ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΟΙΚΟΓΕΝΗΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ: ΔΙΑΓΝΩΣΗ-ΘΕΡΑΠΕΙΑ

Ευάγγελος Λυμπερόπουλος

Καθηγητής Παθολογίας-Μεταβολικών Νοσημάτων Ιατρικής Σχολής Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών
Α΄ Προπαιδευτική Παθολογική Κλινική, ΓΝΑ 'Λαϊκό'
European Atherosclerosis Society Executive Committee member (2024-2027)

EAS
European Atherosclerosis Society

ΠΕΡΙΣΤΑΤΙΚΟ

- Ασθενής 48 ετών έρχεται με T-CHOL 350 mg/dL, TGs 100 mg/dL, HDL-CHOL 50 mg/dL & LDL CHOL 280 mg/dL

1ο ΒΗΜΑ: ΑΠΟΚΛΕΙΣΜΟΣ ΔΕΥΤΕΡΟΠΑΘΟΥΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑΣ

ΑΠΟΚΛΕΙΣΜΟΣ ΔΕΥΤΕΡΟΠΑΘΟΥΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑΣ

- ✓Υποθυρεοειδισμός (TSH)
- ✓Χολόσταση (αλκαλική φωσφατάση)
- ✓Νεφρωσικό σύνδρομο (λεύκωμα ούρων)

DIAGNOSTIC WORK-UP

- Εργαστηριακές εξετάσεις κ.φ.
- Μη καπνιστής
- BMI 25 Kg/m^2
- ΑΠ 120/80 mmHg

2ο ΒΗΜΑ: ΑΤΟΜΙΚΟ & ΟΙΚΟΓΕΝΕΙΑΚΟ ΙΣΤΟΡΙΚΟ

Διαγνωστικές ερωτήσεις

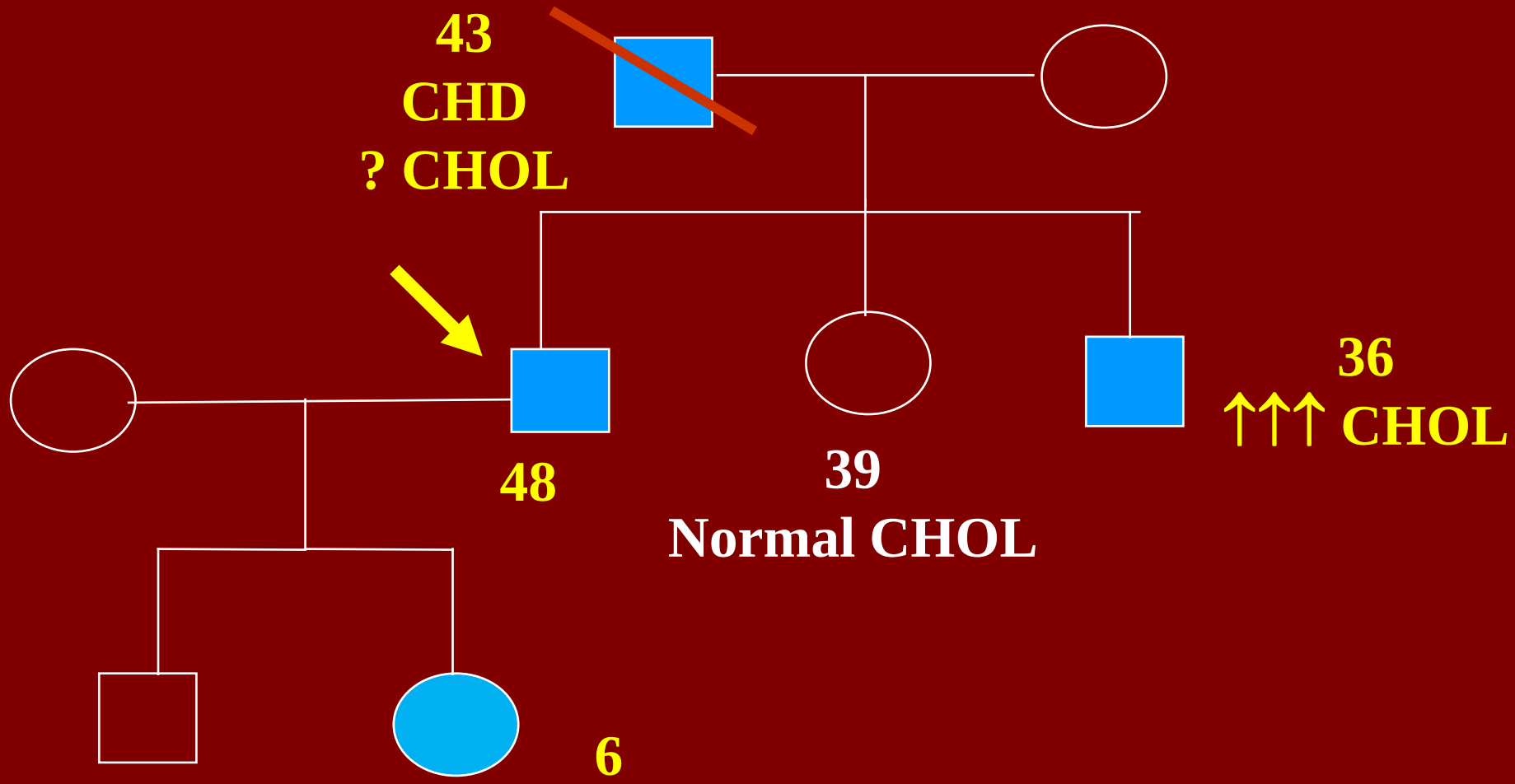
1) Έχει ο ασθενής ατομικό ιστορικό CVD;

2) Τι LDL χοληστερόλη και ιστορικό CVD έχουν οι γονείς;

2) Τι LDL χοληστερόλη και ιστορικό CVD έχουν τα αδέρφια του;

3) Τι LDL χοληστερόλη και ιστορικό CVD έχουν τα παιδιά του;

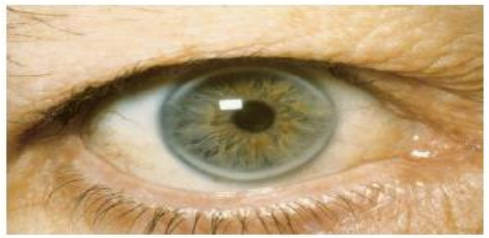
FAMILY TREE

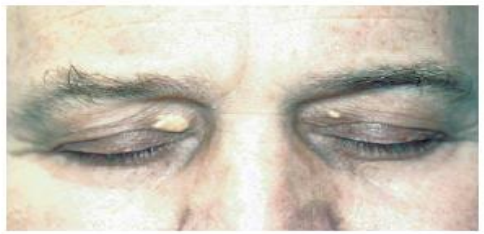

43
CHD
? CHOL
48
39
Normal CHOL
36
↑↑↑ CHOL
8
Normal CHOL
6
LDL CHOL 160 mg/dL

3ο ΒΗΜΑ: ΦΥΣΙΚΗ ΕΞΕΤΑΣΗ

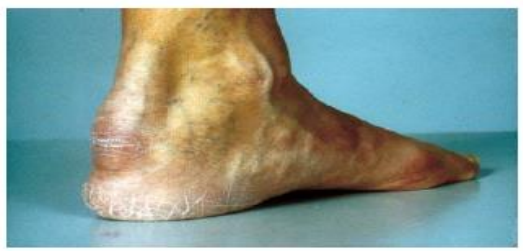
Consider FH

Clinical evidence of:

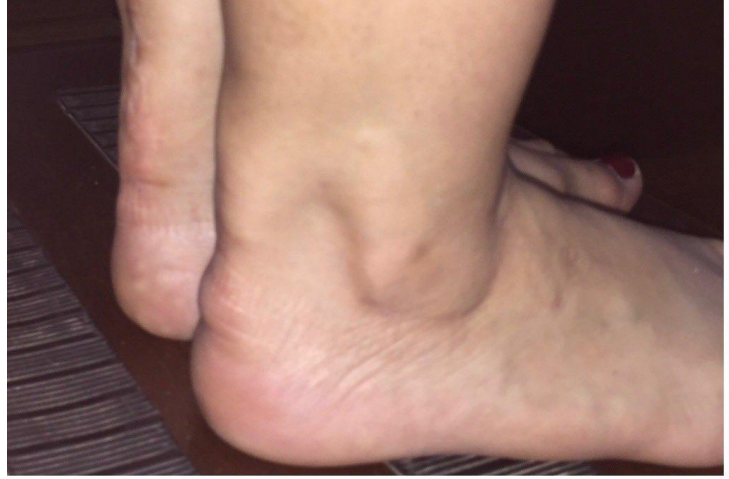
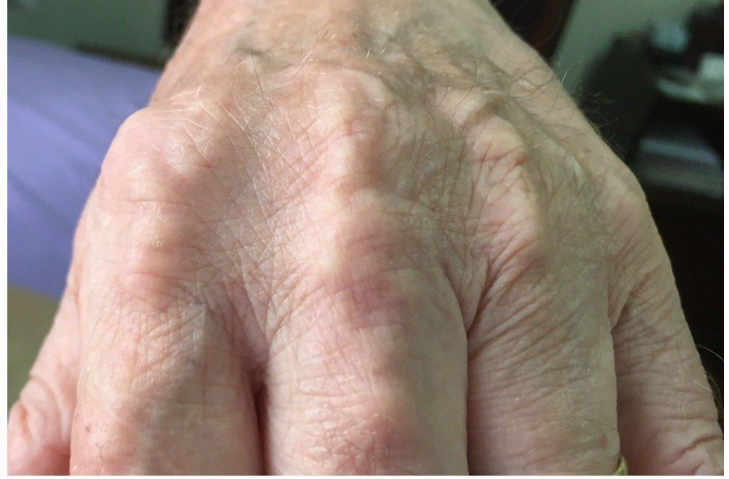
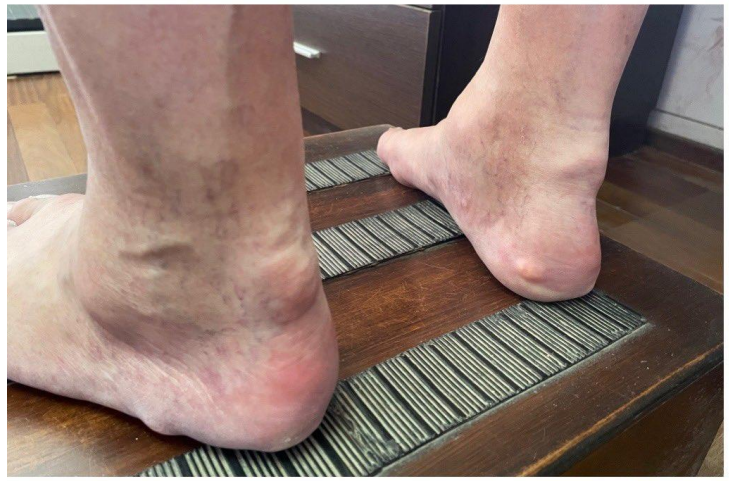
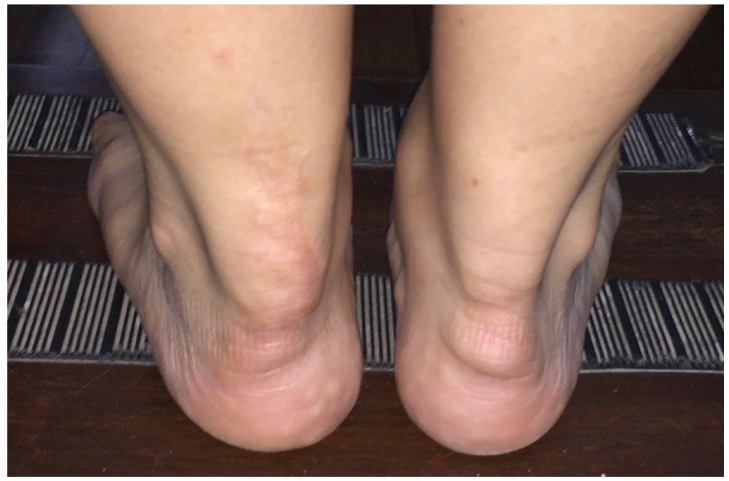
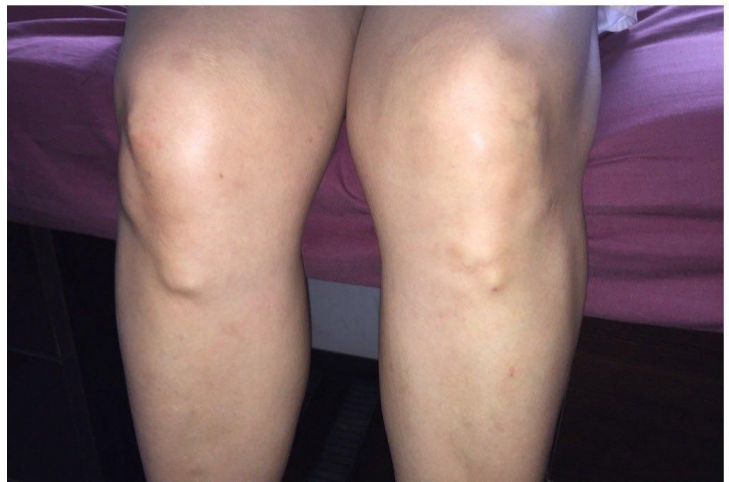
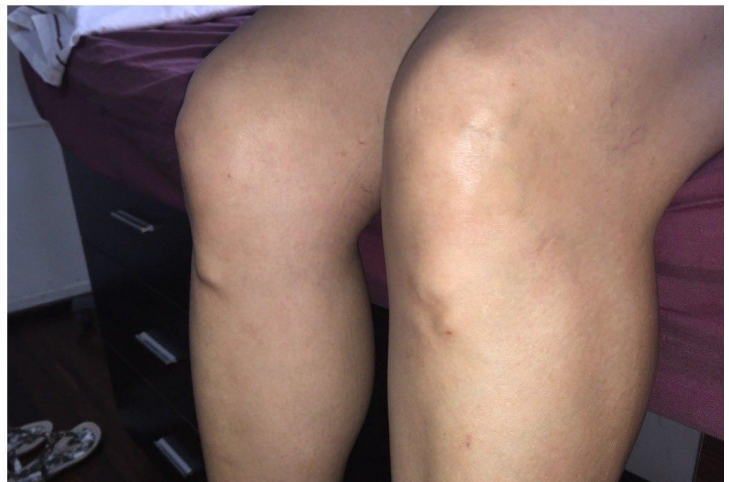




- Corneal Arcus
- Xanthelasma
- Tendon xanthomas in the hands and Achilles tendons



EAS

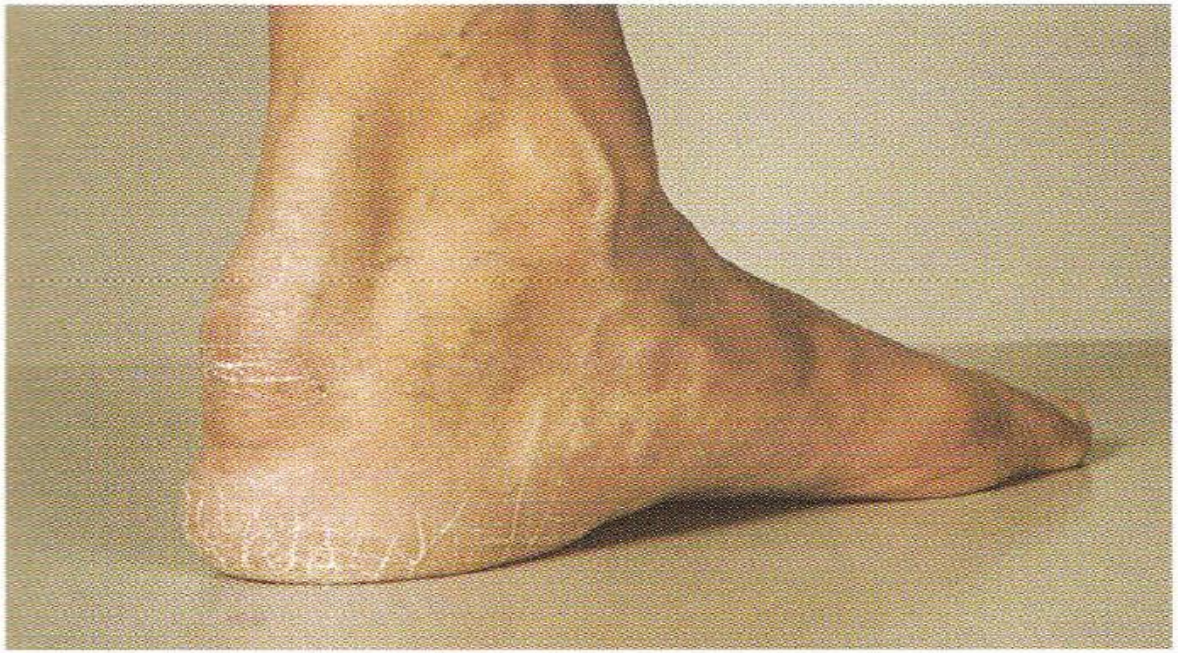


Plate 1 *Achilles tendon xanthoma (heterozygous familial hypercholesterolaemia)*

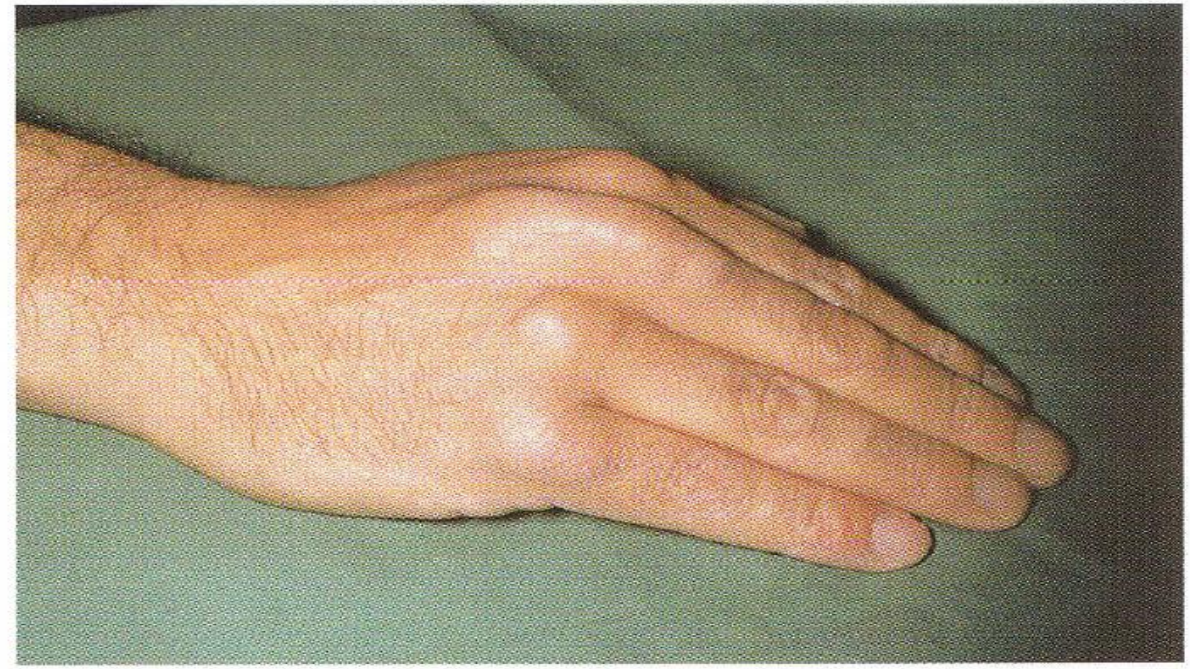
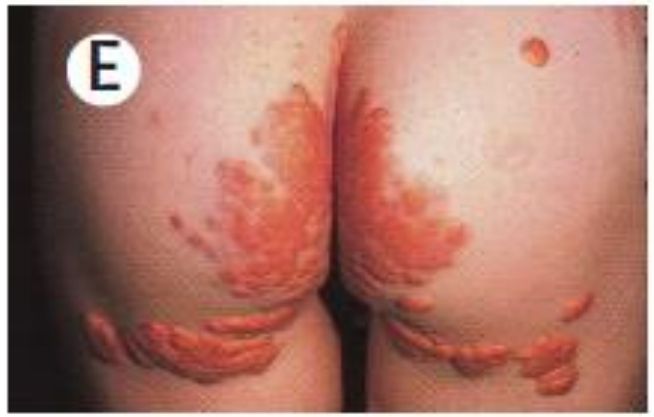
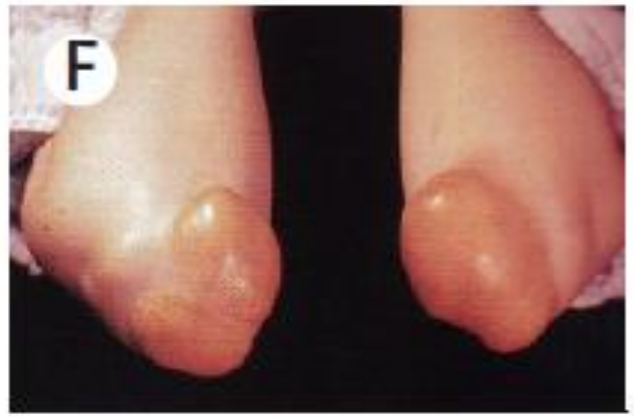
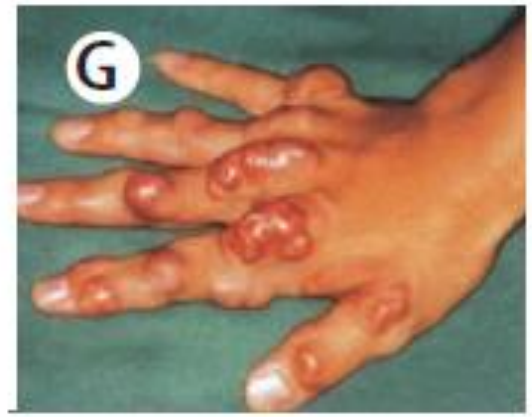


Plate 3 *Tendon xanthomata on dorsum of hand (heterozygous familial hypercholesterolaemia) (courtesy of Dr J. Barth)*

ΦΥΣΙΚΗ ΕΞΕΤΑΣΗ HoFH



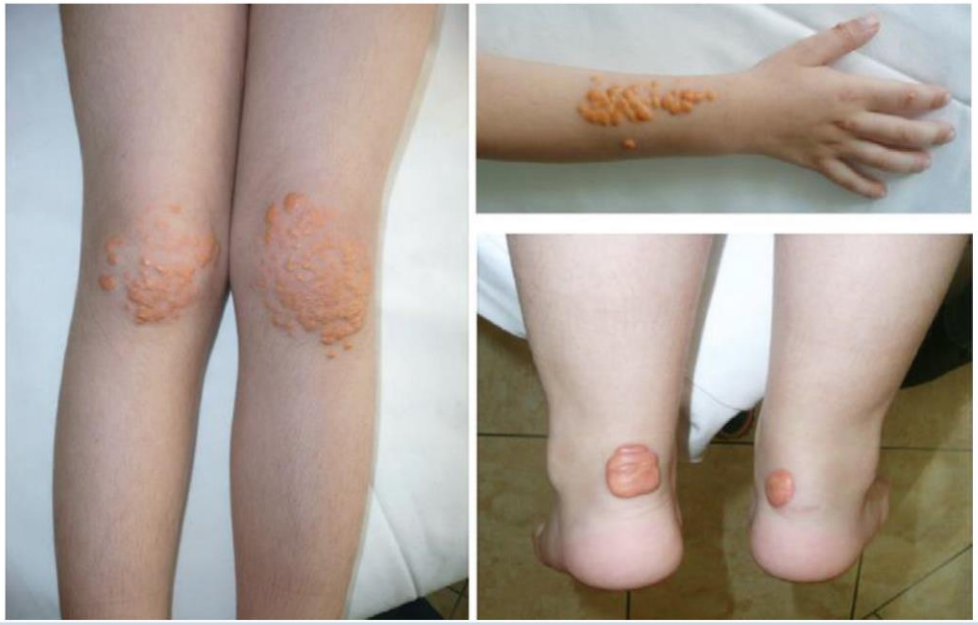




Homozygous FH
A *horrible* inherited metabolic disease

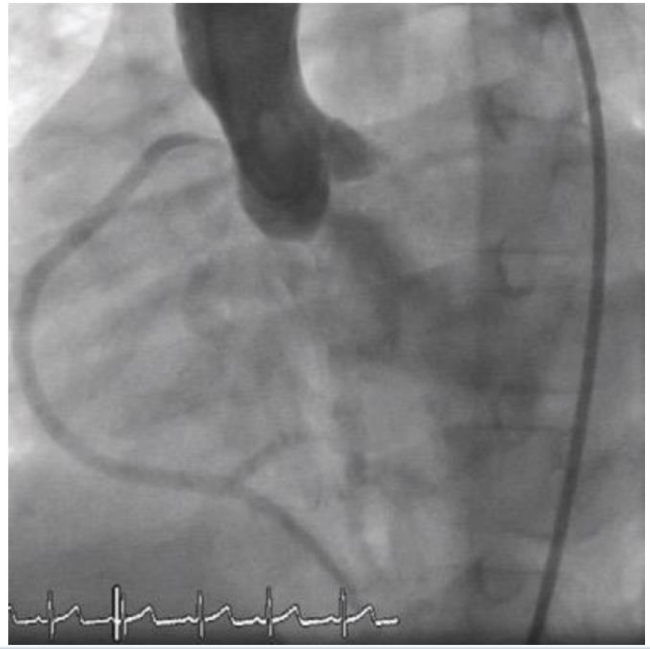
Case report:

- 5-year-old boy with HoFH
- Treated with colestyramine
- LDL 26 mmol/L *(2314 mg/dl)*



Follow-up:

- Acute ischaemic cardiac event; complete obstruction of the left coronary artery
- Died from second MI after three months



Macchiaiolo M e.a. Lancet, 2012;379:1330

4ο ΒΗΜΑ: ΔΙΑΓΝΩΣΗ

ΟΙΚΟΓΕΝΗΣ (50% των 1ου βαθμού συγγενών)

+

ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ (LDL-C >190 mg/dL ενήλικοι ή >160 mg/dL παιδιά)

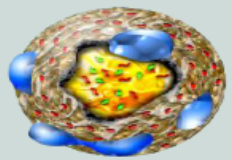
=

ΟΙΚΟΓΕΝΗΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ (FH)

European Heart Journal

DUTCH FH CRITERIA

Feature	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men <55 years, females <60 years) OR First-degree relative with known LDL-C above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C above the 95th percentile for age and sex	2
Clinical history	
Premature coronary artery disease (men <55 years, females < 60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, females <60 years)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
LDL-C (mmol/L) – 5.5 or higher – 6.5 to 8.4 – 5.0 to 6.4 – 4.0 to 4.9	 8 5 3 1
DNA analysis: functional mutation in the *LDLR*, *APOB* or *PCSK9* gene	8



Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria:

- **Definite FH = total score greater than 8**
- **Probable FH = total score between 6 and 8**
- **Possible FH = total score between 3 and 5**
- **Unlikely FH = total score of less than 3**

Hellenic Atherosclerosis Society

Ελληνική Εταιρεία Αθηροσκλήρωσης

Carrier 10:19 PM

Criteria

Group 1: Family History

- Children aged <18 years with LDL-C >95th percentile by gender and age for country (>160 mg/dL; 4.1 mmol/L)

Group 2: Personal Clinical History

Group 3: Physical Exam

Group 4: LDL-C Level

Group 5: Genetic Testing

- Causative mutation in LDLR, ApoB or PCSK9 genes

View Your Score

0

Unlikely FH

Carrier 10:18 PM

Home

The FH Calculator application is an easy way for Medical Practitioners to calculate accurately the possibility of Familial Hypercholesterolemia using the Dutch criteria.

This application is sponsored by the Hellenic Atherosclerosis Society

www.atherosclerosis.gr

This application does not provide full diagnosis of FH and is for educational purpose only.

Take FH Test

Family History + Hypercholesterolemia = FH in Children*

- Cholesterol testing should be used to make a phenotypic diagnosis

  - 5 mmol/L (190 mg/dL), 2 successive occasions over 3 months
  - 4 mmol/L (160 mg/dL) AND family history of premature CVD ± baseline high cholesterol in one parent
  - 3.5 mmol/L (130 mg/dL) AND positive genetic diagnosis in the family

- Rule out secondary causes (thyroid, liver or renal dysfunction, concomitant medication, obesity)
- Genetic testing confirms the diagnosis (after parental testing)
- If a parent died from CHD, a child even with moderate hypercholesterolaemia should be tested genetically for FH and inherited elevation in Lp(a).

*FH Foundation

Diagnosis of HoFH according to the criteria recommended by the EAS Consensus Panel

Box 1 Criteria for the diagnosis of homozygous familial hypercholesterolaemia

- Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus

OR

- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years

or

  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

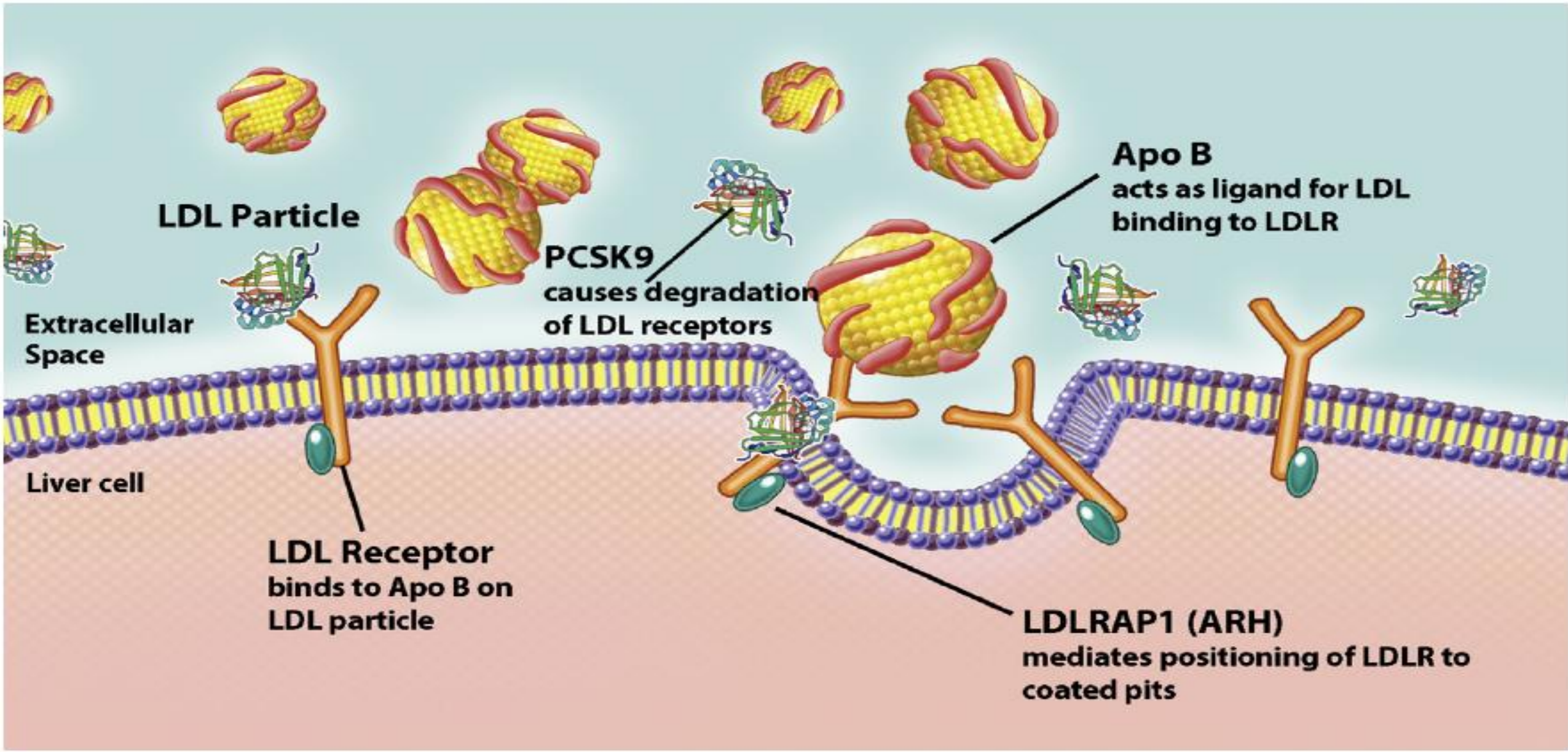
* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

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

EAS

5ο ΒΗΜΑ: ΓΕΝΕΤΙΚΗ ΔΙΑΓΝΩΣΗ [ΟΧΙ ΑΠΑΡΑΙΤΗΤΗ]

Figure 2 Major Molecular Causes of Familial Hypercholesterolemia



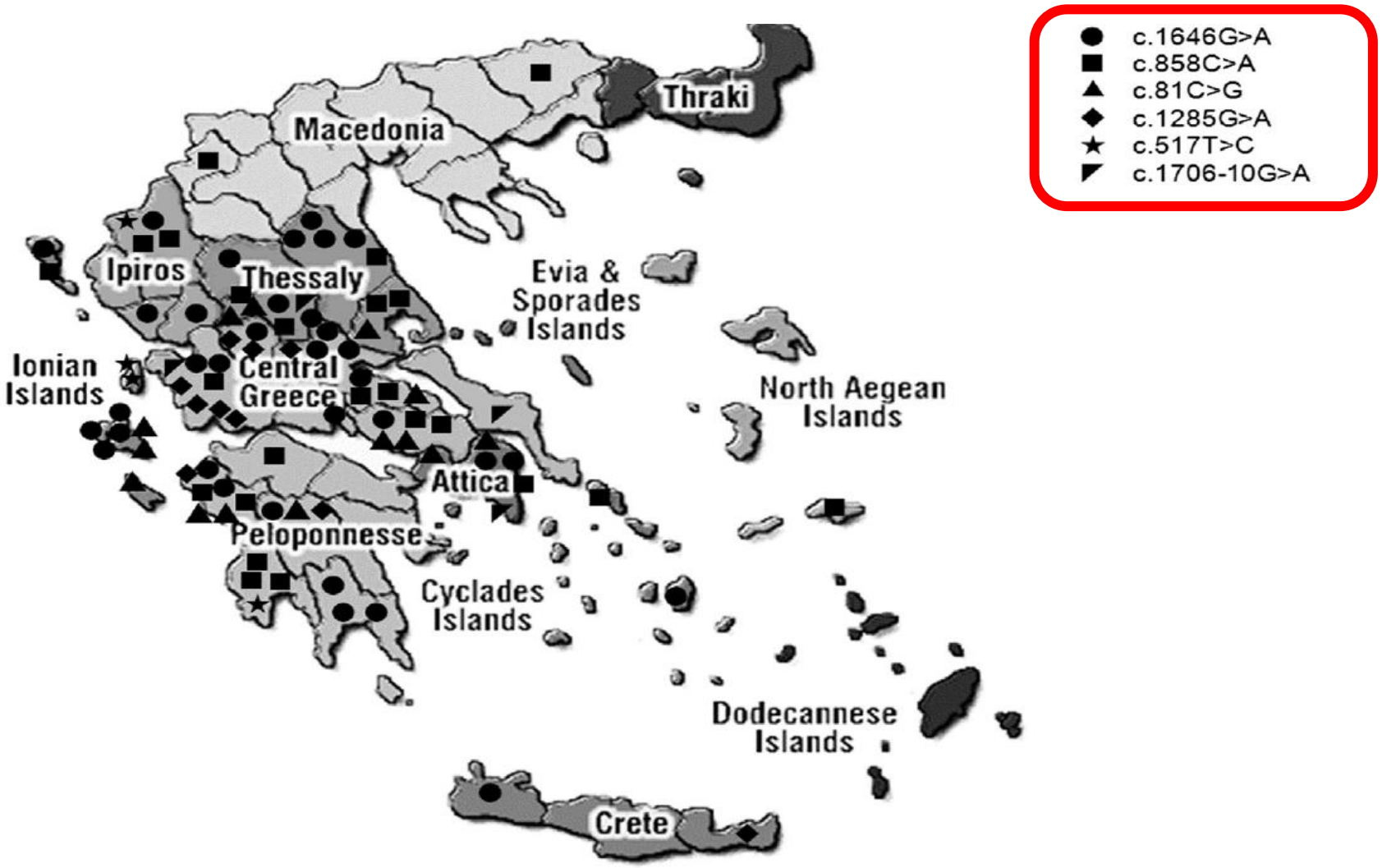
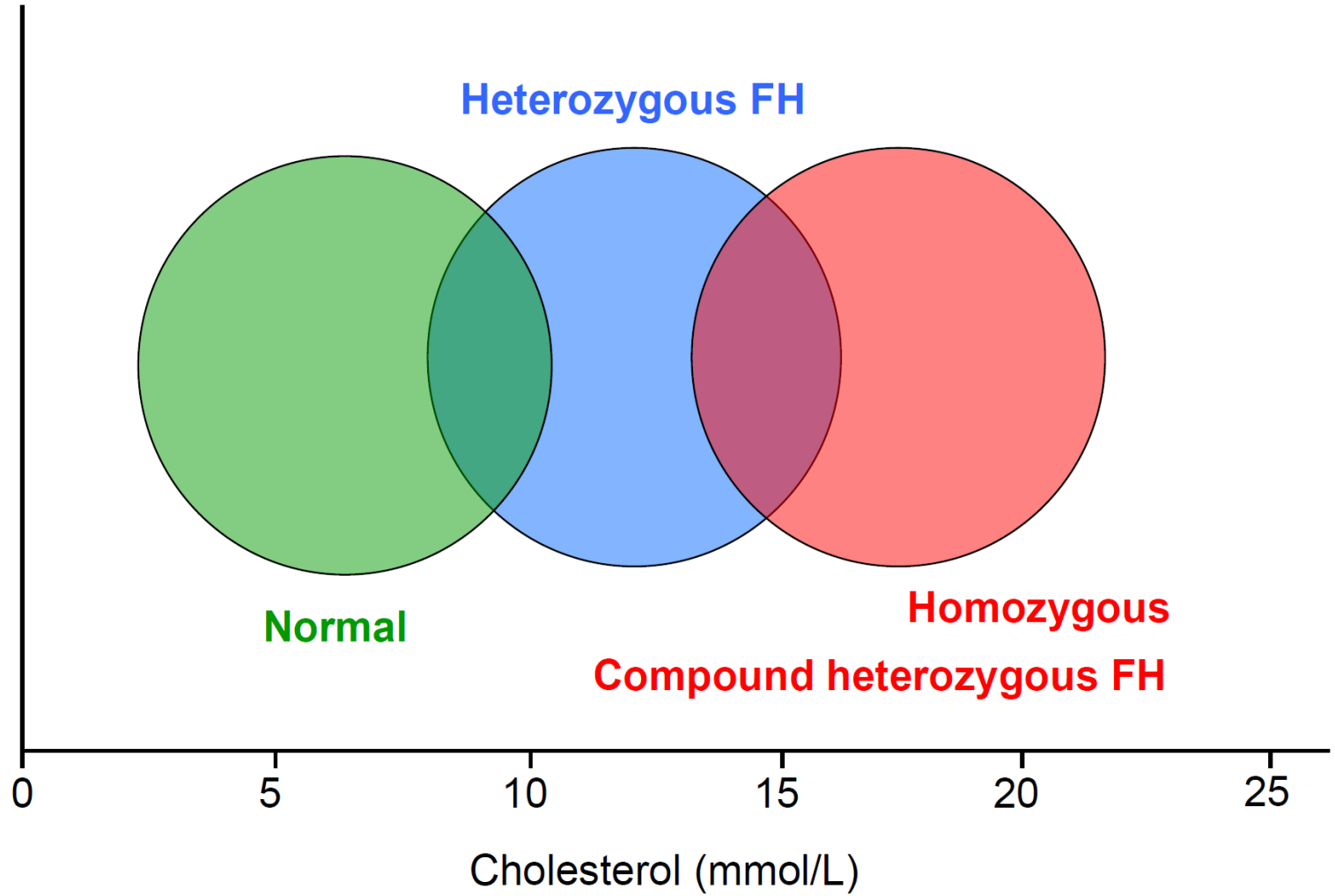


Fig. 2. Geographic distribution of the six most common *LDLR* mutations in Greece. The distribution of mutations is only shown for the index cases with determined exact origin. Four patients originating from Minor Asia carried the mutations c.1646G > A ($n = 2$), and c.81C > G ($n = 2$), and one patient originating from Cyprus carried the mutation c.1646G > A (data not shown in figure).

FH



Adapted from Cuchel M, *Eur Heart J* 2014;35:2146-57

ΤΙ ΣΗΜΑΙΝΕΙ ΝΑ ΕΧΕΙ ΚΑΠΟΙΟΣ ΟΙΚΟΓΕΝΗ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ;

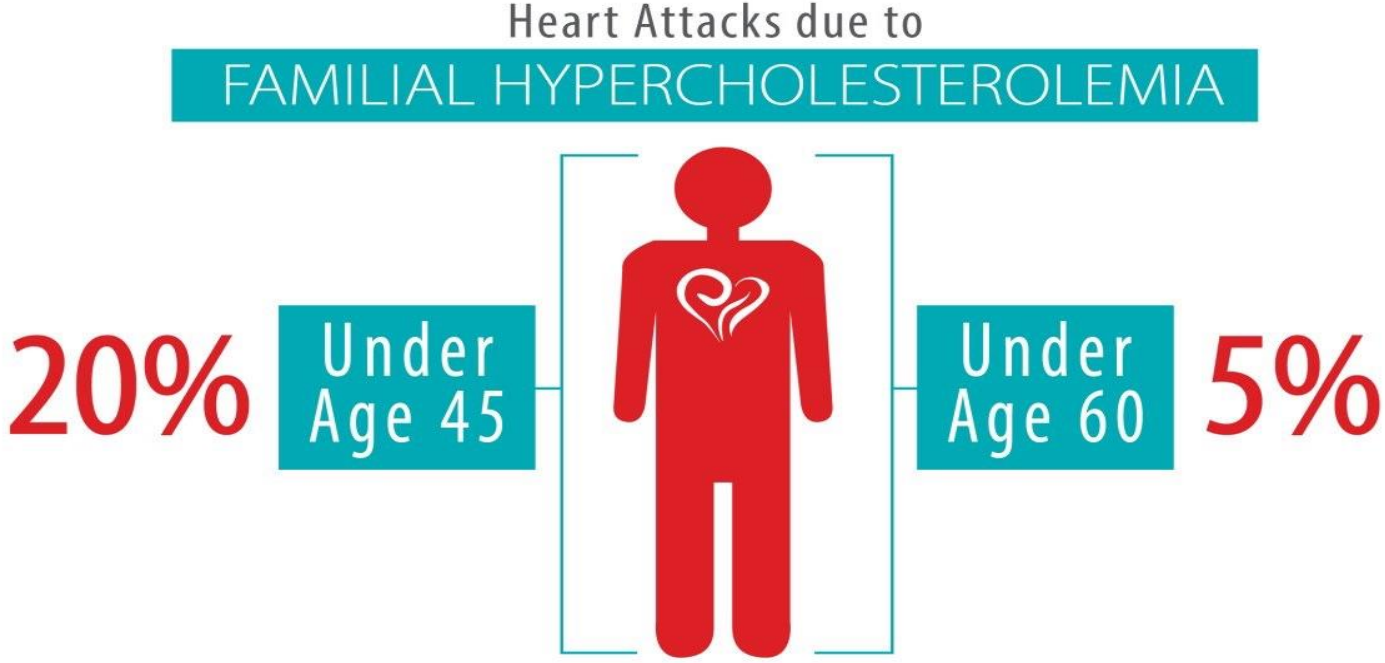
Heterozygous FH

- 20-fold increased risk of CVD
- If untreated:
  - Men have 50% risk of CVD by age 50
  - Women have 30% risk of CVD by age 60
- Many HeFH patients present with established CVD (angina, MI)

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

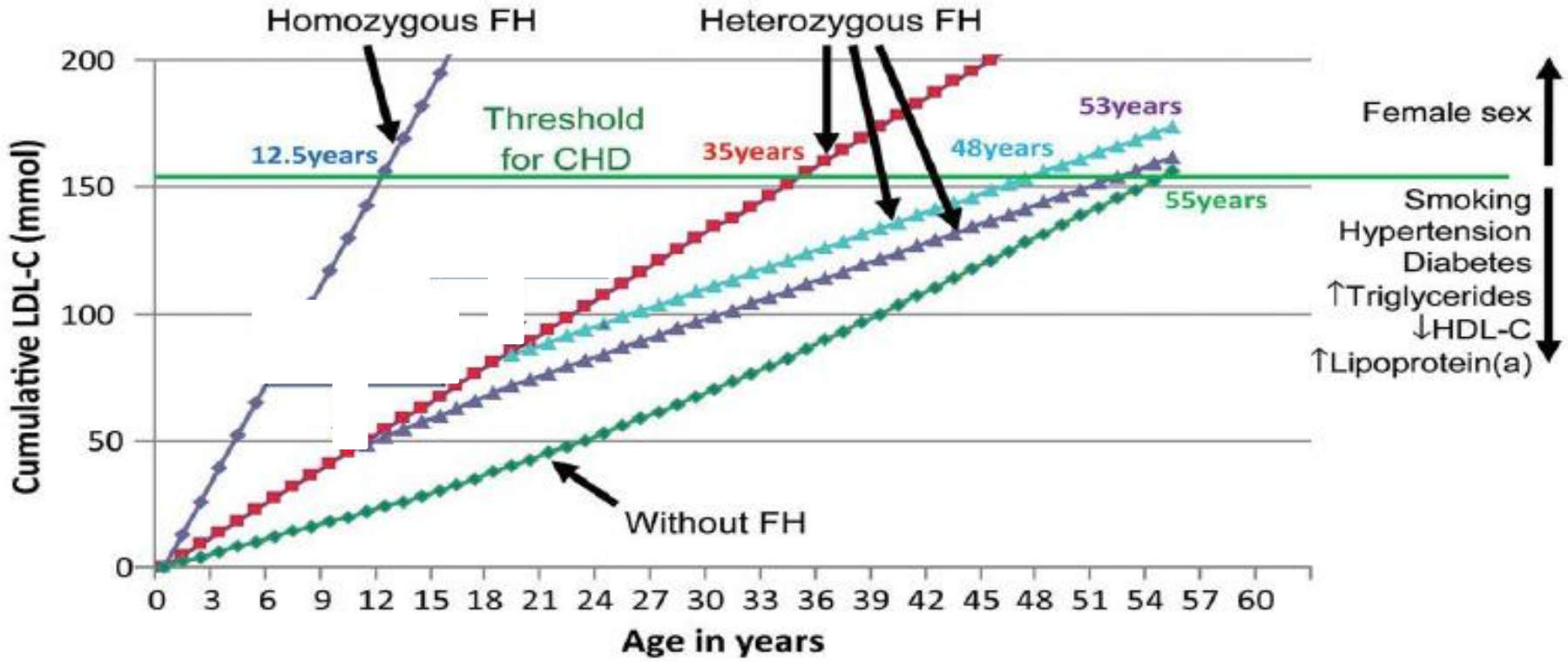
"About 5% of heart attacks under age 60 and as many as 20% under age 45 are due to FH"



Hopkins P, Toth P. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011 Jun;5(3 Suppl):S9–17.

LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy.

European Heart Journal



Adapted from Steve Humphries 2013

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

N=320, STEMI<35 yrs

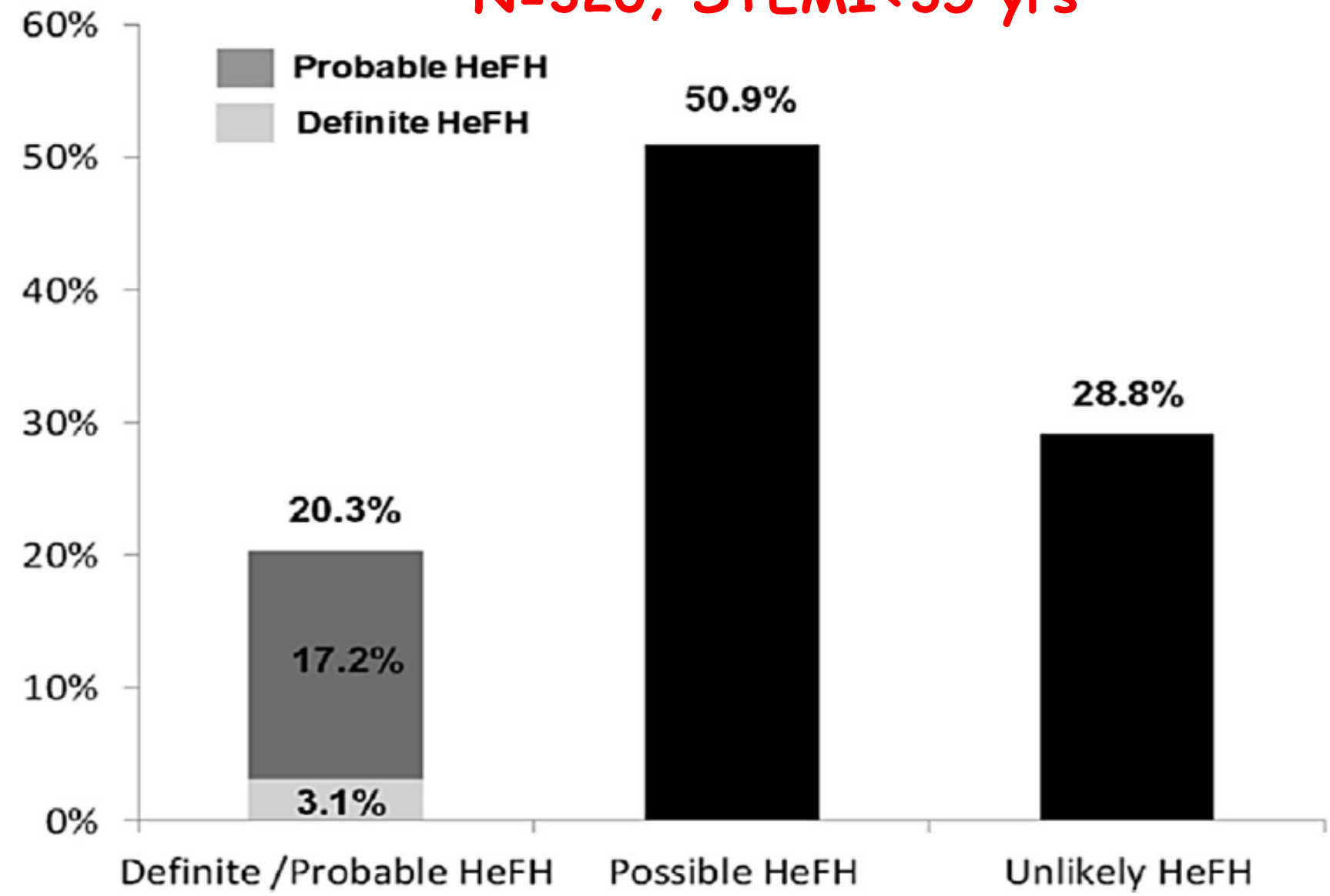


Fig. 1. Prevalence of heterozygous familial hypercholesterolaemia (HeFH) based on Dutch Lipid Clinic Network algorithm among patients with very early ST-segment elevation myocardial infarction.

L.S. Rallidis et al. / Atherosclerosis 249 (2016) 17–21

ΠΟΣΟ ΣΥΧΝΟ ΕΙΝΑΙ ΤΟ ΝΟΣΗΜΑ ΣΤΟΝ ΠΛΗΘΥΣΜΟ;

FH is more common than other genetic disord

Η ΠΙΟ ΣΥΧΝΗ ΓΕΝΕΤΙΚΗ ΝΟΣΟΣ ΤΟΥ ΜΕΤΑΒΟΛΙΣΜΟΥ

Wiegman A, et al. Eur Heart J. 2015;36:2425-2437

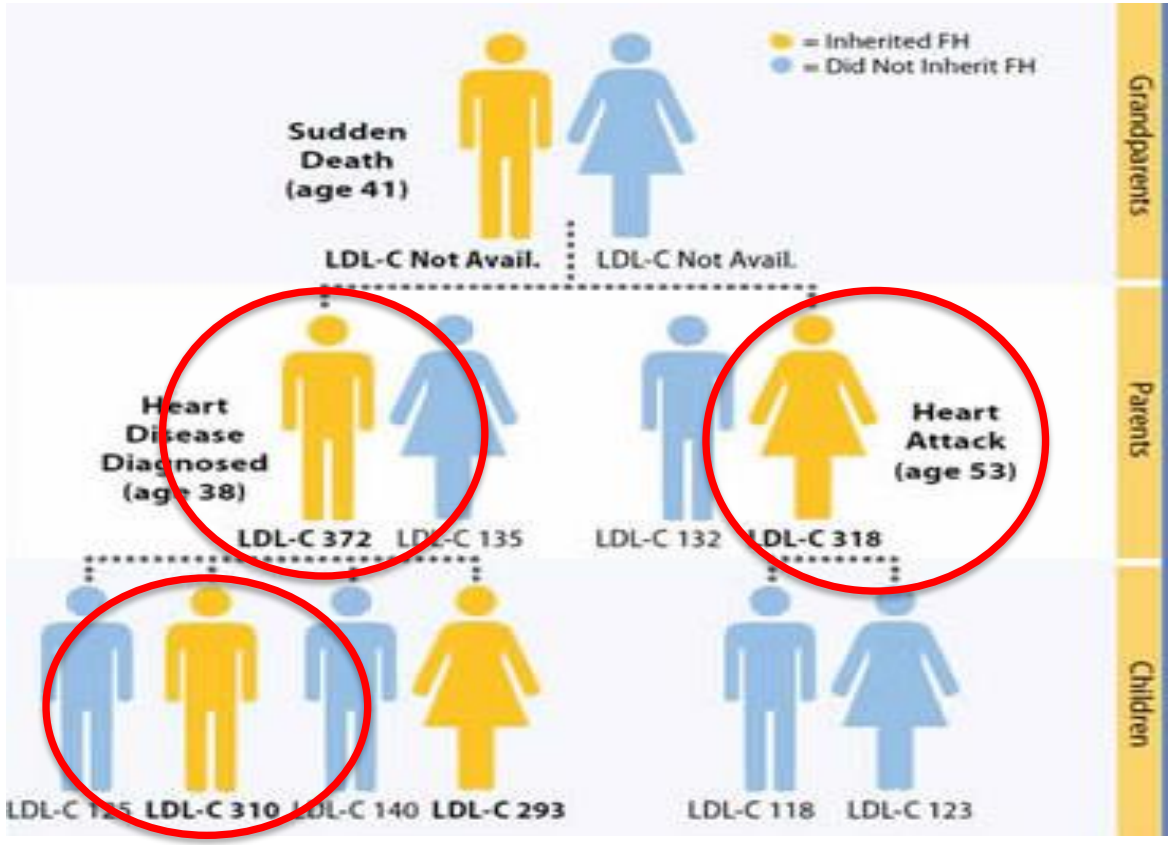
What Is the Prevalence of Familial Hypercholesterolemia?

Arterioscler Thromb Vasc Biol. 2021;41:2629–2631. DOI: 10.1161/ATVBAHA.121.316862

ΕΧΕΙ ΤΕΡΑΣΤΙΑ ΣΗΜΑΣΙΑ Η ΕΓΚΑΙΡΗ ΑΝΙΧΝΕΥΣΗ ΤΩΝ ΑΤΟΜΩΝ ΤΟΥ ΠΛΗΘΥΣΜΟΥ ΠΟΥ ΕΧΟΥΝ ΟΙΚΟΓΕΝΗ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ ΠΡΟΚΕΙΜΕΝΟΥ ΝΑ ΕΦΑΡΜΟΣΘΟΥΝ ΚΑΤΑΛΛΗΛΑ ΠΡΟΛΗΠΤΙΚΑ ΜΕΤΡΑ ΑΠΟ ΤΗΝ ΠΑΙΔΙΚΗ ΗΛΙΚΙΑ

CASCADE SCREENING

Cardiologist/ Lipidologist



Cardiologist

Pediatrician

Adapted from http://pcna.net/patients---preventive-cardiovascular-nurses-association/familial-hypercholesterolemia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Child–Parent Familial Hypercholesterolemia Screening in Primary Care

We obtained capillary blood samples to measure cholesterol levels and to test for familial hypercholesterolemia mutations in 10,095 children 1 to 2 years of age during routine immunization visits. Children were considered to have positive

CONCLUSIONS

Child–parent screening was feasible in primary care practices at routine child immunization visits. For every 1000 children screened, 8 persons (4 children and 4 parents) were identified as having positive screening results for familial hypercholesterolemia and were consequently at high risk for cardiovascular disease. (Funded by the Medical Research Council.)

The overall mutation prevalence was 1 in 273 children

Types of Screening

Cholesterol Screening

Age	Type	Criteria
≥ 2 yrs of age	Selective	• 1 or both biologic parents known to have hypercholesterolemia or are receiving LLM; or • Family history of premature CVD (i.e. men < 55 yrs; women < 65 yrs); or • Whose family history is unknown (e.g. children who were adopted).
≥ 10 yrs of age*	Universal	• Regardless of general health or the presence/absence of CVD risk factors. • If normal, repeat every 5 yrs.

*Selective screening if clinically indicated.

LLM = lipid-lowering medications; CVD = cardiovascular disease

National Lipid Association Annual Summary of Clinical Lipidology 2017. J of Clinical Lipidology (2016) , S1-S50

FH Paediatric Screening
Moving Prevention From Evidence to Action:
Overcoming the Barriers to Implementation

Hybrid Event under the **Auspices of the Czech EU Presidency**

6th September 2022

FH Europe
The European FH Patient Network

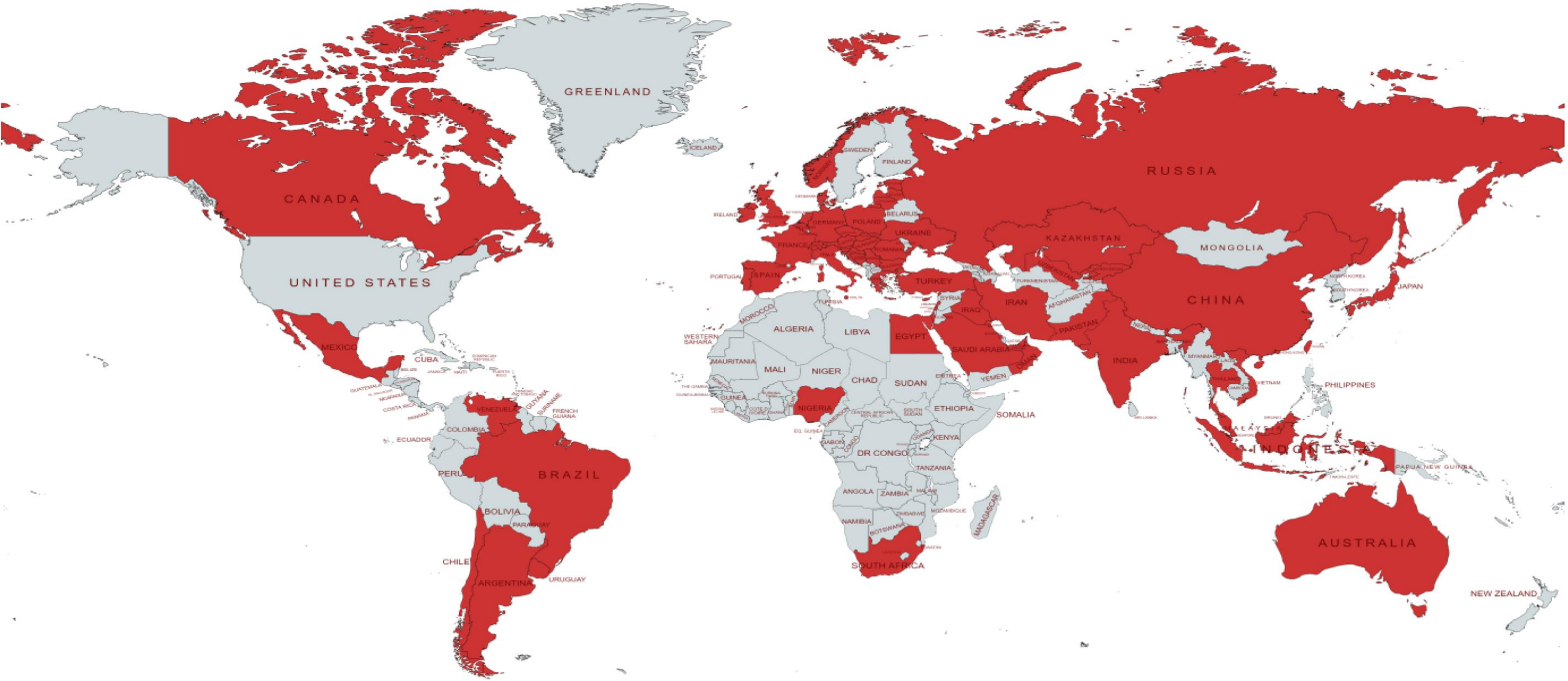
EU2022.CZ

EAS FHSC

The EAS Familial Hypercholesterolaemia Studies Collaboration

FH Global Registry

The EAS FHSC now spans 69 countries (shaded map) and includes 82 Lead Investigators; specifically the National Lead Investigators are listed here. EAS FHSC Registry includes approximately 70,000 cases across 66 countries.



THE LANCET

Articles

Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)

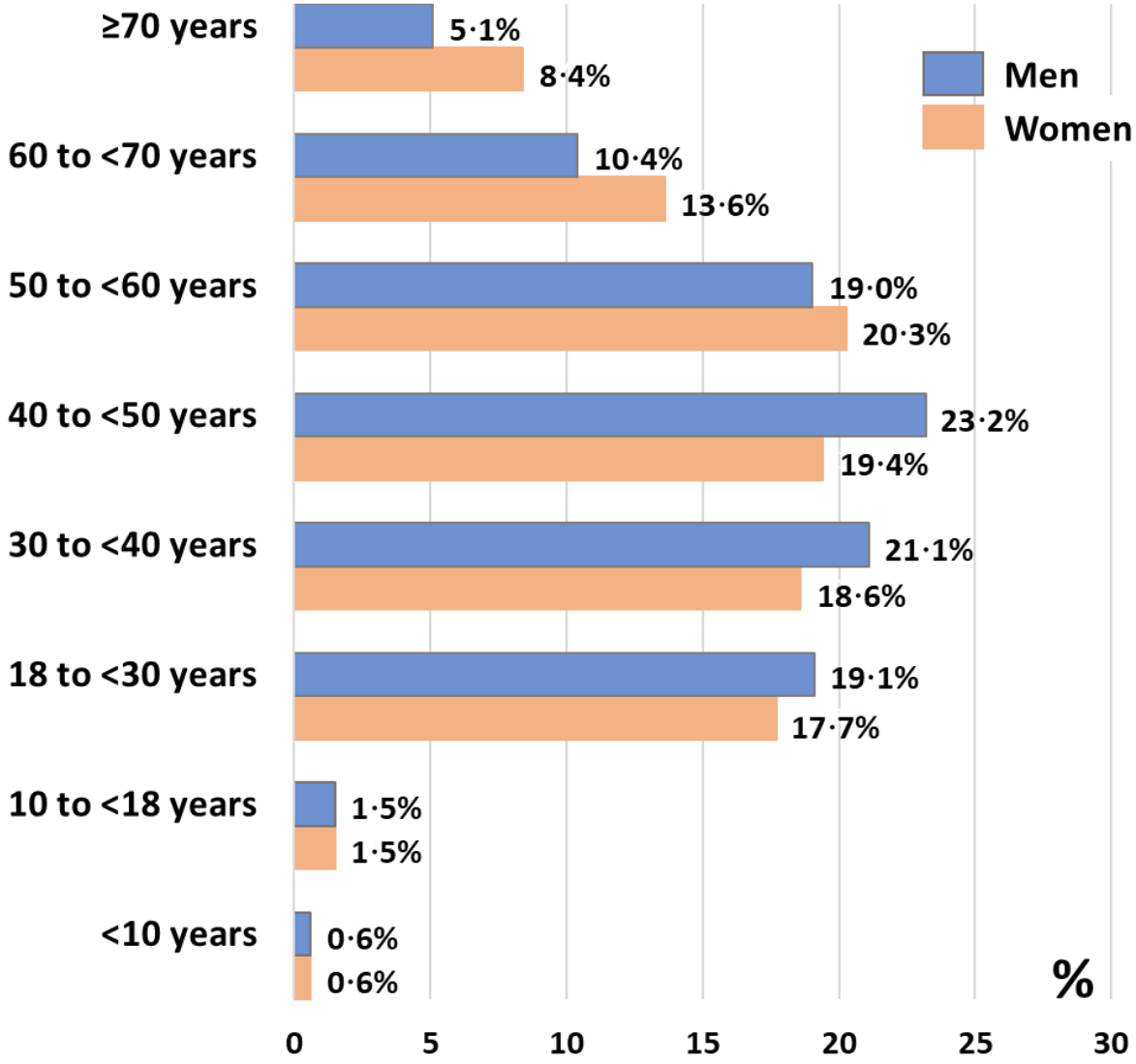
*EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)**

Vallejo-Vaz AJ, Stevens CAT, Lyons ARM, Dharmayat KS, Freiberger T, Hovingh GK, Mata P, Raal FJ, Santos RD, Soran H, Watts GF, Abifadel M, Aguilar-Salinas CA, Alhabib KF, Alkhnifsawi M, Almahmeed W, Alnouri F, Alonso R, Al-Rasadi K, Al-Sarraf A, Al-Sayed N, Araujo F, Ashavaid TF, Banach M, Béliard S, Benn M, Binder CJ, Bogsrud MP, Bourbon M, Chlebus K, Corral P, Davletov K, Descamps OS, Durst R, Ezhov M, Gaita D, Genest J, Groselj U, Harada-Shiba M, Holven KB, Kayikcioglu M, Khovidhunkit W, Lalic K, Latkovskis G, Laufs U, **Liberopoulos E,** Lima-Martinez MM, Lin J, Maher V, Marais AD, März W, Mirrakhimov E, Miserez AR, Mitchenko O, Nawawi H, Nordestgaard BG, **Panayiotou AG,** Paragh G, Petrulioniene Z, Pojskic B, Postadzhiyan A, Raslova K, Reda A, Reiner Z, Sadiq F, Sadoh WE, Schunkert H, Shek AB, Stoll M, Stroes E, Su TC, Subramaniam T, Susekov AV, Tilney M, Tomlinson B, Truong TH, Tselepis AD, Tybjærg-Hansen A, Vázquez Cárdenas A, Viigimaa M, Wang L, Yamashita S, Tokgozoglu L, Catapano AL, Ray KK;

On behalf of the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) Investigators.

EAS FHSC Investigators. *Lancet* 2021; 398(10312):1713-1725. doi: 10.1016/S0140-6736(21)01122-3.

Age at FH diagnosis among Adults with HeFH



n = 30,560 participants

Age at FH diagnosis

Median 44.4 years (IQR 32.5 – 56.5)

Men	**43.0 years** (32.0 – 54.4)
Women	**46.0 years** (33.0 – 58.3)

Mean difference: –2.5 years (95%CI –2.8, –2.1)

40.2% diagnosed **age <40 years**
(Men: 42.3%; Women: 38.4%)

2.1% diagnosed **age <18 years**

EAS FHSC Investigators. *Lancet* 2021;398(10312):1713-1725.

HELLAS FH REGISTRY

EAS FHSC
International collaboration towards understanding the contemporary burden of Familial Hypercolesterolaemia

Ελληνική Εταιρεία Αθηροσκλήρωσης
Hellenic Atherosclerosis Society

Ελληνική Εταιρία Αθηροσκλήρωσης

Τίτλος Μελέτης

Εθνικό Μητρώο Καταγραφής Ασθενών με Οικογενή Υπερχοληστερολαιμία –
The Hellenic Familial Hypercholesterolemia Registry: "Hellas-FH"

ΠΡΩΤΟΚΟΛΛΟ ΜΗΤΡΩΟΥ ΚΑΤΑΓΡΑΦΗΣ ΑΣΘΕΝΩΝ

Εξέλιξη HELLAS-FH Registry

3255

2020
EAS FHSC

2018
1000 ΑΣΘΕΝΕΙΣ

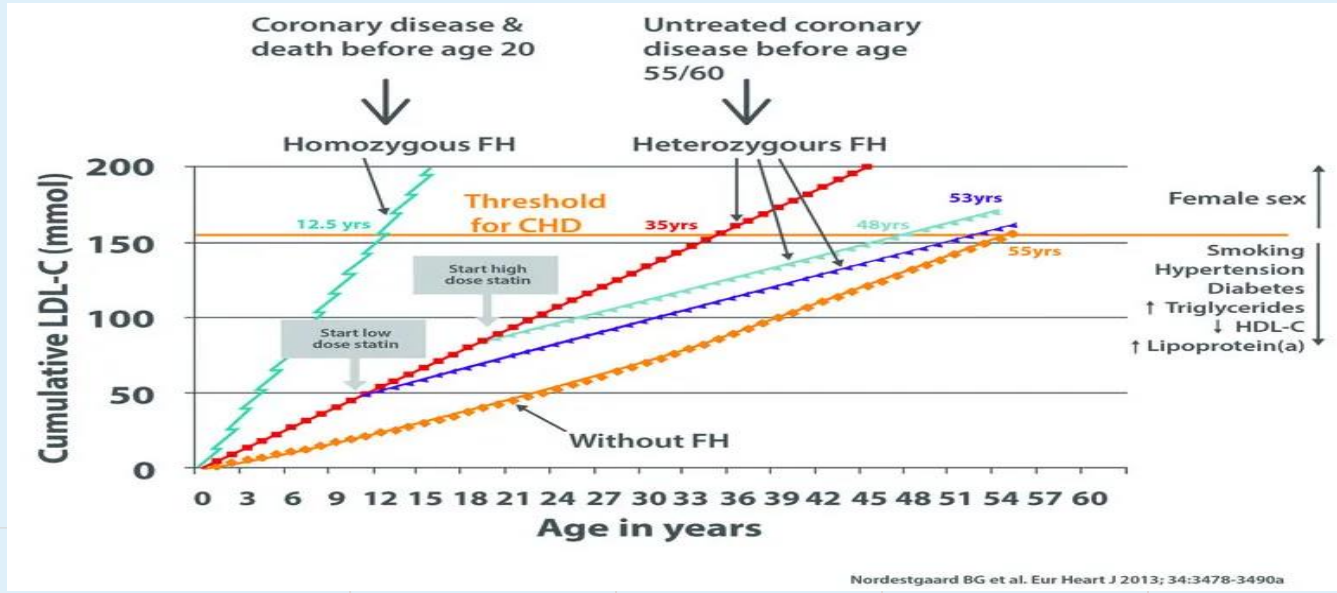
2016
Έναρξη μητρώου

HELLAS FH REGISTRY

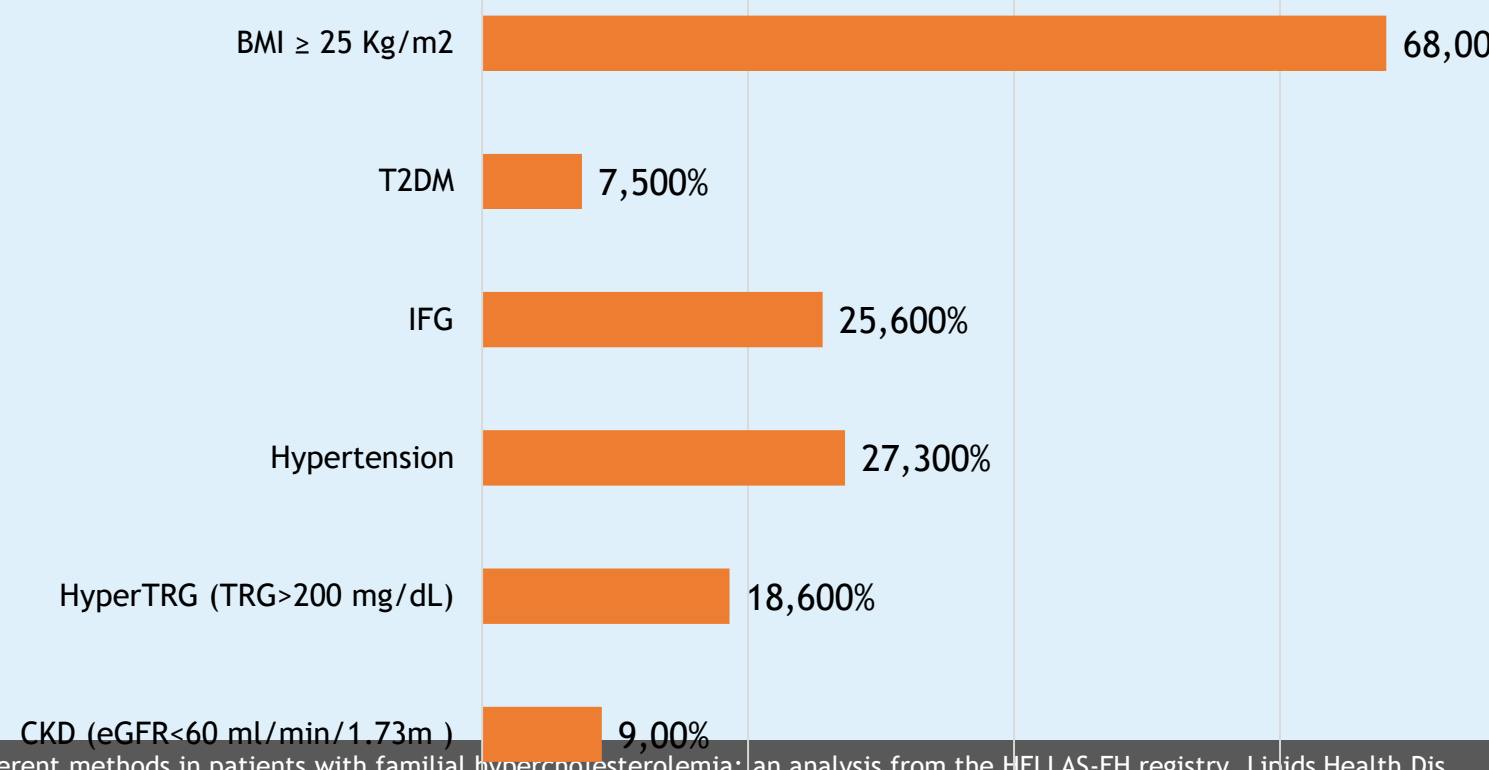
HELLAS-FH: Results

- Οι ασθενείς με FH καθυστερούν να διαγνωσθούν

44 έτη



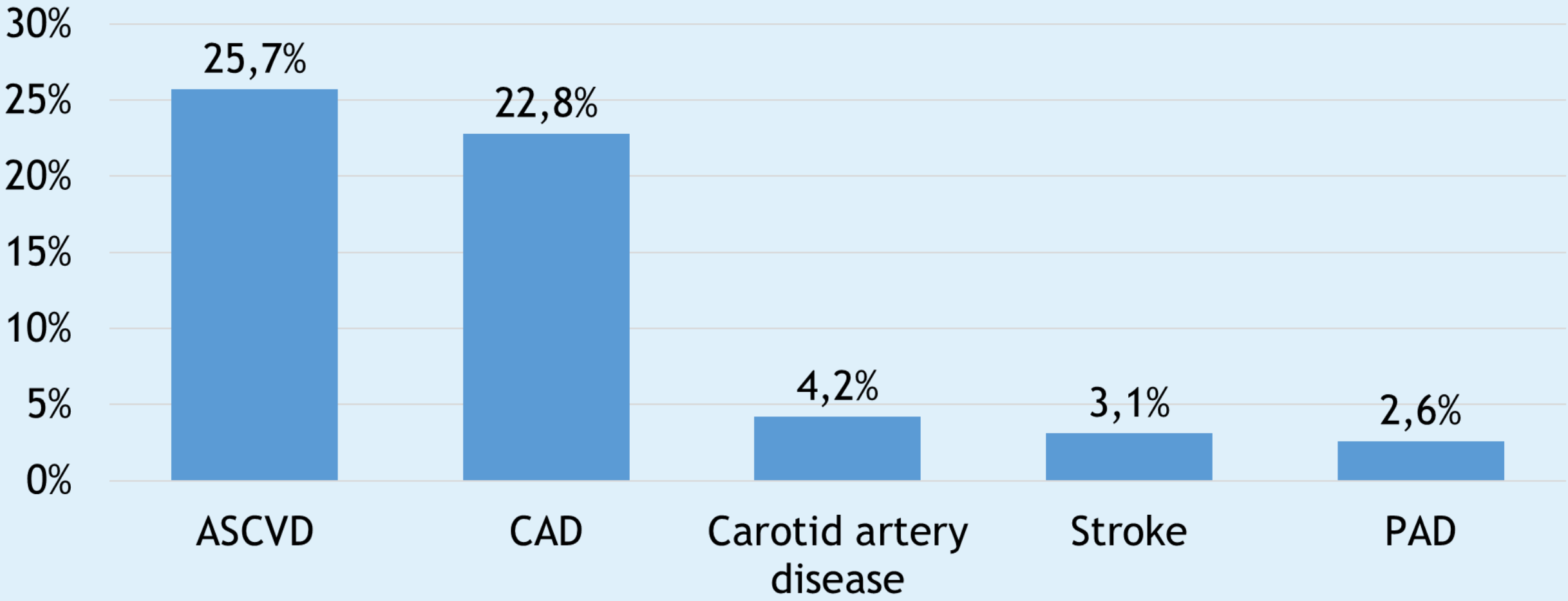
- Οι ασθενείς με FH έχουν συχνά συνοσηρότητες



Rizos CV et al. Achieving low-density lipoprotein cholesterol targets as assessed by different methods in patients with familial hypercholesterolemia: an analysis from the HELLAS-FH registry. Lipids Health Dis. 2020 May 28;19(1):114.

HELLAS-FH: Results

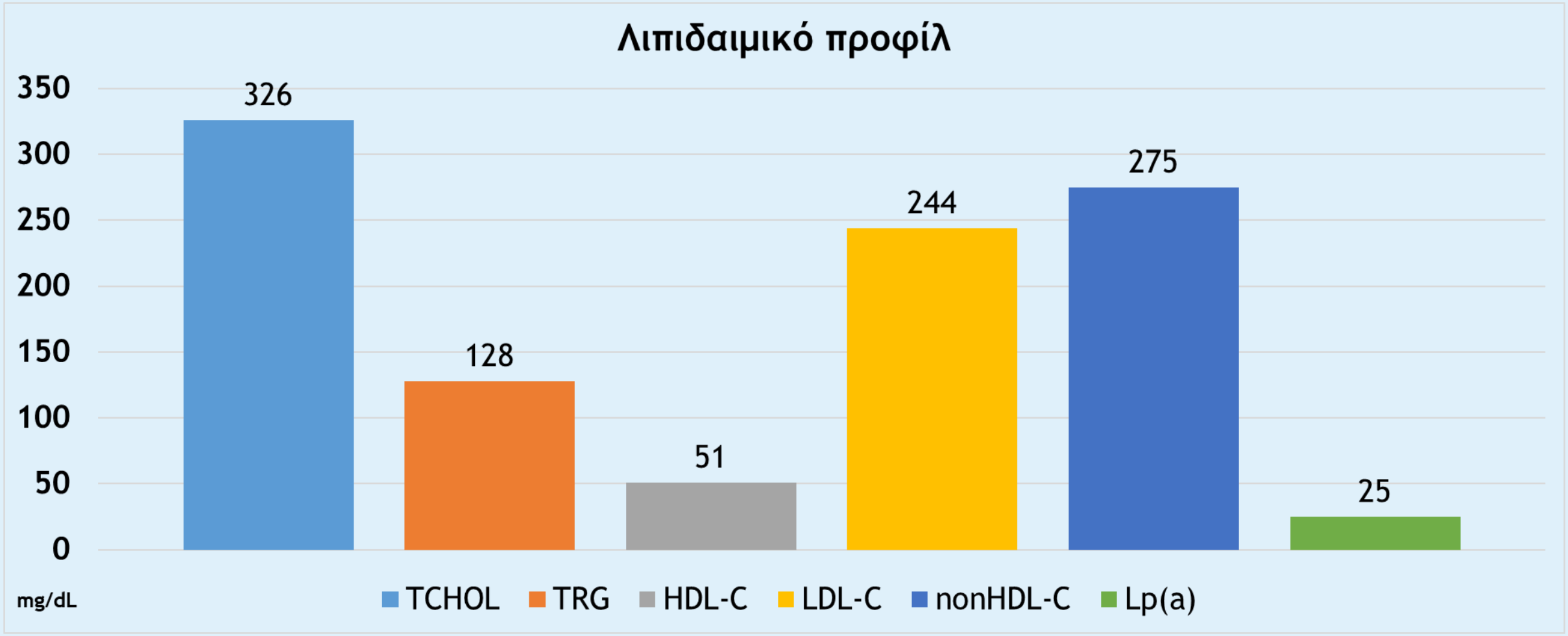
- Οι ασθενείς με FH έχουν αυξημένο επιπολασμό ASCVD



Rizos CV et al. Achieving low-density lipoprotein cholesterol targets as assessed by different methods in patients with familial hypercholesterolemia: an analysis from the HELLAS-FH registry. Lipids Health Dis. 2020 May 28;19(1):114.
Anagnostis P et al. Prevalence of Non-coronary Heart Disease in Patients with Familial Hypercholesterolemia: An Analysis from the HELLAS-FH. Curr Pharm Des. 2021;27(21):2537-2544.

HELLAS-FH: Results

- Οι ασθενείς με FH έχουν πολύ αυξημένα επίπεδα χοληστερόλης



Rizos CV et al. Achieving low-density lipoprotein cholesterol targets as assessed by different methods in patients with familial hypercholesterolemia: an analysis from the HELLAS-FH registry. Lipids Health Dis. 2020 May 28;19(1):114.

www.hellasfh.gr

HellasFH

ΠΑΓΚΟΣΜΙΑ ΗΜΕΡΑ
ΟΙΚΟΓΕΝΟΥΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑΣ
Familial Hypercholesterolemia (FH)

24 ΣΕΠΤΕΜΒΡΙΟΥ

Μάθε τι σημαίνει, μπορεί να σε αφορά!

www.hellasfh.gr

Τι είναι η ΟΙΚΟΓΕΝΗΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ (FH);

Είναι η πιο συχνή **κληρονομική** νόσος του μεταβολισμού (1:250 άτομα).
Οι άνθρωποι με οικογενή υπερχοληστερολαιμία έχουν γεννηθεί
με πολύ αυξημένα επίπεδα LDL ("κακής") χοληστερόλης.

Πρώιμα Καρδιακά Επεισόδια

Άνδρες με FH χωρίς θεραπεία έχουν 50% πιθανότητα να εμφανίσουν καρδιακό επεισόδιο έως την ηλικία των 50 ετών.

Γυναίκες με FH χωρίς θεραπεία έχουν 30% πιθανότητα να εμφανίσουν καρδιακό επεισόδιο έως την ηλικία των 60 ετών.

Αυξημένος Κίνδυνος

Καρδιακού Επεισοδίου

Εγκεφαλικού Επεισοδίου

Πρόωρος θάνατος

ΓΝΩΡΙΣΤΕ ΤΑ ΣΗΜΑΔΙΑ

Πολύ υψηλή LDL ("κακή") χοληστερόλη σε μικρή ηλικία.
>160 mg/dL στα παιδιά
>190 mg/dL στους ενήλικες

Οζίδια
στο δέρμα
στους τένοντες
στα βλέφαρα

Γεροντότοξο:
Εμφάνιση λευκού δακτυλίου στον βολβό των ματιών.

ΘΕΡΑΠΕΙΑ

Φαρμακευτική αγωγή (στατίνες, δέσμευση χολικών οξέων, αναστολείς απορρόφησης της χοληστερόλης, αναστολείς PCSK9)

Θεραπεία αφαίρεσης της LDL από την κυκλοφορία του αίματος σε πολύ σοβαρές περιπτώσεις

Διατροφή & άσκηση

Συνεχής παρακολούθηση

Αν ένας από τους δύο γονείς πάσχει από Οικογενή Υπερχοληστερολαιμία, υπάρχει 50% πιθανότητα το κάθε παιδί να την κληρονομήσει. Σκεφτείτε τον έγκαιρο έλεγχο των παιδιών, αν πάσχετε από την ασθένεια.

HoFH

Ομόζυγη Οικογενής Υπερχοληστερολαιμία

μια σπάνια θανατηφόρα μορφή Οικογενούς Υπερχοληστερολαιμίας

ΕΙΝΑΙ ΠΑΓΚΟΣΜΙΑ

Η HoFH είναι μια σπάνια πάθηση που επηρεάζει περίπου 1 στους 300.000 ανθρώπους παγκοσμίως.

ΕΙΝΑΙ ΚΛΗΡΟΝΟΜΙΚΗ

Η HoFH είναι κληρονομική. Αν κληρονομήσεις την μετάλλαξη και από τους δύο γονείς τότε πάσχεις από Ομόζυγο Οικογενή Υπερχοληστερολαιμία

ΜΠΟΡΕΙ ΝΑ ΔΙΑΓΝΩΣΘΕΙ

Για την διάγνωση της HoFH χρειάζεται μια απλή εξέταση αίματος, μια κλινική εξέταση από τον γιατρό και ένα οικογενειακό ιστορικό. Η HoFH μπορεί να επιβεβαιωθεί με γενετικό έλεγχο. Τα κλινικά σημεία και τα συμπτώματα της HoFH, ακόμα και οι τιμές της LDL χοληστερόλης, διαφέρουν σε κάθε άνθρωπο.

ΠΡΟΚΑΛΕΙ ΠΡΩΙΜΗ ΝΟΣΟ

Εάν αφεθεί χωρίς θεραπεία, είναι πιθανό να εμφανισθεί καρδιακή προσβολή ή αιφνίδιος θάνατος ή στένωση της αορτικής βαλβίδας ακόμα και στην εφηβεία.

ΕΞΑΙΡΕΤΙΚΑ ΥΨΗΛΗ ΧΟΛΗΣΤΕΡΟΛΗ

Η HoFH οδηγεί σε επιθετική αθηροσκλήρωση (βλάβη των αρτηριών από την εναπόθεση λιπιδίων στο τοίχωμά τους).

Η HoFH ΘΕΡΑΠΕΥΕΤΑΙ

Η αλλαγές στον τρόπο ζωής δεν αρκούν για να θεραπεύσουν μια τόσο σοβαρή πάθηση.. Απαιτείται ένας σωστός συνδυασμός φαρμακευτικής αγωγής και σε ορισμένες περιπτώσεις LDL αφαίρεσης από το αίμα. Πάντα να συμβουλεύεστε το γιατρό σας.

ΘΕΡΑΠΕΙΕΣ

Η χορήγηση υπολιπιδαιμικής θεραπείας είναι πολύ αποτελεσματική. Περιλαμβάνει την χορήγηση στατινών, εζετιμίμπης, κολεσεβαλάμης, αναστολέων της PCSK9 και λομιταπίδης.

LDL ΑΦΑΙΡΕΣΗ

Με αυτή τη διαδικασία αφαιρείται η LDL από το αίμα.

Ελληνική Εταιρεία Αθηροσκλήρωσης, Ίωνος Δραγούμη 3, Αθήνα, ΤΚ. 11528, Τηλ. 2017210055, E-mail: info@atherosclerosis.gr

ΠΩΣ ΘΑ ΘΕΡΑΠΕΥΣΟΥΜΕ ΤΟΝ ΑΣΘΕΝΗ;

Atherosclerosis Plus 55 (2024) 74–92

Contents lists available at ScienceDirect

Atherosclerosis Plus

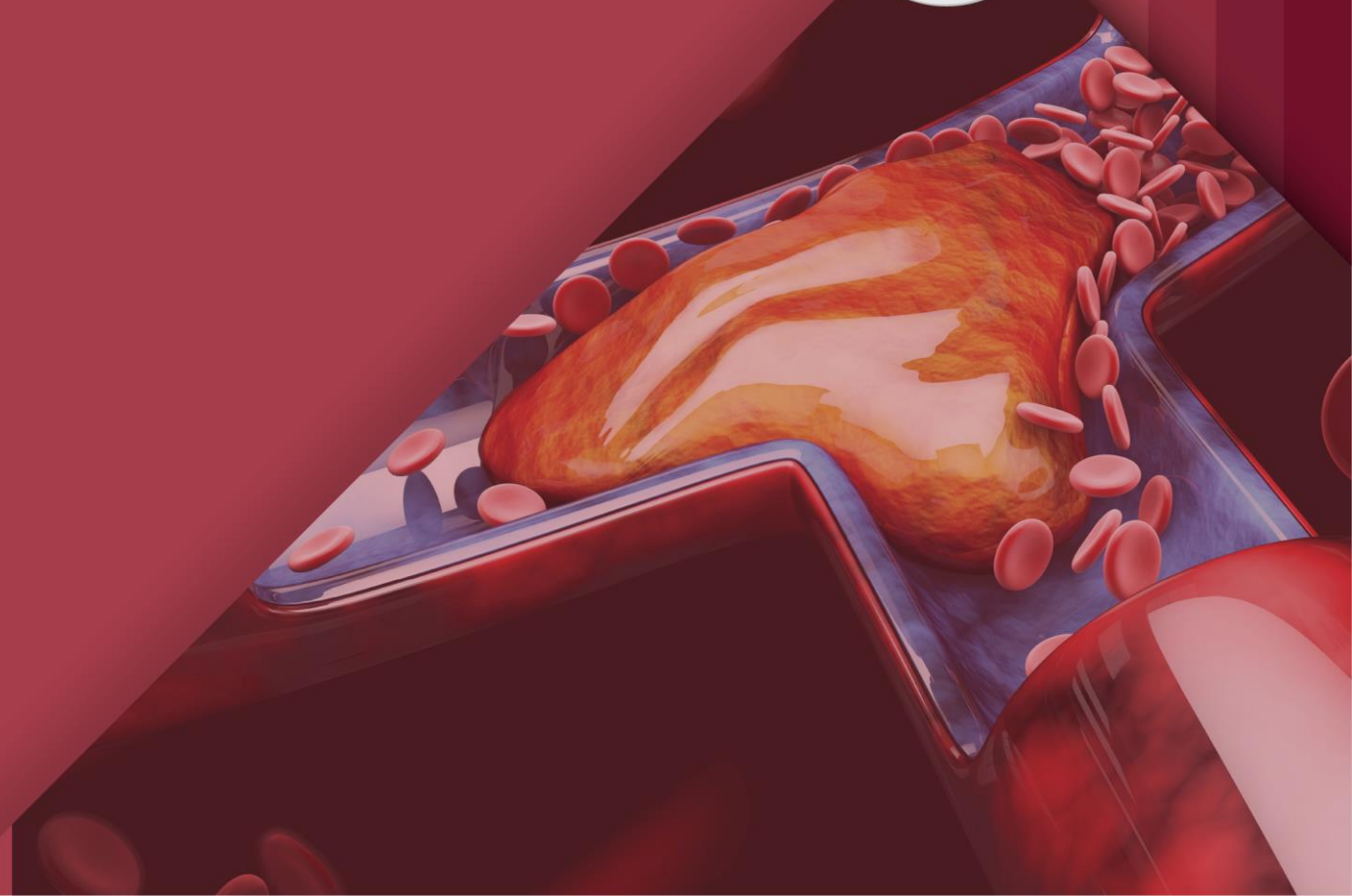
journal homepage: www.elsevier.com/locate/atherosclerosis

Executive summary of the Hellenic Atherosclerosis Society guidelines for the diagnosis and treatment of dyslipidemias - 2023

Katsiki N[a,b,1], Filippatos Td[c,1], Vlachopoulos C[d], Panagiotakos D[e], Milionis H[f], Tselepis A[g], Garoufi A[h], Rallidis L[i], Richter D[j], Nomikos T[e], Kolovou G[k], Kypreos K[b,l], Chrysohoou C[m], Tziomalos K[n], Skoumas I[o], Koutagiar I[p], Attilakos A[q], Papagianni M[r], Boutari C[s], Kotsis V[t], Pitsavos C[u], Elisaf M[v,2], Tsioufis K[w], Liberopoulos E[x,*]

https://atherosclerosis.gr/slide-set-anatheorimenon-kateythyntirion-odigion/

Hellenic Atherosclerosis Society Guidelines for the Diagnosis & Treatment of Dyslipidemias 2023



LDL-C TARGETS 2023

CVD RISK

VERY HIGH RISK

- ESTABLISHED ASCVD
- DIABETES WITH TARGET ORGAN DAMAGE or ≥3 MAJOR RISK FACTORS
- FAMILIAL HYPERCHOLESTEROLEMIA PLUS ≥1 MAJOR RISK FACTOR
- CKD 4-5
- HELLENIC SCORE II ≥10%

↓ LDL-C <55 mg/dL
PLUS
LDL-C >50%

HIGH RISK

- SEVERE RISK FACTOR
- FH WITHOUT ANY MAJOR RISK FACTOR
- DIABETES ≥10 YEARS PLUS ≥1 MAJOR RISK FACTOR
- CKD 3
- AUTOIMMUNE RHEUMATIC DISEASE/HIV INFECTION
- HELLENIC SCORE II ≥5-<10%

↓ LDL-C <70 mg/dL
PLUS
LDL-C ~50%

MODERATE RISK

- DIABETES <10 YEARS IN PATIENTS <50 YEARS
- HELLENIC SCORE II ≥1-<5%

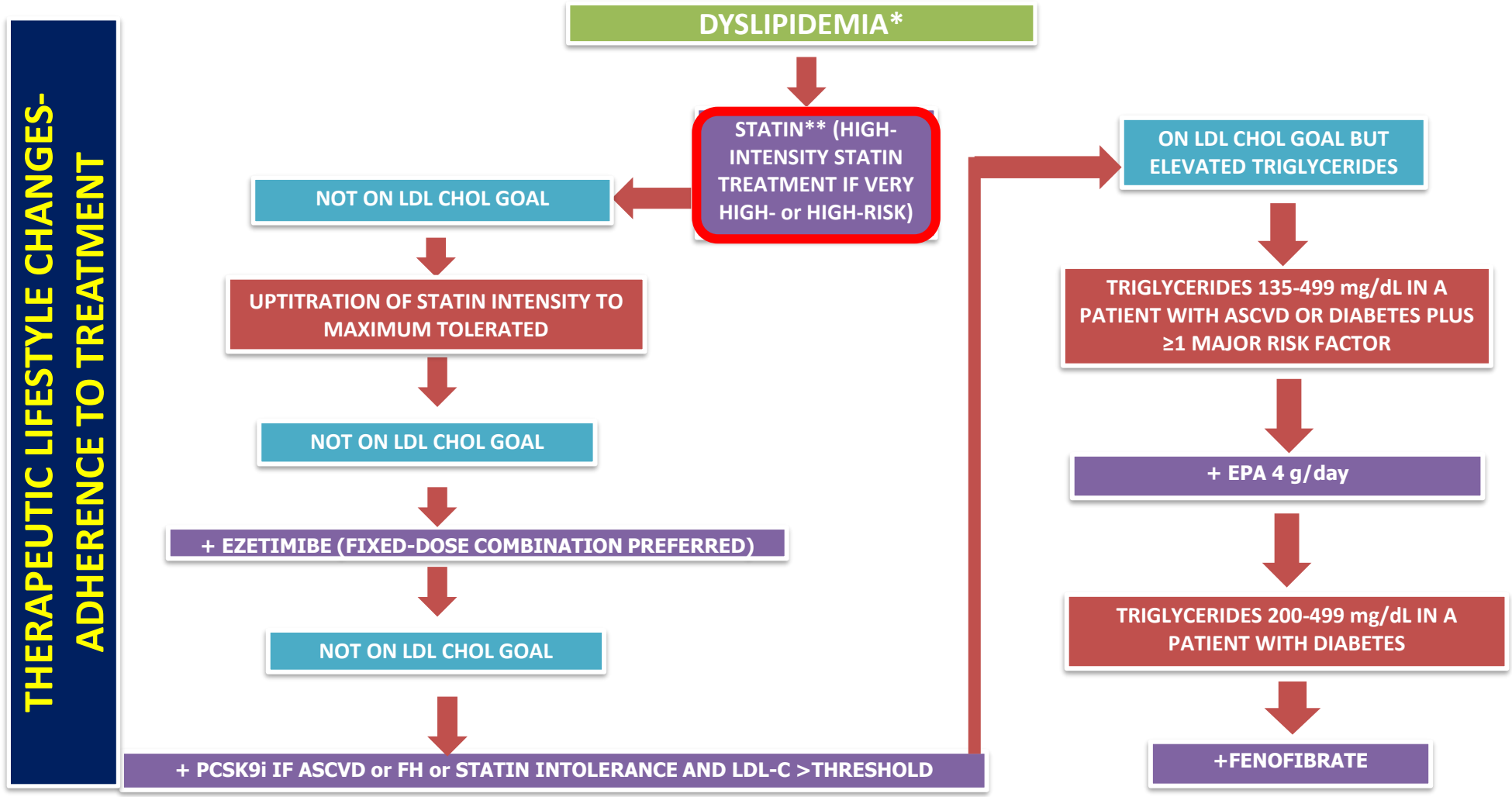
LDL-C <100 mg/dL

LOW RISK

HELLENIC SCORE II <1%

LDL-C <116 mg/dL

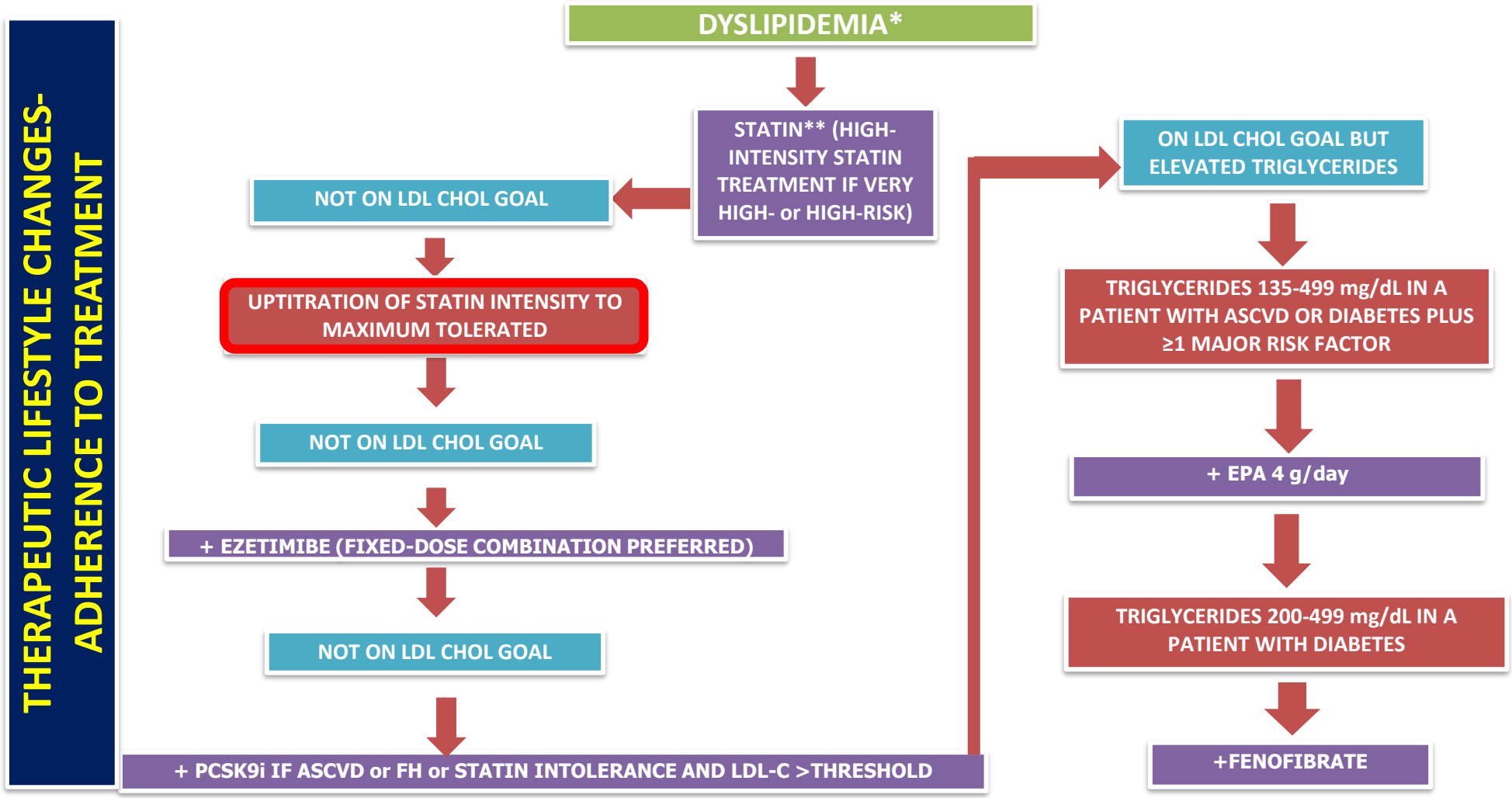
ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA 2023



*IF TRIGLYCERIDES>500 mg/dL → START IMMEDIATELY WITH FENOFIBRATE + STATIN ± HIGHLY PURIFIED OMEGA-3 FATTY ACIDS

**IF LDL-C>110 mg/dL IN A PATIENT WITH ASCVD →START IMMEDIATELY WITH HIGH INTENSITY STATIN PLUS EZETIMIBE (FIXED-DOSE COMBINATION PREFERRED)

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA 2023



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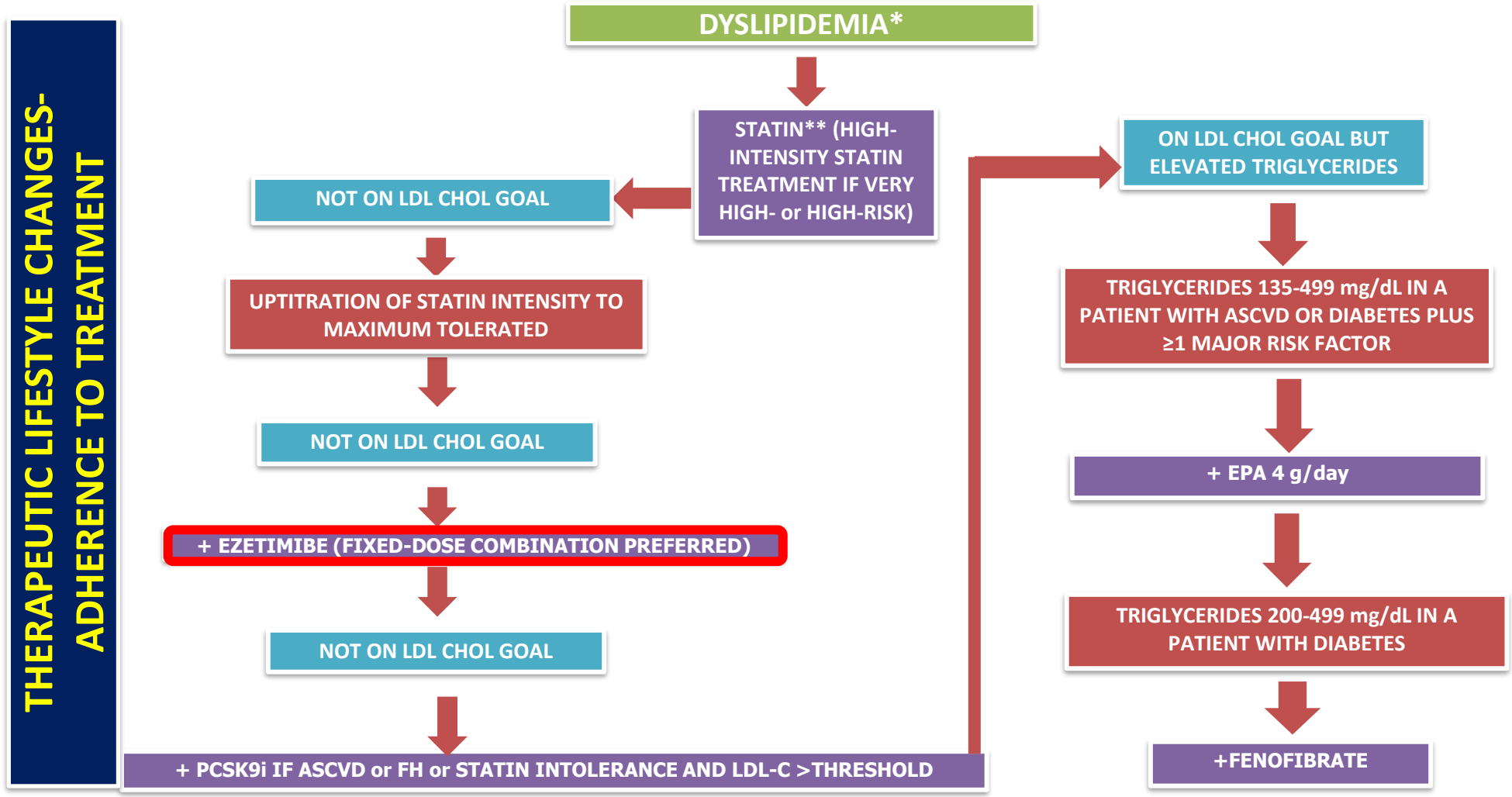

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ΑΝΤΙΜΕΤΩΠΙΖΟΝΤΑΣ ΤΟΝ ΑΣΘΕΝΗ ΜΕ ΟΙΚΟΓΕΝΗ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ

ROSUVASTATIN 40 mg X 1

↓ LDL CHOL κατά ~55% → LDL CHOL 126 mg/dL

ΑΜΕΣΗ ΕΝΑΡΞΗ!

ΕΠΙΤΥΓΧΑΝΟΝΤΑΣ ΤΟΥΣ ΣΤΟΧΟΥΣ ΤΗΣ ΘΕΡΑΠΕΙΑΣ

ΠΡΟΣΘΗΚΗ EZETIMIBE 10 mg X 1

↓ LDL CHOL κατά 20% ⇒ LDL CHOL 101 mg/dL

ΠΡΟΣΟΧΗ! ΣΥΜΒΟΥΛΗ ΓΙΑ ΔΙΑΚΟΠΗ ΣΤΑΤΙΝΗΣ + ΕΖΕΤΙΜΙΜΠΗΣ ~3 ΜΗΝΕΣ ΠΡΙΝ ΠΡΟΓΡΑΜΜΑΤΙΣΜΟ ΕΠΟΜΕΝΗΣ ΚΥΗΣΗΣ

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ΣΤΗ ΔΙΑΡΚΕΙΑ ΤΗΣ ΚΥΗΣΗΣ ΚΑΙ ΤΗΣ ΓΑΛΟΥΧΙΑΣ ΕΠΙΤΡΕΠΕΤΑΙ ΜΟΝΟ Η ΚΟΛΕΣΕΒΕΛΑΜΗ-LDL ΑΦΑΙΡΕΣΗ ΣΕ ΒΑΡΙΕΣ ΠΕΡΙΠΤΩΣΕΙΣ

FDA U.S. FOOD & DRUG ADMINISTRATION

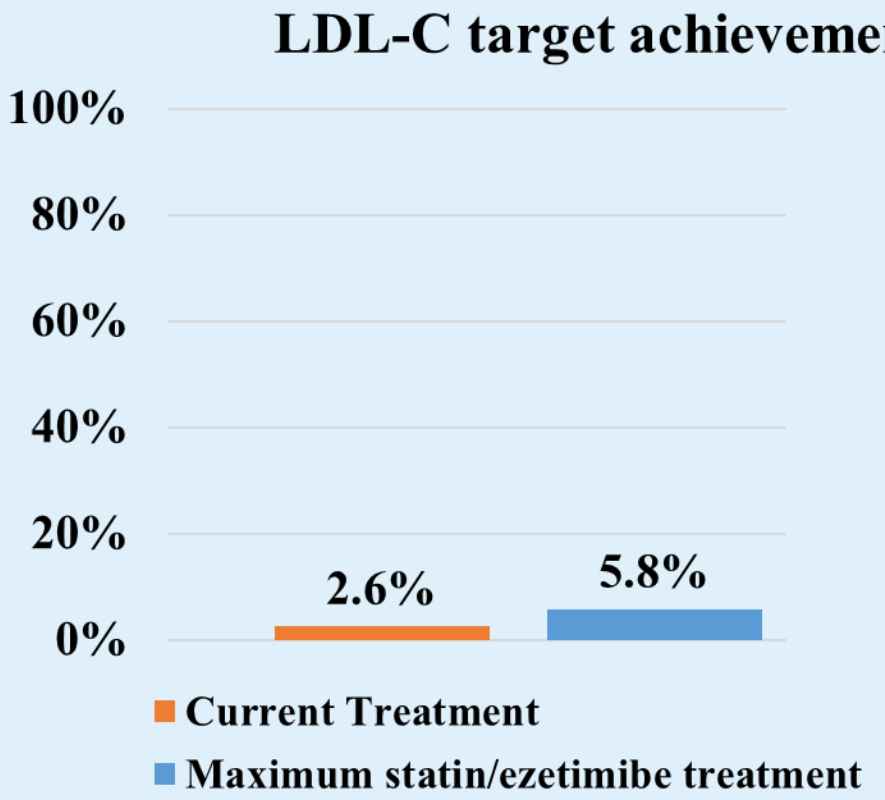
Statins: Drug Safety Communication - FDA Requests Removal of Strongest Warning Against Using Cholesterol-lowering Statins During Pregnancy

[Posted 07/20/2021]

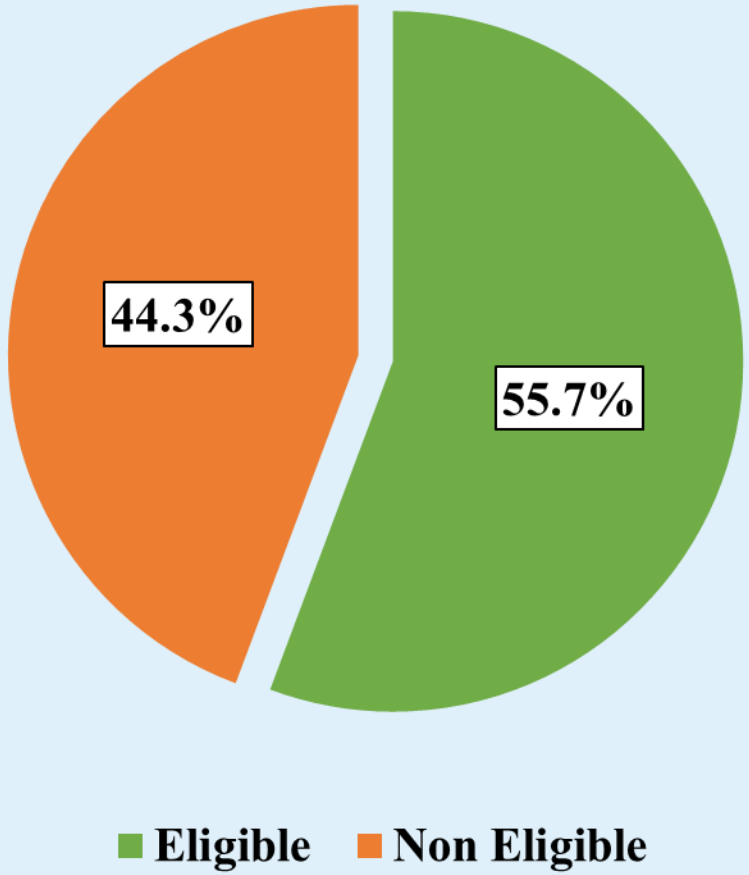
FDA expects removing the contraindication will enable health care professionals and patients to make individual decisions about benefit and risk, especially for those at very high risk of heart attack or stroke. This includes patients with homozygous familial hypercholesterolemia and those who have previously had a heart attack or stroke.

HELLAS-FH: Results

- Οι ασθενείς με FH χρήζουν επιπρόσθετης υπολιπιδαιμικής θεραπείας

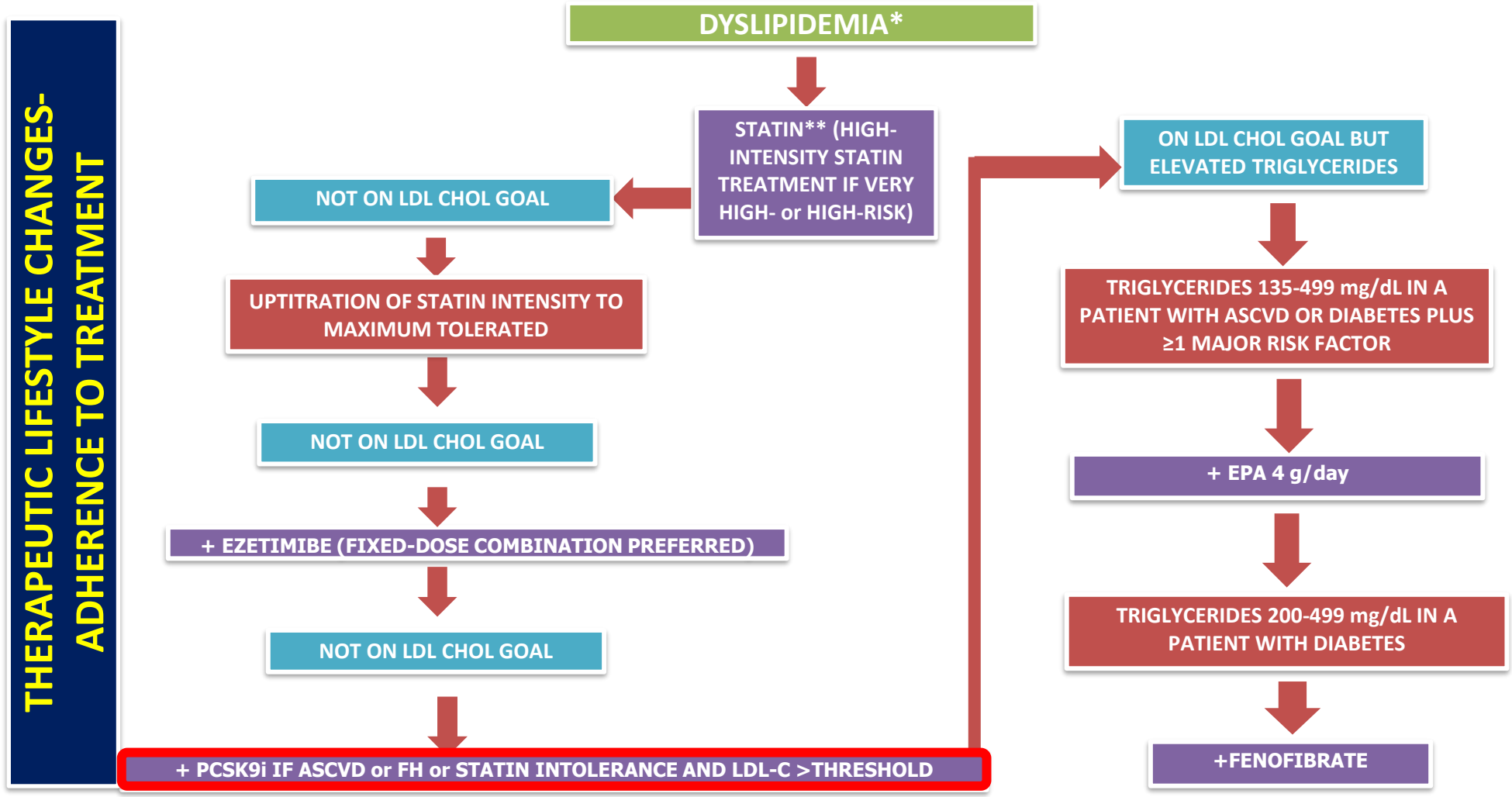


- Οι ασθενείς με FH συχνά χρήζουν θεραπείας με PCSK9i



Rizos CV et al. LDL cholesterol target achievement in heterozygous familial hypercholesterolemia patients according to 2019 ESC/EAS lipid guidelines: Implications for newer lipid-lowering treatments. Int J Cardiol. 2021 Oct 21:S0167-5273(21)01578-3. doi: 10.1016/j.ijcard.2021.10.024

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA 2023



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**IF LDL-C>110 mg/dL IN A PATIENT WITH ASCVD →START IMMEDIATELY WITH HIGH INTENSITY STATIN PLUS EZETIMIBE (FIXED-DOSE COMBINATION PREFERRED)

ELIGIBLE PATIENTS FOR PCSK9 INHIBITORS

1. ASCVD PLUS FH OR RECURRENT/PROGRESSIVE DISEASE DURING THE LAST 2 YEARS OR PREMATURE ASCVD (MEN <45/WOMEN <55 YEARS) WITH LDL-C ≥70 mg/dL

2. OTHER ASCVD AND LDL-C ≥100 mg/dL

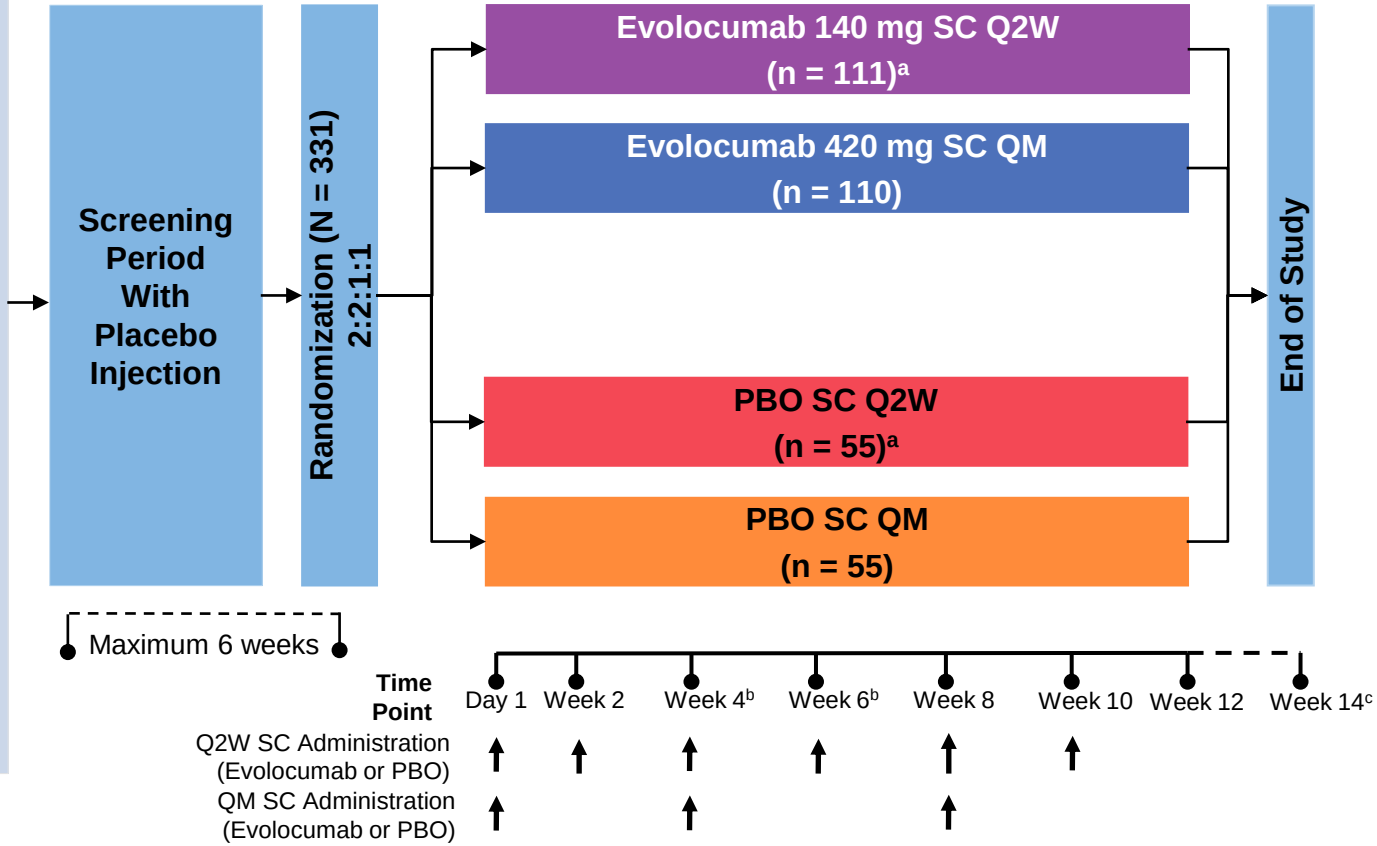
3. FAMILIAL HYPERCHOLESTEROLEMIA AND LDL-C ≥100 mg/dL

ON HIGH-INTENSITY STATIN TREATMENT (ATORVASTATIN 40/80 mg, ROSUVASTATIN 20/40 mg) PLUS EZETIMIBE 10 mg OR MAXIMUM TOLERATED STATIN PLUS EZETIMIBE WHEN STATIN INTOLERANT

RedUction of LDL-C With PCSK9 InhibiTion in HEteRozygous Familial HyperchOlesteRolemia Disorder Study-2 (RUTHERFORD-2)

Key Inclusion Criteria
- Patients 18–80 years with HeFH
- Stable dose of statin with/without approved lipid-lowering therapy for ≥ 4 weeks before screening

Key Exclusion Criteria
- Known clinical/genetic diagnosis of homozygous FH
- NYHA class III or IV HF; LVEF < 30%
- Acute or unstable cardiac event within 3 months of randomization
- Uncontrolled hypertension; type1DM; moderate-to-severe renal dysfunction; active liver disease (> 2 x ULN); CK > 3 x ULN

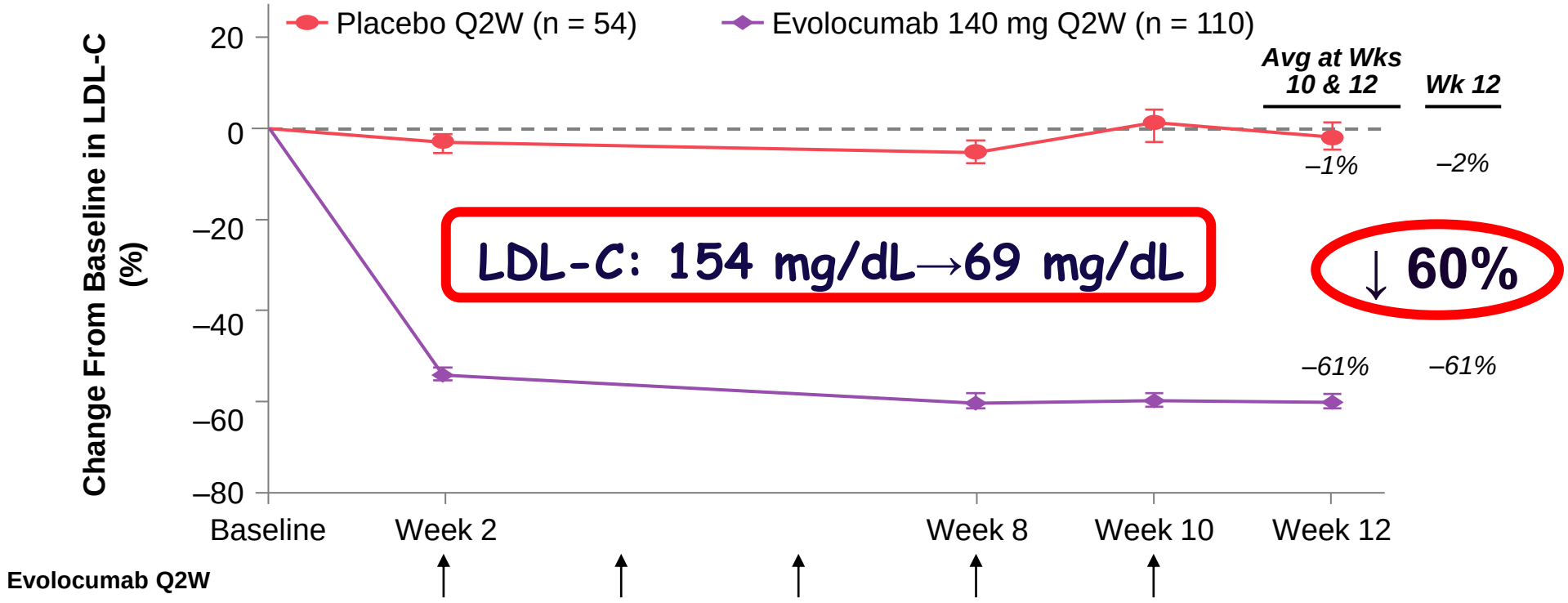


[a]One patient in each of the Q2W dosing groups withdrew consent before treatment and did not receive study drug; the remaining 329 patients received ≥ 1 dose of study drug. [b]Injections were self-administered at home. [c]Final AE data were collected by telephone for patients who received the study drug Q2W.

AE = adverse event; CK = creatine kinase; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PBO = placebo; Q2W = once every 2 weeks; QM = once monthly; SC = subcutaneous; type 1 DM = type 1 diabetes mellitus; ULN = upper limit of normal.

Raal FJ, et al. *Lancet*. 2015; 385:331-340.

Evolocumab Q2W Significantly Reduces LDL-C by 61% in Patients With HeFH



The treatment difference of evolocumab compared with placebo at the mean of weeks 10 and 12 and at week 12 was –60% and –59%, respectively (*P* < 0.0001)

The arrows below the graph represent time points of evolocumab administration. Error bars are standard errors. The percentage change in LDL-C was ascertained by the Friedewald formula, with reflexive testing through preparative ultracentrifugation when the calculated LDL-C was ≤ 40 mg/dL (1.0 mmol/L) or triglyceride concentration was ≥ 400 mg/dL (4.5 mmol/L).

Avg = average; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Q2W = once every 2 weeks; Wk = week.

Adapted from Raal FJ, et al. *Lancet*. 2015;385:331-340.

ΕΠΙΤΥΓΧΑΝΟΝΤΑΣ ΤΟΥΣ ΣΤΟΧΟΥΣ ΤΗΣ ΘΕΡΑΠΕΙΑΣ

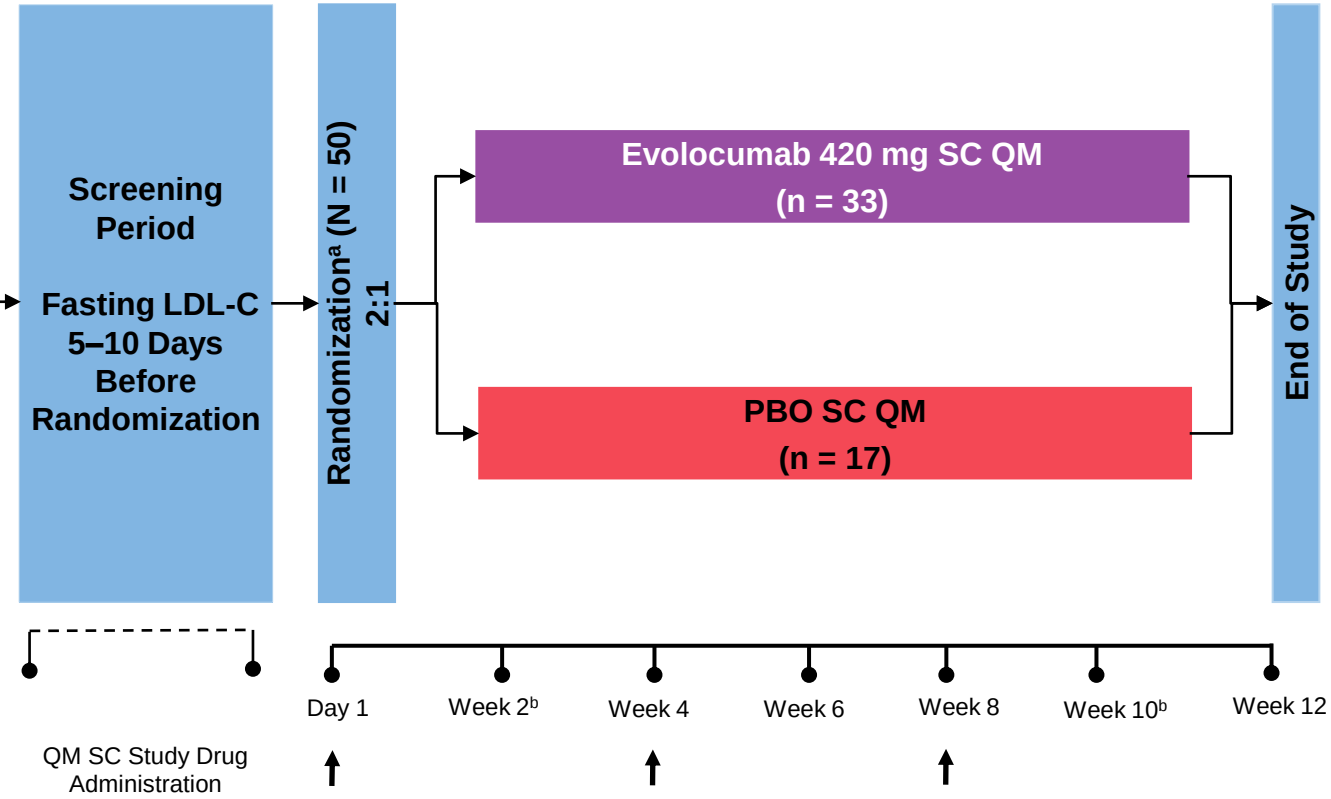
ΠΡΟΣΘΗΚΗ EVOLOCUMAB 140 mg Q2W

↓ LDL CHOL κατά 60% → LDL CHOL 41 mg/dL

Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities Part B (TESLA)

Key Inclusion Criteria
- Male and female ≥ 12 to ≤ 80 years with **homozygous FH**
- Fasting LDL-C ≥ 130 mg/dL
- Fasting TG ≤ 398 mg/dL
- Body weight ≥ 88 pounds

Key Exclusion Criteria
- Lipoprotein apheresis within 8 weeks before screening
- Use of mipomersen or lomitapide within the preceding 5 months
- NYHA class III or IV HF; LVEF < 30%
- Uncontrolled serious cardiac arrhythmia/MI in past 3 months
- Uncontrolled hypertension



[a]Randomization stratified by screening LDL-C (< 425 mg/dL or ≥ 425 mg/dL)
[b]Week 2 and week 10 study visits were optional. 1 mmol/L LDL-C = 38.6 mg/dL; 1 mmol/L TG = 88.5 mg/dL.

AE = adverse event; FH = familial hypercholesterolemia; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PBO = placebo; QM = once monthly; SC = subcutaneous.

Raal FJ, et al. *Lancet*. 2015; 385:341-350.

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

Frederick J Raal, Narimon Honarpour, Dirk J Blom, G Kees Hovingh, Feng Xu, Rob Scott, Scott M Wasserman, Evan A Stein, for the TESLA Investigators*

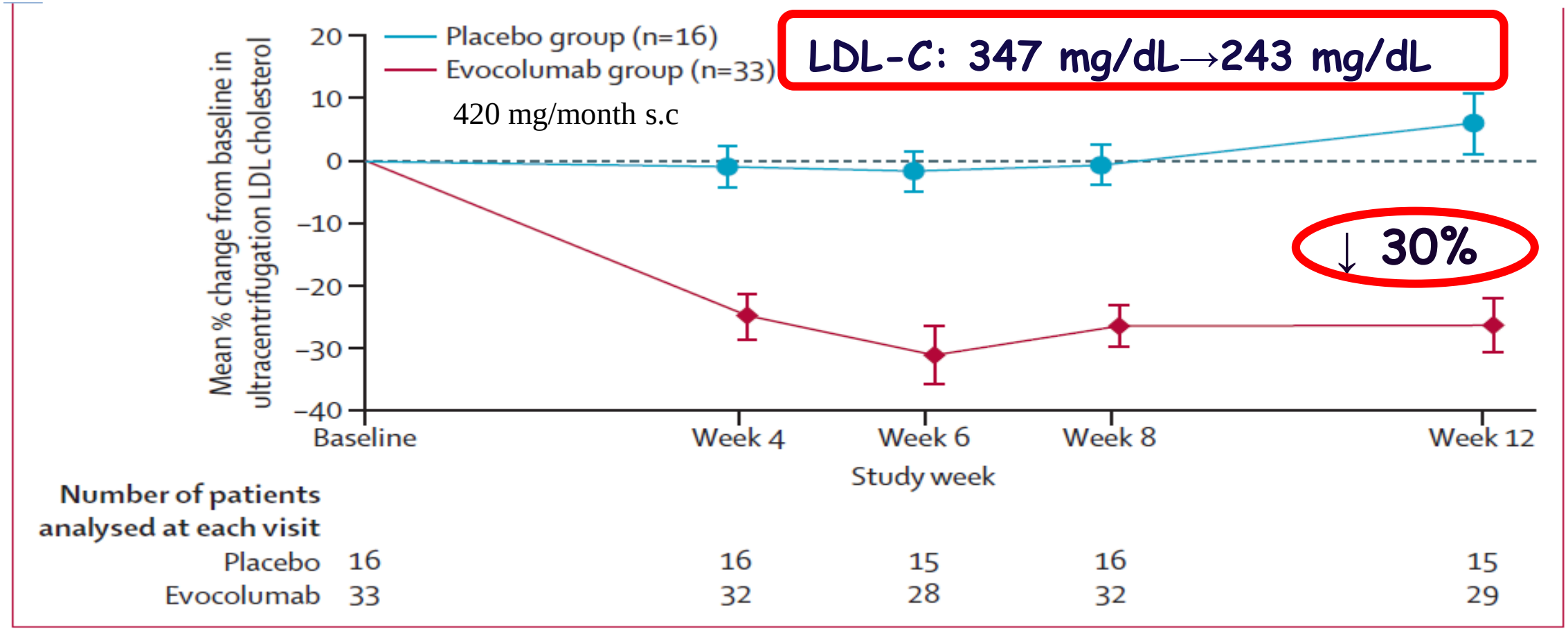
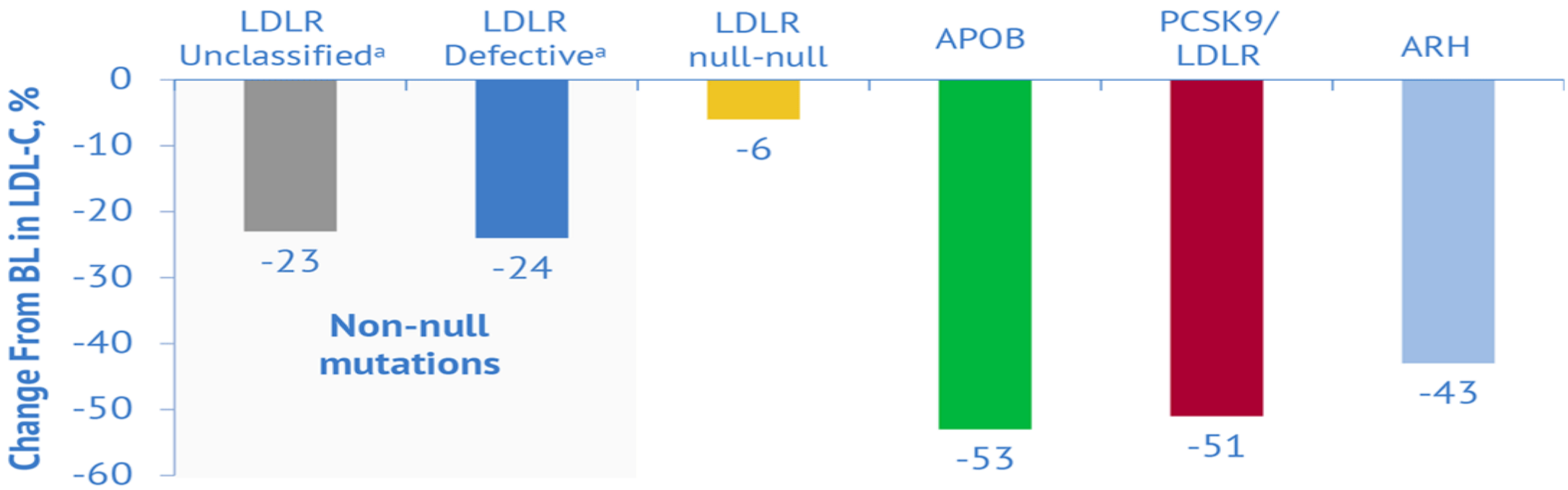


Figure 2: Mean percentage change in ultracentrifugation LDL cholesterol concentration from baseline to week 12

www.thelancet.com Published online October 2, 2014

Impact of Mutation Status on Therapeutic Efficacy of PCSK9 Inhibitors

TAUSSIG: Evolocumab in Patients With HoFH (N = 54)[6]



Patients with LDLR null-null mutations experienced lower reduction in LDL-C levels

[a] One or both alleles.

The NEW ENGLAND JOURNAL of MEDICINE

Evolocumab in Pediatric Heterozygous FH

DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

157

Patients 10–17 years of age with heterozygous familial hypercholesterolemia

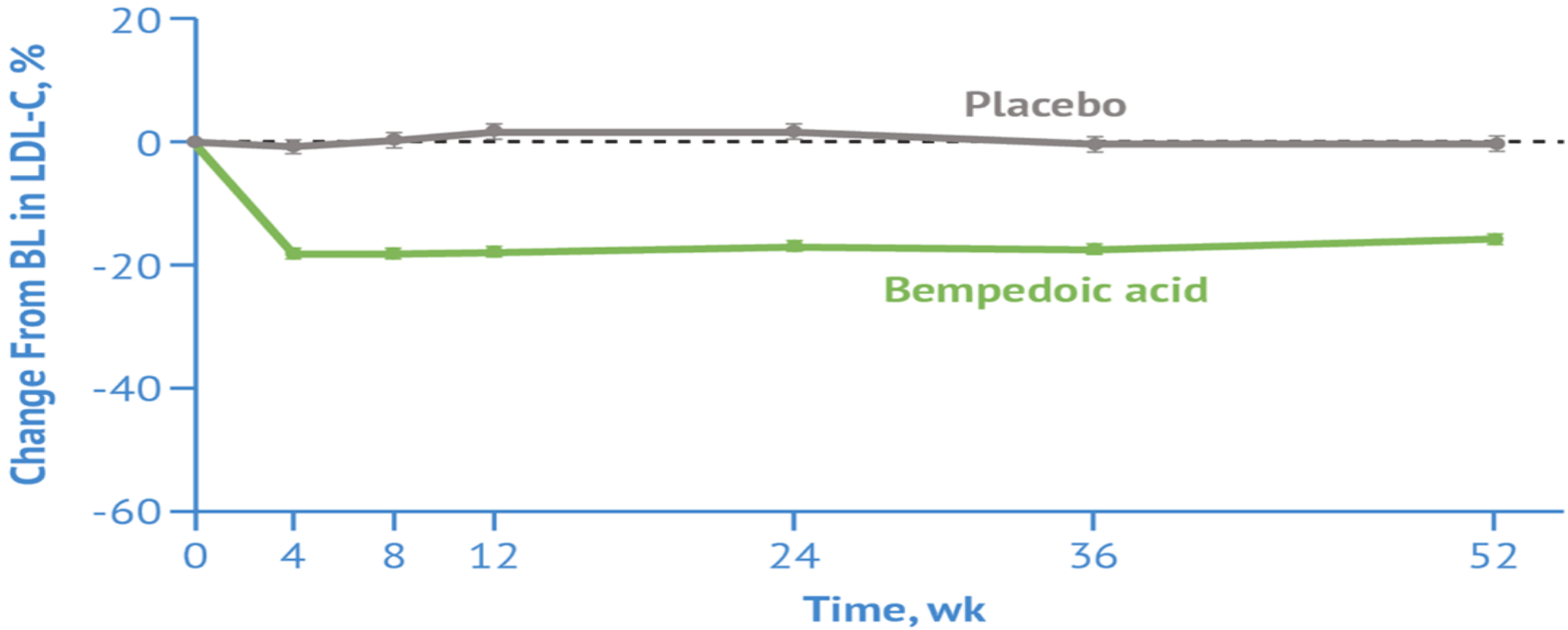
	Subcutaneous Evolocumab (420 mg/mo)	Subcutaneous Placebo
	 N=104	 N=53
Percent change in LDL cholesterol, baseline to 24 wk	**–44.5%**	**–6.2%**
	Difference, –38.3 percentage points; 95% CI, –45.5 to –31.1; P<0.001	
Absolute change in LDL	**–77.5 mg/dl**	**–9.0 mg/dl**
	Difference, –68.6 mg/dl; 95% CI, –83.1 to –54.0; P<0.001	

In pediatric patients with FH, evolocumab effectively reduced LDL cholesterol levels.

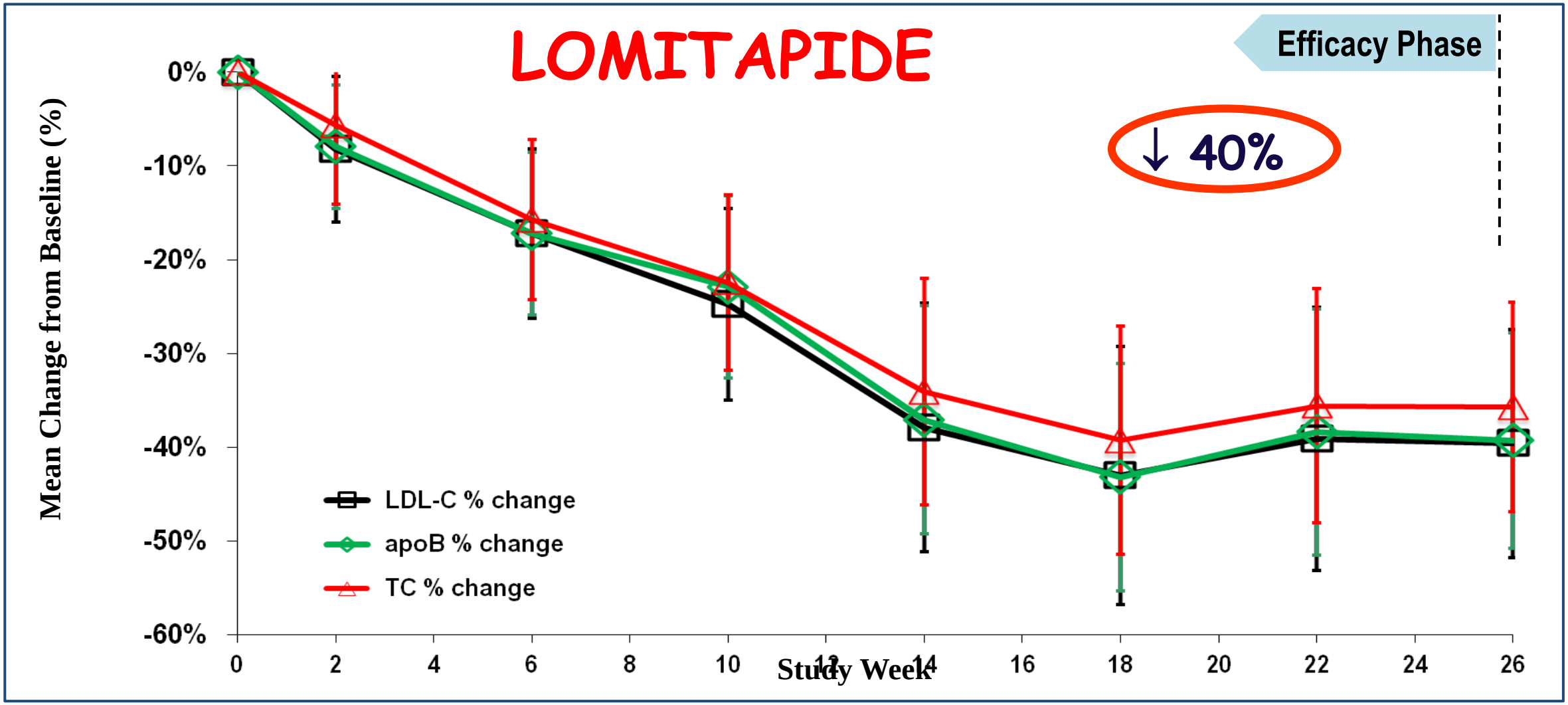
R.D. Santos et al. 10.1056/NEJMoa2019910

ΑΛΛΑ ΦΑΡΜΑΚΑ ΓΙΑ ΤΗΝ ΟΙΚΟΓΕΝΗ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ

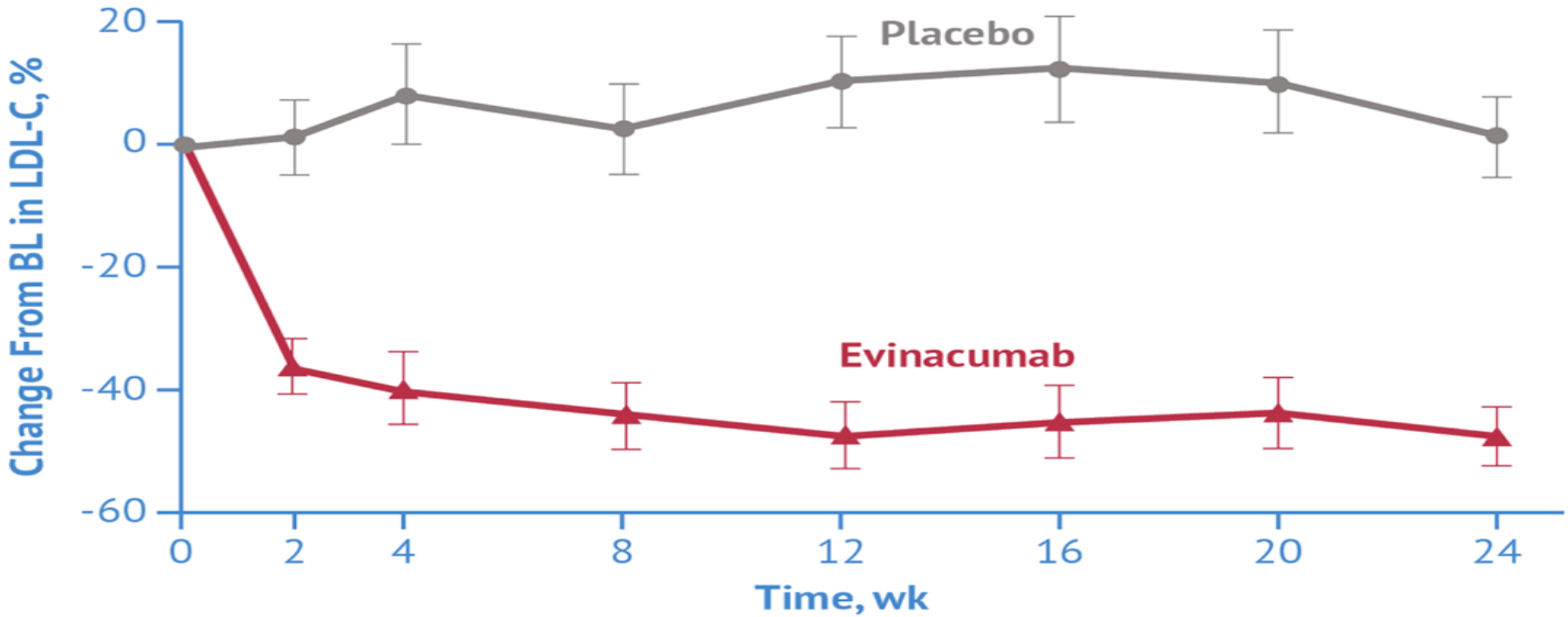
Bempedoic Acid and Reduction in LDL-C in HeFH[16]



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



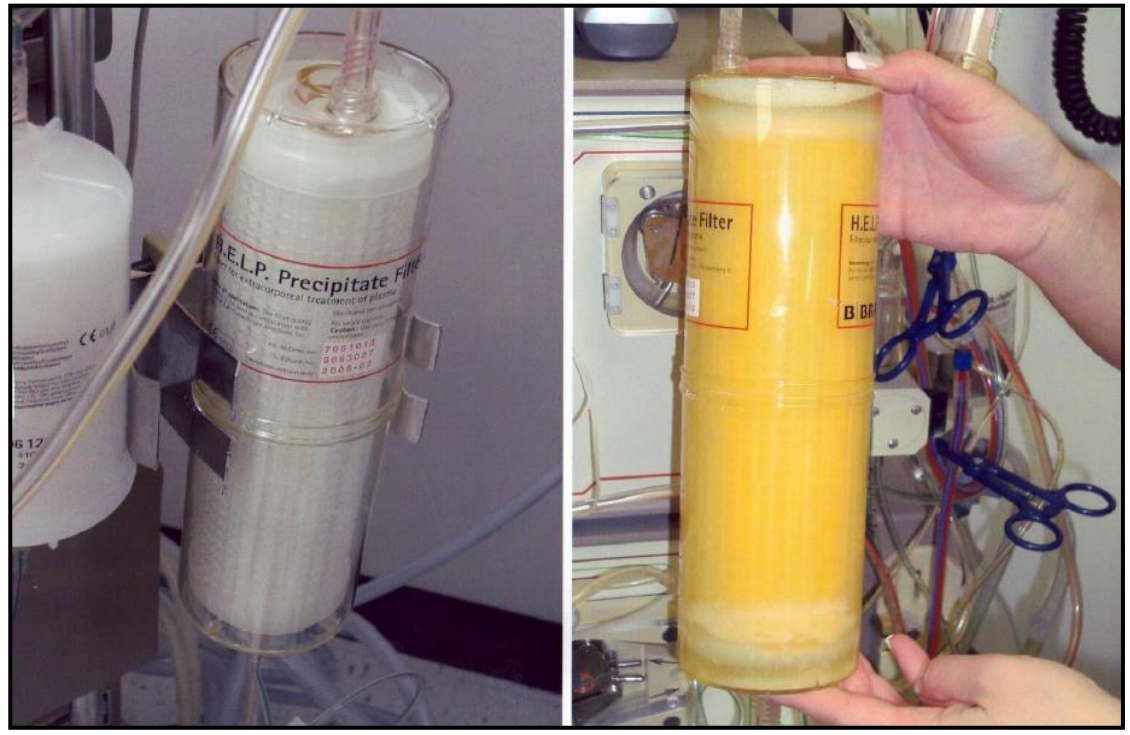
Evinacumab and Reduction in LDL-C in HoFH[13]



LDL-C was lower in the evinacumab group vs placebo for both null-null and non-null variants

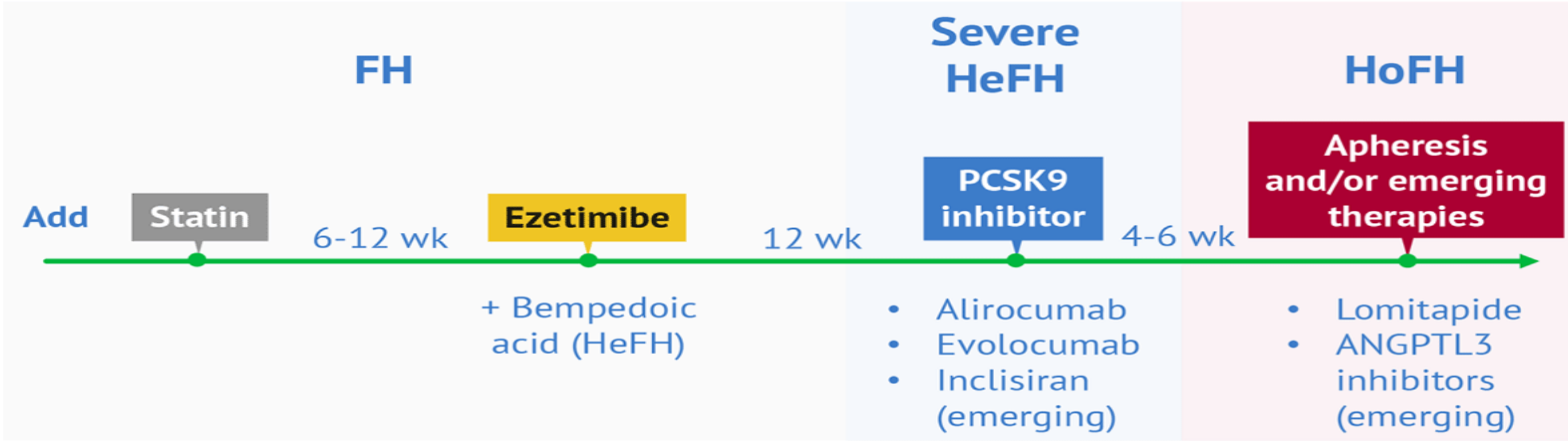
LDL apheresis is current standard of care for HoFH

When LDL-C> 300 mg/dL on maximum therapy (or >200 mg/dL if CVD present)



Treatment Algorithm for Severe FH

TARGET 70 mg/dL (ACC/AHA)[3] or 55 mg/dL (ESC/EAS)[4]



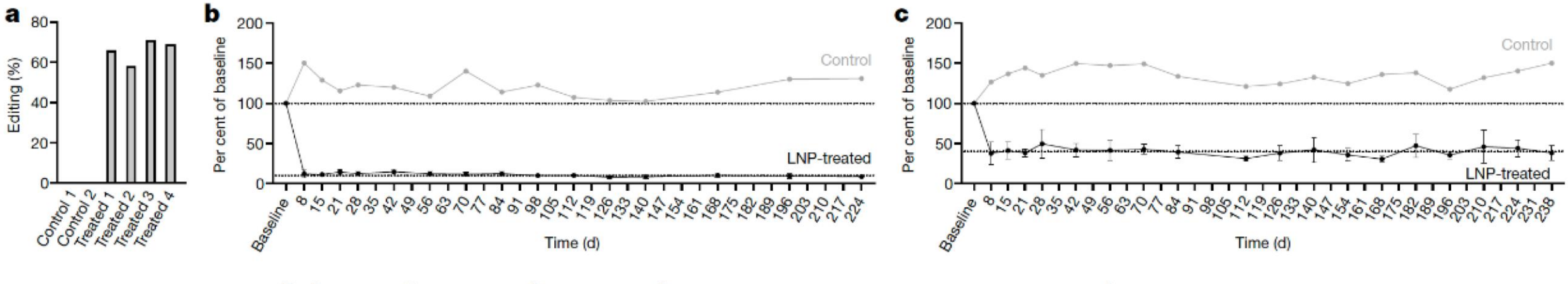
The Future

CrisprCas9 gene editing (in primates)

PCSK9 gene editing

% PCSK9 reduction

% LCL-C reduction



knockdown of *PCSK9* in the liver after a single infusion of lipid nanoparticles, with concomitant reductions in blood levels of PCSK9 and low-density lipoprotein cholesterol of approximately 90% and about 60%, respectively; all of these changes remained stable for at least 8 months after a single-dose treatment. In addition to

Musunuru, Nature 2021

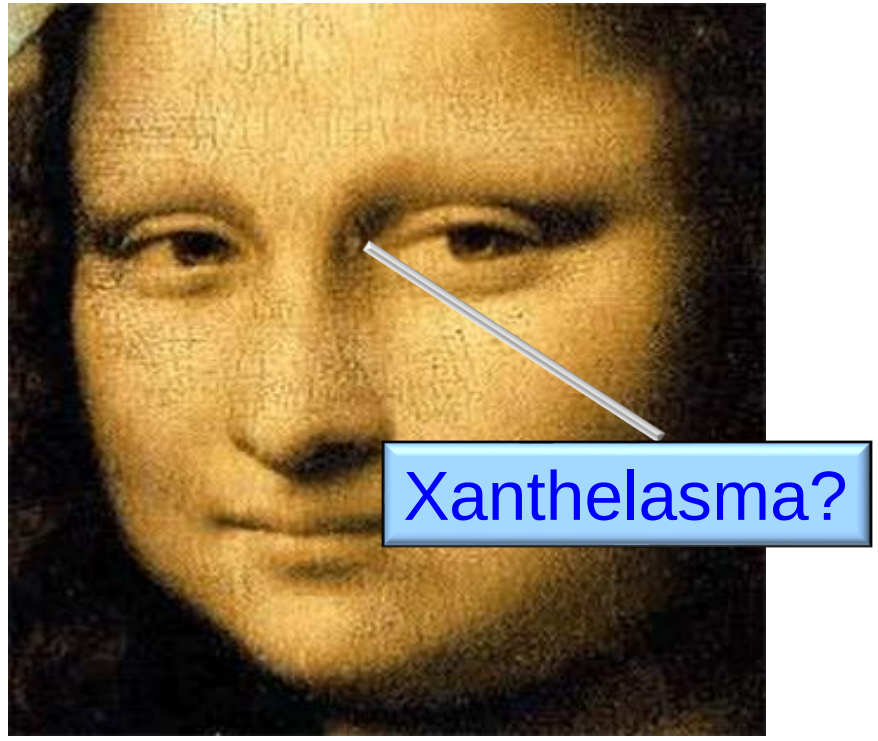
ΣΥΜΠΕΡΑΣΜΑΤΑ

ΟΙΚΟΓΕΝΗΣ ΥΠΕΡΧΟΛΗΣΤΕΡΟΛΑΙΜΙΑ

1. Το πιο συχνό γενετικό νόσημα του μεταβολισμού
2. Πρώιμη καρδιαγγειακή νόσος
3. Οι περισσότεροι ασθενείς δεν έχουν διαγνωσθεί και δεν λαμβάνουν θεραπεία
4. Οι περισσότεροι ασθενείς που λαμβάνουν θεραπεία έχουν τιμές LDL-C εκτός στόχου

ΓΗ: Η ΝΟΣΟΣ ΕΙΝΑΙ ΠΑΝΤΟΥ ΓΥΡΩ ΜΑΣ ΚΑΙ ΑΦΑΙΡΕΙ ΖΩΕΣ!

Madonna Lisa Maria di Gherardini
Born Florence 1479
Died 1516 age 37 years



Dequker et al 2004, Medical Archaelogy IMAJ

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EAS ADVANCED COURSE IN "RARE LIPID DISORDERS"

Friday September 27, 2024, Royal Olympic Hotel, Athens - Greece

Course directors:
Evangelos Liberopoulos, Haralampos Milionis

Language: English

https://eas-society.org/education/rare-lipid-disorder-courses/

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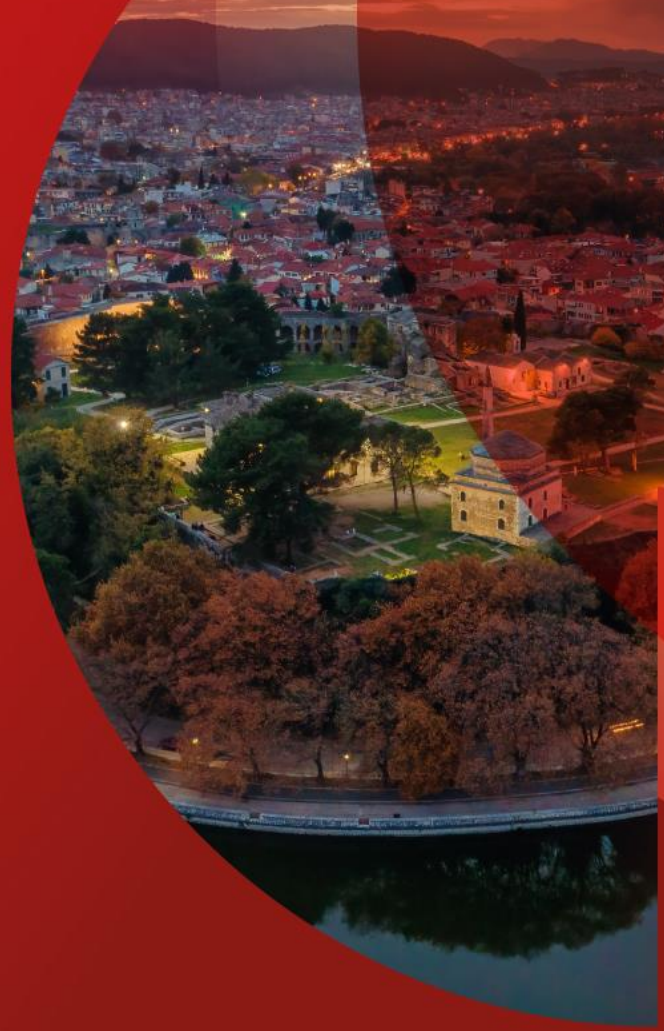

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