Επεμβατικές θεραπείες για την αντιμετώπιση των δυσλιπιδαιμιών

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- In the latest guidelines an LDL-C target of <70 mg/dL and <55 mg/dL, respectively, is recommended for patients at high and very high ASCVD risk.

ESC, 2019

Άτομα με οικογενή υπερχοληστερολαιμία

Recommendations for the detection and treatment of patients with heFH

It is recommended that a diagnosis of FH is considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C [in adults >5 mmol/L (>190 mg/dL), in children >4 mmol/L (>150 mg/dL)], and in first-degree relatives of FH patients.	I	C
It is recommended that FH should be diagnosed using clinical criteria and confirmed, when possible, via DNA analysis.	I	C
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and that those with no prior ASCVD or other risk factors are treated as high-risk.	I	C
For FH patients with ASCVD who are at very-high risk, treatment to achieve a ≥50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with a statin from 8–10 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (<135 mg/dL) at >10 years of age.	IIa	C

Άτομα με σακχαρώδη διαβήτη

Recommendations for the treatment of dyslipidaemias in DM

In patients with T2DM at very-high risk[c], an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.[34,418,432]	I	A
In patients with T2DM at high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.[418]	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.[c] [427]	I	A
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.[33,299]	IIa	B
Statin therapy is not recommended in premenopausal patients with diabetes who are considering pregnancy or are not using adequate contraception.	III	C
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or an LDL-C level >2.5 mmol/L, as long as pregnancy is not being planned.	IIb	C

Άτομα με στεφανιαία νόσο

↓ LDL-C

>/=50% και LDL-C <55 mg/dL

ASCVD pts who experience a second vascular event within 2 years while taking maximally tolerated statin-based therapy

↓ LDL-C reduction

LDL-C goal <40 mg/dL

Άτομα με υπερλιποπρωτεϊναιμία (α)

Recommendations for lipid analyses for cardiovascular disease risk estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

	Γενικά	Υπόψιν	Εφαρμογή
Διατροφή	Μεσογειακή διατροφή	Καρύδια, σπόροι, αβοκάντο. Ψάρια (ειδικά λιπαρά), άπαχο κρέας, πουλερικά, Περιορισμός έτοιμων φαγητών	Τροφές ολικής αλέσεως, φρούτα, λαχανικά. Όχι ζάχαρη, αλάτι, λίπη. Όριο στις τροφές με χαμηλές φυτικές ίνες, στις πατάτες, στις τηγανιτές τροφές, στο πρόχειρο φαγητό (fast-food) και στην κατανάλωση αλκοολούχων ποτών
Σωματική Άσκηση	≥3 φορές την εβδομάδα. Μείωση μεγάλων χρονικών διαλυμάτων χωρίς άσκηση	Αρχικά μικρής διάρκειας και έντασης και σταδιακά αύξησή τους	150-300 λεπτά την εβδομάδα μέτριας ή 75-150 λεπτά την εβδομάδα έντονης άσκησης Αερόβια άσκηση ≥.2 φορές την εβδομάδα
Ύπνος	Διάρκεια 6-8 ώρες	Έλεγχος για υπνική άπνοια	Απώλεια σωματικού βάρους εάν χρειάζεται Αποφυγή υπνωτικών χαπιών
Κάπνισμα	Όχι κάπνισμα ή ουσίες με νικοτίνη	Αποφυγή έκθεσης στο παθητικό κάπνισμα	Η νικοτίνη σε οποιαδήποτε μορφή σχετίζεται με αρτηριοσκλήρωση

Φάρμακα

Νικοτινικό οξύ
Φιβράτες
Αναστολείς απορρόφησης της Χ
Σατίνες
Ω-3 ΛΟ
Αναστολείς PCSK9
Αναστολείς MTP
Αναστολείς Apo CIII
Αναστολείς ANGPTL3

Πολύ υψηλού κινδύνου	Υψηλού κινδύνου	Μετρίου κινδύνου	Χαμηλού κινδύνου
Αλλαγή τρόπου ζωής + Ισχυρή στατίνη	Αλλαγή τρόπου ζωής + Ισχυρή στατίνη	Αλλαγή τρόπου ζωής + Μέσης ισχύς στατίνη	Αλλαγή τρόπου ζωής
Εάν LDL-C >55 mg/dL	Εάν LDL-C >70 mg/dL	Εάν LDL-C >100 mg/dL	Εάν LDL-C >116 mg/dL
Προσθήκη: Εζετιμίμπης, κολεσεβελαμης, μπεμπεδοϊκό οξύ*, PCSK9i	Προσθήκη: Εζετιμίμπης, κολεσεβελαμης, μπεμπεδοϊκό οξύ*, PCSK9i	Άλλαξε σε ισχυρή στατίνη	Προσθήκη μέσης ισχύς στατίνη
Εάν LDL-C >55 mg/dL	Εάν LDL-C >70 mg/dL	Εάν LDL-C >100 mg/dL	Εάν LDL-C >116 mg/dL
Προσθήκη Λομιταπίδης (μόνο στην HoFH) ή **ΛΑ**	Προσθήκη Λομιταπίδης (μόνο στην HoFH) ή **ΛΑ**	Προσθήκη Εζετιμίμπης, κολεσεβελαμης, μπεμπεδοϊκό οξύ* ± PCSK9i	Προσθήκη Εζετιμίμπης, κολεσεβελαμης,

Έλεγχος λιπιδαιμικών παραμέτρων ανά 3-6 μήνες ή νωρίτερα εάν είναι ανάγκη

Ισχυρές στατίνες	Μέτριας ισχύς στατίνη	Εζετιμίμπη	PCSK9i	Κολεσεβελάμη	Μπεμπεδοϊκό οξύ
Ατορβαστατίνη 40-80mg Ροσουβαστατίνη 20-40mg	Ατορβαστατίνη 10-20mg Ροσουβαστατίνη 5-10mg Πραβαστατίνη 20-40mg Σιμβαστατίνη 20-40mg Πιταβαστατίνη 2-4mg Φλουβαστατίνη 80mg	Εζε 10mg	Εβολοκουμάμπη 140mg/2 εβδ. ή 420mg/4 εβδ. Αλιροκουμάμπη 75-150mg/2 εβδ.	Κολεσεβελάμη 3.750mg	Μπεμπεδοϊκό οξύ 180mg


DALI 75

USA:
1) HoFH: LDL-C ≥500 mg/dL on maximal LLT
2) HeFH: LDL-C ≥300 mg/dL (0-1 RF),
LDL-C ≥200 mg/dL (≥2 RFs or ↑Lp(a)
LDL-C ≥160 mg/dL (if at very high risk)

Germany:
1) HoFH
2) Severe hypercholesterolemia (including HeFH): ↑LDL-C on maximal LLT
3) ↑Lp(a): recurrent CVD (clinically and/or on imaging) despite optimal control of all other risk factors and Lp(a) ≥60 mg/dL (143 nmol/L)

Japan:
1) HoFH
2) HeFH: TC ≥250 mg/dL on maximal LLT

United Kingdom:
1) HoFH: LDL-C <50% reduction on maximal LLT or LDL-C ≥350 mg/dL
2) Other hypercholesterolemia (including HeFH): recurrent CVD and LDL-C ≥190 mg/dL or lower if ↑Lp(a) or LDL-C reduction <40%

Australia:
1) HoFH: LDL-C ≥270 mg/dL on maximal LLT
2) HeFH: CVD and LDL-C ≥193 mg/dL on maximal LLT
3) Alternative criteria (HoFH and heFH): <50% reduction on maximal LLT

Spain:
1) HoFH
2) HeFH: LDL-C ≥200 mg/dL with CVD or ≥300 mg/dLwithout CVD

Lipoprotein apheresis: A Hellenic consensus on its clinical use

Kolovou G, Bilianou H, Goumas G, Foussas S, Grapsa E, Garoufi A, Karavolias, G, Kolovou V, Mavrogieni S, Melidonis A, Milionis H, Rallidis L, Richter D, Skoumas I, Tousoulis D, Vlachopoulos C, Liberopoulos E

H J C, 2020

Lipoprotein apheresis: A Hellenic consensus on its clinical use

1a.
HoFH for the primary prevention if LDL-C reduction is <50% under maximum LLT or LDL-C remains ≥250 mg/dL regardless of the response to maximum LLT.

1b.
HoFH for the secondary prevention if LDL-C reduction is <50% under maximum possible LLT or LDL-C remains ≥160 mg/dL regardless of the response to maximum LLT.

2.
Individuals with any other hypercholesterolemia including HeFH: for the secondary prevention, if they are under maximum LLT and 1 of the following:

LDL-C >190 mg/dL
LDL-C reduction <40%
Lp(a) >100 mg/dL (238 nmol/L)

Lipoprotein apheresis: A Hellenic consensus on its clinical use

3a.
Individuals with ↑↑↑Lp(a) [≥180 mg/dL (430 nmol/L)] for the primary prevention if they have LDL-C >190 mg/dL under maximum possible LLT.

3b.
Individuals with DM and Lp(a)>180 mg/dL with i) ASCVD or ii) CKD stage 4 or 5 or iii) urine albumin 24h >300 mg.

4.
Refractory angina, or documented progression of atherosclerotic lesions (cardiac or peripheral arteries)* in nonsmokers, under maximum possible LLT and LDL-C >100 mg/dL (1.8 mmol/L).

Lipoprotein apheresis: A Hellenic consensus on its clinical use

5.
↑↑↑↑ TGs (>880 mg/dL) under maximum LLT or ↑↑ TGs [>440 mg/dL under maximum possible LLT and history of episodes of acute pancreatitis.

6a.
Pregnant women with LDL-C >500 mg/d for the primary prevention

6b.
Pregnant women with LDL-C >190 mg/dL for the secondary prevention

6c.
Pregnant women with ↑↑↑↑ TGs (>880 mg/dL) and history of episodes of acute pancreatitis.

First author	Journal, Published Year	LDL-C reduction	Lp(a) reduction	TG
Gordon B, et al.	Am J Cardiol, 1992	81±5 in HoFH 76±2 in HeFH	68±11, HoFH 65±8, HeFH	59±9 in HoFH 60±9 in HeFH
Thompson GR, et al.	Lancet, 1995	52	22	26
Bambauer R, et al.	Therap Apher, 1997	49.1	30.3	38.4
Mabuchi H, et al.	Am J Cardiol, 1998	58	Not evaluated	53
Jaeger B, et al.	Nat Clin Pract Cardiovasc Med, 2009	64	72	28
Stefanutti C, et al.	Transfus Apher Sci, 2010	30	57.8±9.5	17
Buuren F, et al.	Clin Res Cardiol, Suppl 2012	63.5	60.6	62.3
Kolovou G et al.	Cholesterol, 2012	75±11	Not evaluated	50±16%
Safarova M, et al.	Atheroscler, Suppl 2013	17	73±12	Not provided
Leebmann J, et al.	Circulation, 2013	67.3±10.2	69.6±9.8	Not evaluated
Stefanutti C, et al.	Ther Apher Dial, 2013	67	71	Not provided
Rosada A, et al.	Artif Organs, 2014	60	68	Not change from baseline
Klingel R, et al.	Clin Res Cardiol Suppl, 2015	45*	74	Not provided
Schettler VJJ, et al.	Clin Res Cardiol Suppl, 2017	[68.6]	[70.4]	Not provided
Khan T, et al	Eur Heart J, 2017	[60.5]	[67]	28
Ezhov M. et al	Controlled Clin Trial, 2017	59±14	49±15	67.3±10.2

LA

A single treatment can effectively reduce LDL-C and Lp(a) 50-70%.

LDL-C and Lp(a) levels rebound rapidly after treatment returning to 50-90% of pre-apheresis levels after 4-14 days.

The German Lipoprotein Apheresis Registry

based on more than 15,000 LA procedures, found:

97% decrease in major ASCVD events during the first year of LA vs. 2 years preceding the start of LA*

**Data were obtained prior to the introduction of PCSK9i in Germany.*

Schettler VJ, et al. The German lipoprotein apheresis registry (GLAR) - almost 5 years on. Clin Res Cardiol Suppl. 2017

N=21 with FH

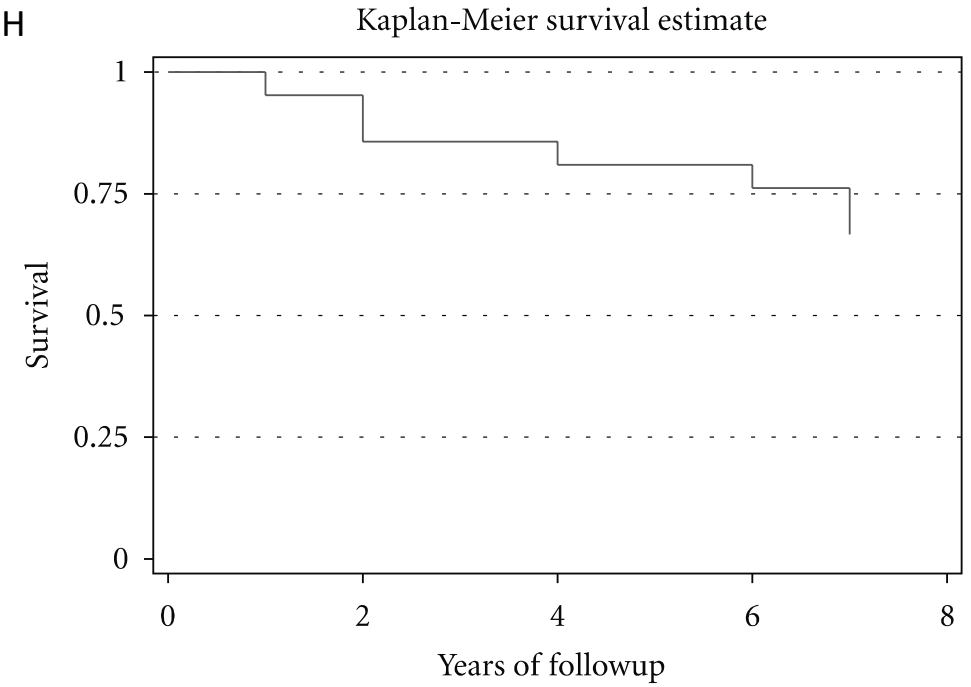

FIGURE 1: Kaplan-Meier survival curve.

Percentage of even-free survival for 7y was 67%
LDL-apheresis-treated 9.5% deaths vs Not-treated 17%
The average annual event rate was 5.5%.

Kolovou, et al. Cholesterol 2012

Gene Therapy

Gene therapy for lipid disorders is still under development.

↓TG gene therapy still presents some difficulties.
↓ LDL gene therapy still presents some difficulties.

Alipogene tiparvovec (*Glybera)*

Περιέχει την παραλλαγή του γονιδίου *LPLS447X* που κωδικοποιεί την LpL
→Φορέας (αδενο-συσχετιζόμενος ιός, *AAV*)

i.m. σε pts FLpL
Γενική αναισθησία →πολλαπλές i.m. σε πολλαπλά σημεία
+ ανοσοκατασταλτικά (ενδεχόμενο απόρριψης)

Η θεράπευα με alipogene tiparvovec μείωνε παροδικά τα TG και την παραγωγή των CM.
Στη διάρκεια 2 χρόνων ↓ 50% νέων επεισοδίων παγκρεατίτιδας

Αποτελεσματική μόνο στους ασθενείς με μεταλλάξεις του γονιδίου *LPL*.
Το κόστος της θεραπείας ήταν 1.000.000 euro ανά ασθενή.

Gene Therapy

↓ LDL

Replacing the defective gene with a functional gene

1995, Liver directed gene therapy → 5 HoFH → inconsistent results

(*short stayed efficacy with ↓ 6-25% LDL-C*)

LDLR Gene Therapy

A recombinant LDLR-expressing agent using the same vector, AAV8.TBG.hLDLR, has entered a phase I clinical trial. In preclinical testing, this agent led to pronounced and sustained metabolic and atherosclerotic effects in humanized models of HoFH