

# **Θεραπευτική Αφαίρεση και Καρδιολογία – Στηθάγχη**

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**7ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΑΙΜΑΦΑΙΡΕΣΗΣ**  
**04-06 Οκτωβρίου 2019**

# Καρδιαγγειακή Νόσος

- CVD kills >4 million people in Europe each year.
- 2.2m women, 1.8m men though mortality <65 years is greater in men (490K vs 193K).
- Substantial mortality changes, especially in Finland, but increased survival so still a major cause of morbidity.
- Improvements in lipid, BP control and smoking, worsening obesity and diabetes.
- Prevention is defined as a coordinated set of actions, at the population level or targeted at the individual, aimed at eradicating, eliminating or minimizing the impact of CV diseases and their related disability.
- Elimination of health risk behaviours has the potential to prevent 80% of CVD and 40% of cancers.

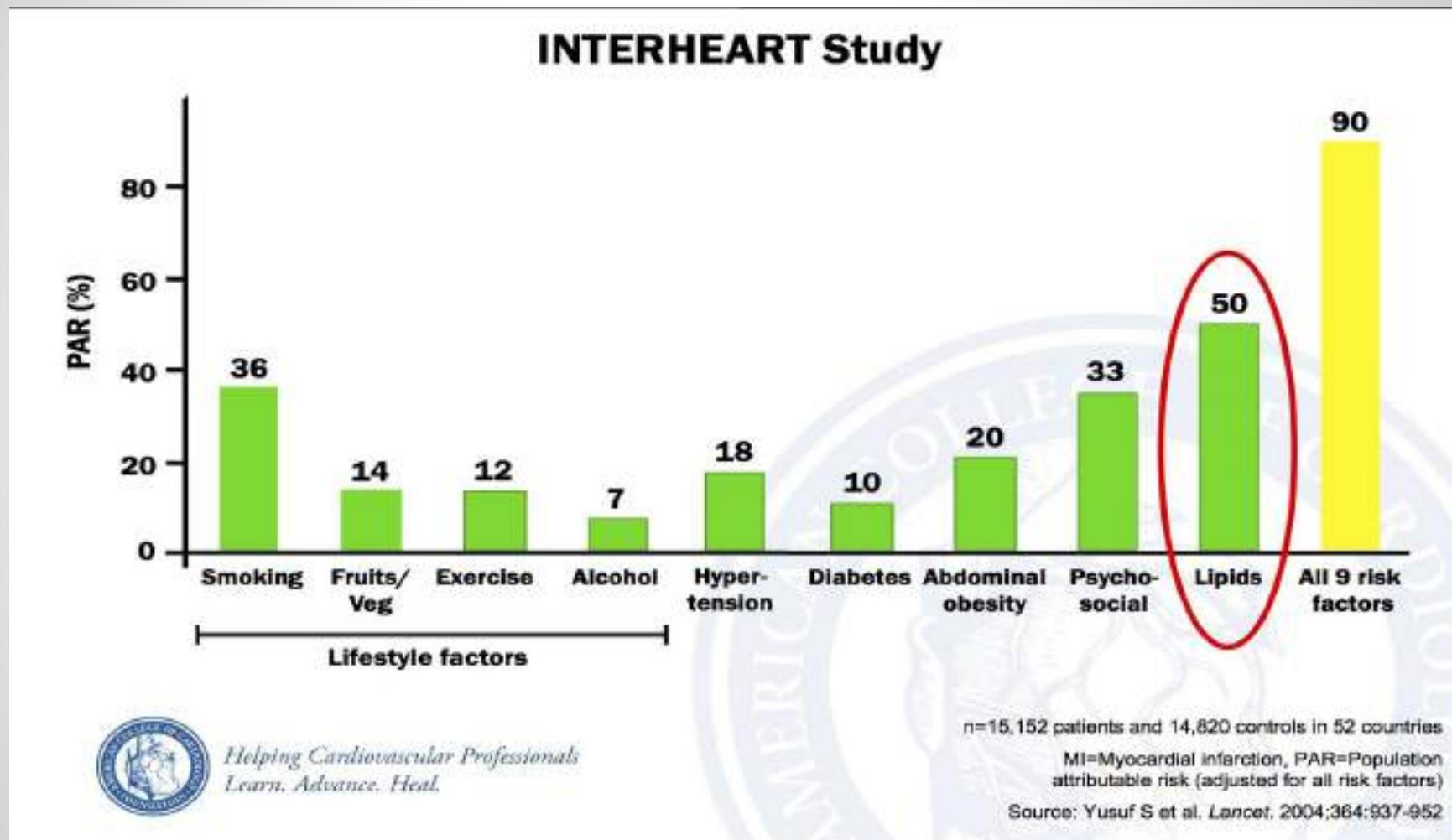


[www.escardio.org/guidelines](http://www.escardio.org/guidelines)

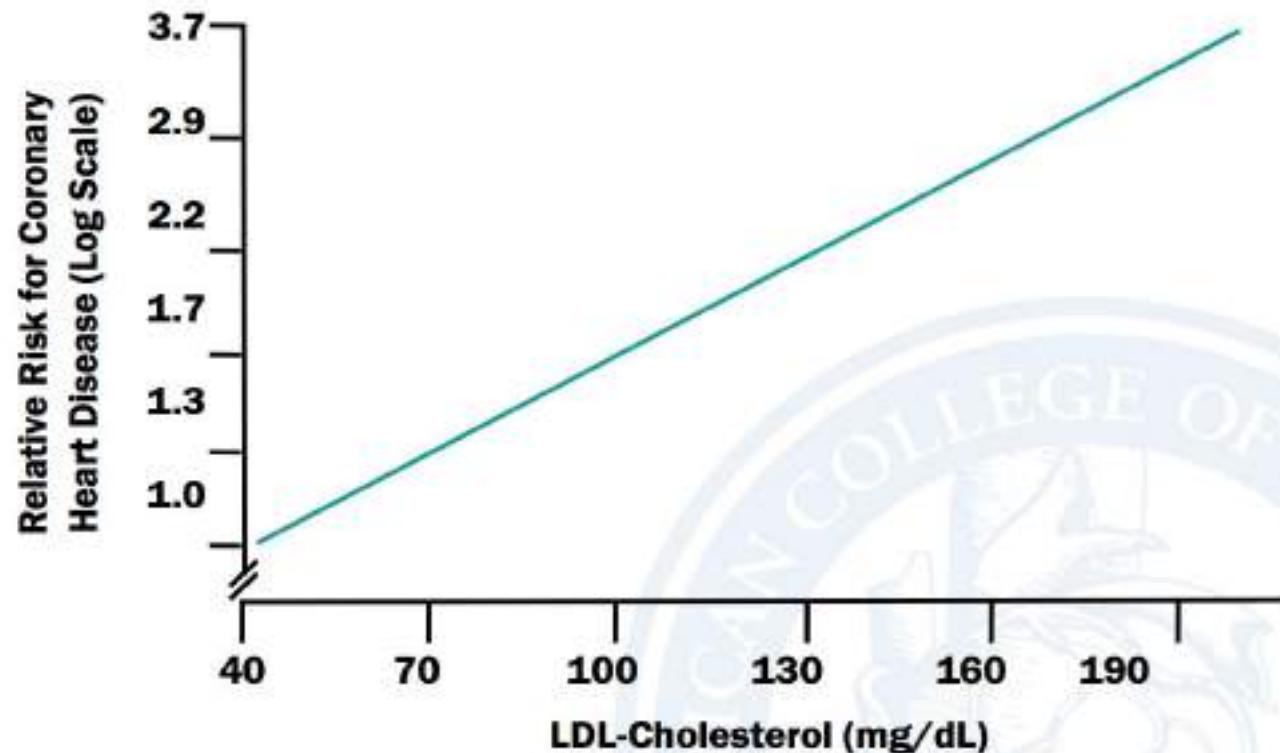
European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272  
Atherosclerosis 253 (2016) 281–344-d doi:10.1016/j.atherosclerosis.2016.08.018



# Αποδοτέος Κίνδυνος OEM



# Στεφανιαία Νόσος και επίπεδα LDL

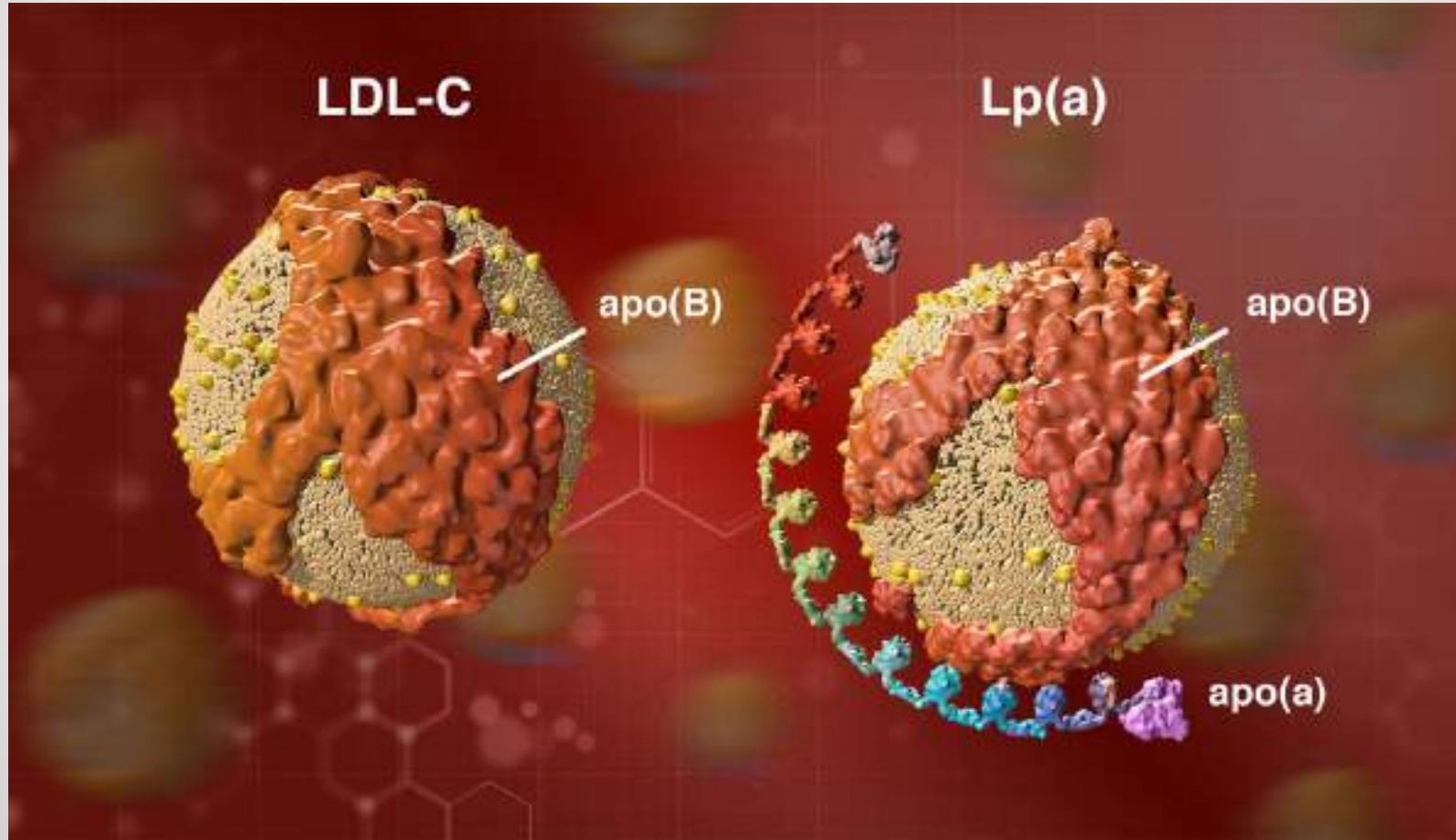


Helping Cardiovascular Professionals  
Learn. Advance. Heal.

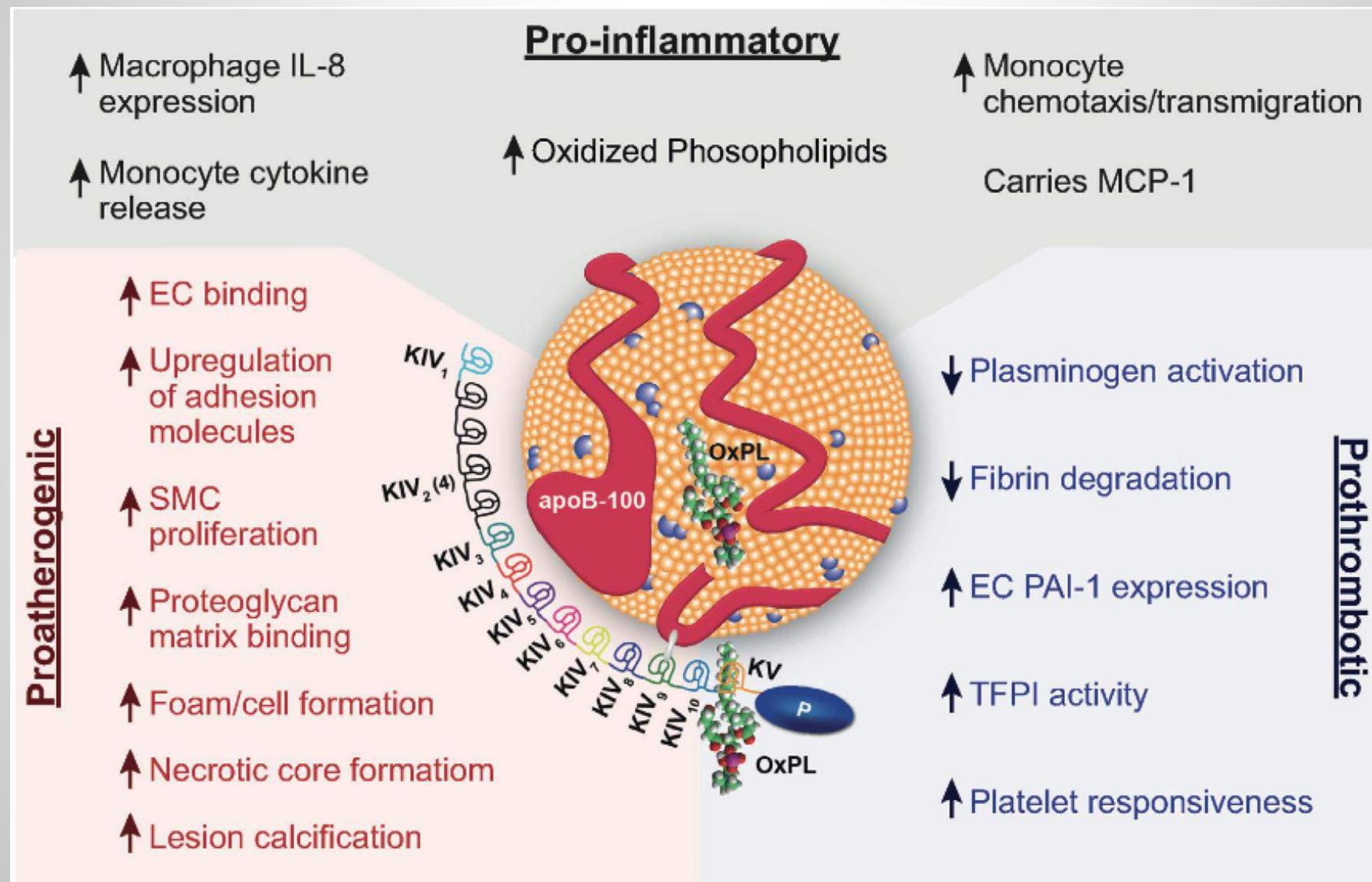
CHD=Coronary heart disease, LDL-C=Low-density lipoprotein cholesterol

Source: Grundy S et al. Circulation 2004;110:227-239

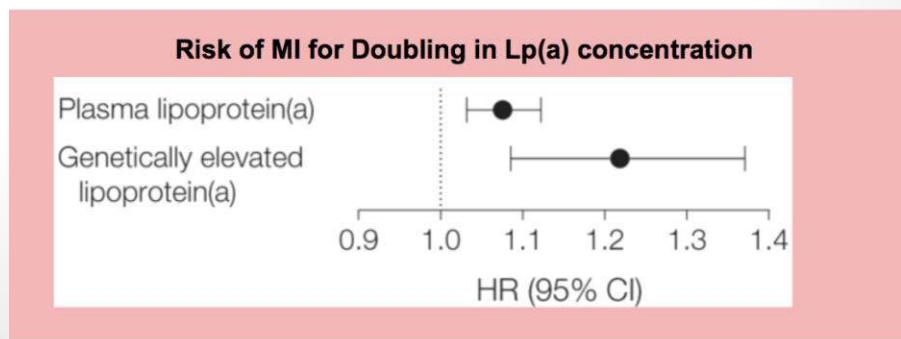
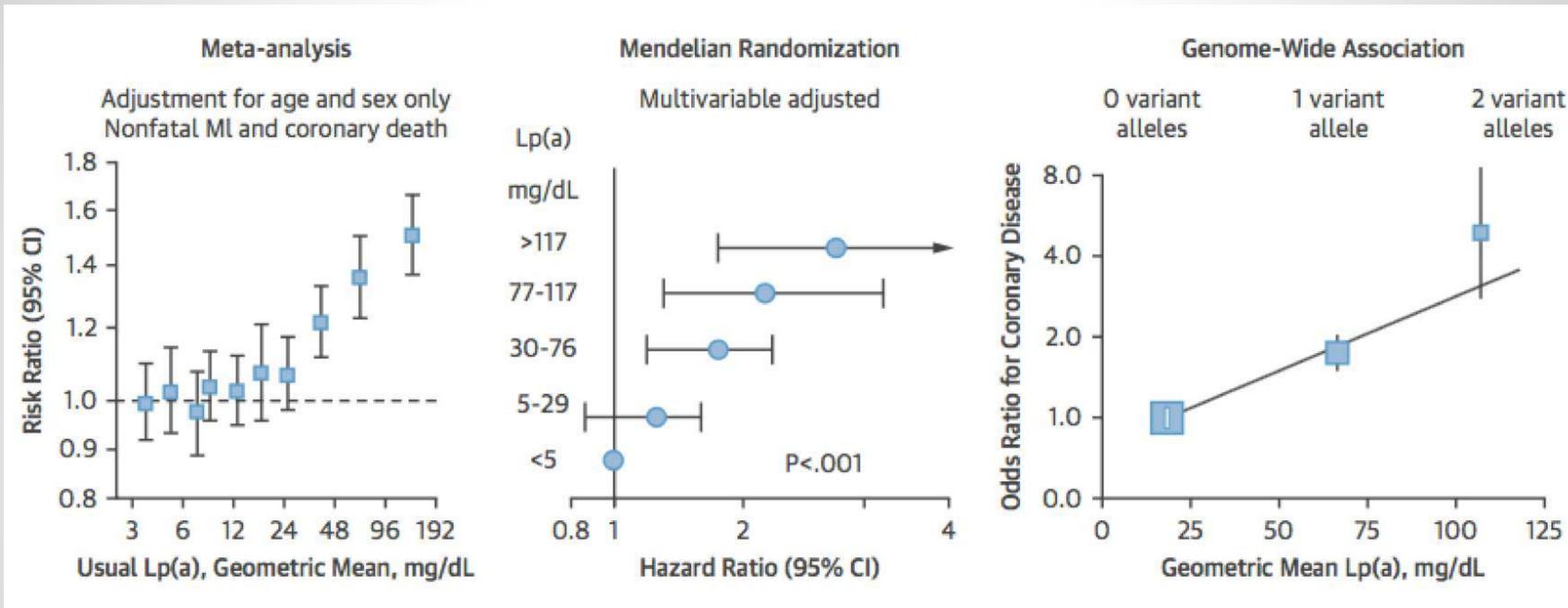
# Στεφανιαία Νόσος και Lp (a)



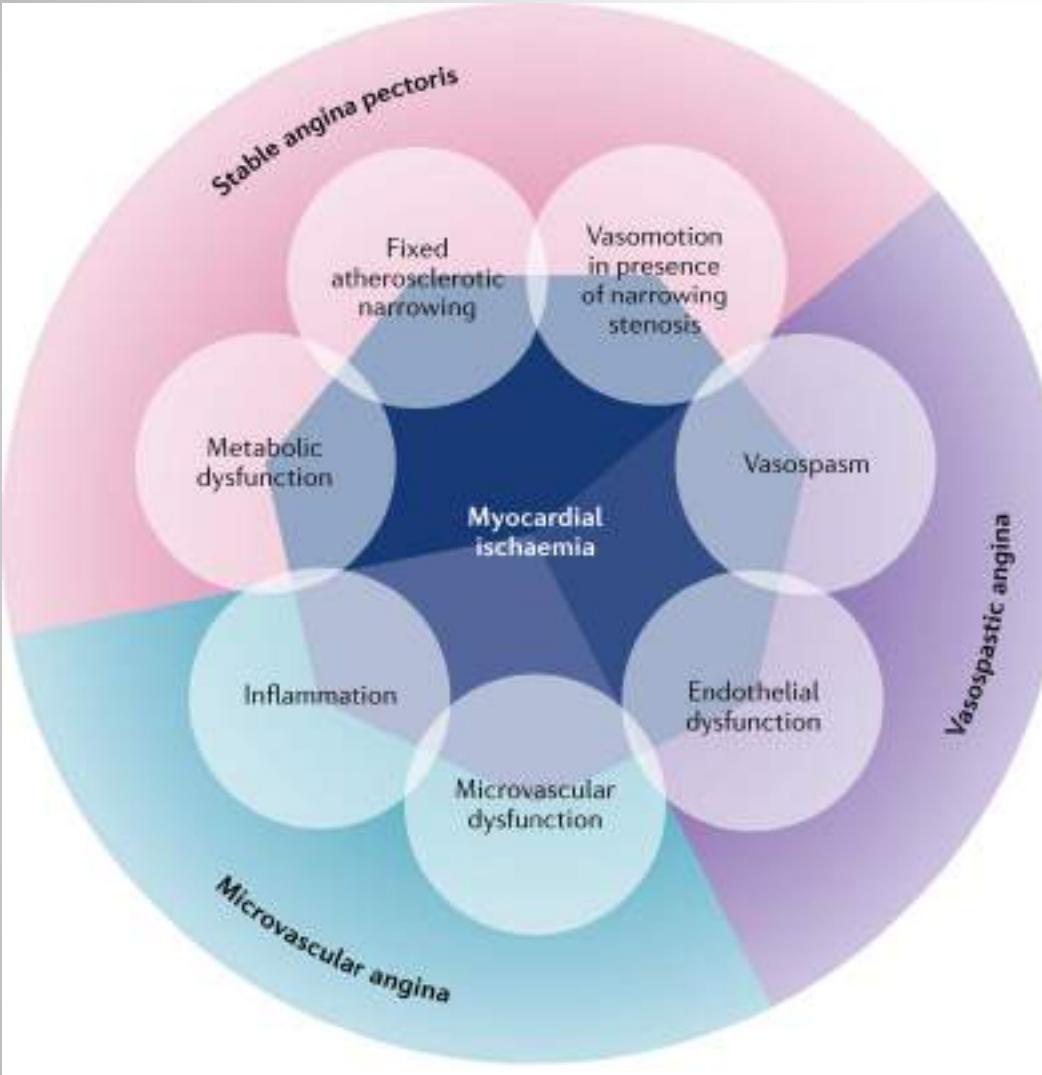
# Στεφανιαία Νόσος και Lp (a)



# Στεφανιαία Νόσος και Lp (a)



# Μυοκαρδιακή Ισχαιμία



Nature Reviews | Cardiology

Ferrari, R. et al. (2017) A 'diamond' approach to personalized treatment of angina  
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2017.131

# Ανθεκτική Στηθάγχη

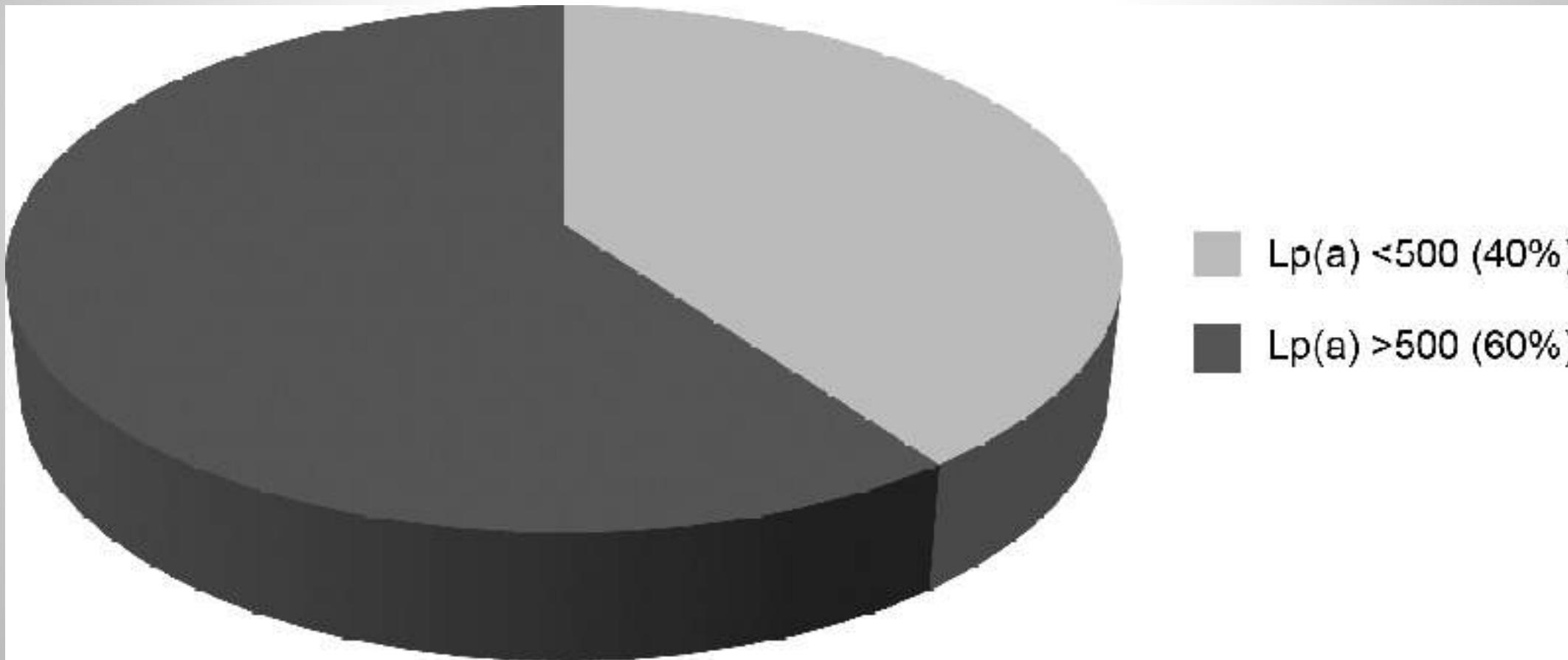
- Refractory angina refers to **long-lasting symptoms (for > 3 months)** due to established reversible ischaemia in the presence of obstructive CAD, which **cannot be controlled** by escalating **medical therapy** with the use of second- and third-line pharmacological agents, **bypass grafting**, or **stenting including PCI of chronic total coronary occlusion**
- Incidence is **growing** with more advanced CAD, multiple comorbidities, and ageing of the population. The quality of life of patients with refractory angina is poor, with **frequent hospitalization** and a high level of resource utilization.

# Ανθεκτική Στηθάγχη

<b>Therapy</b>	<b>Type of therapy</b>	<b>RCT</b>	<b>Type of control group</b>	<b>Number of patients enrolled</b>
External counterpulsation	Enhanced external counterpulsation	MUST <sup>524</sup>	Sham	139
Extracorporeal shockwave	Low-energy extracorporeal shockwave therapy	Not available	Not available	—
Coronary sinus constriction	Reducer device	COSIRA <sup>525</sup>	Sham	104
Neuromodulation	Spinal cord stimulation	STARTSTIM <sup>526</sup>	Not available	68
	Transcutaneous electrical neural stimulation	Not available	Not available	—
	Subcutaneous electrical neural stimulation	Not available	Not available	—
	Sympathectomy	Denby et al. <sup>527</sup>	Placebo	65
Gene therapy	Adenovirus fibroblast growth factor 5	Not available	Not available	—
Autologous cell therapy	Mononuclear bone marrow-derived haematopoietic progenitor cells	RENEW <sup>528</sup>	Placebo	112

# Ανθεκτική Στηθάγχη και Lp (a)

High prevalence of raised lipoprotein(a) in patients  
with refractory angina



High prevalence of raised lipoprotein(a) in patients with refractory angina. Glob Cardiol Sci Pract 2015;  
2015(2): 28.

There is currently no satisfactory pharmacological treatment available which lowers Lp(a), but it can be effectively lowered with **lipoprotein apheresis**, a lipid-lowering **extracorporeal treatment** by which atherogenic **ApoB containing lipoproteins**, including Lp(a) and LDL, are removed from blood or plasma



# Θεραπευτική Αφαίρεση

- Η διαδικασία διαχωρισμού ή απομάκρυνσης επιμέρους στοιχείων του αίματος
- Το αίμα μετά την αφαίρεση του συγκεκριμένου στοιχείου επιστρέφει στον ασθενή



# Θεραπευτική Αφαίρεση

- **Συλλογή στοιχείων αίματος**
  - προγονικά κύτταρα (αυτόλογη ΜΜΟ – **Κυτταρικές Θεραπείες**)
- **Αφαίρεση στοιχείων αίματος(ολική–εκλεκτική)**
  - Ερυθρά (πολυκυτταραιμία)
  - Λευκοκύτταρα (λευχαιμίες – λευκόσταση)
  - Ανοσοσφαιρίνες (υπεργλοιότητα - αυτοαντισώματα)
  - **LDL – λιποπρωτεΐνες**
  - Φάρμακα - Δηλητήρια
- **Αφαίρεση και Αντικατάσταση στοιχείων αίματος**
  - Ερυθρά (Δρεπανοκυτταρική νόσος)
  - Πλάσμα (Θρομβωτική Θρομβοπενική Πορφύρα)



# Θεραπευτική Αφαίρεση - Μέθοδοι



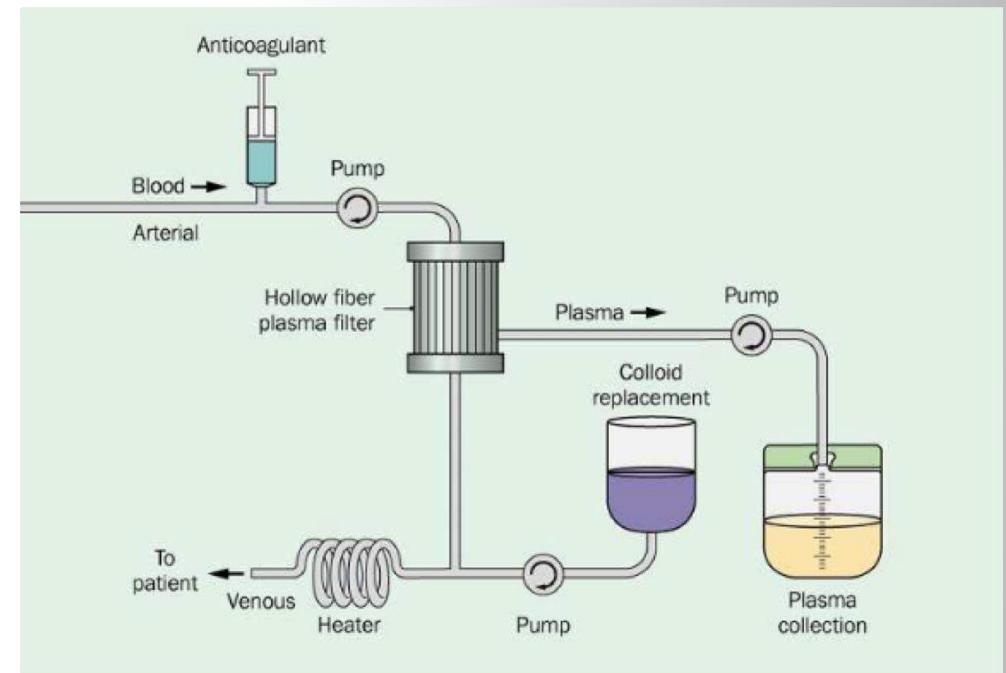
- Τεχνολογία φίλτρων – συνεχούς ροής
- Μηχανισμός φυγοκέντρησης - συνεχούς ή διακεκομένης ροής

Οι δύο τεχνολογίες παρόμοια ασφάλεια –  
αποτελεσματικότητα  
Μόνο τα φυγοκεντρικά μηχανήματα μπορούν να αφαιρέσουν  
κυτταρικά στοιχεία  
Μηχανήματα με φίλτρα μόνο πλασμαφαίρεση



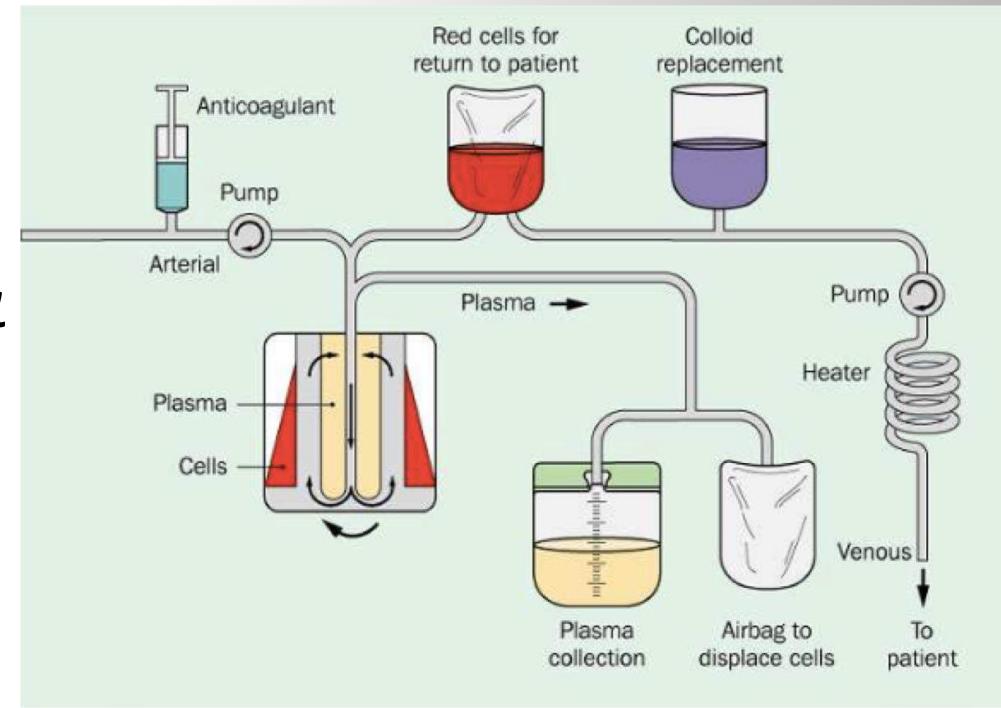
# Θεραπευτική Αφαίρεση- Μέθοδοι

- Τεχνολογία φίλτρων – συνεχούς ροής
- Χορήγηση ηπαρίνης ως αντιπηκτικού παράγοντα
- Κλασικός εξοπλισμός αιμοδιύλισης



# Θεραπευτική Αφαίρεση- Μέθοδοι

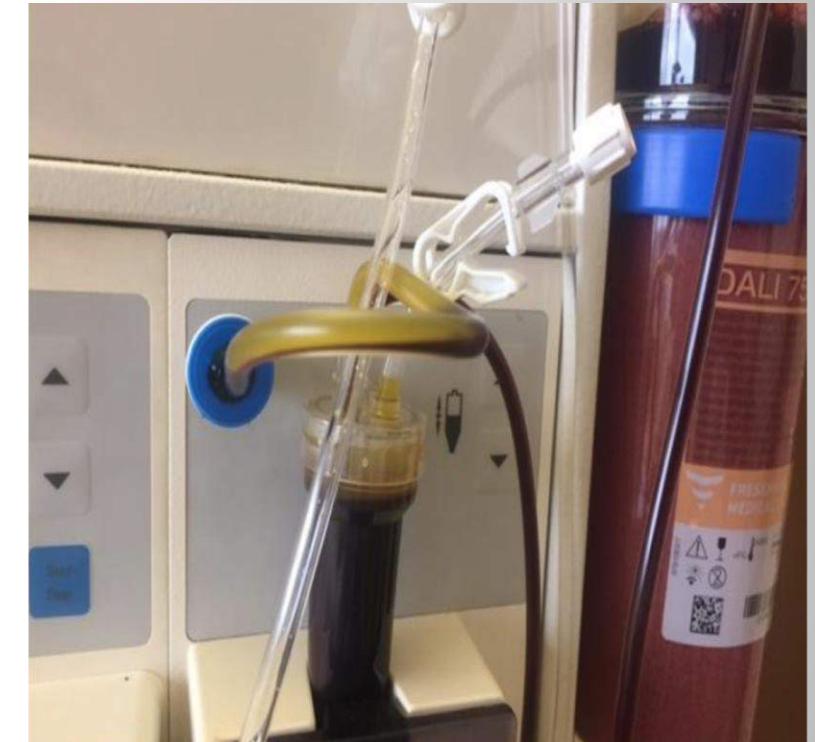
- Μηχανισμός φυγοκέντρησης - συνεχούς ή διακεκομένης ροής – διαχωρισμός στοιχείων αίματος με βάση την πυκνότητα ή το ειδικό βάρος τους



# Θεραπευτική Αφαίρεση Λιποπρωτεΐνών

5 κύριες μέθοδοι :

1. Διήθηση διπλού φίλτρου (DFPP)
2. Ανοσοπροσρόφηση (IMAL)
3. Καθίζηση LDL με τη βοήθεια ηπαρίνης σε χαμηλό pH (HELP)
4. Προσρόφηση λιποπρωτεΐνών από πολυακρυλικό/πολυακρυλαμίδιο (DALI)
5. Προσρόφηση λιποπρωτεΐνών από θειϊκή δεξτράνη (DSA)



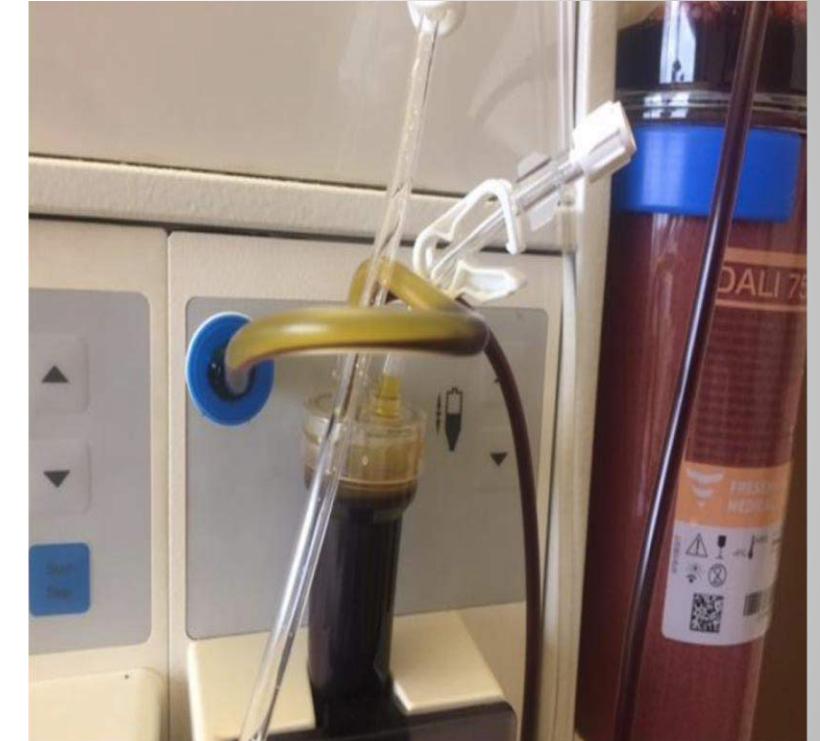
# Θεραπευτική Αφαίρεση

## Λιποπρωτεΐνών

	Cascade filtration (2,500–3,000 mL plasma) reduction of original concentration (%)	Immunoabsorption (4,000–5,000 mL) (%)	Heparin-induced LDL precipitation (HELP) (2,500–3,000 mL) (%)	LDL-adsorption (dextran sulphate) liposorber (2,500–3,000 mL) (%)	LDL hemoperfusion (DALI) 1.6 blood volume (%)
Cholesterol	35–50	30	50	45	60
LDL	30–45	35	45	35–40	60–75
HDL	35–50	20	10–20	—	16–29
Lp(A)	60–70	60	46	60	60–75
Triglycerides	60	60	60	70	ca 40
Fibrinogen	50	10–20	50	30	16
IgM	35	10–20	—	—	21
IgA	55	10–20	—	—	—
Factor VIII	—	10–20	10–20	20	—
C 3	—	—	50	—	—
C 4	—	—	50	—	—
Plasminogen	—	—	50	—	—

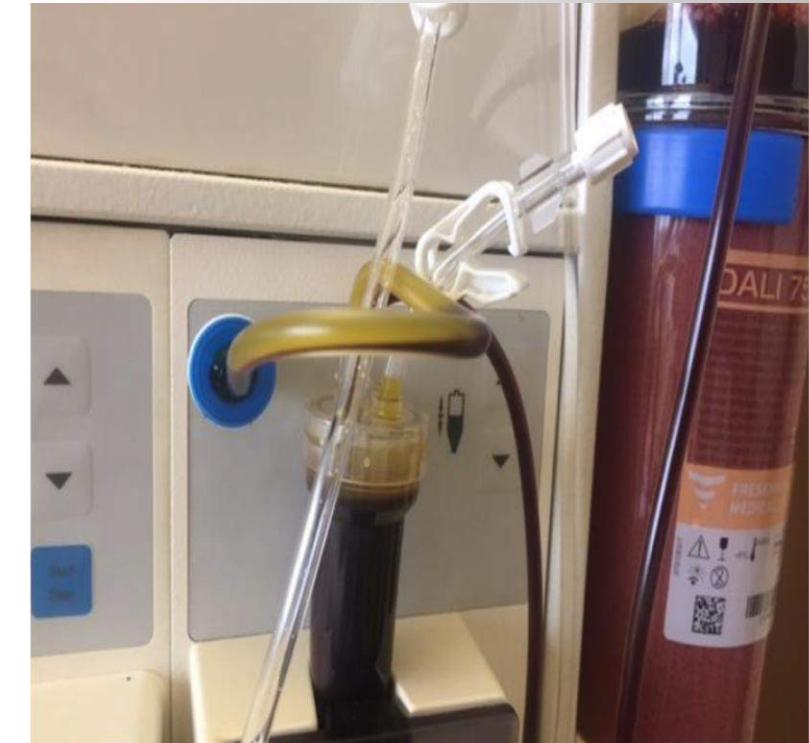
# Θεραπευτική Αφαίρεση Λιποπρωτεΐνών

- A single treatment can effectively reduce serum LDL-C levels by 50-70%.
- LDL-C levels rebound rapidly after treatment returning to 50-90% of pre-apheresis levels after 4-14 days
- Weekly or bi-weekly sessions



# Θεραπευτική Αφαίρεση Λιποπρωτεΐνών

- Potential adverse events of extracorporeal lipid apheresis are **hypotension, nausea and vomiting, flushing, headache, allergic reactions, complaints associated with anticoagulation, and hemolysis**. The incidence of these adverse events is usually **below 5%**.

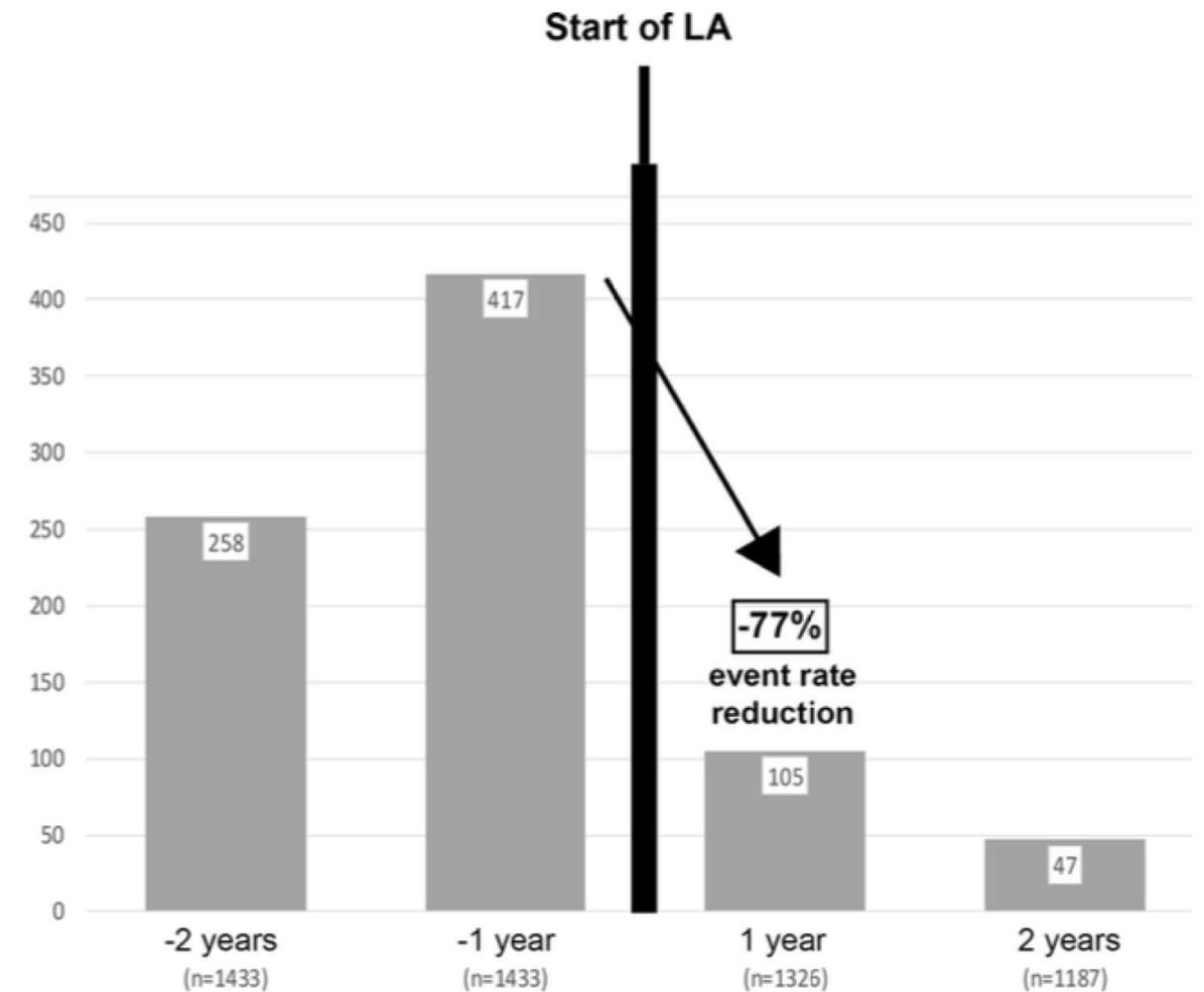


# Θεραπευτική Αφαίρεση Λιποπρωτεΐνών

Although most lipid guidelines mention lipoprotein apheresis as a therapy of **last resort**, they **differ significantly** in defining **which patients to treat** and under what circumstances. This reflects a lack of convincing outcome trials as **most of the evidence supporting the use of lipoprotein apheresis comes from retrospective analyses** or extrapolation of intervention studies using lipid-lowering drugs.

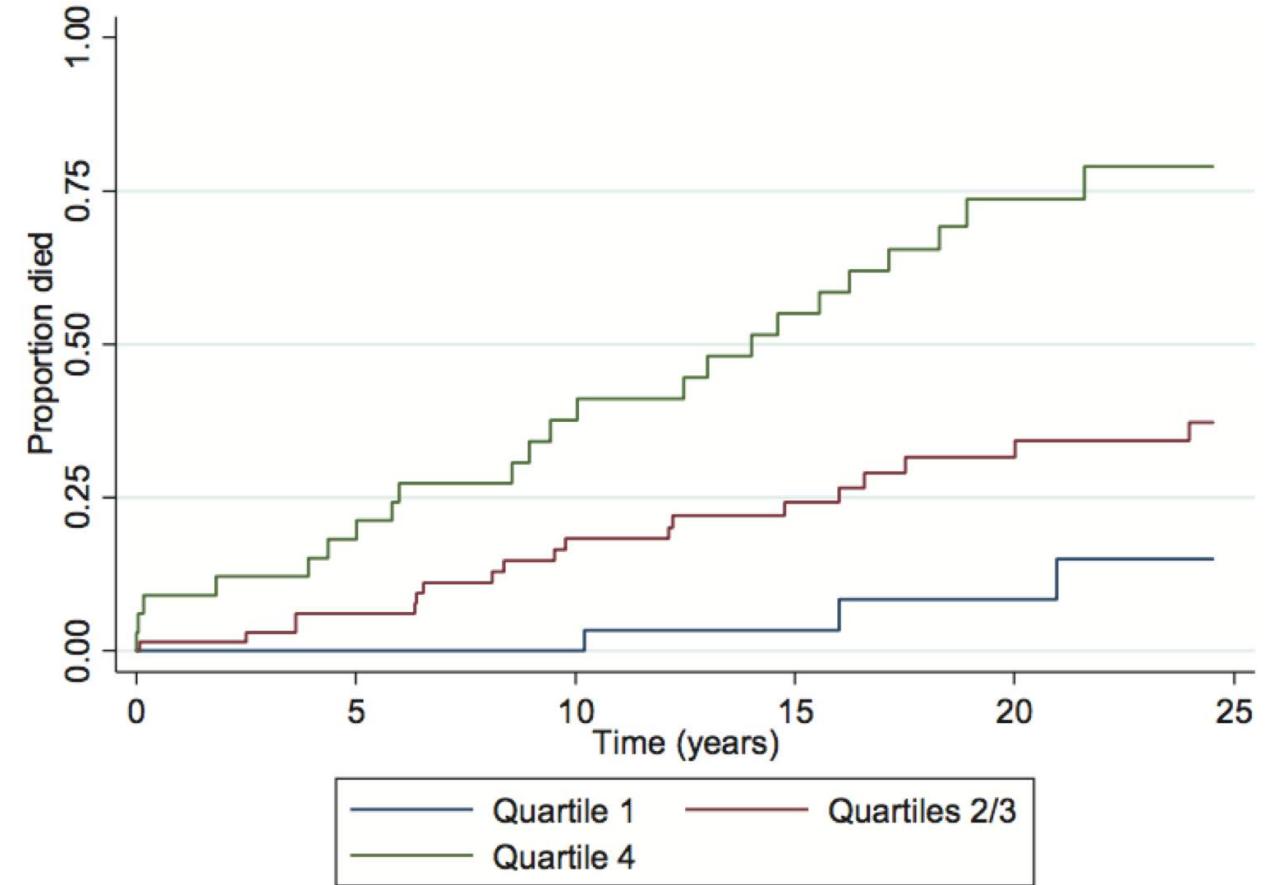
# The German Lipoprotein Apheresis Registry (GLAR)

2012–2016, 71 German apheresis centers collected retrospective and prospective observational data of **1435 patients** undergoing lipoprotein apheresis (LA) treatment of **high LDL-C levels and/or high Lp (a) levels** suffering from cardiovascular disease (CVD) or progressive CVD



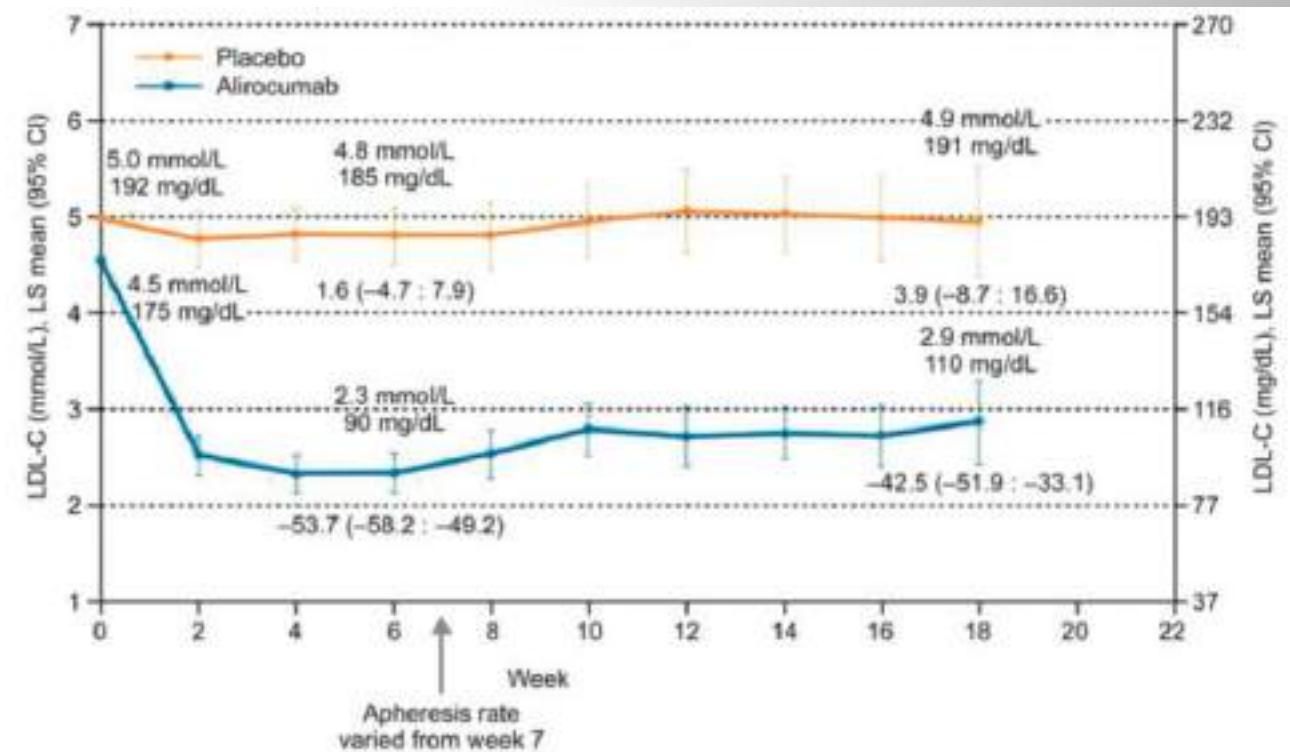
## Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol

- In homozygotes failing to . achieve target levels of LDL with high-dose statins and ezetimibe, additional therapy is required.  
**In addition to lipoprotein apheresis**, current options are the PCSK9 inhibitor (except in receptor-negative homozygotes) and either lomitapide or mipomersen



# Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial

- Double-blind study in 62 HeFH patients undergoing regular weekly or Q2W lipoprotein apheresis
- alirocumab 150 mg ( $n = 41$ ) or placebo ( $n = 21$ ) Q2W subcutaneously for 18 weeks
- 63,4% discontinuation LA
- 36,6% continuation LA



## Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial

- 50 eligible patients (aged  $\geq 12$  years) with homozygous familial hypercholesterolaemia, on stable lipid-regulating therapy for at least 4 weeks, and not receiving lipoprotein apheresis, were randomly allocated to evolocumab 420 mg or placebo every 4 weeks for 12 weeks.
- evolocumab significantly reduced LDL cholesterol at 12 weeks by 30.9%

### Patients with defective/defective status

Ultracentrifugation LDL cholesterol

5 patients

8 patients

15·1% (-1·2 to 31·3)

-31·8% (-44·9 to -18·8)

Apolipoprotein B

8·9% (-4·4 to 22·2)

-29·5% (-40·2 to -18·8)

Lipoprotein(a)

9·8% (-9·3 to 28·9)

-10·0% (-25·4 to 5·3)

### Patients with unclassified mutation status†

Ultracentrifugation LDL cholesterol

6 patients

16 patients

3·8% (-20·7 to 28·3)

-17·9% (-36·0 to 0·3)

Apolipoprotein B

-0·2% (-21·3 to 20·9)

-16·4% (-32·3 to -0·6)

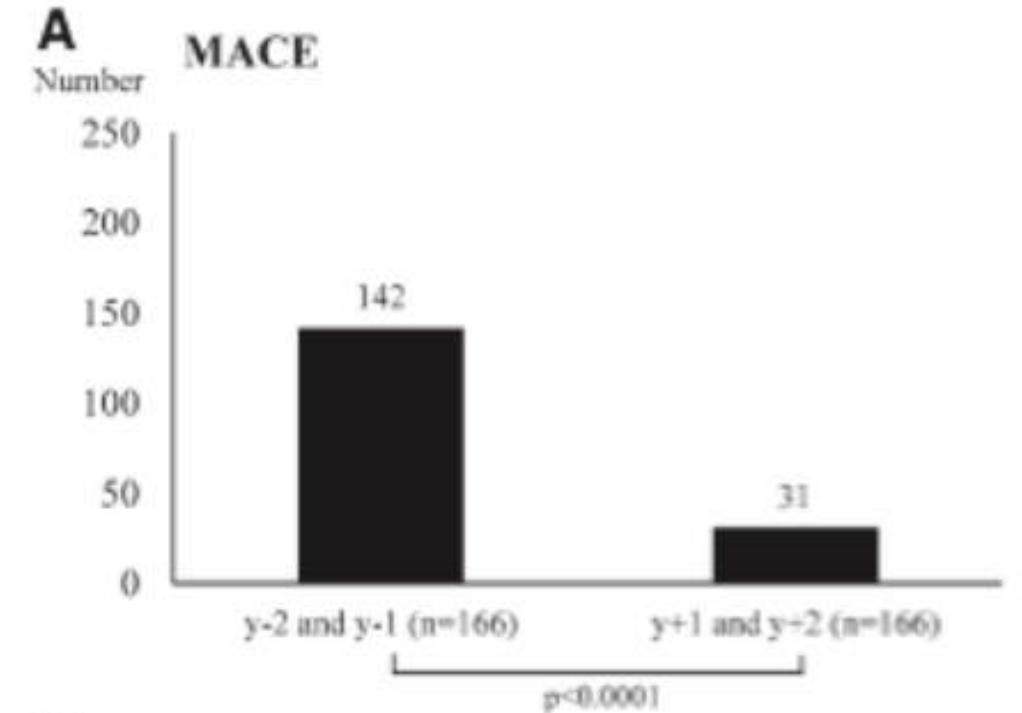
Lipoprotein(a)

-2·0% (-21·7 to 17·8)

-5·4% (-21·7 to 10·8)

## Lipoprotein Apheresis in Patients With Maximally Tolerated Lipid-Lowering Therapy, Lipoprotein(a)-Hyperlipoproteinemia, and Progressive Cardiovascular Disease

- a **prospective observational** multicenter study, **170** patients were investigated who commenced LA because of **Lp(a)-hyperlipoproteinemia** and progressive **cardiovascular disease**.
- Weekly sessions
- Baseline Lp (a) 110 mg/dl



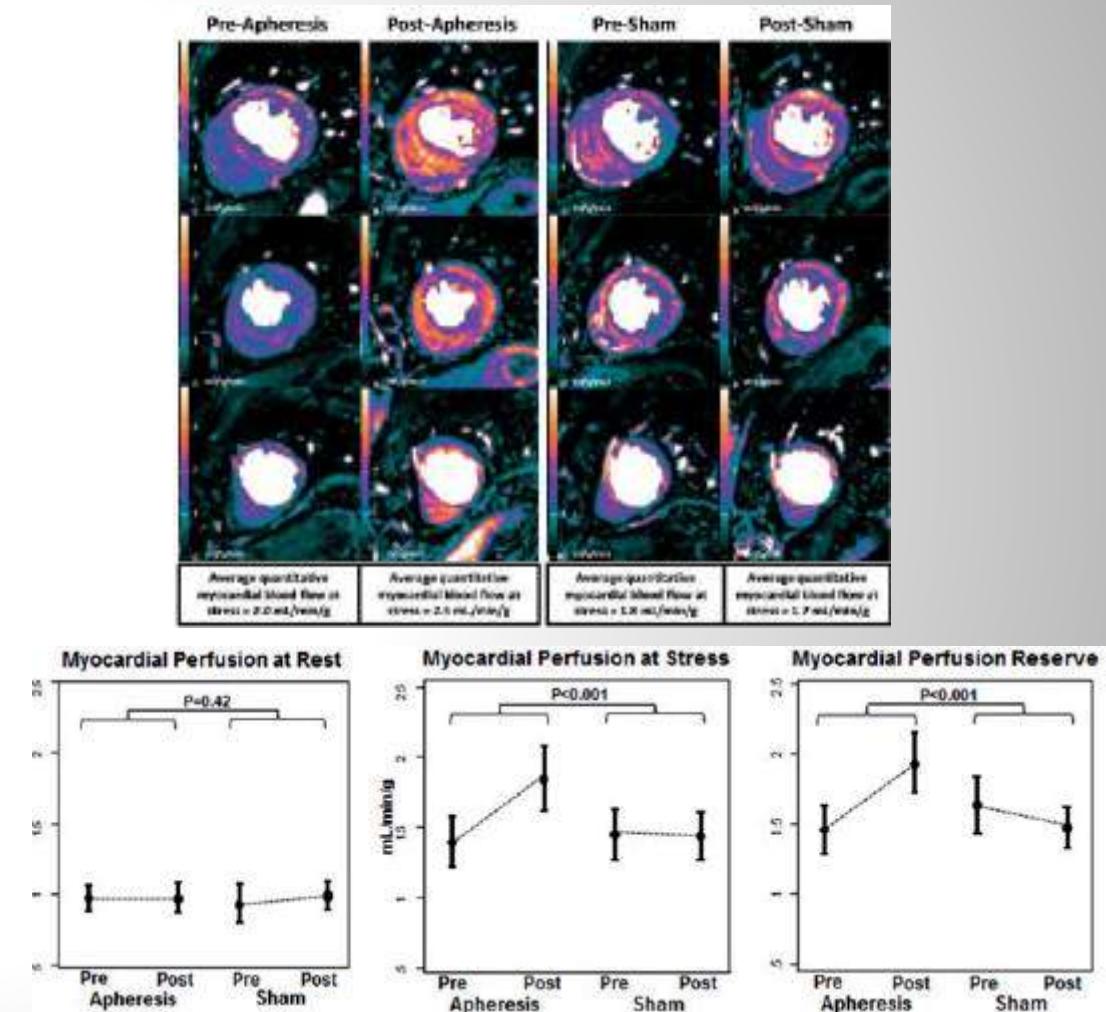
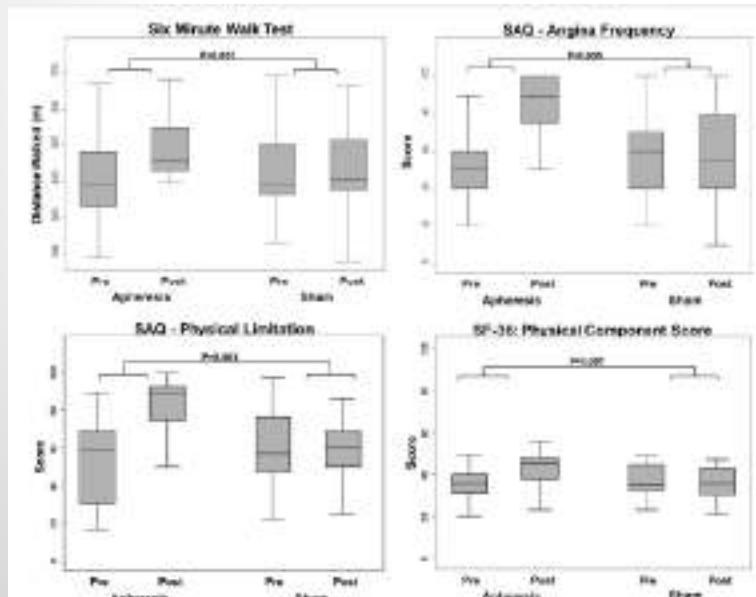
## Apheresis as novel treatment for refractory angina with raised lipoprotein(a): a randomized controlled cross-over trial

- a single-blinded **randomized** controlled trial in 20 patients with refractory angina and raised lipoprotein(a)  $> 500 \text{ mg/L}$ , with 3 months of blinded **weekly** lipoprotein apheresis or **sham**, followed by crossover.
- The primary endpoint was change in quantitative **myocardial perfusion reserve** (MPR) assessed by cardiovascular magnetic resonance.
- Secondary endpoints included measures of atheroma burden, exercise capacity, symptoms and quality of life.

# Apheresis as novel treatment for refractory angina with raised lipoprotein(a): a randomized controlled cross-over trial

- Baseline Lp (a) 110mg/dl
- Baseline LDL 100mg/dl
- Weekly sessions apheresis/sham

3 months



## Apheresis as novel treatment for refractory angina with raised lipoprotein(a): a randomized controlled cross-over trial

- Lipoprotein apheresis removes ApoB containing lipoproteins from whole blood which lowers Lp(a), but also lowers LDL.
- open to interpretation whether the effect is mediated by Lp(a) reduction, LDL reduction or both
- Removal from blood of factors other than lipoproteins, including fibrinogen, coagulation factors, thrombogenic factors, complement factors, inflammatory factors and adhesion molecules

# Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue

**TABLE I. Indications for Therapeutic Apheresis—ASFA 2013 Categories [1]**

Category	Description
I	<b>Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.</b> <i>Example: plasma exchange in Guillain-Barre syndrome as 1st-line standalone therapy; plasma exchange in myasthenia gravis as 1st-line in conjunction with immunosuppression and cholinesterase inhibition</i>
II	<b>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</b> <i>Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease</i>

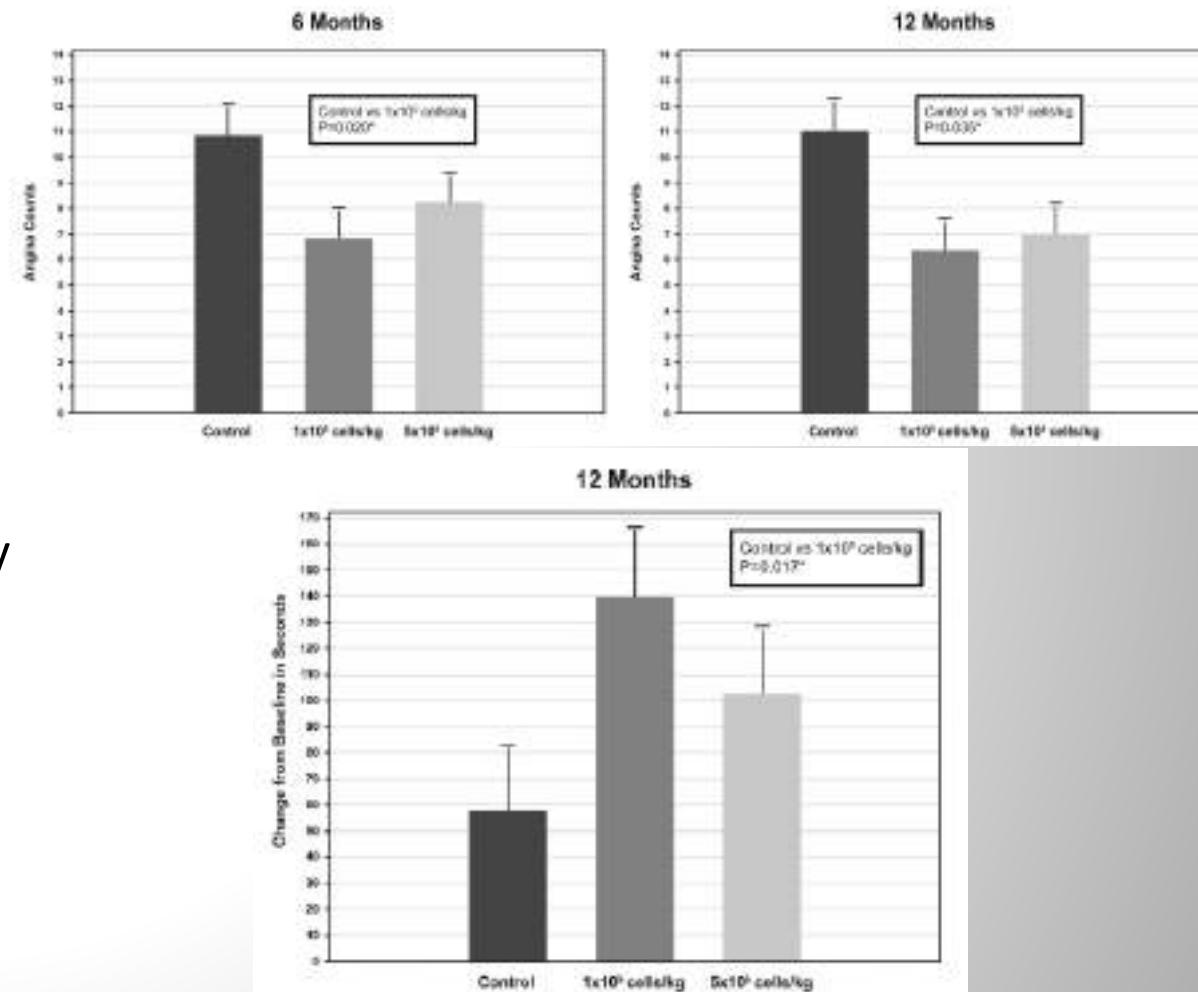
Familial hypercholesterolemia	LDL apheresis LDL apheresis TPE	Homozygotes Heterozygotes Homozygotes with small blood volume	I II II	1A 1A 1C
Lipoprotein (a) hyperlipoproteinemia	LDL apheresis		II	1B
USA	<ul style="list-style-type: none"> <li>• Homozygous FH: LDL c <math>\geq</math> 500 mg/dl (12.9 mmol/L) on maximal possible drug therapy</li> <li>• Heterozygous FH: LDL c <math>\geq</math> 300 mg/dl (7.8 mmol/L) (0–1 additional risk factor), LDL c <math>\geq</math> 200 mg/dl (5.2 mmol/L) (<math>\geq</math> 2 additional risk factors or additional high lipoprotein(a)), LDL <math>\geq</math> 160 mg/dl (4.1 mmol/L) (if at very high risk)</li> </ul>			
Germany	<ul style="list-style-type: none"> <li>• Homozygous FH</li> <li>• Severe hypercholesterolaemia (including but not restricted to heterozygous FH): LDL c elevated on maximal possible drug therapy (taking the overall risk of the patient into account)</li> <li>• Lipoprotein(a): progressive CVD (clinically and on imaging) despite optimal control of all other risk factors and lipoprotein(a) <math>\geq</math> 60 mg/dl</li> </ul>			
Japan	<ul style="list-style-type: none"> <li>• Homozygous FH</li> <li>• Heterozygous FH: total cholesterol <math>\geq</math> 250 mg/dl (6.5 mmol/L) on maximal possible drug therapy</li> </ul>			
UK	<ul style="list-style-type: none"> <li>• Homozygous FH: LDL c reduction <math>&lt;</math> 50% on max. drug therapy or LDL c <math>\geq</math> 350 mg/dl (9.1 mmol/L)</li> <li>• Other hypercholesterolaemia (including heterozygous FH): CVD progression and LDL c <math>\geq</math> 190 mg/dl (4.9 mmol/L) or lower if lipoprotein(a) elevated or LDL c reduction <math>&lt;</math> 40%</li> </ul>			

# Ανθεκτική Στηθάγχη

Therapy	Type of therapy	RCT	Type of control group	Number of patients enrolled
External counterpulsation	Enhanced external counterpulsation	MUST <sup>524</sup>	Sham	139
Extracorporeal shockwave	Low-energy extracorporeal shockwave therapy	Not available	Not available	—
Coronary sinus constriction	Reducer device	COSIRA <sup>525</sup>	Sham	104
Neuromodulation	Spinal cord stimulation	STARTSTIM <sup>526</sup>	Not available	68
	Transcutaneous electrical neural stimulation	Not available	Not available	—
	Subcutaneous electrical neural stimulation	Not available	Not available	—
	Sympathectomy	Denby et al. <sup>527</sup>	Placebo	65
Gene therapy	Adenovirus fibroblast growth factor 5	Not available	Not available	—
Autologous cell therapy	Mononuclear bone marrow-derived haematopoietic progenitor cells	RENEW <sup>528</sup>	Placebo	112

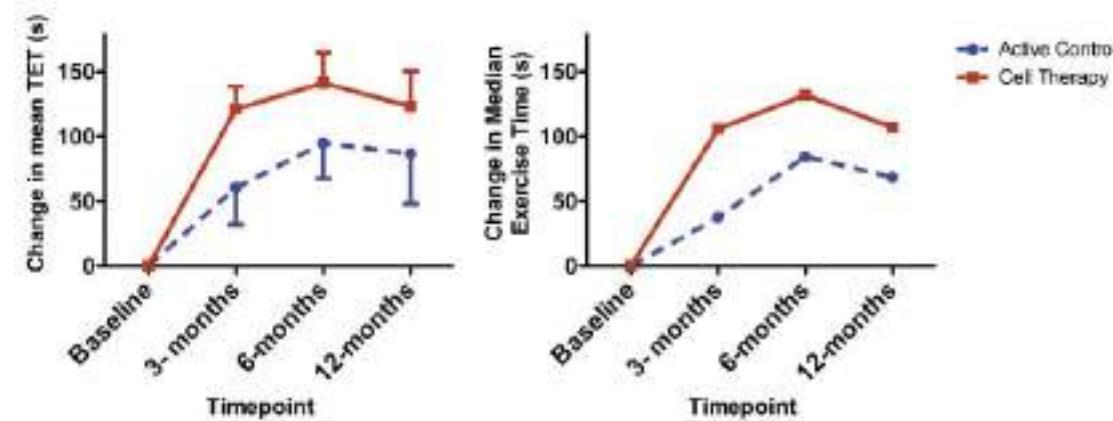
## Intramycocardial, Autologous CD34 Cell Therapy for Refractory Angina - ACT34-CMI

- ACT34-CMI study was a **prospective, double-blind, randomized**, controlled clinical trial conducted at 26 centers in the United States. **167 patients with refractory angina received mobilized autologous CD34 cells or an equal volume of diluent (placebo)**
- The primary outcome measure was weekly angina frequency 6 months after treatment
- mobilization with G-CSF administered subcutaneously for 4 or 5 days, and **leukapheresis** was performed on the 5th day



## The RENEW Trial Efficacy and Safety of Intramyocardial Autologous CD34 Cell Administration in Patients With Refractory Angina

- a randomized, double-blind, multicenter trial comparing IM CD34 administration with no intervention (open-label standard of care) or IM placebo injections (active control). The primary efficacy endpoint was change in TET at 12 months
- 112 of planned 444 enrolled
- All blinded patients underwent cell mobilization with G-CSF (5 mg/kg subcutaneously) for 4 days followed by apheresis on day 5
- Due to early termination, RENEW was underpowered to assess adequately the efficacy of IM administration of autologous CD34 cells for the treatment of refractory angina
- **angina frequency was improved at 6 months** (relative risk: 0.63, p=0.05)
- **safe** compared with both open-label standard of care and active control (major adverse cardiovascular events 67.9% [standard of care], 42.9% (active control), 46.0% [CD34]



# Impact of Cell Therapy on Myocardial Perfusion and Cardiovascular Outcomes in Patients With Angina Refractory to Medical Therapy

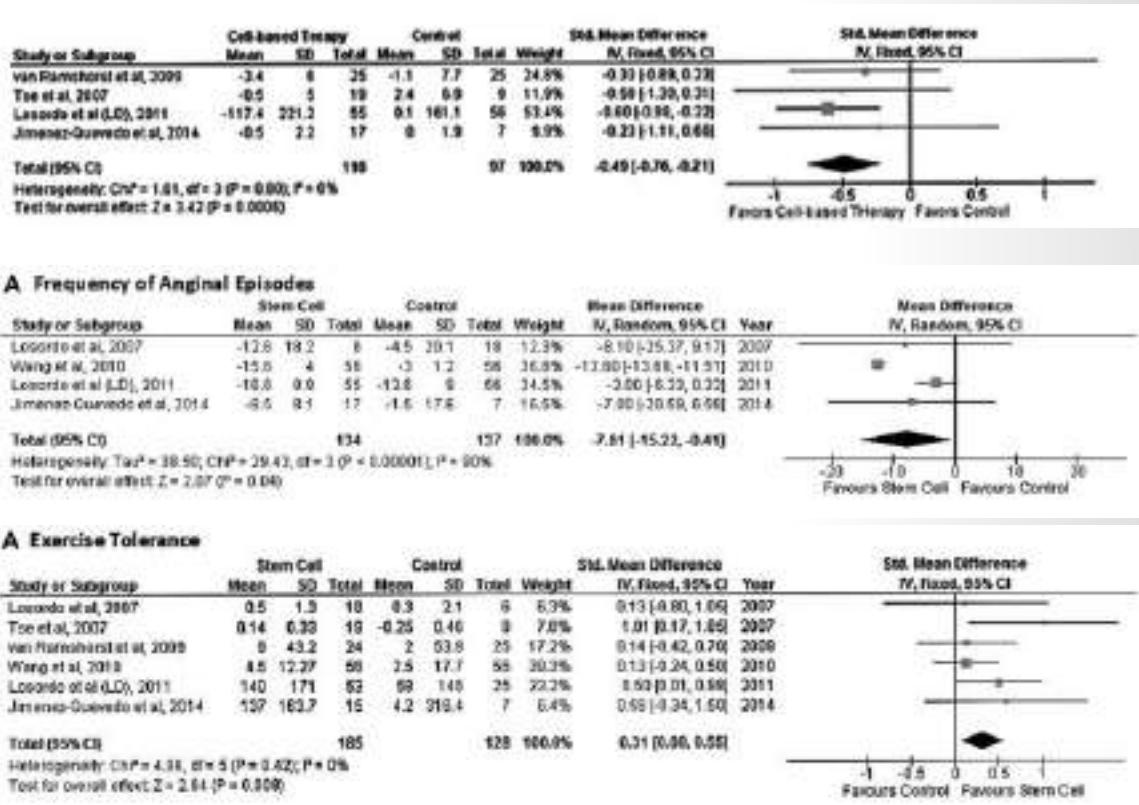
## A Systematic Review and Meta-Analysis

6 trials comprising 353 participants (4/6 Apheresis)

Βελτίωση μυοκαρδιακής αιμάτωσης έναντι OMT (SPECT)

Ελάττωση συχνότητας στηθαγχικών επεισοδίων έναντι OMT

Βελτίωση ανοχής στην άσκηση έναντι OMT



# Συμπεράσματα

- Η ΘΑ εξακολουθεί να αποτελεί ύστατη θεραπευτική επιλογή σε περιπτώσεις ετερόζυγης υπερχοληστερολαιμίας ή άλλης μορφής δυσλιπιδαιμίας με ανεπαρκή ανταπόκριση στη φαρμακευτική αγωγή ή κακή ανοχή σε αυτή
- Η ΘΑ αποτελεί βασική θεραπευτική επιλογή σε ομόζυγη οικογενή υπερχοληστερολαιμία
- Χρήση σε παιδιά (σε αντίθεση με λομιταπίδη) και εγκύους
- Ο ρόλος της σε αμιγώς αυξημένη Lp(a) και ανθεκτική στη θάγχη απομένει να προσδιοριστεί
- Κυτταρικές θεραπείες βασισμένες στην Αφαίρεση είναι δυνατό να συμβάλουν στην επιτυχή αντιμετώπιση της ανθεκτικής στη θάγχης

Ευχαριστώ για την προσοχή