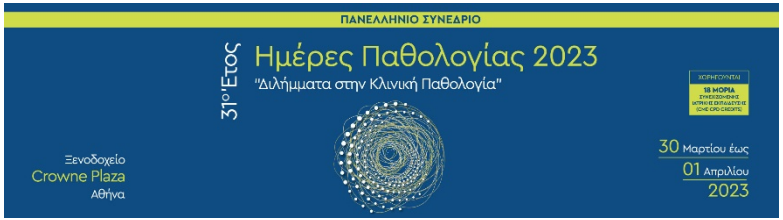
Σύγχρονη Στρατηγική Αντιμετώπισης Παραγόντων Καρδιαγγειακού Κινδύνου

Υπερλιπιδαιμία

Dimitrios Terentes-Printzios, MD, PhD
Interventional Cardiologist-Academic Scholar
Executive Editor of the Hellenic Journal of Cardiology
First Department of Cardiology, Hippokration Hospital, Medical School, National and Kapodistrian University of Athens, Greece



1st April 2023, Athens

Declaration of interest

I have no conflicts of interest.

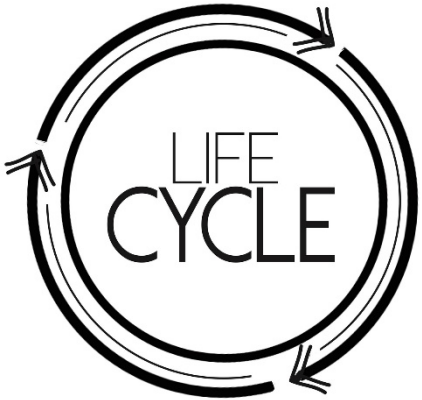
Δυσλιπιδαιμίες 2023

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (E Society (EAS)

Developed with the special contrib for Cardiovascular Prevention & R

Authors/Task Force Members: Alberico L. Ian Graham* (Chairperson) (Ireland), Guy (Sweden), M. John Chapman (France), Hei (The Netherlands), Catriona S. Jennings (U Terje R. Pedersen (Norway), Željko Reine Marja-Riita Taskinen (Finland), Lale Tokgo Verschuren (The Netherlands), Charalamb (UK), Jose Luis Zamorano (Spain)



5 χρόνια

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

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)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)

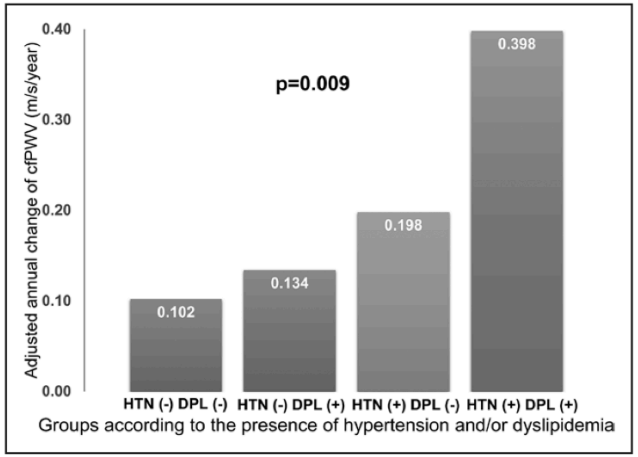
Δυσλιπιδαιμίες 2023

- Γιατί αυτούς τους στόχους;
- Τι έχουμε πετύχει στην πραγματικότητα;
- Οι λύσεις - το μέλλον

Δυσλιπιδαιμίες 2023

- **Γιατί αυτούς τους στόχους;**
- **Τι έχουμε πετύχει στην πραγματικότητα;**
- **Οι λύσεις - το μέλλον**

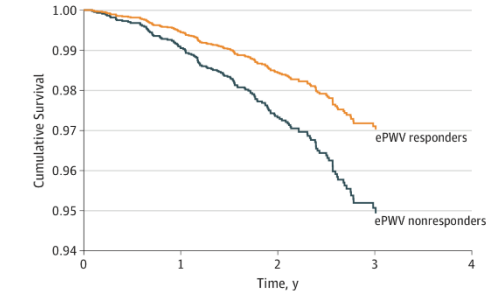
Dyslipidemia increases our vascular age!



Terentes-Printzios D, Vlachopoulos C, et al. Hypertension 2017

PROGNOSTIC Value of (estimated) PWW

Figure 3. Effect of the Response of Estimated Pulse Wave Velocity (ePWV) to 12 Months of Treatment on All-Cause Death in the Standard Treatment Group



No. at risk

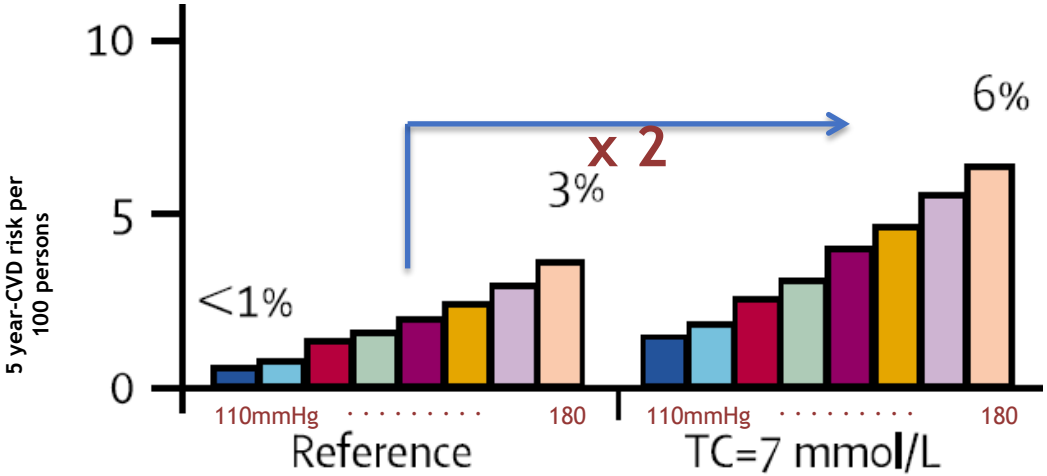
ePWV nonresponders	1909	1862	1246	320
ePWV responders	2305	2249	1581	434

Analysis of SPRINT data

- 8450 hypertensives. Follow-up: 2 years.

Vlachopoulos C / Terentes-Printzios D et al. JAMA NTW open 2019

High cholesterol doubles the CV risk of hypertensive pts



Predictive 5-year CV risk of patients with respective SBP of 110, 120, 130, 140, 150, 160, 170 and 180 mm Hg

Jackson et al. *Lancet*. 2005;365(9457):434-441.

CV risk groups 2019 ESC/EAS Guidelines

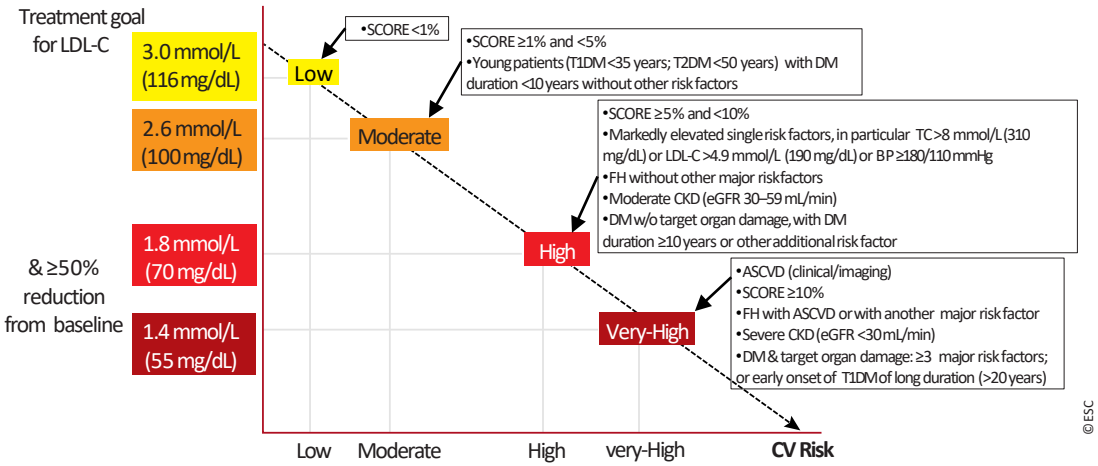
Very high risk	High risk	Moderate risk	Low risk
People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound • DM with target organ damage,* or at least three major risk factors, or early onset of T1DM of long duration (>20 years) • Severe CKD (eGFR <30 mL/min/1.73 m^2) • A calculated SCORE ≥10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor	**People with:** • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30–59 L/min/1.73 m^2) • A calculated SCORE ≥ 5% and <10% for 10-year risk of fatal CVD	• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors • Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD	• Calculated SCORE <1% for 10-year risk of fatal CVD

- *Defined as microalbuminuria, retinopathy, or neuropathy.

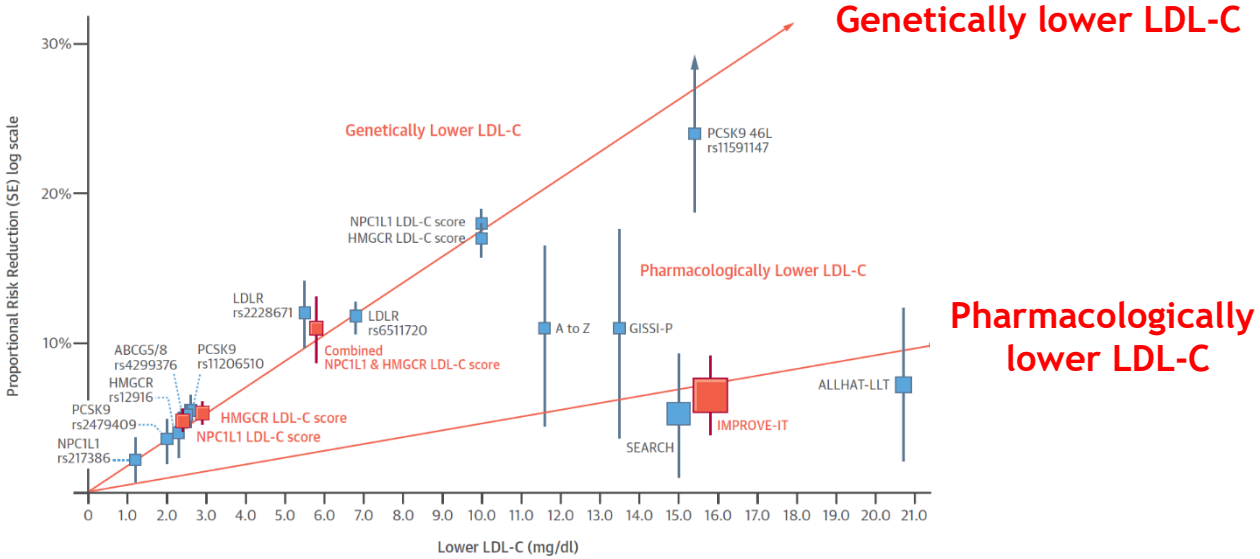
ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM =type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.

Adapted from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



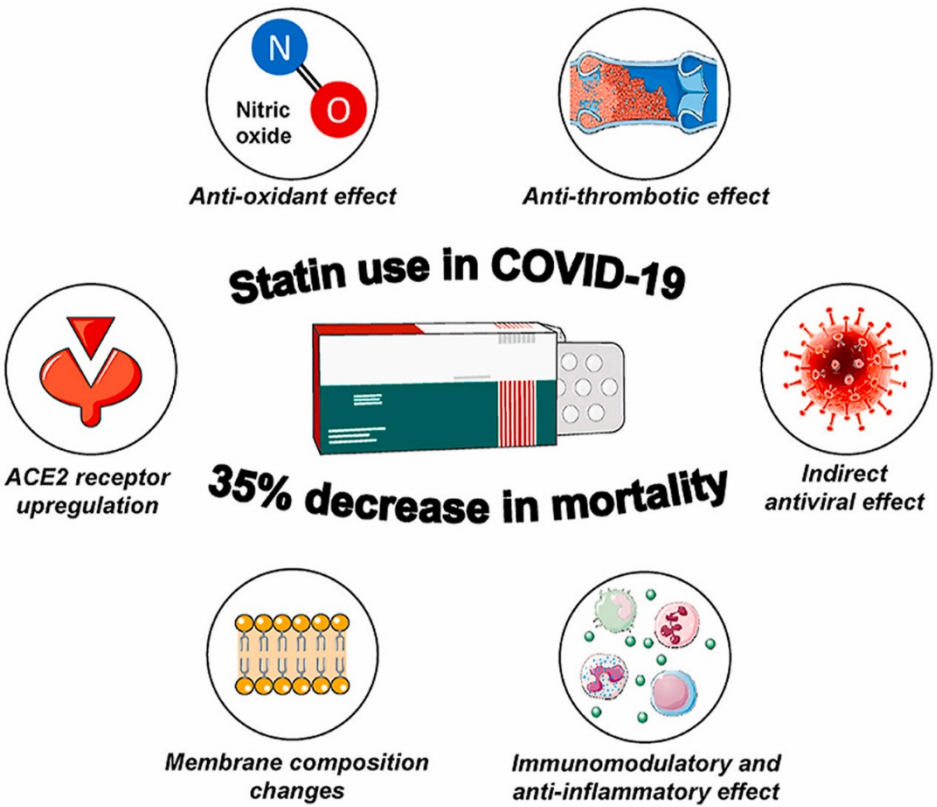
Lower LDL-C is associated with increased risk reduction



[To convert, 100 mg/dL=2.59 mmol/L].
CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error.

Ference BA, et al. J Am Coll Cardiol 2015;65:1552-61.

Statins work in other settings as well



Statin therapy was associated with 35% decrease in the adjusted risk of mortality in hospitalized COVID-19 patients.

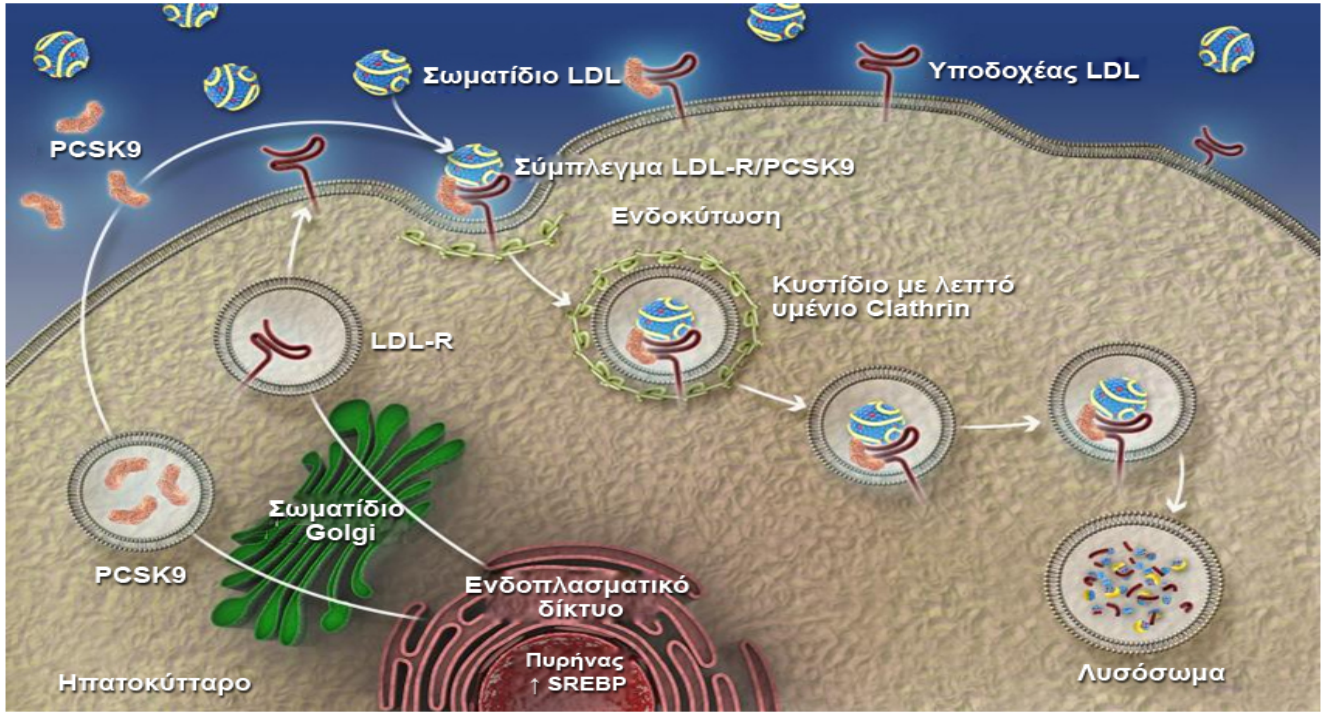
Kollias A, et al. Atherosclerosis 2021

LDL-C is a major contributor to atherosclerotic progression

LDL-C levels and atherosclerosis progression in coronary artery IVUS studies

A-Plus, Avasimibe and Progression of Lesions on Ultrasound; ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; LDL-C, low-density lipoprotein cholesterol; REVERSAL, Reversal of Atherosclerosis With Aggressive Lipid-Lowering; IVUS, intravascular ultrasound..Sipahi I, et al. Cleve Clin J Med 2006;10:937–44; Nissen SE, et al. JAMA 2006;295:1556–65.

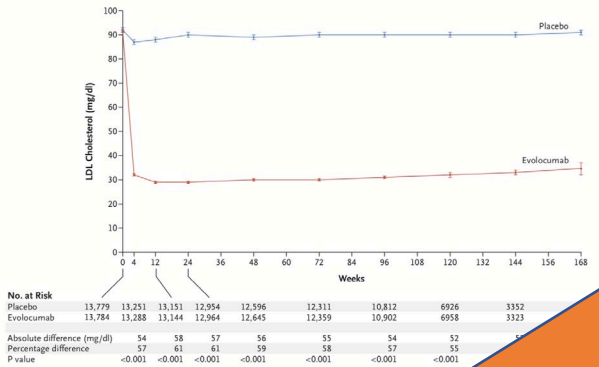
PCSK9 Regulates the Recycling of LDLR by Targeting the LDLR for Degradation



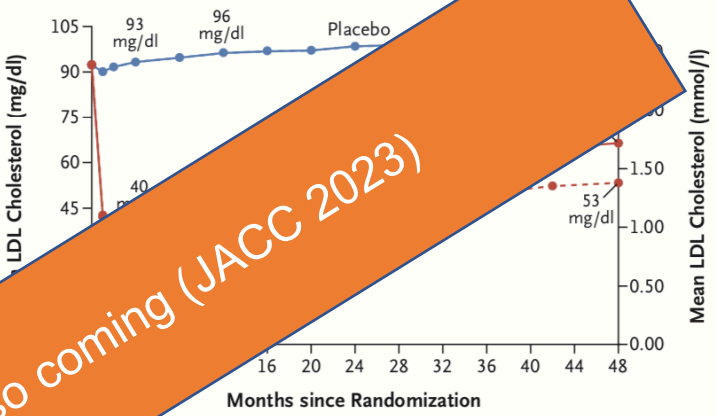
1. Abifadel M, et al. *Nat Genet*. 2003;34:154-156. **2.** Lagace TA, et al. *J Clin Invest*. 2006;116:2995-3005.
3. Maxwell KN, et al. *PNAS*. 2005;102:2069-2074. **4.** Mayne J, et al. *Clin Chem*. 2011;57:1415-1423.

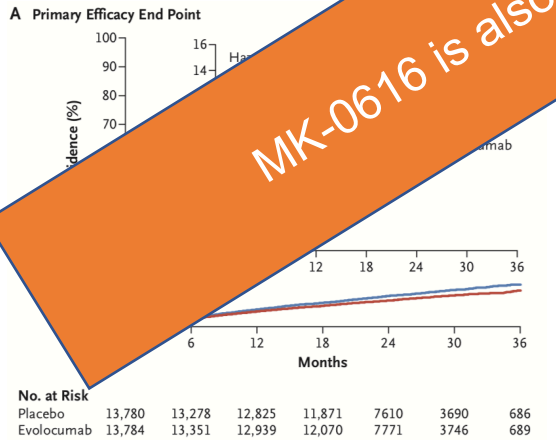
PCSK9i

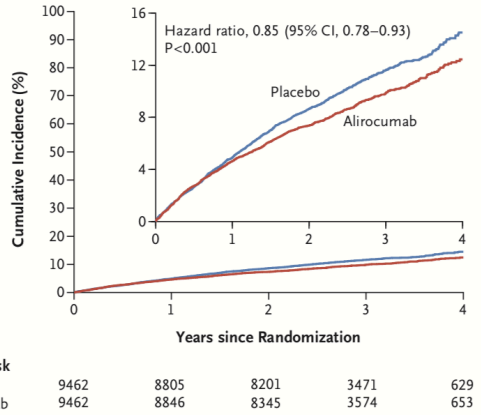
EVOLOCUMAB (FOURIER)



ALIROCUMAB (ODYSSEY OUTCOMES)







MK-0616 is also coming (JACC 2023)

NEJM 2017

NEJM 2018

New recommendations

Cardiovascular imaging for assessment of ASCVD risk
Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.

Cardiovascular imaging for assessment of ASCVD risk
CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.

Lipid analyses for CVD risk estimation
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.

Πέρα από την LDL

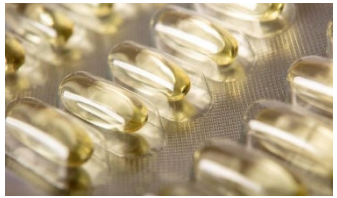
υπερτριγλυκεριδαιμία

Ω-3

tctMD/the heart beat

NEWS

Prescription Omega-3 Fatty Acids Cut Cardiovascular Events: REDUCE-IT



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

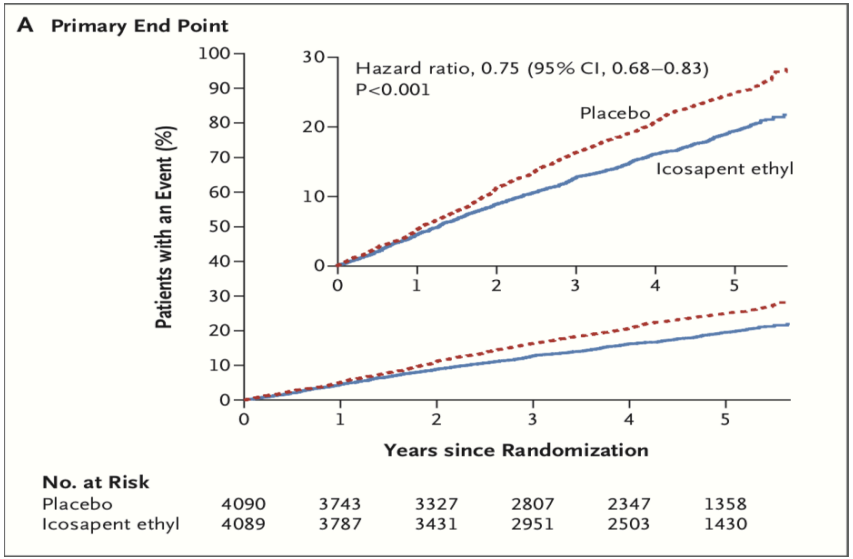
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Results



A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001)

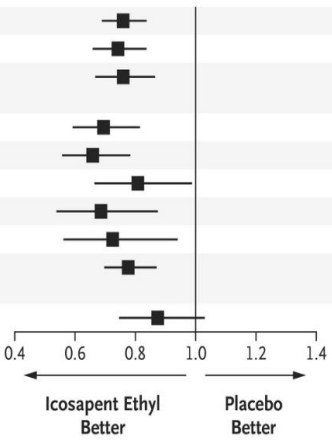
Bhatt et al., NEJM.2018

The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Results

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



Hierarchical Testing of End Points.
Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapentethyl group than in the placebo group.

Bhatt et al., NEJM.2018

The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Σκέψεις για την αποτελεσματικότητα και την ασφάλεια

- **25% ελάττωση του σχετικού κινδύνου** στο πρωτεύον καταληκτικό σημείο (μείζονα καρδιαγγειακά συμβάματα, μη θανατηφόρο ΟΕΜ, μη θανατηφόρο ΑΕΕ, επαναγγείωση στεφανιαίων αγγείων)
- Η αποτελεσματικότητα (25% RRR) συγκρίνεται με αυτή της **ατορβαστατίνης!**
- **Καλά ανεκτή αγωγή**,με παρόμοια ποσοστά παρενεργειών με την ομάδα που έλαβε placebo.
- **Γιατί πέτυχε αυτή η μελέτη;** Υψηλή δόση (4-g daily) ενώ οι περισσότερες προγενέστερες μελέτες με omega-3 λιπαρά (όπως πρόσφατα στην **ASCEND trial**) χρησιμοποιήθηκαν πολύ χαμηλότερες δόσεις.

Bhatt et al., NEJM.2018

Θεραπευτικοί στόχοι

Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

REDUCE-IT trial

2019 ESC/EAS Guidelines for the management of Dyslipidaemias

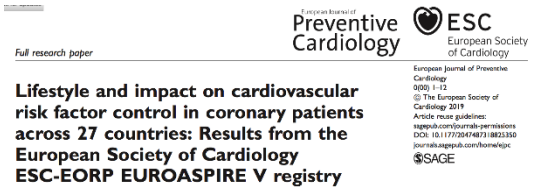
Δυσλιπιδαιμίες 2023

- Γιατί αυτούς τους στόχους;
- **Τι έχουμε πετύχει στην πραγματικότητα;**
- Οι λύσεις - το μέλλον

LDL-C level targets in daily practice

Are we doing enough?

EUROASPIRE V : Blood Pressure and Cholesterol Control Rates in Patients with CHD



8261 patients with CAD

- Although [illegible] patients were using lipid-lowering [illegible]
- [illegible]ere taking high-intensity [illegible] drug combinations
- [illegible]ssure >140/90 mmHg
- [illegible] had LDL-C ≥1.8 mmol/L
- [illegible]ients during interview said that [illegible]re compliant (probably highly [illegible]verestimated number!)

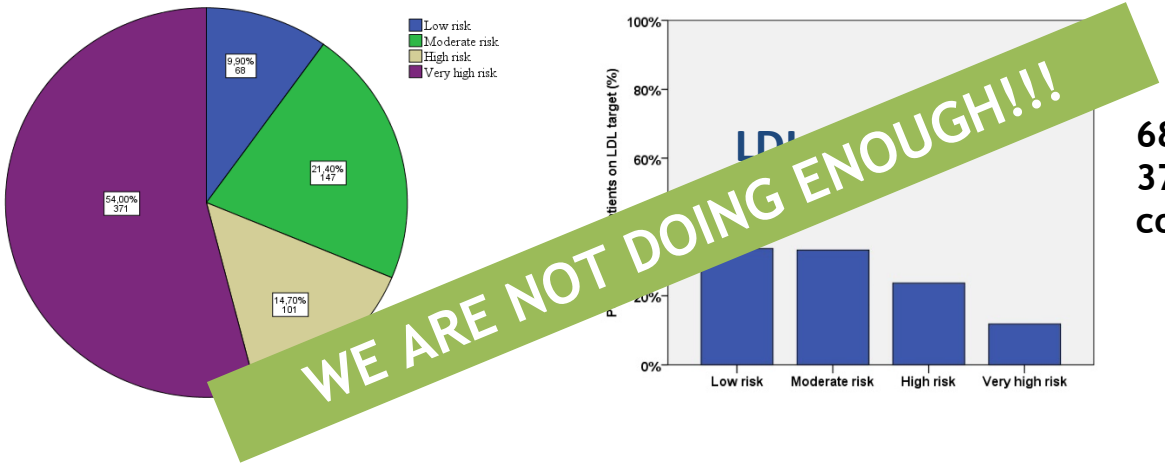
EUROASPIRE V
Suboptimal lipid control in secondary prevention!

LDL-C level targets in daily practice

Are we doing enough?

More than half of the pts are already at high risk BEFORE the ACS
(PHAETHON study)

(partly) because they do not reach targets



687 ACS pts
37 centers
countrywide

Vlachopoulos C, et al. Curr Vasc Pharmacol 2017

Dyslipidemia: How big is the problem in Greece?

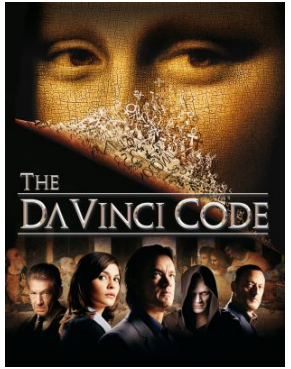
Are we doing enough?

These recent epidemiological data showed a higher rate of dyslipidemia in Greece than in other national and international surveys, with less use of drug treatment, and certainly contributed to the recent reclassification of the Greek population from low to medium cardiovascular risk

Stergiou G, et al. Hellenic J Cardiol 2023

LDL-C level targets in daily practice

Are we doing enough?



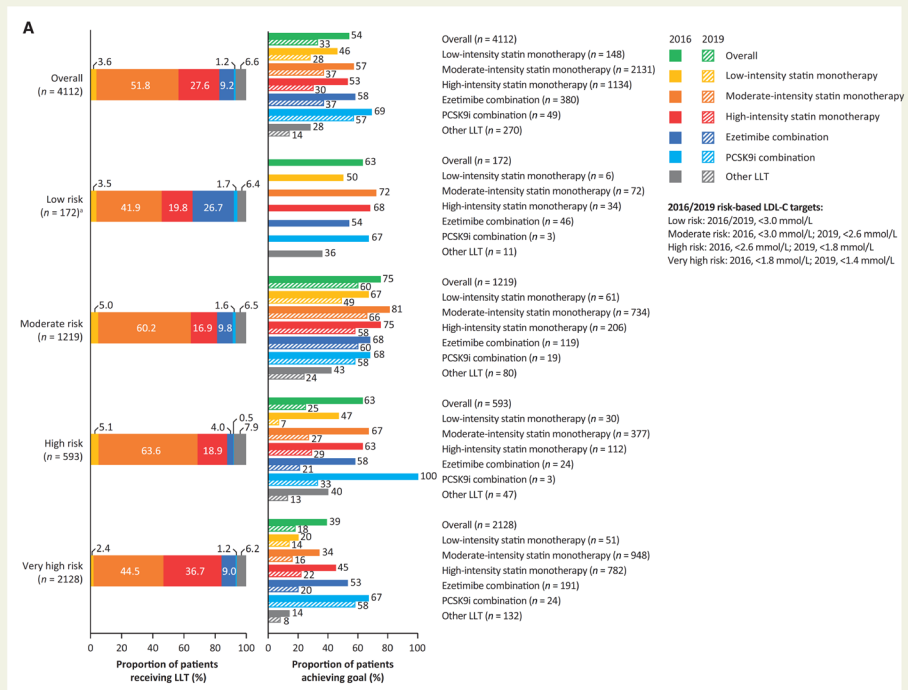


Figure 2 European Society of Cardiology/European Atherosclerosis Society 2016 and 2019 risk-based low-density lipoprotein cholesterol goal attainment among patients stabilized on lipid-lowering regimens summarized by level of risk and statin regimen. (A) The overall group summarized by level of risk and statin regimen (*B*) The Primary prevention group summarized by level of risk and statin regimen. (*C*) The established atherosclerotic

Gaps between clinical guidelines and clinical practice for lipid management across Europe persist

Even with optimized statins, greater utilization of non-statin LLT is likely needed to reduce these gaps for patients at highest risk.

Ray et al., EJPC 2021

LDL-C level targets in daily practice

Why are we not doing enough?

- physician inertia
- deficiencies of health-care systems
- need for multiple medications
- poor patient adherence to therapy

Δυσλιπιδαιμίες 2023

- Γιατί αυτούς τους στόχους;
- Τι έχουμε πετύχει στην πραγματικότητα;
- **Οι λύσεις - το μέλλον**

LDL-C level targets in daily practice

Solutions – Making physician/patient interaction effective

Box 10 Methods for enhancing adherence to lifestyle changes

1. Explore motivation and identify ambivalence. Weigh pros and cons for change, assess and build self-efficacy and confidence, and avoid circular discussion.
2. Offer support, and establish an alliance w… …t and his/her family.
3. Involve the partner, other h… …mbers, or caregiver who may be influential in the lifesty… …ent.
4. Use the **OARS** … …en-ended questions, **A**ffirmation, **R**eflective list… …arising when discussing behaviour changes (www.smartrec… …y.org/wp-content/uploads/2017/03/UsingMIinSR.pdf).
5. Tailor advice to an individual patient's culture, habits, and situation.
6. Use **SMART** goal setting (negotiate goals for change that are **S**pecific, **M**easurable, **A**chievable, **R**ealistic, and **T**imely). Follow-up on goals and record progress on a shared record.

IT TAKES TIME !!!

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 level targets in daily practice

Is adherence important?

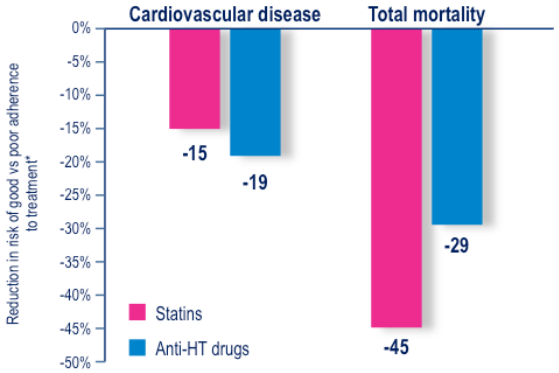
Meta-analysis of 44 prospective studies comprising **1,978,919** non-overlapping participants with CVD:

- **135,627 CVD events**
- **94,126** cases of **all-cause mortality**.

Only **60%** of the included patients were **good adherents***

9.1% of all events that occur are due to poor adherence in patients with prescribed cardiovascular medications.

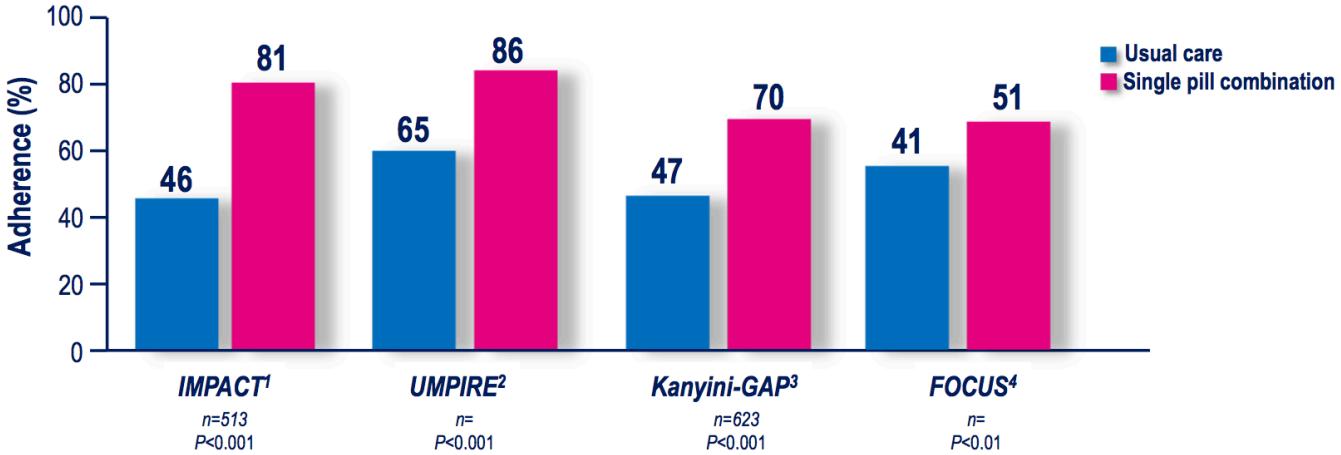
*Good adherence: ≥80% taking medication.



Chowdhury et al. Eur Heart J 2013

Single pill combinations

Percentage adherence to single-pill combination vs usual care in high CVD risk or established CVD[1-5]



Overall adherence improved by 44%[5]

(95% CI 26% to 65%) vs usual care in patients with cardiovascular (CV) disease or high CV risk, n=3338

1. Selak. BMJ. 2014;348:g3318 2. Thom S et al. JAMA. 2013;310(9):918-929. 3. Patel A et al. Europ J Prev Cardiol. 2015;27(7):920-930 4. Castellano JM et al. J Am Coll Cardiol. 2014;(64):613-621. 5. Huffman MD. PLOS Med. 2015;12(8):e1001862. 6. Huffman M, et al. Lancet 2017;389:1055-65

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

Expert Consensus for the Management of Dyslipidemias in ACS

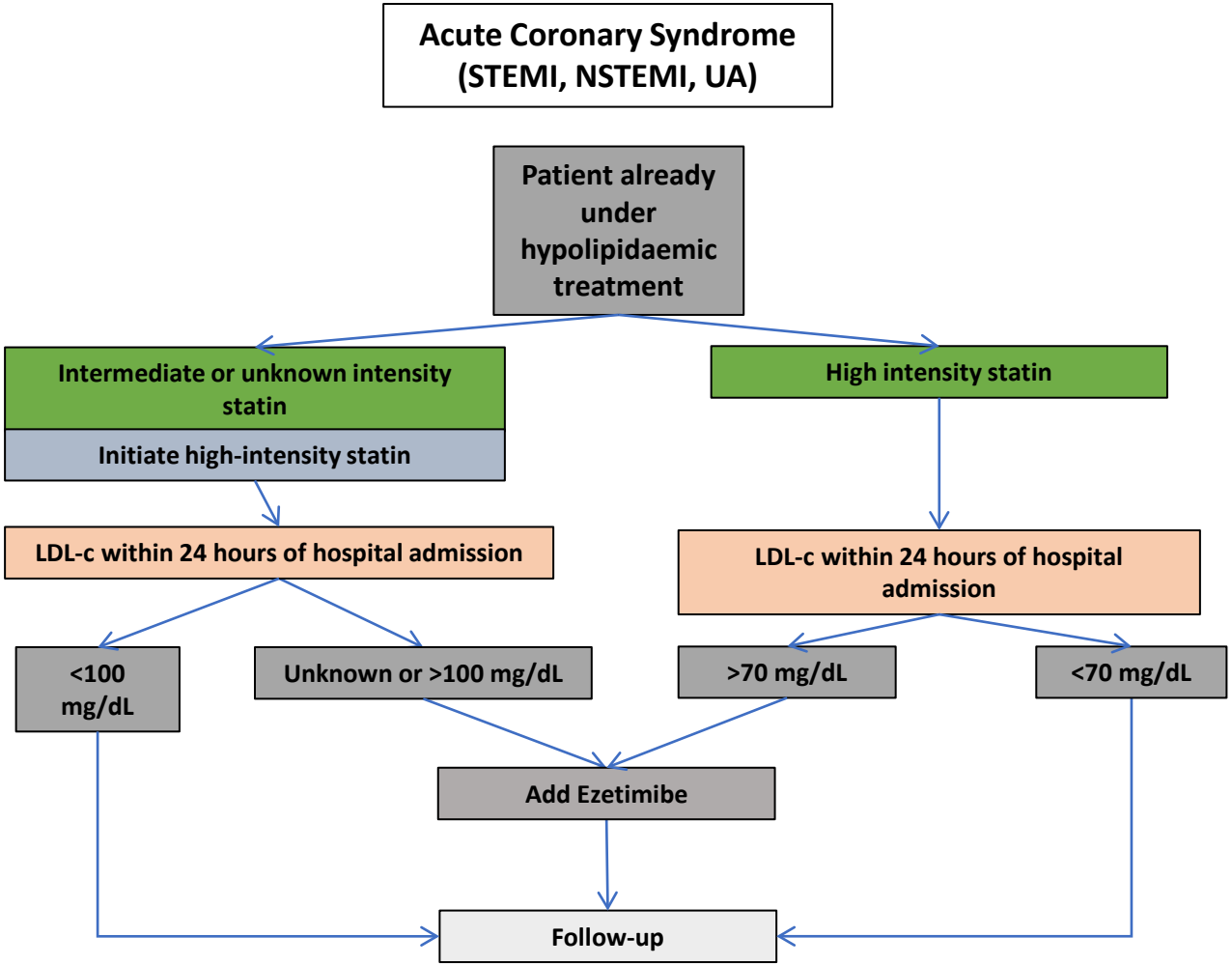
Βλαχόπουλος Χ*, Ραλλίδης Λ*, Άθυρος Β, Αλεξόπουλος Δ, Ανδρικόπουλος Γ, Βάρδας Π, Γανωτάκης Ε, Γουδέβενος Ι, Ελισάφ Μ, Ζάχαρης Ε, Κανακάκης Ι, Καρβούνης Χ, Κολοβού Γ, Λυμπερόπουλος Ε, Μακρυλάκης Κ, Μιχάλης Λ, Πίτσαβος Χ, Ρίχτερ Δ, Σκουλαρίγκης Ι, Σκούμας Ι, Τζιακάς Δ, Τζιόμαλος Κ, Τούτουζας Κ, Τσελέπης Α, Τσιούφης Κ, Φούσας Σ, Χάχαλης Γ, Λεκάκης Ι, Τούσουλης Δ.

Υπό την Αιγίδα:
της Α' και Β' Καρδιολογικής Κλινικής Πανεπιστημίου Αθηνών,
της Ελληνικής Καρδιολογικής Εταιρείας,
της Ελληνικής Εταιρείας Αθηροσκλήρωσης
και της Ελληνικής Εταιρείας Λιπιδιολογίας, Αθηροσκλήρωσης και Αγγειακής Νόσου

ΕΛΛΗΝΙΚΗ ΚΑΡΔΙΟΛΟΓΙΚΗ ΕΠΙΘΕΩΡΗΣΗ ΕΚΕ

Ιούλιος - Αύγουστος 2016
2016; 57(4): 302-315

* ισότιμη συμμετοχή


Acute Coronary Syndrome (STEMI, NSTEMI, UA)
Patient already under hypolipidaemic treatment
Intermediate or unknown intensity statin
Initiate high-intensity statin
High intensity statin
LDL-c within 24 hours of hospital admission
LDL-c within 24 hours of hospital admission
<100 mg/dL
Unknown or >100 mg/dL
>70 mg/dL
<70 mg/dL
Add Ezetimibe
Follow-up

‘Statin-ology’

DAILY EXPRESS

THE WORLD'S GREATEST NEWSPAPER express.co.uk WEATHER: SUNSHINE AND SHOWERS FRIDAY JULY 14, 2017 55p

NOW 10p CHEAPER THAN THE DAILY MAIL AND 15p CHEAPER THAN THE DAILY MIRROR AND TEN TIMES BETTER

TRAVEL BOSSES BAN STAFF FROM CALLING PASSENGERS LADIES AND GENTLEMEN

SEE PAGE 2

GET A SET OF TRIMMING SHEARS FOR JUST £19.99 WAS £40

SEE PAGE 10

STATINS: NEW HEALTH ALERT

Study says heart pills do you more harm than good

By Giles Sheldrick

STATINS fail to slash deaths from heart disease and do more harm than good, a major study claims.

Analysis showed those who suffer a heart attack and take a daily cholesterol-busting pill for five years will increase their life expectancy by just four days.

The research casts fresh doubt on the benefits of statins, prescribed to six million people in the UK and has reignited the debate over their true worth.

A coalition of experts in Britain and the US joined forces to declare there is "no consistent evidence" that the pills reduce death rates.

They claimed that the pro-statin lobby is funded by pharmaceutical giants and simply based on "cherry-picked science".

The senior medics suggest the simplest and safest way to achieve a healthy heart is through better diet and more exercise.

Consultant cardiologist Dr Aseem Malhotra, the report's author, said: "It's clear appropriate

TURN TO PAGE 4

KATHERINE JENKINS Surprise new face of BBC's Songs Of Praise

SEE PAGE 7

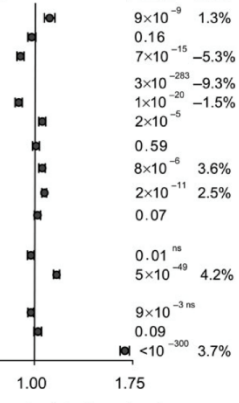
European Heart Journal (2016) **37**, 908–916
doi:10.1093/eurheartj/ehv641

CLINICAL RESEARCH
Prevention and epidemiology

Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study

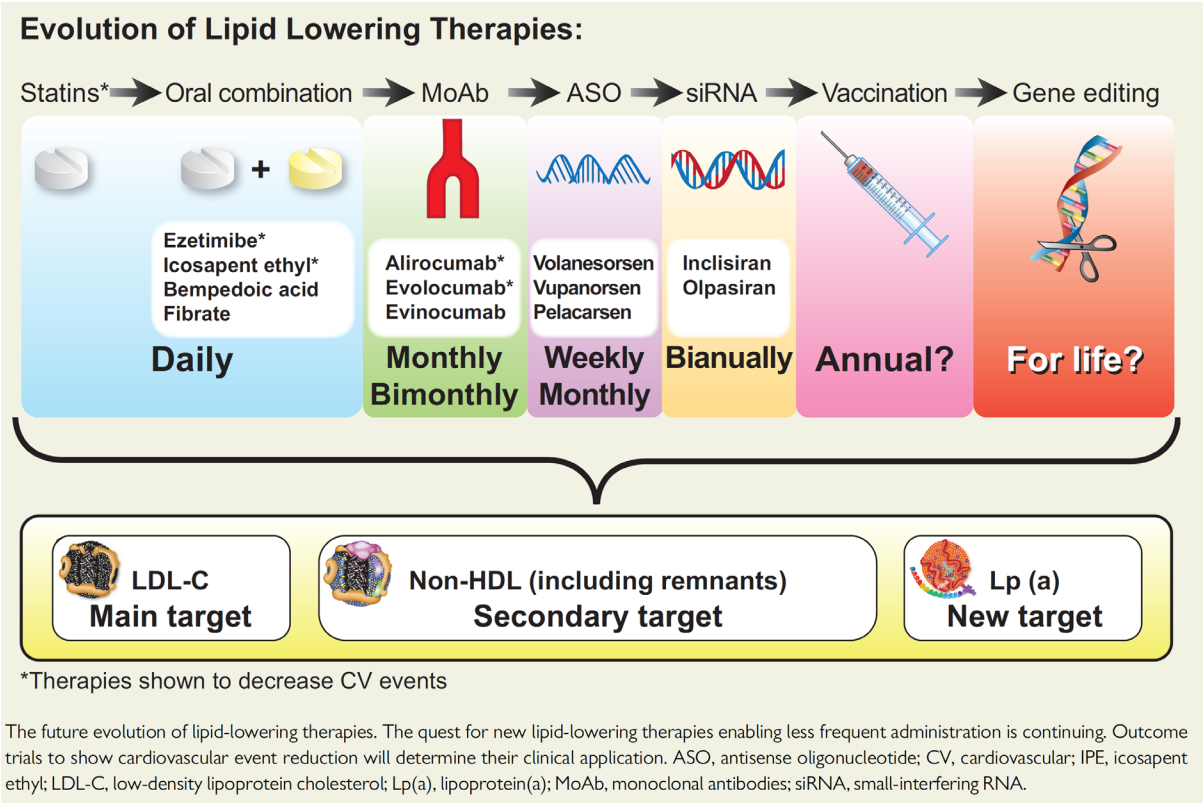
Sune Fallgaard Nielsen and Børge Grønne Nordestgaard*

Predictor	Odds ratio for early statin discontinuation with 95% confidence interval	*P*-value	PAR
Negative nationwide statin-related news story	1.09 (1.06–1.12)	9×10^{-9}	1.3%
Neutral nationwide statin-related news story	0.98 (0.96–1.01)	0.16	
Positive nationwide statin-related news story	0.92 (0.90–0.94)	7×10^{-15}	–5.3%
Cardiovascular disease before statin dispense	0.73 (0.72–0.74)	3×10^{-283}	–9.3%
Diabetes before statin dispense	0.91 (0.90–0.93)	1×10^{-20}	–1.5%
Calendar year	1.04 (1.02–1.07)	2×10^{-5}	
Percentage of population using a statin	1.00 (0.99–1.02)	0.59	
Statin dose in first dispense, DDD#	1.04 (1.02–1.06)	8×10^{-6}	3.6%
Male sex	1.05 (1.03–1.06)	2×10^{-11}	2.5%
Age at start of statin therapy	1.02 (1.00–1.03)	0.07	
Residential area, < 12,000 residents	1.00 (ref)		
12,000-100,000 residents	0.98 (0.96–1.00)	0.01 ns	
>100,000 residents	1.13 (1.11–1.15)	5×10^{-49}	4.2%
Education, primary or high-school	1.00 (ref)		
Vocational training	0.98 (0.96–0.99)	9×10^{-3} ns	
College degree	1.02 (1.00–1.04)	0.09	
Other ethnicity than Danish descent	1.67 (1.63–1.71)	$<10^{-300}$	3.7%



Non-statin future therapies

These LLTs from the future are what keeps me going



The future evolution of lipid-lowering therapies. The quest for new lipid-lowering therapies enabling less frequent administration is continuing. Outcome trials to show cardiovascular event reduction will determine their clinical application. ASO, antisense oligonucleotide; CV, cardiovascular; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MoAb, monoclonal antibodies; siRNA, small-interfering RNA.

Non-statin future therapies

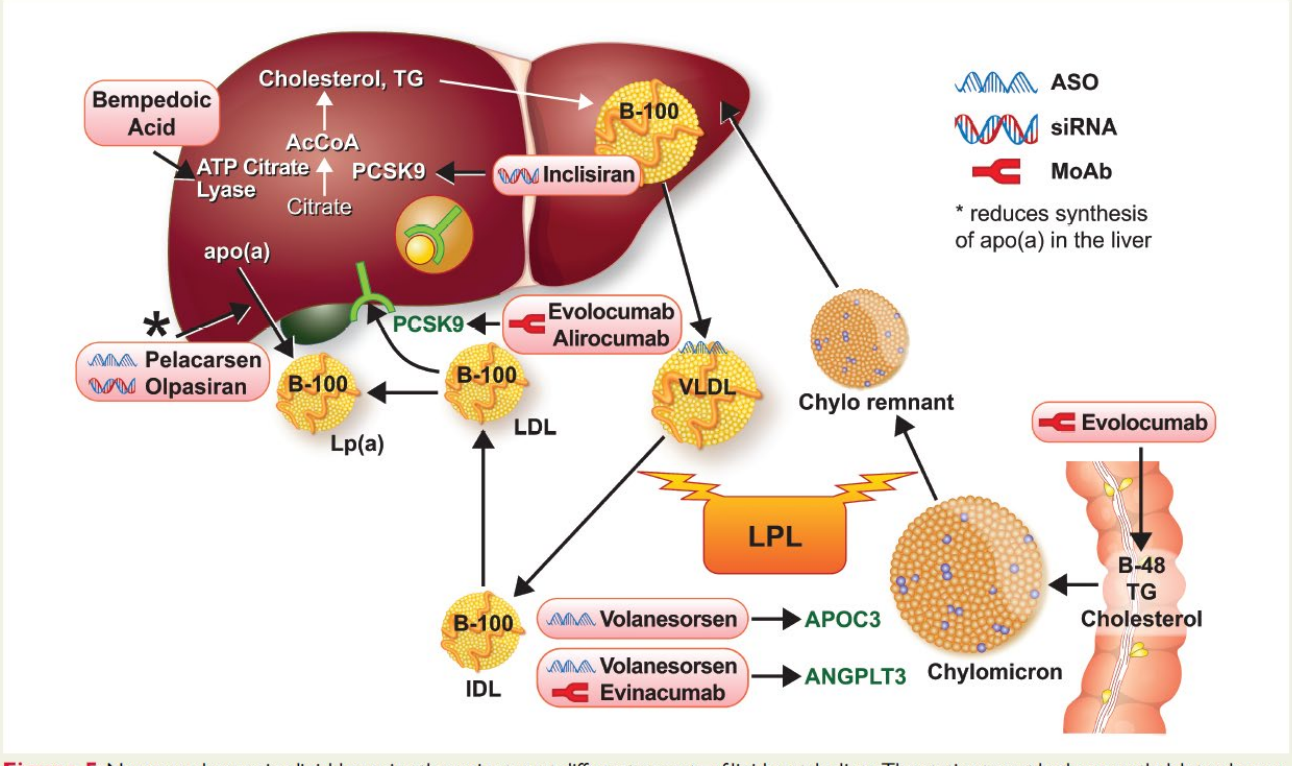


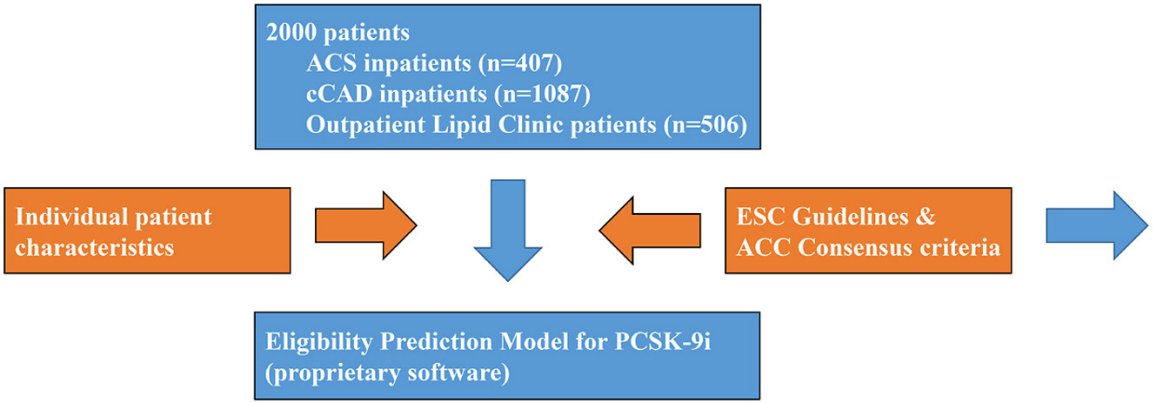
Figure 5 Newer and emerging lipid-lowering therapies target different aspects of lipid metabolism. The statins target hydroxymethylglutaryl coenzyme A reductase. The newer and emerging agents target other aspects of lipid metabolism as shown here. B48 refers to the shorter form of apolipoprotein B produced by RNA editing in the intestine. B100 refers to the longer form produced in the liver. See the list for explanations of other abbreviations.

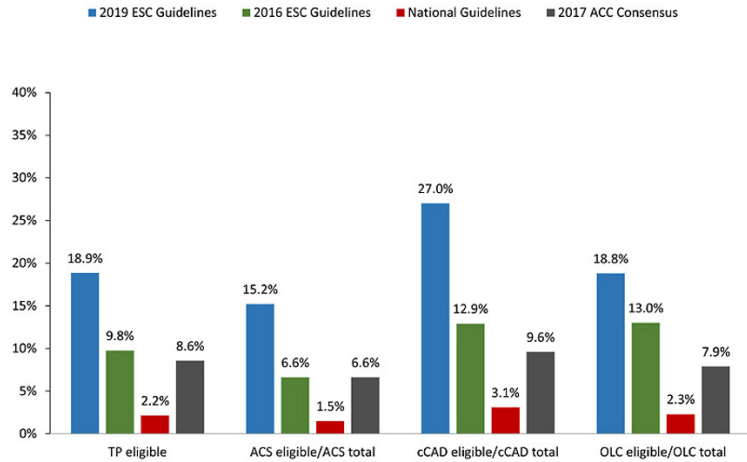
Multiple pathways are being targeted

Tokgozoglu L et a;. EHJ 2022

LDL-C level targets in daily practice

Solutions – Intensification of therapy





- 2,000 patients
- Proprietary adjustable prediction software
- Estimation of pts at goal with intensification of therapy (**maximum statin dose+ezetimibe**)

Dima I, et al. Atherosclerosis 2020

Μελέτες κόστους/αποτελεσματικότητας

Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes

Circ Cardiovasc Qual Outcomes. 2019;12:e005404. DOI: 10.1161/

See Editorial by Nasir et al

BACKGROUND: Atherosclerotic cardiovascular disease remains a major cause of death and disability, especially for high-risk familial hypercholesterolemia individuals. PCSK9i (proprotein convertase subtilisin kexin type 9 inhibitors) reduce low-density lipoprotein cholesterol levels and cardiovascular event rates. However, PCSK9i prescriptions are rejected at high rates by payers, and use is often delayed or eventually abandoned as a treatment option. We tested the hypothesis that acute coronary syndromes, coronary interventions, stroke, and cardiac arrest are more prevalent in patients with rejected or abandoned PCSK9i prescriptions

Kelly D. Myers, BS*
Niloofar Farboodi, MSc, MPH*
Mkaya Mwamburi, MD, PhD, MA
William Howard, PhD
David Staszak, PhD
Samuel Gidding, MD
Seth J. Baum, MD
Katherine Wilemon, BS
Daniel J. Rader, MD

Μελετήθηκαν 140.000 ασθενείς στους οποίους είχε συνταγογραφηθεί η εβολοκουμάμπη στις ΗΠΑ σε διάστημα 2 ετών (2015-2017). 4 στα 5 περιστατικά απορρίφθηκαν

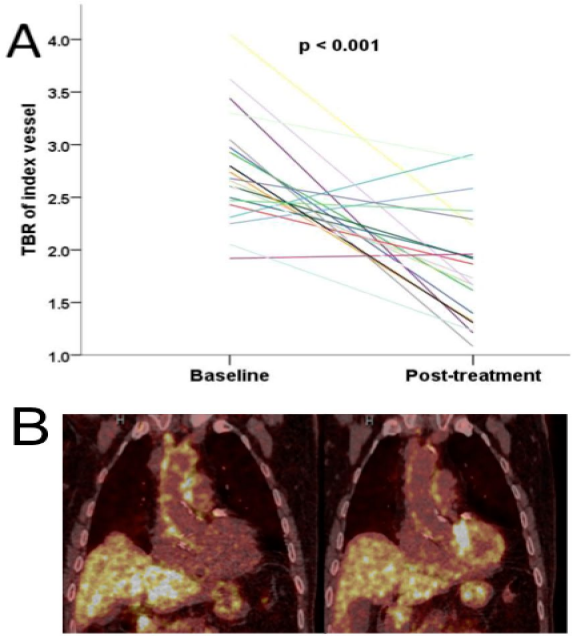
Συγκρινόμενο με την ομάδα στην οποία αποζημιώθηκε το φάρμακο για 12 μήνες αυτοί που δεν το έλαβαν είχαν αυξημένα ΚΑ συμβάντα κατά 16-21 %.

PCSK9i and aortic inflammation

Long term administration of proprotein convertase subtilisin/kexin type 9 inhibitors reduces arterial 18F-fluoro-2-deoxy-D-glucose (FDG) uptake

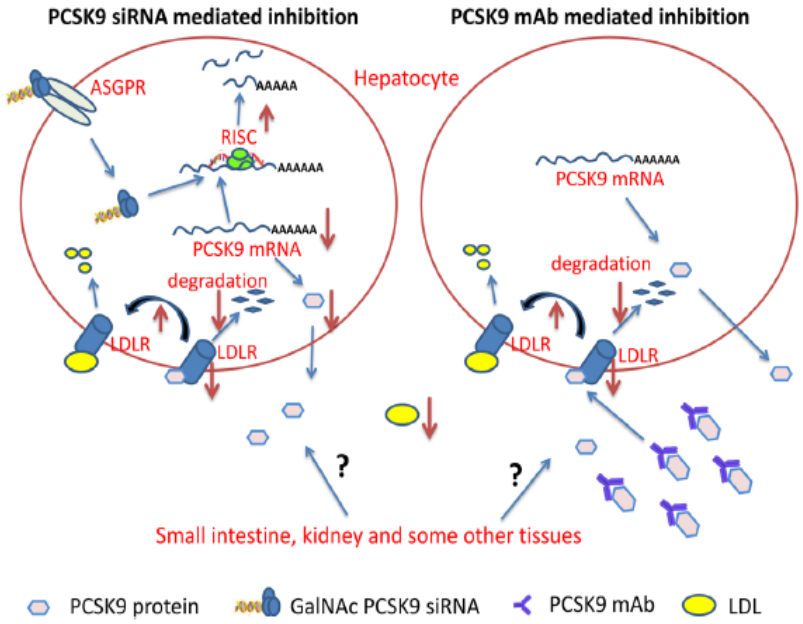
- 21 patients with stable CVD not on low density lipoprotein cholesterol target
- FDG PET/CT imaging was performed and high sensitivity interleukin-1β (hs-IL-1β) and IL-6 (hs-IL-6) were measured at baseline and 12 months after treatment with either alirocumab (n=9, 75 or 150 mg every 2 weeks) or evolocumab (n=12, either 140 mg every 2 weeks or 420 mg once monthly).

- **significant reduction of arterial FDG uptake independently of LDL-c change.**
- **significant reduction of hs-IL-1β.**



Vlachopoulos/Koutagiar et al. JACC Img 2019

Non-statin therapies



Circres.ahajournals.org

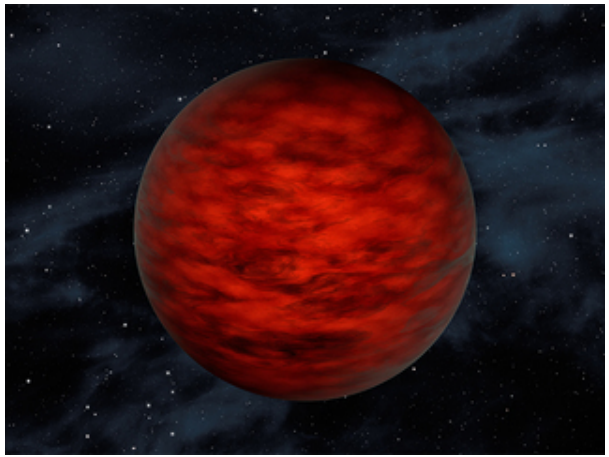
Inclisiran: Small interfering RNA molecule (siRNA) which inhibits the synthesis of PCSK9.

Reduction of LDL up to 50%

One-Year Follow-up of the ORION-1 Randomized Phase II Clinical Trial

501 participants randomised to Inclisiran or placebo

- ONE dose 200, 300 or 500mg at Day 1
- TWO doses 100, 200 or 300mg at Day 1 and 90



Time-averaged reduction in LDL-C levels over 1 year after a single dose ranged from 29.5% to 38.7% ($P < .001$ between groups) and from 29.9% to 46.4% ($P < .001$ between groups) for those who received 2 doses.

JAMA, September 2019

Πέρα από την LDL

HDL
Όσο υψηλότερη τιμή, τόσο καλύτερα;

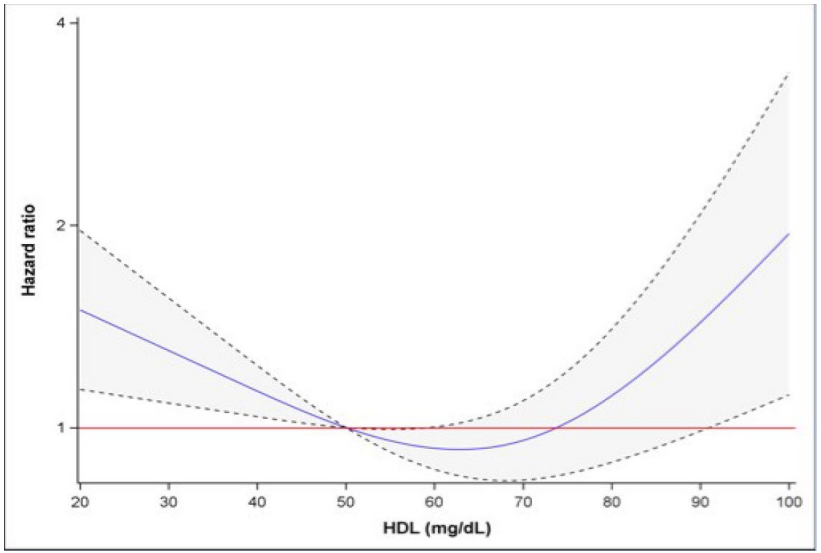
Elevated HDL-C is associated with adverse cardiovascular outcomes

5,965 individuals (mean age 63.3±12.4 years, 35% female, 23% African American)

Median follow-up of 3.9 years; 769 CV death/non-fatal MI events

Individuals were stratified by HDL-C categories (<30, 31–40, 41–50, 51–60 and ≥60 mg/dL)

- **U-shaped" association between HDL-C and CV death/non-fatal MI**
- **HDL-C <30 mg/dL and ≥60 mg/dL ➡ ▲risk of all-cause mortality and CV death / non-fatal MI** (HR 1.62; 95% CI=1.16–2.26, p=0.005 and HR 1.44; 95% CI = 1.01–2.06, p=0.04 respectively)



Allard-Ratick et al. ESC 2018

Πέρα από την LDL

HDL

CETP-inhibitors

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

HDL

Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

Recommendations if drug treatment of low high-density lipoprotein cholesterol is considered

Recommendations	Class [a]	Level [b]
Statins and fibrates raise HDL-C with a similar magnitude and these drugs may be considered.	IIb	B
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B

Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes - ACCELERATE

Principal Findings:

The trial was terminated early due to futility

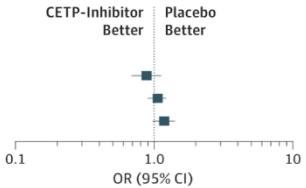
The primary outcome, cardiovascular death/MI/stroke/coronary revascularization/unstable angina for evacetrapib vs. placebo was **12.8% vs. 12.7%**, p = 0.85

Components of the primary outcome (for evacetrapib vs. placebo):

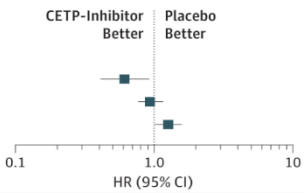
- CV death: 7.2% vs.7.3%, p = 0.73
- MI: 4.2% vs. 4.2%, p = 0.97
- Stroke: 1.5% vs. 1.6%, p = 0.82

Effect of genotyping:
single-nucleotide polymorphism (SNP) in the *ADCY9* gene (rs1967309) among 1,427 cases and 1,532 matched controls

Study and Genotype	OR (95% CI)	Interaction *P* Value[a]	*P* Value For Trend[b]
ACCELERATE		.17	.06
AA	0.88 (0.69-1.12)		
AG	1.04 (0.90-1.21)		
GG	1.18 (0.98-1.41)		



Study and Genotype	HR Reduction, % (CI)	Interaction *P* Value[a]	*P* Value For Trend[b]
dal-OUTCOMES		NA	.001
AA	0.61 (0.41-0.92)		
AG	0.94 (0.77-1.16)		
GG	1.27 (1.02-1.58)		



JAMA Cardiology 2018

Σκέψεις πάνω στη HDL

- **Οι πολύ υψηλές τιμές HDL δεν είναι τόσο αθώες**
- **Απουσία κλινικού οφέλους από τη θεραπευτική παρέμβαση στα επίπεδα HDL**
- **Σημασία έχουν τα επίπεδα ή η μορφολογία-λειτουργικότητα της HDL;**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Ray KK, et al., for the CLEAR Harmony Trial

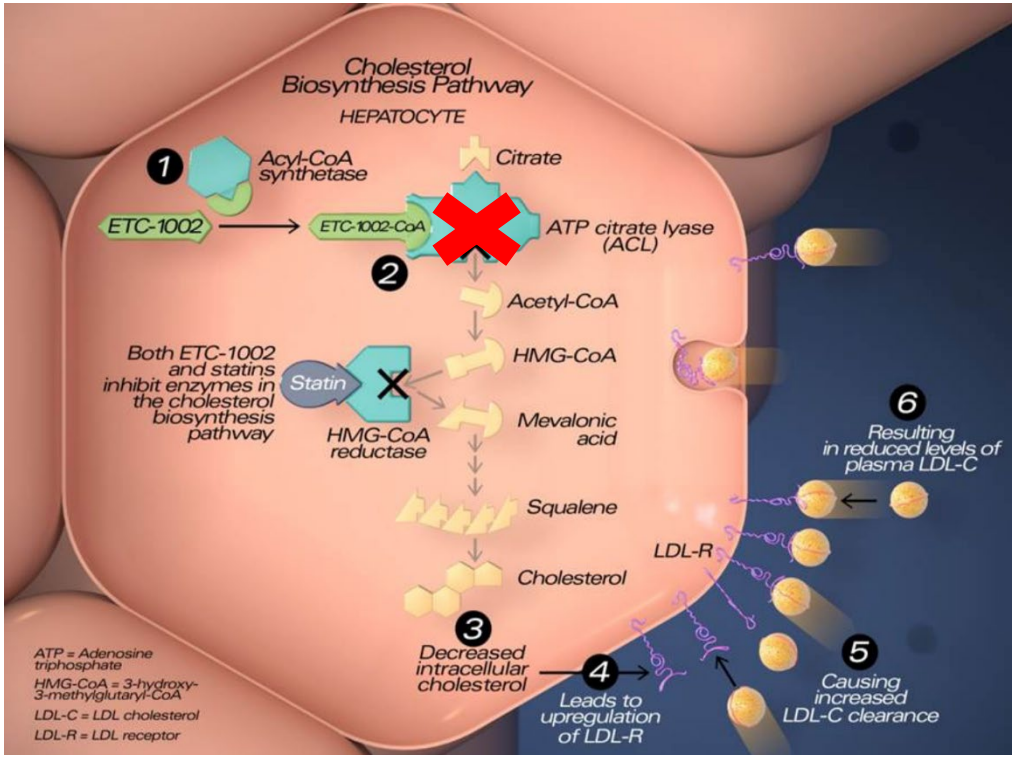
BACKGROUND

- Bempedoic acid, an inhibitor of ATP citrate lyase, reduces levels of low-density lipoprotein (LDL) cholesterol.

- **BUT:** limited data regarding the safety and efficacy of bempedoic acid treatment in long-term studies involving patients with hypercholesterolemia who are receiving guideline-recommended statin therapy.

N Engl J Med 2019; 380:1022-1032

Bempedoic acid - Mechanism of action



Bempedoic acid is converted to its active moiety primarily in the liver, and inhibits adenosine triphosphate citrate lyase (ACL)—an enzyme two steps upstream from HMG-CoA reductase, the target of statins—along the cholesterol biosynthesis pathway.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

RESULTS – SAFETY (Primary Endpoint)

Variable*	Patients, %		*P* value†
	Placebo (n=742)	Bempedoic Acid (n=1487)	
Any AE	78.7	78.5	NS
Serious AE	14.0	14.5	NS
AE leading to discontinuation of study drug	7.1	10.9	0.005

- Similar rates of adverse events; 78.5% in the bempedoic acid group and 78.7% in the placebo group)
- Similar rates of serious adverse events; Bempedoic acid [14.5%] and [14.0%] placebo group
- BUT adverse events leading to **discontinuation of the regimen was higher in the bempedoic acid group** than in the placebo group [10.9%] vs.[7.1%], as was the incidence of GOUT ([1.2%] vs. [0.3%]).

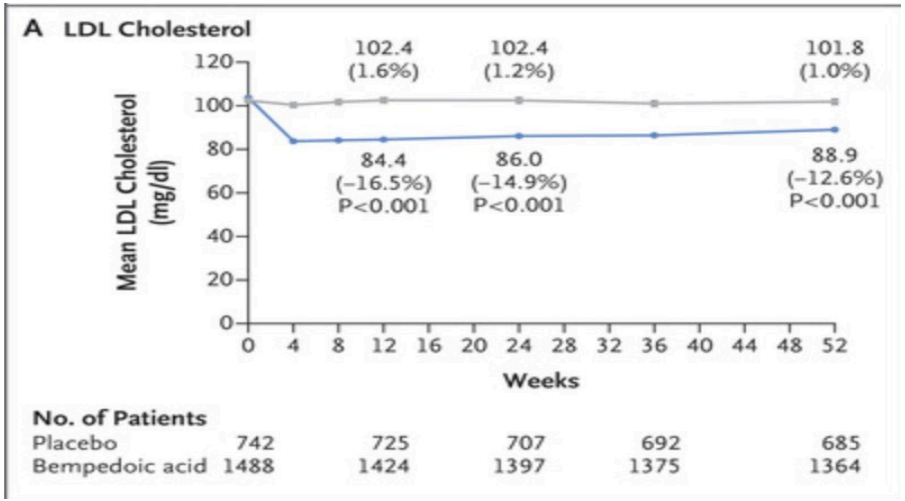
Ray KK, et al., N Engl J Med 2019; 380:1022-1032

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

RESULTS – EFFICACY (Secondary endpoint)



At week 12, bempedoic acid **reduced the mean LDL cholesterol level by 19.2** mg per deciliter, representing a change of **−16.5% from baseline** (difference vs. placebo in change from baseline, −18.1 percentage points; 95% confidence interval, −20.0 to −16.1; P<0.001)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Conclusions

CLEAR Harmony provides the largest evidence to date that BA is safe as an adjunct to a guideline-based statin regimen

- ✓ Adverse event profile of BA was generally similar to that of placebo
- ✓ Background statin intensity did not influence the safety profile of BA

BA reduced LDL-C at week 12 by 18.1% (ITT) and 19.8% (on-treatment)

- ✓ Significant reductions in LDL-C were observed through to week 52
- ✓ BA also significantly lowered non-HDL-C, total cholesterol, apoB, and hsCRP

❖ BA provides an additional therapeutic option to safely lower LDL-C in high ASCVD risk patients treated with statins

Ray KK, et al., N Engl J Med 2019; 380:1022-1032

Conclusions

- We are entering a new era in lipid lowering.
- Efforts to personalize therapy and target the right patient at the right time include further refinement of risk stratification tools including genetic risk scores and the integration of imaging studies to management decisions.
- While statins remain the first choice for lipid lowering, the availability of complementary therapies allow for individual tailoring according to the needs of the patient


Thank you