ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΓΩΓΗ ΑΣΘΕΝΩΝ ΜΕ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ

Ο ρόλος των στατινών

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Ειδική Γραμματέας της Ελληνικής Εταιρείας Αθηροσκλήρωσης

European Association for the Study of Obesity (EASO) National Fellow

International Atherosclerosis Society (IAS)-Europe: Executive Board Member

International Lipid Expert Panel (ILEP) Member

INTERNATIONAL HELLENIC UNIVERSITY

European University Cyprus

EASO European Association for the Study of Obesity

IAS INTERNATIONAL ATHEROSCLEROSIS SOCIETY

HELLENIC ATHEROSCLEROSIS SOCIETY 25-5-02

International ILEP Lipid Expert Panel

Δήλωση συμφερόντων

429 δημοσιεύσεις στο PubMed, >9,000 αναφορές, H-index: 49

- Associate Editor of ***Angiology***
- Associate Editor of the ***Journal of Diabetes Complications***
- Associate Editor of the ***Hormones-International Journal of Endocrinology and Metabolism***

- Section Editor of ***Archives of Medical Science***

- Book Review and News and Views Editor of ***Current Vascular Pharmacology***
- Editorial Board Member of ***Metabolism Clinical and Experimental*** and ***Current Medical Research and Opinion***

- Η ΝΚ έχει συμμετάσχει σε κλινικές μελέτες, συνέδρια ή/και έχει δώσει ομιλίες χρηματοδοτούμενες από Amgen, Astra-Zeneca, Boehringer Ingelheim, Elpen, Libytec, Novartis, Novo Nordisk, Sanofi, Vianex και Viatris

STANFORD UNIVERSITY NAMES WORLD'S TOP 2% SCIENTISTS, 2023

Posted on **October 4, 2023**

On 4 October 2023, Elsevier published data-update for "Updated science-wide author databases of standardized citation indicators.

Θεραπεία με στατίνη

Hellenic Atherosclerosis Society

• GUIDELINES •

Hellenic Atherosclerosis Society Guidelines for the Diagnosis and Treatment of Dyslipidemias - 2023

Katsiki N*, Filippatos TD*, Vlachopoulos C, Panagiotakos D, Milionis H, Tselepis A, Garoufi A, Rallidis L, Richter D, Nomikos T, Kolovou G, Kypreos K, Chrysohoou C, Tziomalos K, Skoumas I, Koutagiar I, Attilakos A, Papagianni M, Boutari C, Kotsis V, Pitsavos C, Elisaf M, Tsioufis K, Liberopoulos E

*Equal contribution

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. HELLENIC SCORE II ≥10%
II. High ASCVD risk group	1. HELLENIC SCORE 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. HELLENIC SCORE 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	HELLENIC SCORE II <1%

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

LDL-C TARGETS 2023

Hellenic Atherosclerosis Society

CVD RISK

VERY HIGH RISK	HIGH RISK	MODERATE RISK	LOW 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%	• 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%	• DIABETES <10 YEARS IN PATIENTS <50 YEARS • HELLENIC SCORE II ≥1-<5%	HELLENIC SCORE II <1%
↓ LDL-C <55 mg/dL PLUS LDL-C >50%	↓ LDL-C <70 mg/dL PLUS LDL-C ~50%	LDL-C <100 mg/dL	LDL-C <116 mg/dL

Έναρξη υπολιπιδαιμικής αγωγής

Hellenic Atherosclerosis Society

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

Στόχοι υπολιπιδαιμικής αγωγής

ΤΙΜΕΣ ΑΝΑΦΟΡΑΣ ΕΡΓΑΣΤΗΡΙΑΚΩΝ ΕΞΕΤΑΣΕΩΝ - ΕΝΗΛΙΚΕΣ

Lipid parameter	Result	Target values*
TOTAL CHOLESTEROL (mg/dL)		<170 (DEPENDING ON LDL-C TARGET)
LDL CHOLESTEROL (mg/dL)**		<55 FOR VERY HIGH-RISK PATIENTS <70 FOR HIGH-RISK PATIENTS <100 FOR MODERATE RISK PATIENTS <116 FOR LOW-RISK PATIENTS
TRIGLYCERIDES (mg/dL)		<150
HDL CHOLESTEROL (mg/dL)		>40 FOR MEN >50 FOR WOMEN

*TARGET VALUE IS DEFINED BY THE PHYCISIAN BASED ON CVD RISK
**IF LDL-C>190 mg/dL, FH SHOULD BE EXCLUDED
**Lp(a) >180 mg/dL IS ASSOCIATED WITH VERY HIGH CVD RISK

ΤΙΜΕΣ ΑΝΑΦΟΡΑΣ ΕΡΓΑΣΤΗΡΙΑΚΩΝ ΕΞΕΤΑΣΕΩΝ - ΕΝΗΛΙΚΕΣ

Lipid parameter	Result	Target values*
NON-HDL CHOLESTEROL (mg/dL)		<85 FOR VERY HIGH-RISK PATIENTS <100 FOR HIGH-RISK PATIENTS <130 FOR MODERATE RISK PATIENTS
ApoB (mg/dL)		<65 FOR VERY HIGH-RISK PATIENTS <80 FOR HIGH-RISK PATIENTS <100 FOR MODERATE RISK PATIENTS
Lp(a) (mg/dL)***		<30

*TARGET VALUE IS DEFINED BY THE PHYCISIAN BASED ON CVD RISK
**IF LDL-C>190 mg/dL, FH SHOULD BE EXCLUDED
**Lp(a) >180 mg/dL IS ASSOCIATED WITH VERY HIGH CVD RISK

Θεραπευτική αντιμετώπιση δυσλιπιδαιμίας

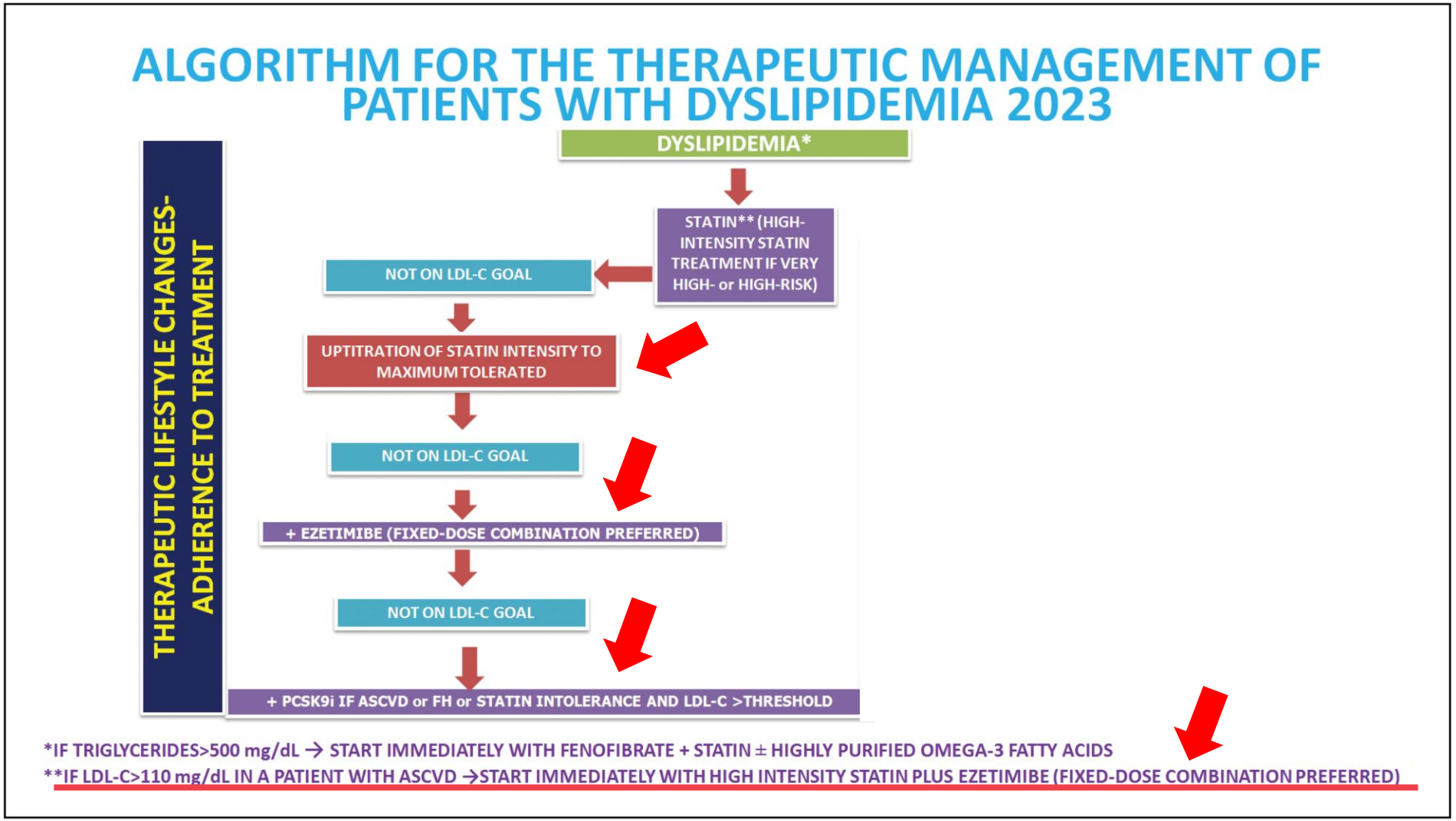

FIGURE 10. Proposed treatment algorithm.

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

Συμφωνία (Consensus) Ειδικών για την Αντιμετώπιση της Δυσλιπιδαιμίας σε Ασθενείς με Οξύ Στεφανιαίο Σύνδρομο – Update 2022

Χαράλαμπος Βλαχόπουλος*, Λουκιανός Ραλλίδης*, Χρήστος Μιχαλακέας, Δημήτριος Αλεξόπουλος, Γεώργιος Ανδρικόπουλος, Εμμανουήλ Βαβουρανάκης, Γεώργιος Γιαννακούλας, Άννα Δαγρέ, Ευάγγελος Ζάχαρης, Χαράλαμπος Καρβούνης, Νίκη Κατσίκη, Γενοβέφα Κολοβού, Μιχαήλ Κουτούζης, Γεώργιος Κοχιαδάκης, Ευάγγελος Λυμπερόπουλος, Αικατερίνη Νάκα, Περικλής Νταβλούρος, Χριστόδουλος Παπαδόπουλος, Φραγκίσκος Παρθενάκης, Σωτήριος Πατσιλινάκος, Ευάγγελος Πισιμίσης, Δημήτριος Ρίχτερ, Εμμανουήλ Σκαλίδης, Ιωάννης Σκουλαρίγκης, Ιωάννης Σκούμας, Δημήτριος Τζιακάς, Κωνσταντίνος Τζιόμαλος, Κωνσταντίνος Τούτουζας, Κωνσταντίνος Τσιούφης, Γεράσιμος Φιλιππάτος, Λάμπρος Μιχάλης*, Ιωάννης Κανακάκης*

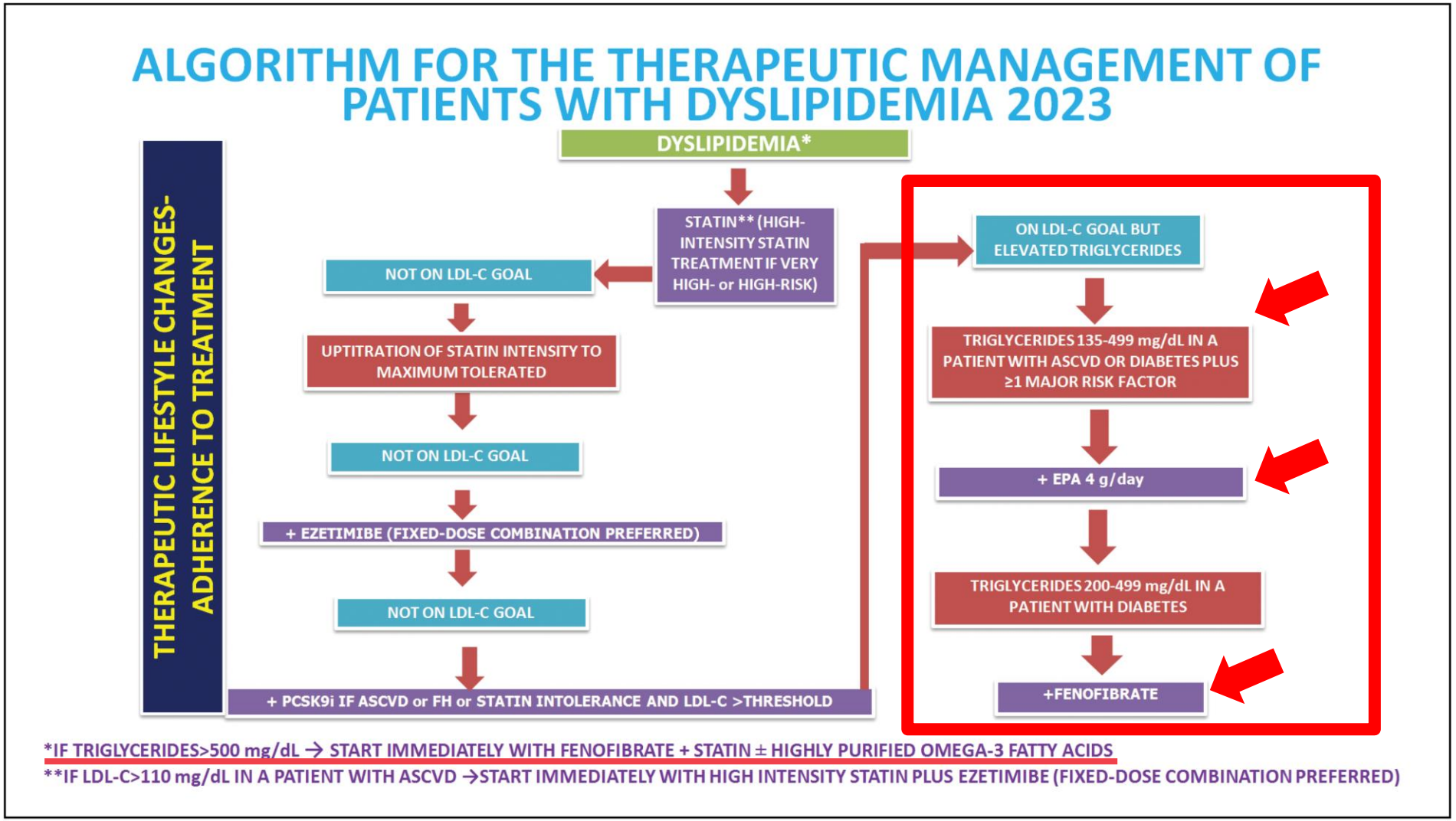

FIGURE 10. Proposed treatment algorithm.

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

Δυσανεξία στις στατίνες

23 Statin Intolerance - Statin-Associated Muscle Symptoms

Hellenic Atherosclerosis Society

TABLE 48. Definitions of statin-associated muscle symptoms proposed by the EAS consensus panel.

Symptoms	CK levels	Incidence	Terminology	Comments
Muscle symptoms	Normal	3-5%	Myalgia	Causality is uncertain
Muscle symptoms	CK >ULN and <10 x ULN	3-5%		Commonly due to exercise or physical activity, but also may be statin-related
Muscle symptoms	CK >10 x ULN and <40 x ULN	0.1-0.2%	Myositis or myopathy	May be statin-related but may be associated with underlying muscle disease
Muscle symptoms	CK >40 x ULN	1 per 10,000 person-years	Rhabdomyolysis when associated with creatinine elevation and/or myoglobinuria	Referral for hospital admission
None	CK >ULN		Asymptomatic CK increase	Raised CK may be incidental finding. Consider checking thyroid function or may be exercise-related

CK: creatine kinase; ULN: upper limit of normal

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CK: creatine kinase; ULN: upper limit of normal

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None	CK >ULN		Asymptomatic CK increase	Raised CK may be incidental finding. Consider checking thyroid function or may be exercise-related

CK: creatine kinase; ULN: upper limit of normal

TABLE 49. Proposed score system that assesses the probability of muscle symptoms to be statin-related.

Parameter	Score
Distribution of symptoms	
• Symmetric, hip flexors or thighs	3
• Symmetric, calves	2
• Symmetric, upper proximal extremities	2
• Not specific to any area, asymmetric or intermittent	1
Timing of symptom onset	
• <4 weeks	3
• >4-12 weeks	2
• >12 weeks	1
Timing of muscle symptoms improvement after statin withdrawal (de-challenge)	
• <2 weeks	2
• 2-4 weeks	1
• No improvement >4 weeks	0
Re-challenge with a statin	
• Same symptoms recur in <4 weeks	3
• Same symptoms recur in 4-12 weeks	1
• Same symptoms recur in >12 weeks or symptoms do not recur	0

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Likelihood that patient's muscle symptoms are due to statin use	
• Probable	9-11
• Possible	7-8
• Unlikely	<7

TABLE 50. Conditions that increase the risk of statin-associated myopathy.

Patient-related risk factors
1. Age >80 years
2. Hypothyroidism
3. Impaired renal or liver function
4. Female sex
5. Low body mass index
6. Diabetes
7. Polypharmacy
8. Strenuous exercise
9. Vitamin D deficiency
10. Acute infection
11. Heavy alcohol consumption (alcohol is a direct muscle toxin)
12. Drug abuse (cocaine, amphetamines, heroin)
13. Impaired renal or hepatic function
14. Biliary tract obstruction
15. Inflammatory or inherited metabolic muscle defects (McArdle disease, carnitine palmityl transferase II deficiency)
16. Surgery with high metabolic demands
17. History of pre-existing/unexplained muscle/joint/tendon pain

Risk factors predisposing to statin interactions

Co-administration with:

1. Cytochrome P-450 3A4 inhibitors including:
   - Macrolide antibiotics: azithromycin, clarithromycin, erythromycin
   - Cyclosporine
   - Antifungals: fluconazole*, itraconazole, ketoconazole*
   - Antivirals (protease inhibitors): amprenavir, indinavir, nelfinavir, ritonavir
   - Amiodarone
   - Calcium antagonists (diltiazem, verapamil) [weak inhibitors]
   - Warfarin*
   - Colchicine
   - Grapefruit juice (if >1 L/day)
2. Glucuronidation inhibitors: gemfibrozil
3. Nicotinic acid

*also metabolized through the cytochrome P-450 2C9

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TABLE 51. Managing the patient with statin-associated muscle symptoms (SAMS).

1. Reassess the benefit of statin therapy
2. Reassure patient that statins are very safe and effective drugs and that muscle symptoms are reversible
3. Aggressive health-diet changes
Eliminate contributing factors (e.g., hypothyroidism, vitamin D deficiency, other drugs that may interact with statins [**Table *52***])
Confirm the diagnosis
a) dechallenge: discontinue statin and wait (usually 4-6 weeks) until complete resolution of symptoms + normalization of CK
b) rechallenge: try a second (usually different) statin at low dose (after dechallenge). If this is tolerated:
b1) statin can be up-titrated to achieve LDL-C goal, or as much LDL-C reduction can be achieved with minimal muscle complaints, or
b2) statin remains at low or moderate dose and ezetimibe ± colesevelam are added
4. If a second statin causes recurrence of muscle symptoms, try low dose of atorvastatin (5-10 mg) or rosuvastatin (5 mg) on alternate days or twice weekly. This approach lowers LDL-C by 25-35% and is tolerated by the majority (~80%) of intolerant to statin patients. For further LDL-C reduction, statin should be combined with ezetimibe ± colesevelam
5. If alternate low dose of statin is not tolerated (i.e., the patient is intolerant to 3rd introduction of statin), then no other attempt with statin should be tried
6. In statin-intolerant patients ("totally" or "partially") consider:
a) ezetimibe or combination of ezetimibe with colesevelam (in totally intolerant patient) and
b) a PCSK9 inhibitor (alirocumab or evolocumab) if despite low statin dose (in partially intolerant patients) + ezetimibe ± colesevelam, LDL-C remains >100 mg/dL in patients with established cardiovascular disease or >130 mg/dL in high-risk patients
c) bempedoic acid is a promising alternative to statin treatment in patients with SAMS

CK: creatine kinase; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

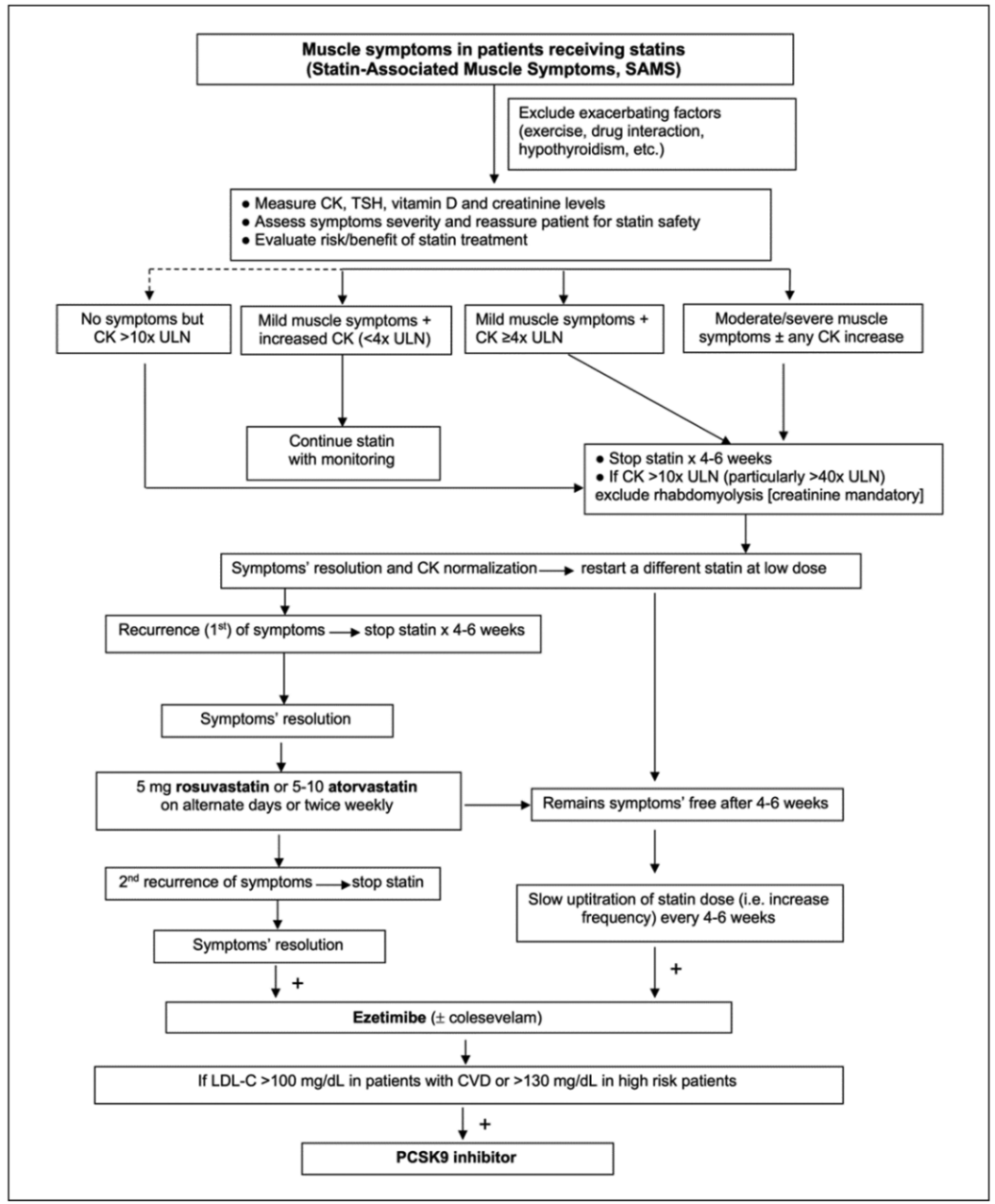

FIGURE 8. Algorithm for the management of patients with statin-associated muscle symptoms

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 type 9

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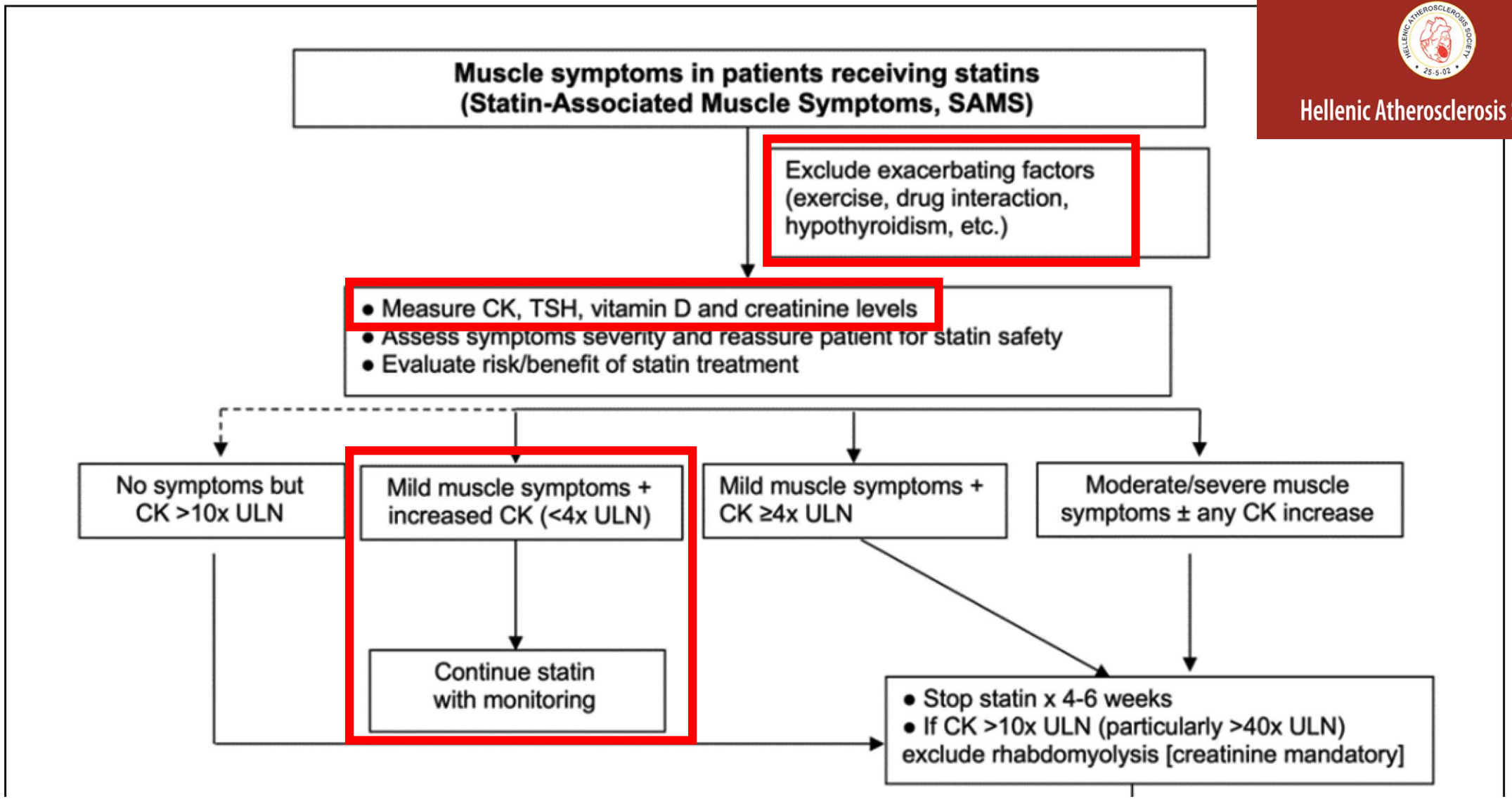


Αύξηση τρανσαμινασών

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

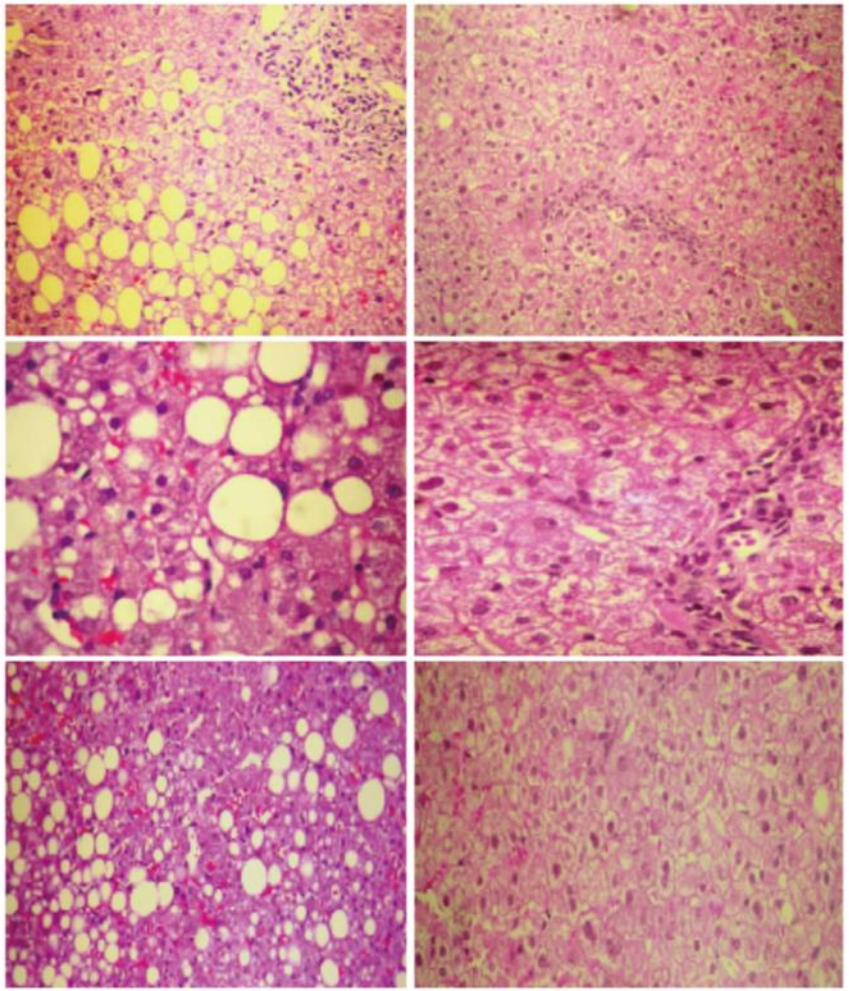
The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

European Heart Journal (2019) **00**, 1–78

8.1.4.2 Adverse effects on the liver. The activity of alanine aminotransferase (ALT) in plasma is commonly used to assess hepatocellular damage. Mild elevation of ALT occurs in 0.5–2.0% of patients on statin treatment, more commonly with potent statins or high doses. The common definition of clinically relevant ALT elevation has been an increase of three times the ULN on two consecutive occasions. Mild elevation of ALT has not been shown to be associated with true hepatotoxicity or changes in liver function. Progression to liver failure is exceedingly rare, therefore routine monitoring of ALT during statin treatment is no longer recommended.[243] Patients with mild ALT elevation due to steatosis have been studied during statin treatment and there is no indication that statins cause any worsening of liver disease.[244–246]

Επιπρόσθετο όφελος αγωγής με ροσουβαστατίνη

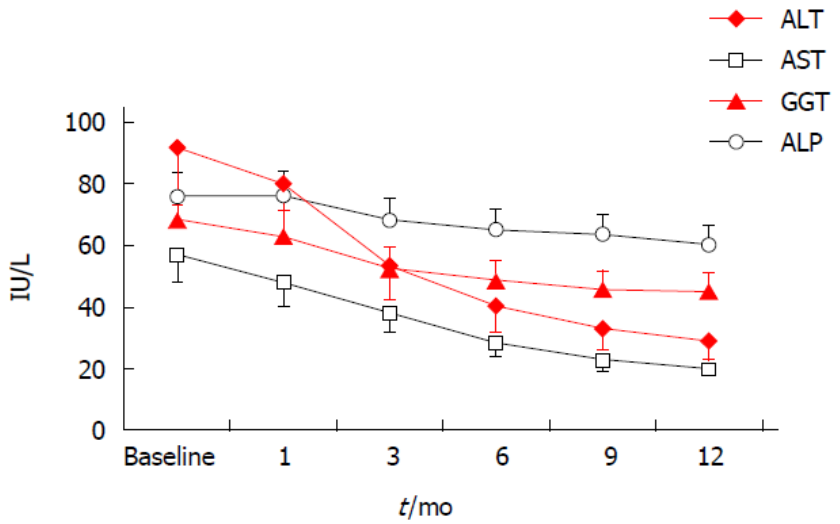
NASH resolution following rosuvastatin 10 mg/d monotherapy



Prospective Study

Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome

Konstantinos Kargiotis, Vasilios G Athyros, Olga Giouleme, Niki Katsiki, Evangelia Katsiki, Panagiotis Anagnostis, Chrysoula Boutari, Michael Doumas, Asterios Karagiannis, Dimitri P Mikhailidis



World J Gastroenterol 2015 July 7; 21(25): 7860-7868

METABOLISM CLINICAL AND EXPERIMENTAL 71 (2017) 17–32

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An Expert Panel Statement

Vasilios G. Athyros[a,*,1], Theodore K. Alexandrides[b], Helen Bilianou[c], Evangelos Cholongitas[d], Michael Doumas[a], Emmanuel S. Ganotakis[e,2], John Goudevenos[f], Moses S. Elisaf[g], Georgios Germanidis[h], Olga Gioulleme[a], Asterios Karagiannis[a], Charalambos Karvounis[i], Niki Katsiki[a], Vasilios Kotsis[j], Jannis Kountouras[a], Evangelos Liberopoulos[g], Christos Pitsavos[k], Stergios Polyzos[l], Loukianos S. Rallidis[m], Dimitrios Richter[n], Apostolos G. Tsapas[o], Alexandros D. Tselepis[p], Konstantinos Tsioufis[k], Konstantinos Tziomalos[q], Themistoklis Tzotzas[r], Themistoklis G. Vasiliadis[j], Charalambos Vlachopoulos[k], Dimitri P. Mikhailidis[s,1], Christos Mantzoros[t,1]

Katsiki N, Mikhailidis DP. Abnormal Peri-Organ or Intra-Organ Fat Deposition and Vascular Risk. Angiology. 2018;69(10):841-842.

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Katsiki N, Perez-Martinez P. Drug therapy for ectopic fat: myth or reality? Expert Rev Cardiovasc Ther. 2017;15(2):71-72.

Katsiki N, Imprialos K, Vlachopoulos C. Editorial: Arterial Stiffness, Central Haemodynamics and Non-Alcoholic Fatty Liver Disease: Links with Cardiovascular Risk and Effects of Drug Treatment. Curr Vasc Pharmacol. 2018;16(4):401-404.

Katsiki N, Purrello F, Tsioufis C, Mikhailidis DP. Cardiovascular disease prevention strategies for type 2 diabetes mellitus. Expert Opin Pharmacother. 2017;18(12):1243-1260.

Katsiki N, Athyros VG, Mikhailidis DP. Non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: Effects of statins and antidiabetic drugs. J Diabetes Complications. 2017;31(3):521-522.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

European Heart Journal (2019) **00**, 1–78

Monitoring liver and muscle enzymes

How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?

- Before treatment.
- Once, 8–12 weeks after starting a drug treatment or after dose increase.
- Routine control of ALT thereafter is not recommended during statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended.

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European Heart Journal (2019) **00**, 1–78

Monitoring liver and muscle enzymes

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

If ALT <3× ULN:

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

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European Heart Journal (2019) **00**, 1–78

Monitoring liver and muscle enzymes

If ALT rises to ≥3× ULN

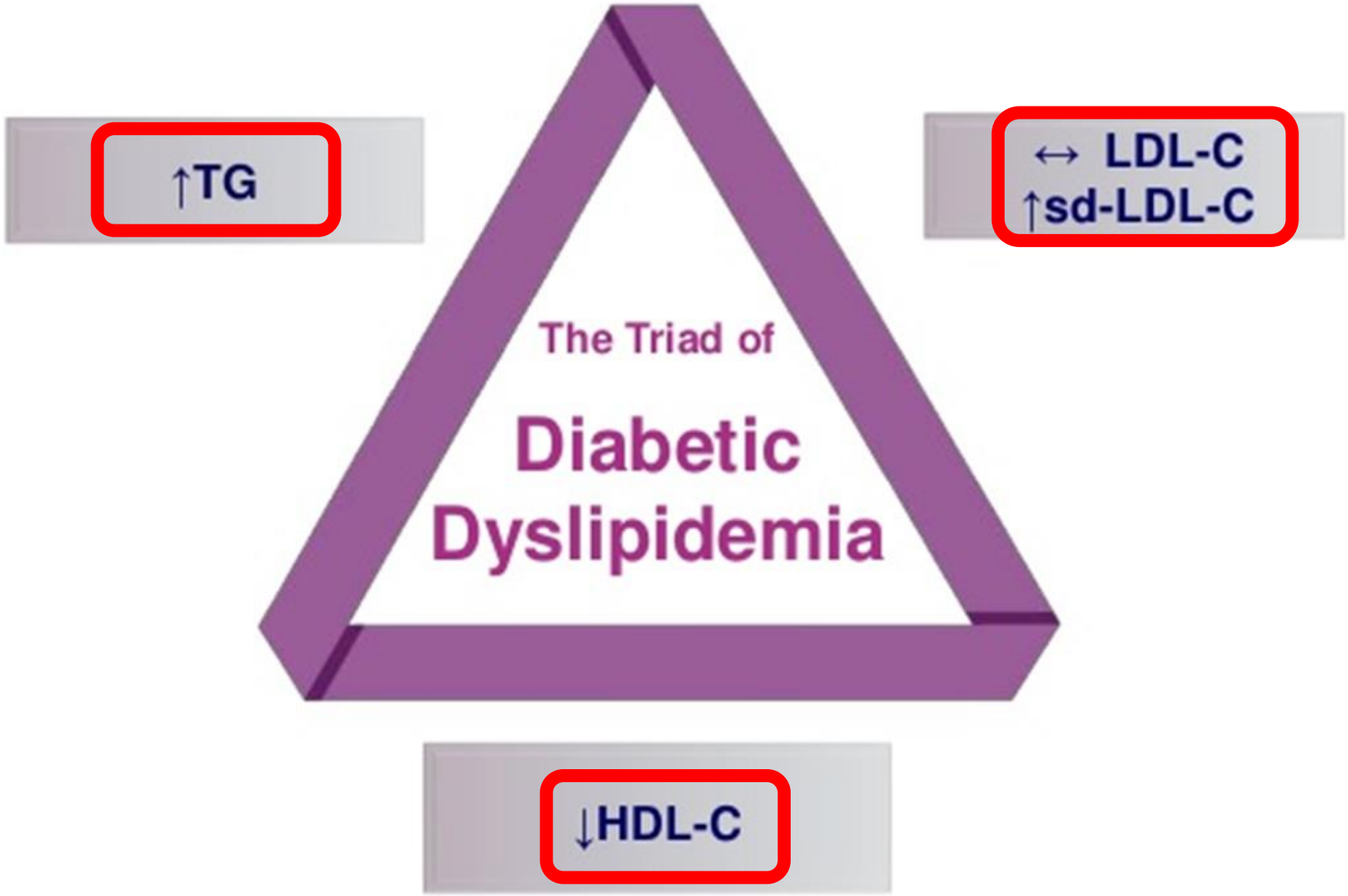
- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

Διαφορές στατινών

Statins

Pharmacologic properties	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Prodrug	No	No	Yes	No	No	No	Yes
Half-life (hours)	14	2.3	3	12	1.3–2.7	29	3
logD* + pH: 7.4	1.53	1.75	2.59	1.50	–0.47	–0.25	2.44
Lipophilicity	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
CYP substrate	3A4	2C9	3A4	Glucuronidation	Sulfation	Unchanged	3A4
Active metabolites	Active	Inactive	Active	Active (minor)	Inactive	Active (minimal)	Active
Protein binding (%)	98	>98	>95	96	50	90	95–98
Renal excretion	<2	6	10	2	20	10	13
Fecal excretion	>98	93	83	79	70	90	60

***Vasc Health Risk Manag*. 2016; 12: 153 - 61**


↑TG
↔ LDL-C
↑sd-LDL-C
The Triad of
Diabetic
Dyslipidemia
↓HDL-C

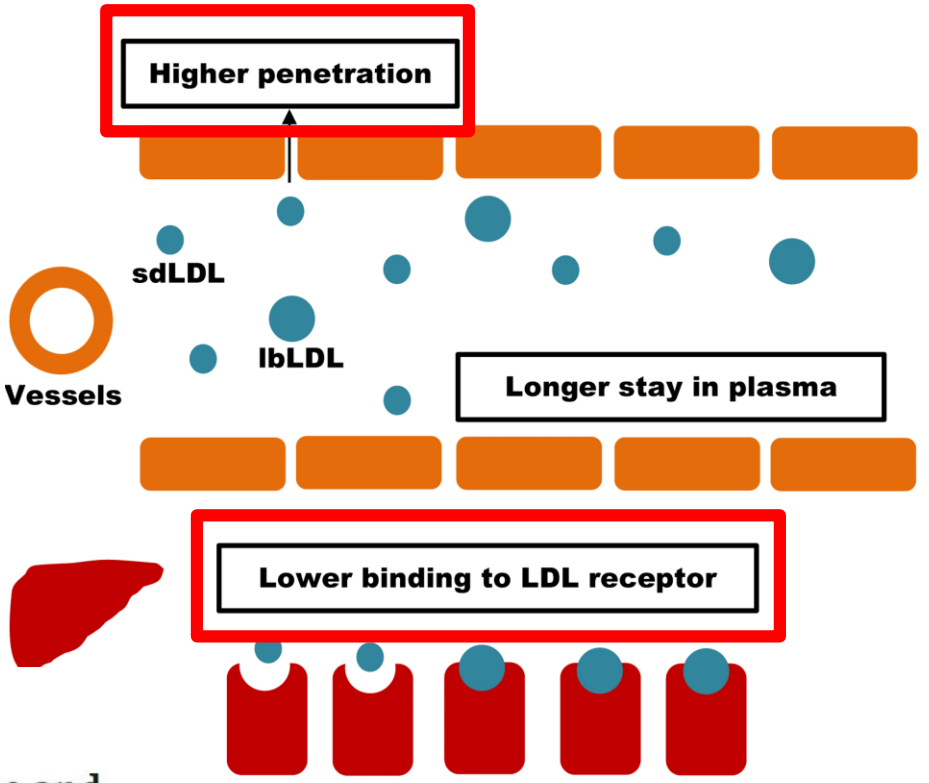
Διείσδυση υπενδοθηλιακά
Μειωμένη πρόσδεση στον LDL υποδοχέα

Cureus. 2023 Jan 18;15(1):e33924. doi: 10.7759/cureus.33924. eCollection 2023 Jan.

Small Dense Low-Density Lipoprotein Level in Newly Diagnosed Type 2 Diabetes Mellitus Patients With Normal Low-Density Lipoprotein

Conclusions

Newly diagnosed T2DM patients with blood lipids within an optimum or near-optimum level may have a higher percentage of sdLDL-C when compared with healthy controls. Hence, they may have a higher risk of atherosclerosis and cardiovascular disease risks despite having an LDL-C level that is considered normal or near-optimal. Hence, the sdLDL-C may be a hidden risk factor among patients otherwise of the "not at risk" category. However, the test for sdLDL-C is still costly for patients in developing countries. Clinicians dealing with patients with T2DM may consider the sdLDL-C level for patients who can afford the test for detecting a potential risk factor for cardiovascular diseases, which is not commonly practiced regularly.



Review > Curr Opin Cardiol. 2017 Jul;32(4):422-429. doi: 10.1097/HCO.0000000000000407.

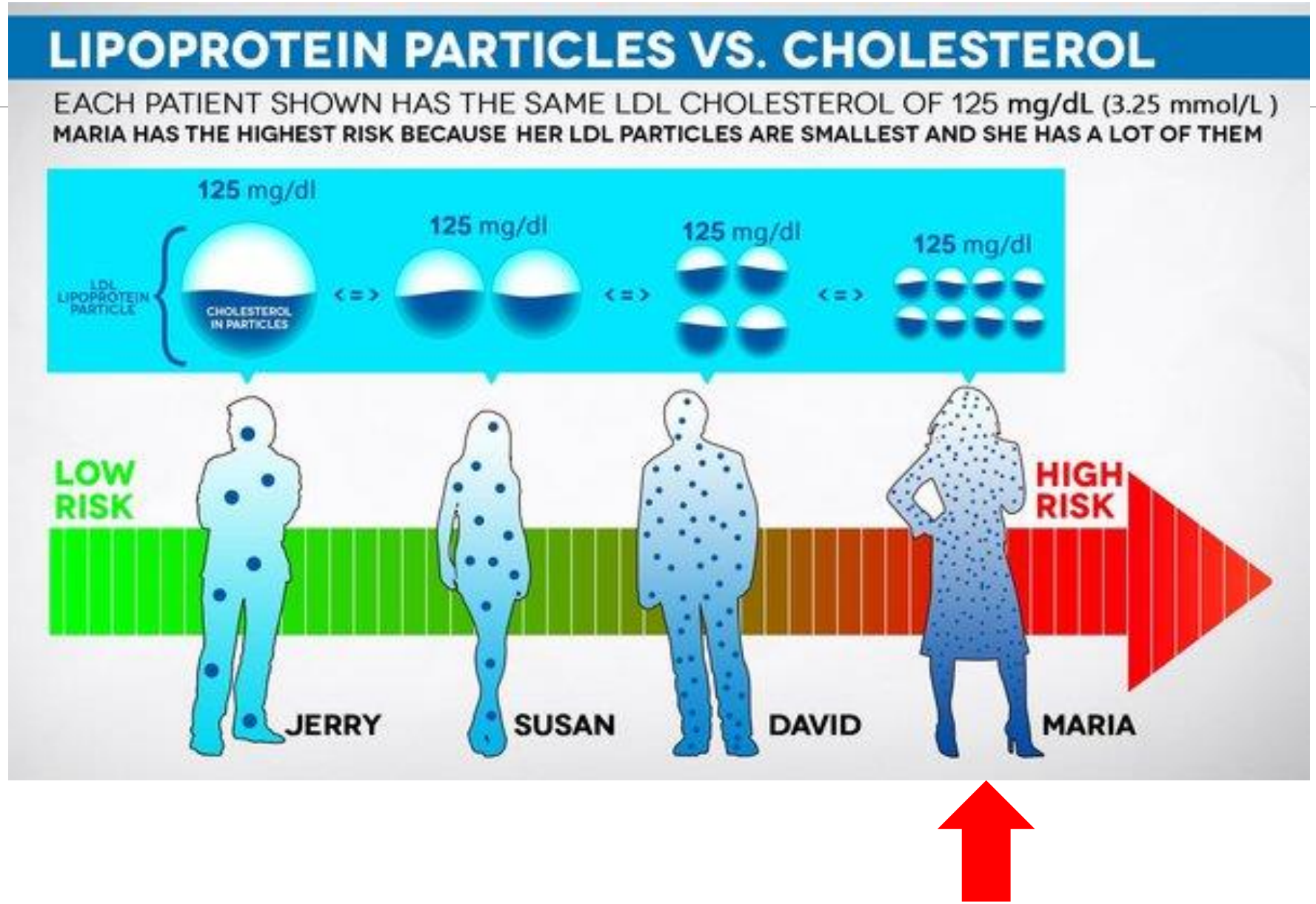
Dyslipidaemia in type 2 diabetes mellitus: bad for the heart

Niki Katsiki [1], Nikolaos Tentolouris, Dimitri P Mikhailidis

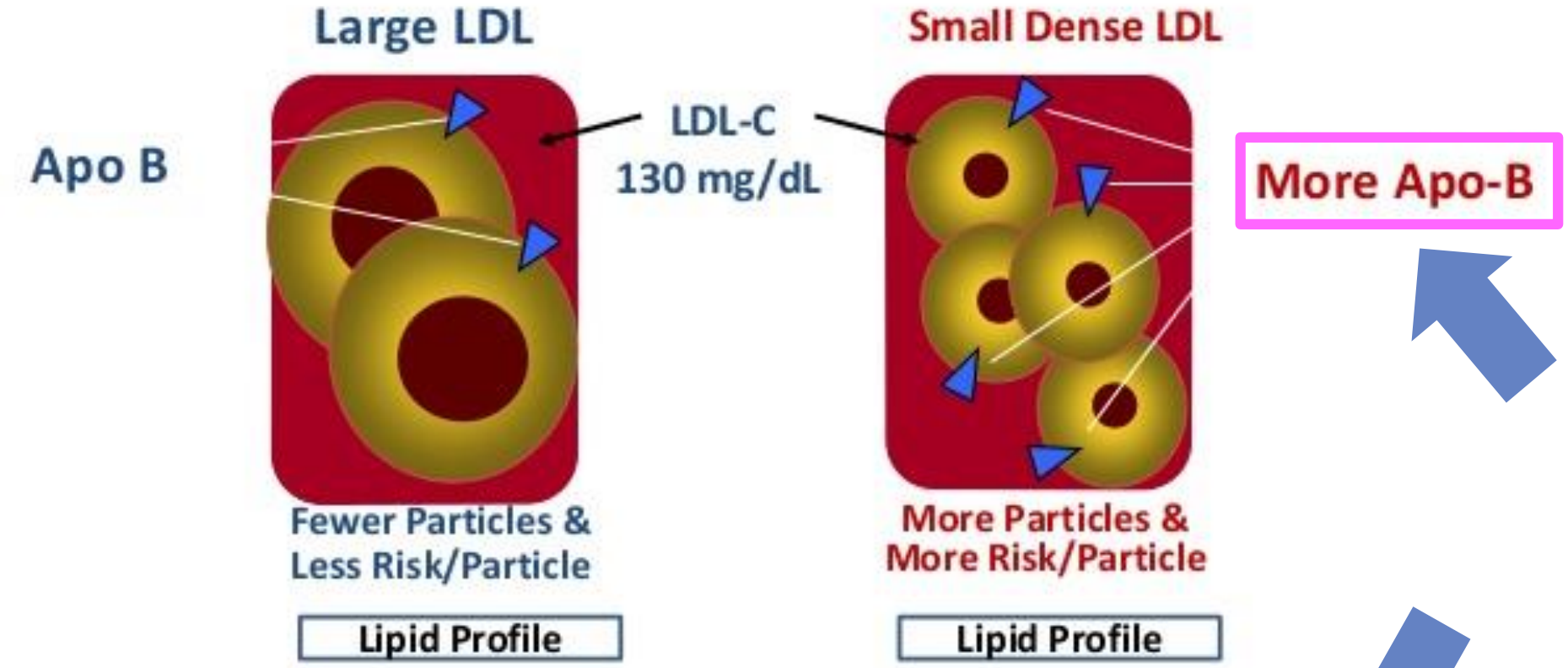
Review > Nutrients. 2013 Mar 18;5(3):928-48. doi: 10.3390/nu5030928.

Lipoprotein subfractions in metabolic syndrome and obesity: clinical significance and therapeutic approaches

Dragana Nikolic [1], Niki Katsiki, Giuseppe Montalto, Esma R Isenovic, Dimitri P Mikhailidis, Manfredi Rizzo


LIPOPROTEIN PARTICLES VS. CHOLESTEROL
EACH PATIENT SHOWN HAS THE SAME LDL CHOLESTEROL OF 125 mg/dL (3.25 mmol/L)
MARIA HAS THE HIGHEST RISK BECAUSE HER LDL PARTICLES ARE SMALLEST AND SHE HAS A LOT OF THEM
125 mg/dl
125 mg/dl
125 mg/dl
125 mg/dl
LDL LIPOPROTEIN PARTICLE
CHOLESTEROL IN PARTICLES
LOW RISK
HIGH RISK
JERRY
SUSAN
DAVID
MARIA

Same LDL-C Levels, Different Cardiovascular Risk.



TC	198 mg/dL	TC	210 mg/dL
LDL-C	130 mg/dL	LDL-C	130 mg/dL
TG	90 mg/dL	TG	250 mg/dL
HDL-C	50 mg/dL	HDL-C	30 mg/dL
Non–HDL-C	148 mg/dL	Non–HDL-C	180 mg/dL

Otvos JD, et al. *Am J Cardiol.* 2002;90:22i-29i.

European Heart Journal (2019) **00**, 1–78

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

8.1.2.2 Triglycerides. Statins usually reduce TG levels by 10–20% from baseline values.[199] More potent statins (atorvastatin, rosuvastatin, and pitavastatin) demonstrate robust lowering of TG levels, especially at high doses and in patients with elevated TGs (HTG), in whom the absolute risk, and therefore the absolute risk reduction, is larger.

REVIEW Open Access

Personalized management of dyslipidemias in patients with diabetes—it is time for a new approach (2022)

Maciej Banach[1,2,3*†], Stanisław Surma[4,5†], Zeljko Reiner[6], Niki Katsiki[7,8], Peter E. Penson[9,10], Zlatko Fras[11,12], Amirhossein Sahebkar[13,14], Francesco Paneni[15,16], Manfredi Rizzo[17,18] and John Kastelein[19]

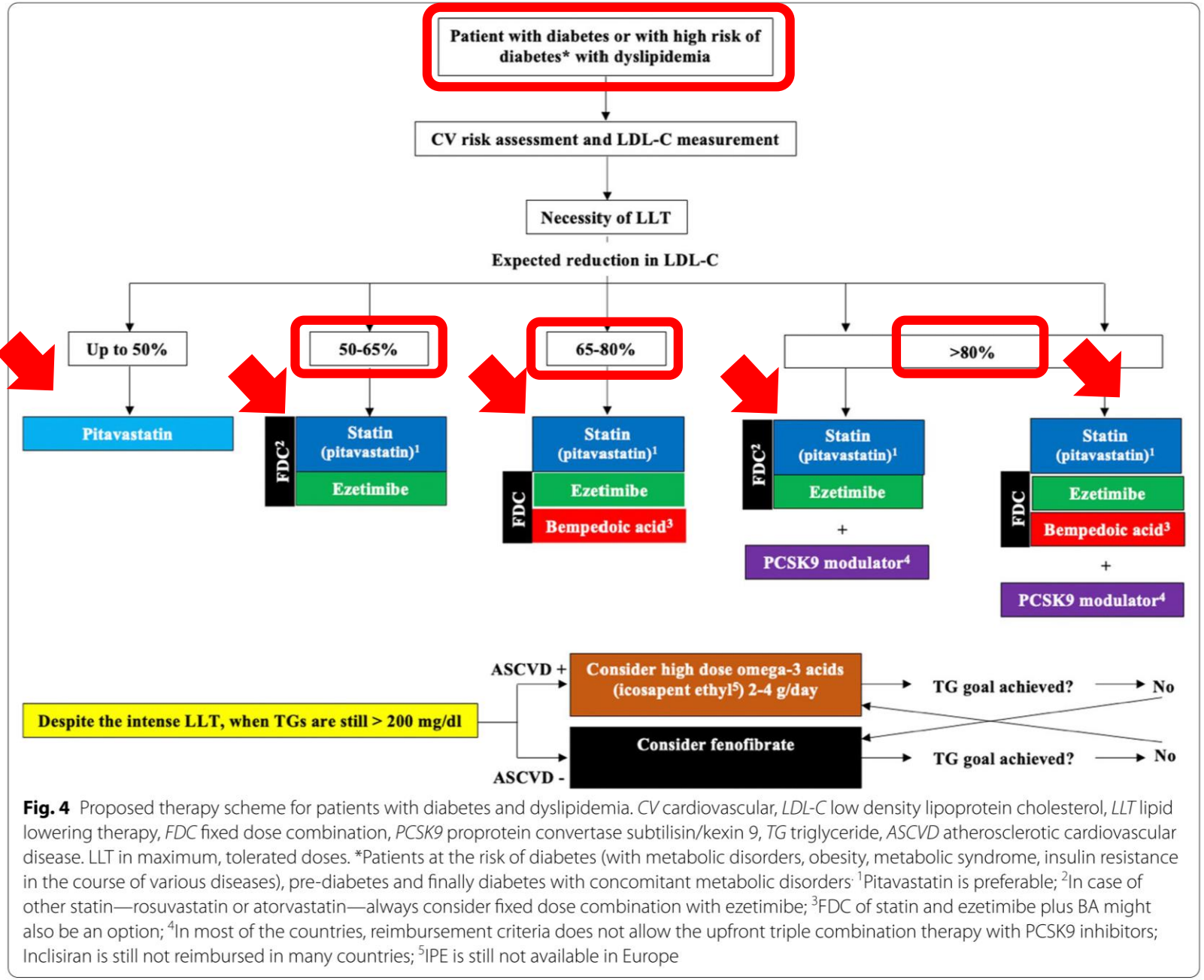


Fig. 4 Proposed therapy scheme for patients with diabetes and dyslipidemia. *CV* cardiovascular, *LDL-C* low density lipoprotein cholesterol, *LLT* lipid lowering therapy, *FDC* fixed dose combination, *PCSK9* proprotein convertase subtilisin/kexin 9, *TG* triglyceride, *ASCVD* atherosclerotic cardiovascular disease. LLT in maximum, tolerated doses. *Patients at the risk of diabetes (with metabolic disorders, obesity, metabolic syndrome, insulin resistance in the course of various diseases), pre-diabetes and finally diabetes with concomitant metabolic disorders. [1]Pitavastatin is preferable; [2]In case of other statin—rosuvastatin or atorvastatin—always consider fixed dose combination with ezetimibe; [3]FDC of statin and ezetimibe plus BA might also be an option; [4]In most of the countries, reimbursement criteria does not allow the upfront triple combination therapy with PCSK9 inhibitors; Inclisiran is still not reimbursed in many countries; [5]IPE is still not available in Europe

Εργαστηριακή παρακολούθηση

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TABLE 56. Laboratory follow-up in patients on hypolipidemic drug treatment.

At diagnosis: TC, TGs, HDL-C, LDL-C, Lp(a), glucose, eGFR, AST, ALT, CK, TSH

LDL-C: low-density lipoprotein cholesterol

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TABLE 56. Laboratory follow-up in patients on hypolipidemic drug treatment.

At diagnosis: TC, TGs, HDL-C, LDL-C, Lp(a), glucose, eGFR, AST, ALT, CK, TSH

↓

8 ± 4 weeks following treatment initiation or intensification: TC, TGs, HDL-C, LDL-C, glucose, eGFR, ALT, CK (if myalgias are reported)

LDL-C: low-density lipoprotein cholesterol

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TABLE 56. Laboratory follow-up in patients on hypolipidemic drug treatment.

At diagnosis: TC, TGs, HDL-C, LDL-C, Lp(a), glucose, eGFR, AST, ALT, CK, TSH

↓

8 ± 4 weeks following treatment initiation or intensification: TC, TGs, HDL-C, LDL-C, glucose, eGFR, ALT, CK (if myalgias are reported)

↓

Every 12 months when on treatment target: TC, TGs, HDL-C, LDL-C, glucose, eGFR, ALT (if evidence of liver injury), CK (if myalgias are reported)

LDL-C: low-density lipoprotein cholesterol

Τρίτη ηλικία

17 Management of Dyslipidemia in the Elderly

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TABLE 26. Recommendations for the management of dyslipidemia in the elderly.

Recommendation	Class of recommendation
Lipid-lowering treatment must aim at LDL-C levels <55, <70 and <100 mg/dL in very high, high, and moderate risk elderly patients (≤ 75 years old).	I
In very high- and high-risk elderly patients (≤ 75 years old), a reduction in baseline LDL-C levels by >50% is recommended	I

LDL-C: low-density lipoprotein cholesterol

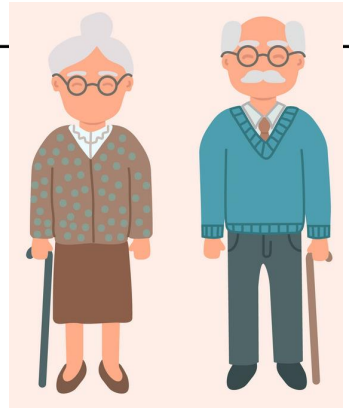
17 Management of Dyslipidemia in the Elderly

Hellenic Atherosclerosis Society

TABLE 26. Recommendations for the management of dyslipidemia in the elderly.

Recommendation	Class of recommendation
In very high- and high-risk elderly patients >75 years old, initiation of statin therapy should be considered	IIa
In the presence of renal impairment and/or drug interactions, statin therapy must be initiated at a low dose, and then titrated, if needed, to attain LDL-C target	I

LDL-C: low-density lipoprotein cholesterol



Review > Expert Rev Clin Pharmacol. 2018 Mar;11(3):259-278.
doi: 10.1080/17512433.2018.1425138. Epub 2018 Jan 12.

Dyslipidaemia in the elderly: to treat or not to treat?

Niki Katsiki [1], Genovefa Kolovou [2], Pablo Perez-Martinez [3], Dimitri P Mikhailidis [4]

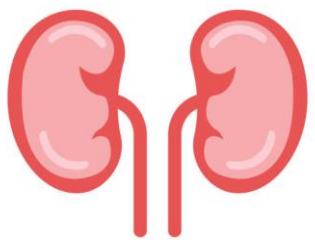
Χρόνια νεφρική νόσος

Hellenic Atherosclerosis Society

15 Management of Dyslipidemia in Patients with CKD

TABLE 24. Recommendations for dyslipidemia management in patients with CKD.

Recommendations	Class of recommendation
Stage 3 CKD patients (eGFR 30-59 mL/min/1.73 m^2) are considered at high risk. LDL-C reduction of ≥50% from baseline and LDL-C goal <70 mg/dL (1.8 mmol/L) are recommended	I
Stage 4-5 CKD patients (eGFR <30 mL/min/1.73 m^2) are at very high risk; LDL-C reduction of ≥50% from baseline and LDL-C goal <55 mg/dL (1.4 mmol/L) are recommended	I



eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

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15 Management of Dyslipidemia in Patients with CKD

TABLE 24. Recommendations for dyslipidemia management in patients with CKD.

Recommendations	Class of recommendation
In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, lipid-lowering therapy should be continued	IIa
In patients with CKD without ASCVD who require dialysis, statin treatment should not be initiated	III
In adult kidney transplant recipients, statin treatment should be considered	IIa

eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

Review > Expert Opin Pharmacother. 2019 Nov;20(16):2007-2017.
doi: 10.1080/14656566.2019.1649394. Epub 2019 Aug 6.

Lipid-lowering agents for concurrent cardiovascular and chronic kidney disease

Niki Katsiki [1], Dimitri P Mikhailidis [2], Maciej Banach [3 4]

Agent	Renal Excretion	General Population Dosing, Not CKD-Specific	Dosing Adjustments in CKD
Atorvastatin	<2%	10-80 mg daily	No adjustment
Fluvastatin	5%	40 mg bid or XL 80 mg daily	Use with caution in severe renal impairment
Lovastatin	10%	20-80 mg daily	Use with caution in CrCl <30
Pravastatin	20%	40-80 mg daily	Initial dose of 10 mg daily with significant impairment
Rosuvastatin	10%	5-40 mg daily	5-10 mg daily in CrCl <30
Simvastatin	13%	10-40 mg daily	Initial dose of 5 mg daily with CrCl <30
Niacin	60%-76%	250-3,000 mg daily in divided doses	No adjustment; use with caution
Colesevelam	None	4-8 g 1-2 times daily	No adjustment; use with caution
Ezetimibe	11%	10 mg daily	No adjustment
Fenofibrate	60%	Varies with formulation	Varies with formulation; use generally contraindicated in CrCl <30 and dialysis
Gemfibrozil	70%	600 mg bid	No adjustment
Fish Oil/Omega-3	None	4 g daily	No adjustment

10-20 mg

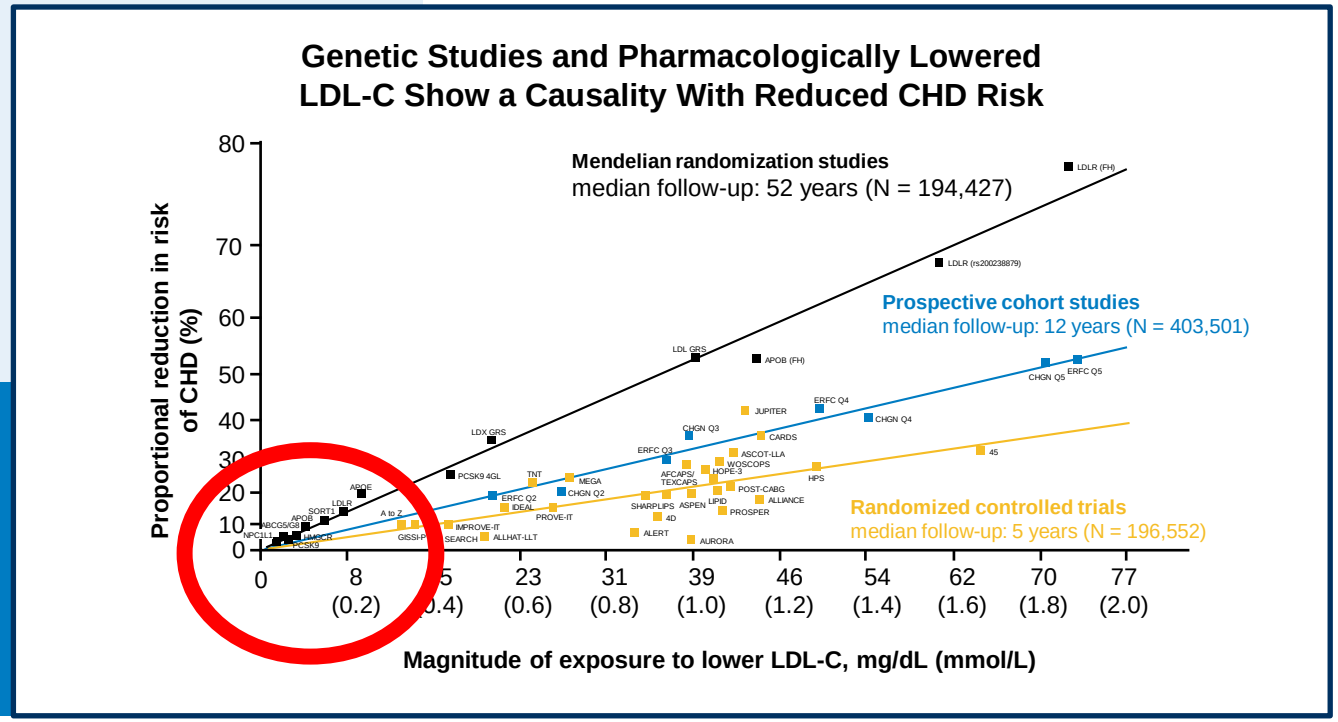
Πόσο χαμηλά είναι ασφαλές;

Plasma LDL-C Concentrations Are Associated With a Dose-Dependent Increase in the Risk of ASCVD

The lower the better

A meta-analysis of 49 studies demonstrated a consistent dose-dependent log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD

Reducing plasma LDL-C levels with a statin leads to dose-dependent reduction in the risk of major ASCVD events that is proportional to the absolute magnitude of the reduction in achieved LDL-C



ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.
Ference BA, et al. *Eur Heart J*. 2017;38:2459-2472.

Lowering of LDL-C to < 25 mg/dL (< 0.6 mmol/L) Was Not Associated With a Higher Rate of Neurocognitive Events

Pooled data from 14 phase 2 and 3 studies were analyzed to evaluate the safety of alirocumab in patients with at least two consecutive LDL-C values of <25 or <15 mg/dL (<0.6 or <0.4 mmol/L), with follow-up of up to 104 weeks

LDL-C levels of <25 or <15 mg/dL (<0.6 or <0.4 mmol/L) were not associated with an increased rate of neurologic and neurocognitive events

AEs of interest, % (n)	Pooled control (n = 1,894)	Alirocumab			
		Overall alirocumab (n = 3,340)	LDL-C ≥ 25 mg/dL (≥ 0.6 mmol/L) (n = 2,501)	LDL-C < 25 mg/dL (< 0.6 mmol/L) (n = 839)	LDL-C < 15 mg/dL (< 0.4 mmol/L) (n = 314)
Neurologic events	3.7 (71)	4.0 (134)	4.2 (105)	2.4 (20)	2.9 (9)
Peripheral neuropathy	3.3 (63)	3.2 (106)	3.4 (84)	1.7 (14)	2.2 (7)
Neurocognitive disorders	0.9 (17)	1.0 (32)	10 (26)	0.6 (5)	0.3 (1)
Amnesia	0.3 (5)	0.2 (6)	0.2 (5)	0.1 (1)	0
Aphasia	0	< 0.1 (2)	< 0.1 (1)	0.1 (1)	0
Confusional state	0.2 (3)	0.2 (8)	0.3 (7)	0.1 (1)	0
Dementia	0.1 (2)	< 0.1 (1)	0	0.1 (1)	0
Frontotemporal dementia	0	< 0.1 (1)	0	0.1 (1)	0.3 (1)

AE, adverse event; LDL-C, low-density lipoprotein cholesterol.

Robinson JJ, et al. *J Am Coll Cardiol*. 2017;69(5):471-482.

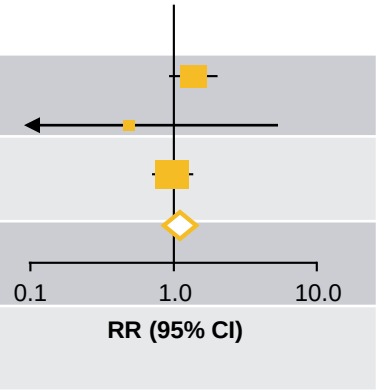
In a Meta-analysis of Recent CV Outcomes Trials, Further Lowering of LDL-C to <20 mg/dL (<0.5 mmol/L) Was Not Associated With Increased Risk of Hemorrhagic Stroke

Safety outcome	Patients with event, no.		Meta-analysis data	P value
	Experimental arm	Control arm	RR (95% CI)	
Hemorrhagic stroke	132	118	1.11 (0.87–1.43)	0.40

LDL-C lowering was not associated with an increased risk of hemorrhagic stroke

Hemorrhagic Stroke

Trial	RR (95% CI)
IMROVE-IT	1.37 (0.93–2.03)
FOURIER	0.49 (0.04–5.38)
REVEAL	0.98 (0.71–1.36)
Overall	1.11 (0.87–1.43)



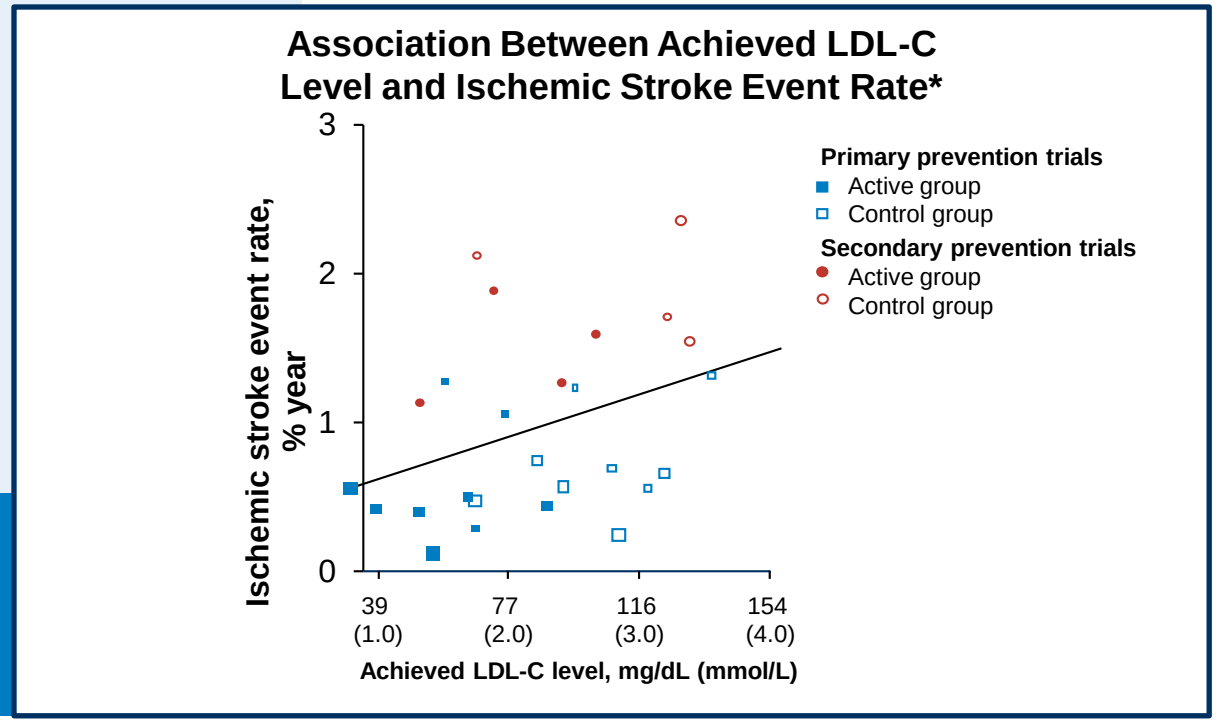
CI, confidence interval; CV, cardiovascular; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; IMPROVE-IT, Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin; LDL-C, low-density lipoprotein cholesterol; REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification; RR, risk ratio.
Sabatine MS, et al. *JAMA Cardiol*. 2018;3(9):823-828.

Achievement of Very Low LDL-C Was Associated With a Reduction in Ischemic Stroke Risk

A meta-analysis of 222,149 participants in 23 randomized trials evaluated the association between achieved LDL-C levels and stroke risk

Evaluated trials were categorized according to achieved LDL-C levels: < 50 mg/dL (< 1.3 mmol/L), 50–70 mg/dL (1.3–1.8 mmol/L), and > 70 mg/dL (> 1.8 mmol/L)

For ischemic stroke, each 39 mg/dL (1 mmol/L) decrease in LDL-C was associated with a risk reduction of 28.6% (95% CI: -0.019–0.591, *P* = 0.065)



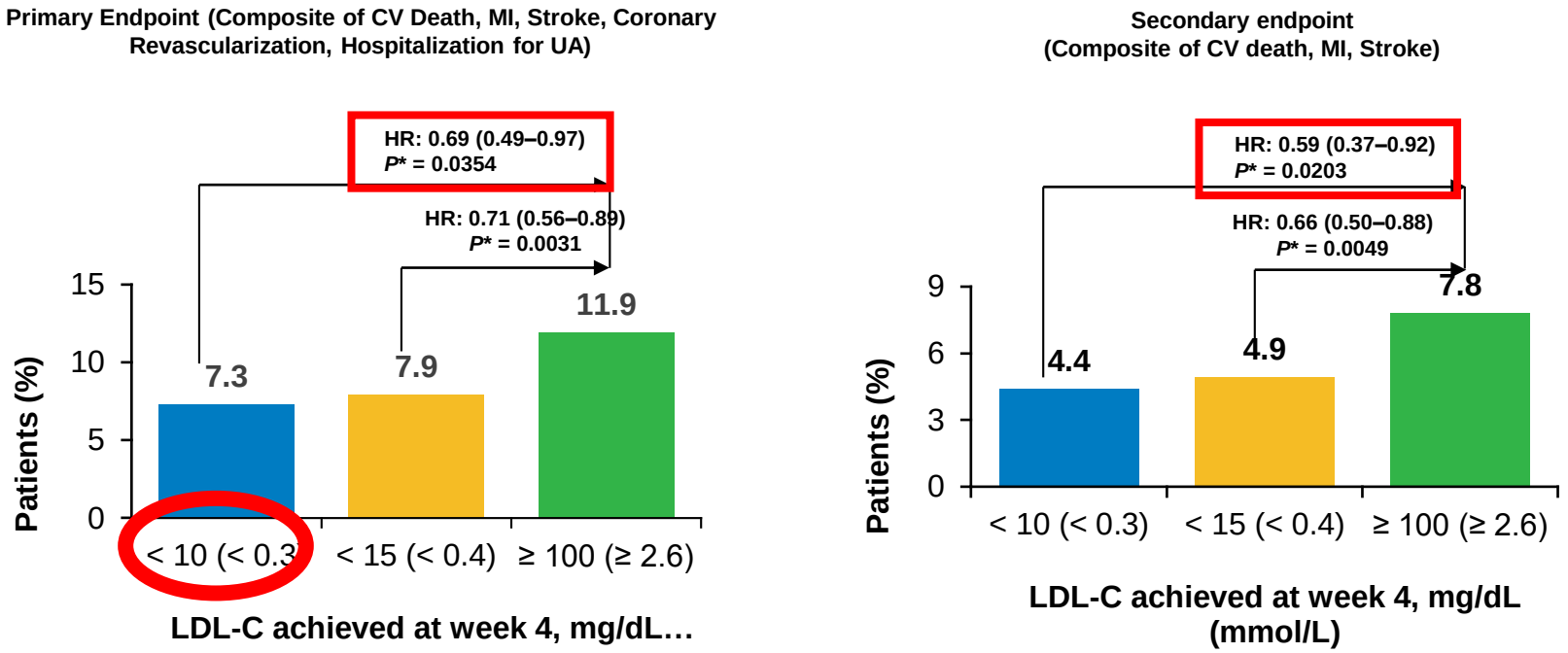
*The size of each square on the graph indicates the weight of each trial, which was derived from the inverse of variance of the event rate of each trial.
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.
Shin J, et al. *Eur J Prev Cardiol*. 2019. Epub ahead of print.

In PROFICIO, No New Safety Signals Were Observed in Evolocumab Patients Who Achieved Very Low LDL-C Levels

AE or laboratory parameter	Lowest LDL-C achieved and treatment group									
	< 25 mg/dL (< 0.6 mmol/L)		≥ 25 mg/dL (≥ 0.6 mmol/L) and < 40 mg/dL (< 1.0 mmol/L)		All patients with < 40 mg/dL (< 1.0 mmol/L)		≥ 40 mg/dL (≥ 1.0 mmol/L)			
	Initial parent trials*	OLE‡	Initial parent trials*	OLE‡	Initial parent trials*	OLE‡	Initial parent trials*	OLE‡	Initial parent trials*	OLE‡
	Any evolocumab N = 1,609	Evolocumab + SOC N = 773	Any evolocumab N = 956	Evolocumab + SOC N = 759	Any evolocumab N = 2,565	Evolocumab + SOC N = 1,532	Any evolocumab N = 1,339	Evolocumab + SOC N = 1,426	Any control† N = 2,038	SOC N = 1,459
Any AE, %	51.4	70.2	50.4	69.2	51.0	69.7	52.1	71.1	50.0	66.6
AEs leading to discontinuation of IP	1.2	1.0	1.0	1.8	1.2	1.4	3.1	3.7	0	N/A§
SAEs	2.9	7.8	2.4	7.1	2.7	7.4	2.6	8.2	2.0	7.8
Neurocognitive AEs, %	0.06	0.5	0	1.2	0.04	0.8	0.3	1.0	0.3	0.3
Muscle-related AEs, %	4.5	5.2	3.9	7.1	4.2	6.1	6.6	6.9	4.8	6.2
CK > 5 x ULN, %	0.6	0.4	0.4	0.9	0.5	0.7	1.0	0.5	0.7	1.1
CK > 10 x ULN, %	0.2	0.1	0.1	0.4	0.2	0.3	0.3	0.2	0.2	0.5
ALT or AST > 3 x ULN, %	0.4	0.9	0.3	0.8	0.4	0.8	0.5	1.3	0.9	1.2
Total bilirubin > 2 x ULN, %	0.3	0.4	0.1	0.3	0.2	0.3	0	0.1	0.1	0.1

*Median study exposure: 3 months. †Control placebo and/or ezetimibe. ‡Year 1 SOC-controlled period of OLE studies, median study exposure: 11 months. §Not applicable, SOC group did not receive IP.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; OLE, open-label extension; PROFICIO, Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 in Different Populations; SAE, serious adverse event; SOC, standard of care; ULN, upper limit of normal.
Toth PP. *Circulation*. 2017;135:1819-1831.

Achievement of Ultra-low LDL-C Levels in FOURIER Further Reduced the Risk of Major CV Events



Major CV events progressively declined with lower achieved LDL-C at week 4

*P value compared with the group achieving an LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) at 4 weeks.
CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; UA, unstable angina.
Giugliano RP, et al. *Lancet.* 2017;390:1962-1971.

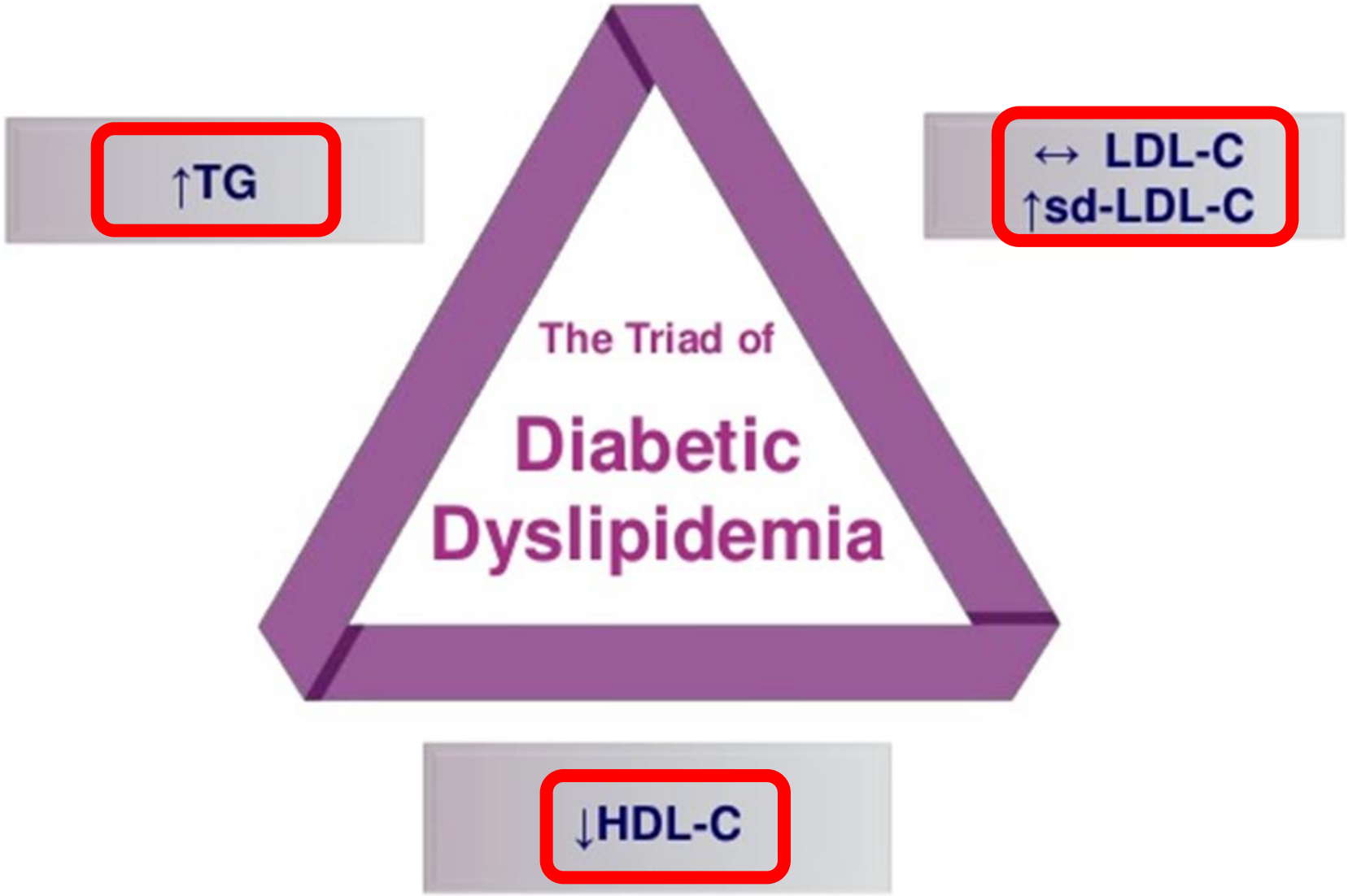

↑TG
↔ LDL-C
↑sd-LDL-C
The Triad of
Diabetic
Dyslipidemia
↓HDL-C

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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

Ευχαριστώ πολύ για την προσοχή σας!