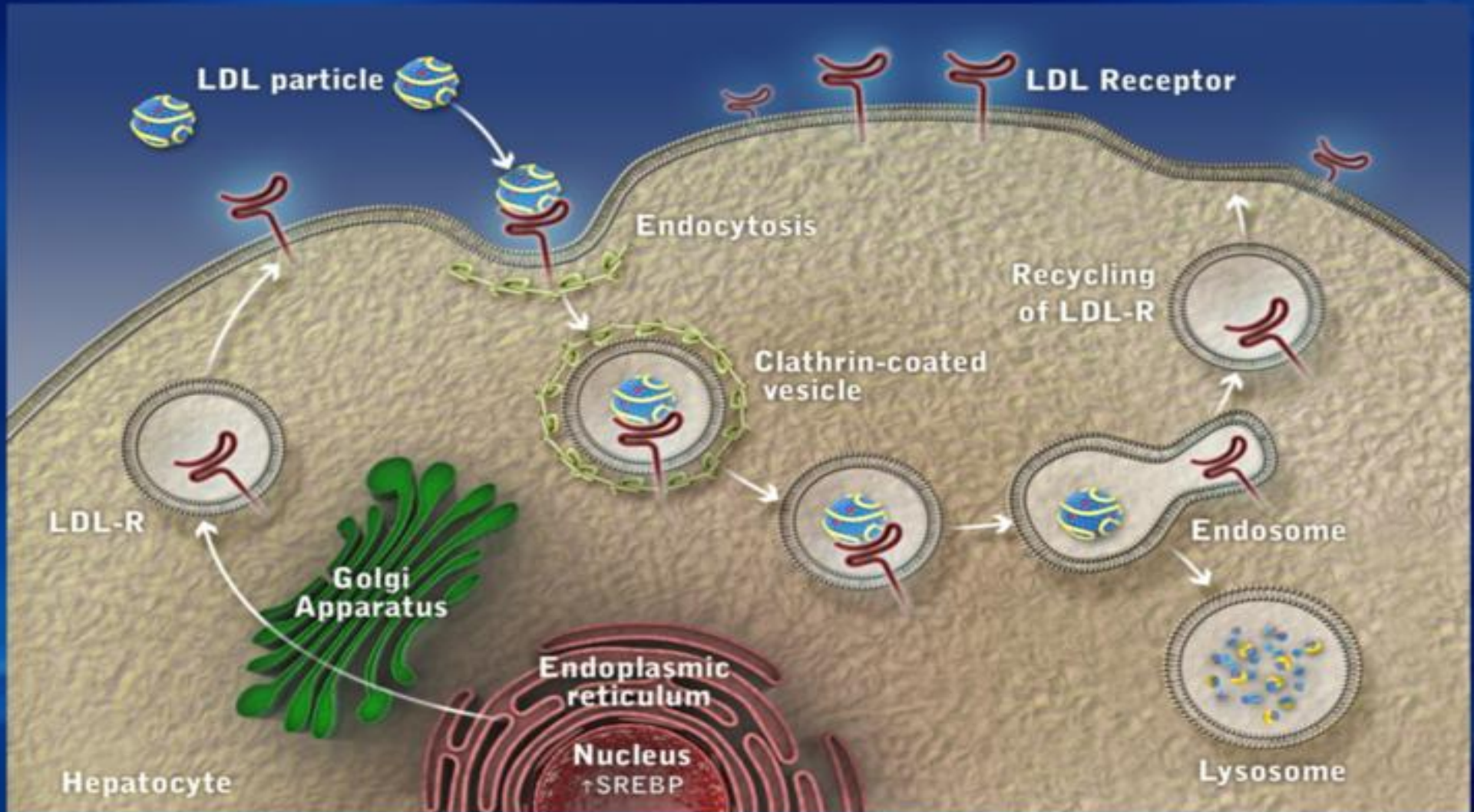


Hepatic LDLRs Play a Central Role in Cholesterol Homeostasis

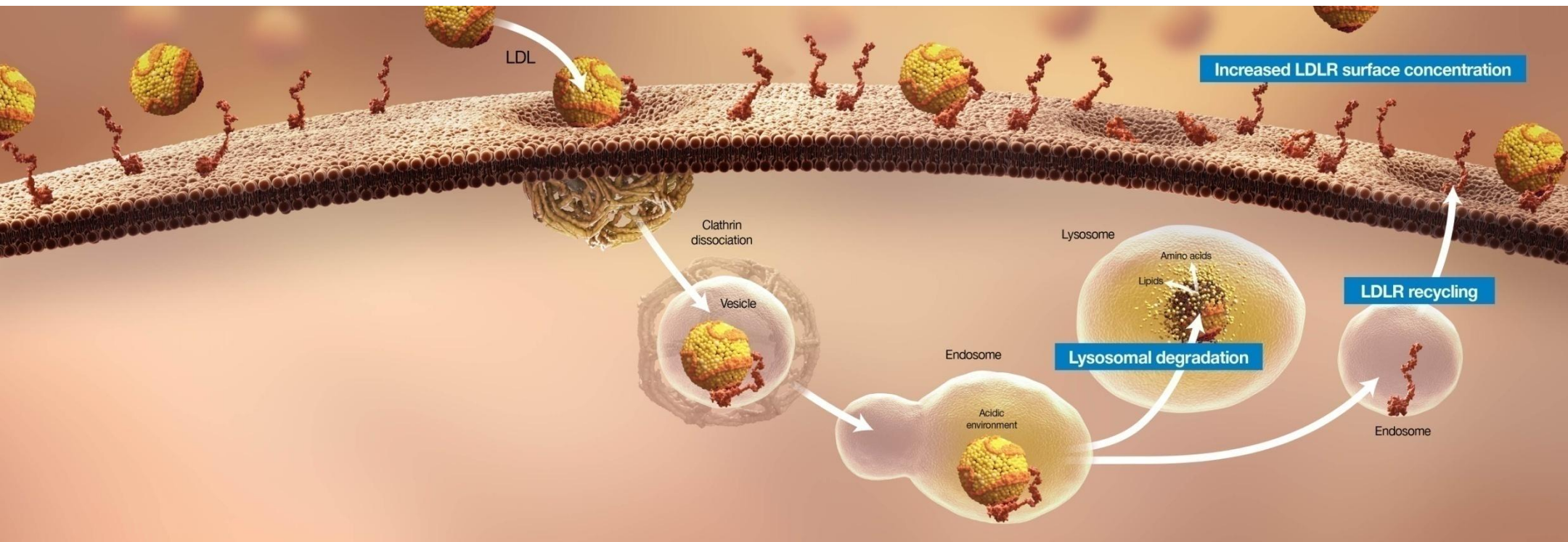


1. Brown MS, et al. *Proc Natl Acad Sci* 1979;76:3330-3337.
2. Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
3. Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.

LDL Receptor Function and Life Cycle



Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles



1. Brown MS, et al. *Proc Natl Acad Sci U S A*. 1979;76:3330-3337.
2. Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.
3. Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

PCSK9

❑ Ένζυμο που συνδέεται με τους LDL υποδοχείς και αυξάνει την αποδόμηση τους

❑ Γλυκοπρωτεΐνη (692 αμινοξέα) που ανήκει στην οικογένεια των πρωτεασών της σερίνης που ονομάζονται proproteain convertase (PC)

❑ Το γονίδιο που κωδικοποιεί την πρωτεΐνη βρίσκεται στο χρωμόσωμα 1 (1P32)

❑ Εκφράζεται σε πολλά όργανα-κυρίως όμως στο ήπαρ

PCSK9



Σύνδεση με τους LDL
υποδοχείς

Σύμπλοκο PCSK9 / LDLR



Αποδόμηση στα λυσοσώματα

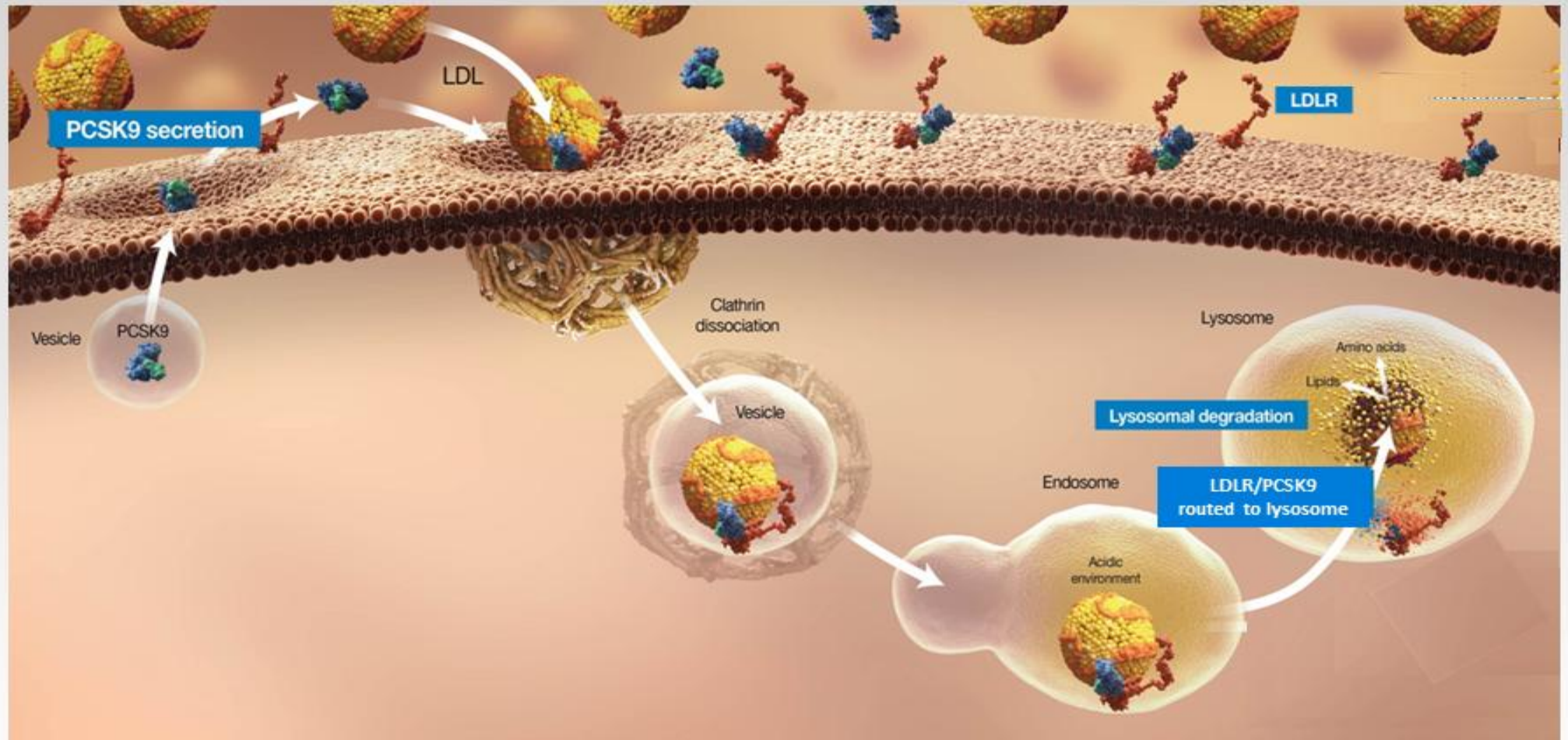


↓ LDL-R

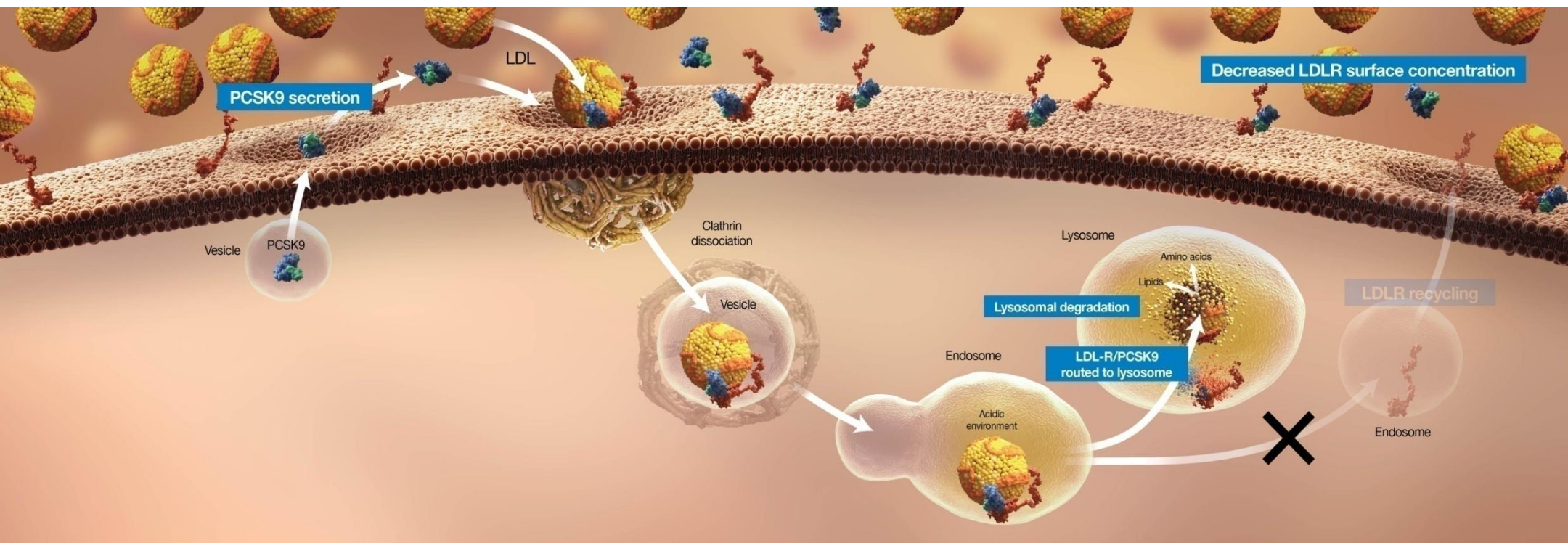


↑ LDL CHOL

PCSK9 Regulates Surface LDLRs by Increasing Their Lysosomal Degradation

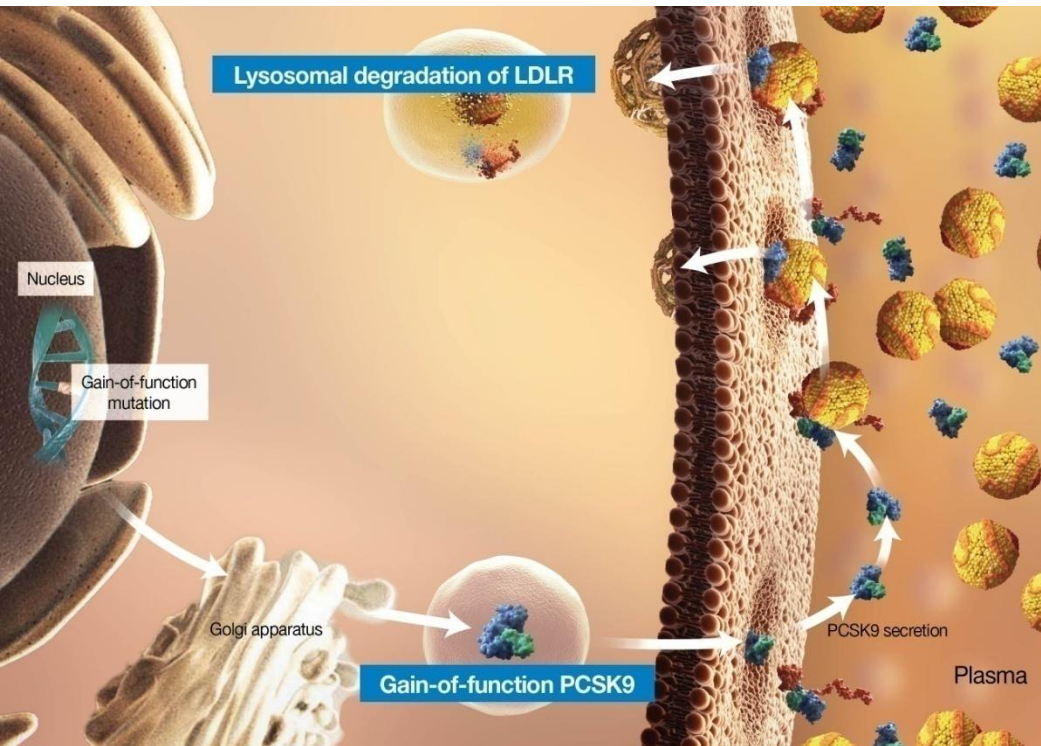


PCSK9 Regulates the Surface Expression of LDLRs by Targeting for Lysosomal Degradation

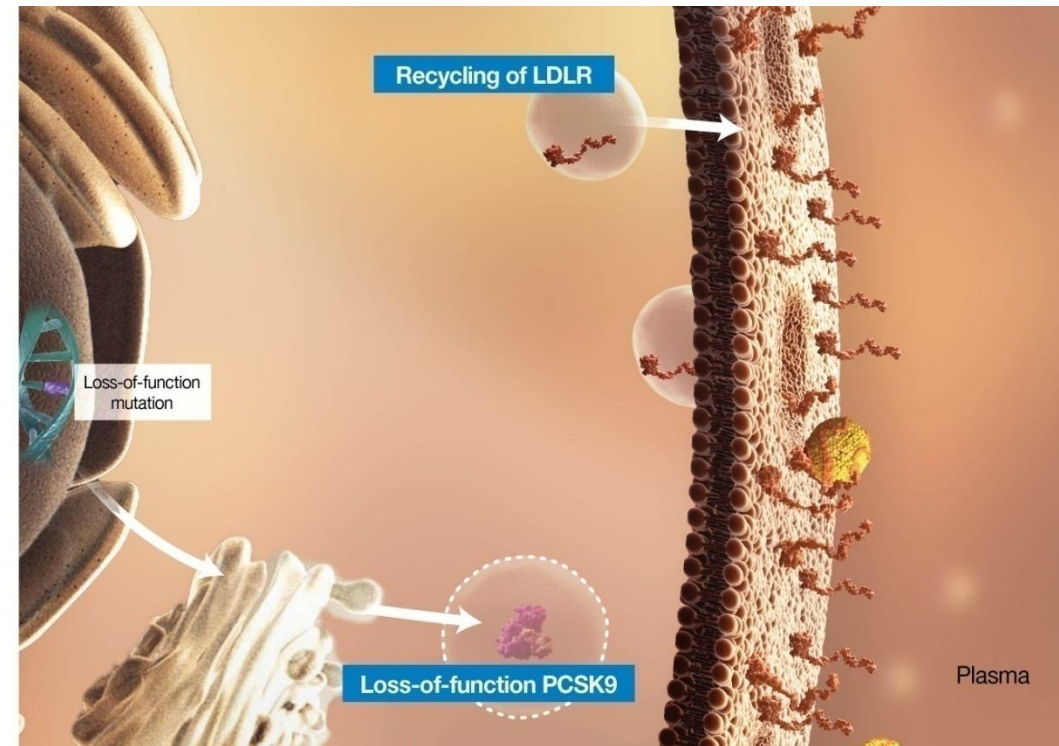


1. Qian YW, et al. *J Lipid Res.* 2007;48:1488-1498.
2. Horton JD, et al. *J Lipid Res.* 2009;50:S172-S177.
3. Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels



PCSK9 Gain of Function = Less LDLRs



PCSK9 Loss of Function = More LDLRs

Gain-of-Function Mutations in PCSK9 Cause Autosomal-Dominant Hypercholesterolemia* (ADH)

PCSK9 Variant	Population	Clinical Characteristics
D374Y	British, Norwegian families, 1 Utah family	Premature CHD Tendon xanthomas Severe hypercholesterolemia
S127R	French, South African, Norwegian families	Tendon xanthomas; CHD, early MI, stroke
R215H	Norwegian family	Brother died at 31 from MI; strong family history of CVD

- Associated with:
 - High serum LDL-C²
 - Premature CHD and MI²
 - In vitro testing in many identified mutations show decreased levels of LDLRs³

1. Abifadel M, et al. *Hum Gen.* 2009;30:520-529.

2. Horton JD, et al. *J Lipid Res.* 2009;50:S172-S177.

3. Cameron J, et al. *Hum Mol Genet.* 2006;15:1551-1558.

*For a full list of ADH mutations, please see refer to Abifadel reference.

Loss-of-Function Mutations in PCSK9 Are Associated With Decreased LDL-C and CHD Risk

PCSK9 Variant	Population	LDL-C	CHD Risk
R46L	ARIC, DHS	↓ 15% ¹	↓ 47% ¹
Y142X or C679X	ARIC, DHS	↓ 28%-40% ^{1,2}	↓ 88% ¹
R46L	CGPS	↓ 11% ³	↓ 46% ³

- Heterozygous LOF mutations found in 1% to 3% of population¹
- Associated with
 - Lower serum LDL-C¹
 - Lower incidence of coronary heart disease¹
- PCSK9 null individual identified (compound heterozygote for two inactivating mutations)
 - No detectable circulating PCSK9 with strikingly low LDL-C (14 mg/dL)⁴
 - Healthy and fertile college graduate in apparent good health⁴
- Inhibiting LDLR/PCSK9 interaction may lower plasma LDL-C levels⁵

LOF = loss of function.

1. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272.

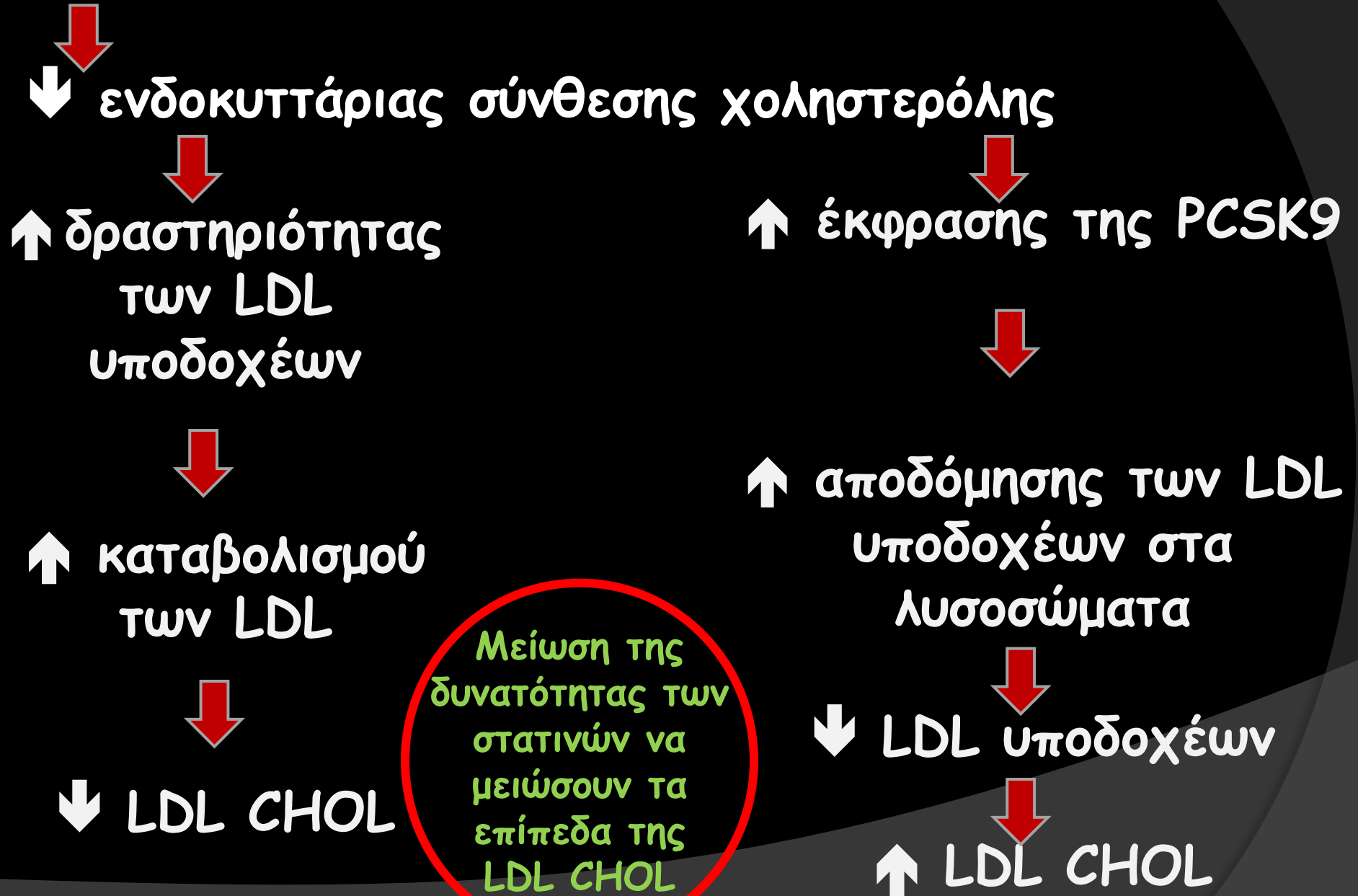
2. Cohen J, et al. *Nat Genet*. 2005;37:161-165.

3. Benn M, et al. *J Am Coll Cardiol*. 2010;55:2833-2842.

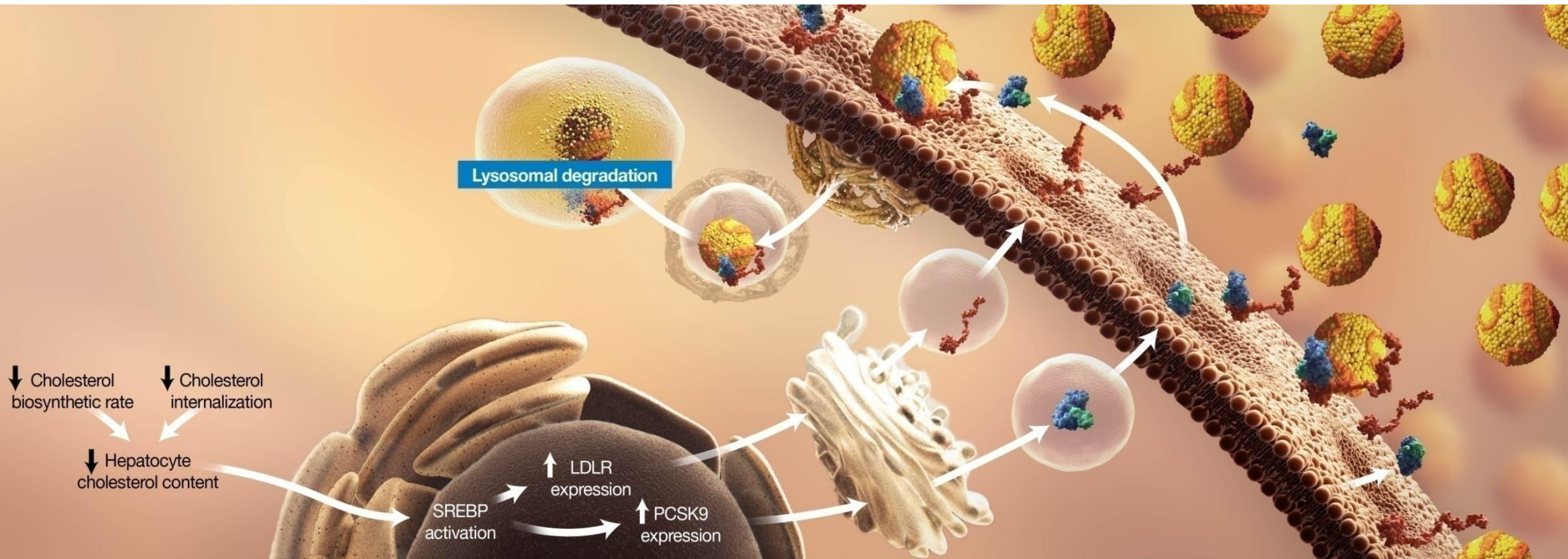
4. Zhao et al. *Am Journal of Hum Gen*. 2006;79:514-534.

5. Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.

ΣΤΑΤΙΝΕΣ



LDLR and PCSK9 Expression Are Both Upregulated When Intercellular Cholesterol Levels Are Low



*[SREBP] = sterol regulatory element-binding protein.

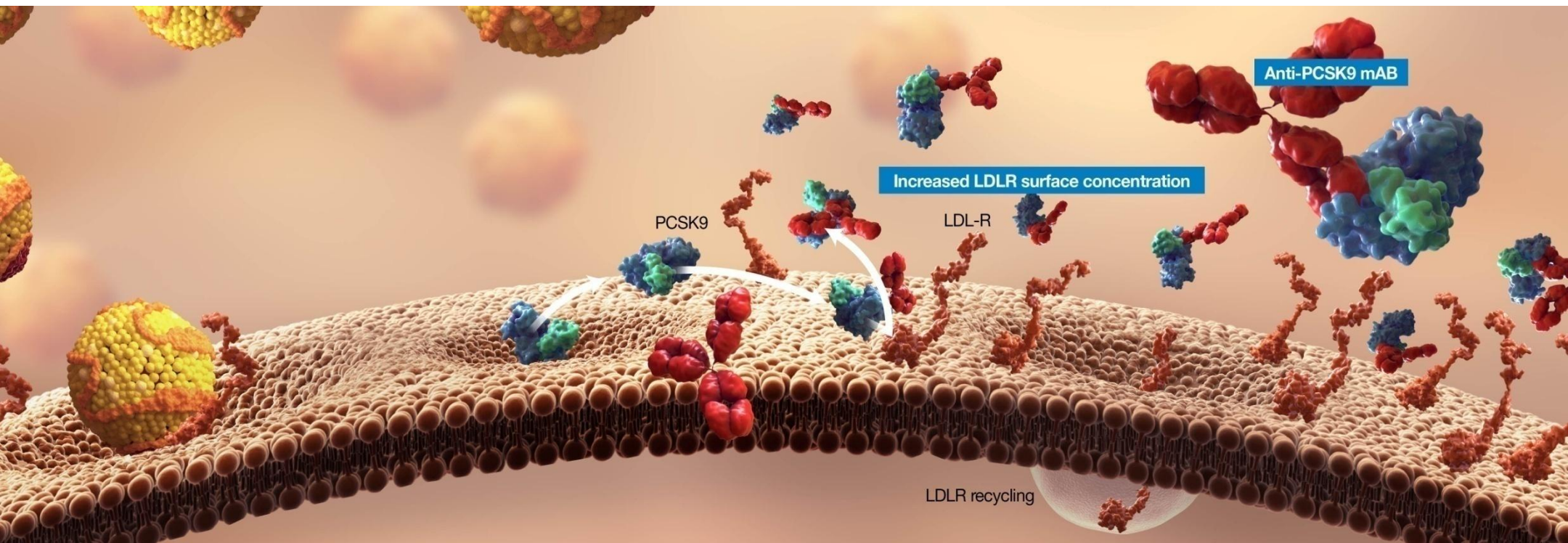
1. Goldstein JL, et al. *Arterioscler Thromb Vasc Biol.* 2009;29:431-438.
2. Dubuc G, et al. *Arterioscler Thromb Vasc Biol.* 2004;24:1454-1459.

Οι στατίνες επιτυγχάνουν το στόχο της υπολιπιδαιμικής αγωγής σε ένα σχετικά μικρό ποσοστό ασθενών υψηλού κινδύνου - ανάγκη χορήγησης υψηλών δόσεων - δοσοεξαρτώμενες ανεπιθύμητες ενέργειες ΤΟΥΣ

ΓΙΑ ΤΗΝ ΕΠΙΤΕΥΞΗ ΤΩΝ ΣΤΟΧΩΝ ΤΗΣ ΥΠΟΛΙΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ

Ανάγκη χορήγησης υποχοληστερολαιμικών
φαρμάκων με διαφορετικό μηχανισμό δράσης

Blockade of PCSK9/LDLR Interaction May Lower LDL Levels

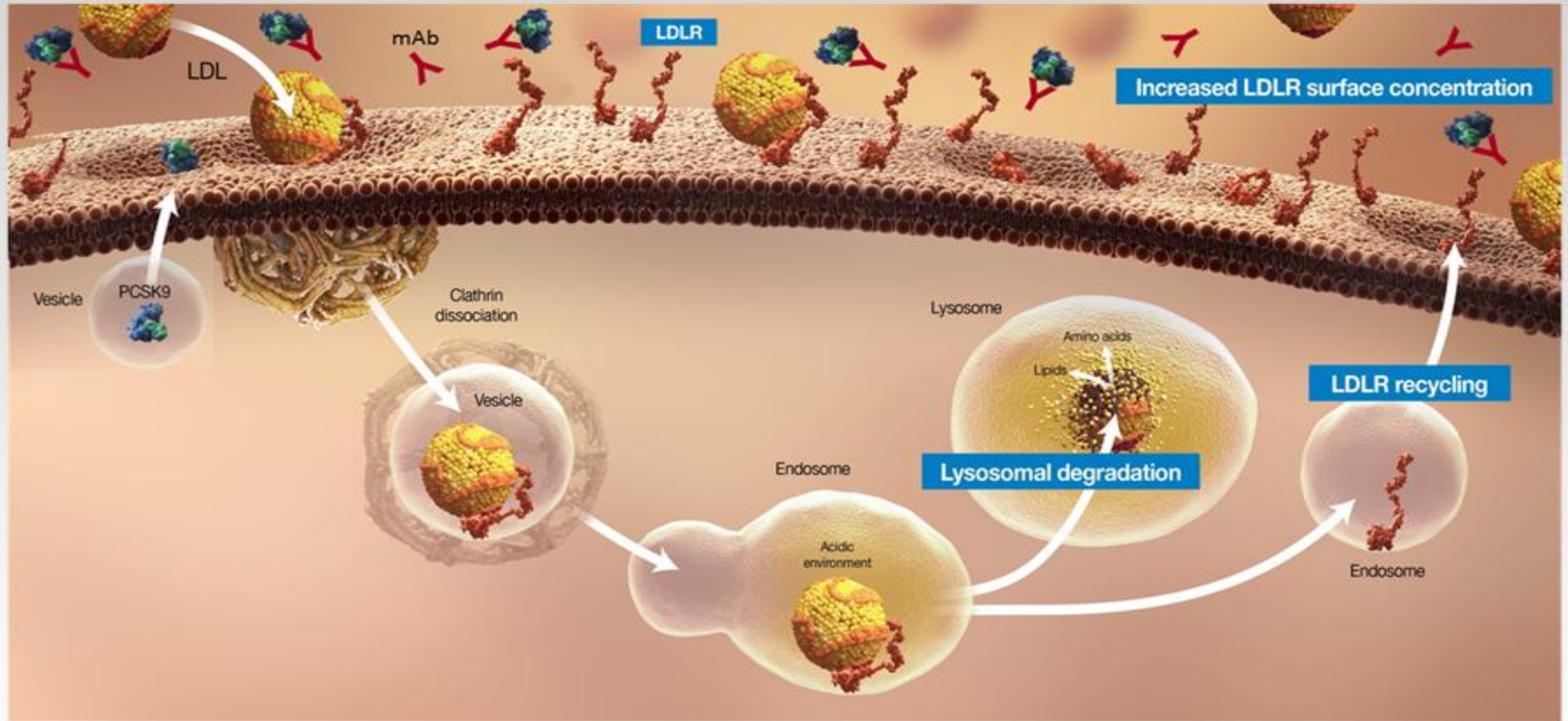


1. Chan JC, et al. *Proc Natl Acad Sci U S A*. 2009;106:9820-9825.

PCSK9 INHIBITORS

Μονοκλωνικά αντισώματα που εμποδίζουν την αλληλεπίδραση της PCSK9 (proprotein convertase subtilisin/kexin 9) με τον LDL υποδοχέα

Impact of PCSK9 Monoclonal Antibodies on LDL Receptor Surface Concentrations



ΕΠΙΤΕΥΞΗ ΤΩΝ ΣΤΟΧΩΝ ΤΗΣ ΥΠΟΛΙΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ

PCSK9 inhibitors

+

ΣΤΑΤΙΝΗ

EVOLOCUMAB VS EZETIMIBE
IN HYPERCHOLESTEROLEMIC SUBJECTS UNABLE
TO TOLERATE EFFECTIVE STATINS DOSES
GAUSS-2 TRIAL (n=307)

Evolocumab 140mg/2 εβδομάδες ή evolocumab
420mg/4 εβδομάδες vs ezetimibe 10mg

Evolocumab: ↓ LDL CHOL κατά 53-56%

Δ με ezetimibe κατά 37-39%

Muscle adverse events: evolocumab 12% vs
ezetimibe 23%

JACC 2014;63: 2541-2548

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

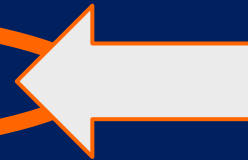
A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

Dirk J. Blom, M.D., Ph.D., Tomas Hala, M.D., Michael Bolognese, M.D.,
Michael J. Lilestol, M.D., Phillip D. Toth, M.D.,
Lesley Burgess, M.B., B.Ch., M.Med., Ph.D., Richard Ceska, M.D., Ph.D.,
Eli Roth, M.D., Michael J. Koren, M.D., Christie M. Ballantyne, M.D.,
Maria Laura Monsalvo, M.D., Kate Tsirtsonis, M.Sc., Jae B. Kim, M.D.,
Rob Scott, M.D., Scott M. Wasserman, M.D., and Evan A. Stein, M.D., Ph.D.,
for the **DESCARTES** investigators*

This article was published on March 29,
2014, at NEJM.org.

Ασθενείς υπό αγωγή με ATORVA (10 ή 80mg/d) ή
συνδυασμό ATORVA (80mg/d) + ezetimibe (10mg/d)
Evolocumab vs placebo
(420mg/4 εβδομάδες), n=901

↓ LDL CHOL κατά 57%, $p < 0.001$



Ανεπιθύμητες ενέργειες: ρινοφαρυγγίτιδα, οσφυαλγία,
γριπώδης συνδρομή

N Engl J Med 2014;370: 1809-1819

REDUCTION IN LIPOPROTEIN (a) WITH PCSK9 MONOCLONAL ANTIBODY EVOLOCUMAB (AMG 145)

n=1359 άτομα

Evolocumab (140mg/2 weeks) ⇒ ↓ Lp(a) κατά 29.5%

Evolocumab (420mg/4weeks) ⇒ ↓ Lp(a) κατά 24.5%

Η μείωση της Lp(a) συσχετίζονται με τις ποσοστιαίες μειώσεις της LDL CHOL

ENOLOCUMAB (AMG 145) ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ (ΜΕΛΕΤΗ OSLER)

Μια μελέτη 52 εβδομάδων , n=1104,
420mg /4 εβδομάδες

↓ LDL CHOL κατά 52.3%
ΑΠΟΤΕΛΕΣΜΑΤΙΚΗ ΚΑΙ ΑΣΦΑΛΗΣ ΑΓΩΓΗ

ΕΠΙΤΕΥΞΗ ΣΤΟΧΟΥ ΥΠΟΛΙΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ ΣΕ ΑΤΟΜΑ ΥΨΗΛΟΥ ΚΙΝΔΥΝΟΥ

LAPLACE-TIMI 57 TRIAL

>90% των ασθενών πέτυχε το στόχο
LDL CHOL <70mg/dl

ΜΟΝΟΘΕΡΑΠΕΙΑ ΜΕ ΕΒΟΛΟCUMΑΒ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ

ΜΕΛΕΤΗ MENDEL-2

n=614 , ΕΒΟΛΟCUMΑΒ 120mg /2 εβδομάδες ή 420
mg / 4 εβδομάδες:

↓ LDL CHOL κατά 55-57% vs placebo

↓ LDL CHOL κατά 38% vs ezetimibe

EVOLOCUMAB OR EZETIMIBE +
STATIN THERAPY ΣΕ ΑΣΘΕΝΕΙΣ
ΜΕ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ
LAPLACE -2 Randomized clinical trial

Evolocumab:

- ↓ LDL CHOL κατά 66%-75% / 2 εβδομάδες
- ↓ LDL CHOL κατά 63%-75% / 4 εβδομάδες

AMG-145: A PCSK9 INHIBITOR

- ❑ Χορηγείται υποδόρια κάθε 2/4 εβδομάδες
- ❑ Αποτελεσματική μείωση της LDL CHOL σε ασθενείς με ή χωρίς FH, ακόμα και σε ασθενείς με ομόζυγη FH
- ❑ Ιδιαίτερα αποτελεσματικό φάρμακο σε συνδυασμό με στατίνες (\pm ezetimibe)



Clinical update

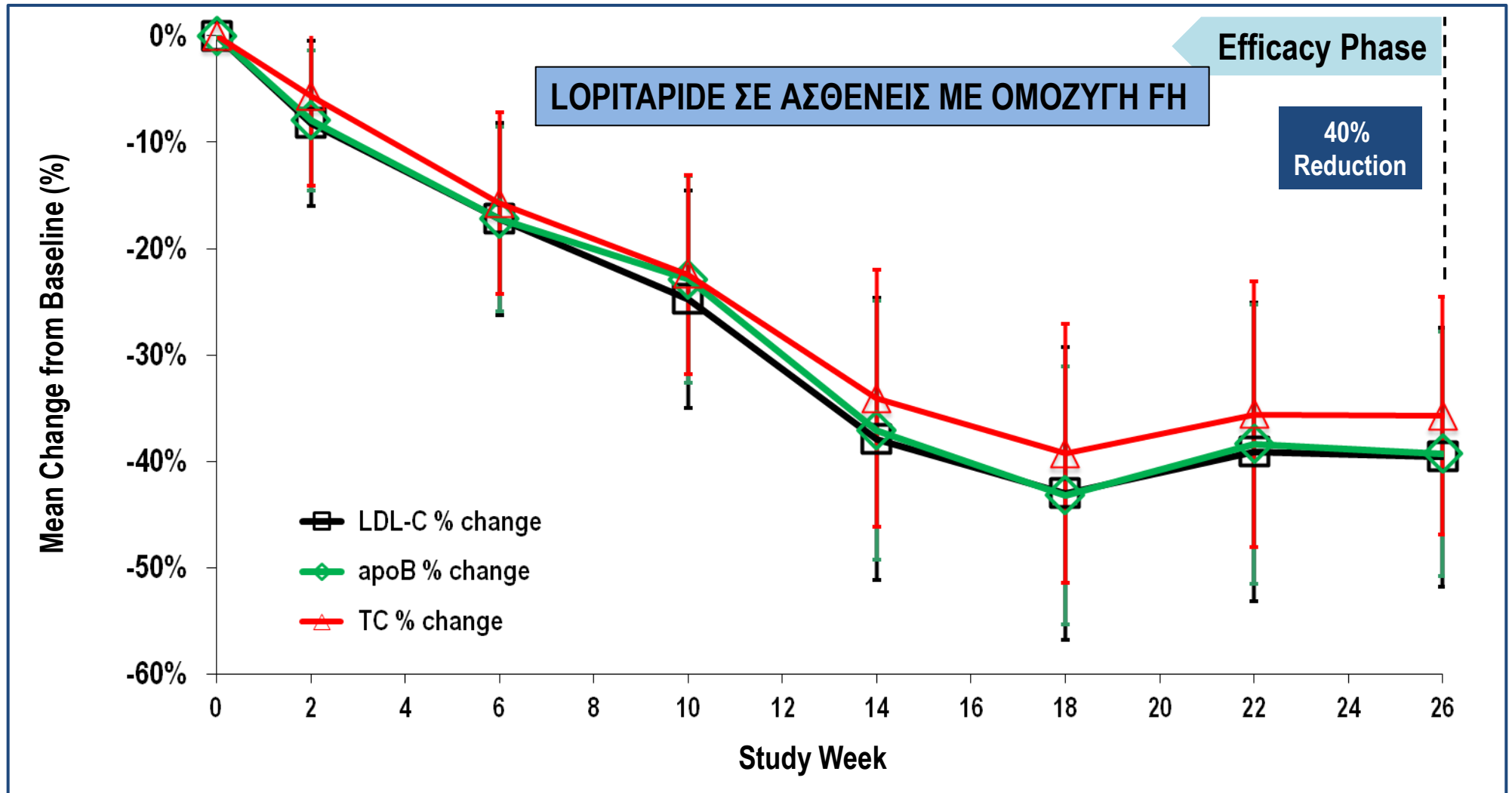
Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

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Mean % Change in TC, LDL-C, and Apo B Through the Efficacy Phase (ITT, LOCF)



Lomitapide should be approved for HoFH in Europe, EMA advised

LOJUXTA, Aegerion Pharmaceuticals

London, UK - The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended that the **lomitapide** preparation Lojuxta (Aegerion Pharmaceuticals) be approved "as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low-density-lipoprotein apheresis in adult patients with homozygous familial hypercholesterolemia (HoFH)" [1]. Such recommendations are usually adopted officially by the EMA.

The "positive opinion" rendered by the CHMP follows FDA approval of the same company's lomitapide preparation Juxtapid for the same indication in December 2012, as reported by [heartwire](#). The FDA's advisory panel had recommended its approval by a vote of 13 to 2.

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