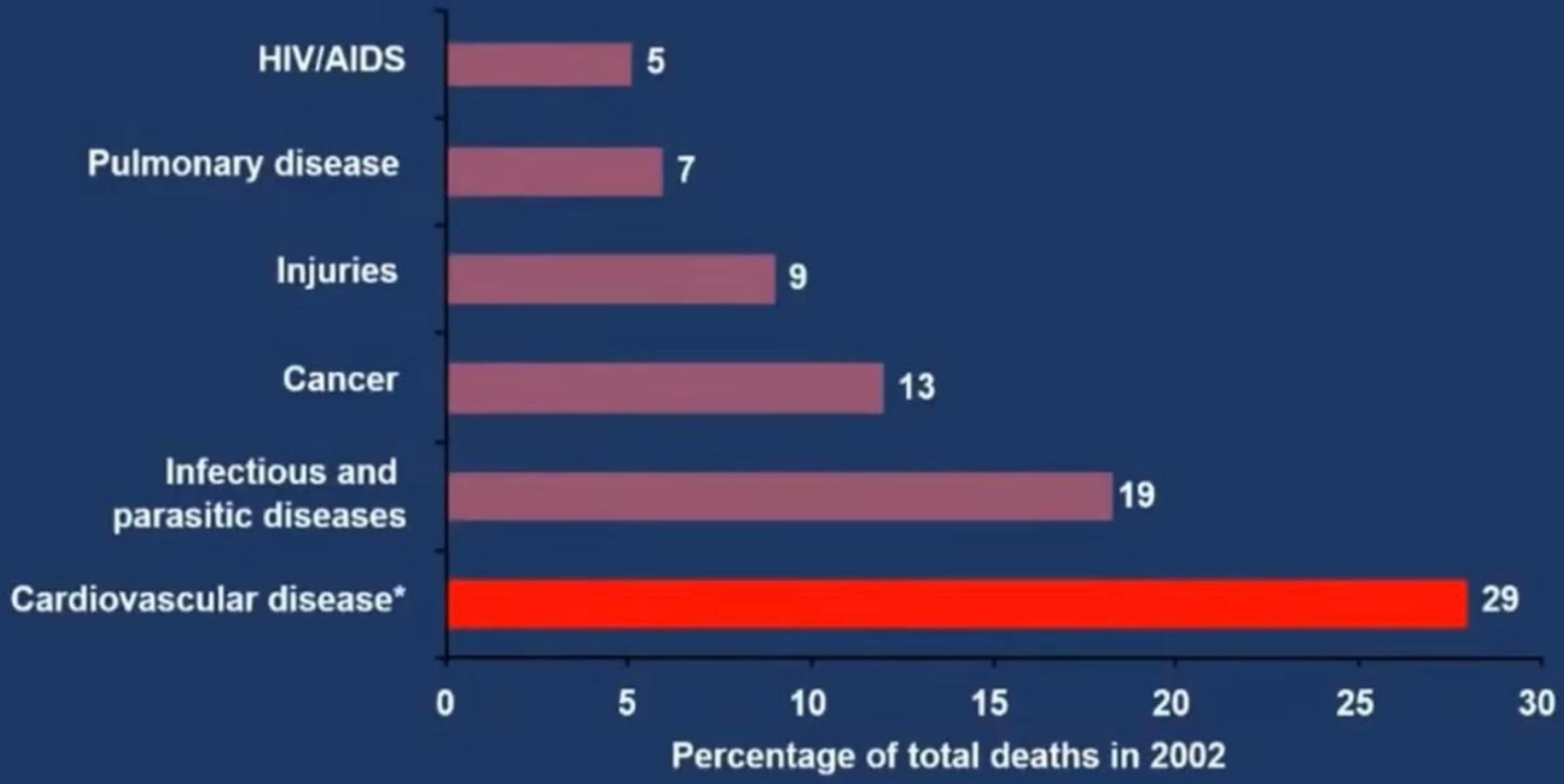
Θεραπευτικός αλγόριθμος αντιμετώπισης υπερλιπιδαιμίας

Ροδιτάκης Γιώργος

Παθολόγος

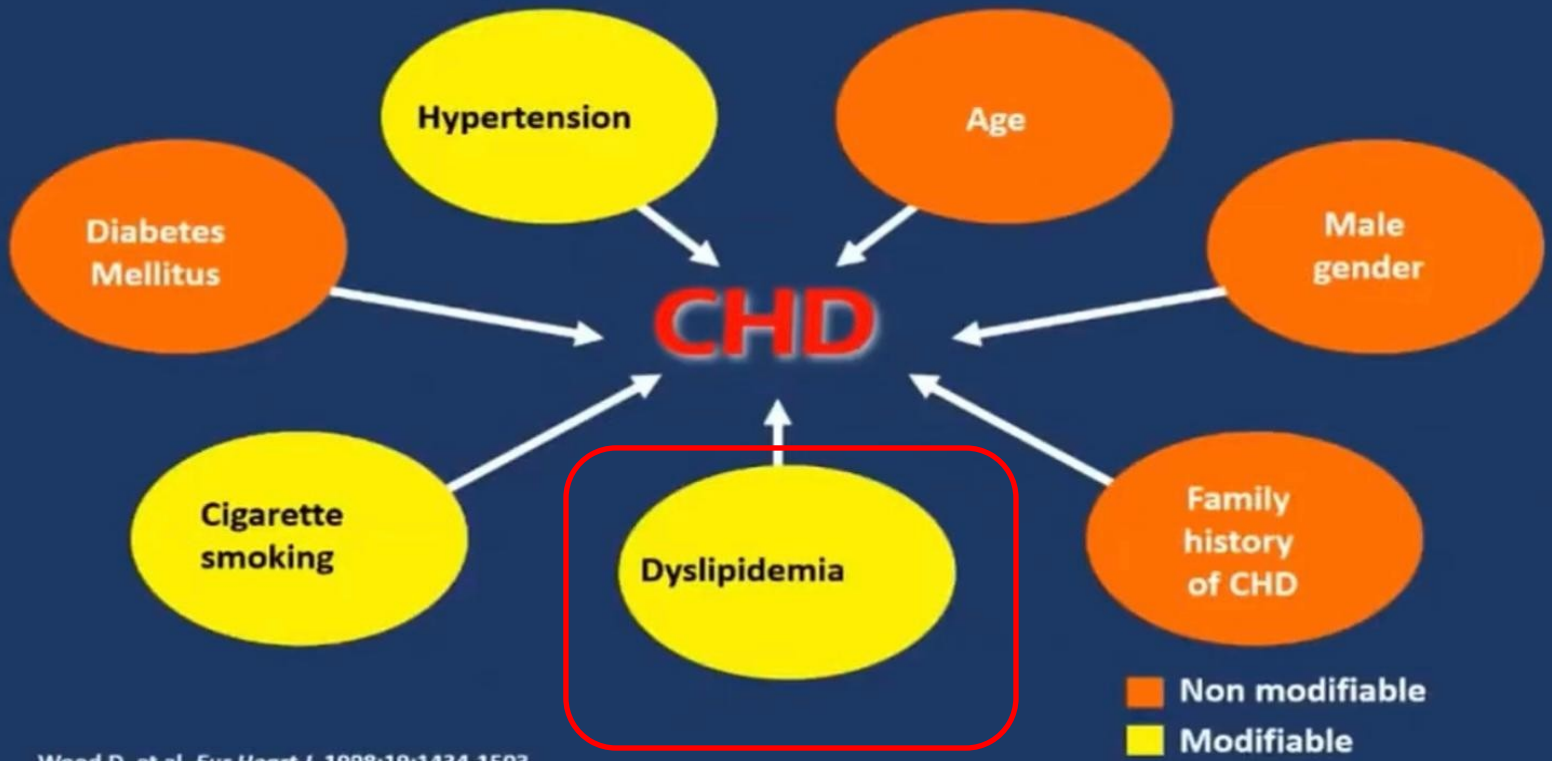
Μέλος Ελληνικής Εταιρείας Αθηροσκλήρωσης

Cardiovascular Disease is the Leading Cause of Death Worldwide[1]



*Ischemic heart disease, cerebrovascular disease, hypertensive heart disease, inflammatory heart disease and rheumatic heart disease

Primary Risk Factors For CHD



Wood D, et al. *Eur Heart J.* 1998;19:1434-1503.

The 3 Lipoproteins That Cause ASCVD

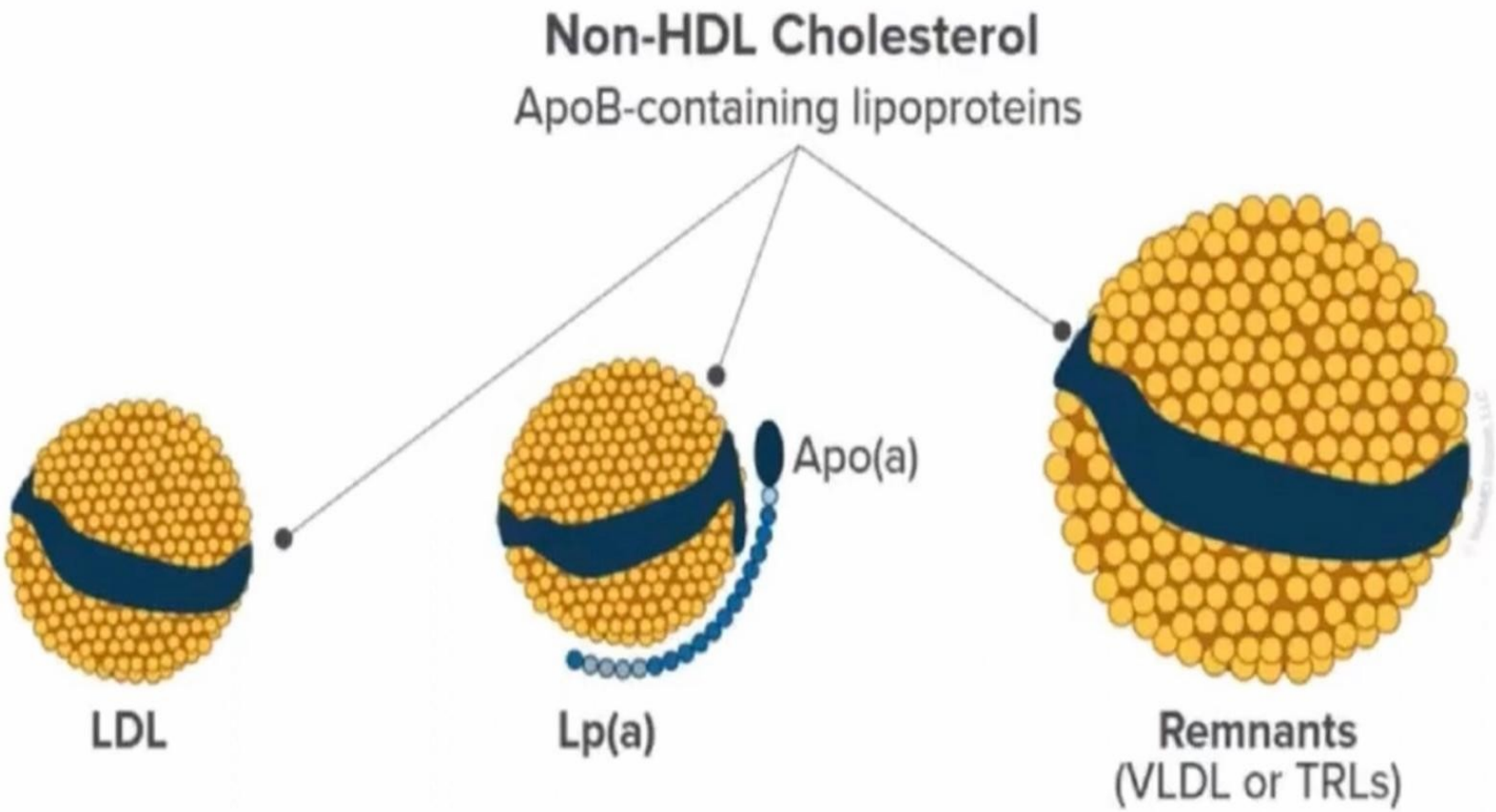
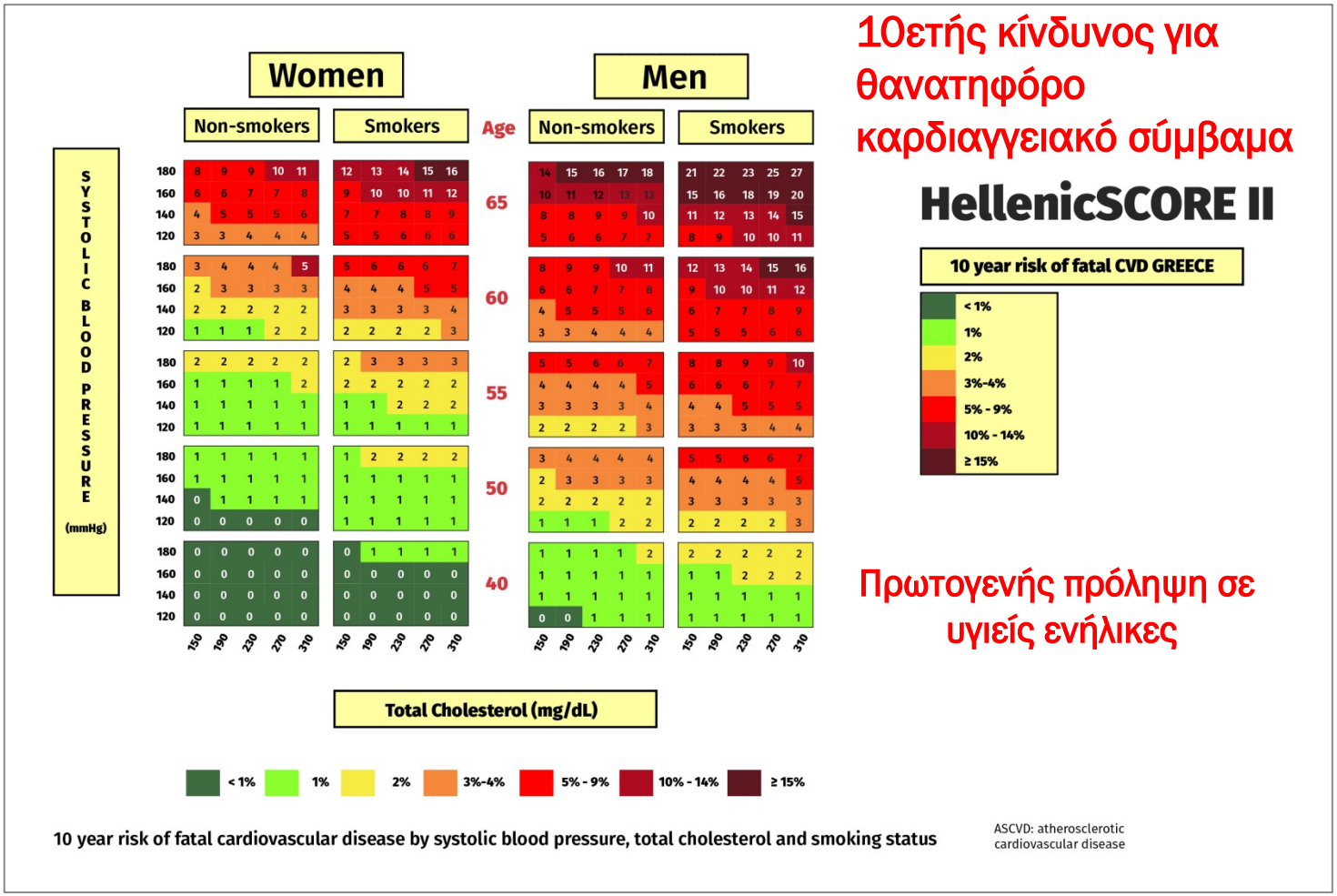


Image courtesy of Børge Nordestgaard, MD, DMSc.

Nordestgaard BG. *Circ Res.* 2016;118:547-563; Nordestgaard BG, et al. *Atherosclerosis.* 2020;294:46-61.

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

10ετής κίνδυνος για θανατηφόρο καρδιαγγειακό σύμβαμα



Πρωτογενής πρόληψη σε υγιείς ενήλικες

Figure 2. HellenicSCORE II – 10-year risk of fatal ASCVD in Greece. (*Adapted from Panagiotakos et al*[15])

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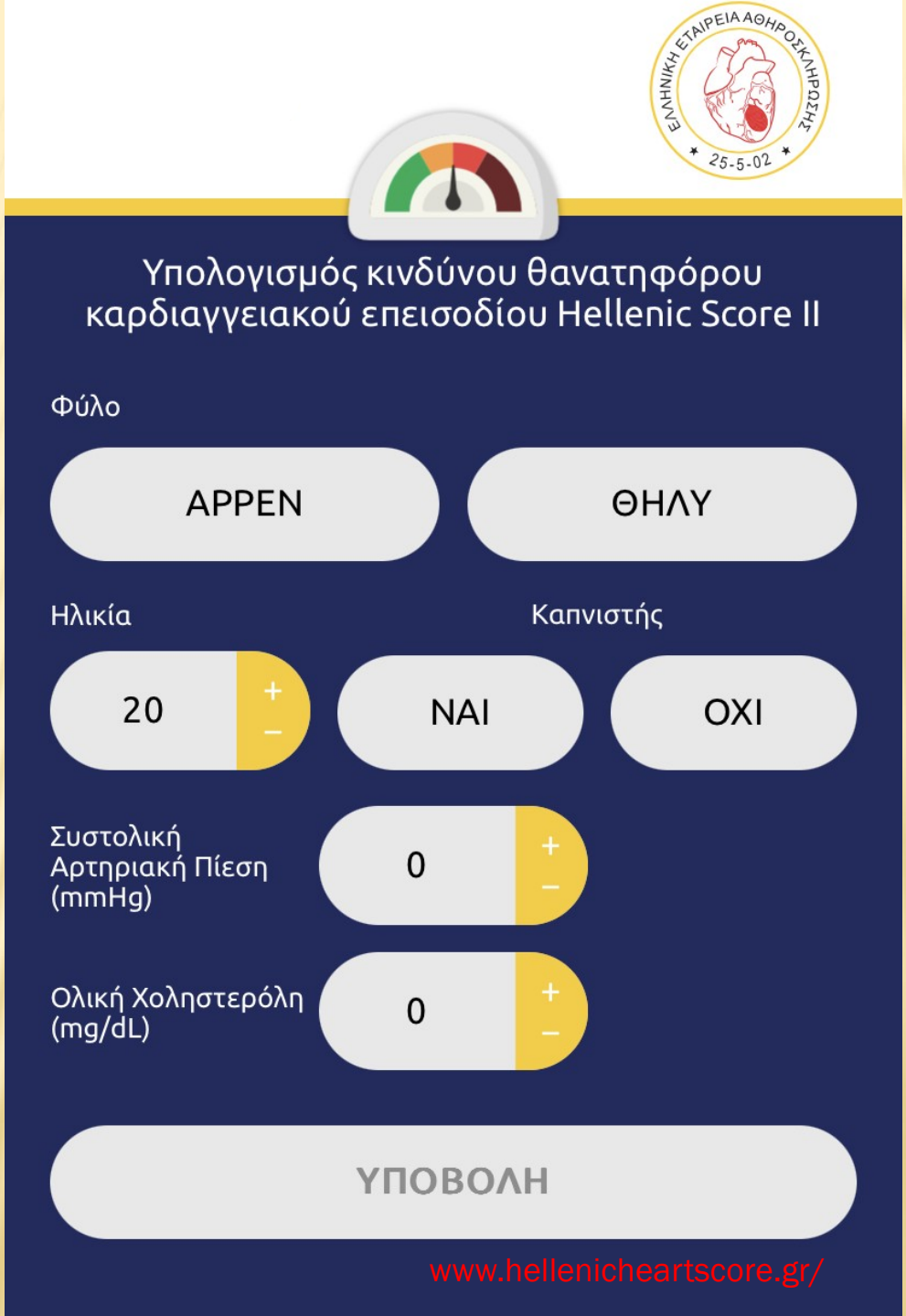
ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΘΗΡΟΣΚΛΗΡΩΣΗΣ
25-5-02
Υπολογισμός κινδύνου θανατηφόρου καρδιαγγειακού επεισοδίου Hellenic Score II
Φύλο
ΑΡΡΕΝ
ΘΗΛΥ
Ηλικία
20
Καπνιστής
ΝΑΙ
ΟΧΙ
Συστολική Αρτηριακή Πίεση (mmHg)
0
Ολική Χοληστερόλη (mg/dL)
0
ΥΠΟΒΟΛΗ
www.hellenicheartscore.gr/

TABLE 1. Parameters that increase ASCVD risk and should be considered as risk modifiers in individuals at low or moderate risk.

Social deprivation
Obesity, especially central obesity
Physical inactivity
Family history of premature ASCVD (men: <55 years; women: <60years)
Major psychiatric disorders
Atrial fibrillation
Left ventricular hypertrophy
Obstructive sleep apnoea syndrome
Non-alcoholic fatty liver disease
History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia

Parameters that increase ASCVD risk and should be considered as risk modifiers in individuals at low or moderate risk

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TABLE 1. Parameters that increase ASCVD risk and should be considered as risk modifiers in individuals at low or moderate risk (*continued*).

High-risk race/ethnicities (e.g., South Asian ancestry)

Lipid-related markers

- Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL)
- non–HDL-C >190 mg/dL
- Elevated Lp(a) ≥50 mg/dL or ≥125 nmol/L
- Elevated apoB ≥130 mg/dL (if measured)

Other biomarkers/imaging (if measured or done):

- Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
- ABI <0.9
- Arterial (carotid and/or femoral) plaque burden on ultrasonography
- CAC score assessment with CT

ASCVD: atherosclerotic cardiovascular disease; non-HDL-C: non high-density lipoprotein cholesterol; Lp(a): lipoprotein a; apoB: apolipoprotein B; ABI: ankle brachial index; CAC: coronary artery calcium; CT: computed tomography

Parameters that increase ASCVD risk and should be considered as risk modifiers in individuals at low or moderate risk

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ASCVD risk groups.

TABLE 53. ASCVD risk groups.

ASCVD Risk group	Patient characteristics
I. Very high ASCVD risk	1. Established CHD 2. Ischemic stroke/TIA 3. Atherosclerotic arterial stenosis >50% 4. Abdominal aortic aneurysm 5. Familial hypercholesterolemia with ≥1 major risk factor 6. Diabetes type 2 with target organ damage or ≥3 major risk factors (age, smoking, atherogenic dyslipidemia, hypertension, obesity) or diabetes type 1 >20 years duration 7. Chronic kidney disease stage 4 (eGFR <30 mL/min/1.73 m^2) 8. HellenicSCORE II ≥10% 9. Peripheral artery disease

ASCVD risk groups.

TABLE 53. ASCVD risk groups (*continued*).

ASCVD Risk group	Patient characteristics
II. High ASCVD risk group	1. HellenicSCORE II ≥ 5-10% 2. At least one severe risk factor (stage 3 hypertension, extreme smoking, LDL-C>190 mg/dL) 3. Familial hypercholesterolemia without any major risk factor 4. Diabetes >10 years duration with 1-2 major risk factors (age, smoking, atherogenic dyslipidemia, hypertension, obesity) 5. Chronic kidney disease stage 3 (eGFR 30-60 mL/min/1.73 m^2) 6. Autoimmune diseases/HIV infection
III. Moderate ASCVD risk group	1. HellenicSCORE II ≥ 1-5% 2. Diabetes <10 years duration in persons <45 years (type 2) or <35 years (type 1) without any major risk factors
IV. Low ASCVD risk group	HellenicSCORE II <1%

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; TIA: transient ischemic attack; LDL-C: low-density lipoprotein cholesterol

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA - 2023

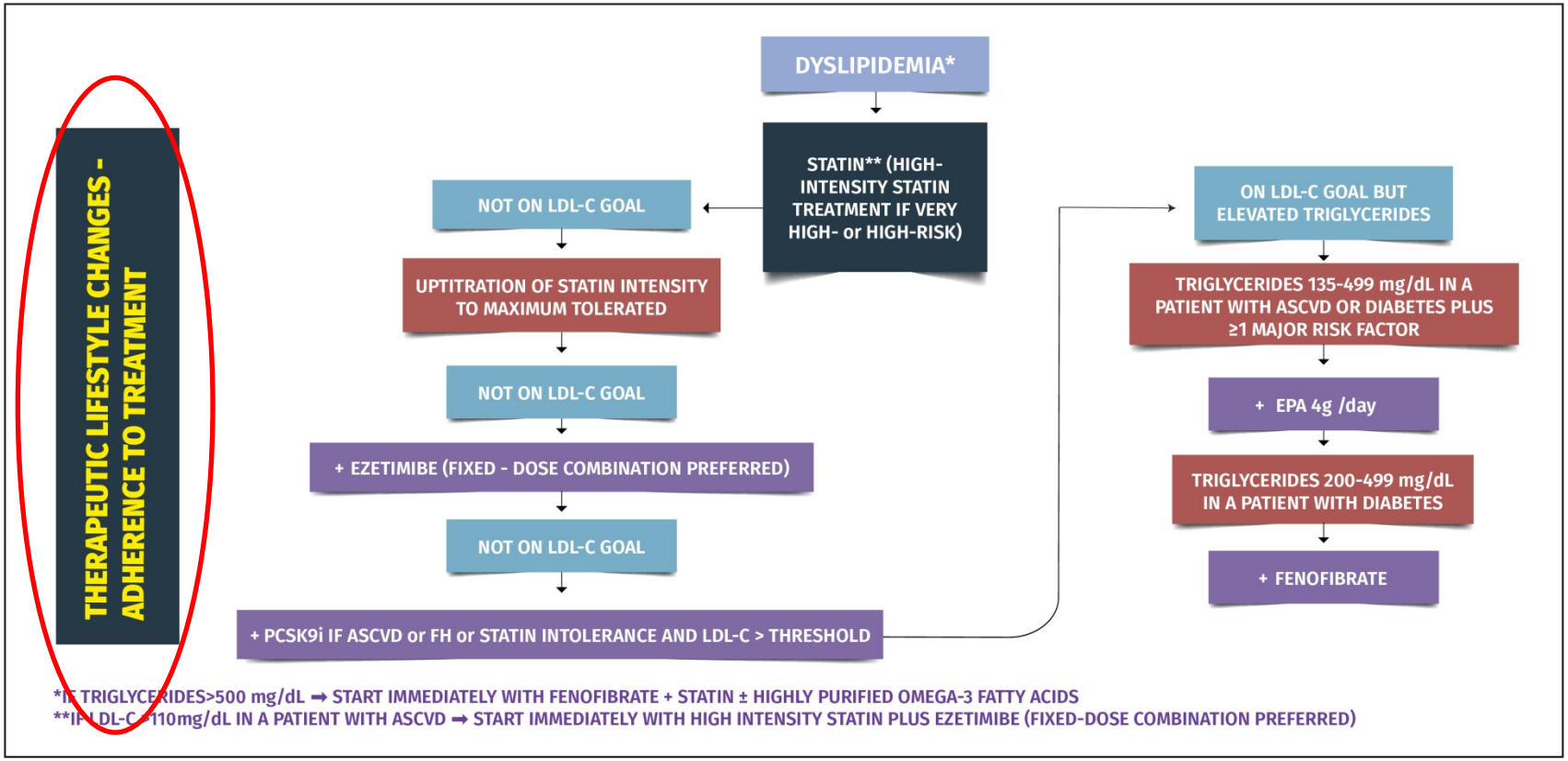

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FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol;
CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

Treatment targets and goals for cardiovascular disease prevention (1)

EAS ESC European Society of Cardiology

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	3.5–7 hours moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg[a]

[a] Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Dietary recommendations for patients with dyslipidemia

TABLE 5. Dietary recommendations for patients with dyslipidemia.

Recommendation	Class of recommendation
Individualized nutritional counseling should be provided by a registered nutritionist to all patients with dyslipidemia for sustainable dietary changes. The nutritionist should collaborate with the clinicians to achieve the maximal benefit	IIa
Dietary fat is recommended to be consumed mainly via vegetable oils, fish and nuts. A total fat intake higher than 35% of total energy intake should be avoided, especially for people with mild to moderate hypercholesterolemia	I
Patients with FH should restrict total fat to 20-35% of total energy intake, keeping in mind that very low-fat diets have the risk of inadequate intake of lipid soluble vitamins	IIa
SFA, MUFA and PUFA are recommended not to exceed 7, 20 and 10% of energy intake, respectively	I
The intake of omega-6 PUFA is recommended to range from 5 to 10% of energy intake, while that of omega-3 PUFA between 0.6-2.0%. A minimum intake of 500 mg/day EPA+DHA, preferably from fish, is recommended	I
Most carbohydrates are recommended to derive from unprocessed, non-refined food sources providing high amounts of dietary fibers with a hypocholesterolemic action and preventing increase of TG and decrease of HDL-C	I
Sugars, including those found in foods, should not exceed 10% of energy intake from food sources. A lower intake is needed for patients with atherogenic dyslipidemia (such as those with metabolic syndrome and T2D)	IIa

TABLE 5. Dietary recommendations for patients with dyslipidemia (*continued*).

The consumption of trans fatty acids is recommended not to exceed 1% of energy intake	I
Hypercholesterolemic patients should limit dietary cholesterol consumption to no more than 300 mg/day	IIa
Legumes, vegetables, fruits and wholegrain cereals intake is recommended for the daily consumption of >25 g/day of dietary fibers. The inclusion of 3 g/day of oat and barley soluble fibers can lower LDL-C	I
The addition of 2 g/day of plant sterols/stanols in the diet of hypercholesterolemic patients (including patients with FH), in the form of supplements or functional foods, can significantly enhance LDL-C lowering combined with pharmaceutical treatment	IIb
The general population should consume 2-3 servings (150 g of cooked fish) preferably from fatty fish (e.g., sardines, anchovies, salmon) to achieve a daily consumption of 500 mg EPA-DHA. Higher doses of long-chain omega-3 fatty acids (2-4 g) from supplements, fish oils or enriched foods are required for a clinically significant improvement of hypertriglyceridemia	IIa
The daily consumption of 40-60 g/day of nuts (preferably walnuts, almonds, hazelnuts and flaxseed) can exert a meaningful reduction of LDL-C, especially in hypercholesterolemic patients	IIb
Social drinkers can moderately consume alcoholic beverages providing 20 g alcohol/day for men and 10 g alcohol/day for women. Wine is the recommended alcoholic beverage due to its cardioprotective properties. People with elevated TG must abstain from alcohol consumption	I

SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; T2D: type 2 diabetes; LDL-C: low-density lipoprotein cholesterol

TABLE 6. Recommendations for physical activity and exercise in patients with dyslipidemia.

Recommendation	Class of recommendation
Regular physical activity can favorably alter lipids and lipoproteins. Patients with dyslipidemia must be encouraged to achieve at least 30 min/day of physical activity	I
A hypocholesterolemic effect can be attained by 40 min/day of moderate to intense aerobic training for >3 days/week	I
Moderate-intensity aerobic exercise 150 min/week, separated in sessions of 30 min, can favorably modify cardiometabolic health, including lipid profile	I
Muscle-strengthening resistance training should be considered at least twice per week at a moderate intensity.	IIa
Patients who are reluctant to follow structured exercise programs should be encouraged to participate in supervised recreational team sports activities	IIa

Recommendations for physical activity and exercise in patients with dyslipidemia

Laboratory follow-up in patients on hypolipidemic drug treatment

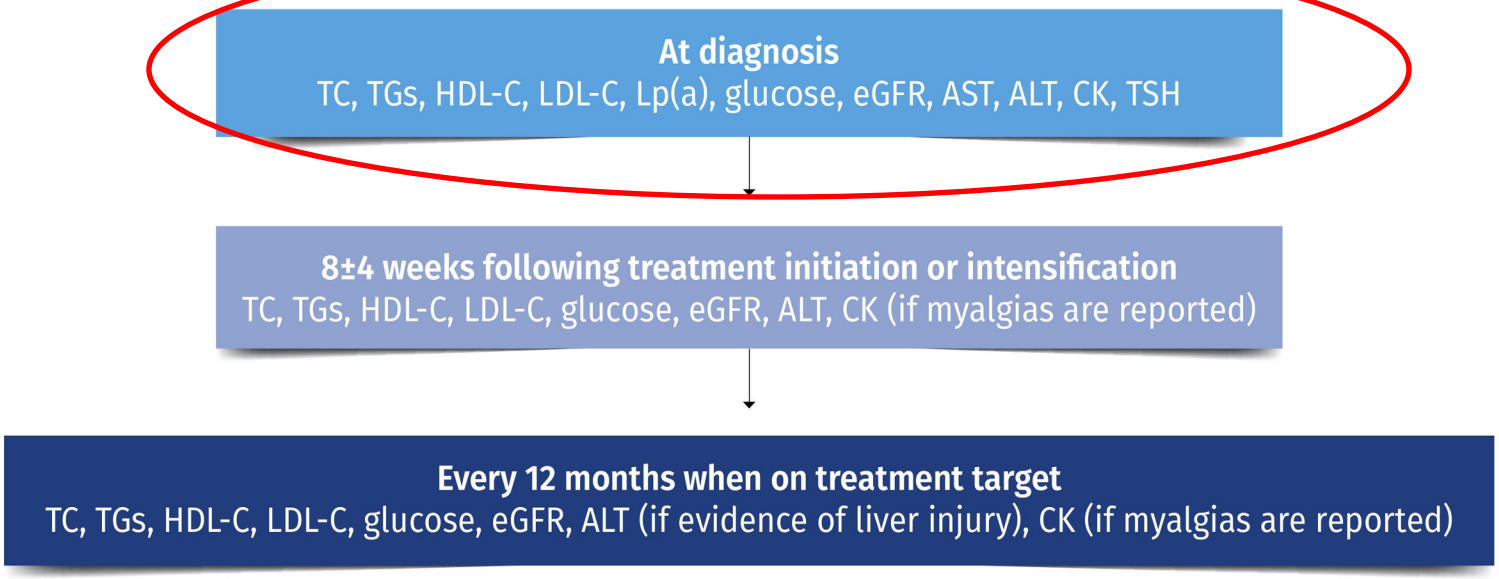

FIGURE 12: Laboratory follow-up in patients on hypolipidemic drug treatment

LDL-C TARGETS 2023

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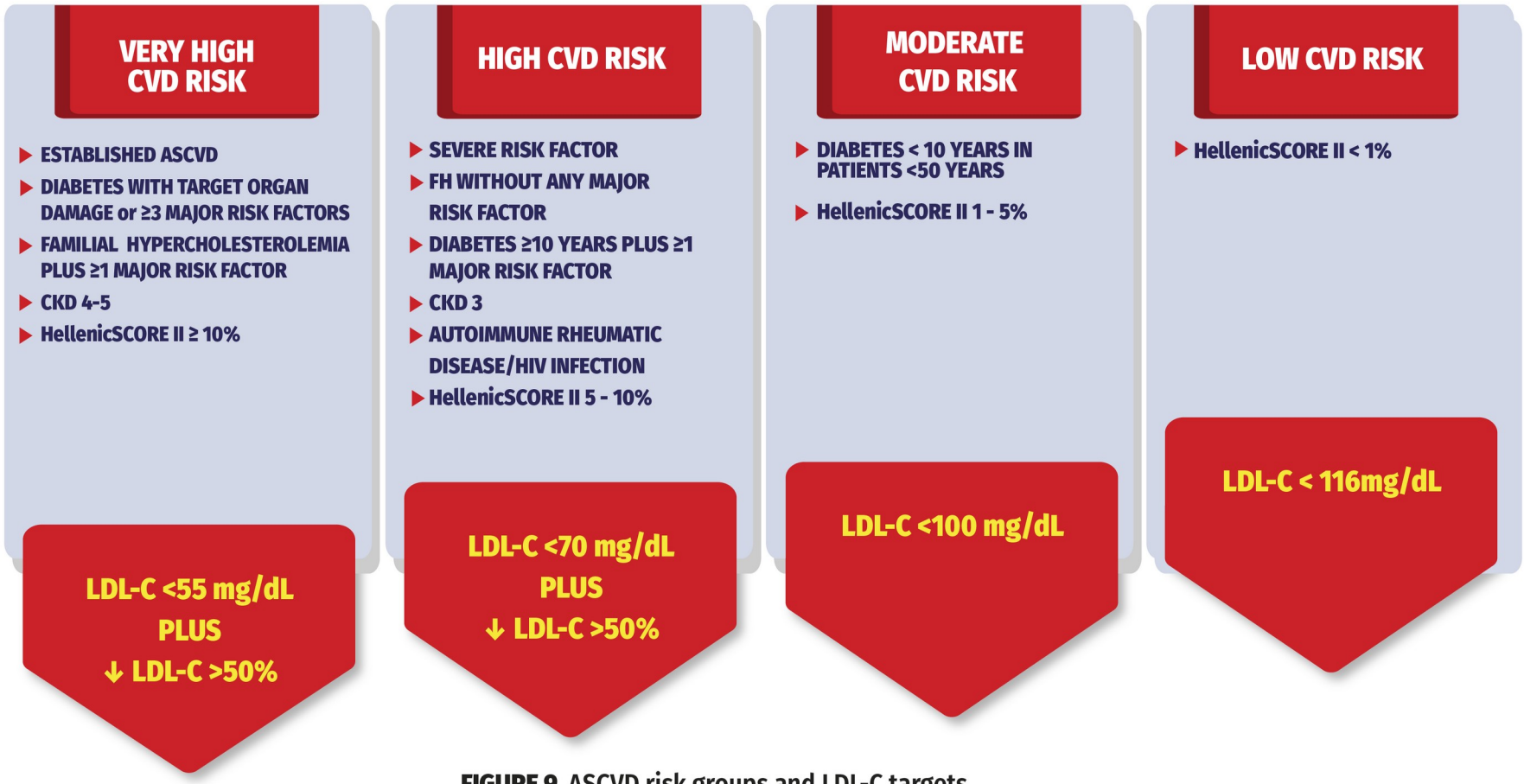
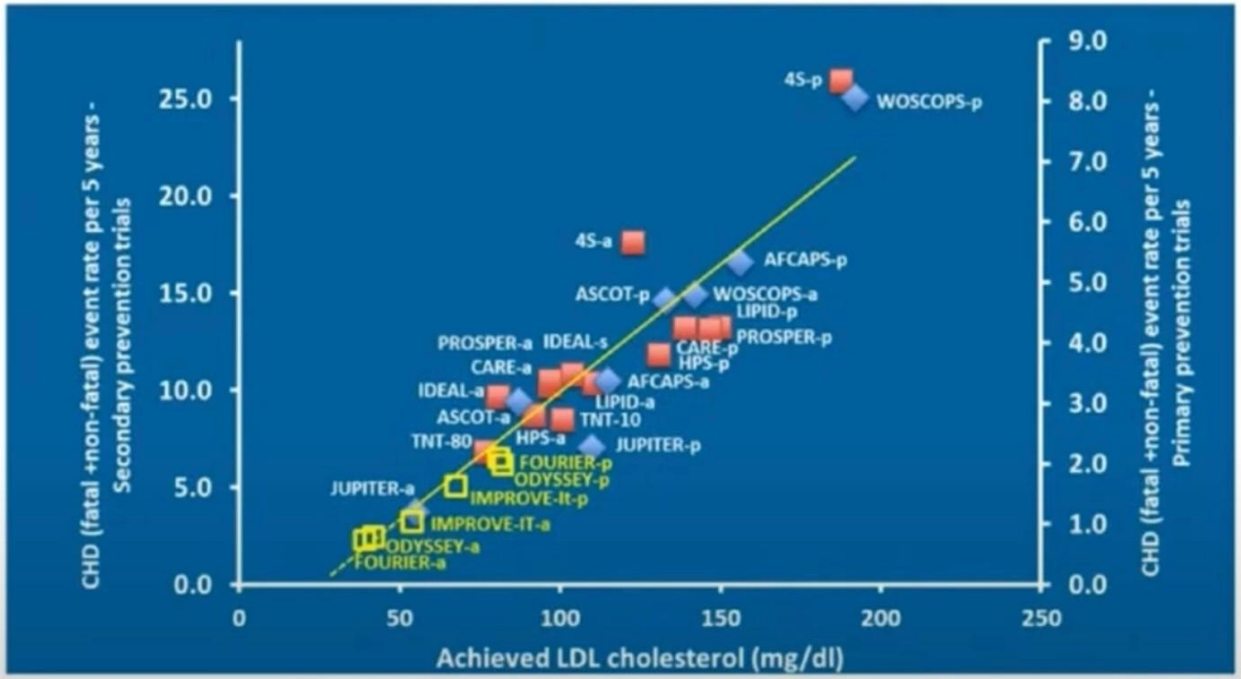


FIGURE 9. ASCVD risk groups and LDL-C targets

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia

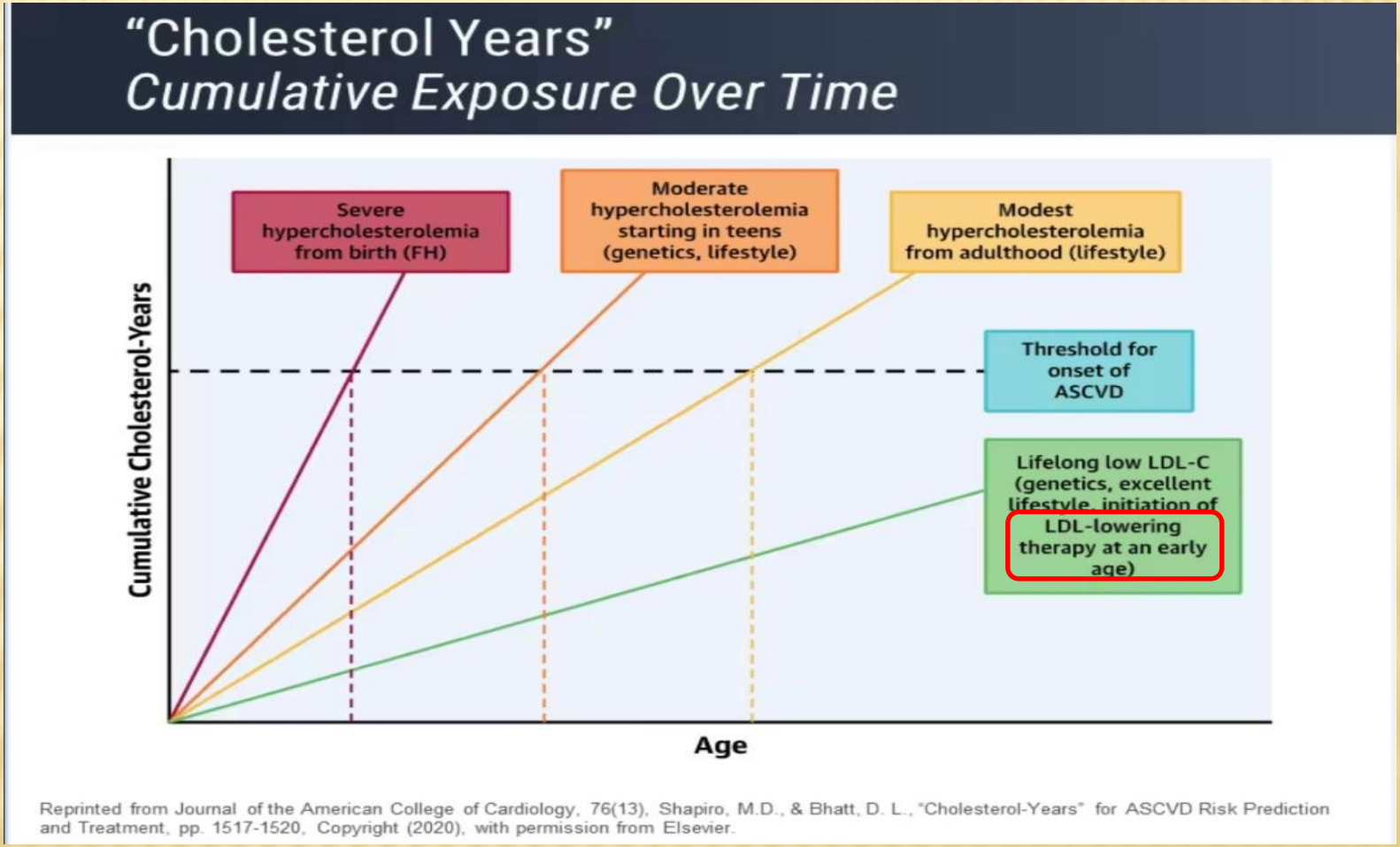
THE LOWER THE BETTER!!

Impact of Lower LDL-C on Outcomes



Slide courtesy of C. Packard. Modified from Ference BA, et al. *Eur Heart J.* 2017;38:2459-2472; Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397; Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722; Schwartz GG, et al. *N Engl J Med.* 2018;379;2097-2107.

THE EARLIER THE BETTER!



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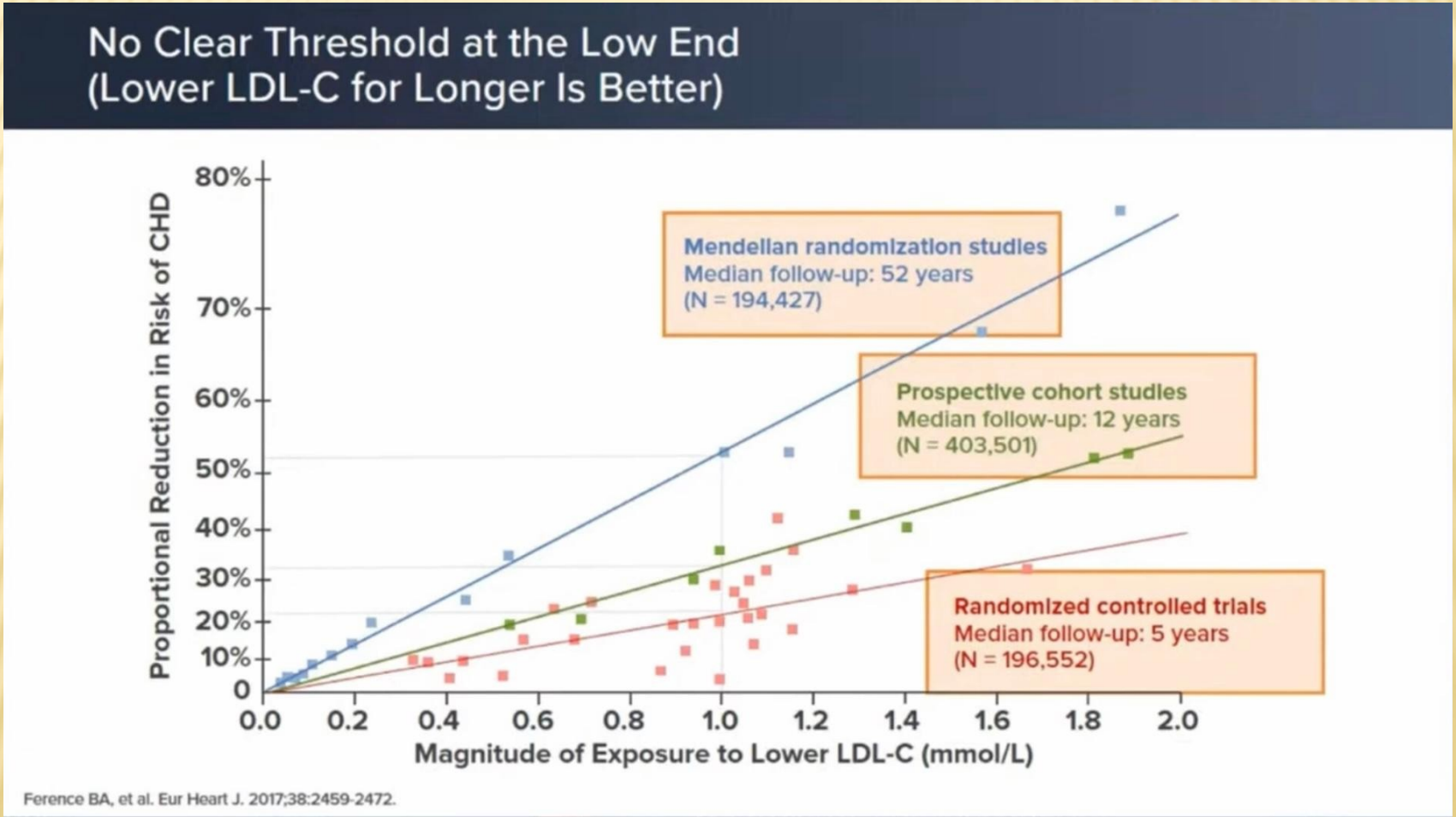
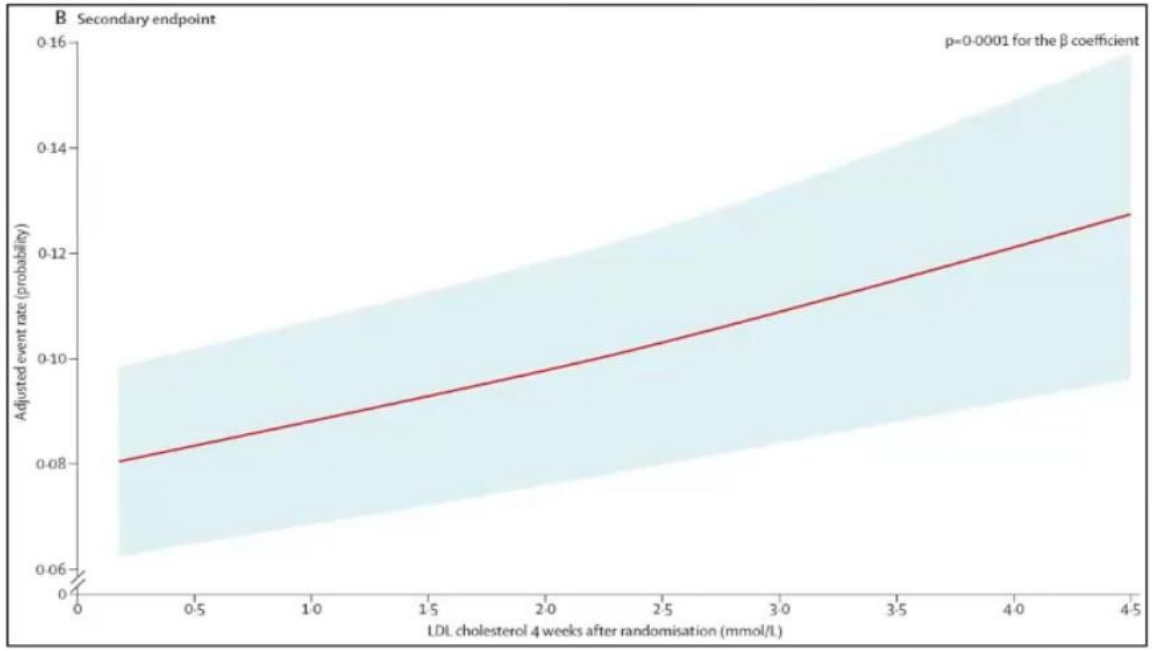
THE LONGER THE BETTER!!



Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

- 10% είχαν LDL-χολ <20 mg/dL
- **Όφελος και για επίπεδα LDL-χολ <10 mg/dL**
- Απουσία ανεπιθύμητων ενεργειών σε πολύ χαμηλά επίπεδα LDL-χολ



Glugliano RP. Lancet 2017;390(10106):1962-71

Recommendations for treatment goals for low-density lipoprotein cholesterol (2)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B
In patients at high risk, an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

LDL-C treatment goals for different ASCVD risk groups.

TABLE 54. LDL-C treatment goals for different ASCVD risk groups.

ASCVD Risk group	LDL-C treatment target	Initiation of lipid-lowering drug treatment	Class of recommendation
I. Very high ASCVD risk	<55 mg/dL AND >50% LDL-C reduction from baseline	Immediate + therapeutic lifestyle changes	I
II. High ASCVD risk	<70 mg/dL AND >50% LDL-C reduction from baseline	Immediate + therapeutic lifestyle changes	I
III. Moderate ASCVD risk group	<100 mg/dL	3 months following therapeutic lifestyle changes	I
IV. Low ASCVD risk group	<116 mg/dL	3-6 months following therapeutic lifestyle changes	IIa

LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA - 2023

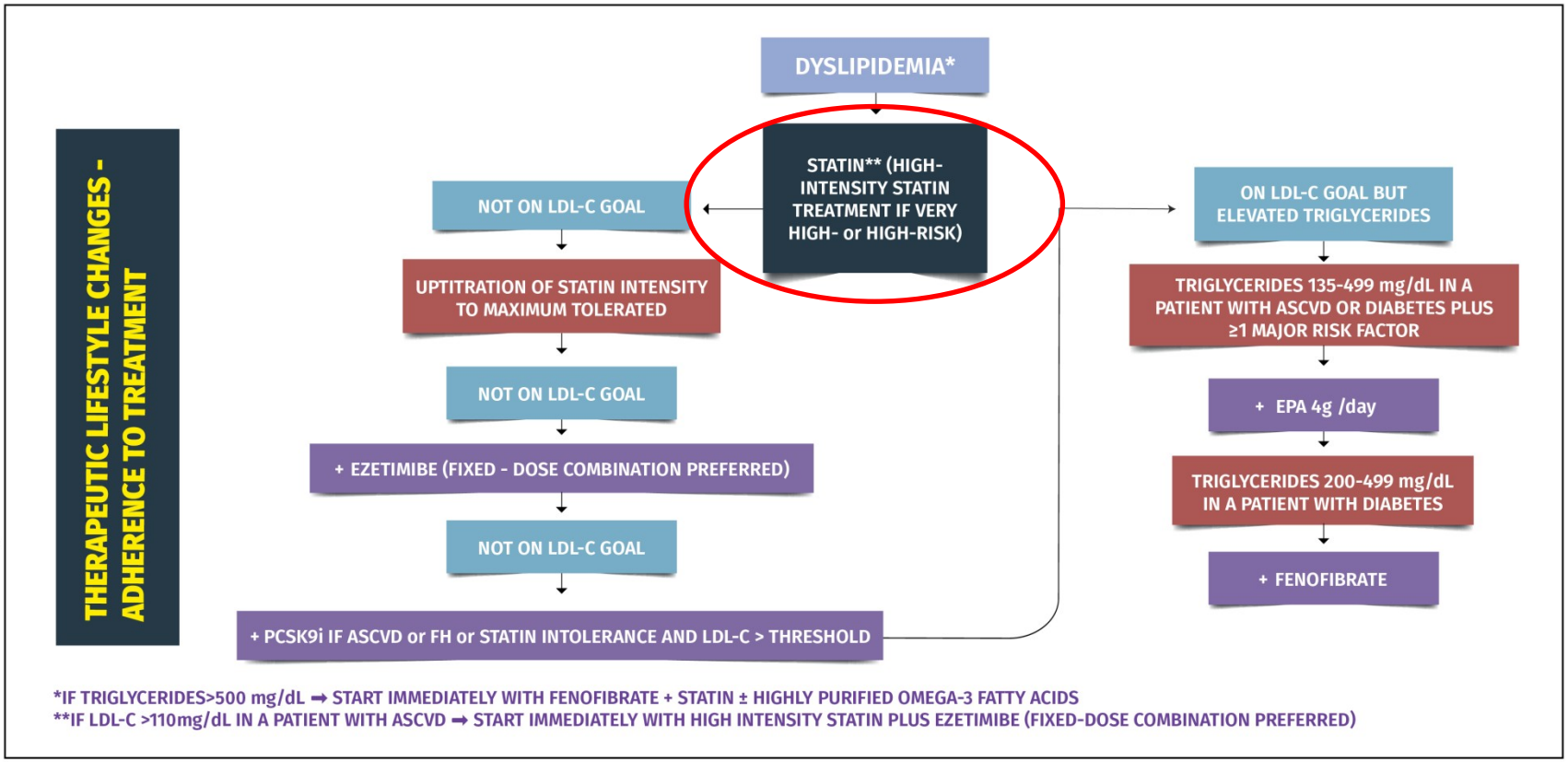


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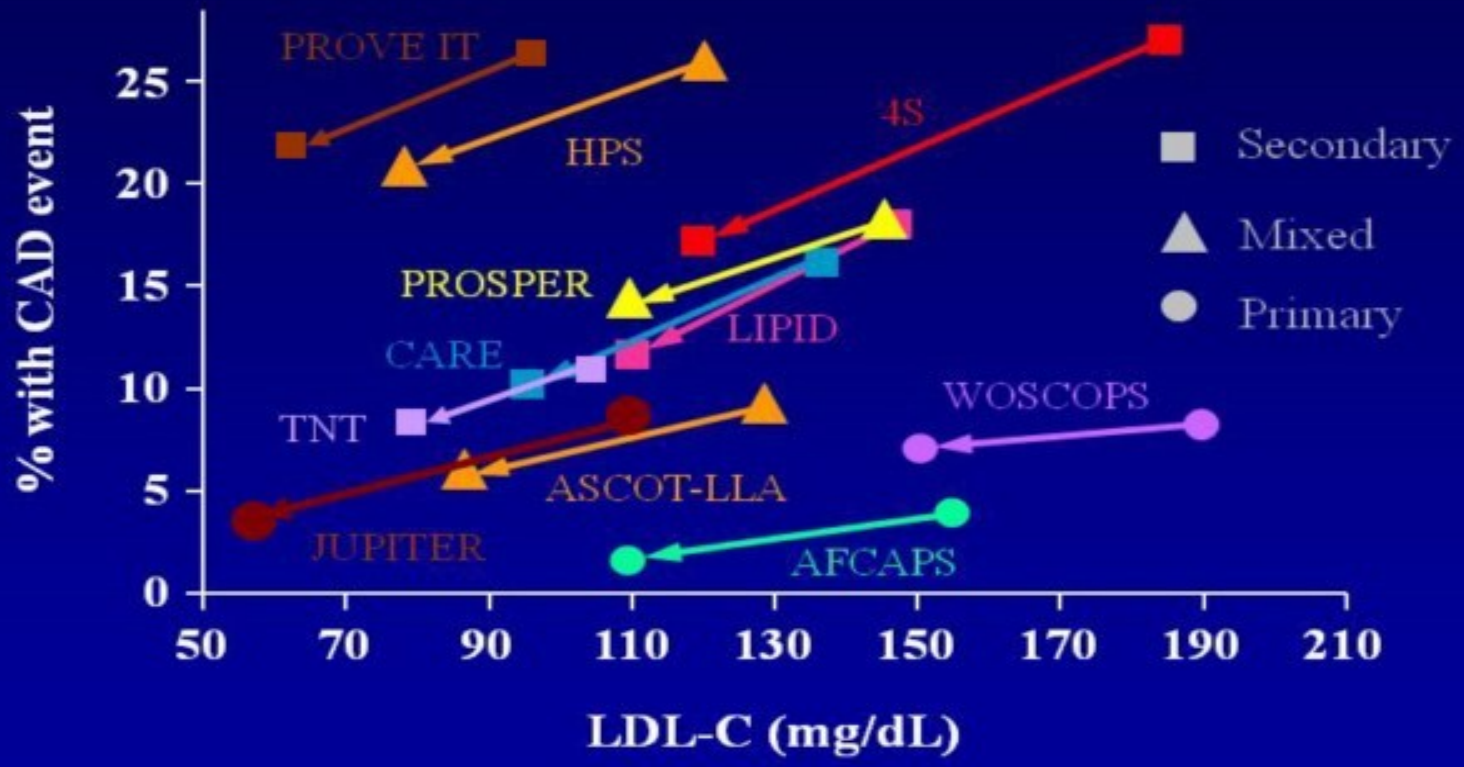
FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

ΣΤΑΤΙΝΕΣ

- Μειώνουν την ενδογενή σύνθεση χοληστερόλης και αυξάνουν την πρόσληψη της χοληστερόλης από το πλάσμα μέσω των LDLR
- Μειώνουν την LDL 20-50%, μικρή επίδραση σε HDL, δοσοεξαρτώμενη στα TG
- Διπλασιασμός δόσης επιπλέον μείωση LDL κατά 6%

Major Statin Trials

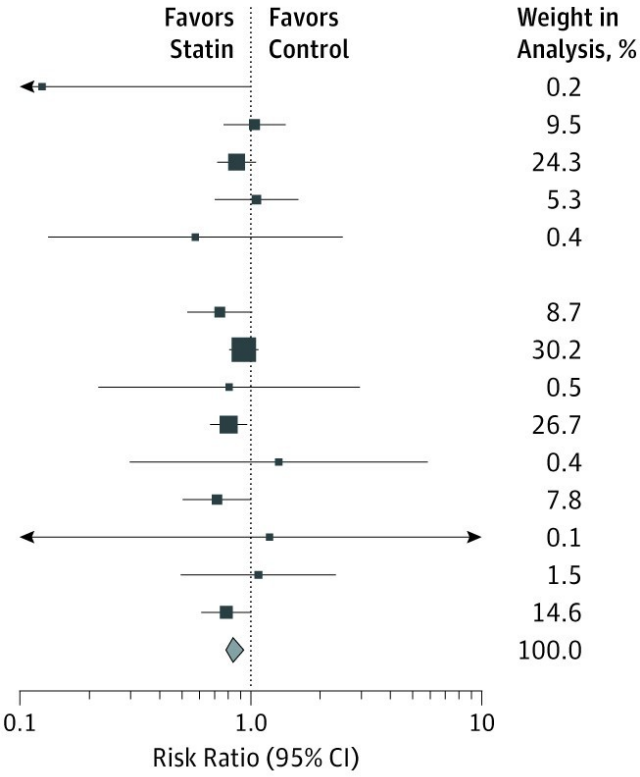


A All-cause mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)
ACAPS,[18] 1994	3	1/460 (0.22)	8/459 (1.7)	0.12 (0.02-0.99)
AFCAPS/TexCAPS,[19] 1998	5	80/3304 (2.4)	77/3301 (2.3)	1.04 (0.76-1.41)
ASCOT-LLA,[20] 2003	3	185/5168 (3.6)	212/5137 (4.1)	0.87 (0.71-1.05)
ASPEN,[21] 2006	4	44/959 (4.6)	41/946 (4.3)	1.06 (0.70-1.60)
Beishuizen et al,[23] 2004	2	3/103 (2.9)	4/79 (5.1)	0.58 (0.13-2.50)
Bone et al,[24] 2007	1	0/485 (0)	0/119 (0)	Not estimable
CARDS,[26] 2004	4	61/1428 (4.3)	82/1410 (5.8)	0.73 (0.53-1.01)
HOPE-3,[14] 2016	6	334/6361 (5.3)	357/6344 (5.6)	0.93 (0.81-1.08)
HYRIM,[28] 2005	4	4/283 (1.4)	5/285 (1.8)	0.81 (0.22-2.97)
JUPITER,[29] 2008	2	198/8901 (2.2)	247/8901 (2.8)	0.80 (0.67-0.96)
KAPS,[30] 1995	3	4/214 (1.9)	3/212 (1.4)	1.32 (0.30-5.83)
MEGA,[31] 2006	5	55/3866 (1.4)	79/3966 (2.0)	0.71 (0.51-1.00)
METEOR,[32] 2007	2	1/700 (0.14)	0/281 (0)	1.21 (0.05-29.5)
Prevend-IT,[34] 2004	4	13/433 (3.0)	12/431 (2.8)	1.08 (0.50-2.34)
WOSCOPS,[35] 1995	5	106/3302 (3.2)	135/3293 (4.1)	0.78 (0.61-1.01)
Total (95% CI)		1089/35 967 (3.0)	1262/35 164 (3.6)	0.86 (0.80-0.93)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{13} = 11.07$ ($P = .60$); $I^2 = 0\%$

Test for overall effect: $z = 3.63$ ($P < .003$)



Roger Chou, MD[1,2,3]; Tracy Dana, MLS[1]; Ian Blazina, MPH[1]; et al

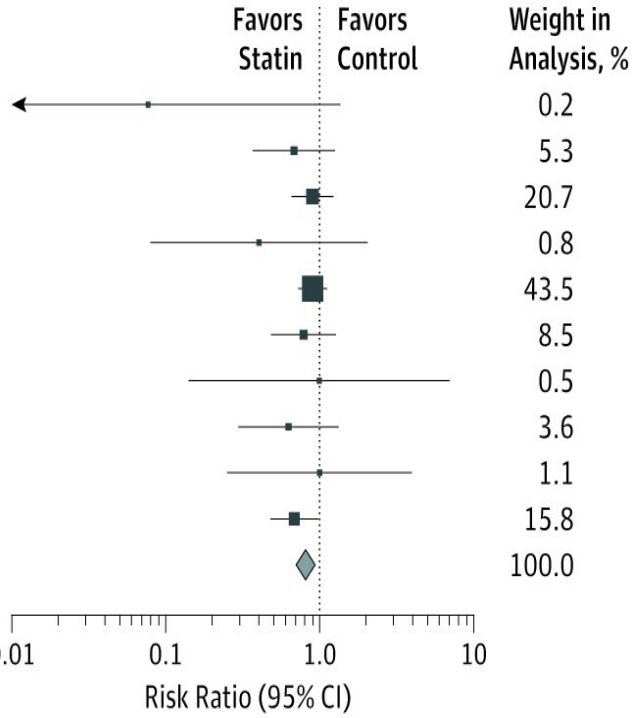
JAMA 2016

B Cardiovascular mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	0/460 (0)	6/459 (1.3)	0.08 (0.004-1.36)	0.2
AFCAPS/TexCAPS,[19] 1998	5	17/3304 (0.51)	25/3301 (0.76)	0.68 (0.37-1.26)	5.3
ASCOT-LLA,[20] 2003	3	74/5168 (1.4)	82/5137 (1.6)	0.90 (0.66-1.23)	20.7
ASTRONOMER,[22] 2010	4	2/134 (1.5)	5/135 (3.7)	0.40 (0.08-2.04)	0.8
HOPE-3,[14] 2016	6	154/6361 (2.4)	171/6344 (2.7)	0.90 (0.72-1.11)	43.5
JUPITER,[29] 2008	2	29/8901 (0.33)	37/8901 (0.42)	0.78 (0.48-1.27)	8.5
KAPS,[30] 1995	3	2/214 (0.93)	2/212 (0.94)	0.99 (0.14-6.97)	0.5
MEGA,[31] 2006	5	11/3866 (0.28)	18/3966 (0.45)	0.63 (0.30-1.33)	3.6
Prevend-IT,[34] 2004	4	4/433 (0.92)	4/431 (0.93)	1.00 (0.25-3.95)	1.1
WOSCOPS,[35] 1995	5	50/3302 (1.5)	73/3293 (2.2)	0.68 (0.48-0.98)	15.8
Total (95% CI)		343/32 143 (1.1)	423/32 179 (1.3)	0.82 (0.71-0.94)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_9 = 6.38$ ($P = .70$); $I^2 = 0\%$

Test for overall effect: $z = 2.78$ ($P = .005$)



Roger Chou, MD[1,2,3]; Tracy Dana, MLS[1]; Ian Blazina, MPH[1]; et al
JAMA 2016

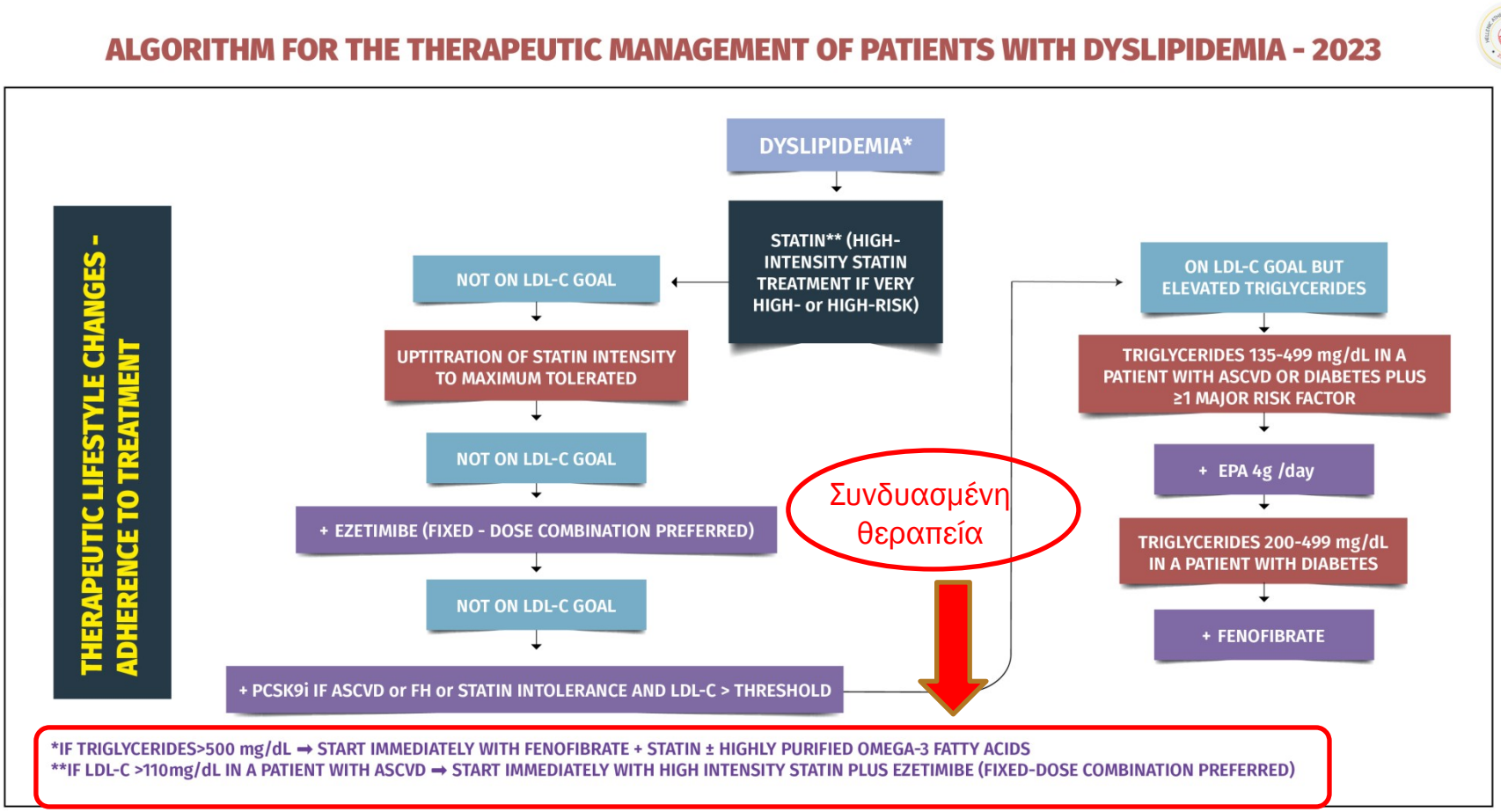


FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol;
CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA - 2023

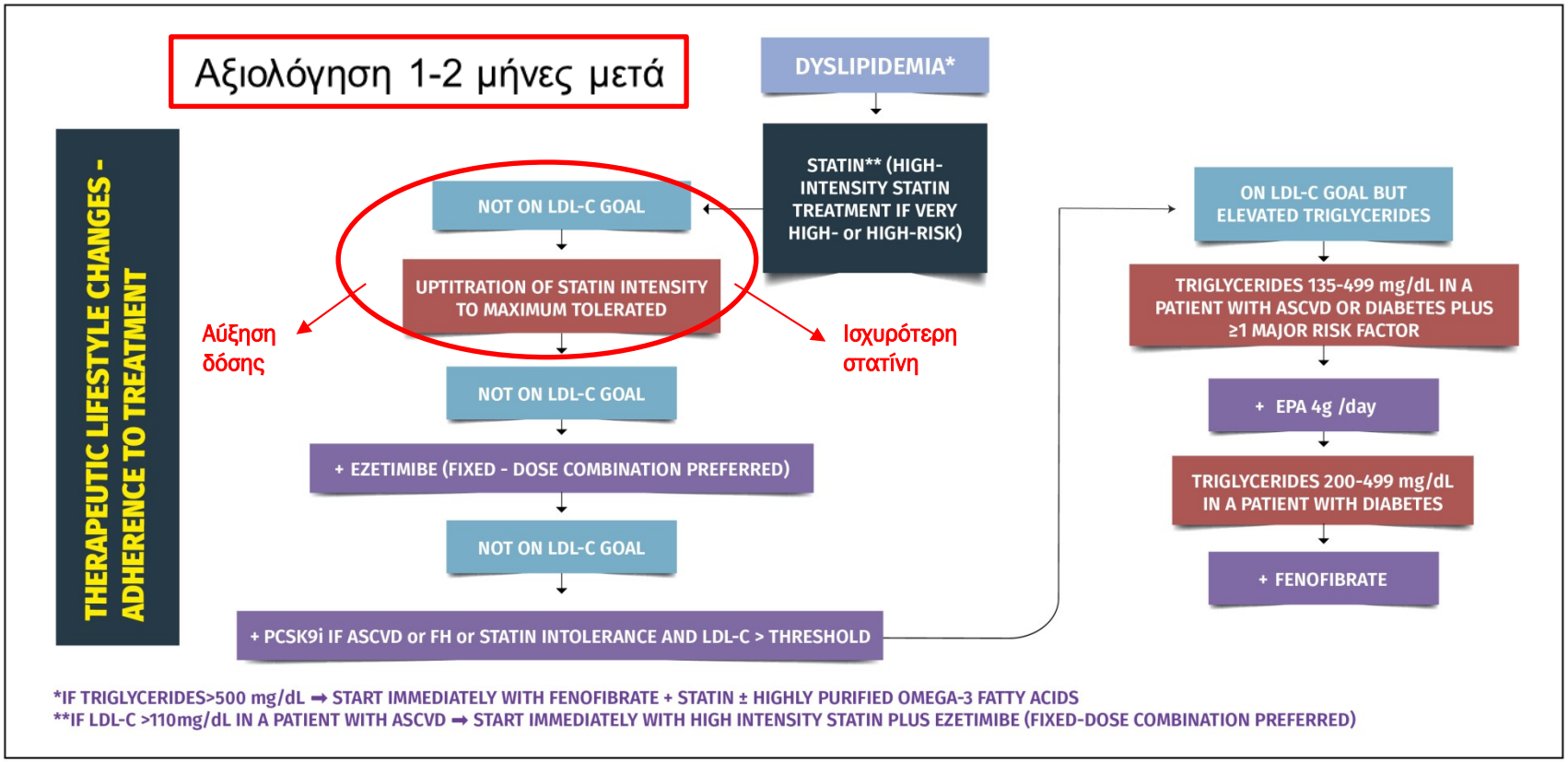


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FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

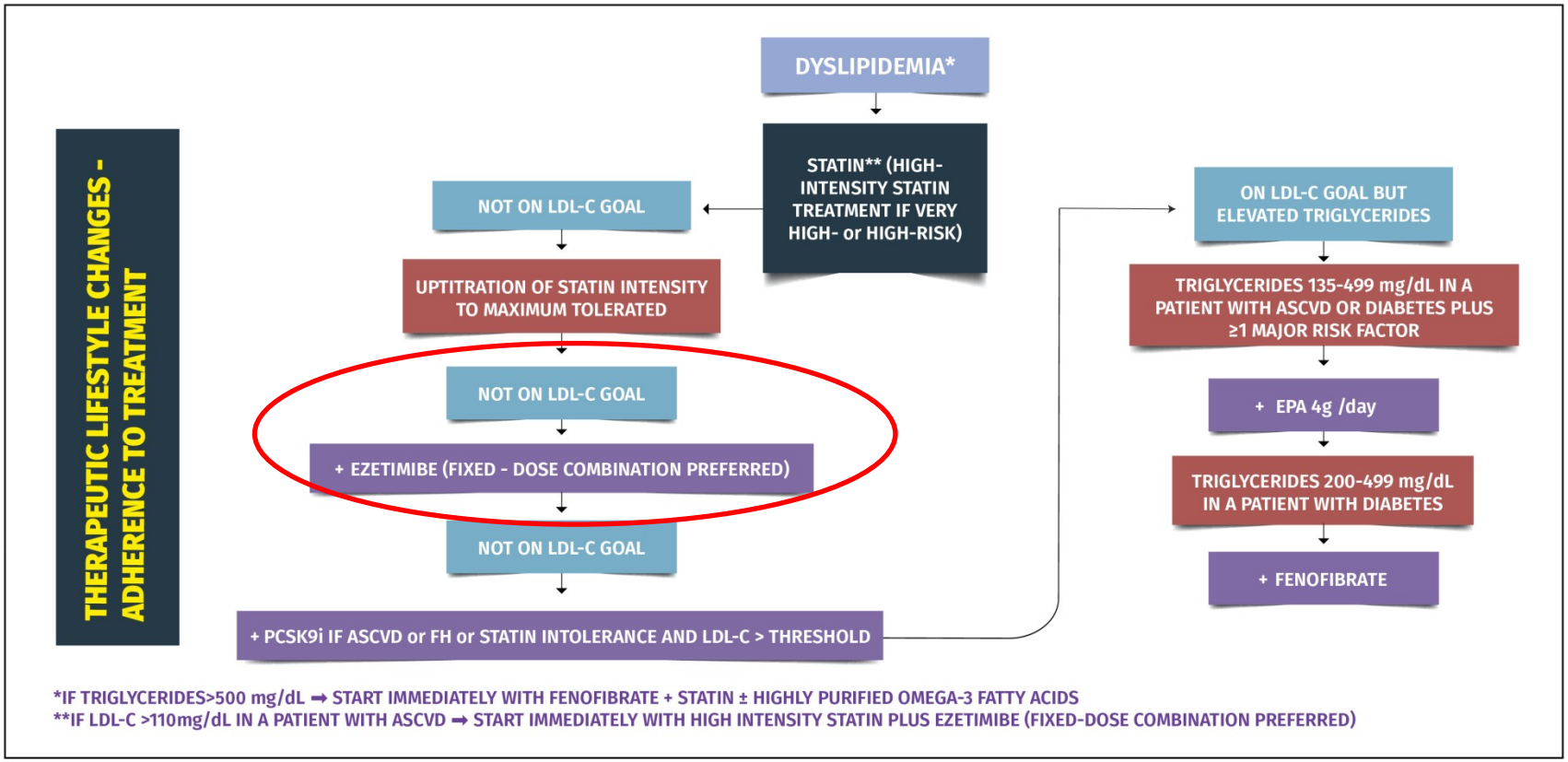
Intensity of statin treatment.

TABLE 55. Intensity of statin treatment.

High intensity (LDL-C reduction >50%)	Moderate intensity (LDL-C reduction 30-50%)	Low intensity (LDL-C reduction <30%)
Atorvastatin 40-80 mg	Atorvastatin 10-30 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40 mg	Fluvastatin 40 mg
	Lovastatin 40 mg	
	Fluvastatin XL80 mg	
	Pitavastatin 1-4 mg	

LDL-C: low-density lipoprotein cholesterol

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA - 2023



Hellenic Atherosclerosis Society

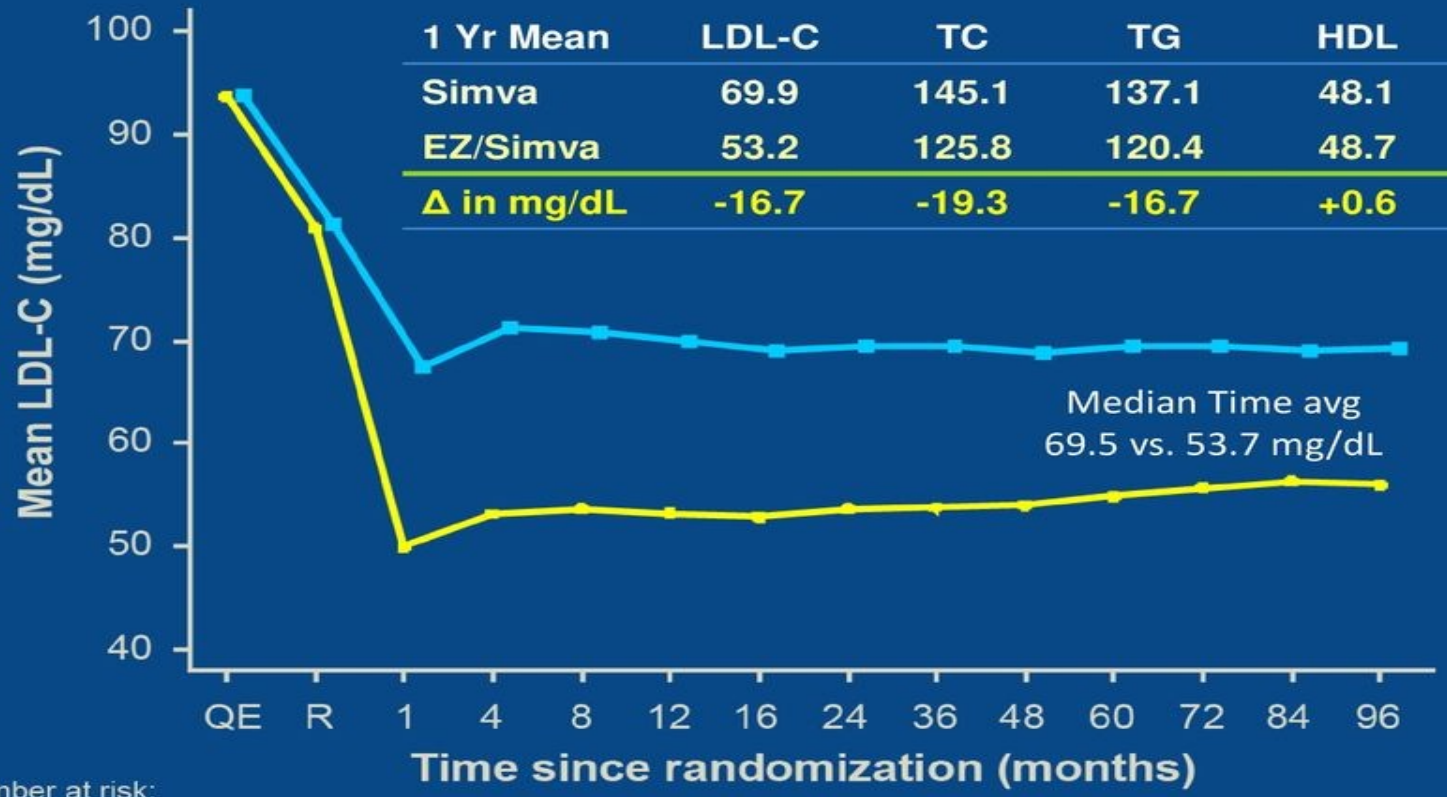
FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol;
CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

ΕΖΕΤΙΜΙΜΠΗ

- Παρεμποδίζει την απορρόφηση της χοληστερόλης στο έντερο
- Επιπλέον μείωση LDL 10-20% όταν προστεθεί στην αντιλιπιδαιμική αγωγή
- Μείωση καρδιαγγειακών συμβαμάτων

IMPROVE-IT: LDL-C and Lipid Changes

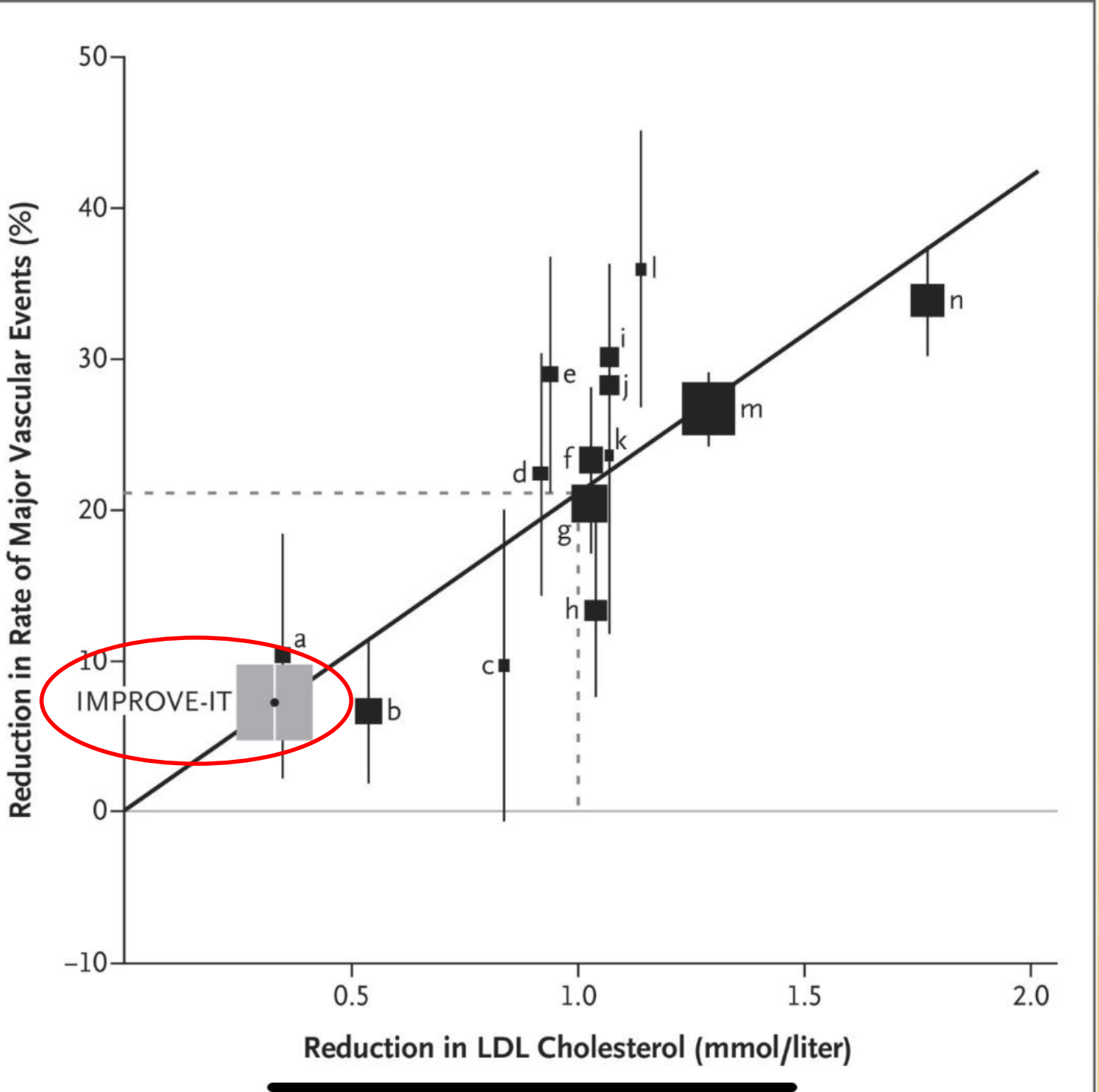
1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



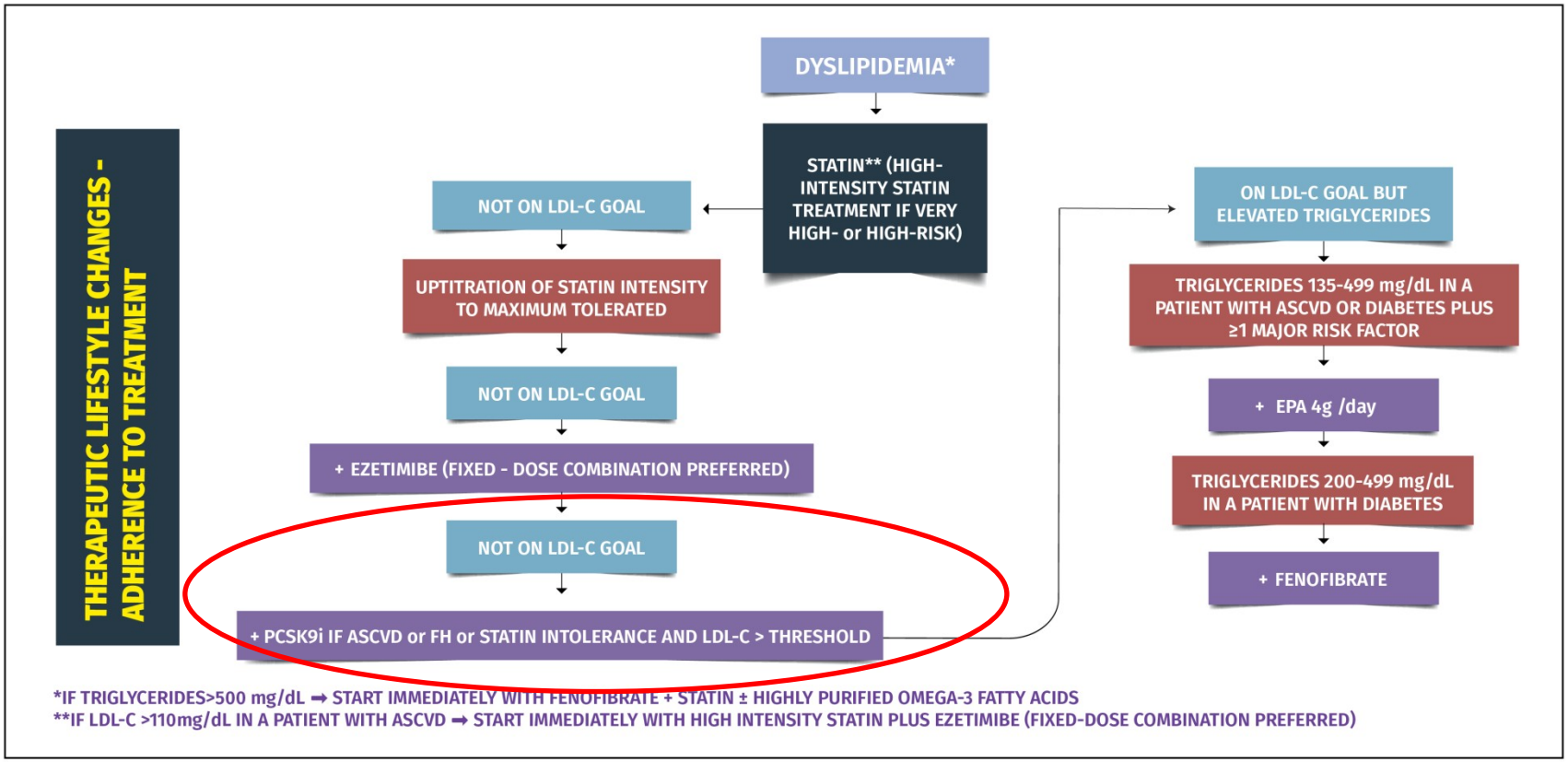
Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Cannon CP presented AHA late breaking clinical trials Nov 19, 2014


50
40
30
20
10
0
−10
Reduction in Rate of Major Vascular Events (%)
IMPROVE-IT
a
b
c
d
e
f
g
h
i
j
k
l
m
n
0.5
1.0
1.5
2.0
Reduction in LDL Cholesterol (mmol/liter)

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA - 2023

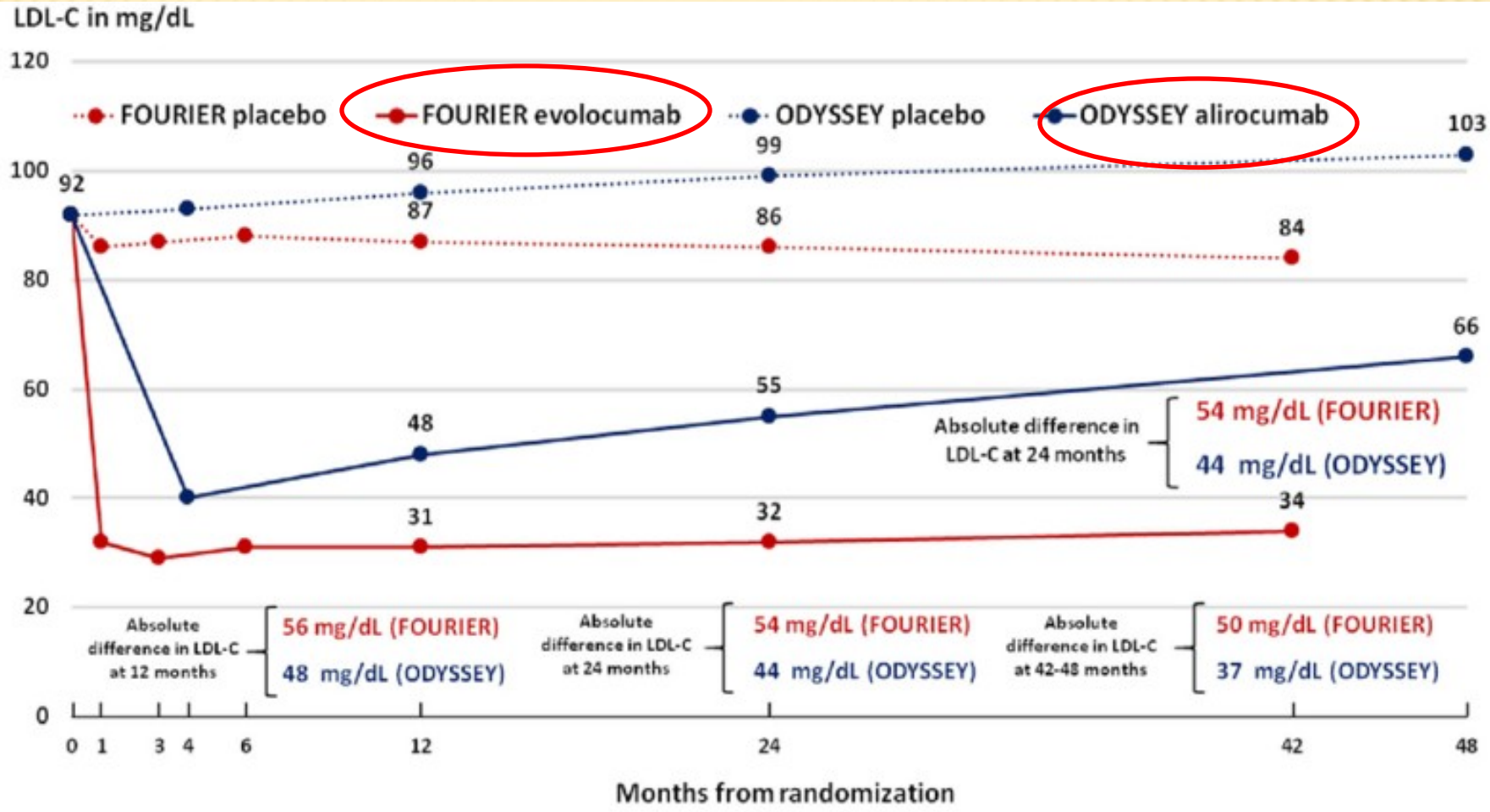


Hellenic Atherosclerosis Society

FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

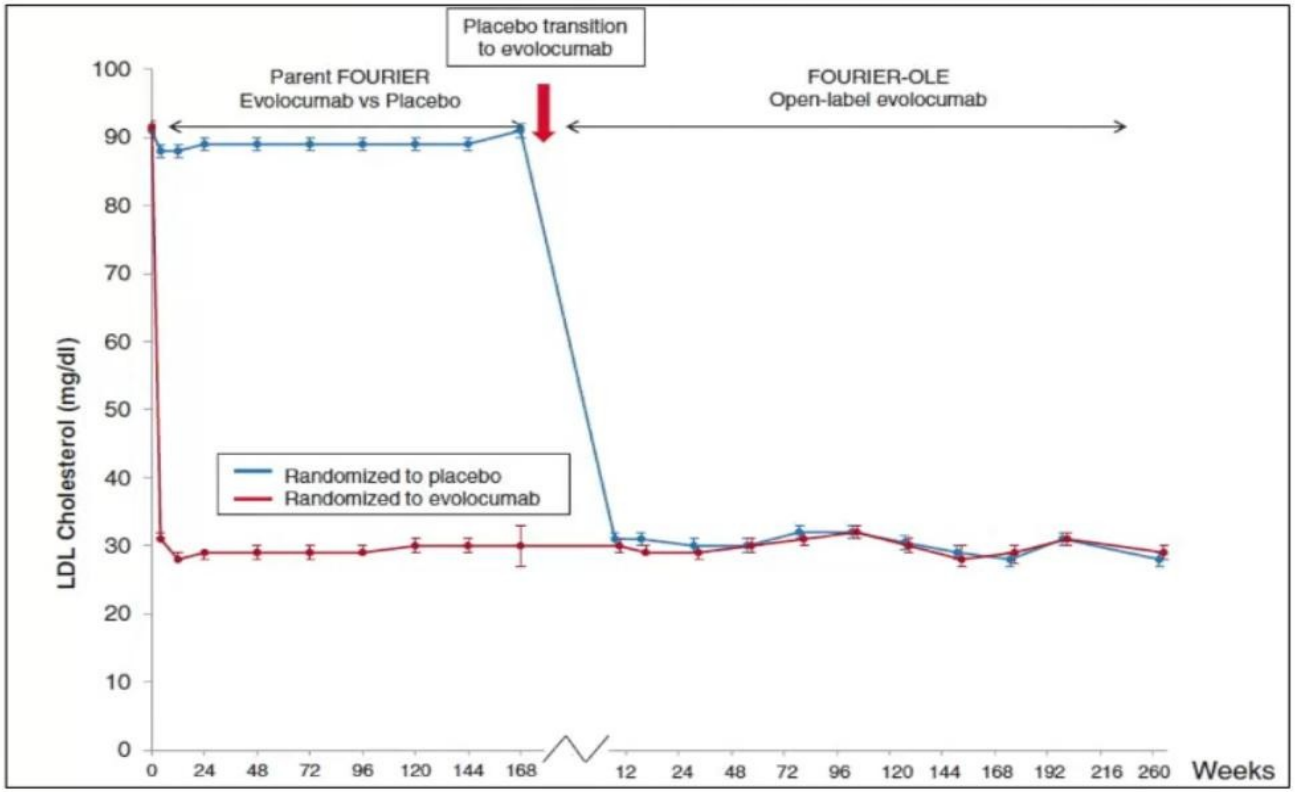
ΑΝΑΣΤΟΛΕΙΣ PCSK9

- Μείωση της PCSK9
- Αύξηση αριθμού και δραστηριότητας LDLR
- Αύξηση καταβολισμού LDL
- Μείωση της LDL >60%



Remo H. M. Furtado . Robert P. Giugliano Cardiol Ther (2020)

Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease



- Δεν παρατηρήθηκαν αξιόλογες ανεπιθύμητες ενέργειες

O'Donghue ML. Circulation 2022;146: 1109-19

ELIGIBLE PATIENTS FOR PCSK9 INHIBITORS

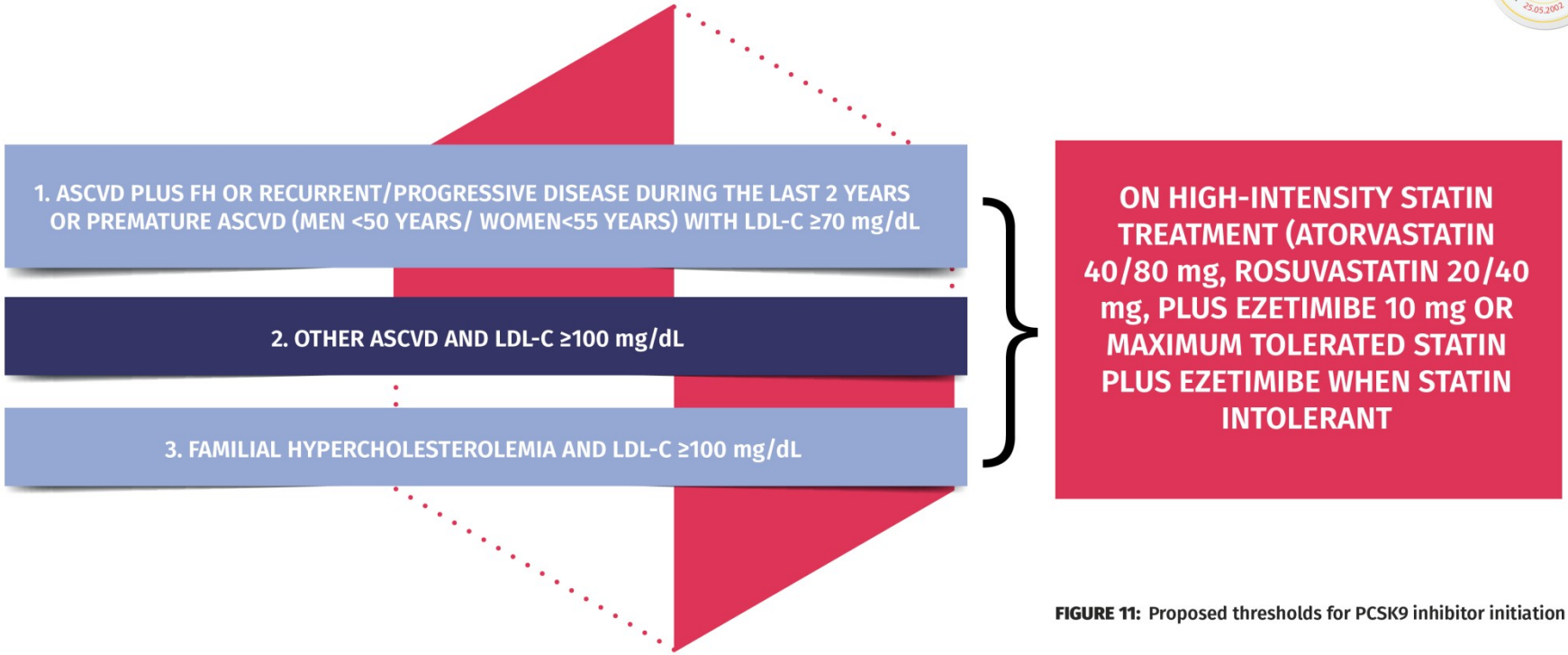


FIGURE 11: Proposed thresholds for PCSK9 inhibitor initiation

PCSK9: proprotein convertase subtilisin/ kexin type 9; ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia

Intensity of LLT

Treatment	Average LDL-C Reduction, %
Moderate-intensity statin	~30
High-intensity statin	~50
High-intensity statin + ezetimibe	~65
PCKK9-targeted siRNA therapy	~50[b]
PCSK9 inhibitor	~60
PCSK9 inhibitor + high-intensity statin	~75
PCSK9 inhibitor + high-intensity statin + ezetimibe	~85

siRNA, small interfering RNA.
a. Mach F, et al. Eur Heart J. 2020;41:111-188; b. Ray KK, et al. Lancet Diabetes Endocrinol. 2023;11:109-119.

Recommendations for drug treatments of patients with hypertriglyceridaemia (1)

EAS ESC European Society of Cardiology

Υψηλά επίπεδα TG αυξάνουν τον καρδιαγγειακό κίνδυνο αλλά το όφελος από τη μείωσή τους δεν έχει πλήρως τεκμηριωθεί

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (>200 mg/dL)).	I	B
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with statin.	IIa	B

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

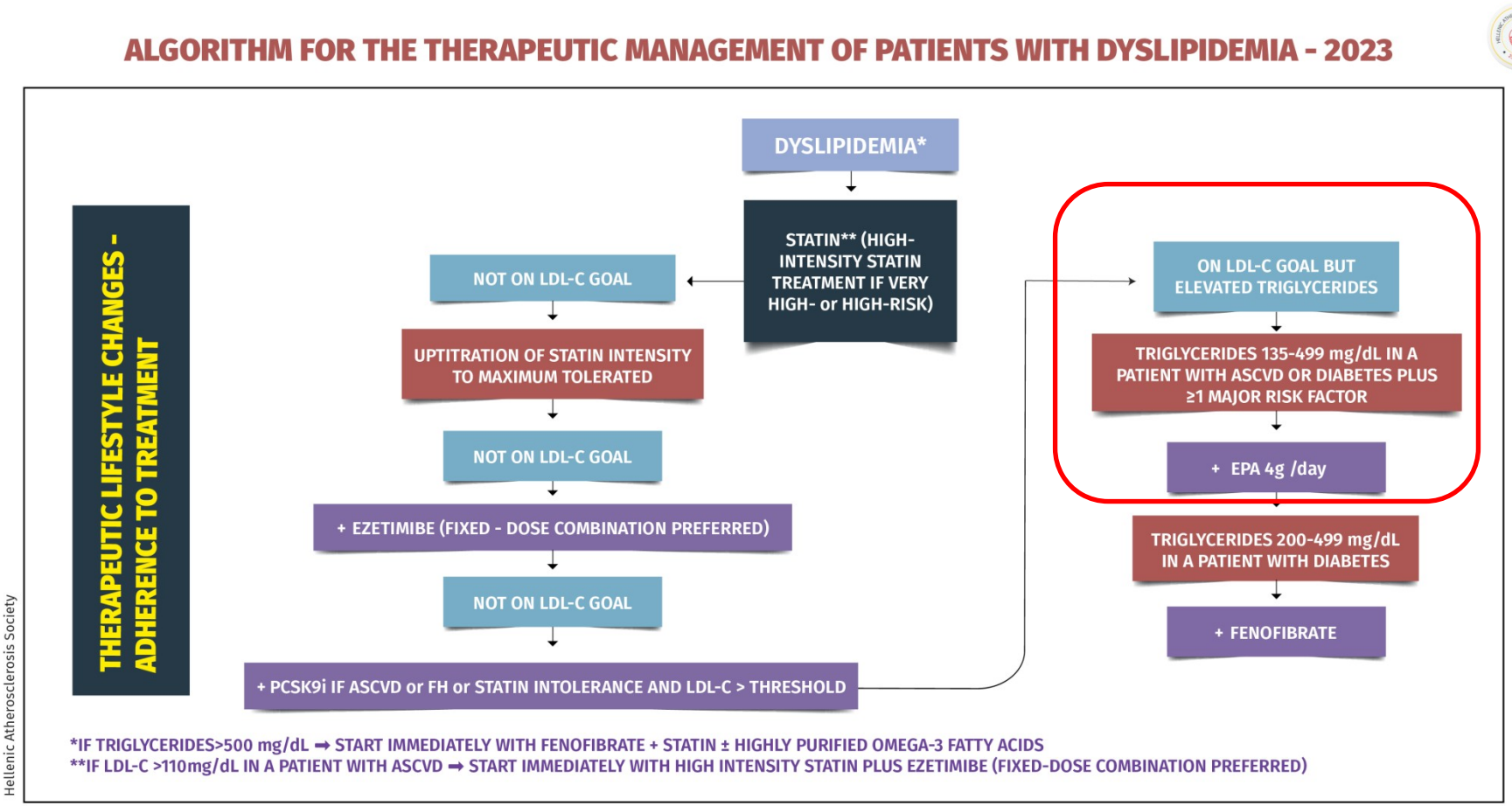


FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

2019

REDUCE-IT USA

Results From the 3,146 Patients Randomized in the United States

AMERICAN COLLEGE of CARDIOLOGY

Multicenter, randomized, double-blind, placebo-controlled clinical trial

Objective: To assess the degree of benefit of icosapent ethyl for cardiovascular risk reduction in the USA.

3,146 patients

Inclusion criteria: Patients with CVD or with diabetes and other risk factors, on statin therapy and elevated triglyceride levels (135-499 mg/dl).

Icosapent ethyl (n=1,548)	VS	Placebo (n=1,598)

PRIMARY OUTCOME

18.2	CV death, non-fatal MI or stroke, revascularization or unstable angina HR 0.69; 95% CI 0.59-0.80; P<0.001	24.7

SECONDARY OUTCOME

12.1	CV death, non-fatal MI, or non-fatal stroke % HR 0.69; 95% CI 0.57-0.83; P<0.001	16.6
7.2	All-cause mortality % HR 0.70; 95% CI 0.55-0.90; P=0.004 USA vs Non-USA, $P_{interaction}$=0.02	9.8

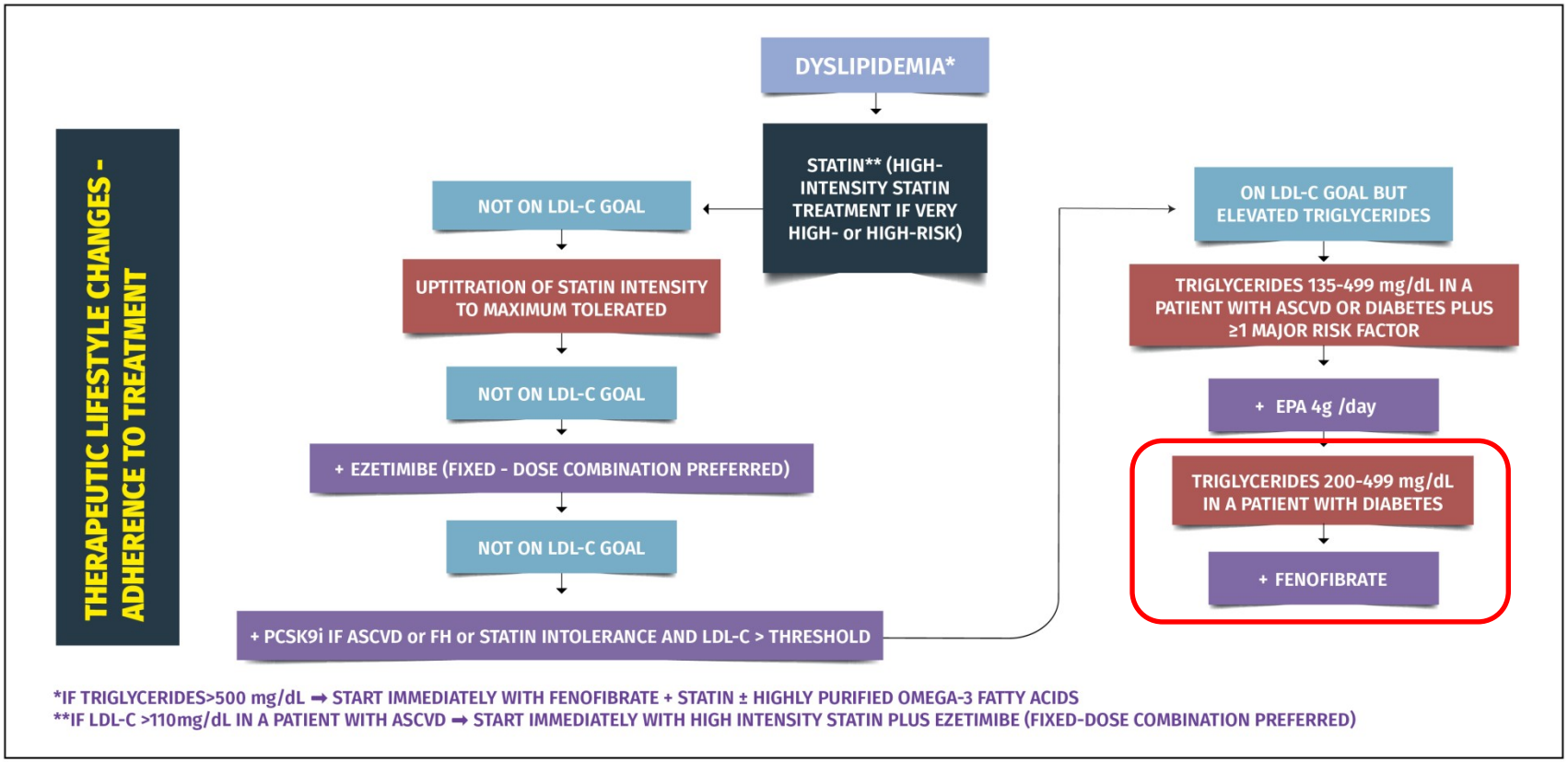
Conclusion: The prespecified subgroup analysis of the USA cohort of the REDUCE-IT trial demonstrated particularly robust reductions in the primary and key secondary endpoints including the individual endpoints such as all-cause mortality.

Bhatt DL, Miller M, Brinton EA, et al., on behalf of the REDUCE-IT Investigators. REDUCE-IT USA: Results From the 3,146 Patients Randomized in the United States. *Circulation* 2019;Nov 11:[Epub ahead of print].

STRENGTH		REDUCE-IT
EPA + DHA carboxylic acids	Omega-3 preparation	Icosapent ethyl
Corn oil	Placebo used	Mineral oil
49.9%	High-intensity statin	30%
55.9%	% with ASCVD	70.7%
70.1%	% with diabetes	58.5%
239 mg/dL	Baseline triglycerides	216 mg/dL
3.2 years	Median follow-up	4.9 years
HR (95% CI)	**RESULTS**	HR (95% CI)
0.99 (0.90-1.09)	Overall	0.75 (0.68-0.83)
1.16 (0.95-1.41)	Primary prevention	0.88 (0.70-1.10)
0.94 (0.84-1.05)	Secondary prevention	0.73 (0.65-0.81)
0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5		0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5
EPA+DHA Better / Placebo Better		EPA Better / Placebo Better

Μελέτες με χαμηλότερες δόσεις ω3 λιπαρών οξέων χωρίς καρδιαγγειακό όφελος

ALGORITHM FOR THE THERAPEUTIC MANAGEMENT OF PATIENTS WITH DYSLIPIDEMIA - 2023



Hellenic Atherosclerosis Society

FIGURE 10. Proposed treatment algorithm.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid

2022

PROMINENT TRIAL

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

Multinational, double-blind, randomized, controlled trial

Objective: To evaluate pemafibrate compared with placebo among patients with type 2 diabetes and hypertriglyceridemia.

10,497 Patients

Inclusion criteria:
Type 2 diabetes
Triglyceride level 200–499 mg/dL
High-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL

pemafibrate 0.2 mg twice daily (n = 5,240)		placebo (n = 5,257)
	PRIMARY OUTCOME	
3.6	CV death, nonfatal MI, ischemic stroke, or coronary revascularization % p = 0.67	3.5
	SECONDARY OUTCOMES	
-31.1	Median change in triglyceride level from baseline %	-6.9
3.2	Median change in apolipoprotein B level from baseline %	-1.6
10.7	Any adverse renal event p = 0.004	9.6

Conclusion: Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels.

Aruna Das Pradhan et al. NEJM, 2022; 387:1923-1934

Laboratory follow-up in patients on hypolipidemic drug treatment

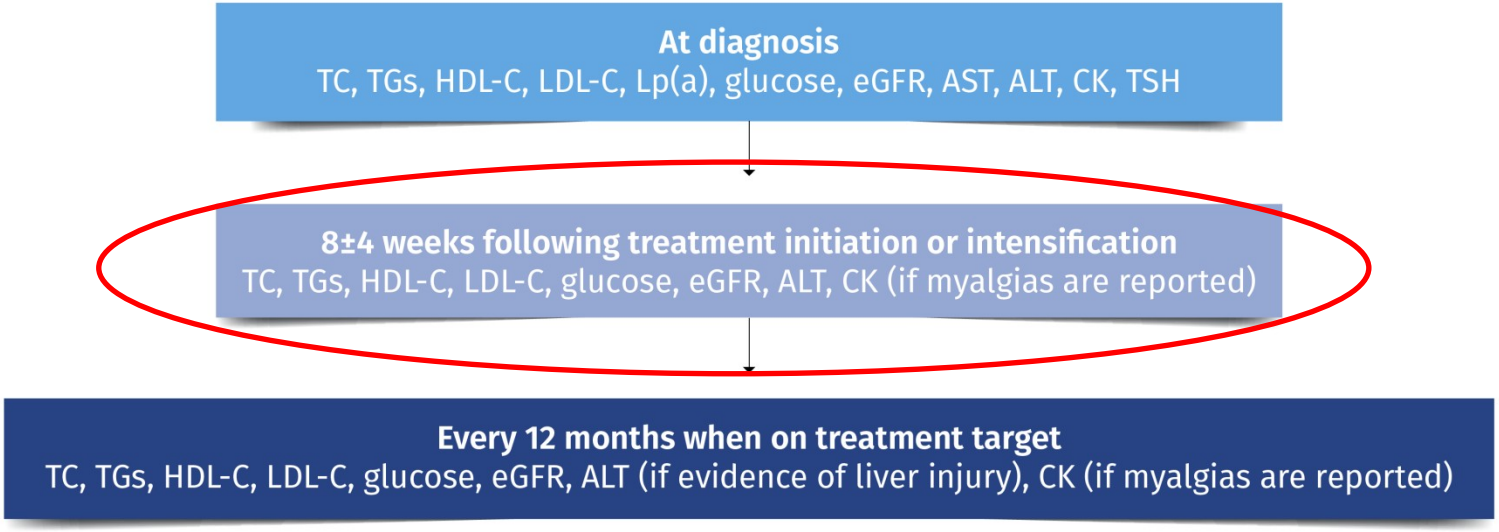


FIGURE 12: Laboratory follow-up in patients on hypolipidemic drug treatment

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (3)

EAS ESC European Society of Cardiology

Monitoring liver and muscle enzymes

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT <3x upper limit of normal (ULN):

- Continue therapy.
- Recheck liver enzymes in 4–6 weeks.

2% των ασθενών θα εμφανίσουν παροδική αύξηση ALT που υποχωρεί στη διάρκεια της θεραπείας

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (4)

EAS ESC European Society of Cardiology

Monitoring liver and muscle enzymes

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT ≥3x ULN:

- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

ΜΥΟΠΑΘΕΙΑ ΑΠΟ ΣΤΑΤΙΝΗ

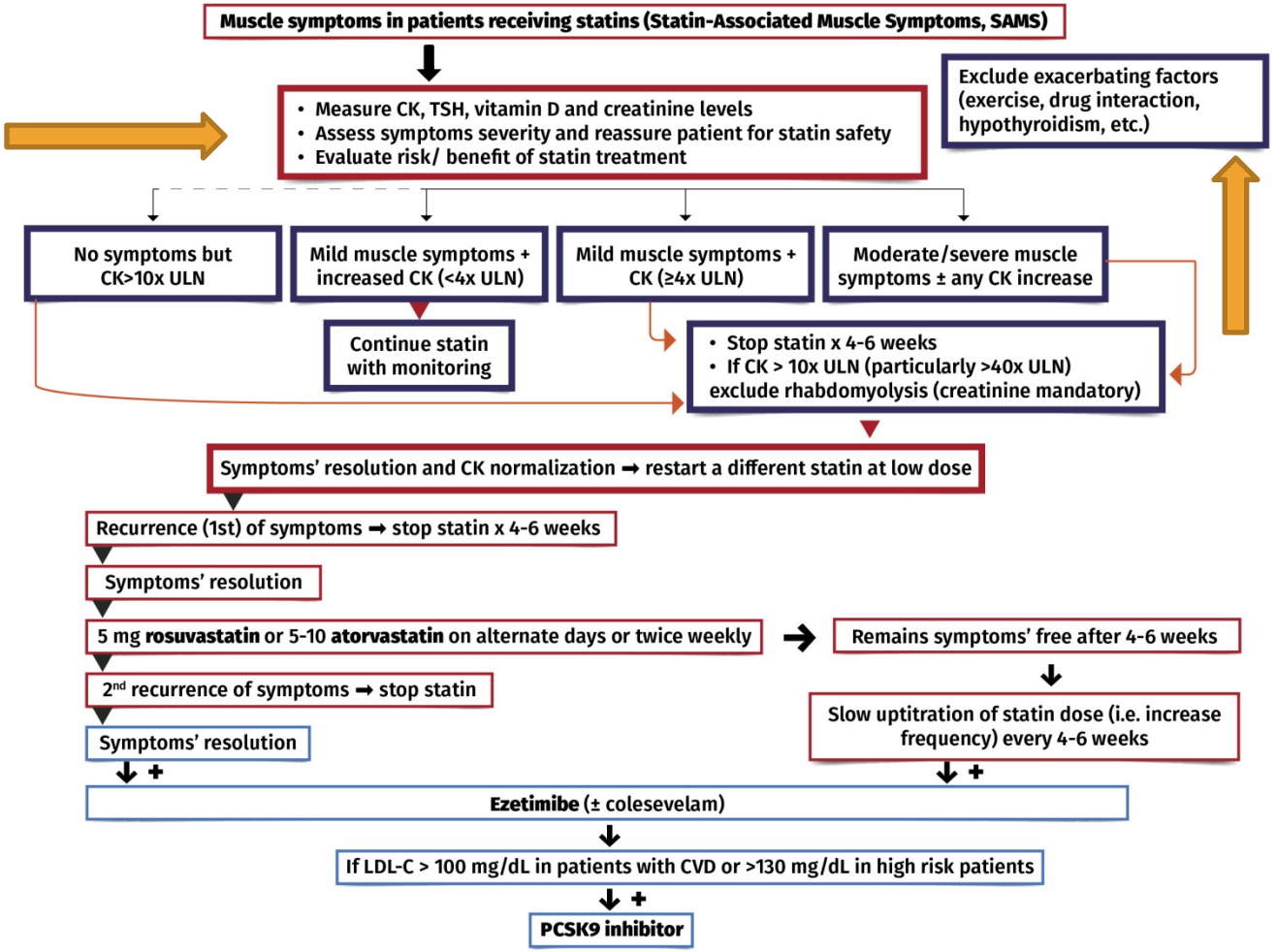


Figure 8. Algorithm for the management of patients with statin-associated muscle symptoms

CK: creatine kinase; ULN: upper limit of normal; TSH: thyroid-stimulating hormone; LDL-C: low-density lipoprotein cholesterol; CVD: cardiovascular disease; PCSK9: proprotein convertase subtilisin/ kexin type9

ΜΥΟΠΑΘΕΙΑ ΑΠΟ ΣΤΑΤΙΝΗ

- CPK>10 ULN
- ΣΟΒΑΡΗ ΜΥΑΛΓΙΑ
- ΗΠΙΑ ΜΥΑΛΓΙΑ ΚΑΙ CPK>4 ULN

ΔΙΑΚΟΠΗ ΣΤΑΤΙΝΗΣ ΚΑΙ ΑΞΙΟΛΟΓΗΣΗ ΣΕ 4-6 W

- ΥΦΕΣΗ ΤΩΝ ΣΥΜΠΤΩΜΑΤΩΝ ΚΑΙ ΑΠΟΚΑΤΑΣΤΑΣΗ ΤΗΣ ΤΙΜΗΣ ΤΗΣ CK

ΕΝΑΡΞΗ ΧΑΜΗΛΗΣ ΕΝΤΑΣΗΣ ΚΑΙ ΣΕ ΧΑΜΗΛΗ ΔΟΣΗ ΣΤΑΤΙΝΗ

- ΣΕ ΥΠΟΤΡΟΠΗ ΕΝΑΡΞΗ ΙΣΧΥΡΗΣ ΣΤΑΤΙΝΗΣ ΣΕ ΧΑΜΗΛΗ ΔΟΣΗ 2-3 ΦΟΡΕΣ ΤΗΝ ΕΒΔΟΜΑΔΑ
- ΣΕ ΕΠΑΝΕΜΦΑΝΙΣΗ ΣΥΜΠΤΩΜΑΤΩΝ **ΔΙΑΚΟΠΗ ΣΤΑΤΙΝΗΣ ΟΡΙΣΤΙΚΑ**

ΕΝΑΡΞΗ ΕΖΕΤΙΜΙΜΠΗΣ ΚΑΙ ΠΡΟΣΘΗΚΗ
ΚΟΛΕΣΕΒΕΛΑΜΗΣ Η/ΚΑΙ ΑΝΑΣΤΟΛΕΑ
PCSK9 ΑΝΑΛΟΓΑ ΜΕ ΤΟΝ ΣΤΟΧΟ ΤΗΣ
LDL ΚΑΙ ΤΟΝ ΚΑΡΔΙΑΓΓΕΙΑΚΟ ΚΙΝΔΥΝΟ

ΕΠΙΤΥΓΧΑΝΕΤΑΙ ΤΕΛΙΚΑ Ο ΣΤΟΧΟΣ ΓΙΑ ΤΗΝ LDL;

ESC European Society of Cardiology

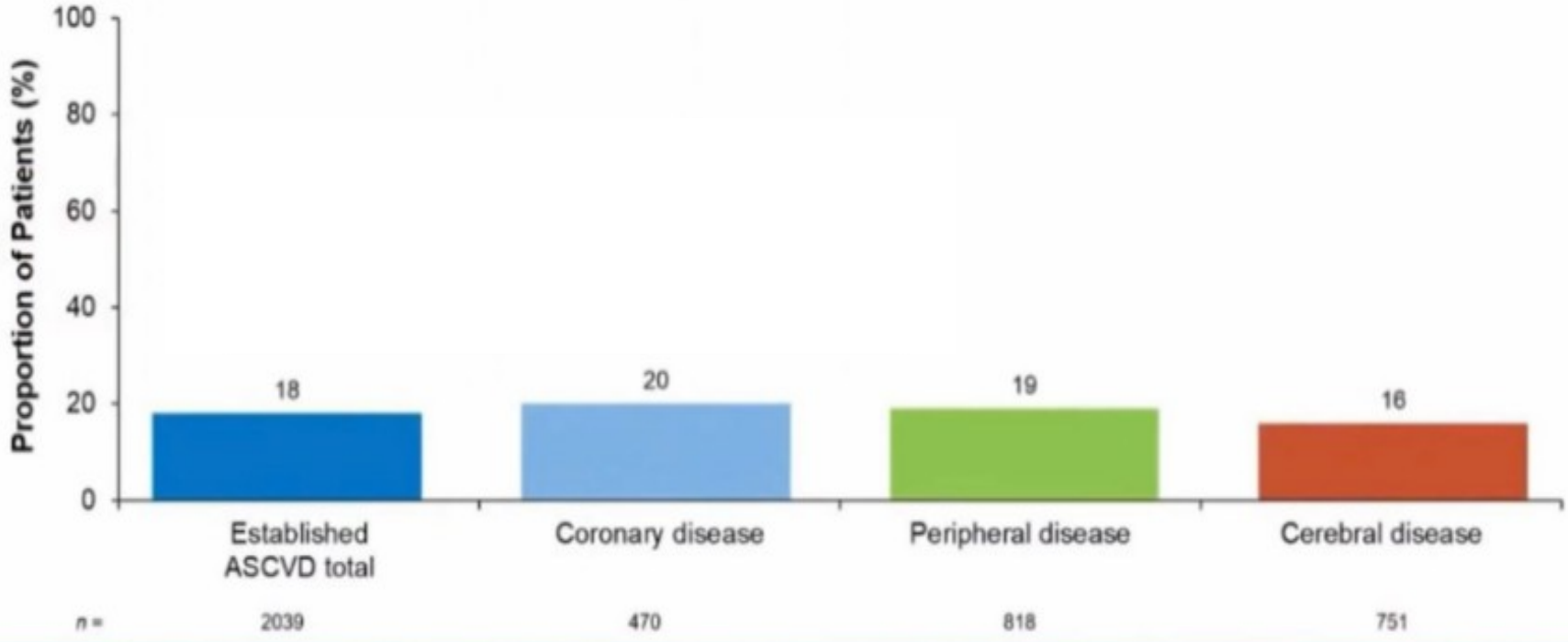
European Journal of Preventive Cardiology (2021) **28**, 1279–1289
doi:10.1093/eurjpc/zwaa047

FULL RESEARCH PAPER

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

Kausik K. Ray[1]*, Bart Molemans[2], W. Marieke Schoonen[3], Periklis Giovas[4], Sarah Bray[5], Gaia Kiru[6], Jennifer Murphy[6], Maciej Banach[7,8,9], Stefano De Servi[10], Dan Gaita[11], Ioanna Gouni-Berthold[12], G. Kees Hovingh[13], Jacek J. Jozwiak[14], J. Wouter Jukema[15], Robert Gabor Kiss[16], Serge Kownator[17], Helle K. Iversen[18,19], Vincent Maher[20,21], Luis Masana[22], Alexander Parkhomenko[23], André Peeters[24], Piers Clifford[25], Katarina Raslova[26], Peter Siostrzonek[27], Stefano Romeo[28,29,30], Dimitrios Tousoulis[31], Charalambos Vlachopoulos[31], Michal Vrablik[32], Alberico L. Catapano[33], and Neil R. Poulter[6]; on behalf of the DA VINCI study†

DA VINCI: Among Patients with Established ASCVD, 18% Achieved the 2019 ESC/EAS Very-High Risk Goal of LDL-C < 1.4 mmol/L (< 55 mg/dL)



In very high risk patients, 2019 goal attainment was approximately half that of 2016 (18% vs 39%).

ASCVD = atherosclerotic cardiovascular disease; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol.
Ray, KK, et al. *Eur J Prev Cardiol.* Suppl 2020. doi:10.1093/eurjpc/zwaa047.

The Future of Lipid-Lowering Strategy to Reduce ASCVD

Start early

Less "atherogenic lipoprotein [ie, LDL-C, TRL, Lp(a)] exposure" leads to prevention of lesion formation

Treat more aggressively

Treat much more aggressively from desirable target to "atherogenic lipoprotein elimination"

Combination therapy + novel nucleic acid therapies

Atherogenic lipoprotein lowering reduces CV risk

Courtesy of Frederick J. Raal, MBBCh, MMed, PhD, FCP(SA), FRCPC, MRCP.

Ευχαριστώ για την προσοχή σας!