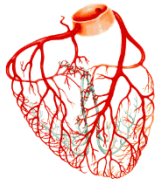
Lipoprotéine (a) et Athérosclérose

Professeur Jean Ferrières

Fédération de Cardiologie et Equipe ARTERRE

INSERM UMR 1295

CHU de Toulouse



Patient en vacances à Bayonne qui après une séance de footing présenté des douleurs thoraciques avec une perte de connaissance accompagnée de convulsions suivies d'un arrêt cardiaque.
Réanimé par son épouse médecin urgentiste avec un low flow pendant 20 minutes.
À l'arrivée du SMUR il bénéficie d'un choc électrique externe avec retour en rythme sinusal et un ECG qui s'inscrit un sous décalage diffus avec un sus-décalage en aVR.
Il est conduit au service de cardiologie de Bayonne où il

bénéficie d'une angiocoronarographie retrouvant une occlusion de l'IVA proximale, une lésion intermédiaire de l'IVA moyenne, une occlusion aiguë de l'IVA distale.
Il a été revascularisé ad hoc sur l'IVA avec mise en place d'un stent.
Pic de troponine à 14 000.
L'échographie de contrôle réalisée à J2 montre une FEVG des 35 à 40 % avec une hypokinésie franche en antérieur et en apical ainsi qu'une hypokinésie de la paroi inféro-septale.
Il a été mis sous traitement de l'insuffisance cardiaque et il a bénéficié d'une LifeVest.
Le patient est par la suite transféré au CHU de RANGUEIL pour la suite de la prise en charge.

Votre patient, **Monsieur** **âgé de 40 ans,** (22/06/1983), a été hospitalisé au sein du Département de Cardiologie Interventionnelle et Structurelle du CHU RANGUEIL, Unité 61 du 03/08/2023 au 07/08/2023 **pour suite de prise en charge d'un ST+ antérieur compliqué d'un ACR**

Le patient n'avait auparavant pas de suivi cardiologique habituel.

Aucun antécédent
- pas d'allergie connue.

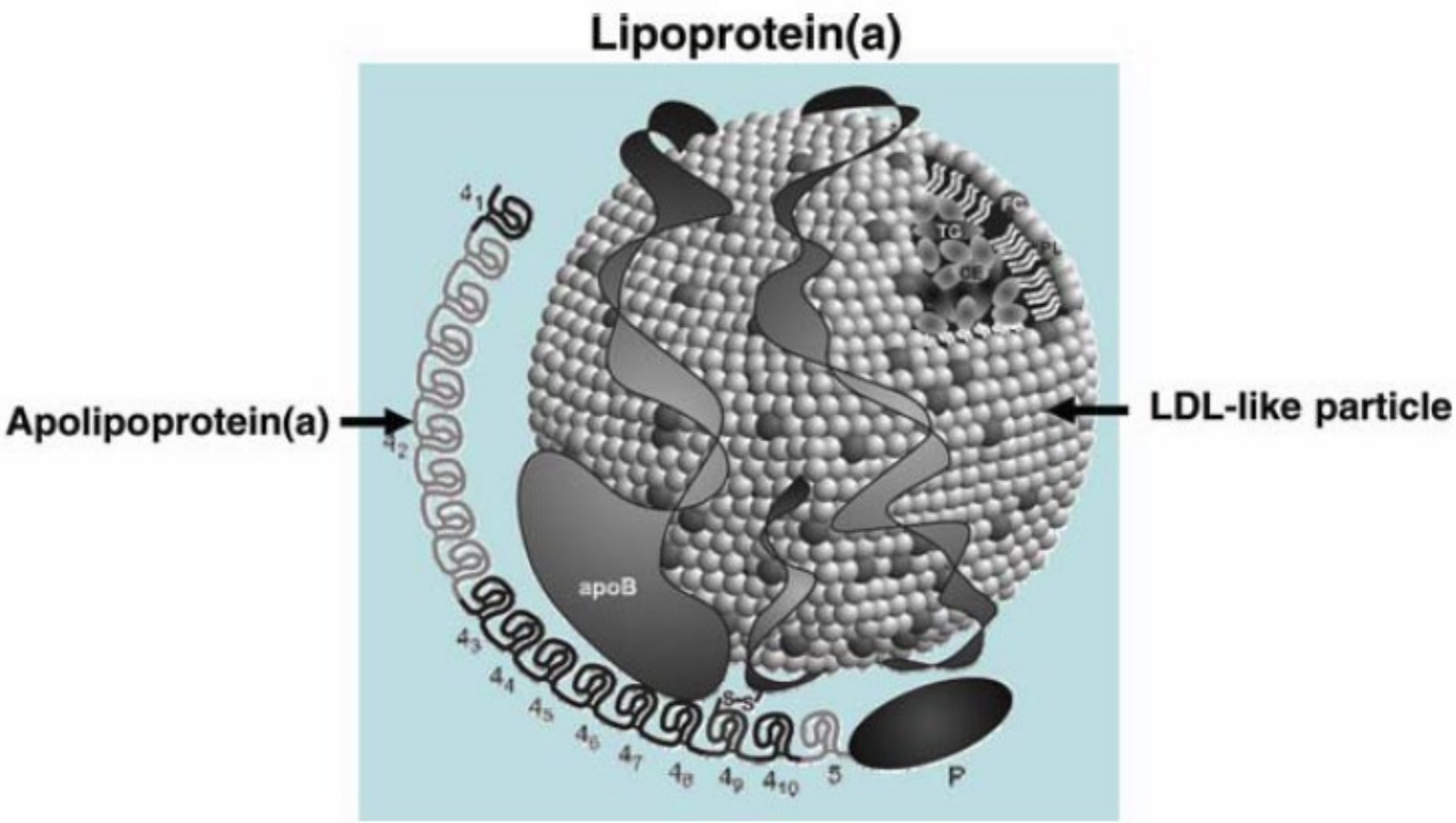
Ses facteurs de risque cardio-vasculaire associent outre son sexe :
- Hérédité cardiovasculaire

° Triglycérides	↑	**2.81**	mmol/l
		soit 2.46	g/l
Technique : Chimie Roche Cobas 8000			
° Cholestérol total		4.77	mmol/l
		soit 1.85	g/l
Technique : Chimie Roche Cobas 8000			
° Cholestérol HDL	↓	**0.87**	mmol/l
		soit 0.34	g/l
Technique : Chimie Roche Cobas 8000			
° Cholestérol VLDL	↑	**1.28**	mmol/l
		soit 0.50	g/l
Technique : Calcul,méth.de Friedwald			
° Cholestérol LDL		2.62	mmol/l
		soit 1.01	g/l
Technique : Calcul,méth.Friedwald si TG<4mmol/l et Planella si 4<TG<10mmol/l *< 4.15 mmol/l (< 1.6 g/l)si pas plus de 2 facteurs de risque.* *< 3.37 mmol/l (< 1.3 g/l)si au moins 3 facteurs de risque.* *< 2.59 mmol/l (< 1 g/l)si antécédents personnels cardio-vasculaires.*			
° Apolipoprotéine A1		1.24	g/l
Technique : Chimie Roche Cobas 8000			
° Apolipoprotéine B		1.13	g/l
Technique : Chimie Roche Cobas 8000			
° Lipoprotéine Lp(a)	↑	**327.20**	nmol/L
		soit 1.36	g/L

La Lipoprotéine (a)

Lipoprotein(a) as a cardiovascular risk factor: current status

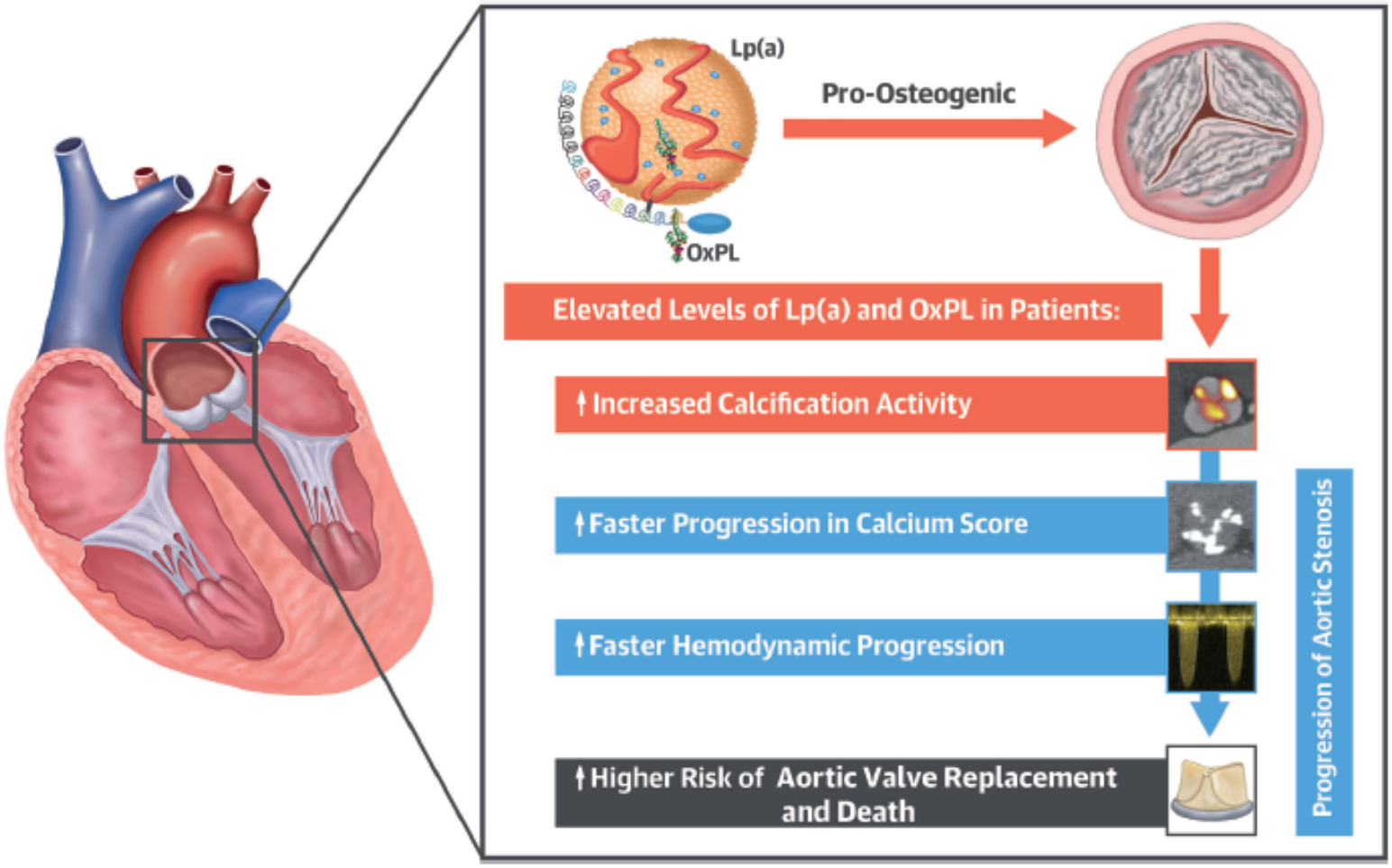
Lipoprotein(a) consists of an LDL-like particle to which apolipoprotein(a) is covalently linked



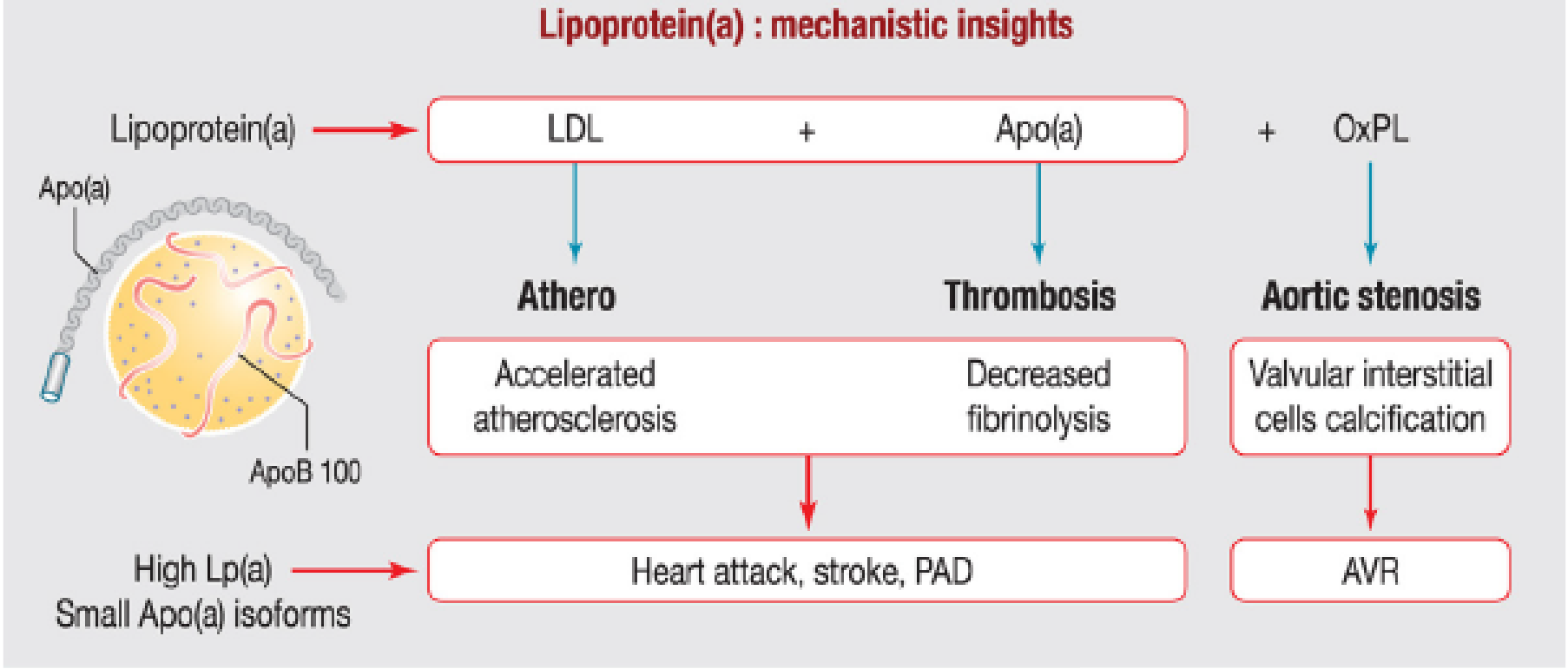
The LDL-like moiety is composed of a central core of cholesteryl esters (CE) and triglycerides (TG) surrounded by phospholipids (PL), free cholesterol (FC), and a single molecule of apolipoprotein B (apoB). Apolipoprotein(a) contains 10 different types of plasminogen kringle 4-like repeats as well as regions homologous to the kringle 5 and protease (P) regions of plasminogen. The kringle 4 type 2 domain (4_2) is present in multiply repeated copies from 2 to >40 that differ in number between apolipoprotein(a) isoforms. Apolipoprotein(a) is linked to apolipoprotein B100 by a single disulfide bond involving an unpaired cysteine residue in kringle 4 type 9. Modified from Koschinsky and Marcovina.

Eur Heart J 2010;31:2844-2853

CENTRAL ILLUSTRATION Lp(a) and OxPL Drive Disease Progression by Aggravating Calcification in Aortic Stenosis Patients



Zheng, K.H. et al. J Am Coll Cardiol. 2019;73(17):2150–62.



Archives of Cardiovascular Disease 114 (2021) 828–847

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Elsevier Masson France EM|consulte www.em-consulte.com/en

ELSEVIER

ORIGINAL ARTICLE

Lipoprotein(a): Pathophysiology, measurement, indication and treatment in cardiovascular disease. A consensus statement from the Nouvelle Société Francophone d'Athérosclérose (NSFA)☆

Lipoprotéine (a) : physiopathologie, indication de dosage et traitement dans les MCV. Déclaration de consensus de la Nouvelle Société Francophone d'Athérosclérose (NSFA)

Vincent Durlach[a], Dominique Bonnefont-Rousselot[b,c], Franck Boccara[d,e], Mathilde Varret[f,g], Mathilde Di-Filippo Charcosset[h,i], Bertrand Cariou[j], René Valero[k], Sybil Charrière[l], Michel Farnier[m,n], Pierre E. Morange[o], Olivier Meilhac[p,q], Gilles Lambert[p,q], Philippe Moulin[l], Philippe Gillery[r], Sophie Beliard-Lasserre[k], Eric Bruckert[s,t], Alain Carrié[u], Jean Ferrières[v], Xavier Collet[w], M. John Chapman[x], Eduardo Anglés-Cano[y,1,*]

International Journal of Cardiology 221 (2016) 537–538

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Correspondence

Real life validation of the European Atherosclerosis Society Consensus Panel lipoprotein(a) threshold of 50 mg/dL

F. Séguro [a,d,1], E. Bérard [b,c,1], V. Bongard [b,c,1], J.B. Ruidavets [b,c,1], D. Taraszkiewicz [d,1], M. Galinier [a,1], D. Carrié [d,1], J. Ferrières [c,d,*,1]

Table 2
Relation between Lp(a) and LDL-C: HR for all-cause and CV mortality (adjusted for age, gender, smoking, diabetes, HTA, use of statins, LDL-C ≥ 4 mmol/L).

	HR	95%CI	p
Total mortality			
Lp(a) ≥ 50 mg/dL	1.52	[1.01–2.26]	0.044
LDL-C > 4 mmol/L	2.02	[1.36–2.99]	<0.01
LDL < 4 mmol/L & Lp(a) < 50 mg/dL	1		
LDL < 4 mmol/L & Lp(a) > 50 mg/dL	2.21	[1.16–4.21]	0.016
LDL > 4 mmol/L & Lp(a) < 50 mg/dL	2.27	[1.42–3.61]	0.001
LDL > 4 mmol/L & Lp(a) > 50 mg/dL	2.94	[1.63–5.29]	<0.001
CV mortality			
Lp(a) ≥ 50 mg/dL	2.58	[1.22–5.48]	0.013
LDL-C > 4 mmol/L	2.16	[0.97–2.28]	0.061
LDL < 4 mmol/L & Lp(a) < 50 mg/dL	1		
LDL < 4 mmol/L & Lp(a) > 50 mg/dL	2.51	[0.72–8.72]	0.148
LDL > 4 mmol/L & Lp(a) < 50 mg/dL	1.99	[0.72–5.45]	0.182
LDL > 4 mmol/L & Lp(a) > 50 mg/dL	5.68	[1.93–16.70]	0.002

American Journal of Preventive Cardiology 23 (2025) 101023

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Association of high lipoprotein (a) level with carotid atherosclerosis and all-cause mortality

Anthony Matta [a,b,c], Dorota Taraszkiewicz [a], Pauline Cougoul [d], Sylvie Lemozy [d], Jean Ferrières [a,*]

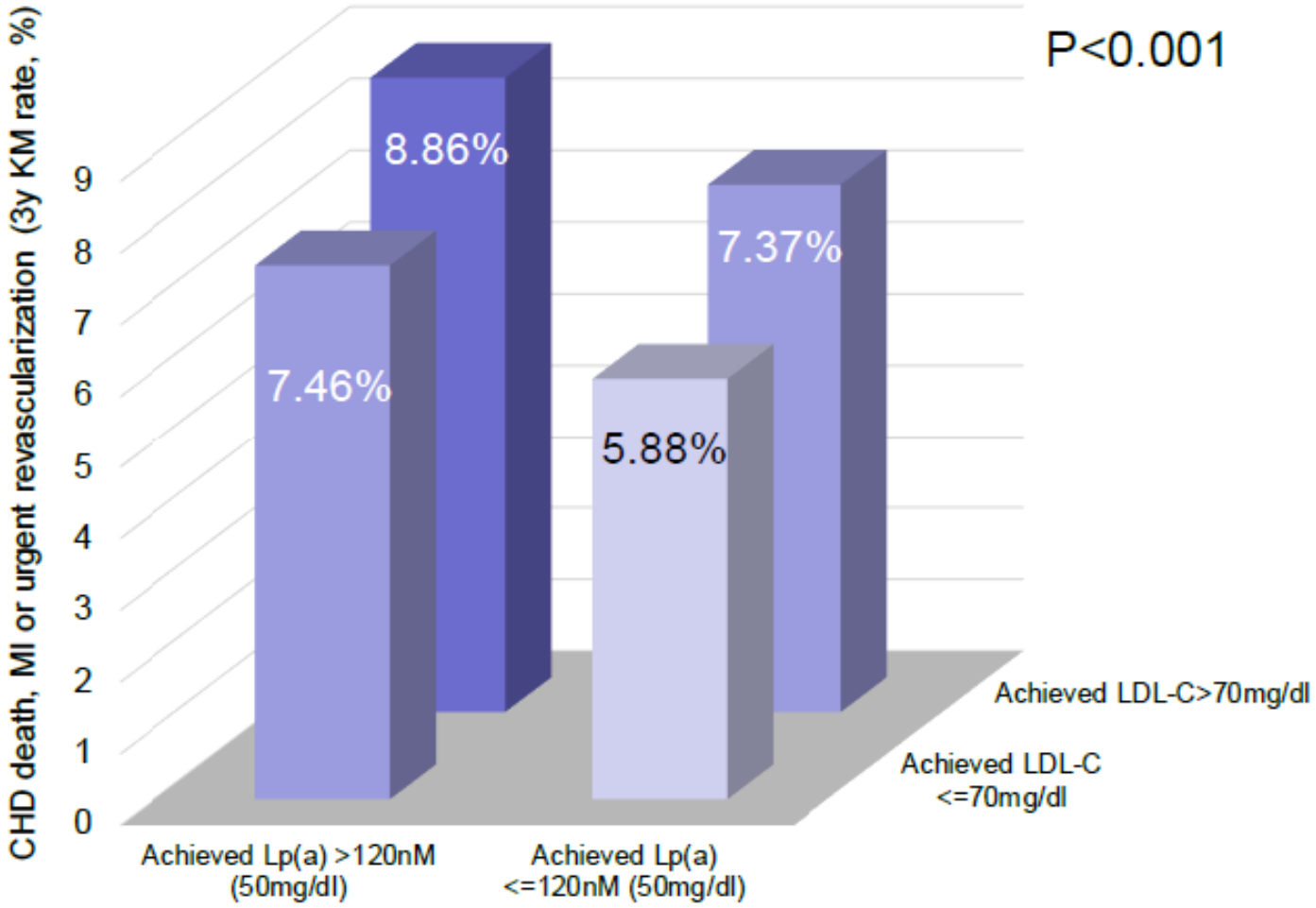
Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

Insights From the FOURIER Trial

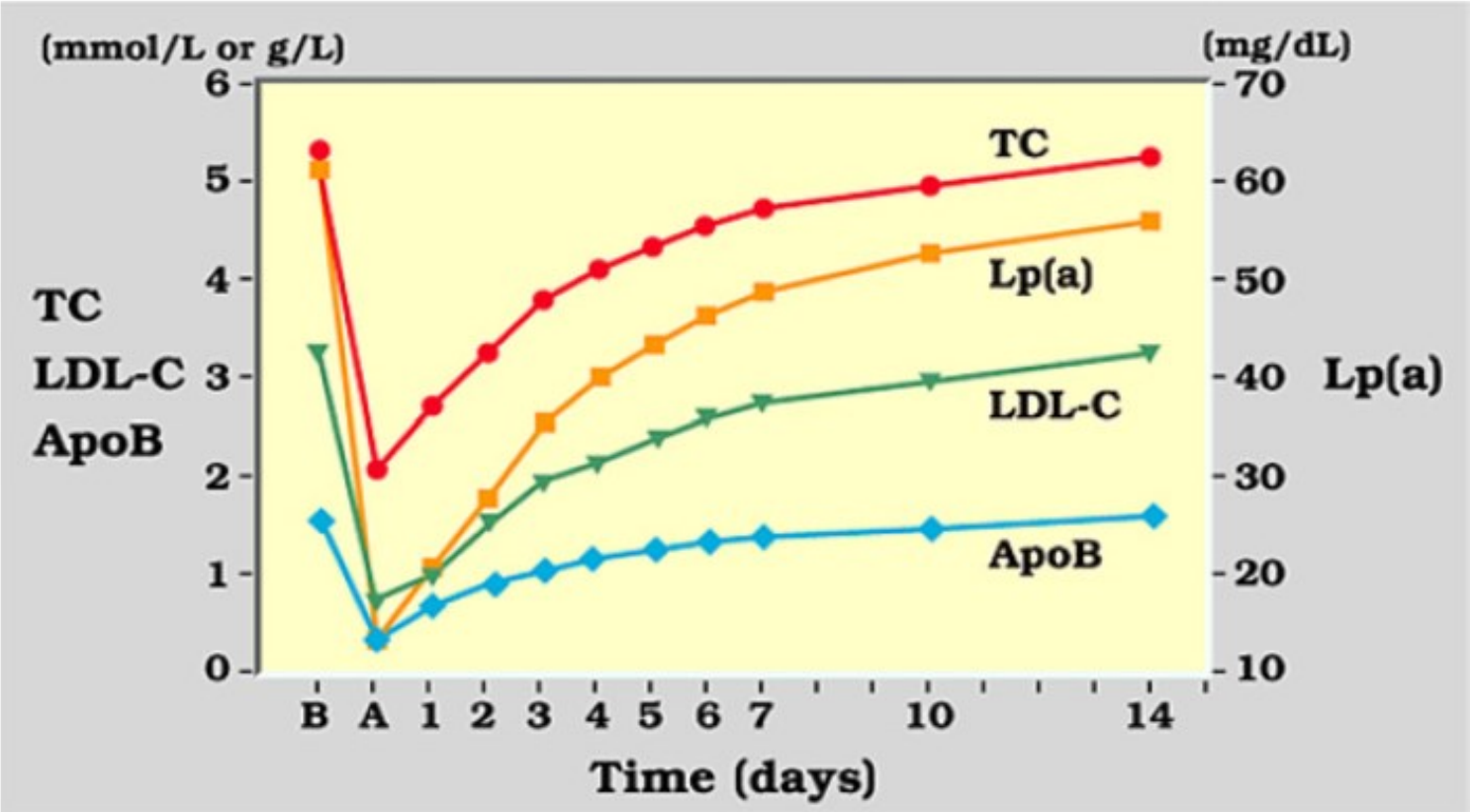
Circulation. 2019;139:1483–1492. DOI: 10.1161/CIRCULATIONAHA.118.037184


P<0.001
CHD death, MI or urgent revascularization (3y KM rate, %)
0
1
2
3
4
5
6
7
8
9
8.86%
7.46%
7.37%
5.88%
Achieved LDL-C>70mg/dl
Achieved LDL-C <=70mg/dl
Achieved Lp(a) >120nM (50mg/dl)
Achieved Lp(a) <=120nM (50mg/dl)

LDL - Apheresis

Emerging low-density lipoprotein (LDL) therapies: Management of severely elevated LDL cholesterol—The role of LDL-apheresis

Time–course effect of LDL-apheresis on lipid levels

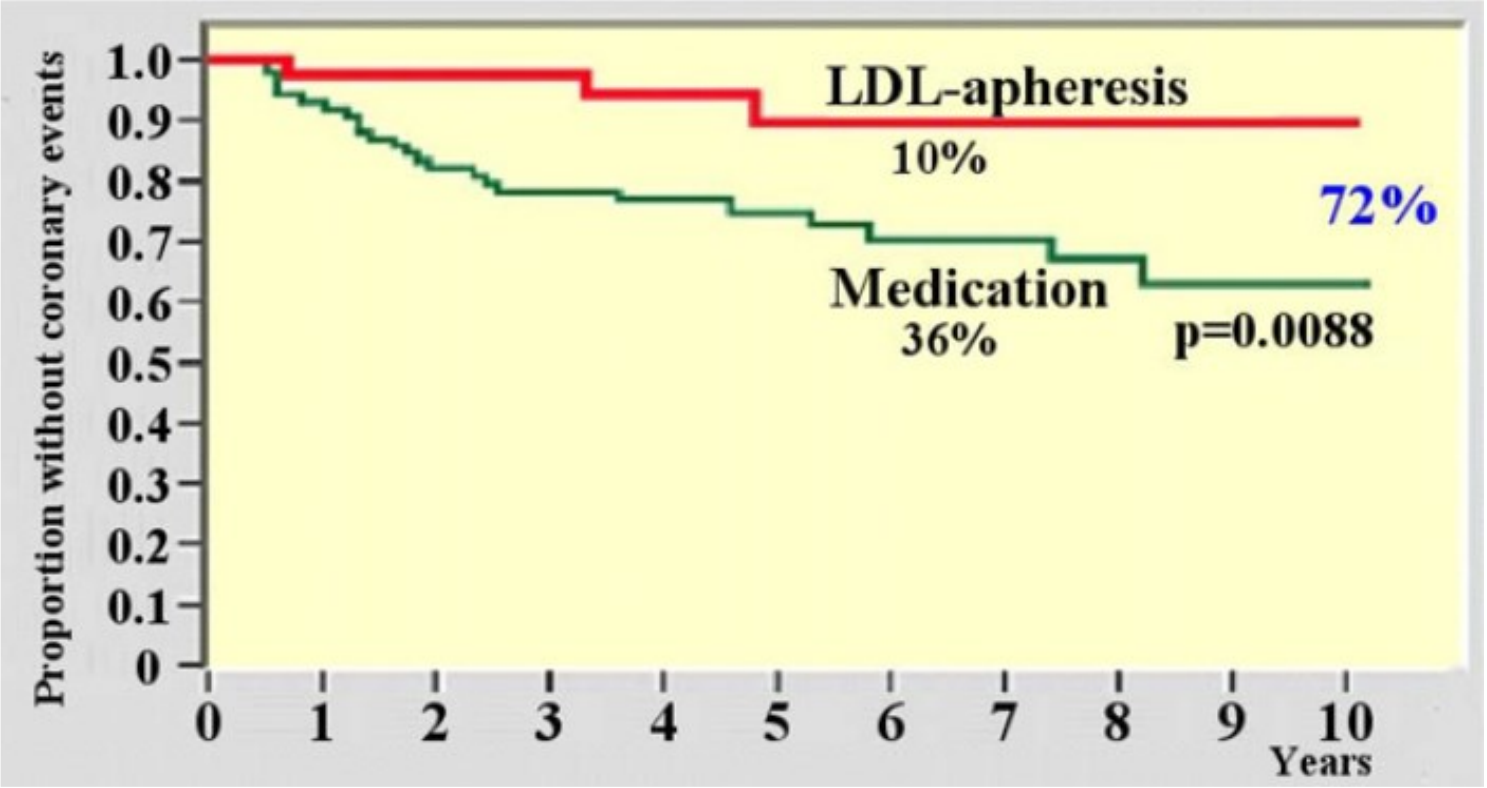


A, immediatley after apheresis; B, immediately before apheresis; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); TC, total cholesterol.

J Clin Lipidol 2013;7:S21-S26

Emerging low-density lipoprotein (LDL) therapies: Management of severely elevated LDL cholesterol—The role of LDL-apheresis

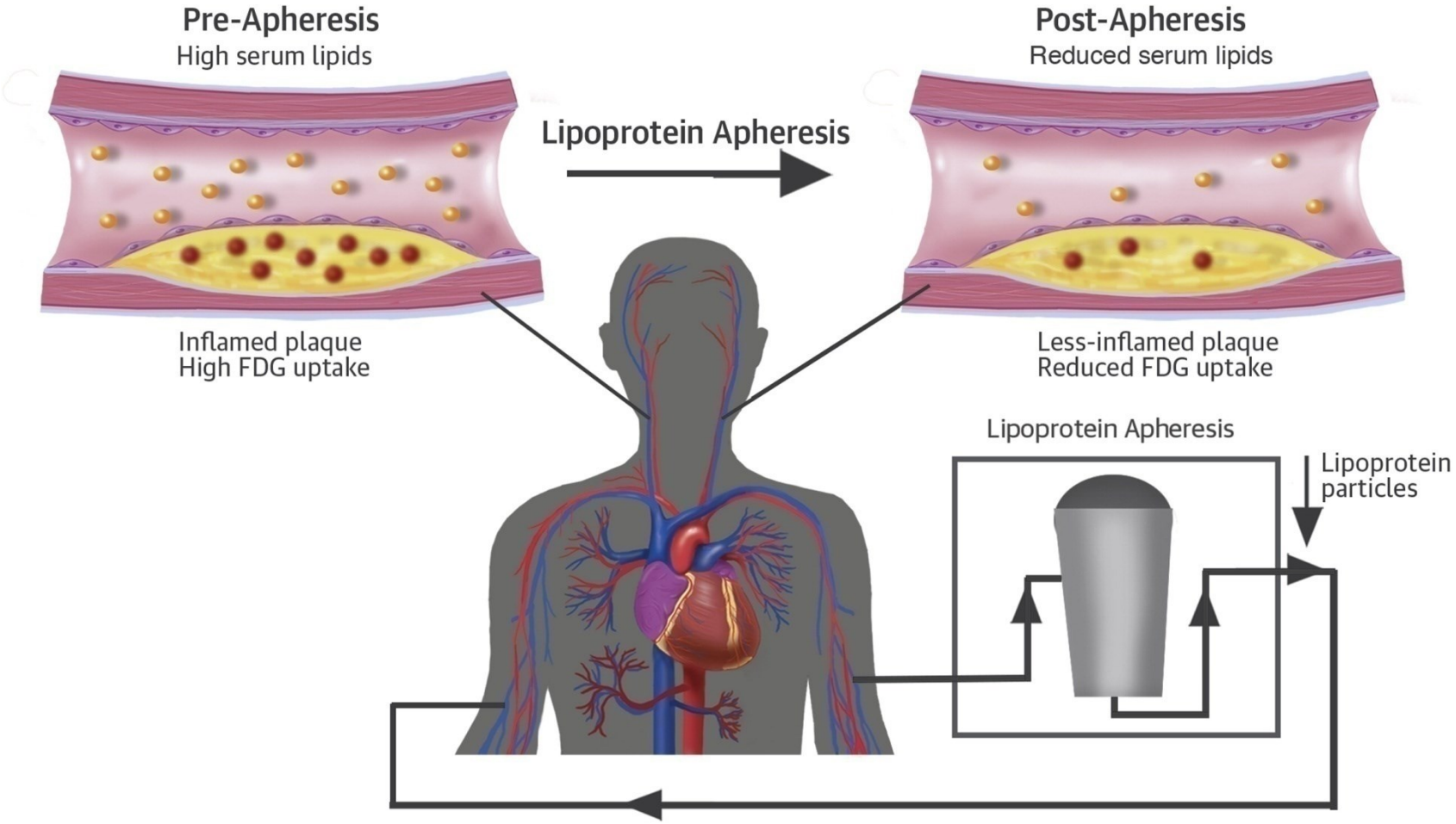
Kaplan-Meier curves for the proportion of patients without coronary events receiving LDL-apheresis in combination with lipid-lowering medications or medications alone



LDL, low-density lipoprotein.
Reprinted with permission from Mabuchi et al.

J Clin Lipidol 2013;7:S21-S26

Impact of Apheresis on Circulating Lipids and Atherosclerotic Inflammation



Familial hypercholesterolemia (FH) is associated with elevated circulating lipids and increased atherosclerotic inflammation. Lipoprotein apheresis in individuals with FH results in a rapid reduction in circulating lipids as well as in a concordant reduction in atherosclerotic inflammation, measured as a decrease in arterial fluorodeoxyglucose uptake.

J Am Coll Cardiol 2014;64:1418-26

Atherosclerosis 398 (2024) 118601

Contents lists available at ScienceDirect

Atherosclerosis

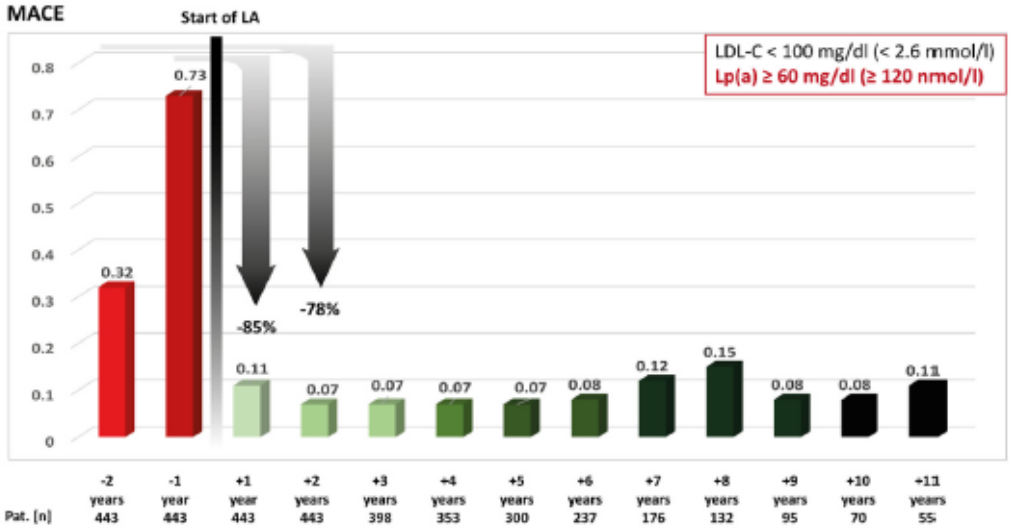
journal homepage: www.elsevier.com/locate/atherosclerosis

The German Lipoprotein Apheresis Registry-Summary of the eleventh annual report

V.J.J. Schettler [a,*], N. Selke [b], S. Jenke [b], T. Zimmermann [c], G. Schlieper [d], W. Bernhardt [d], F. Heigl [e], P. Grützmacher [f], I. Löhlein [g], R. Klingel [h], B. Hohenstein [i], W. Ramlow [j], A. Vogt [k], U. Julius [l], for the Scientific Board of GLAR for the German Apheresis Working Group

Table. 3
Patient's subgroups of GLAR.

Subgroups	Definition	2020	2021	2022
A	**Patients with isolated increase of LDL-C** LDL-C ≥100 mg/dl (≥2,6 mmol/l) Lp(a) < 60 mg/dl (<120 nmol/l)	180	187	171
B	**Patients with isolated increase of Lp(a)** LDL-C <100 mg/dl (<2,6 mmol/l) Lp(a) ≥60 mg/dl (≥120 nmol/l)	500	536	443
C	**Patients with combined increase of LDL-C and Lp(a)** LDL-C ≥100 mg/dl (≥2,6 mmol/l) Lp(a) ≥60 mg/dl (≥120 nmol/l)	228	220	202



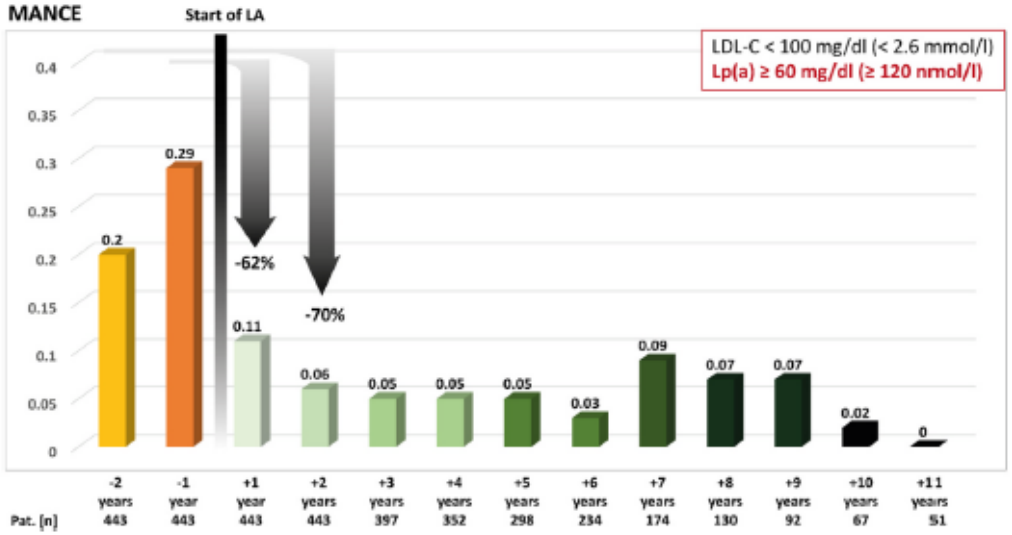


Fig. 3. MACE and MANCE in LA patients with isolated increase of Lp(a) (Group B).

Atherosclerosis 410 (2025) 120508

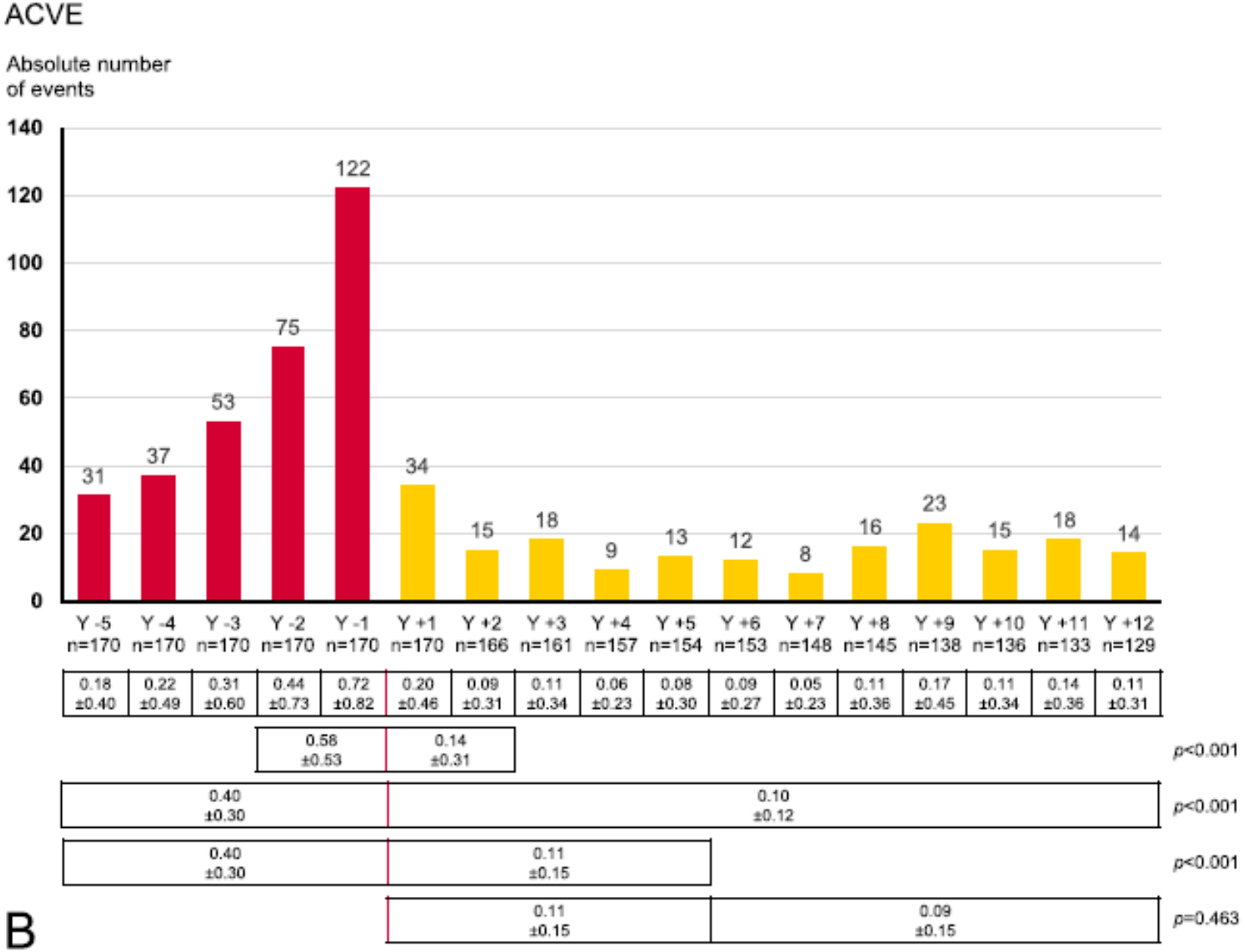
Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

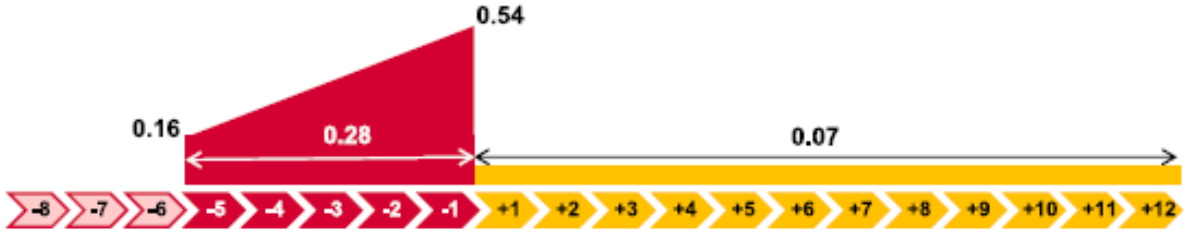
Lipoprotein apheresis for lipoprotein(a)-associated progressive atherosclerotic cardiovascular disease: 12-years follow-up

Reinhard Klingel [a,b,*], Ulrich Julius [c], Wanja M. Bernhardt [d,e,f], Franz Heigl [g], Ralf Spitthoever [h], Josef Leebmann [i], Volker J.J. Schettler [j], Walter Lehmacher [k], Børge G. Nordestgaard [l], Florian Kronenberg [m], Andreas Heibges [a], for the Pro(a)LiFe-Study Group [1]


ACVE
Absolute number of events
140
120
100
80
60
40
20
0
31
37
53
75
122
34
15
18
9
13
12
8
16
23
15
18
14
Y -5 n=170
Y -4 n=170
Y -3 n=170
Y -2 n=170
Y -1 n=170
Y +1 n=170
Y +2 n=166
Y +3 n=161
Y +4 n=157
Y +5 n=154
Y +6 n=153
Y +7 n=148
Y +8 n=145
Y +9 n=138
Y +10 n=136
Y +11 n=133
Y +12 n=129
0.18 ±0.40
0.22 ±0.49
0.31 ±0.60
0.44 ±0.73
0.72 ±0.82
0.20 ±0.46
0.09 ±0.31
0.11 ±0.34
0.06 ±0.23
0.08 ±0.30
0.09 ±0.27
0.05 ±0.23
0.11 ±0.36
0.17 ±0.45
0.11 ±0.34
0.14 ±0.36
0.11 ±0.31
0.58 ±0.53
0.14 ±0.31
p<0.001
0.40 ±0.30
0.10 ±0.12
p<0.001
0.40 ±0.30
0.11 ±0.15
p<0.001
0.11 ±0.15
0.09 ±0.15
p=0.463
B

Pro(a)LiFe study cohort

Lp(a) 224 [174-278] nmol/l
104 [81-130] mg/dl

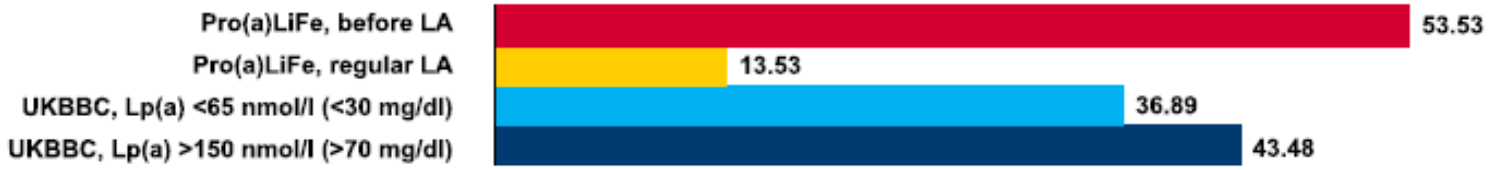


MACE + IS
Mean annual rates

Arrow: 1 study year with respective number

Comparison of Pro(a)LiFe and UKBBC

Pro(a)LiFe: one year before and the first year after initiation of regular LA; UKBBC: the first year after the incident cardiovascular event.



MACE + IS
Incidence rates per 100 patient years

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

To determine the clinical impact of lipoprotein apheresis in patients with refractory angina and raised lipoprotein(a) > 500 mg/L on the primary end point of quantitative myocardial perfusion, as well as secondary end points including atheroma burden, exercise capacity, symptoms, and quality of life.

We conducted a single-blinded randomized controlled trial in 20 patients with refractory angina and raised lipoprotein(a) > 500 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.

The primary endpoint, namely MPR, increased following apheresis (0.47; 95% CI 0.31–0.63) compared with sham (-0.16; 95% CI - 0.33–0.02) yielding a net treatment increase of 0.63 (95% CI 0.37–0.89; $P < 0.001$ between groups). Improvements with apheresis compared with sham also occurred in atherosclerotic burden as assessed by total carotid wall volume ($P < 0.001$), exercise capacity by the 6 min walk test ($P = 0.001$), 4 of 5 domains of the Seattle angina questionnaire (all $P < 0.02$) and quality of life physical component summary by the short form 36 survey ($P = 0.001$).

Lipoprotein apheresis may represent an effective novel treatment for patients with refractory angina and raised lipoprotein(a) improving myocardial perfusion, atheroma burden, exercise capacity and symptoms.

European Heart Journal (2017) **38**, 1561–1569
doi:10.1093/eurheartj/ehx178

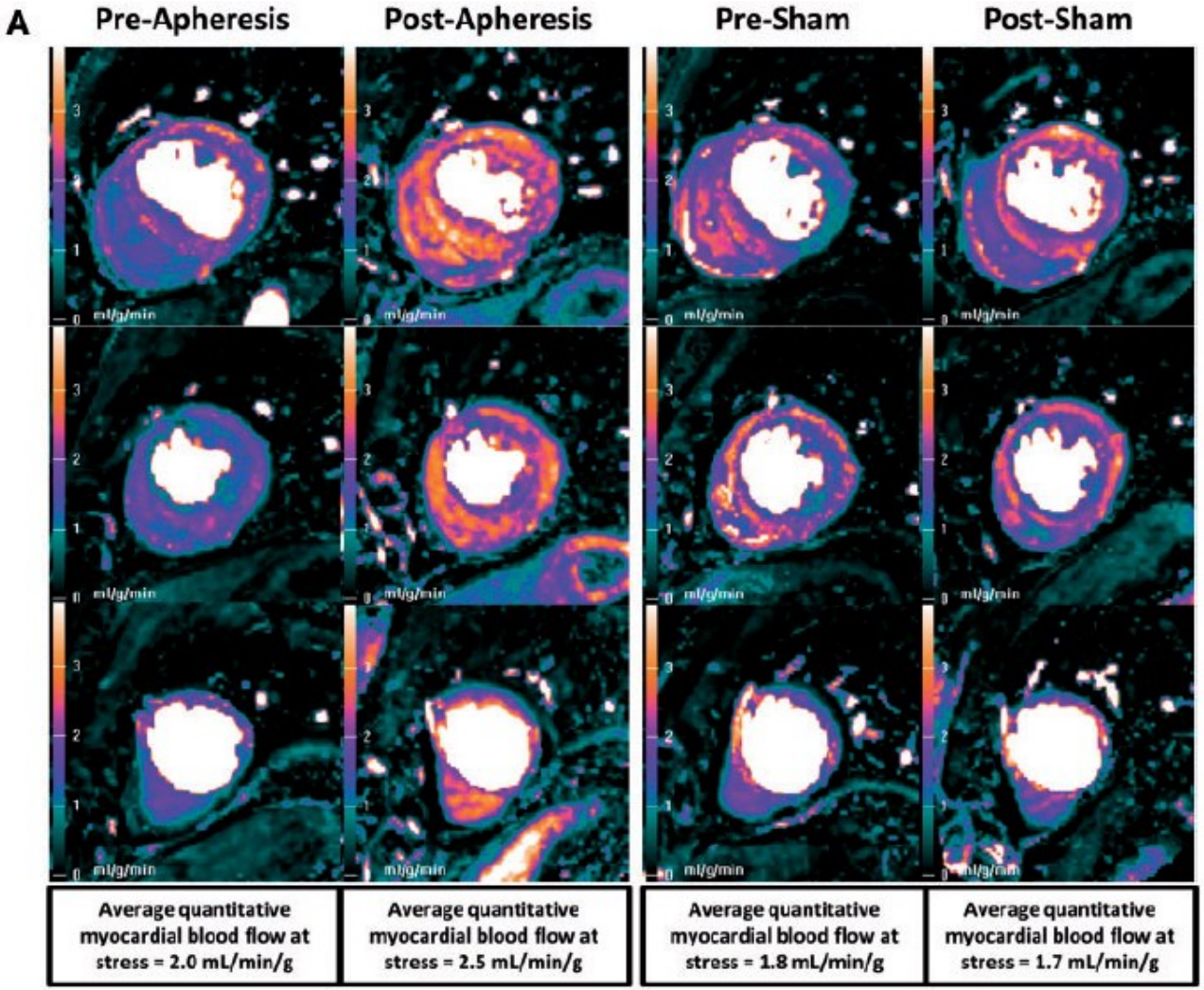


Figure 2 Quantitative CMR perfusion pixel maps pre and post apheresis and pre and post sham (*A*) and group data from myocardial perfusion at rest (left), perfusion with stress (middle) and the myocardial perfusion reserve (right) (*B*). (*A*) Quantitative CMR perfusion pixel maps pre- and post-apheresis and pre- and post-sham. The colour scale shows perfusion from 0–4 mL/g/min as low (black-green), medium (mauve-pink) and high (orange-white), therefore brighter colours represent greater perfusion. In this single patient example, there is clear improvement in stress perfusion after apheresis compared with baseline, but no change is seen during sham treatment. (*B*) Group data are shown from myocardial perfusion at rest

Les nouveaux hypolipidémiants

JAMA Cardiology | Brief Report

Estimation of the Required Lipoprotein(a)-Lowering Therapeutic Effect Size for Reduction in Coronary Heart Disease Outcomes

A Mendelian Randomization Analysis

Claudia Lamina, PhD; Florian Kronenberg, MD; for the Lp(a)-GWAS-Consortium

CONCLUSIONS AND RELEVANCE This mendelian randomization analysis estimated a required Lp(a)-lowering effect size of 65.7 mg/dL to reach the same effect as a 38.67-mg/dL lowering

Agent	Effect on Lp(a)	Clinical benefit by Lp(a) lowering	Evidence
Statin	+0.1%, −24%	None	Meta-analysis *de Boer et al.* [19]
Ezetimibe/fibrates	−7.06%	None	Meta-analysis Awad *et al.* [26]
Bempedoic Acid	+2.4%	None	Secondary analysis of RCT trials *Ridker et al.* [27]
PCSK9 inhibitors	−23%, −27%	Approximately 25% of the cardiovascular benefit of PCSK9i is attributable to Lp(a) lowering when initial levels are high.	Secondary analysis of RCT trials *Bittner et al.* [29] *O'Donoghue et al.* [30]

Lp(a), lipoprotein(a).

Curr Opin Lipidol 2025, 36:130–137
DOI:10.1097/MOL.0000000000000981

Table 2. Key molecules targeting Lp(a) reduction in ongoing phase 3 clinical trials (original)

Agent	Developer	Maximum Lp(a) reduction in phase 1–2 trials	Phase 3 Trial	No of patients	Initiated	Estimated completion	Type of population	Primary outcome
Pelacarsen *ASO*	Novartis, Akcea Therapeutics	–35% – 80%	Lp(a) HORIZON NCT04023552	8323	2019	May 2025	Secondary prevention	Time to CV death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization requiring hospitalization in (1) Lp(a) ≥70 mg/dL and (2) Lp(a) ≥90 mg/dL
Olpasiran *siRNA*	Amgen, Arrowhead Pharmaceuticals	–101%	OCEAN(a) - outcomes NCT05581303	7297	2022	December 2026	Secondary prevention	Time to CHD death, MI, or urgent coronary revascularization
Lepodisiran *siRNA*	Eli Lilly, Dicerna Pharmaceuticals	–97%	ACCLAIM-Lp(a) NCT06292013	12500	2024	March 2029	Primary prevention at high CV risk and secondary prevention	Time to first CV death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization

ASO, antisense oligonucleotides; CHD, coronary heart disease; CV, cardiovascular; Lp(a), lipoprotein(a); MI, myocardial infarction; siRNA, small interfering RNAs.

Curr Opin Lipidol 2025, 36:130–137
DOI:10.1097/MOL.0000000000000981

Lp(a)

Trial	Inclusion Criteria	Intervention	Outcome
Lp(a)HORIZON	Lp(a) ≥70 mg/dL + ASCVD (MI, ischemic stroke, or PAD)	Pelacarsen	4-point MACE (CVD death, nonfatal MI, nonfatal ischemic stroke, coronary revascularization)
ACCLAIM Lp(a)	Lp(a) ≥175 nmol/L + ASCVD or subclinical atherosclerosis or FH or multiple risk factors	Lepodisiran	
MOVE-Lp(a)	Lp(a) ≥175 nmol/L + ASCVD or subclinical atherosclerosis or CKD with diabetes or multiple risk factors	Muvalaplin	
OCEAN(a)	Lp(a) ≥200 nmol/L + CHD (MI or PCI with risk factor)	Olpasiran	CHD death, MI, or urgent revascularization
OCEAN(a)-PreEvent	Lp(a) ≥200 nmol/L + subclinical atherosclerosis or multiple risk factors	Olpasiran	CHD death, MI, or urgent revascularization

FROM THE INSTITUTE OF FORENSIC MEDICINE, UNIVERSITY HOSPITAL, RIKSHOSPITALET, OSLO, NORWAY

A NEW SERUM TYPE SYSTEM IN MAN—THE Lp SYSTEM

By

KÅRE BERG

Received 25.iii.63

The hypothesis for the study was that animals, when given relatively large doses of an isolated protein from one single donor, might be able to develop antibodies against several antigenic groups on this protein, including possible type-specific factors, and that antibodies against all but the latter could be removed by proper absorptions.

The purpose of the present article is to describe a procedure by means of which a specific antibody was produced in rabbits. This antibody

Berg K. A new serum type system in man--the Lp system. *Acta Pathol Microbiol Scand.* 1963;59:369–382. doi: 10.1111/j.1699-0463.1963.tb01808.x