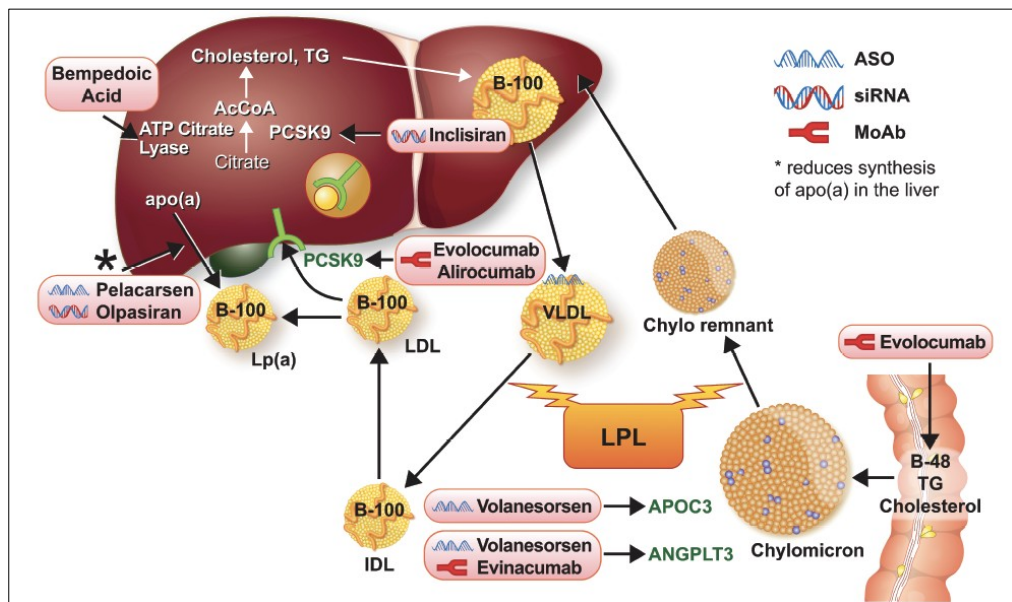


# Νέες αναδυόμενες θεραπείες δυσλιπιδαιμίας



ΛΟΥΚΙΑΝΟΣ ΡΑΛΛΙΔΗΣ, FESC  
ΚΑΘΗΓΗΤΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ  
ΥΠΕΥΘΥΝΟΣ ΥΠΟΛΙΠΙΔΑΙΜΙΚΟΥ ΙΑΤΡΕΙΟΥ/  
ΙΑΤΡΕΙΟΥ ΠΡΩΙΜΗΣ ΣΝ  
ΚΑΙ ΜΟΝΑΔΟΣ ΕΜΦΡΑΓΜΑΤΙΩΝ  
Β' ΚΑΡΔ ΚΛ, ΠΓΝ «ΑΤΤΙΚΟΝ»

ΠΡΟΓΡΑΜΜΑ



**SIMA 23**

Σι-μα Ιητηρ(ιατρός) Μινωική Κρήτη



1ο ΠΟΛΥΘΕΜΑΤΙΚΟ ΣΥΝΕΔΡΙΟ  
ΙΑΤΡΙΚΟΥ ΣΥΛΛΟΓΟΥ ΗΡΑΚΛΕΙΟΥ

# Σύγκρουση συμφερόντων

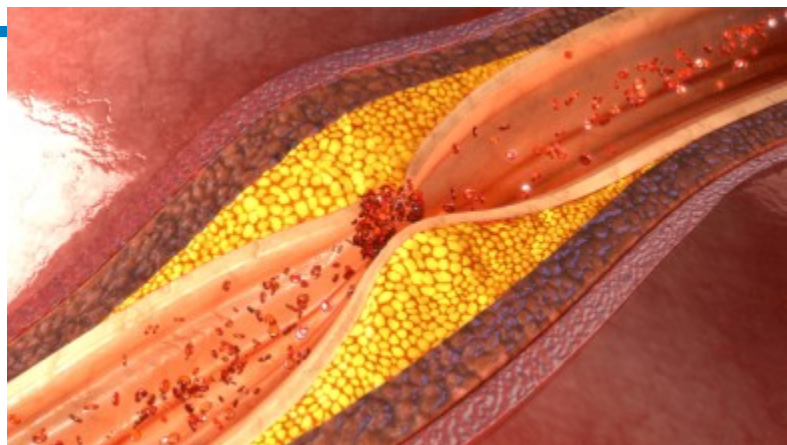
Συμμετοχή σε ομιλίες, honoraria, συμβουλευτικές υπηρεσίες, και κλινικές μελέτες που επιχορηγήθηκαν από φαρμακευτικές εταιρείες, συμπεριλαμβανομένων των Viatris, Vianex, Sanofi, Pfizer, Elpen, Servier και Amgen

ΕΧΩ ΣΤΗΝ ΤΡΑΠΕΖΑ ΕΝΑ ΠΟΣΟ  
ΜΕ ΠΟΛΛΑ ΜΗΔΕΝΙΚΑ!...  
0,00001 ΕΥΡΩ!

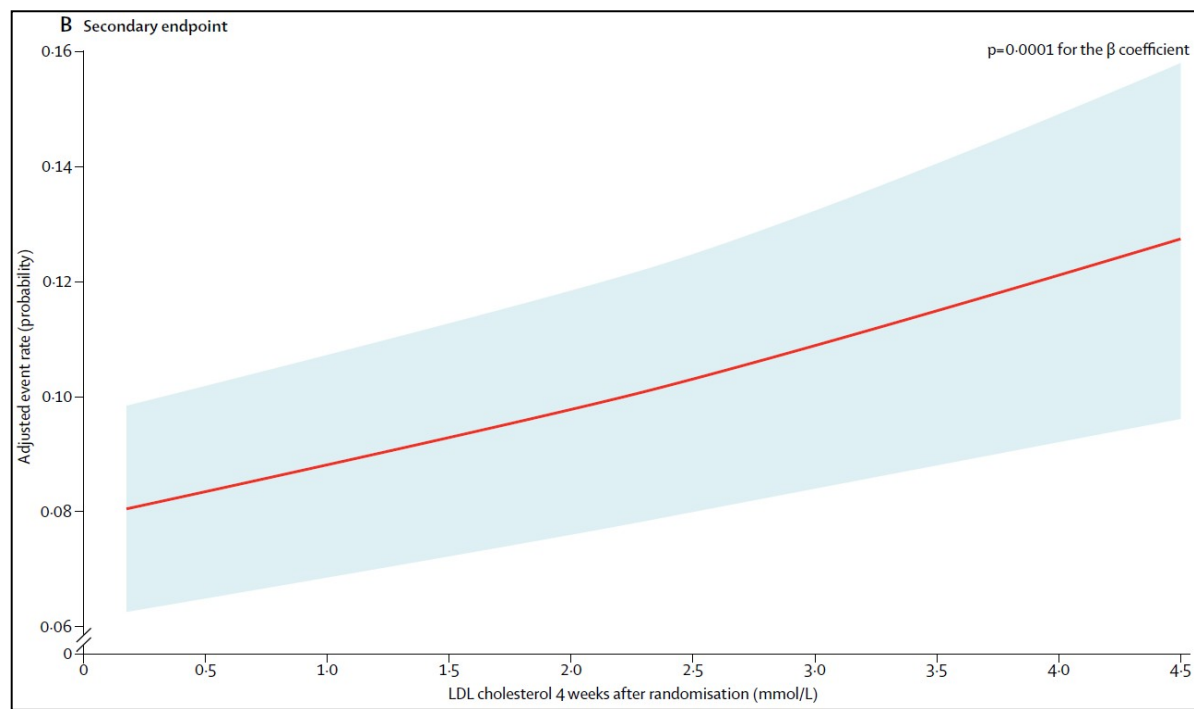
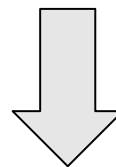


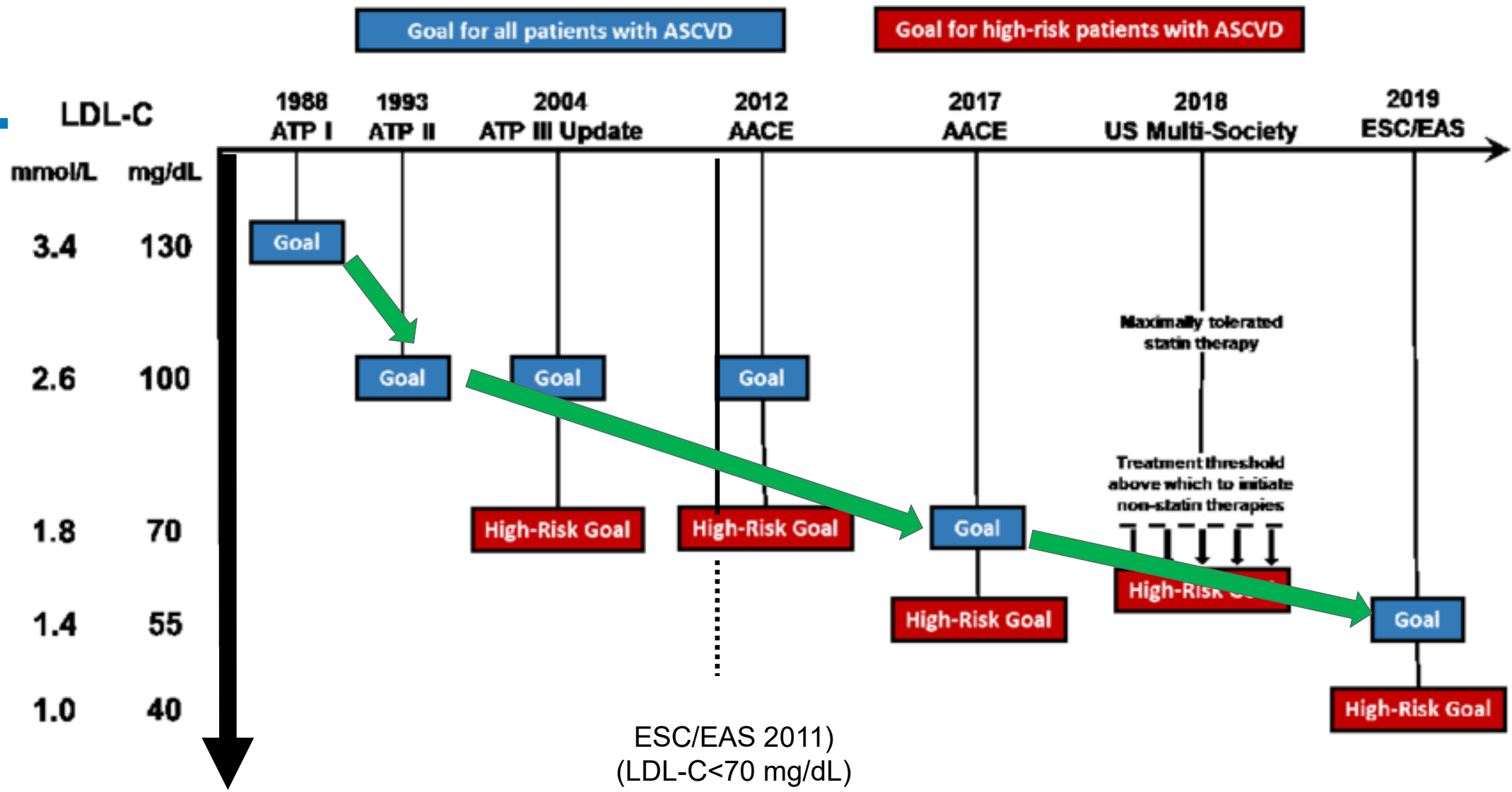


# Η LDL-χ ως αιτιολογικός παράγοντας ΚΑΝ



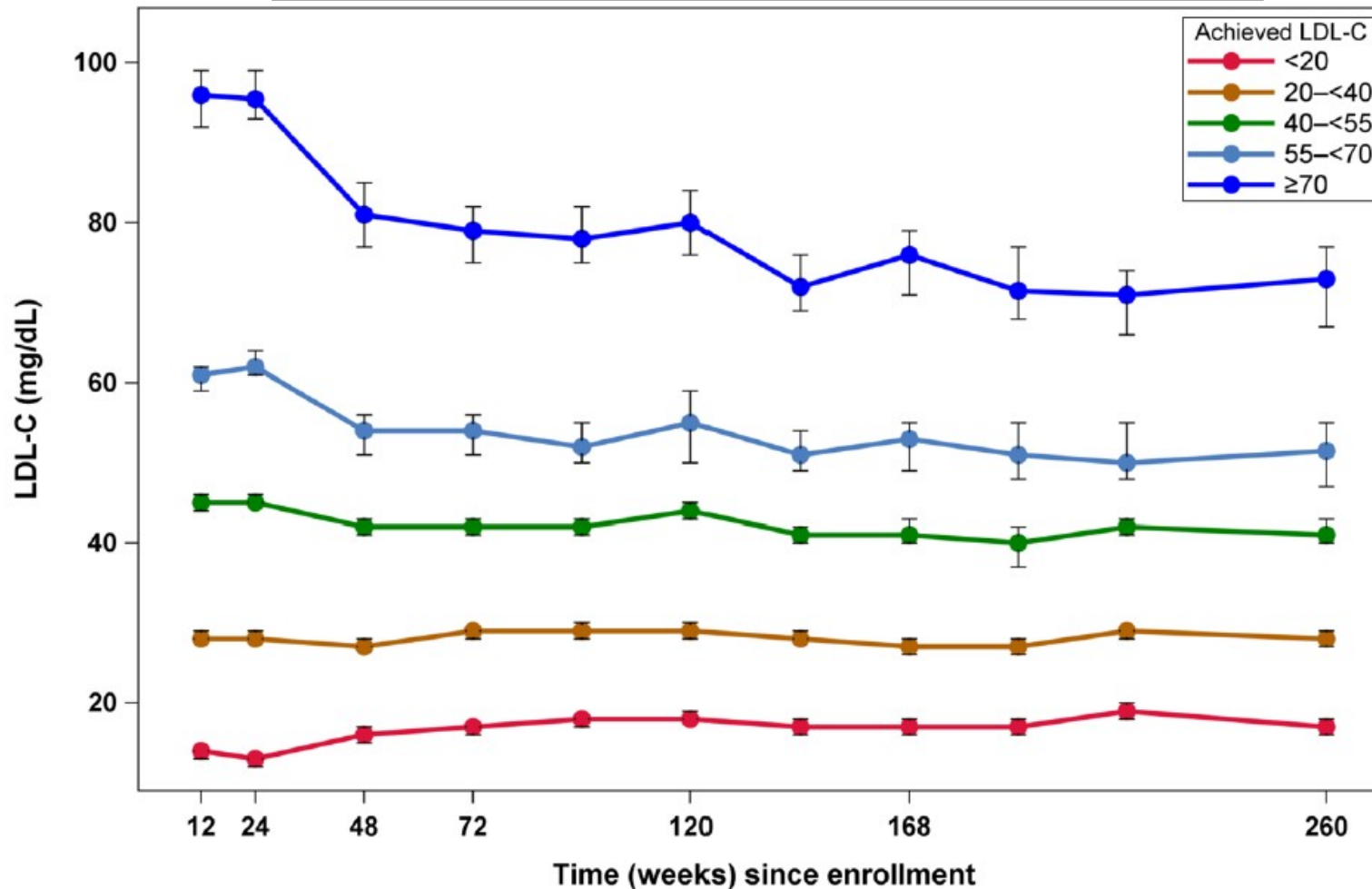
Μέχρι 300 mg% χοληστερίνης αίματος  
δέον να θεωρηθεί φυσιολογικόν  
(Εσωτερική Παθολογία Δανόπουλου 1966)





# Πόσο ασφαλή είναι τα πολύ χαμηλά επίπεδα της LDL-χ?

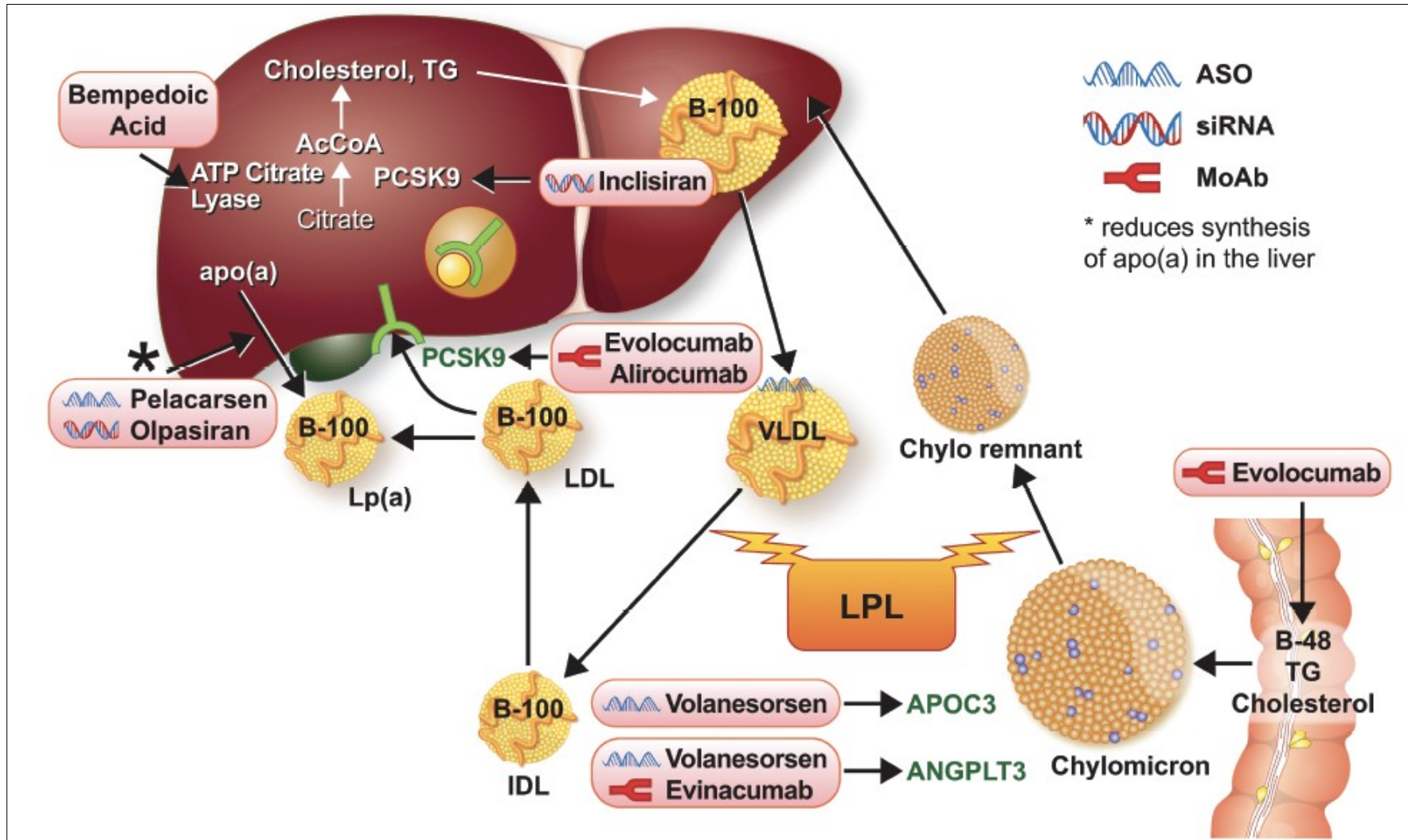
Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE



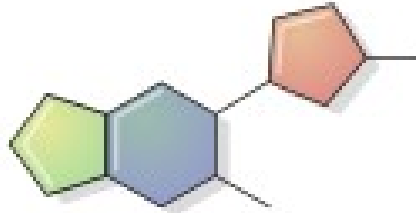
64% <40 mg/dL

24% <20 mg/dL  
(n=1592)

## 2) Νεότερα υπολιπιδαιμικά

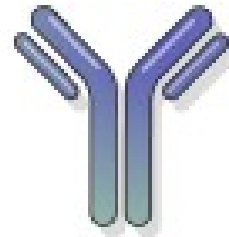


## Small molecules



- Bempedoic acid
- Pemafibrate
- Icosapent ethyl

## Antibodies



- Evinacumab
- Evolocumab
- Alirocumab

## ASO



- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L</sub><sub>RX</sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

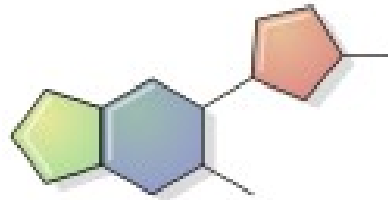
## Proteins and peptides



- CSL-112

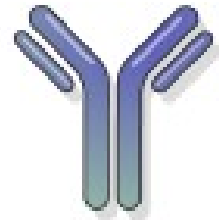


## Small molecules



- Bempedoic acid
- Pemafibrate
- Icosapent ethyl

## Antibodies



- Evinacumab
- Evolocumab
- Alirocumab

## ASO



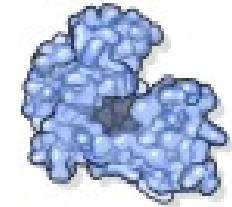
- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L</sub><sub>RX</sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

## Proteins and peptides

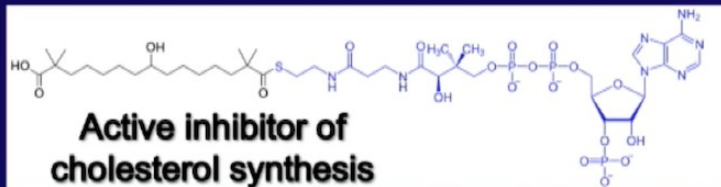
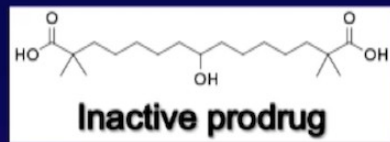
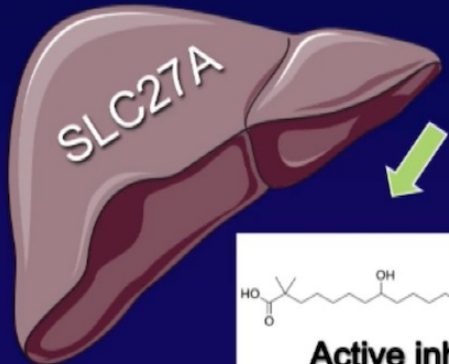


- CSL-112

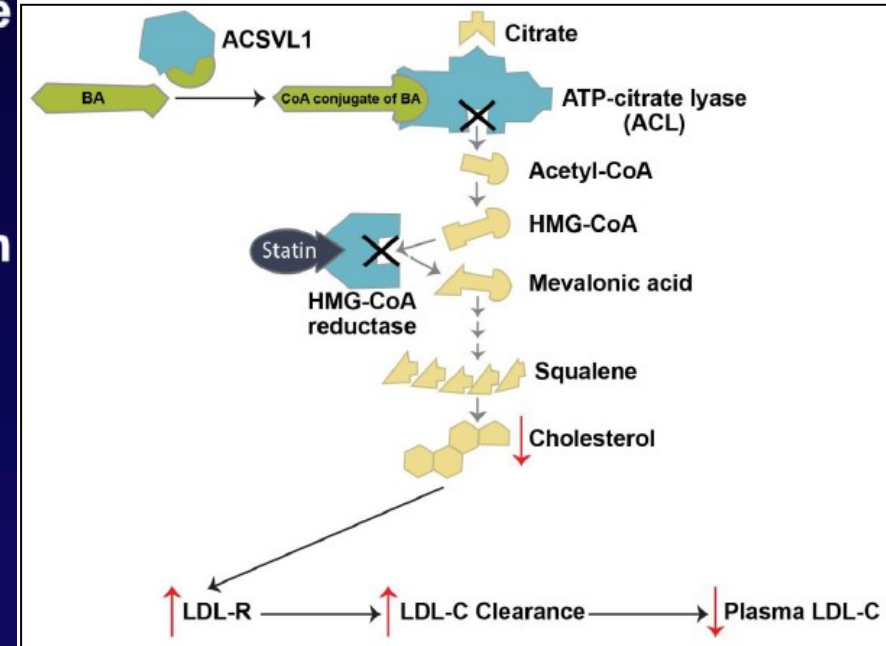
# Μπεμπεδοϊκό οξύ

## Selective Activation of Bempedoic Acid in Hepatocytes

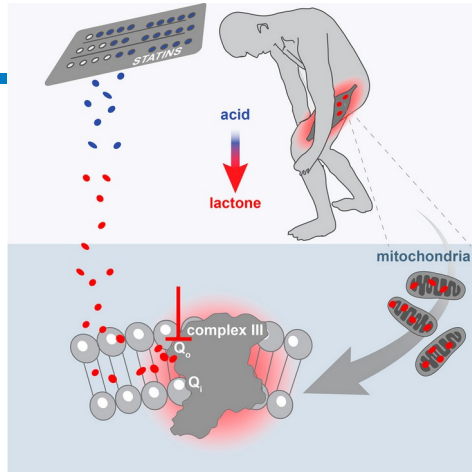
Bempedoic acid is a *pro-drug* that requires conjugation to coenzyme A to form a thioester. Hepatocytes, but not skeletal myocytes express the activating enzyme SLC27A2. This prevents the drug from inhibiting the target enzyme ATP-citrate lyase in myocytes, reducing the likelihood of muscle symptoms encountered with statin therapy.



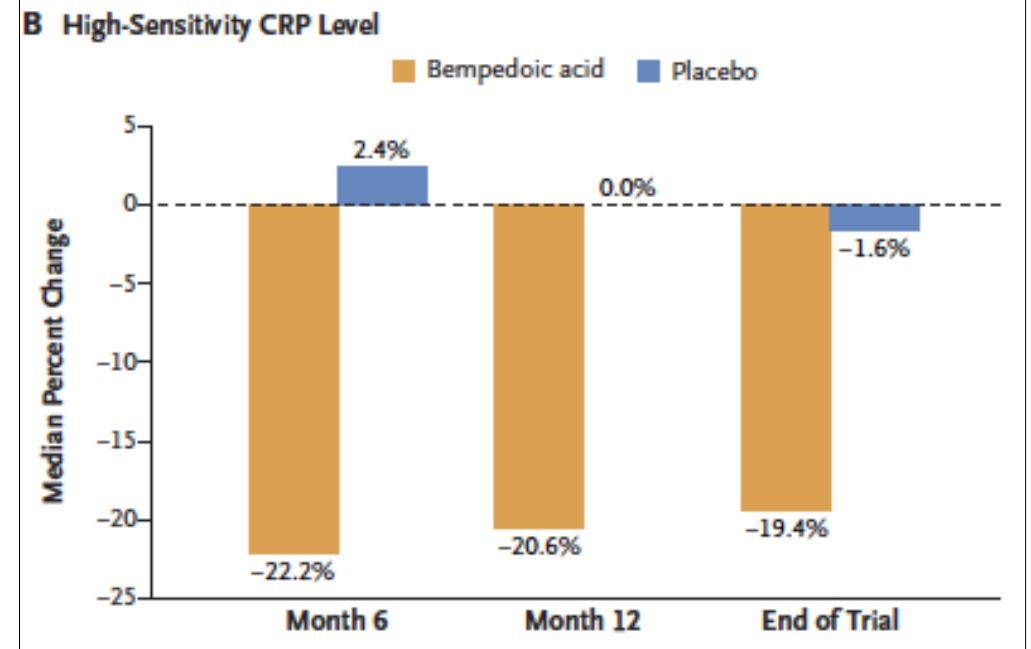
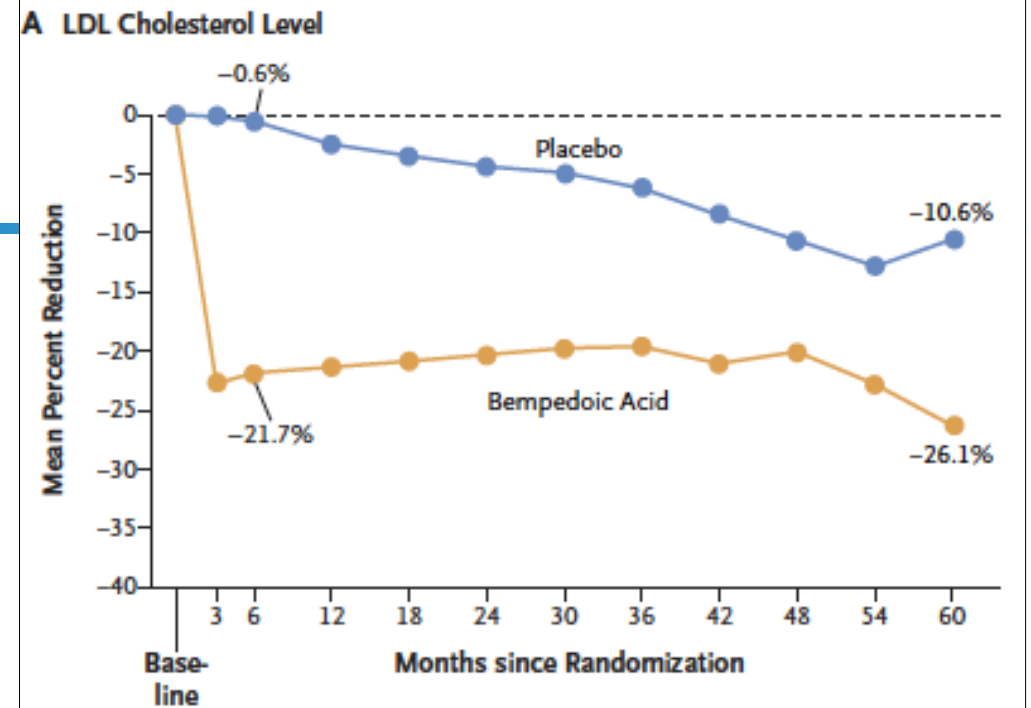
**Activation in liver not muscle**

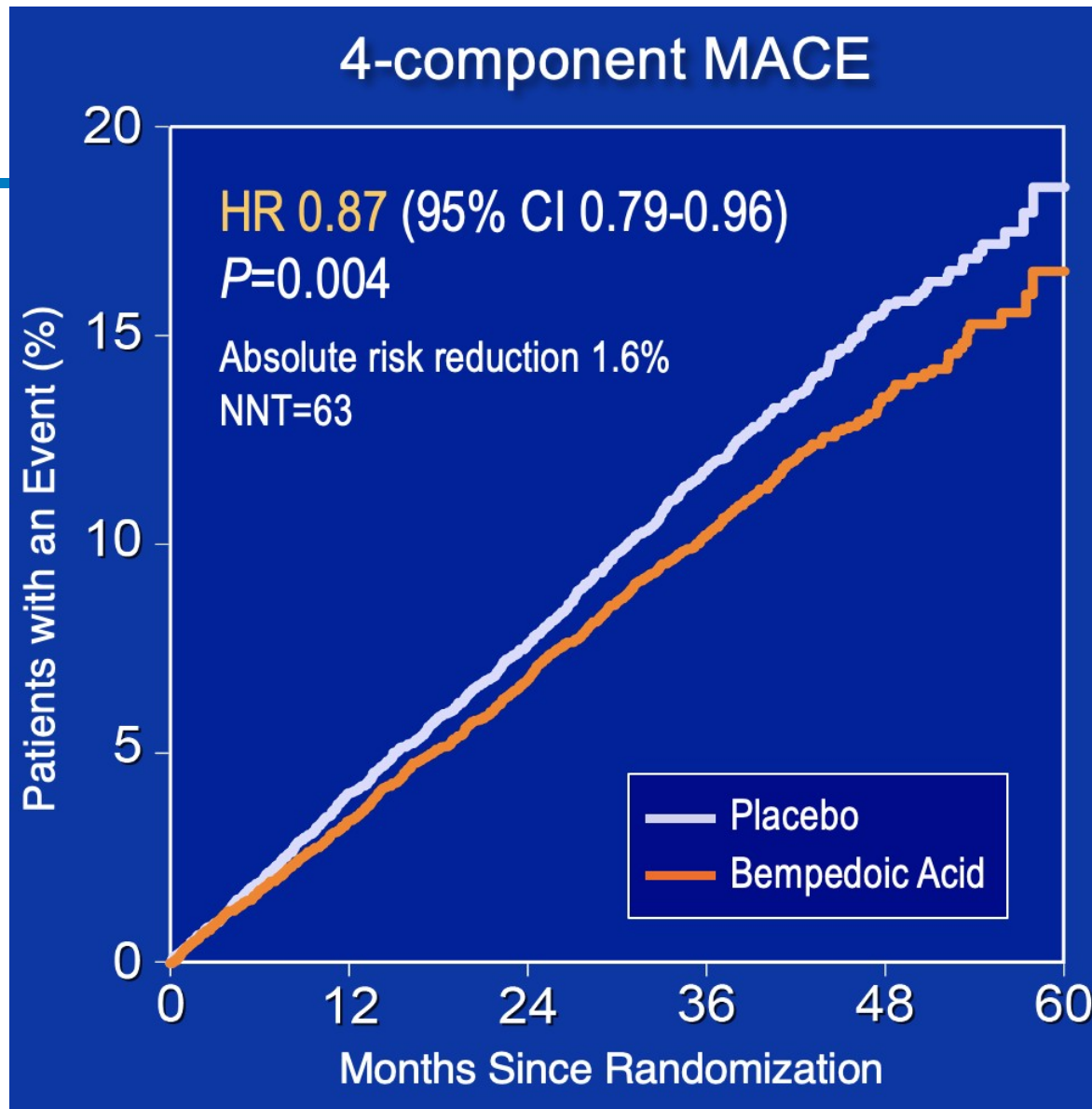


# Clear Outcomes



- 13970 ασθενείς (70% ΚΑΝ) με δυσανεξία στις στατίνες τυχαιοποιήθηκαν σε μπεμπεδοϊκό οξύ ή εικονικό φάρμακο
- Διάρκεια F/U 42 μήνες.
- Πρωταρχικό καταληκτικό σημείο θανατηφόρα και μη ΚΑ συμβάματα



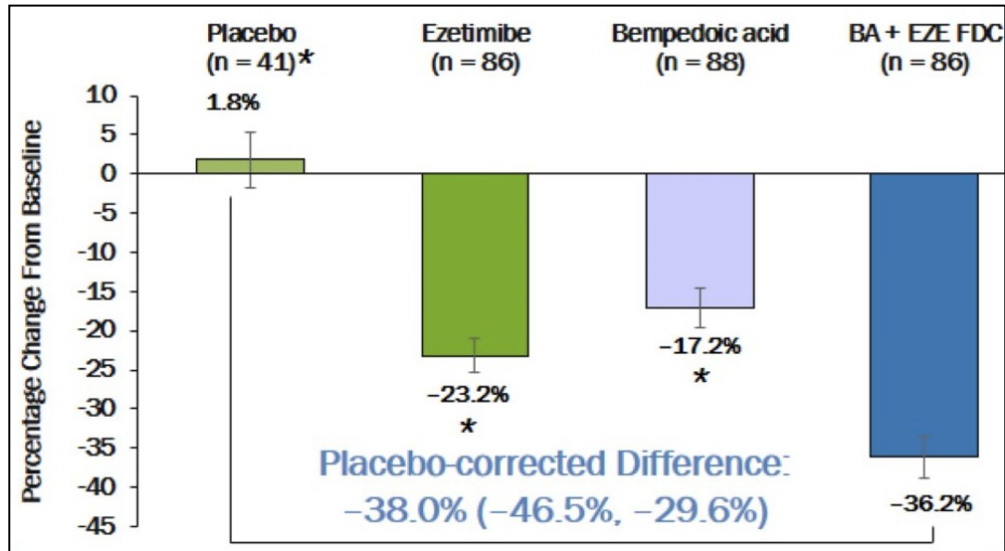


↓  
**13%**

Υψηλότερα ποσοστά ουρικής αρθρίτιδας

## Πόσο ελαττώνει την LDL-χ ο συνδυασμός μπεμπεδοϊκού οξέος + εζετιμίμπη?

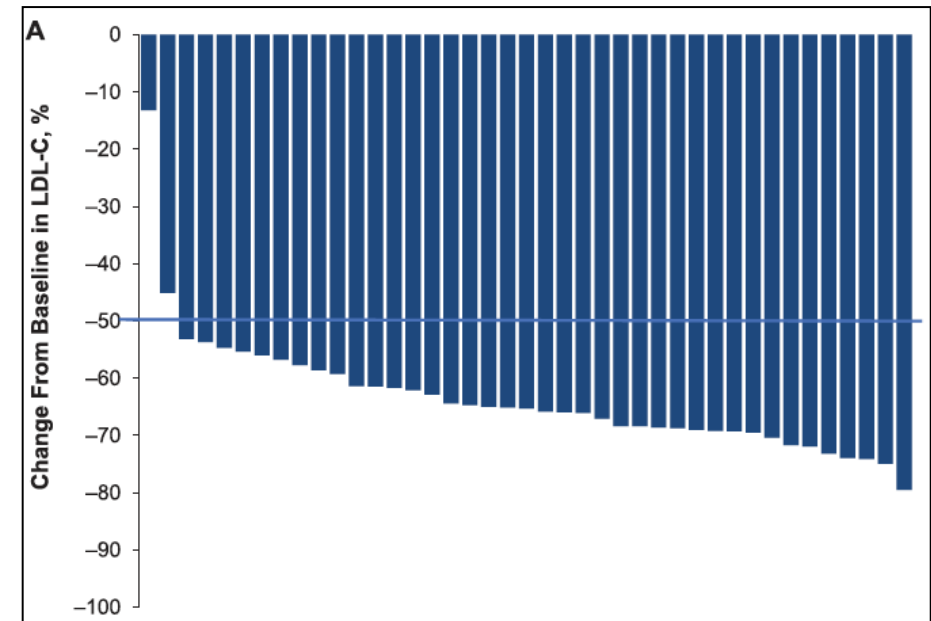
- 301 ασθενείς με FH ή CVD που ελάμβαναν στατίνη (LDL-C =150 mg/dL) τυχαιοποιήθηκαν 2:2:1 συνδυασμό **bempedoic+EZ**, bempedoic, EZ ή εικονικό x 12 εβδομάδες



**LDL-χ κατά 36%**

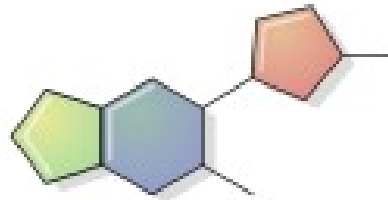
## Πόσο ελαττώνει την LDL-χ ο συνδυασμός μπεμπεδοϊκού οξέος + στατίνη + εζετιμίμπη?

- 63 ασθενείς χωρίς CVD ή ΣΔ με LDL-C =155 mg/dL τυχαιοποιήθηκαν 2:1 σε συνδυασμό **bempedoic (180 mg)+ατορβαστατίνη (20 mg)+EZ** ή εικονικό x 6 εβδ



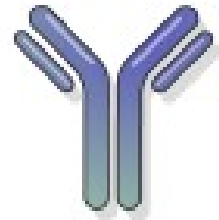
**LDL-χ κατά 60%**

## Small molecules



- Bempedoic acid
- Pemafibrate
- Icosapent ethyl

## Antibodies



- Evinacumab
- Evolocumab
- Alirocumab

## ASO



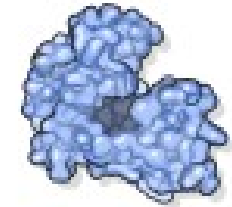
- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L</sub><sub>RX</sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

## Proteins and peptides

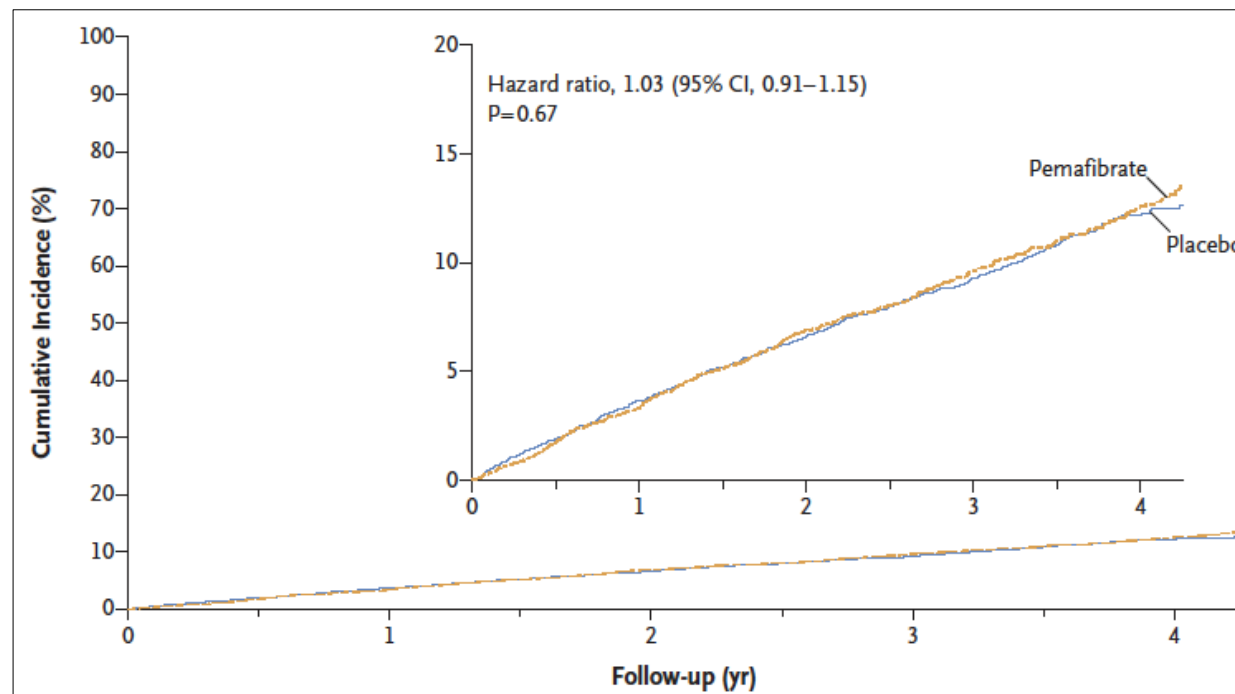


- CSL-112

# Μελέτη PROMINENT και πεμαφιμπράτη

- **10497 άτομα με ΣΔ** (67% με ΚΑΝ) υπό στατίνη, αυξημένα τριγλυκερίδια (270 mg/dL), HDL-χολ=33 mg/dL και LDLχ=78 mg/dL τυχαιοποιήθηκαν σε πεμαφιμπράτη 0,2 gχ2/ημ vs placebo x 3,4 έτη
- Πρωτογενή καταληκτικά σημεία το σύνολο των θανατηφόρων και μη ΚΑ συμβαμάτων

**Ελάττωση τριγλ κατά 26%, αύξηση HDL-χ κατά 5%**



Αυξημένα ποσοστά νεφρικής δυσλειτουργίας και φλεβικής θρομβοεμβολικής νόσου



## The Fibrates Story — A Tepid End to a PROMINENT Drug

Salim S. Virani, M.D., Ph.D.



What do these findings mean for the future of fibrates and other therapies that primarily target triglycerides? First, fibrates should not be used to reduce the risk of atherosclerotic cardiovascular disease among statin-treated patients,

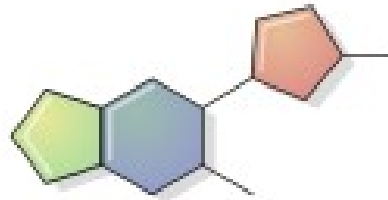


## Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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)]. <sup>355</sup>	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. <sup>194</sup>	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. <sup>305–307,356</sup>	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. <sup>305–307,356</sup>	IIb	C

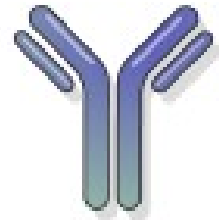
© ESC 2019

## Small molecules



- Bempedoic acid
- Pemafibrate
- Icosapent ethyl

## Antibodies



- Evinacumab
- Evolocumab
- Alirocumab

## ASO



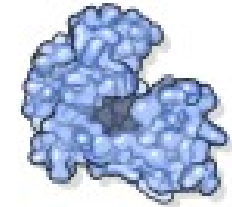
- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L</sub><sub>RX</sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

## Proteins and peptides

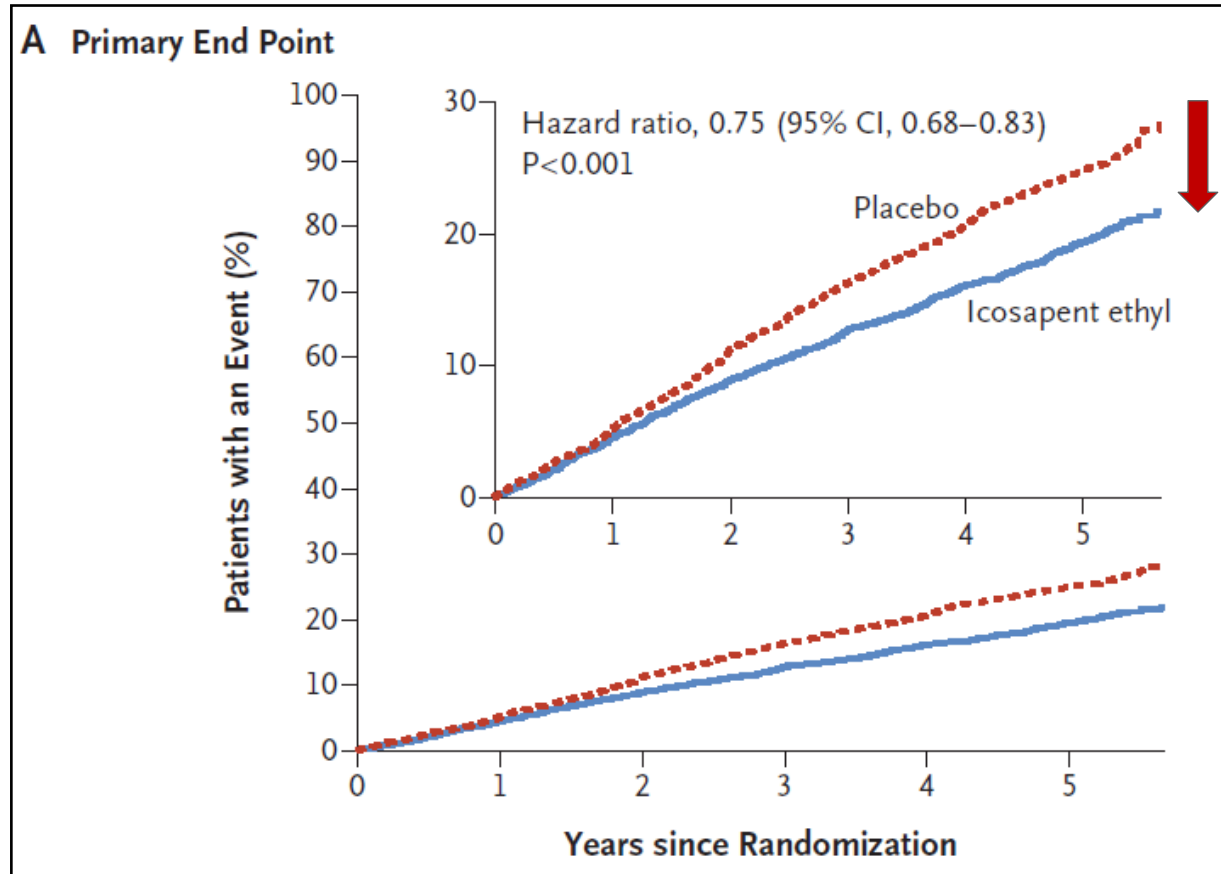


- CSL-112

# Μελέτη REDUCE-IT



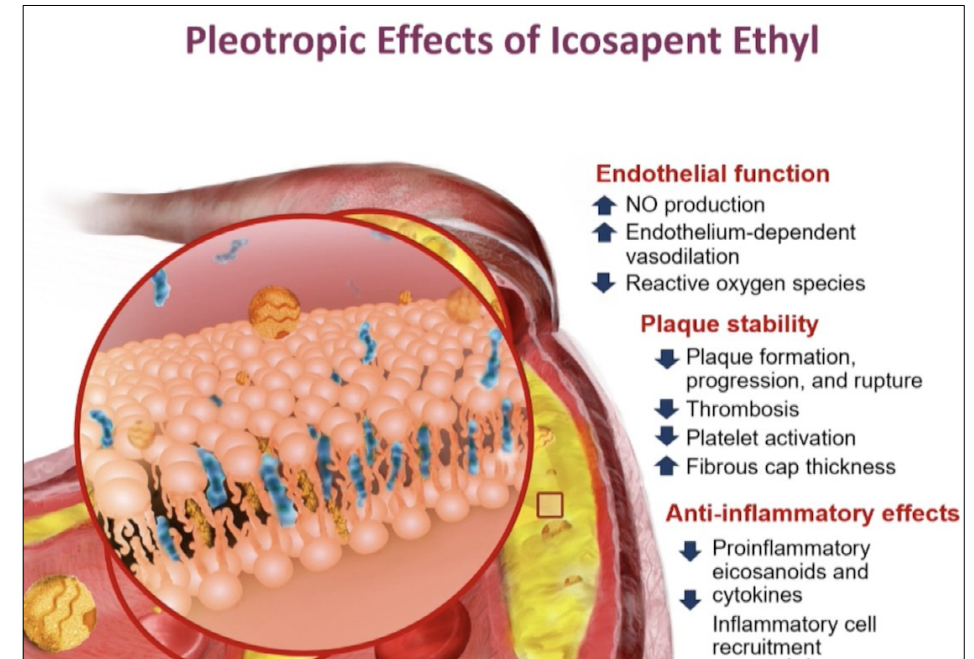
- 8179 ασθ. με ΚΑΝ (70%) ή ΣΔ (60%) υπό στατίνη, με τριγλ/δια 135-499 mg/dL τυχαιοποιήθηκαν σε 4 g icosapent ethyl vs placebo x 5 έτη



**25%**



- Ελάττωση των τριγλυκεριδίων κατά 18%



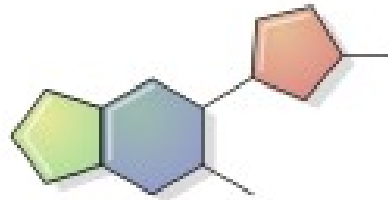
# ESC guidelines: recommendations for use of Icosapent ethyl

## Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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)]. <sup>355</sup>	<b>I</b>	<b>B</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. <sup>194</sup>	<b>IIa</b>	<b>B</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. <sup>305–307,356</sup>	<b>IIb</b>	<b>B</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. <sup>305–307,356</sup>	<b>IIb</b>	<b>C</b>

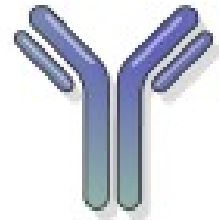
© ESC 2019

## Small molecules



- Bempedoic acid
- Pemafibrate
- Icosapent ethyl

## Antibodies



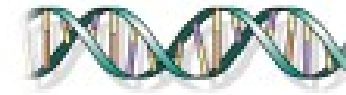
- Evinacumab
- Evolocumab
- Alirocumab

## ASO



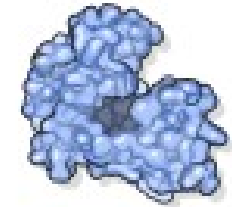
- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L</sub><sub>RX</sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

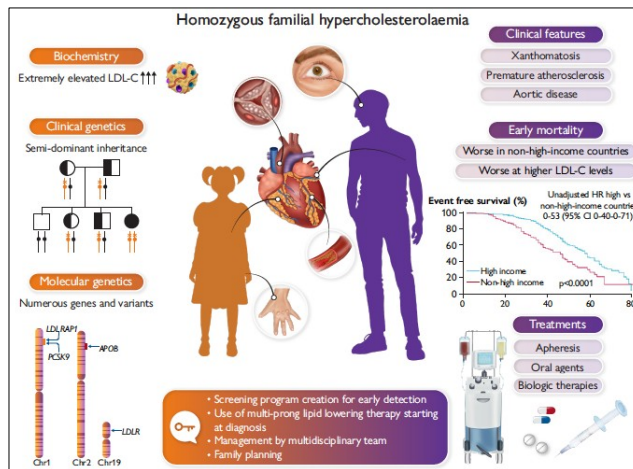
## Proteins and peptides



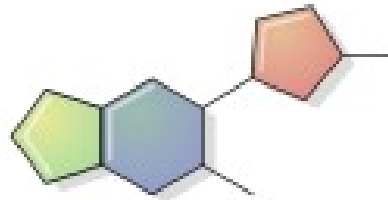
- CSL-112

κατά της ANGPTL3  
(στην hoFH, IV)

κατά της apoCIII

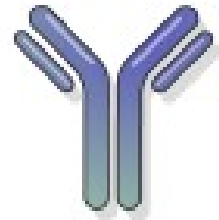


## Small molecules



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## Antibodies



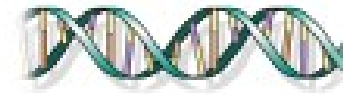
- Evinacumab
- Evolocumab
- Alirocumab

## ASO



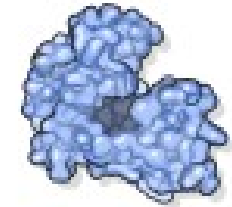
- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L<sub>R</sub></sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

## Proteins and peptides



- CSL-112

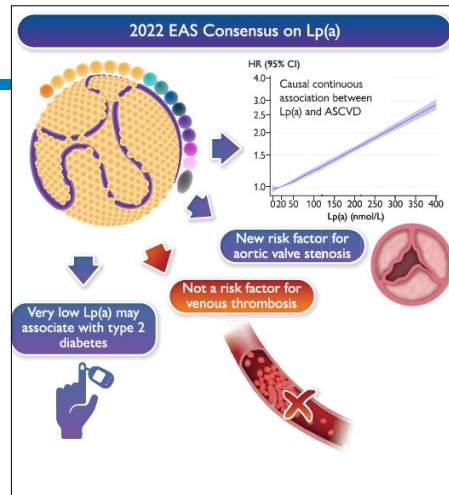
κατά της apo(a)

κατά της PCSK9

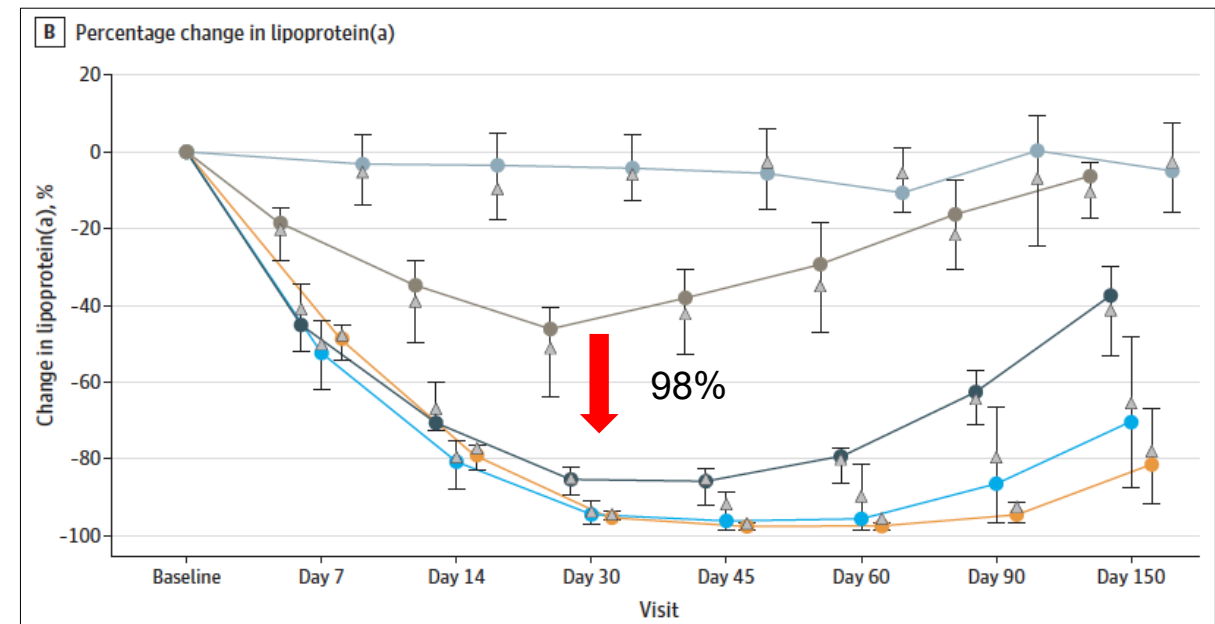
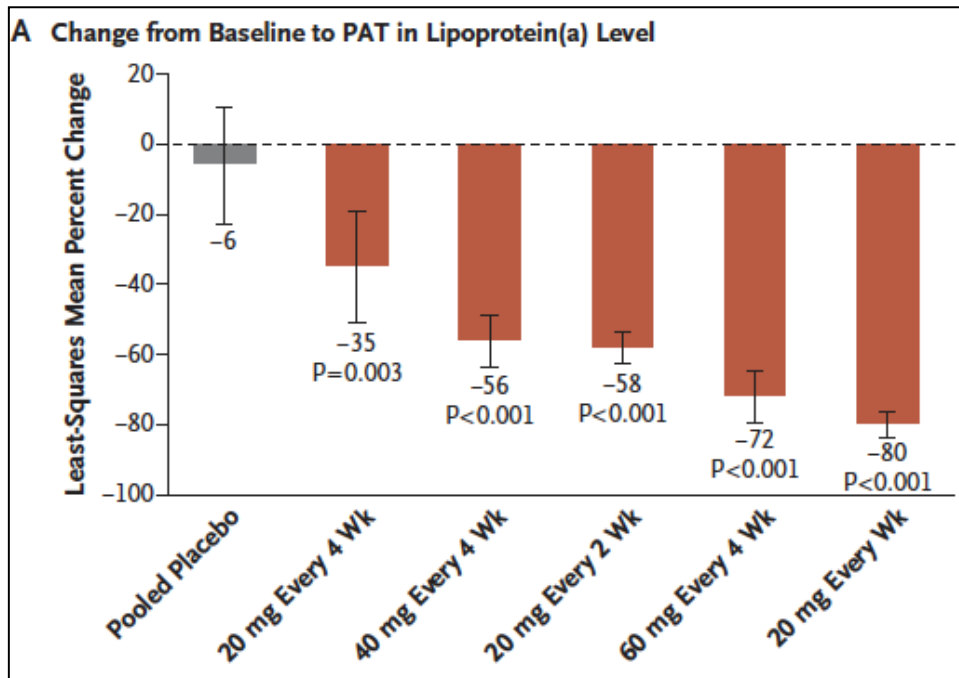
κατά της apo(a)

# Παρεμβάσεις ελάττωσης Lp(a)

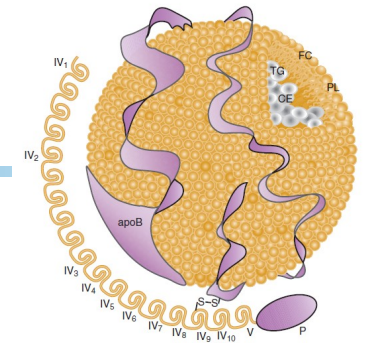
ASO (pelacarsen)



siRNA (olpasiran)



# Μελέτες ελάττωσης της Lp(a) φάσης III



**Pelacarsen:** αντινοσηματικό  
ολιγονουκλεοτίδιο

**Olpasiran:** μικρό παρεμβαλλόμενο  
μόριο RNA

## Lp(a)HORIZON

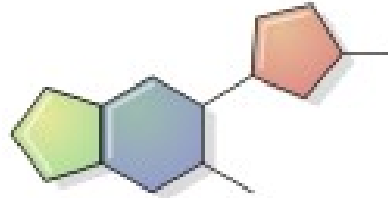
- Inclusion Criteria: History of MI, History of ischemic stroke, history of PAD
- Baseline Cut-Off Lp(a) Value: 175 nmol/L
- Primary Outcome: Composite of cardiovascular death, MI, stroke, and urgent coronary revascularization requiring hospitalization

## OCEAN(a)

- Inclusion Criteria: History of MI, PCI with a high-risk condition
- Baseline Cut-Off Lp(a) Value: 200 nmol/L
- Primary Outcome: Composite of CHD death, MI, or urgent revascularization

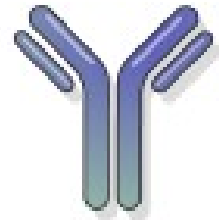


## Small molecules



- Bempedoic acid
- Pemafibrate
- Icosapent ethyl

## Antibodies



- Evinacumab
- Evolocumab
- Alirocumab

## ASO



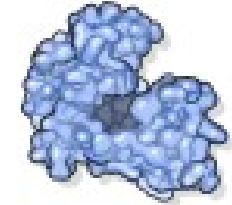
- Volanesorsen
- Vupanorsen
- IONIS-APO(a)<sub>RX</sub>
- IONIS-APO(a)<sub>L</sub><sub>RX</sub>

## siRNA



- Inclisiran
- Olpasiran
- SLN360

## Proteins and peptides

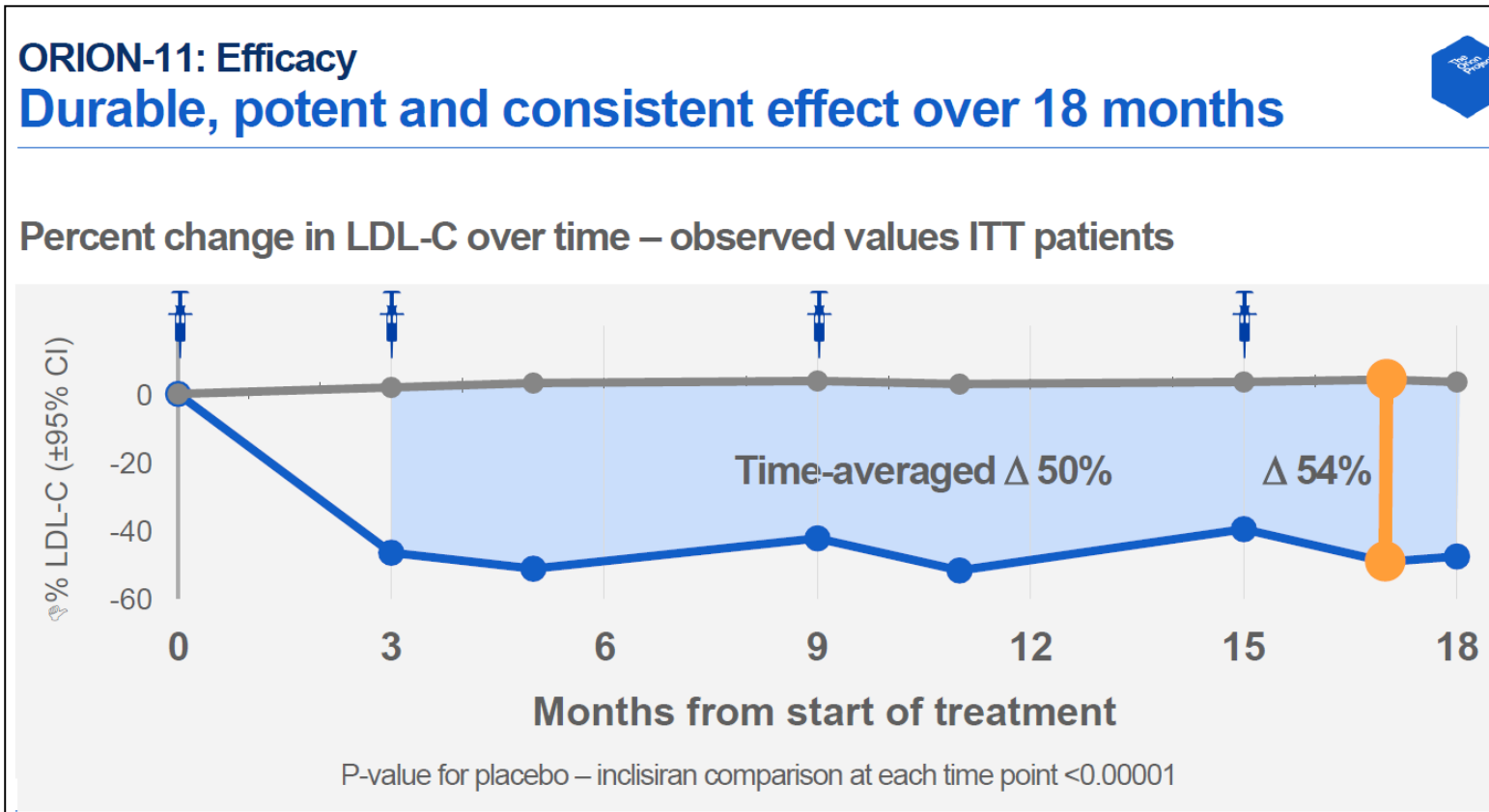


- CSL-112

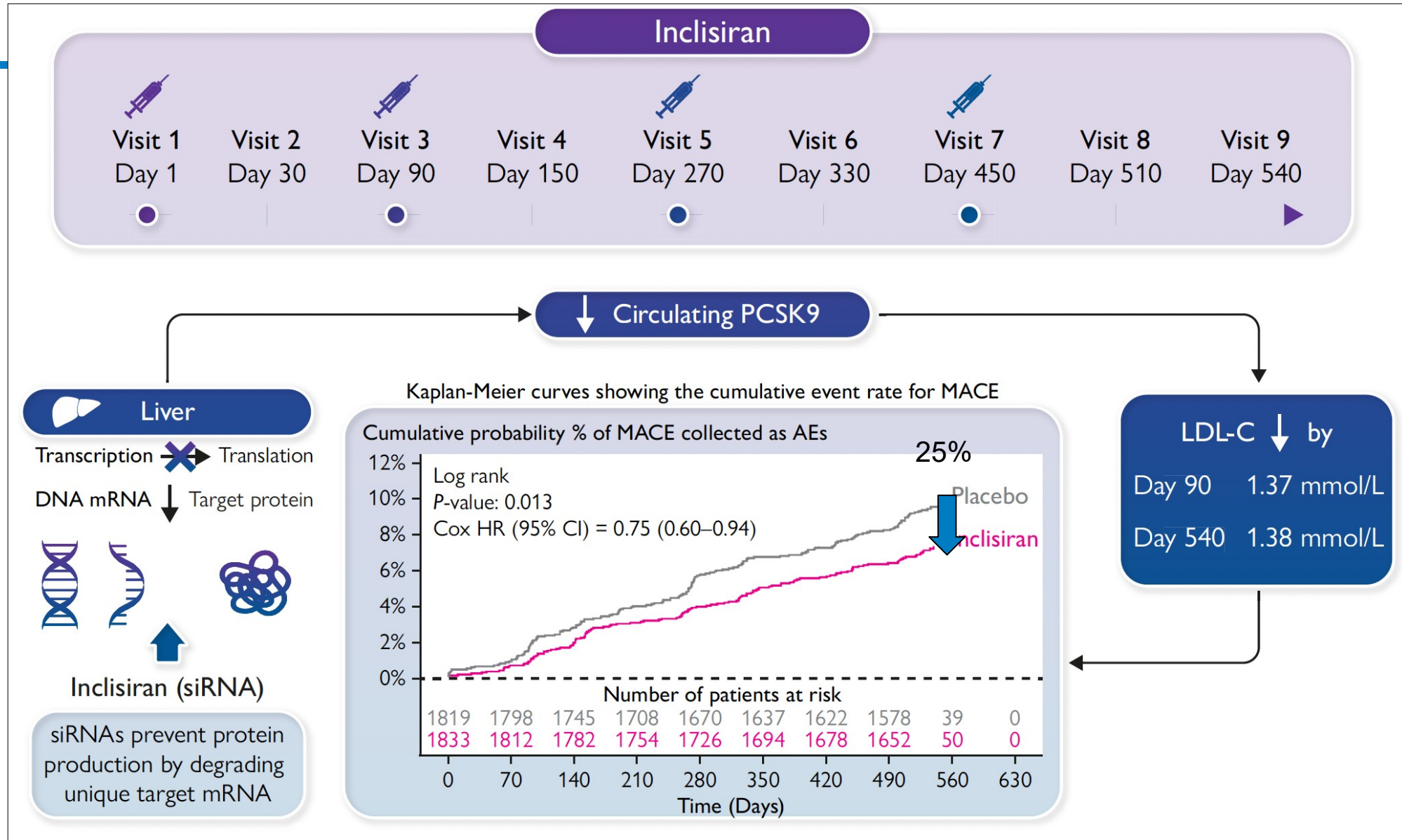
κατά της PCSK9

# Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

- **ORION-10**: 1561 ασθ. με CVD, **ORION-11**: 1617 ασθ. με CVD ή ισοδύναμο CVD, υπό μέγιστη αγωγής στατίνης τυχαιοποιήθηκαν σε 284 mg inclisiran sb έναντι εικονικού φαρμάκου
- Διάρκεια παρέμβασης 15 μήνες



# 3655 ασθενείς από ORION 9, 10, 11, x18 μήνες



# Συμπεράσματα

- 1) Οι πυλώνες της υπολιπιδαιμικής αγωγής είναι οι **στατίνες**, η **εξετιμίμπη** και τα **μονοκλωνικά αντισώματα που αναστέλλουν την PCSK9**
- 2) Για το **inclisiran** (συνταγογραφείται μέσω ΣΗΠ), **pelacarsen** και **olpasiran** αναμένονται αποτελέσματα μελετών κλινικών συμβαμάτων
- 3) Το **μπεμπεδοικό οξύ** φαίνεται να έχει μέση σε ασθενείς υψηλού κινδύνου με δυσανεξία στις στατίνες
- 4) Το **εικοσιπενταενοϊκό αιθύλιο** έχει καρδιοπροστατευτική δράση

Τροποποίηση  
γενετικού υλικού  
(CRISPR τεχνική)

