

ΓΙΕΕΟΥ

Επόπειο Εργασίας
Φερρούρων
Καποδιστριακού
Πανεπιστημίου

4η

Ετήσια Επιστημονική Εκδήλωση
Νεφρολογικού Τμήματος
ΓΝ "Παπαγεωργίου" Θεσσαλονίκης
(στη μνήμη του Γιώργου Σακελλαρίου)

Περί Θεραπευτικής Αφαίρεσης

14-16

Δεκεμβρίου 2018

Ξενοδοχείο Electra Palace
Θεσσαλονίκη



Ελληνική Νεφρολογική
Εταιρεία (ΕΝΕ)



Ελληνική Εταιρεία
Λιμφοφίρεσης

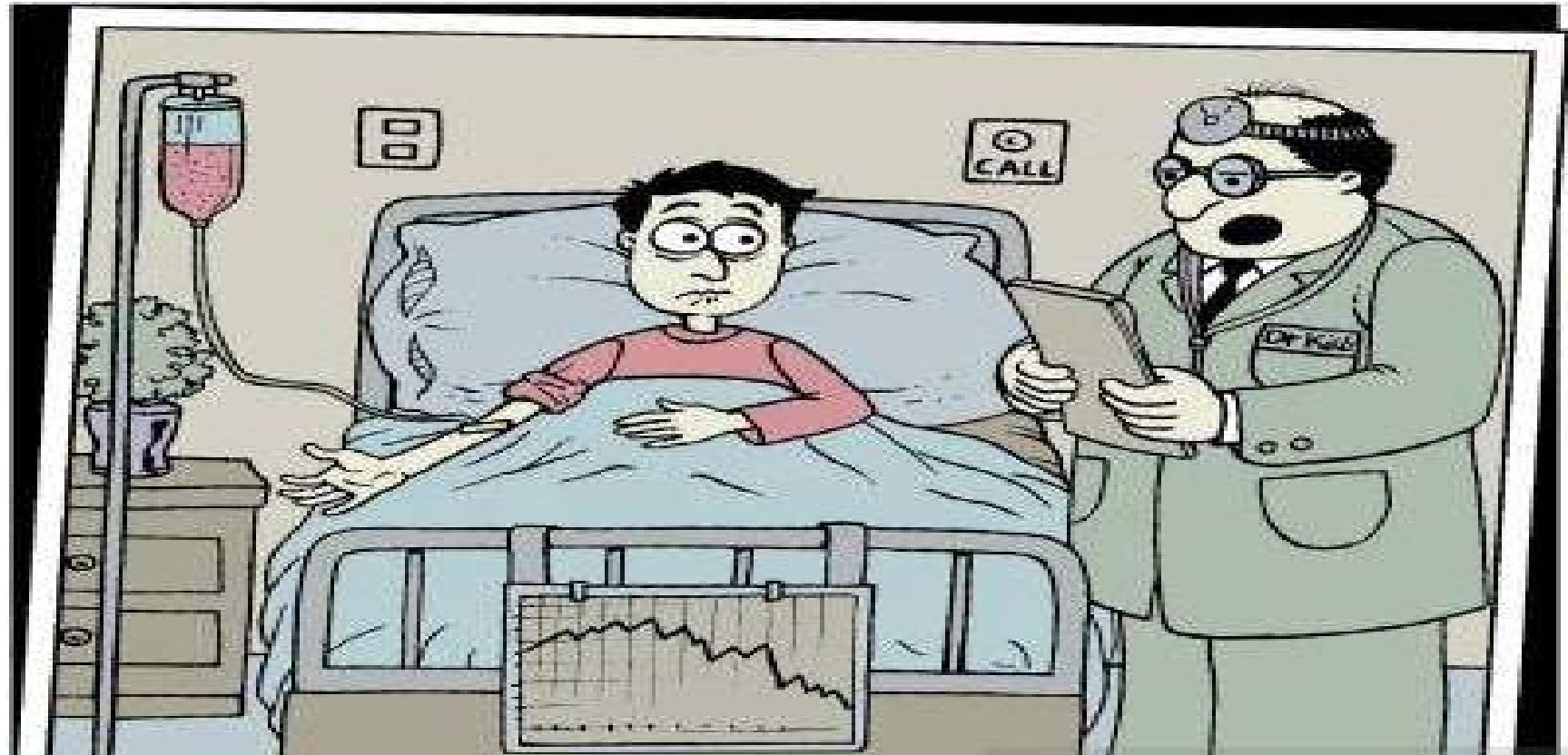


ΓΝ Θεσσαλονίκης
"Παπαγεωργίου"

Η εφαρμογή της
θεραπευτικής
αφαίρεσης στις
δυσλιπιδαιμίες
και διάφορα
«ορφανά»
νοσήματα

Π. Κρίκη

Νεφρολόγος , Π.Γ.Ν.Αλεξανδρούπολης



"The good news is that we're going
to name the disease after you."

Σπάνια νόσος : όταν ο αριθμός των ασθενών
που έχουν προσβληθεί από αυτή είναι
 $< 5/10.000$

RARE DISEASES by the NUMBERS

50%
of the people affected
by rare diseases are children

Approximately
7,000
rare diseases & disorders
have been identified



**30 MILLION
PEOPLE**

In the U.S. are living with
rare diseases



**30 MILLION
PEOPLE**

In Europe are living with
rare diseases

#DYK:
If all of the people with rare diseases
lived in one country, it would be the
**world's 3rd
most populous
country**

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

ΚΑΤΗΓΟΡΙΑ Ι:

ΣΤΑΝΤΑΡ ΚΑΙ ΑΠΟΔΕΚΤΗ ΘΕΡΑΠΕΙΑ

ΚΑΤΗΓΟΡΙΑ ΙΙ:

ΓΕΝΙΚΑ ΑΠΟΔΕΚΤΗ ΘΕΡΑΠΕΙΑ ΩΣ ΥΠΟΣΤΗΡΙΚΤΙΚΗ

N-METHYL-D-ASPARATE RECEPTOR ANTIBODY ENCEPHALITIS

Incidence: Rare	Procedure: TPE	Recommendation: Grade 1C	Category: I
No. of reported patients: 100–300	RCT 0	CT 0	CS 5(22) CR 39(41)

■ Αυτοάνοση νευρολογική διαταραχή : Anti – NMDAR

■ Αγωγή:

- ✓ 1^{ης} γραμμής: CCS, IVIG, **TPE** (5-6ΜΠΜ)
- ✓ 2^{ης} γραμμής : Rituximab ± Cyclophosphamide

Technical notes

Volume treated: 1–1.5 TPV

Frequency: Every other day

Replacement fluid: Albumin

Scwartz et al, J Clin Apheresis 2016

Hyperimmunoglobulinemia

Hyperlipidemia

Idiopathic thrombocytopenic purpura

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ΚΑΤΗΓΟΡΙΑ I:

ΣΤΑΝΤΑΡ ΚΑΙ ΑΠΟΔΕΚΤΗ ΘΕΡΑΠΕΙΑ

ΚΑΤΗΓΟΡΙΑ II:

ΓΕΝΙΚΑ ΑΠΟΔΕΚΤΗ ΘΕΡΑΠΕΙΑ ΩΣ ΥΠΟΣΤΗΡΙΚΤΙΚΗ

Εγκεφαλοπάθεια Hashimoto

Incidence: Rare

Procedure

Recommendation

Category

of reported patients: < 100

RCT

0

CT

0

CS

0

CR

14(15)

- Νευροψυχιατρική συνδρομή με αυξημένους τίτλους αντιθυρεοειδικών αντισωμάτων (πιθανώς ευθυρεοειδικοί οι ασθενείς)

- Αγωγή:

- ✓ 1^{ης} γραμμής: CCS,
- ✓ 2^{ης} γραμμής : IVIG,Cyclophosphamide,AZA, **TPE (3-9ΜΠΜ)**

Technical notes

Volume treated: 1-1.5 TPV

Frequency: Daily to every other day

Replacement fluid: Albumin

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

ΚΑΤΗΓΟΡΙΑ III: ΜΗ ΤΕΚΜΗΡΙΩΜΕΝΗ ΕΝΔΕΙΞΗ		ΚΑΤΗΓΟΡΙΑ IV: ΑΠΟΔΕΔΕΙΓΜΕΝΑ ΧΩΡΙΣ ΑΠΟΤΕΛΕΣΜΑ	
Aplastic anemia or pure RBC	Multifocal osteoporosis of unknown cause	AIDS	
Stiff man Syndrome			
Incidence: 0.1/100,000	Procedure	Recommendation	Category
	TPE	Grade 2C	III
No. of reported patients: < 100	RCT	CT	CR
	0	0	13(14)
		CS	
		5(30)	
<ul style="list-style-type: none"> ■ Νευρολογική αυτοάνοση διαταραχή : antiGlutamic Acid Decarboxylate (antiGAD) ■ Αγωγή: <ul style="list-style-type: none"> ✓ Immune therapy, αντικαταθλιπτικά, μυοχαλαρωτικά, TPE (4-5 σε 8-14 μέρες) 			
Volume treated: 1-1.5 TPV	Frequency: Every 1-3 days		
Replacement fluid: Albumin			
Plasmapheresis encephalitis			
Stiff man syndrome			
Schwartz et al, J Clin Apheresis 2016			

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

ΚΑΤΗΓΟΡΙΑ III: ΜΗΤΕΚΜΗΡΙΩΜΕΝΗ ΕΝΔΕΙΞΗ

ΚΑΤΗΓΟΡΙΑ IV: ΑΠΟΔΕΔΕΙΓΜΕΝΑ ΧΩΡΙΣ ΑΠΟΤΕΛΕΣΜΑ

Δερματομυοσίτιδα/Πολυμυοσίτιδα

Incidence: 1/100,000/yr in adults, 0.4/100,000/yr in children

Procedure	Recommendation	Category
TPE	Grade 2B	IV
ECP	Grade 2C	IV

No. of reported patients: < 100

RCT	CT	CS	CR
1(39)	0	1(3)	2(2)

- Ιδιοπαθής φλεγμονώδης μυοπάθεια ± δερματικές βλάβες
- Αγωγή:
 - ✓ CCS ± AZA, Cyclophosphamide, IVIG, Rituximab
 - ✓ TPE;;;; Rescue therapy;;;;
 - ✓ Αντισώματα: ANA, Anti-Ro, Anti-La, myositis specific antibodies..... Όχι ειδικά
 - ✓ RCT/CR

FAMILIAL HYPERCHOLESTEROLEMIA

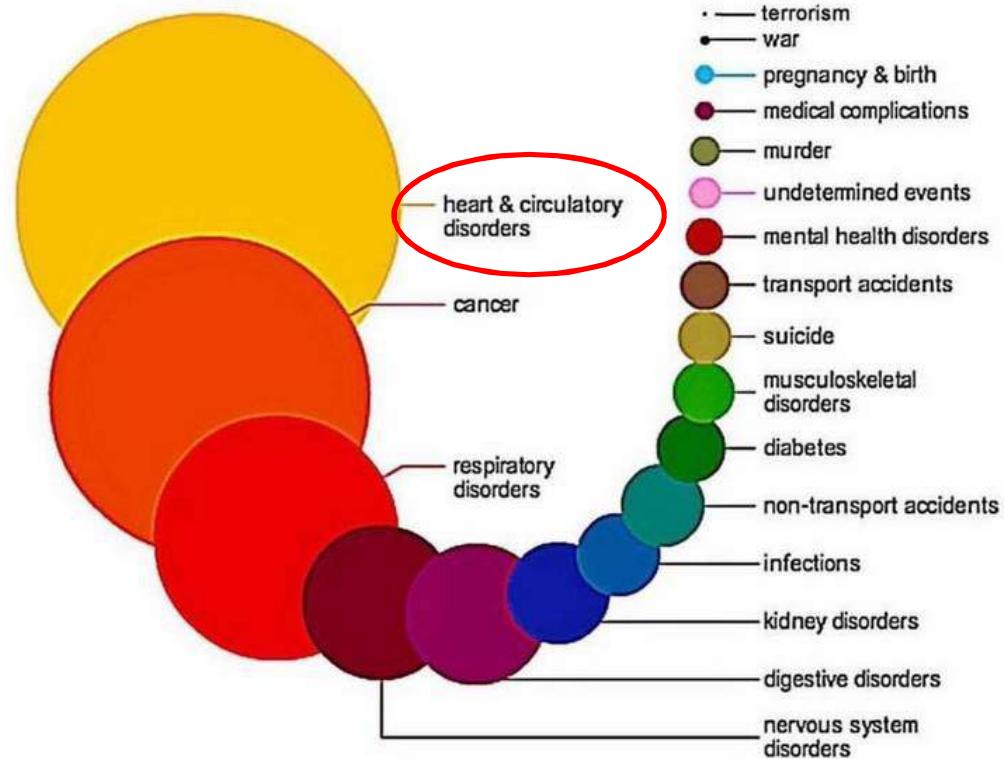
Incidence: Heterozygotes: 200/100,000/year;
Homozygotes: 1/1,000,000/year

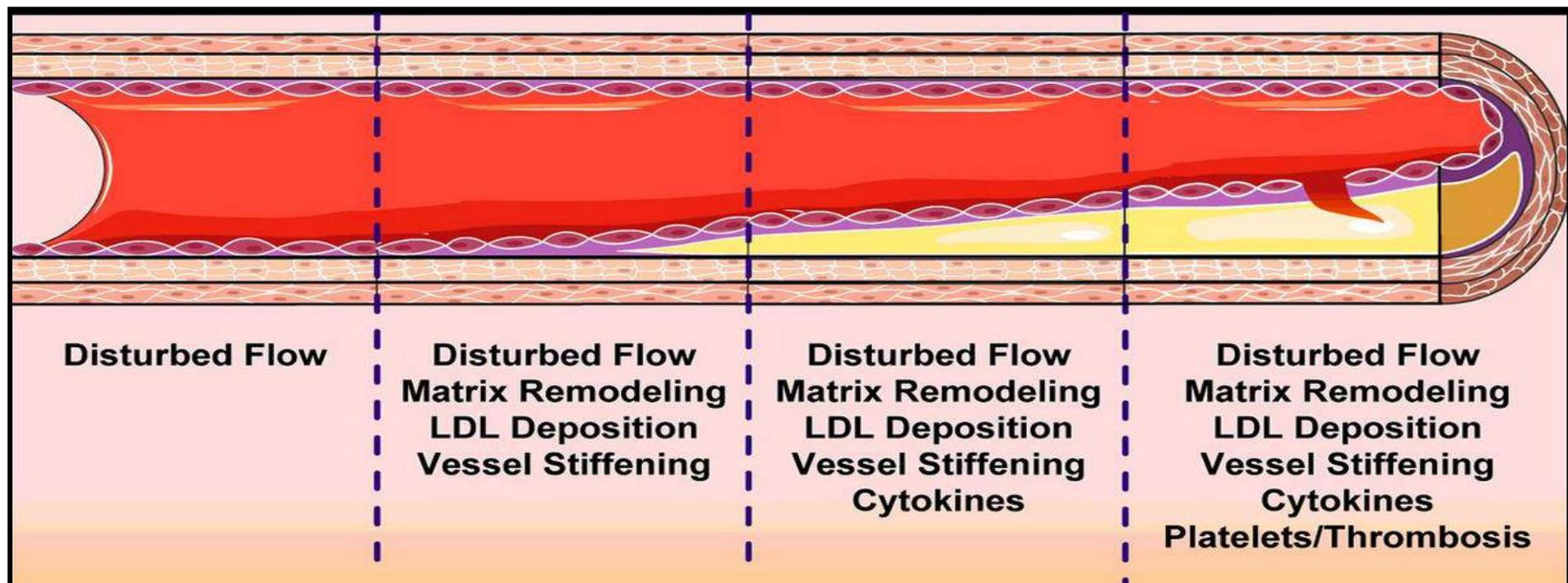
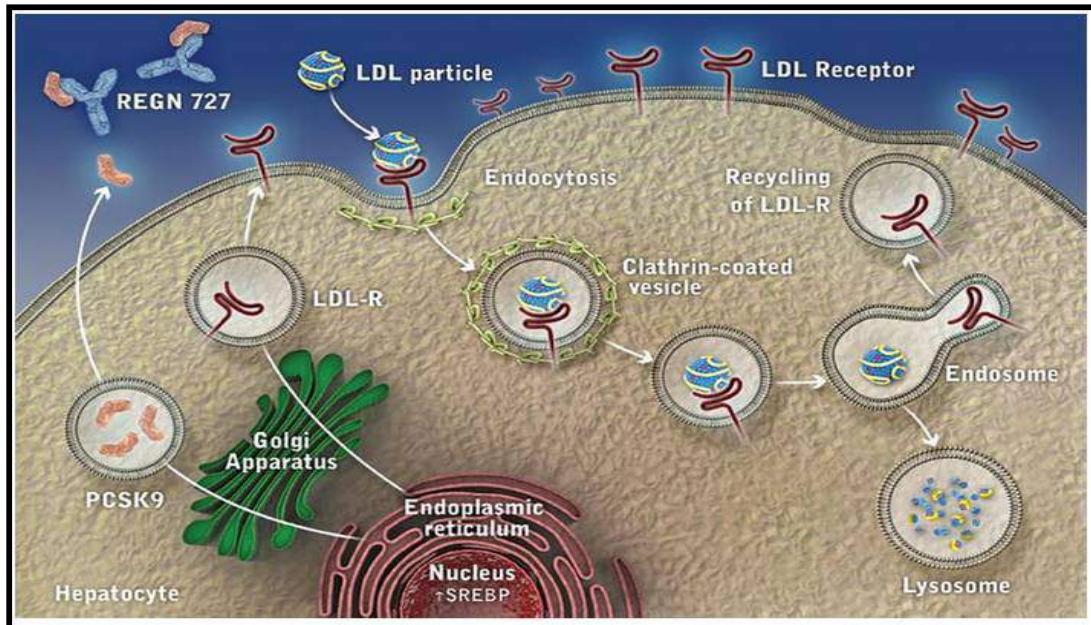
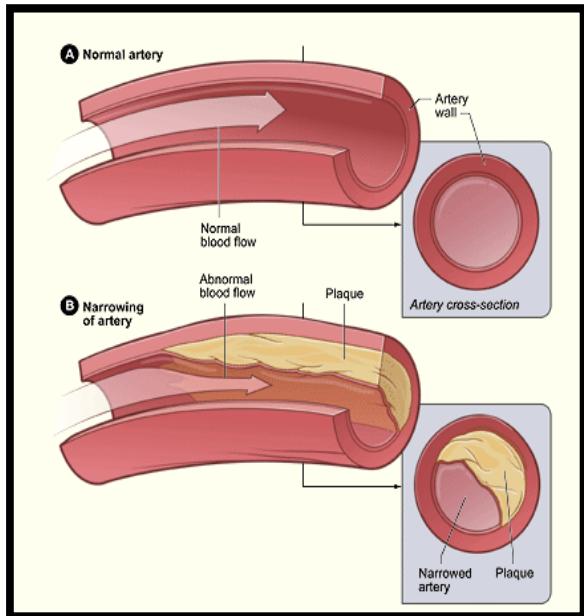
	Indication	Procedure	Recommendation	Category
	Homozygotes ^a	LDL apheresis	Grade 1A	I
	Heterozygotes	LDL apheresis	Grade 1A	II
	Homozygotes with small blood volume ^b	TPE	Grade 1C	II
No. of reported patients: > 300	RCT	CT	CS	CR
LDL apheresis	6(228)	15(308)	22(401)	NA
TPE	0	1(5)	14(62)	NA

^aApproved indications vary among countries, see technical notes below. ^bRelative to manufacturers' recommendation for available selective removal devices.



Leading causes of death in perspective





Δίαιτα

Φαρμακευτική
αύξηση του
μεταβολισμού

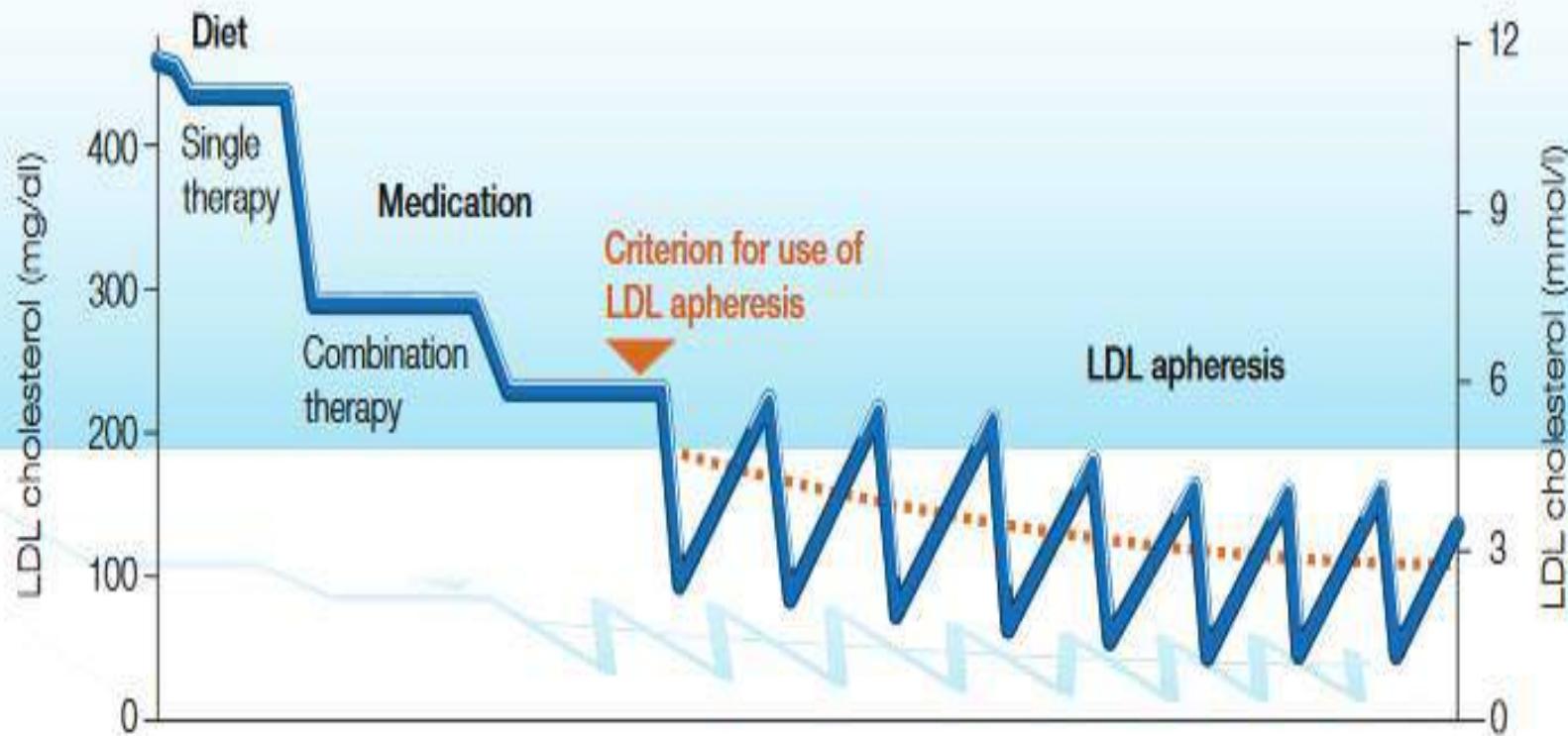
Αναστολή
σύνθεσης

Απομάκρυνση από
τον ενδαγγειακό
χώρο

LDL

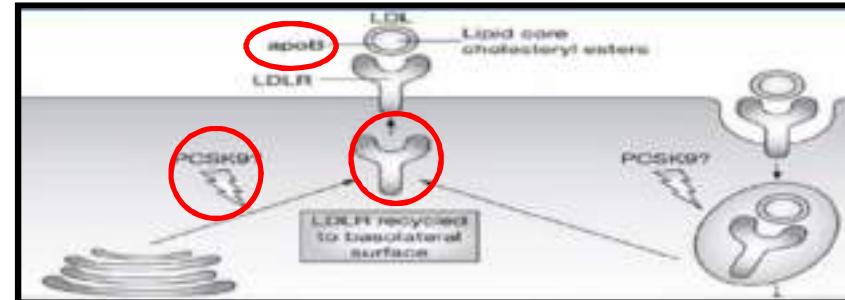
Lp(a)

Therapy stages with hypercholesterolaemia





Οικογενής υπερχοληστερολαιμία



HoFH

1/1000000

LDL : 650-1000mg/dl

Ξανθώματα 4 ετών

20 ετών

HeFH

1/1500

LDL : 250-550 mg/dl

Ξανθώματα 20 ετών

Αθηρωματική νόσος 30

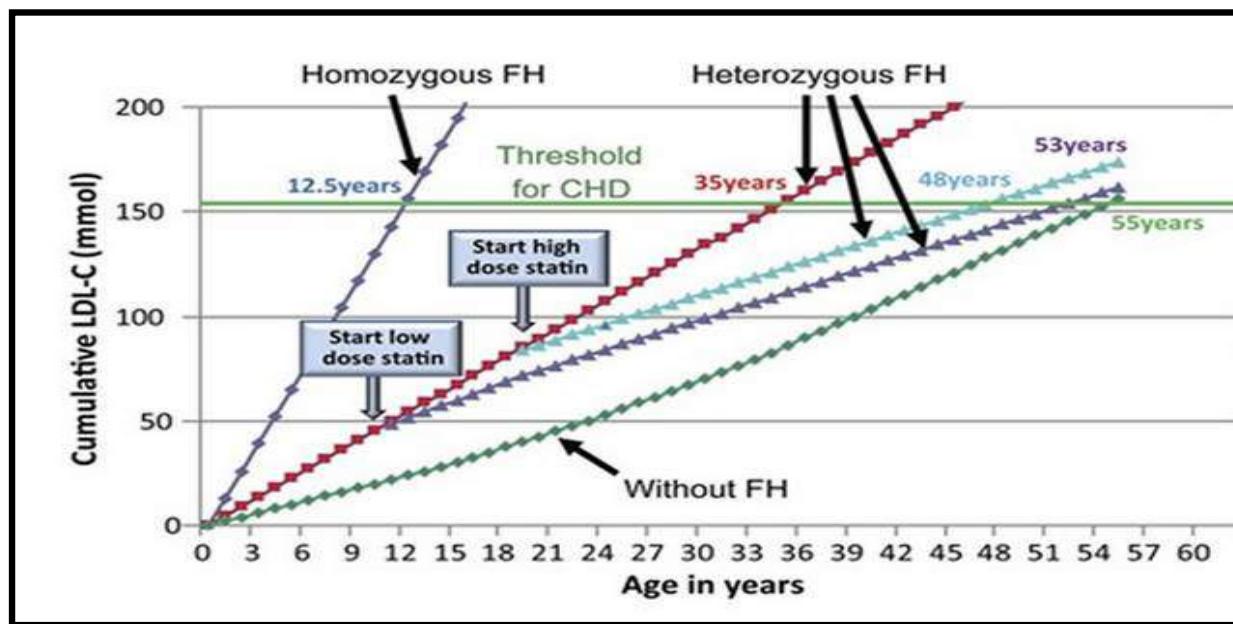
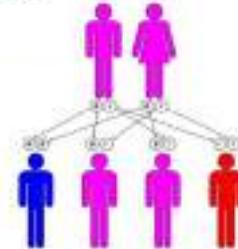


Table 1. Dutch Lipid Clinic Network criteria for the diagnosis of heterozygous familial hypercholesterolemia (hFH).^{33,34}

Criteria	Score
Family history	
First-degree adult relative with	
• Premature coronary and/or vascular disease (male < 55 years; female < 60 years)	1
• LDL-C > 95th percentile for age and gender	1
• Tendon xanthomata and/or arcus cornealis	2
First-degree relative < 18 years with LDL-C > 95th percentile for age and gender	2
Clinical history	
Patient with premature IHD (ages as above)	2
Patient with other premature vascular and/or cerebrovascular disease (ages as above)	1
Physical examination	
Tendon xanthomata	6
Arcus cornealis prior to age 45	4
Laboratory analysis	
LDL-C (mmol/L)	
• ≥8.5	8
• 6.5–8.4	5
• 5.0–6.4	3
• 4.0–4.9	1
DNA analysis	
Genetic test results confirming functional mutation in <i>LDLR</i> , <i>APOB</i> , or <i>PCSK9</i> gene	8

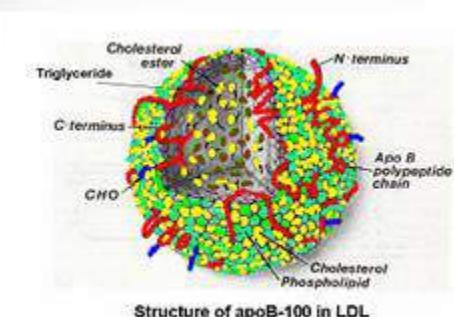
LDL-C = low-density lipoprotein cholesterol; IHD = ischemic heart disease; *LDLR* = low-density lipoprotein receptor; *APOB* = apolipoprotein B-100; *PCSK9* = proprotein convertase subtilisin/kexin 9

SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA¹

Point	Criteria
1	Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) in adults.
2	Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)
3	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.
4	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
5	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.
	Family history of elevated total cholesterol > 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative.
	Family history of elevated total cholesterol > 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.
DIAGNOSIS	
Definite familial hypercholesterolemia = 1+2 or 3	
Possible familial hypercholesterolemia = 1+4 or 5	

¹ Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia.

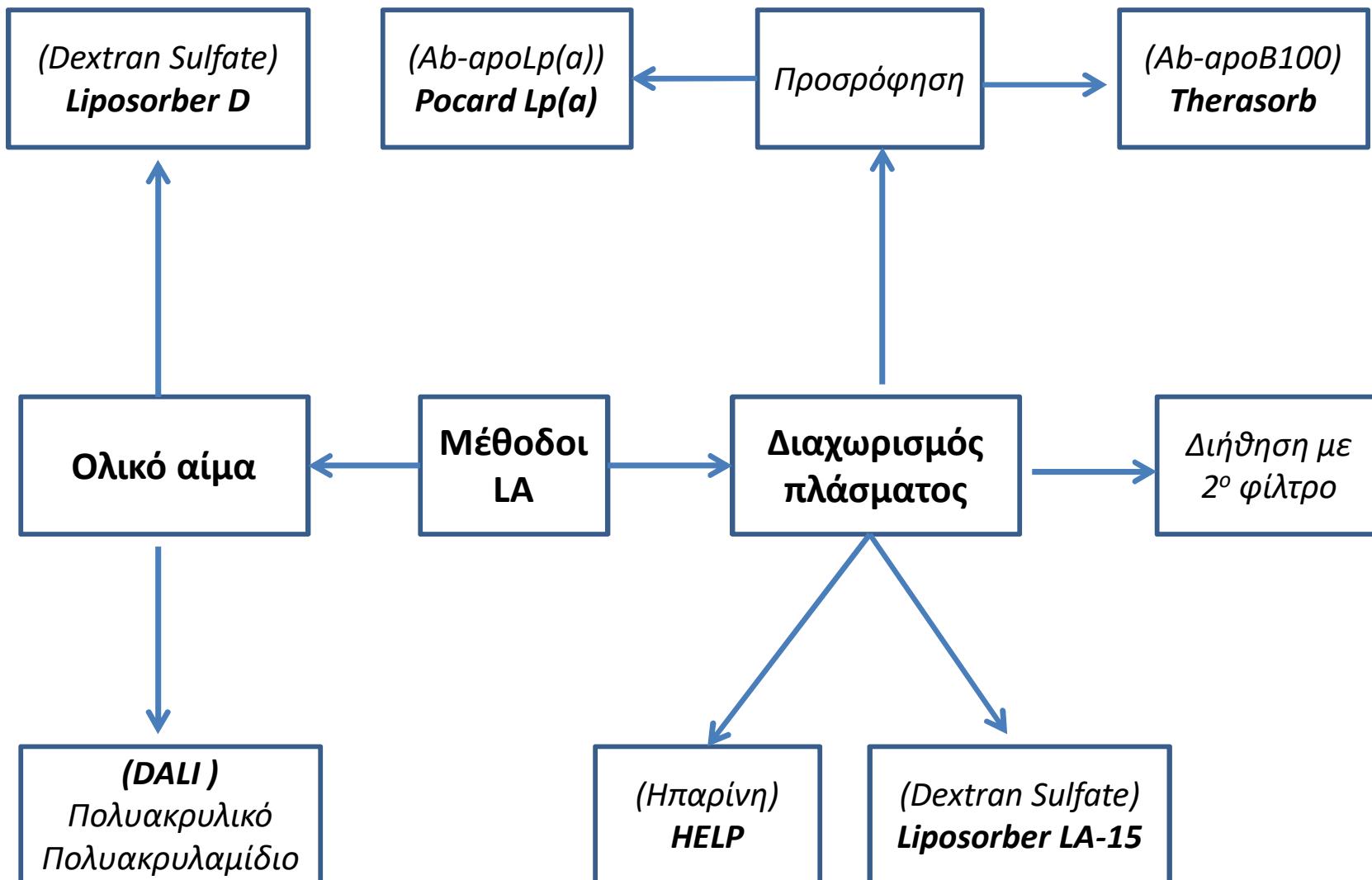
^a HuGE prevalence review. American Journal of Epidemiology. 2004;160:407-420.



LDL-αφαίρεση

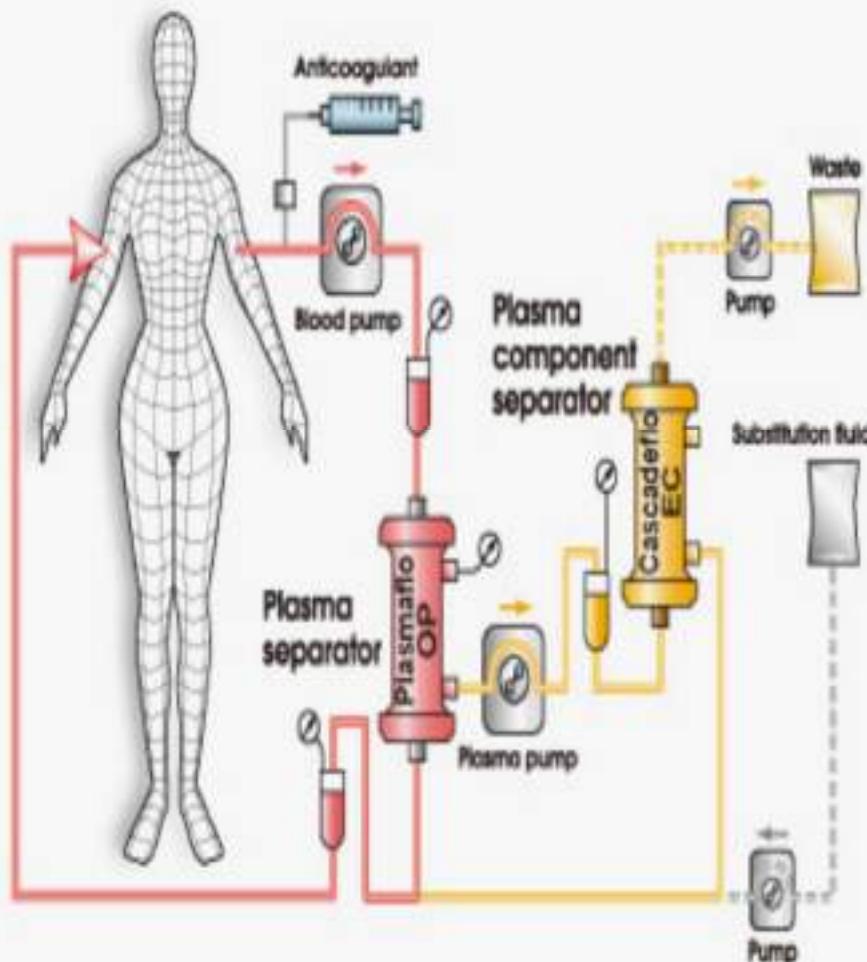
λιποπρωτεΐνική αφαίρεση

Year	Authors	Method	Advantage	Disadvantage
1967	De Gennes et al. [2]	Plasmapheresis	Quick and well-tolerated elimination of pathologic substances	Unselectivity, danger of infection, bleeding, and risks of human albumin
1975	Thompson et al. [3]	Plasmapheresis		
1980	Agishi et al. [4]	Cascade filtration	Semiselectivity	Danger of infection and low effectiveness
1981	Stoffel and Demant [5]	Immunoadsorption	Selectivity, effectiveness, regeneration, and reusability	Expensive technology
1983	Borberg et al. [6]	Immunoadsorption		
1983	Wieland and Seidel [7]	Heparin-induced LDL precipitation (HELP)	Selectivity and effectiveness	Expensive technology
1985	Nose et al. [8]	Thermofiltration	Selectivity and effectiveness	Outdated technology, behavior of macromolecules under heat unknown and not available
1985	Antwiller et al. [9]	Dextran sulfate-induced LDL precipitation	Selectivity and effectiveness	Expensive technology and not available
1987	Mabuchi et al. [10]	Dextran sulfate LDL adsorption (liposorber-LA 15)	Selectivity and effectiveness	Expensive technology
1993	Bosch et al. [11]	LDL hemoperfusion (DALI)	Selectivity, effectiveness, and simple technology	Unknown
2003	Otto et al. [12]	LDL hemoperfusion (liposorber D)	Selectivity, effectiveness, and simple technology	Unknown

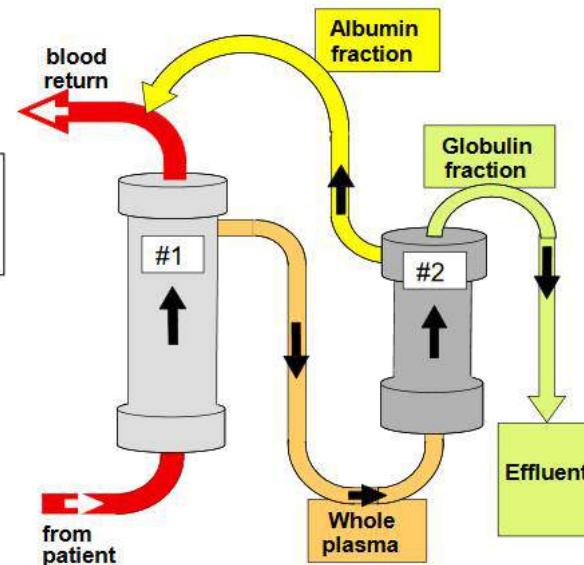


Cascade filtration

Circuit diagram of DFPP

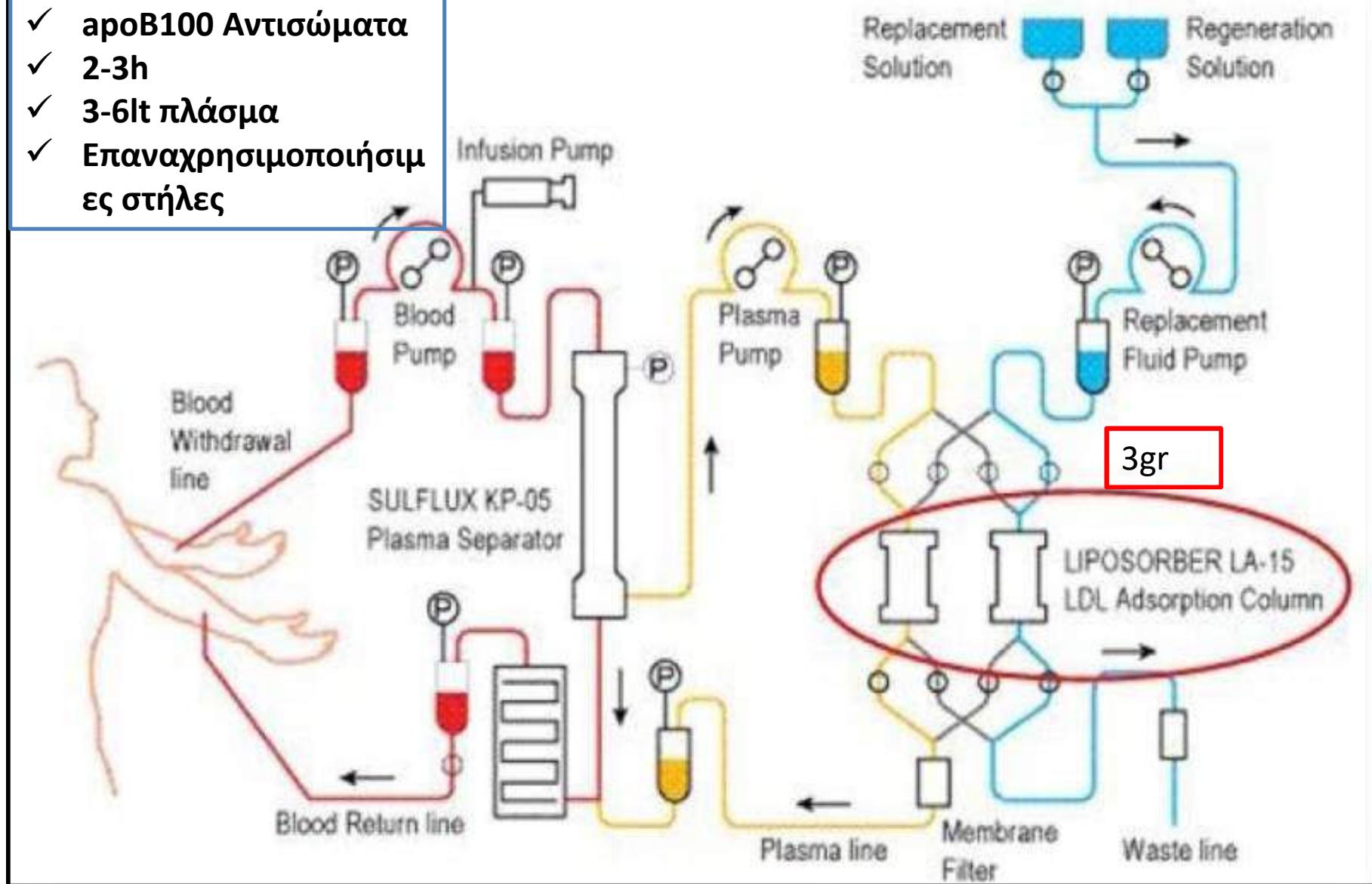


- ✓ 10^6d
- ✓ $\text{LDL} - 2,3 \times 10^6$
- ✓ Απομακρύνονται ινωδιογόνο, HDL, ανοσοσφαιρίνες



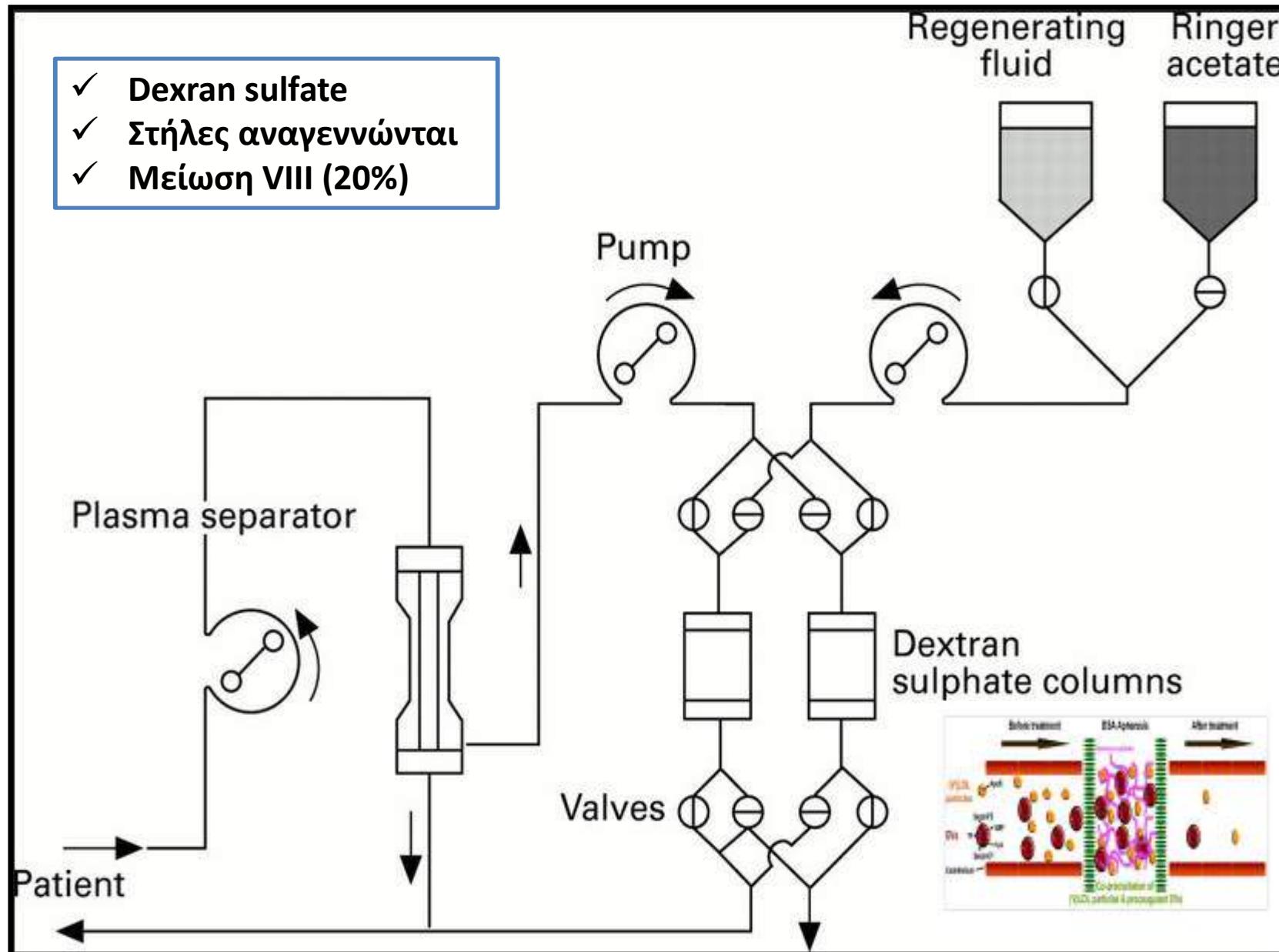
Προσρόφηση

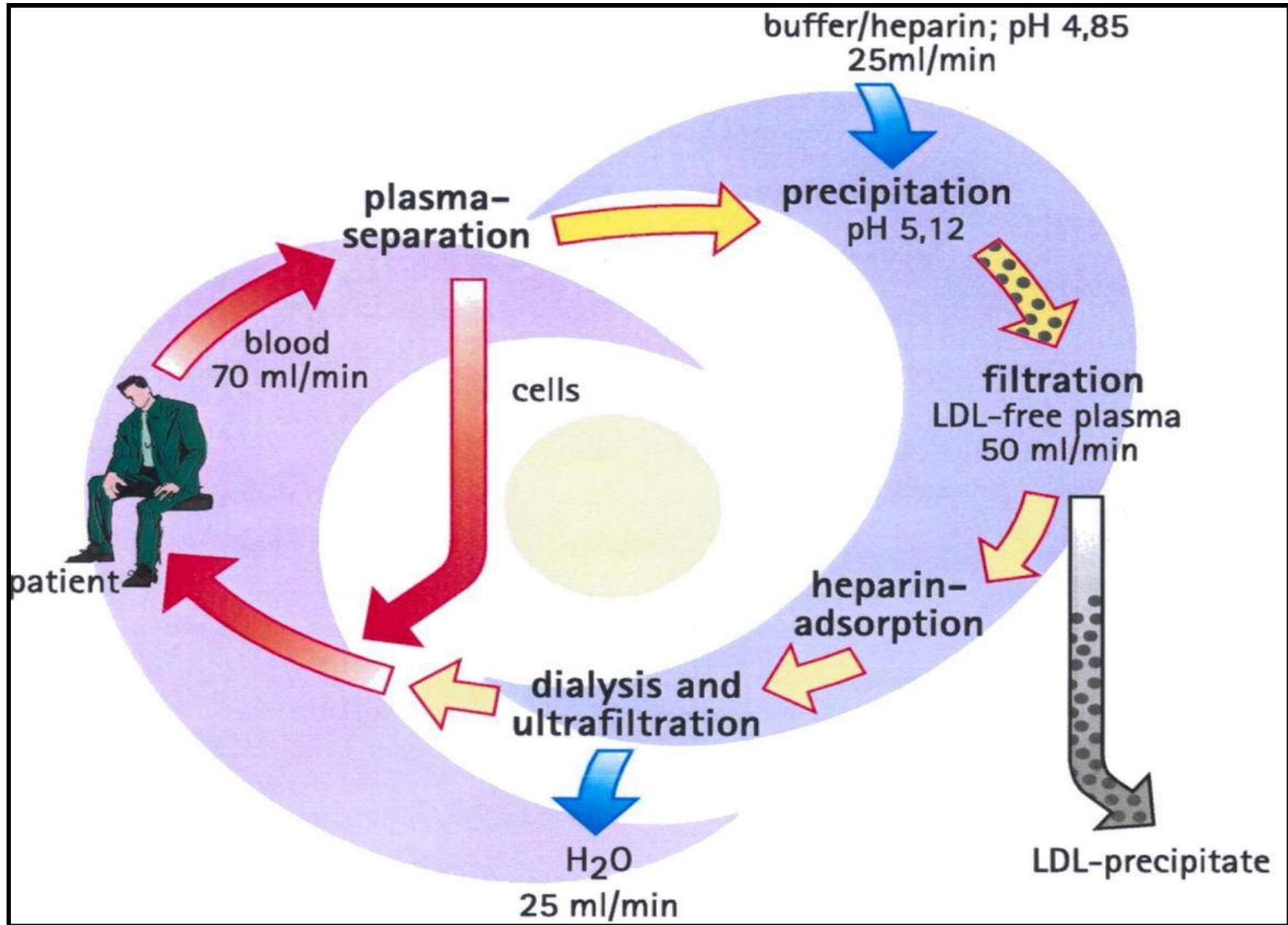
- ✓ apoB100 Αντισώματα
- ✓ 2-3h
- ✓ 3-6lt πλάσμα
- ✓ Επαναχρησιμοποιήσιμες στήλες



Προσρόφηση

- ✓ Dexran sulfate
- ✓ Στήλες αναγεννώνται
- ✓ Μείωση VIII (20%)





Καθίζηση

- ✓ Απομάκρυνση C3-C4,
ινωδιγόνου και
πλασμινογόνου
- ✓ 3 L

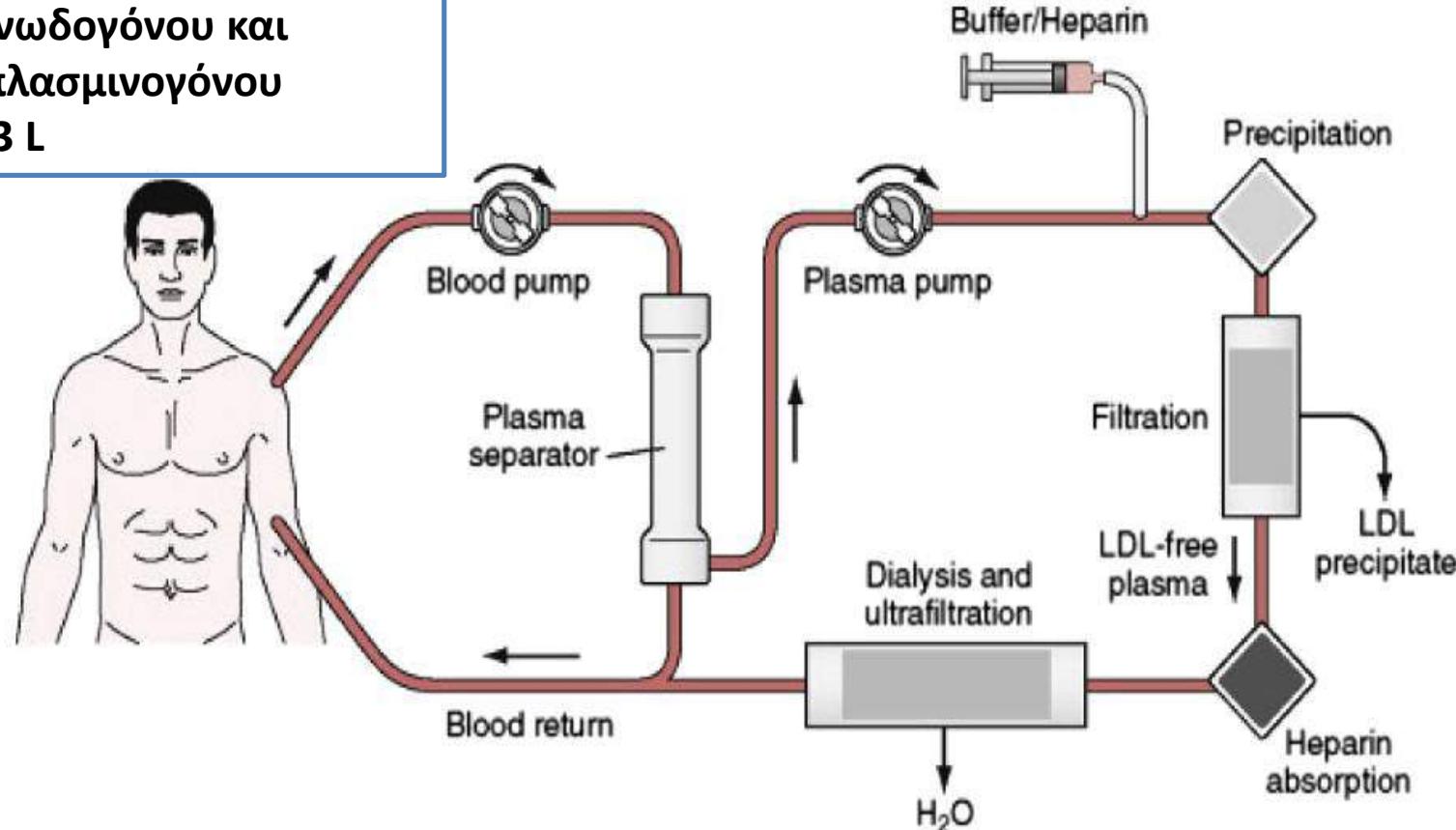
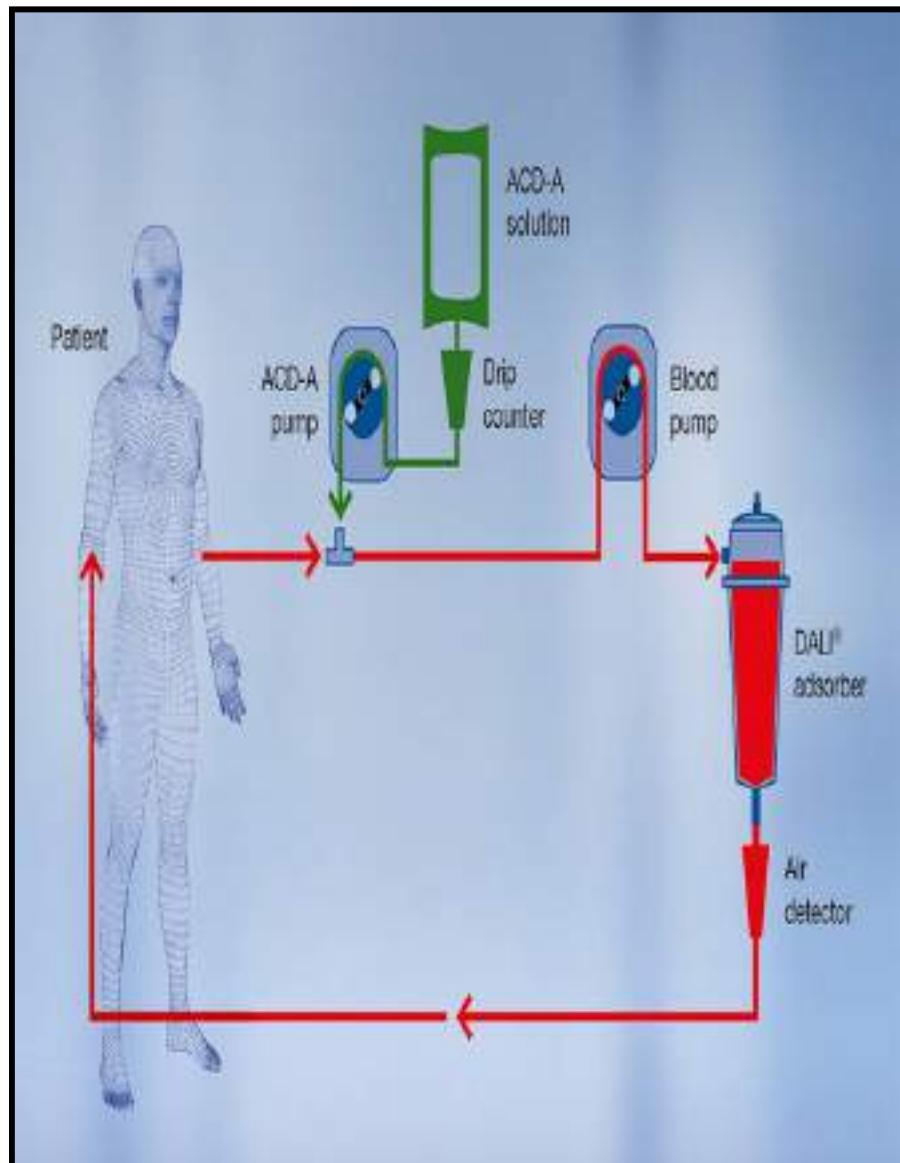


Fig. 1. HELP (Futura). (From Moriarty PM. Low-density lipoprotein apheresis. In: Ballantyne CM, editor. Clinical lipidology: a companion to Braunwald's heart disease. Philadelphia: Saunders Elsevier; 2009. p. 365; with permission.)

DALI (ολικό αίμα)

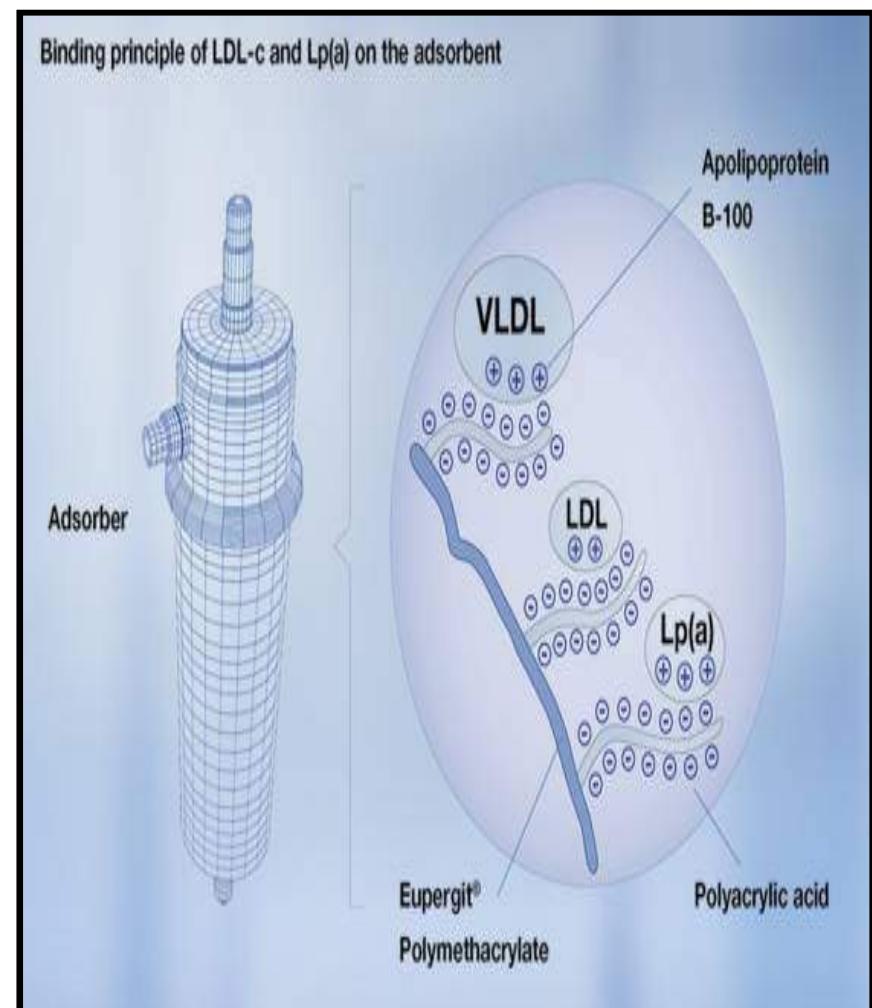


Reductions up to:

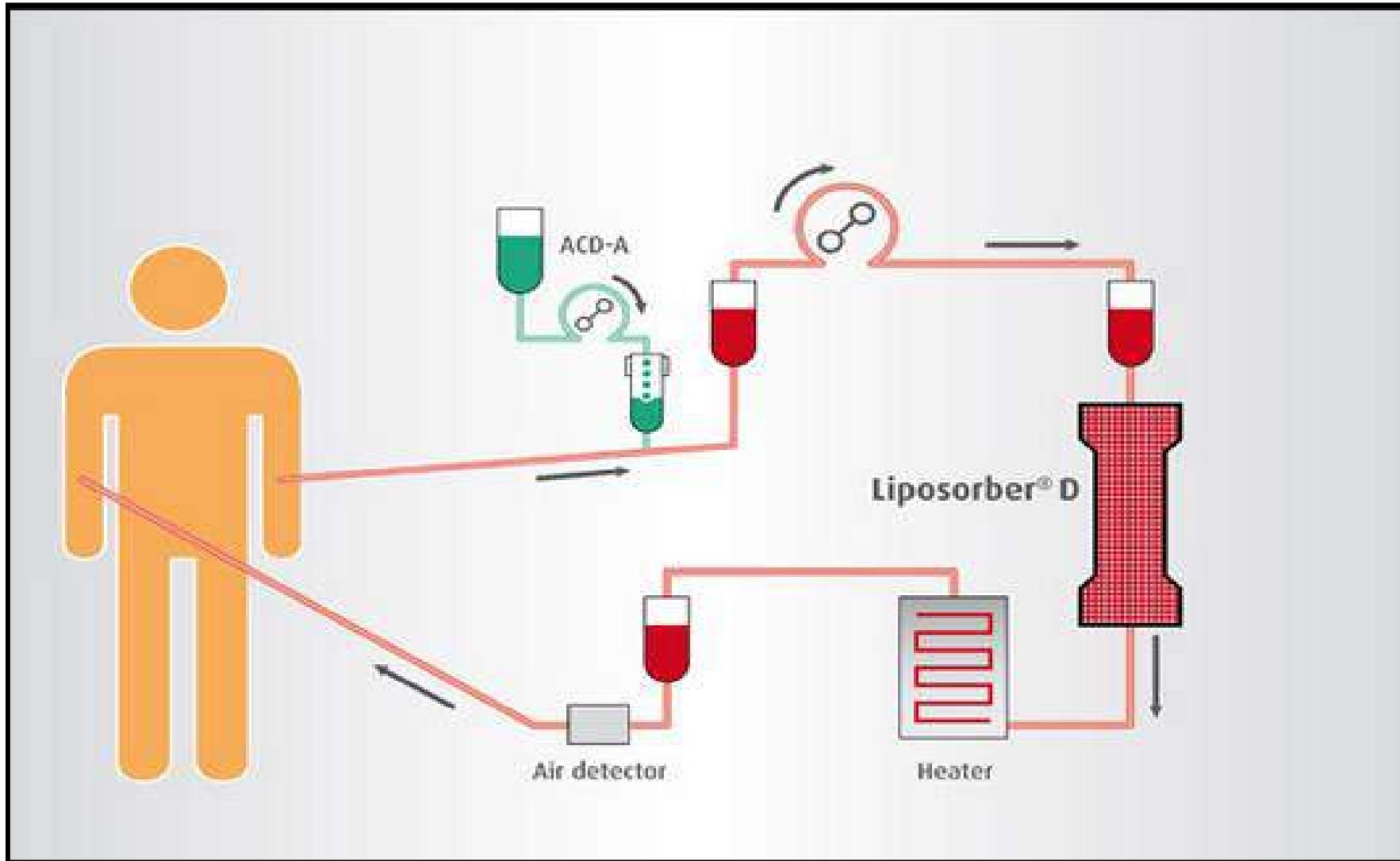
80 % LDL-ch

75 % lipoprotein (a)

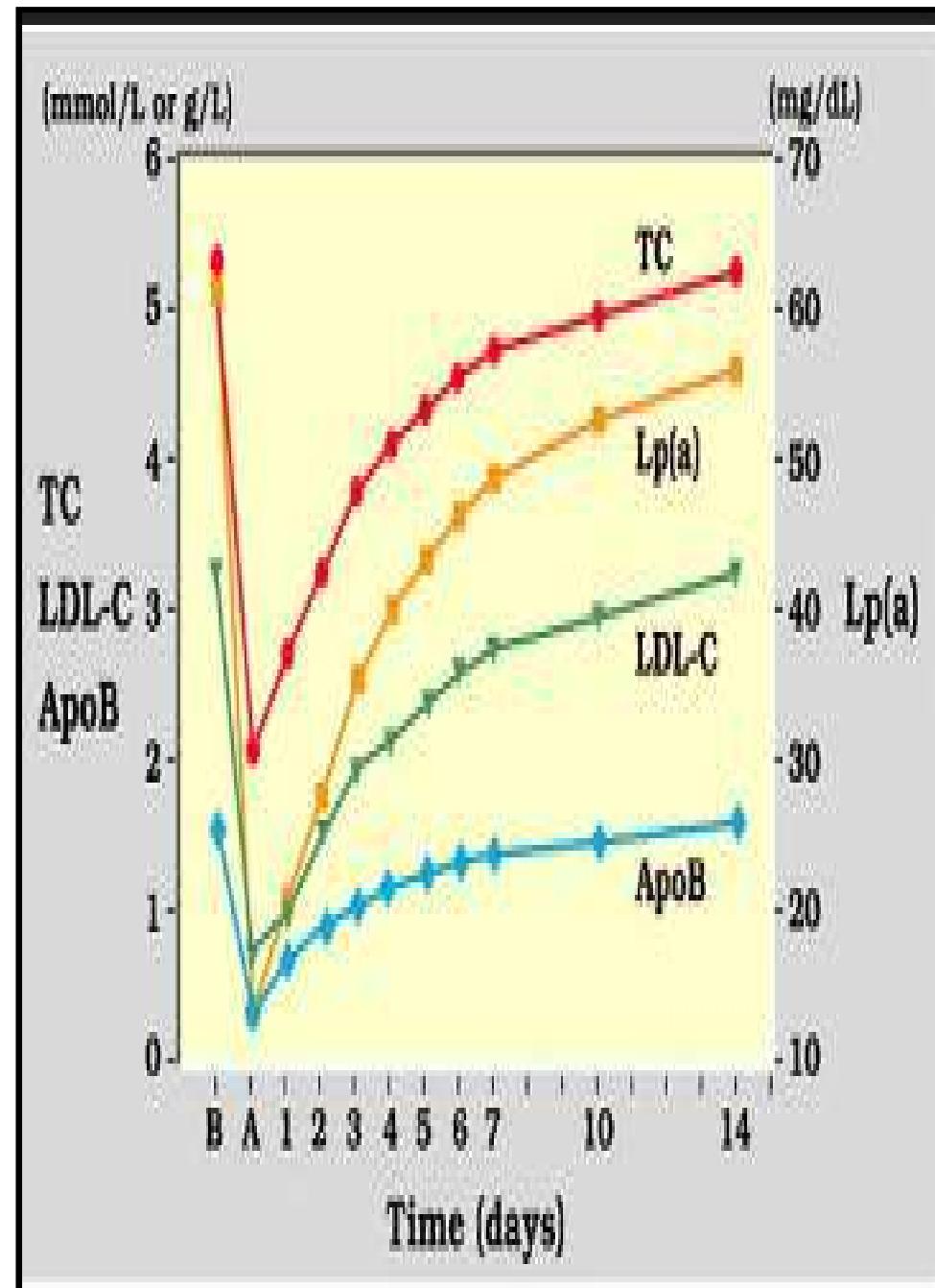
50 % triglycerides



Liposorber D (ολικό αίμα)



- ✓ Επεμβατικές μέθοδοι
- ✓ 2 φλέβες...
αρτηριοφλεβική
αναστόμωση
- ✓ 1,5-4 ώρες
- ✓ Αντιπηξία
- ✓ Όγκος πλάσματος
αίματος



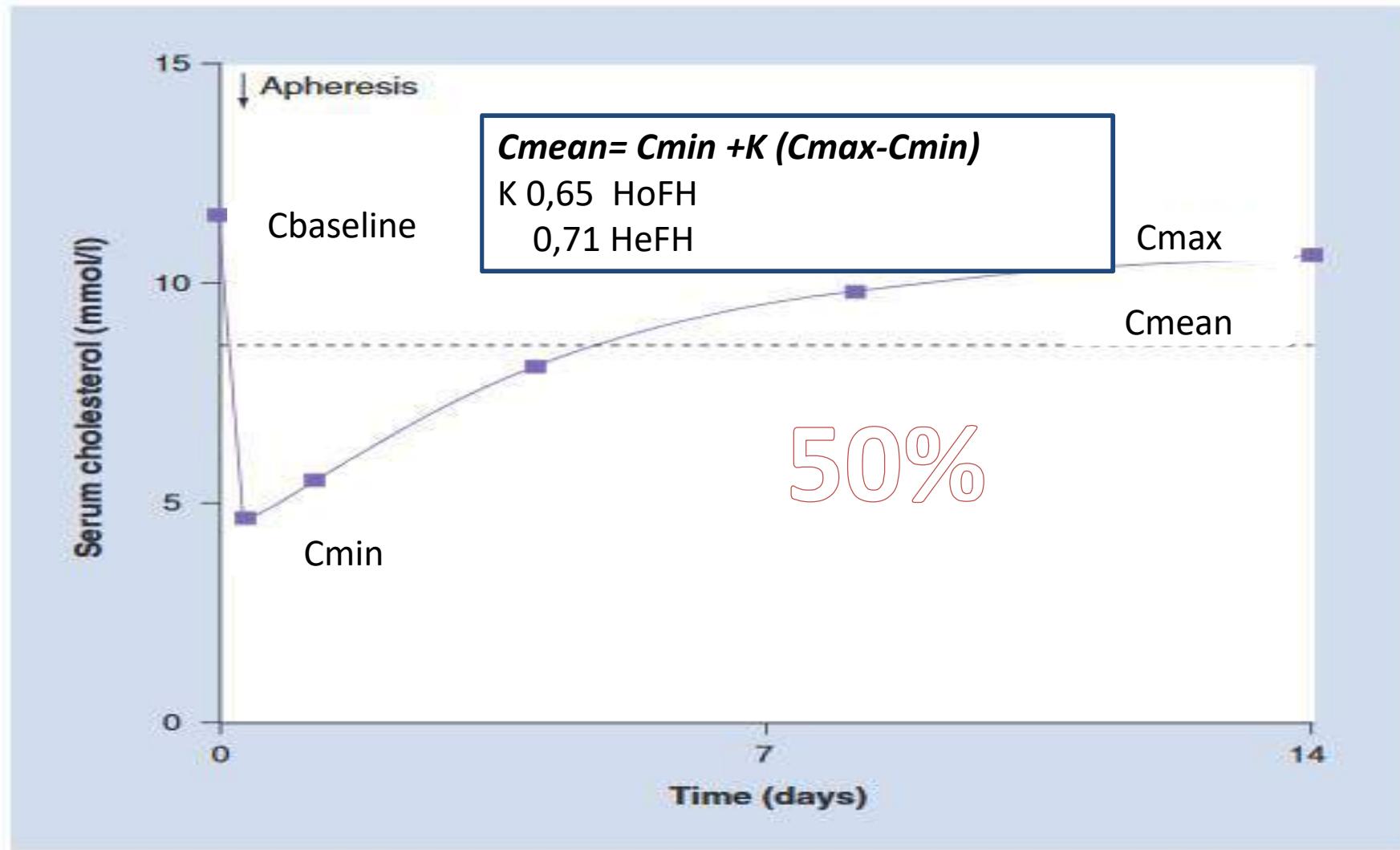
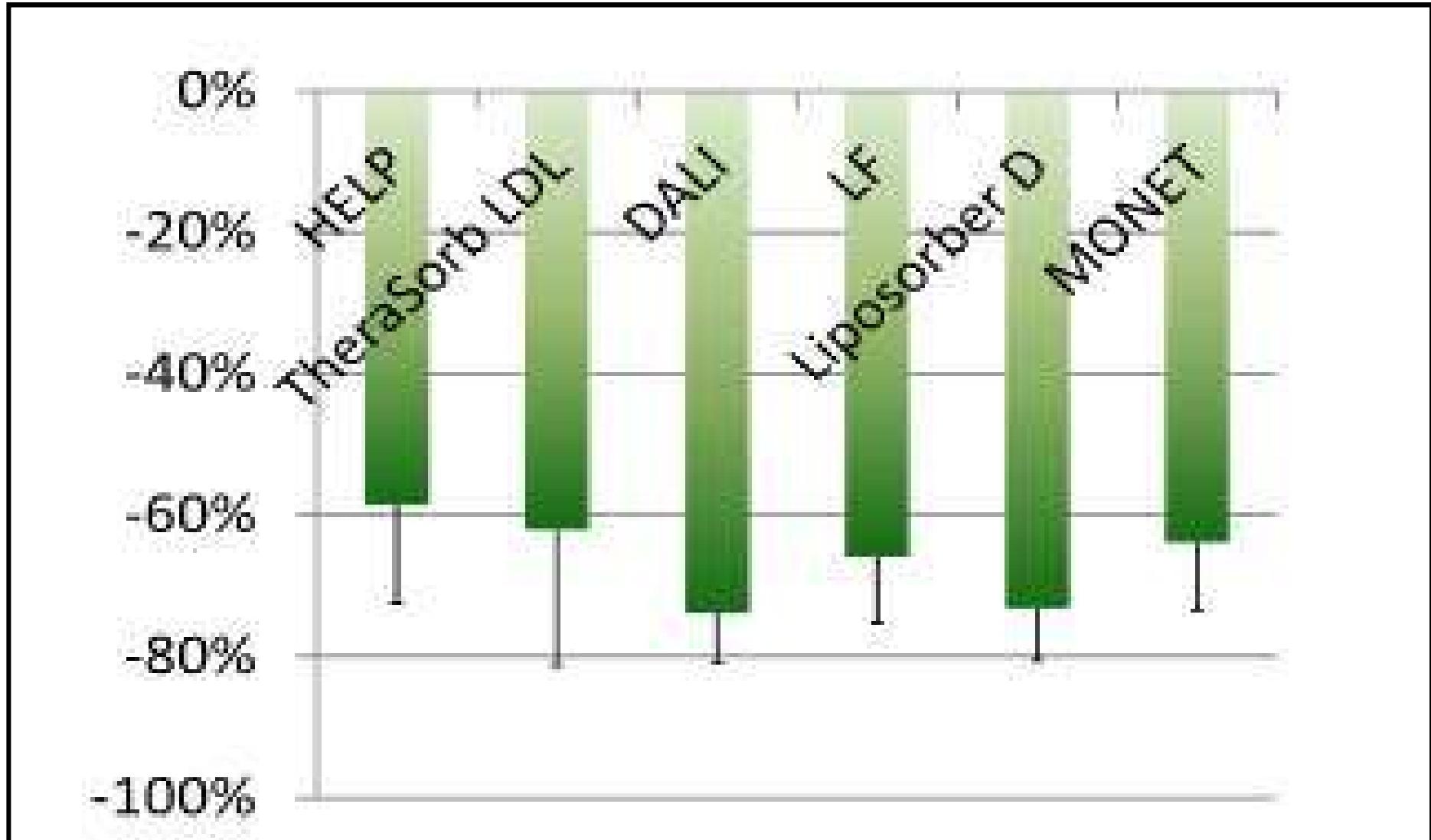


Figure 1. Parameters of the rebound in serum cholesterol during the 2 weeks following an apheresis procedure. C_{mean} is the best index of the average lipoprotein level between consecutive procedures.
 C_{baseline} : Baseline value; C_{max} : Maximum value; C_{mean} : Interval mean; C_{min} : Minimum value.

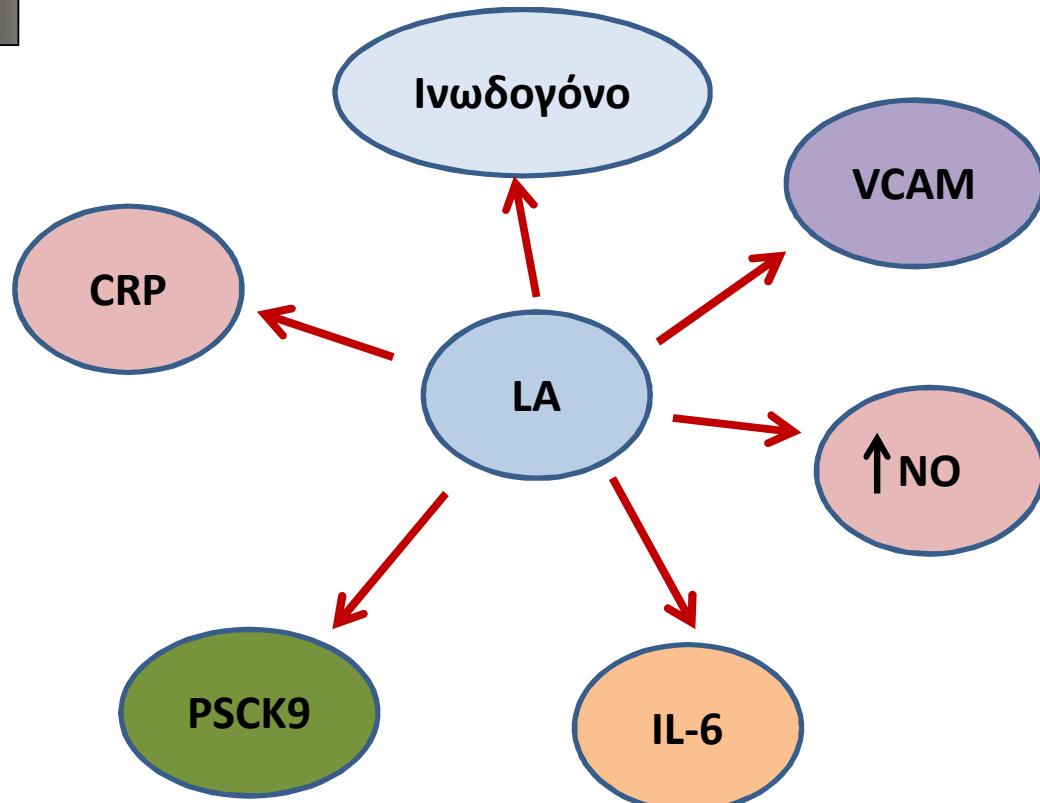
Μείωση LDL



Julius et al, Therapeutic Apheresis and Dialysis 2013



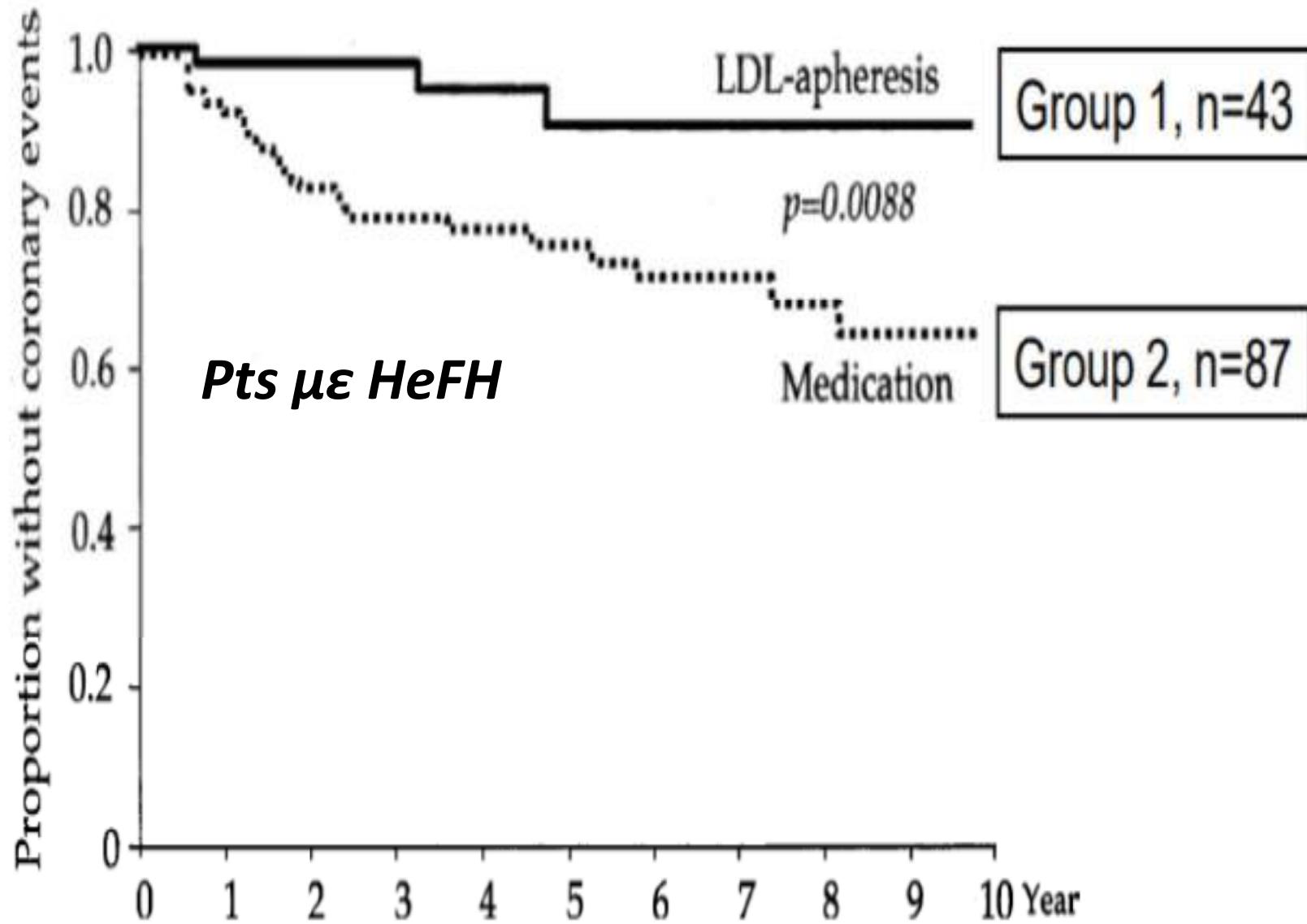
Πλειοτροπικές δράσεις της LA



- ✓ Βελτίωση της αιματικής ροής
- ✓ Θετική επίδραση στο ενδοθήλιο

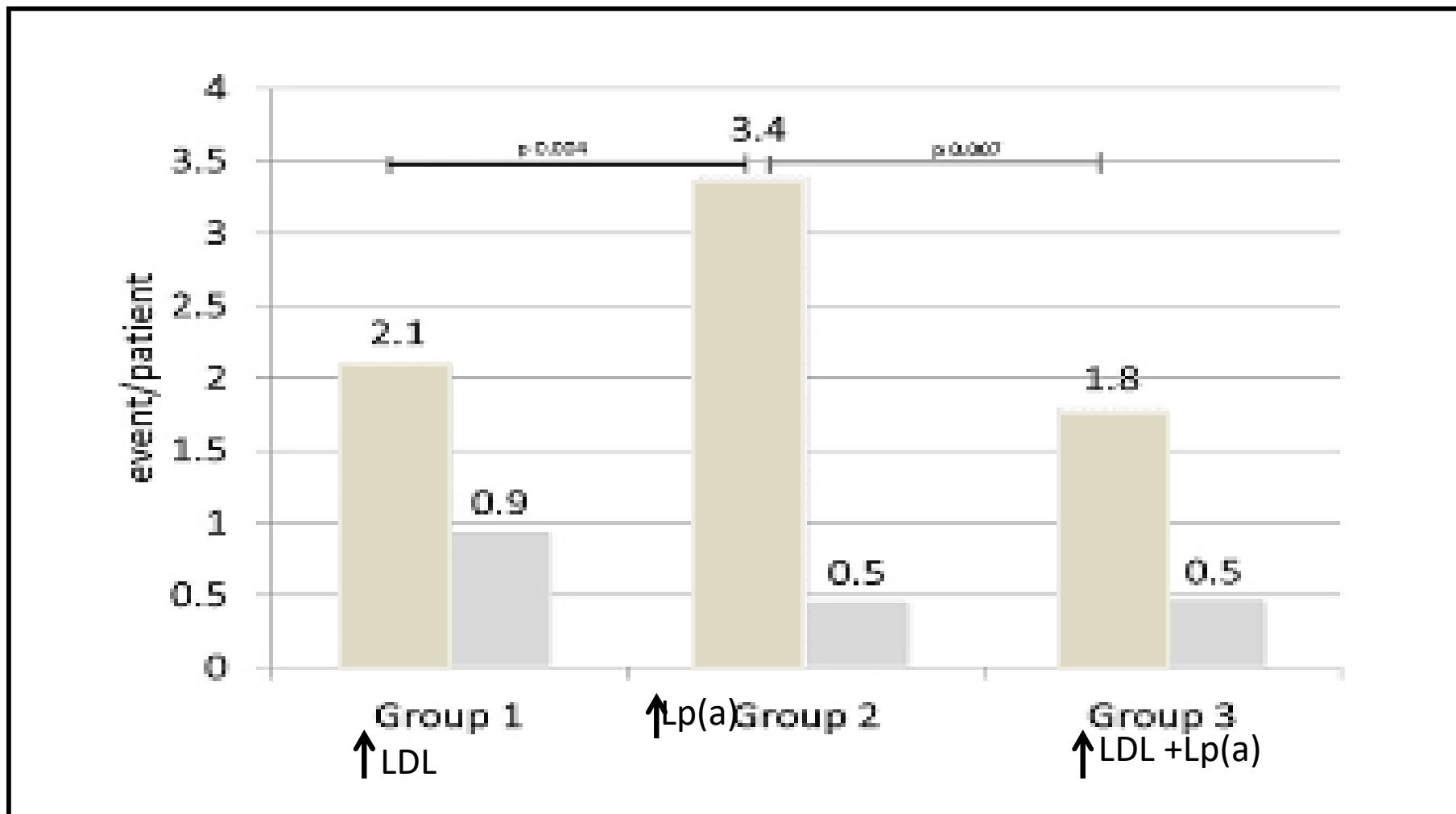
Βελτίωση κλινικών εκδηλώσεων αθηρωμάτωσης;

Stefanutti et al, J Clinical Lipidology 2018



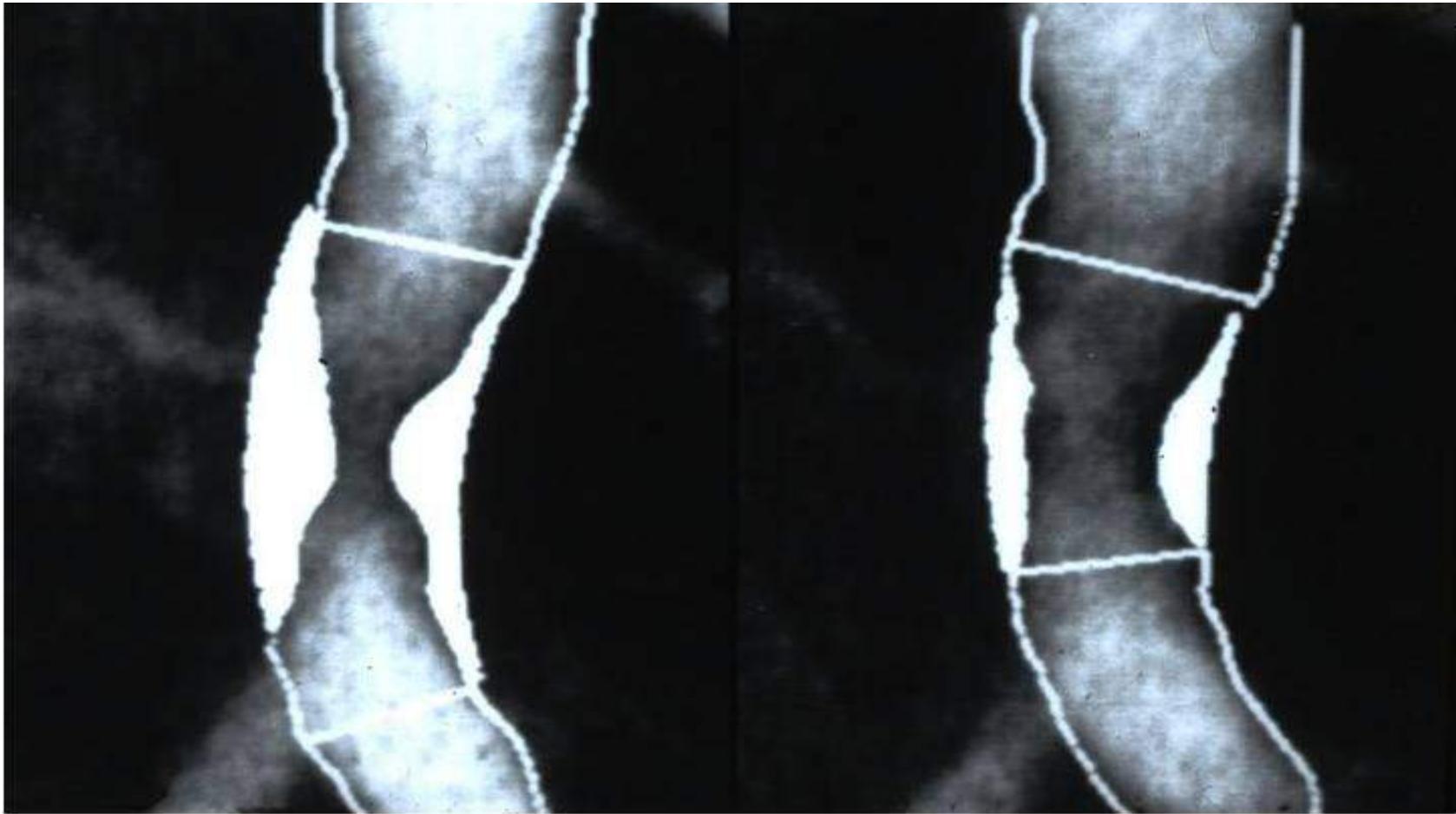
Mabuchi et al, Atherosclerosis 1987

Differences in the atherogenic risk of patients treated by lipoprotein apheresis according to their lipid pattern



Αγγειογραφικά δεδομένα

Μελέτη	Ασθενείς	Μέθοδος	Αποτελέσματα
L-CAPS	25pts HeFH 11 pts	LA+ Simvastatin Simvastatin	Εξέλιξη: 8% vs 64% Σταθεροποίηση: 76% vs 36% Υποστροφή: 16% vs 0
LARS	37pts 7HoFH 25HeFH 5 HCH	Dextran Sulfate LIPOSORBER-LA15	Εξέλιξη :14% Σταθεροποίηση: 38% Υποστροφή: 38%
HELP-Study Group	39/51	HELP	Διατήρηση βλαβών : 57,8% Εξέλιξη βλαβών : 15,5% Υποστροφή : 26,7%
LAARS	42 2 ομάδες	LA Φαρμακευτική αγωγή	Σταθεροποίηση των βλαβών και στις δύο ομάδες

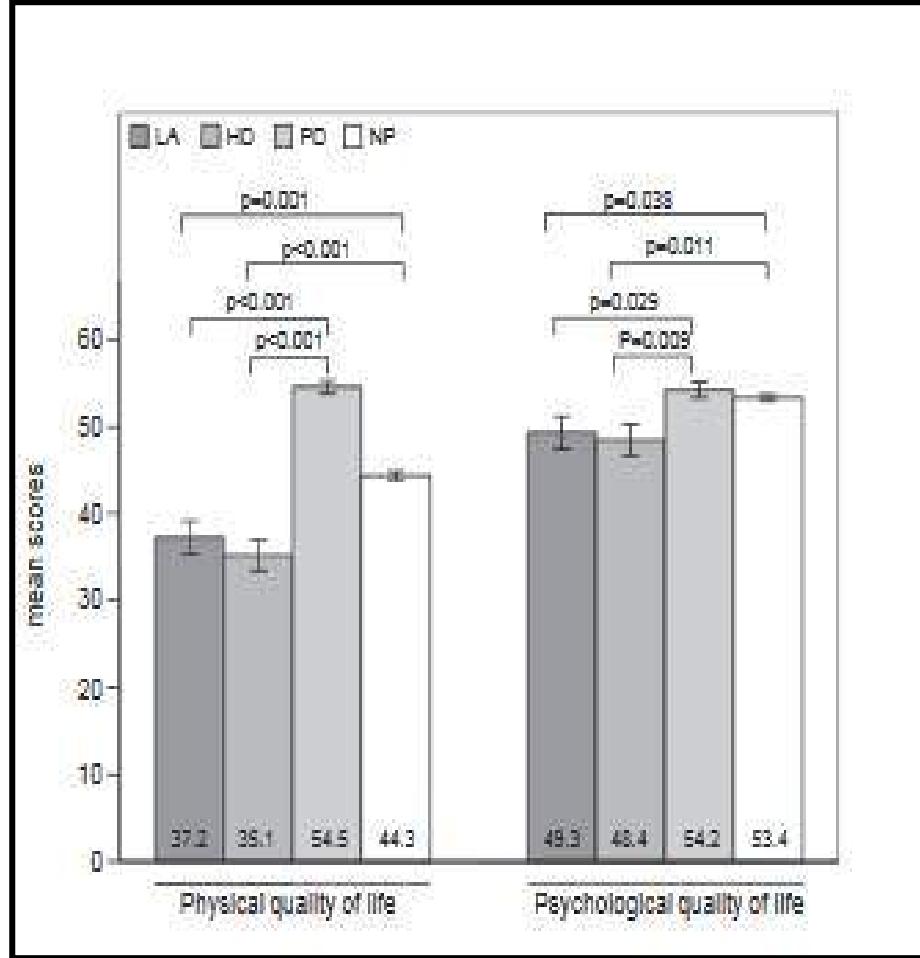


Βελτίωση αιματικής ροής, μείωση του επιπέδου ασβεστοποίησης, βελτίωση περιφερικής αγγειοπάθειας, υποστροφή ξανθωμάτων και των στενώσεων των καρωτίδων και καθυστέρηση της εξέλιξης της αορτικής στένωσης

LA

Αντενδείξεις διενέργειας LA

- ✓ Αδυναμία αγγειακής προσπέλασης
- ✓ Σοβαρή καρδιακή ανεπάρκεια
- ✓ Ανθεκτική υπέρταση
- ✓ Μη συμμόρφωση
- ✓ Μικρό προσδόκιμο επιβίωσης
- ✓ Κακοήθεια
- ✓ Ψυχιατρική διαταραχή



Stasiewski et al, Atheroscl Suppl 2015

FDA	Heart UK	Γερμανία	Ιταλία
<ul style="list-style-type: none"> ✓ HoFH με LDL > 500 mg/dl ✓ HeFH με LDL ≥ 300 mg/dl χωρίς ιστορικό καρδιαγγειακής νόσου ✓ HeFH με LDL ≥ 200 mg/dl με ιστορικό καρδιαγγειακής νόσου 	<ul style="list-style-type: none"> ✓ HoFH με αδυναμία μείωσης της LDL >50% με συμβατική αγωγή ή CHOL >350 ✓ HeFH ή σοβαρή HCH με προοδευτική επιδείνωση ΣΝ και LDL ≥ 194 mg/dl ή μείωση <40% με αγωγή 	<ul style="list-style-type: none"> ✓ HoFH ✓ Σοβαρή HCH χωρίς βελτίωση με μέγιστη αγωγή για ένα χρόνο 	<ul style="list-style-type: none"> ✓ HoFH με LDL ≥ 300 mg/dl ✓ HeFH με LDL ≥ 300 mg/dl ✓ HeFH με LDL ≥ 200 mg/dl και στεφανιαία νόσο ✓ HCH με δύο από τα παρακάτω: <ul style="list-style-type: none"> 1. Μη ανταπόκριση στη θεραπεία 2. Νέα επειδόσιο αγγειοπλαστικής 3. Μεταμόσχευση καρδιάς 4. Σοβαρή αθηροσκλήρυνση

+ Lipoprotein(a) + Heart disease

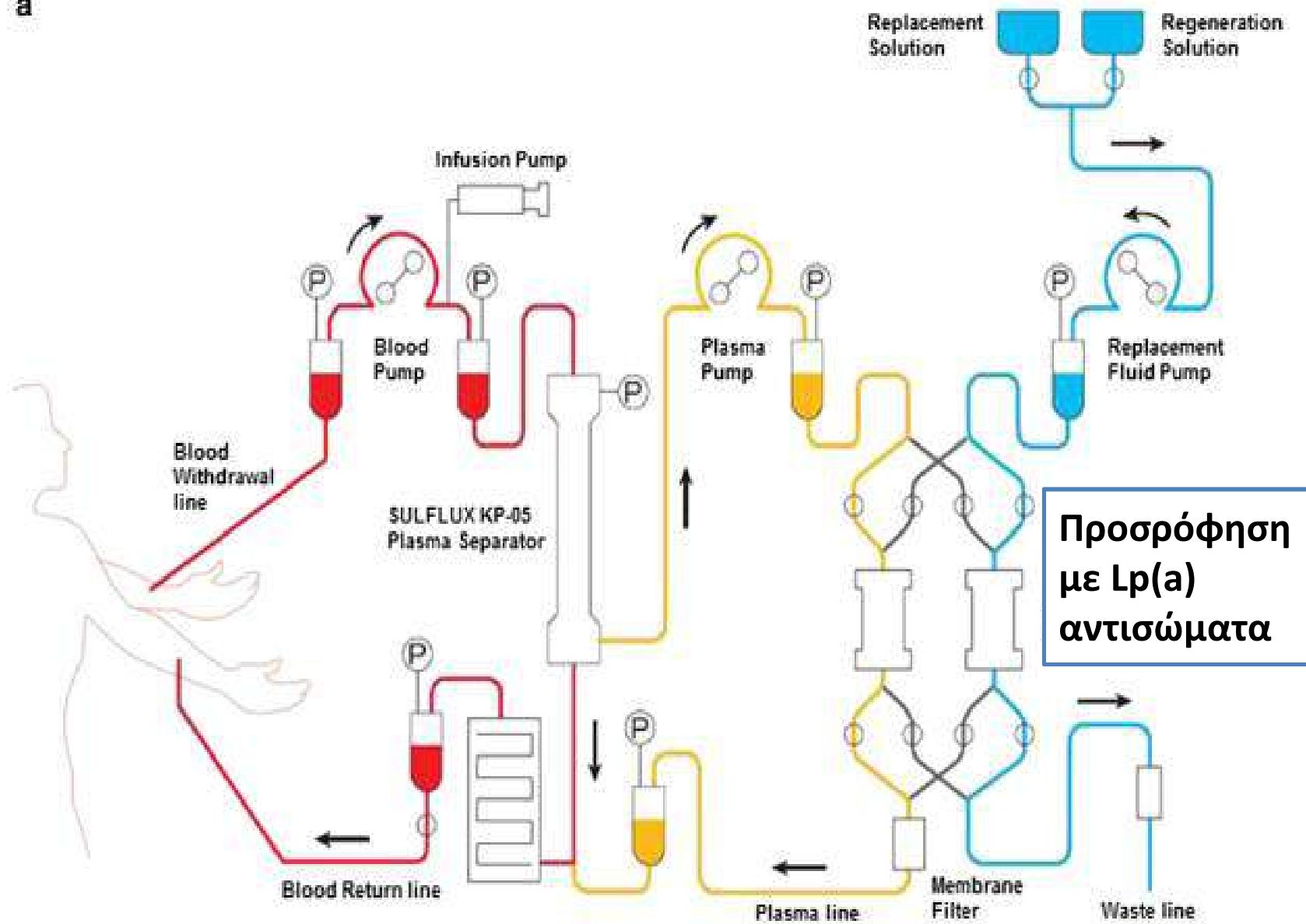


**1 in 14 heart attacks and 1 in 7 cases of aortic valve disease
are due to Lipoprotein(a) cholesterol.**

Μελέτες για Lp(a)- αφαίρεση

Μελέτη	Pro(a)LiFe, Leebmann et al. 2013	Jaeger et al. 2009	Rosada et al. 2014
Περίοδος μελέτης	LA 2008–2010	LA > 3m	LA μεταξύ 1995–2010
Κριτήρια	Lp(a) > 60mg/dl και εξέλιξη καρδιαγγειακής βλάβης παρά τον έλεγχο LDL	Lp(a) > 60mg/dl και εξέλιξη καρδιαγγειακής βλάβης παρά τον έλεγχο LDL	Lp(a) > 60mg/dl με ιστορικό CVE και τουλάχιστον ένα ακόμα επεισόδιο παρά τον έλεγχο LDL
Μείωση CVE	Από 0,42 επεισόδια ανά ασθενή / έτος σε 0,09	Από 0,45 επεισόδια ανά ασθενή / έτος σε 0,10	Από 0,35 επεισόδια ανά ασθενή / έτος σε 0,08

a



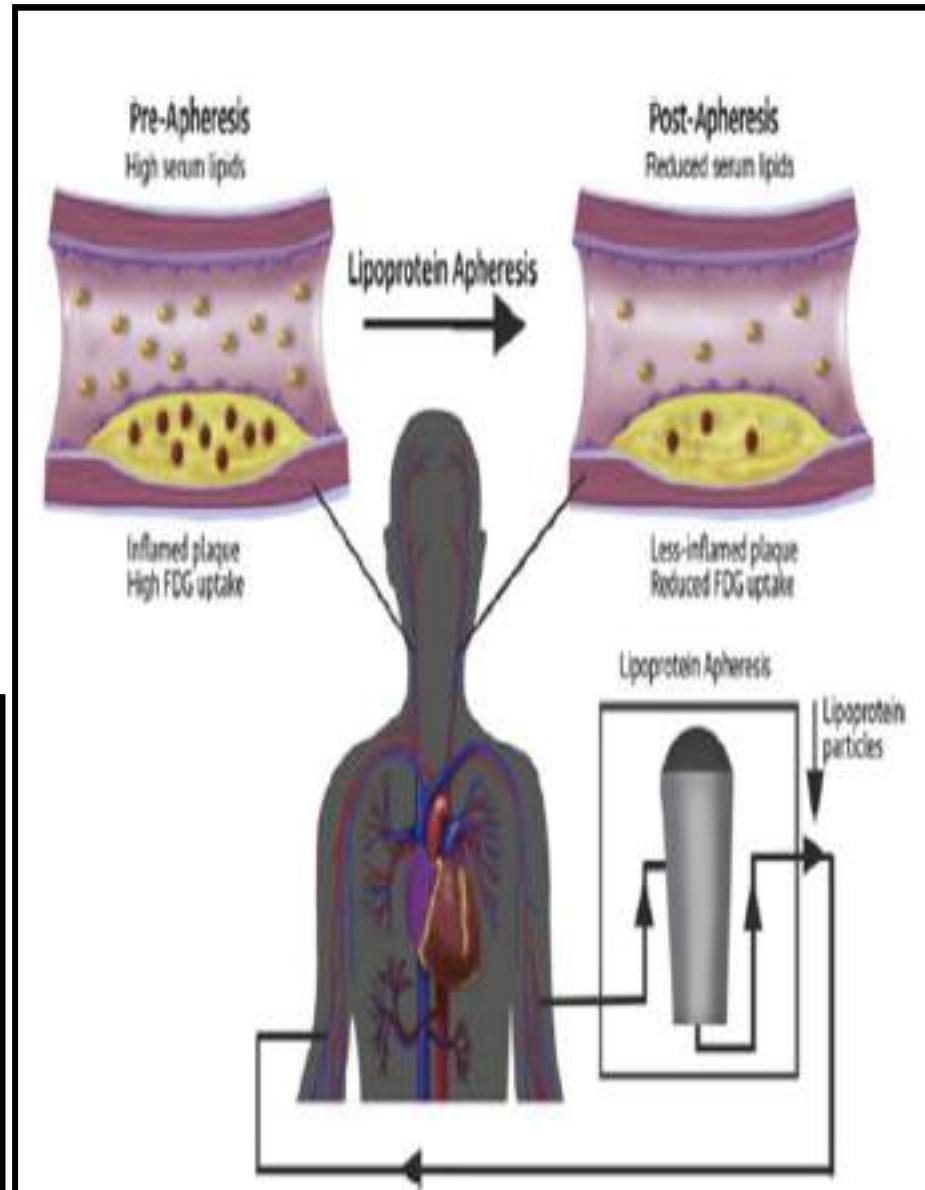
Γερμανία	12/10⁶
Σουηδία	3/10⁶
Ιταλία/ Γαλλία	2/10⁶
Αγγλία	0,6/10⁶
ΗΠΑ	1,3/10⁶

Table 3 LA centers, physicians, and patients in Germany in 2013–2015

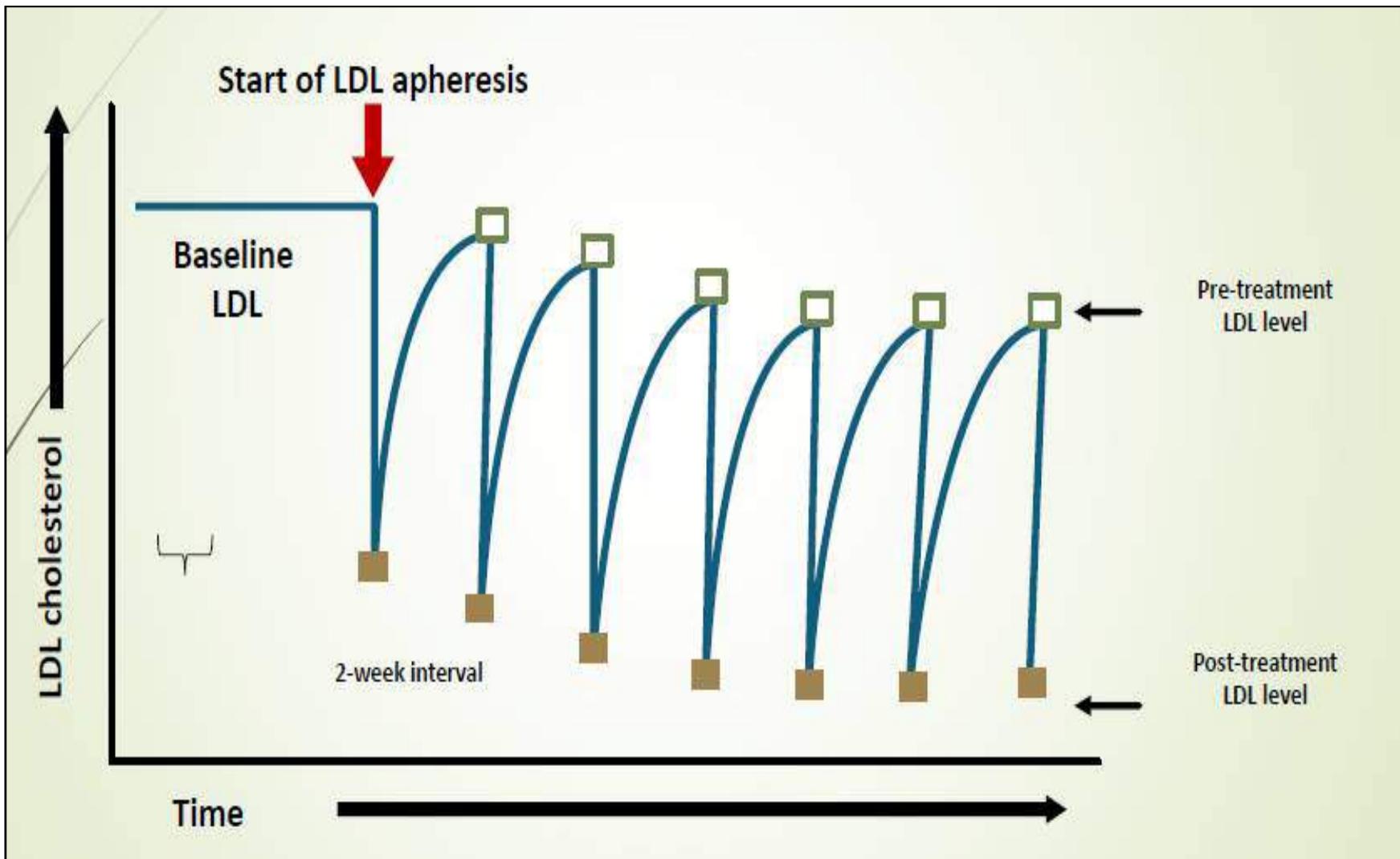
	2013 ^a	2014 ^a	2015 ^b
Centers	218 ^a	325 ^a	378 ^b
Physicians	962 ^a	1,096 ^a	Not known
Patients	2,161 ^a	2,546 ^a	3,197 ^b

Notes: ^aData from Quality report of the National Association of Statutory Health Insurance Physicians (KBV).^{19,49} ^bPreliminary data (personal communication, 2015).

Abbreviation: LA, lipoprotein apheresis.



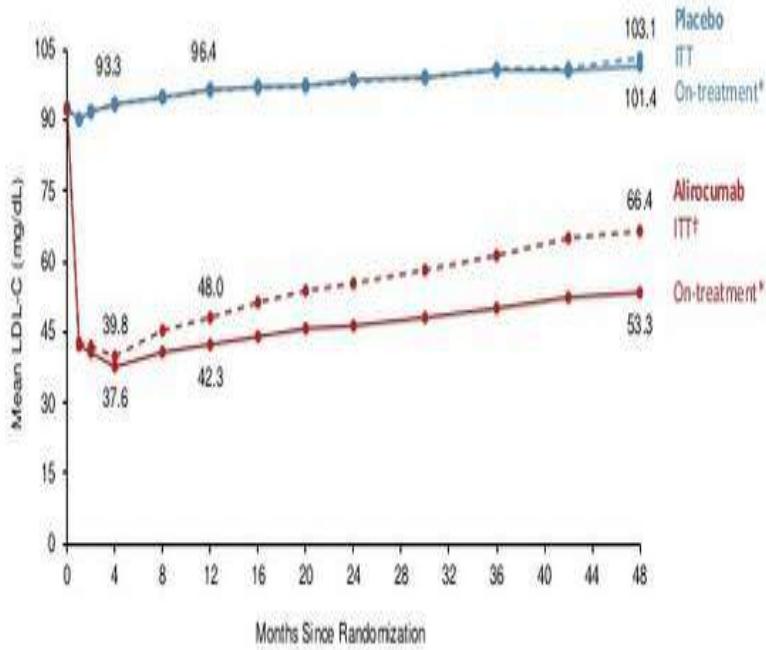
Κόστος





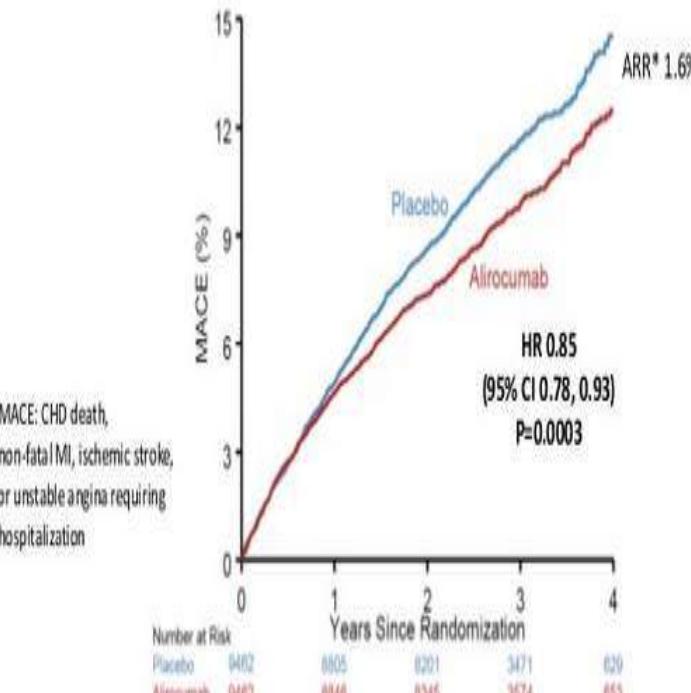
PCSK9 inhibitors

LDL-C: ITT and On-Treatment Analyses



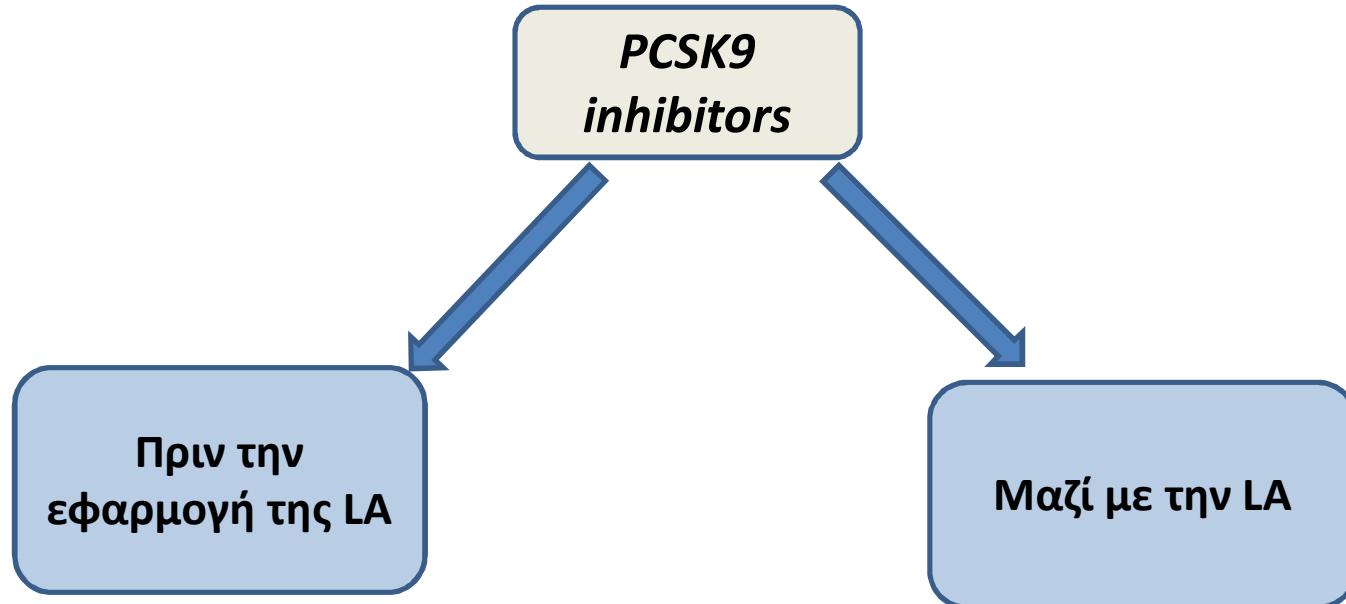
ODYSSEY
OUTCOMES 12

Primary Efficacy Endpoint: MACE

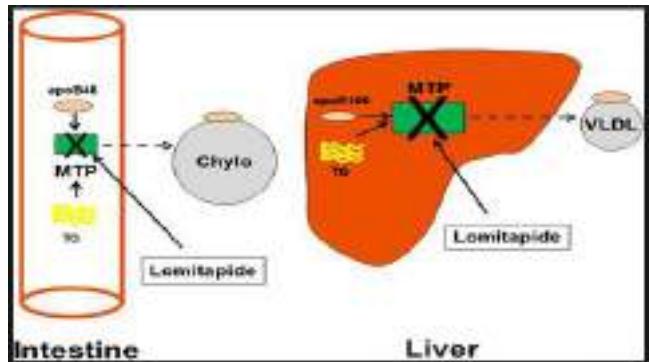


*Based on cumulative incidence

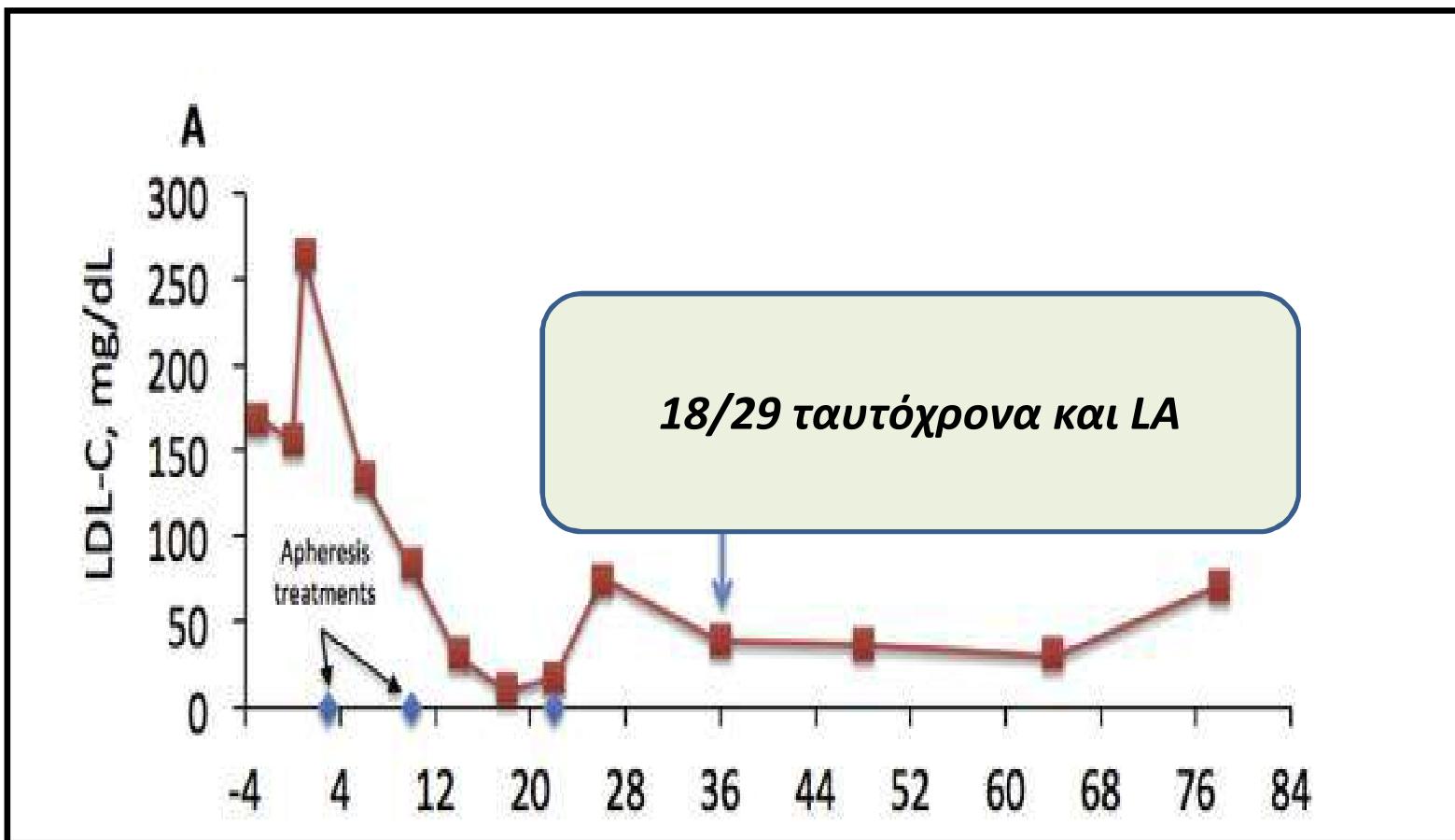
ODYSSEY
OUTCOMES 13



PCSK9 inhibitors και ΛΑ σε σοβαρή ΗCH

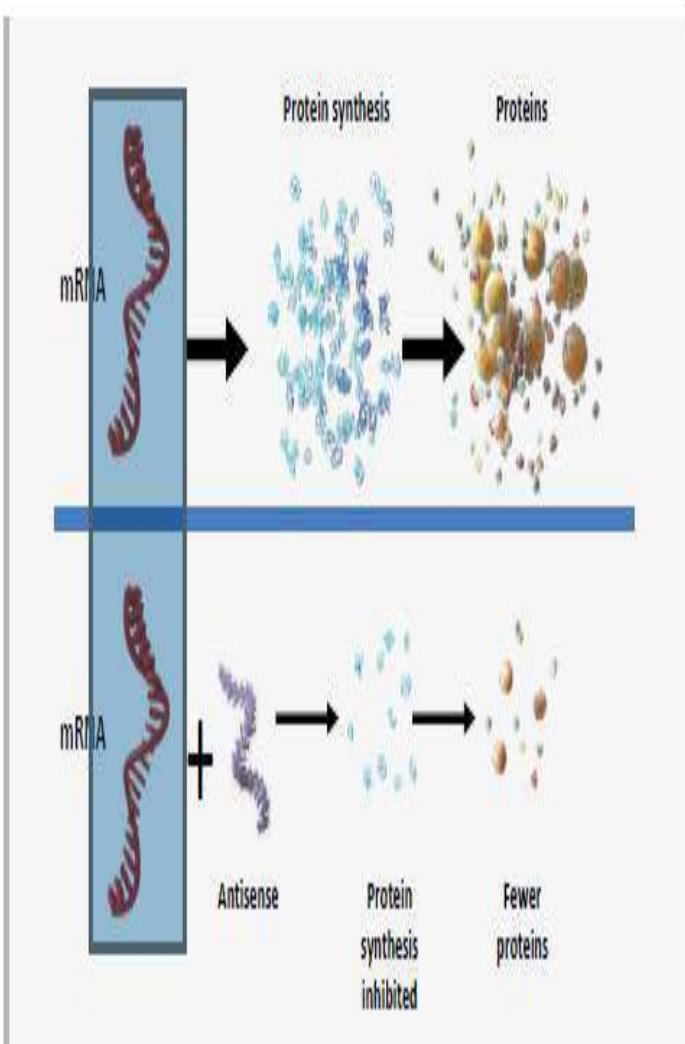


Microsomal Transfer Protein inhibitors (lomitapide)



Cachel et al, J Lancet 2013

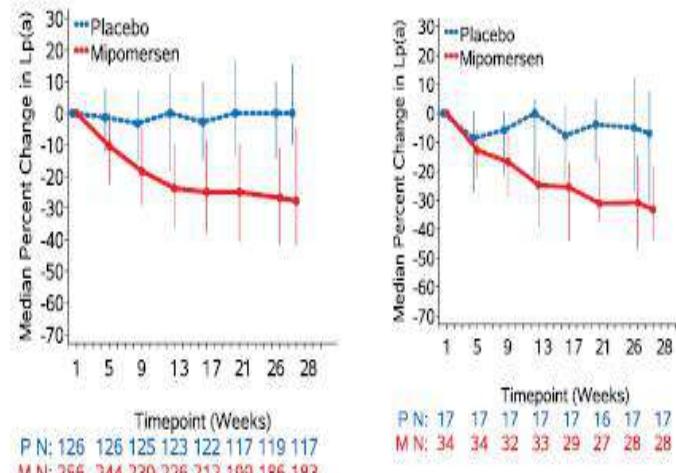
Antisense Oligonucleotide against apo(a) (mipomersen)



Mipomersen, an Antisense Oligonucleotide to Apolipoprotein B-100, Reduces Lipoprotein(a) in Various Populations With Hypercholesterolemia

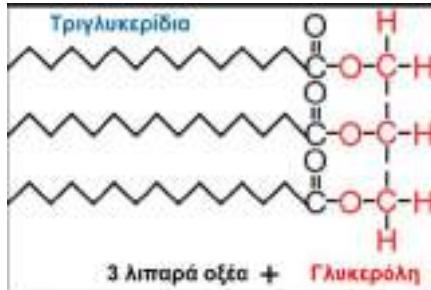
Results of 4 Phase III Trials

Raul D. Santos, Frederick J. Raal, Alberico L. Catapano, Joseph L. Witztum,
Elisabeth Steinhagen-Thiessen, Sotirios Tsimikas



Pooled Population

Homozygous FH



Υπερτριγλυκεριδαιμία

<i>Diseases</i>	<i>Heredity conditions</i>	<i>Medications</i>
<ul style="list-style-type: none"> · Uncontrolled diabetes · Hypertension · CHD · Acute hepatitis · Hepatic disease · Hypothyroidism · Renal disease · Acromegaly · Lipo-dystrophies · Cushing's syndrome · Polycystic ovary Syndrome (PCOS) 	<ul style="list-style-type: none"> -Familial hypertriglyceridemia -Familial dysbeta lipoproteinemia -Familiar lipoprotein lipase deficiency -Type III hyper-lipoproteinemia -Type V hyper-lipoproteinemia 	<ul style="list-style-type: none"> · Antiretroviral drugs · Beta-blockers · Oral contraceptives · Cyclosporine · Diuretics · Estrogen replacement therapy · Glucocorticoids · Antipsychotics · Progesterone · Retinoids · Steroids · Tamoxifen

HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18/100,000/yr		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients: 100–300	RCT 0	CT 1(20)	CS 16(235)	CR 38(39)

TABLE 1. Current available studies on the use of apheresis in the treatment of severe hypertriglyceridemia (sHTG) (only studies with patients n ≥ 10)

Reference	Patients included	Plasma exchange methods	Significant reduction of tryglicerides
Stefanutti et al. (34)	17	Albumin	By 61%
Yeh et al. (22)	18	FFP and albumin, double membrane filtration	By 66% (first setting) and by 83% (second setting)
Yeh et al. (21)	17	FFP and albumin	Significant reduction
Chen et al. (20)	94	FFP and albumin	n.a.
Gubensek et al. (22)	50	Albumin	Significant reduction
Kyriakidis et al. (6)	10	FFP	By 62%

FFP, fresh-frozen plasma; n.a., not available. Reproduced from Ewald and Kloer (20) with kind permission from Springer Science+Business Media.



Κυτοκίνες
Αναπληρώνει την LpL

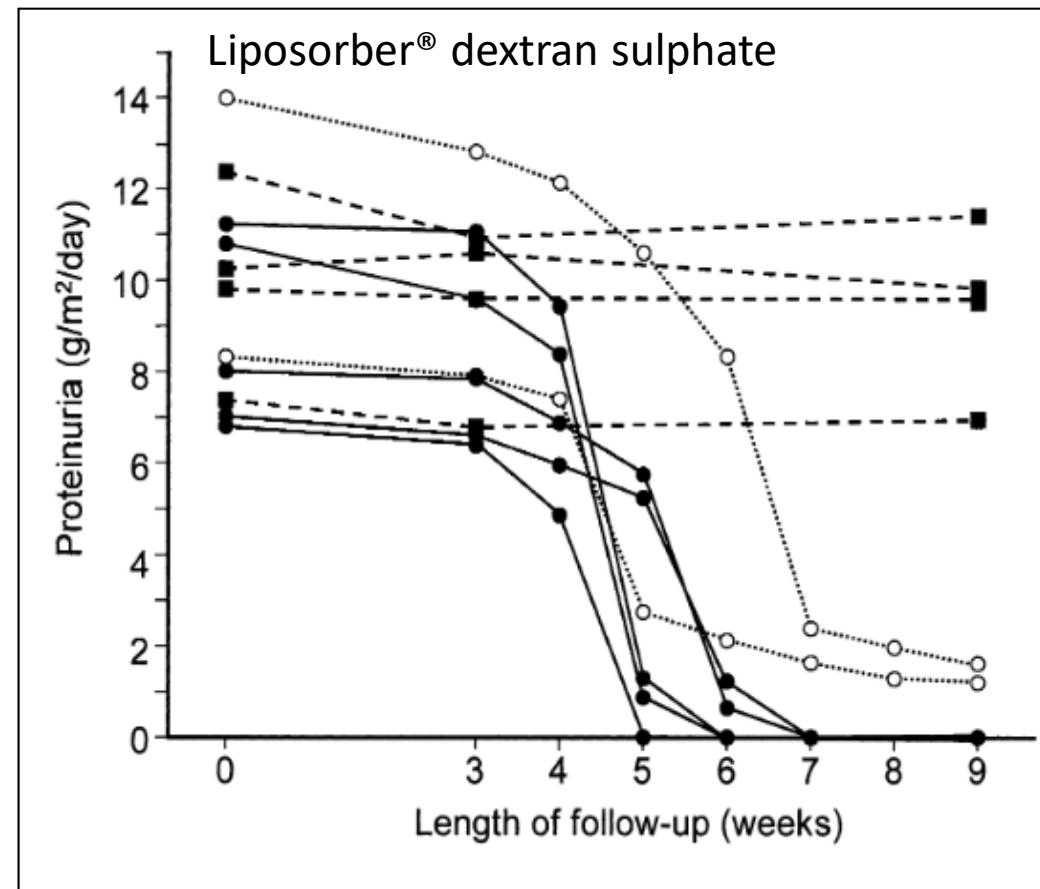
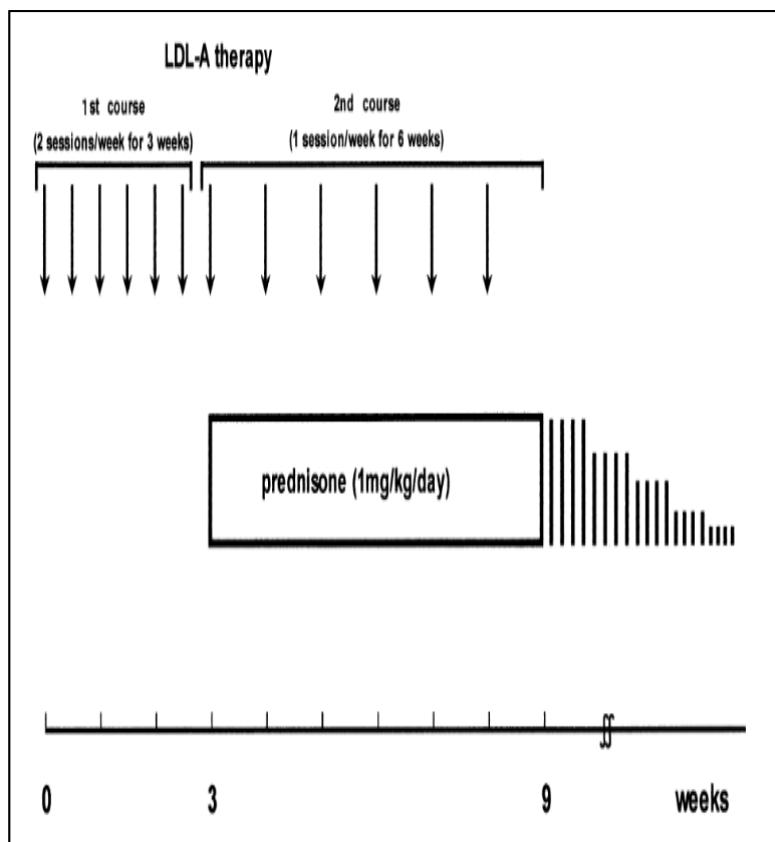
Δεν διαφοροποιεί τη θνητότητα

Volume treated: 1–1.5 TPV
Replacement fluid: Albumin, plasma

Frequency: Therapeutic: daily for 1–3 days depending upon patient course and TG level; Prophylactic: every 2–4 weeks to maintain TG level < 150 mg/dL

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Incidence: 7/1,000,000	Indication	Procedure	Recommendation	Category
	Recurrent in transplanted kidney	TPE	Grade 1B	I
	Steroid resistant in native kidney	LDL Apheresis	Grade 2C	III
No. of reported patients: >300	RCT	CT	CS	CR
Recurrent in transplanted kidney	0	3(48)	49(224)	15(17)
Steroid resistant in native kidney	0	0	1(11)	4(4)



Μείωση
ινδογόνου,
αύξηση NO

Hyperlipidemia · Hypercholesterolemia Abnormal Lipoproteins

↓ Adiponectin, ↑ TNF- α ,
↑ Resistin, ↑ MCP-1, ↑ PAI-1, ↑ RAS

Mesangial Cell Proliferation

Lipoprotein Deposition
in Glomerulus

Lipiduria

Increased Mesangial Matrix

Macrophage Activation

Tubulointerstitial Injury

↑TGF- β , ↑PAI-1,
↑TNF- α , ↑IL-6

↑ROS

Interstitial Fibrosis

Glomerulosclerosis

vascular
endothelium
injury

Atherosclerosis
Hypertension

Progressive Renal Disease

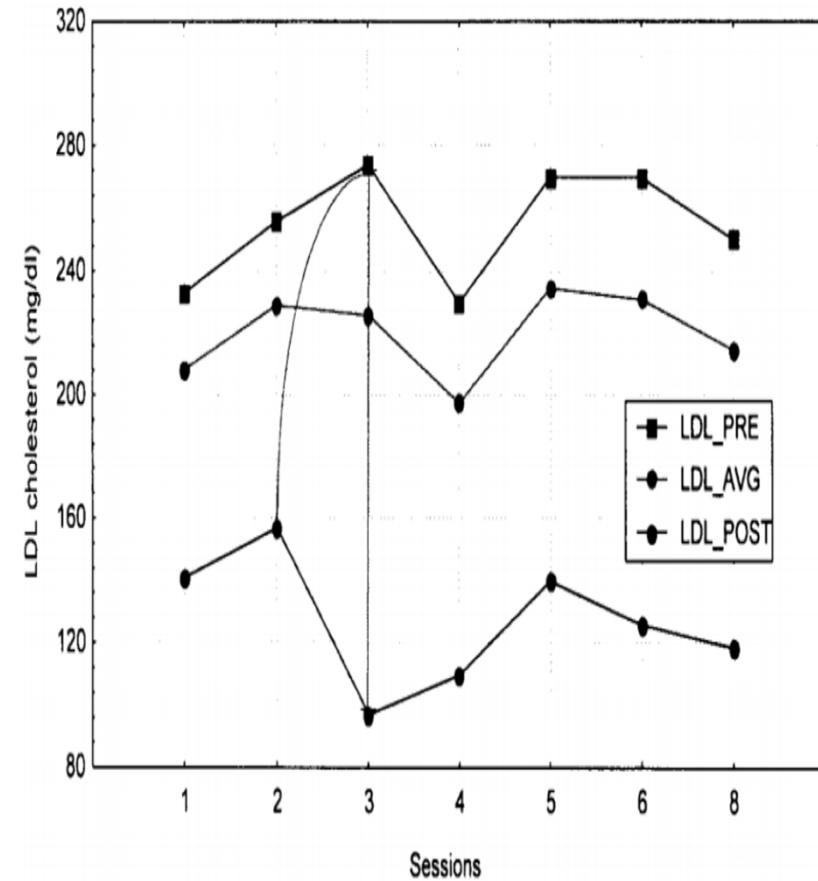
Table 2 Clinical efficacy of LDL-apheresis for nephrotic syndrome (Summary of Clinical Studies before 2007)

Muso et al. Nephron 2001 89 408-415	Stenvinkel et al. Eur J Clin Invest 2000 30 866-870	Yokoyama et al. Clin Nephrol 1998 50 1-7	Muso et al. NDT 1994 9 2257-264	Sakai et al. Jin To Touseki 1994 33 321-328	Hattori et al. Am J Kidney Dis 42 1121-1130
Study design	Study Group: prospective	Prospective	Retrospective	Retrospective	Prospective
No. of cases (control group)	Control group: retrospective 17 (10)	7 (none)	14 (none)	8 (none)	16 (none)
Primary disease (no. of cases)	FSGS (14/9) MCNS(3/1)	MN (3) MCNS(2) IgAGN (1)	FSGS (14) PSL resistant	FSGS(6) MCNS (1) MN + FSGS (1)	FSGS (13) MN (3)
No. of Treatment	2/w × 3 1/w × 6 Total 12	2/w × 3 1/w × 7 Total 13	2/w × 3 Total 6	2-13 7.3 (average)	2/w × 3 Total 6 1/w × 6 Total 12
Concomitant treatment (no. of cases)	PSL 1.0 mg/kg	none (4) PSL(1) PSL + CyA (2)	PSL 0.8 mg/kg	PSL/pulse 1.0 mg/kg	PSL (14) immunosuppressant (10)
Clinical efficacy	Remission 9 Partial remission 4 no effect 4	Remission 2 Partial remission 4 no effect 1	Responded 8 no effect 6	Remission 4 Partial remission 1 no effect 3	Improved 7 Unchanged 3 Worsened 3 unjudgemental 3
Efficacy rate	76 %	86 %	57 %	63 %	PSGS 54 %
Summary	Reduced remission induction period	Increased serum albumin	Increased serum albumin Effective in younger age	Amelioration of ApoB deposition in glomerulus 5 in 6 cases	>50 % reduction of proteinuria in 9 cases
					Effective in PSL resistant juvenile patients

LDL apheresis in the treatment of a patient with resistant nephrotic syndrome

**Antonoglou C, Passadakis P, Kriki P, Paraschou A,
Giannatos V, Kantartzis C, Panagoutsos S, Vargemezis V**
*Division of Nephrology, Democritus University of Thrace,
Alexandroupolis*

3 sessions/wk
5 sessions/2wk
2 sessions/3wk
1 session after 4wks



LDL avg derives from integrating the area under the curve (predicted LDL rebound)

"Rare diseases are rare, but rare disease patients are numerous"

