Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Relatore: Roberto Scicali

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Il dr. ROBERTO SCICALI dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- SANOFI

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Agenda

- Diabetic dyslipidemia
- Role of Lp(a) in diabetic patients
- Target and Therapies of Lp(a)

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REVIEW ARTICLE

MECHANISMS OF DISEASE

The Human Plasma Lipidome

Oswald Quehenberger, Ph.D., and Edward A. Dennis, Ph.D.

N Engl J Med 2011;365:1812-23.

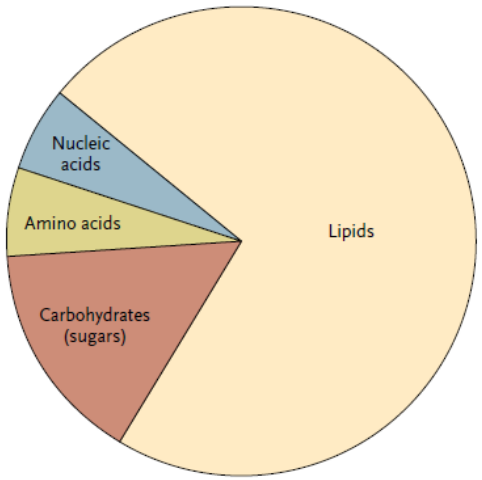

Figure 1. Relative Distribution of Biologic Molecules in Human Plasma.

Amino acids and nucleic acids are shown without consideration of the contribution of proteins and DNA or RNA. The relative distribution is based on weight (grams per deciliter). Data were compiled from Lentner,[1] Wishart et al.,[2] and Quehenberger et al.[3]

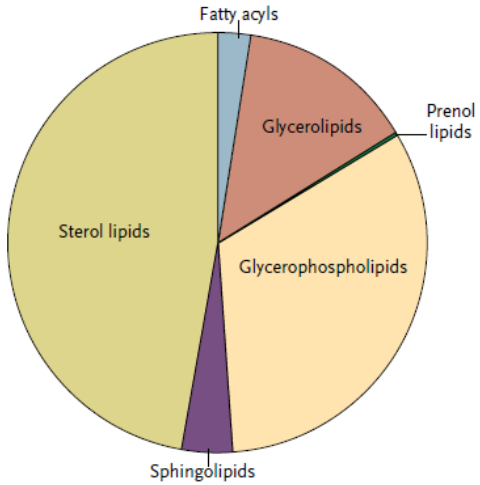

Figure 2. Relative Distribution of Lipids in Human Plasma.

Lipidomic analysis has identified, characterized, and quantified almost 600 lipid molecular species in human plasma.[3] The relative distribution in each category is given on a molar basis. The nomenclature of the lipid categories conforms to the recently developed LIPID MAPS classification system.[6]

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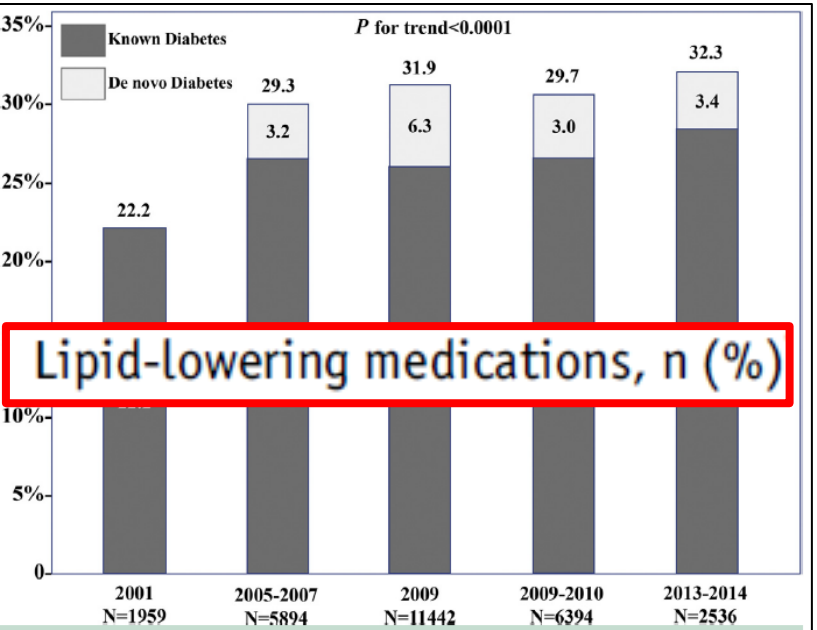
ARTICLE IN PRESS
CLINICAL RESEARCH STUDY
THE AMERICAN JOURNAL of MEDICINE®

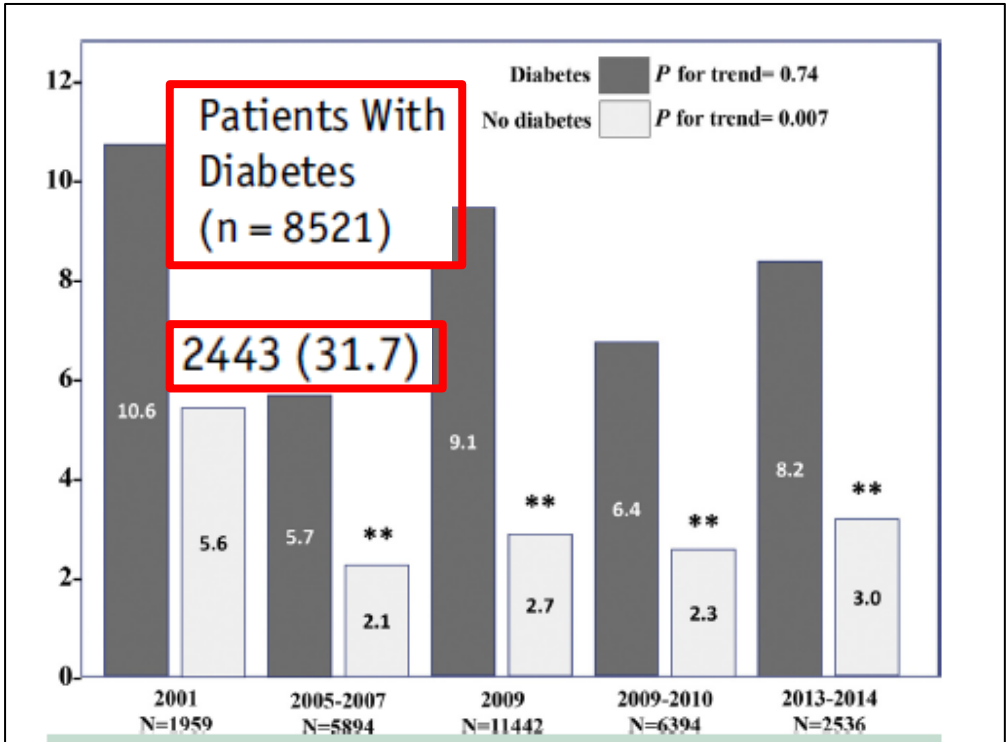
Fifteen-Year Trends of Cardiogenic Shock and Mortality in Patients with Diabetes and Acute Coronary Syndromes

Marco Dauriz, MD,[a] Nuccia Morici, MD,[b,c] Lucio Gonzini, PhD,[d] Donata Lucci, PhD,[d] Antonio Di Chiara, MD,[e] Alessandro Boccanelli, MD,[f] Zoran Olivari, MD,[g] Gianni Casella, MD,[h] Leonardo De Luca, MD,[i] Pierluigi Temporelli, MD,[j] Stefano De Servi, MD,[k] Enzo Bonora, MD,[l] Stefano Savonitto, MD[m,*]



Lipid-lowering medications, n (%)

Figure 1 Nationwide prevalence of diabetes mellitus in 28,225 patients hospitalized for acute coronary syndrome in the Italian Intensive Cardiac Care Units over 2001-2014. The picture shows the overall study-specific prevalence of diabetes mellitus stratified as to whether the diagnosis was already present prior to hospital admission (known diabetes) or it occurred during hospitalization (de novo diabetes), as a combination of data from 5 consecutive nationwide prospective surveys conducted between 2001 and 2014 and comprising 28,225 patients. De novo diabetes evaluated excluding BLITZ-1 study (data on glycemia not available).



Patients With Diabetes (n = 8521)

2443 (31.7)

Figure 2 Cardiogenic shock rates in patients with or without diabetes mellitus in the 5 ICCU registries. Bars are percentages of patients with or without diabetes. *P*-value for comparison within each study: $*P = .0002$; $**P < .0001$.

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REVIEW

OPEN

The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity

Jan Borén[a,b] and Kevin Jon Williams[a,b,c]

Table 1. Reclassification of human epidemiologic risk factors for ASCVD events into causative agents, exacerbating factors, and mere bystander phenomena

Epidemiologic risk factors for ASCVD	Pathophysiologic reclassification	Evidence from human RCTs or human MRS
Elevated plasma concentrations of total cholesterol, LDL-cholesterol, non-HDLc, C-TRL remnants, and apoB	Causative	LDL: proven in RCTs of statins and nonstatins and in MRS; Other apoB-lipoproteins: Proven in MRS
Tobacco smoking	Exacerbating	Lifetime low plasma LDL levels from genetics or unusual lifestyles protect smokers from ASCVD events
Diabetes mellitus	Exacerbating	Likewise for diabetes: lifetime low LDL levels protect patients with diabetes from ASCVD events
Hypertension	Exacerbating	Likewise for hypertension (but extreme hypertension still causes other health problems)
Male sex (age)	Exacerbating	Likewise for elderly men, many of whom no longer develop clinically significant ASCVD
Elevated plasma glucose levels *per se*	Exacerbating	Modest genetic elevations in plasma glucose in MRS detectably increase ASCVD, but in the context of abundant plasma apoB-lipoproteins
Low plasma HDLc concentrations	Exacerbating or bystander	No benefit yet in RCTs of HDLc-raising treatments; no benefit of higher HDLc in MRS

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ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455
ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

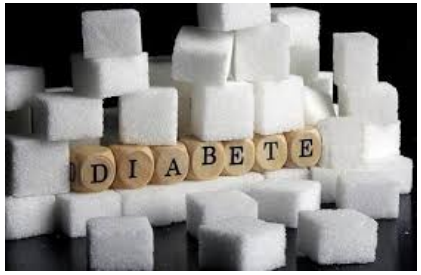

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

©ESC 2019

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.

LDL < 55 mg/dL
Non-HDL < 85 mg/dL
ApoB < 65 mg/dL

LDL < 70 mg/dL
Non-HDL < 100 mg/dL
ApoB < 80 mg/dL

LDL < 100 mg/dL
Non-HDL < 130 mg/dL
ApoB < 100 mg/dL

Target primario - Target secondario

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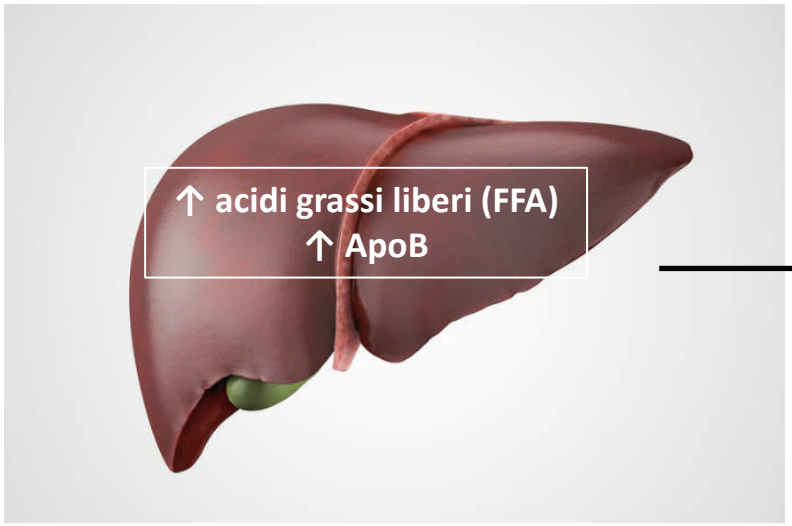
Fisiopatologia della dislipidemia diabetica

Insulino-resistenza

↓



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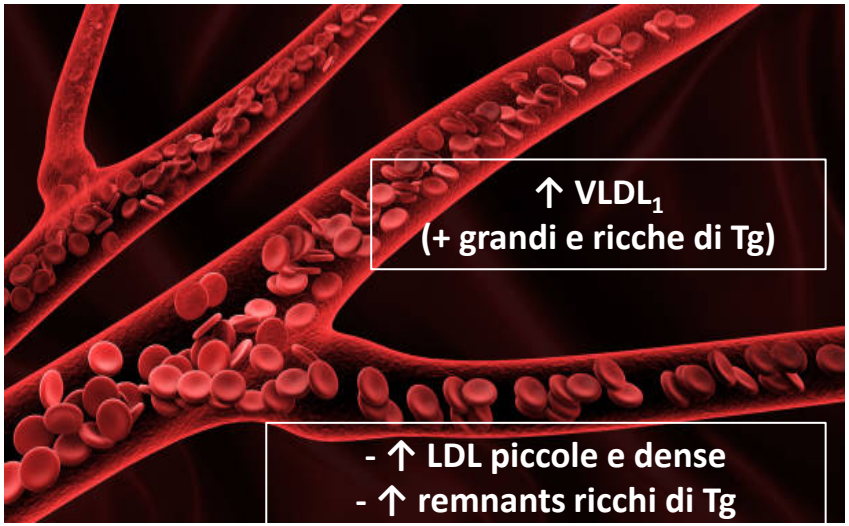

Abnormal hepatic apolipoprotein B metabolism in type 2 diabetes.
Vergès B. Atherosclerosis 2010.

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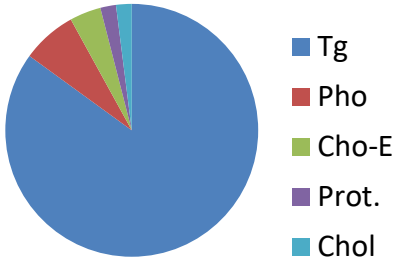
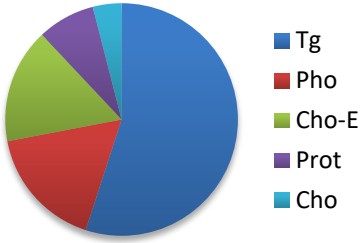
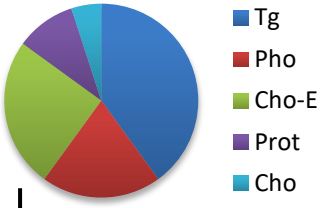
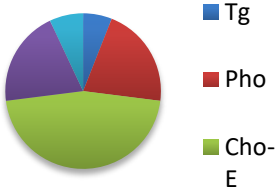
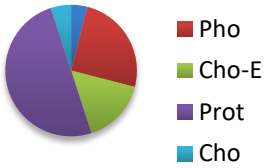
Chilomicroni (remnants) - VLDL - IDL - LDL (Lpa) - HDL











- *Low-density lipoprotein subclass patterns and risk of myocardial infarction*. Austin MA *et al*, JAMA 1988

- *Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women*. Gardner CD, Fortmann SP, Krauss RM, JAMA. 1996

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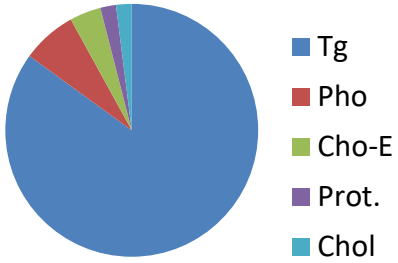

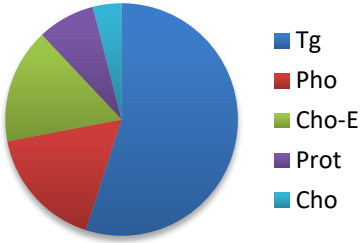

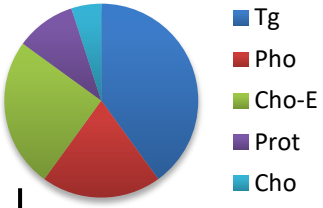

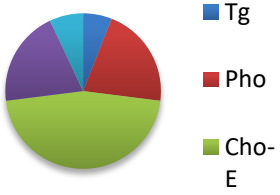

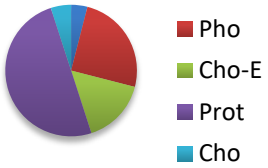

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Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

European Heart Journal (2010) 31, 2844–2853
doi:10.1093/eurheartj/ehq386

CURRENT OPINION

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

Børge G. Nordestgaard[1*], M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Amarenco[8], Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], Petri T. Kovanen[12], Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zeljko Reiner[15], Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg-Hansen[18], for the European Atherosclerosis Society Consensus Panel[†]

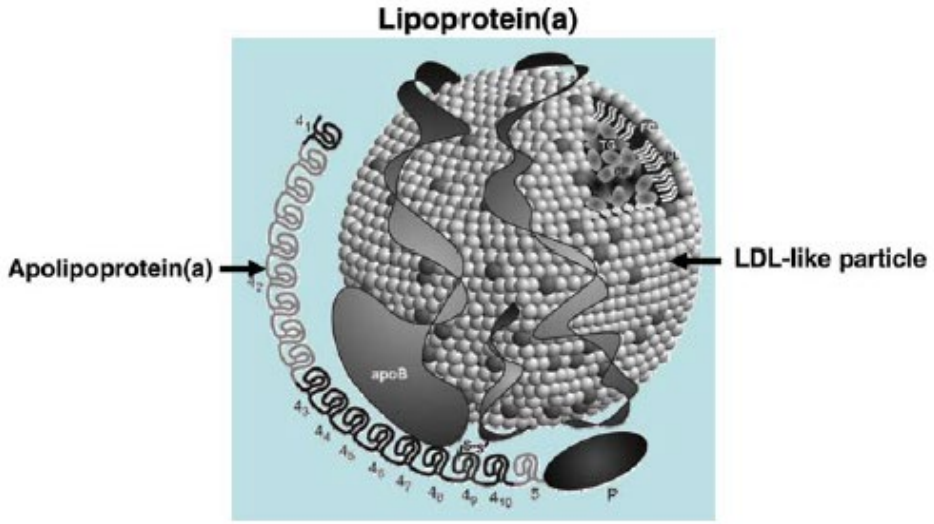

Figure 1 Lipoprotein(a) consists of an LDL-like particle to which apolipoprotein(a) is covalently linked. The LDL-like moiety is composed of a central core of cholesteryl esters (CE) and triglycerides (TG) surrounded by phospholipids (PL), free cholesterol (FC), and a single molecule of apolipoprotein 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.[1] 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.[18]

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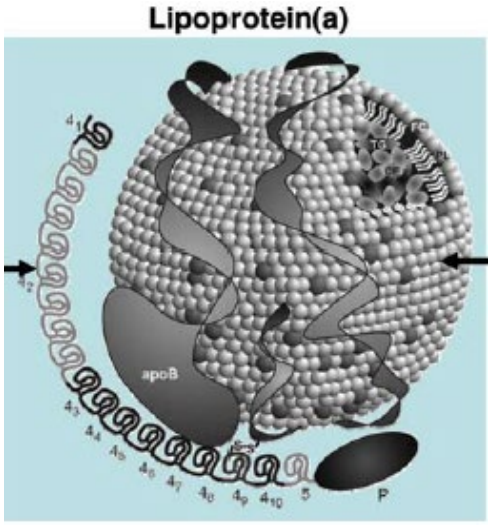
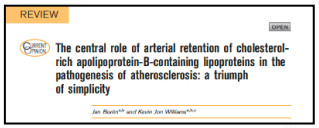


ASCVD

- **CAD**
- **STROKE**
- **PAD**

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?


REVIEW

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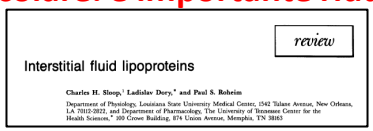
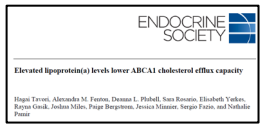

review

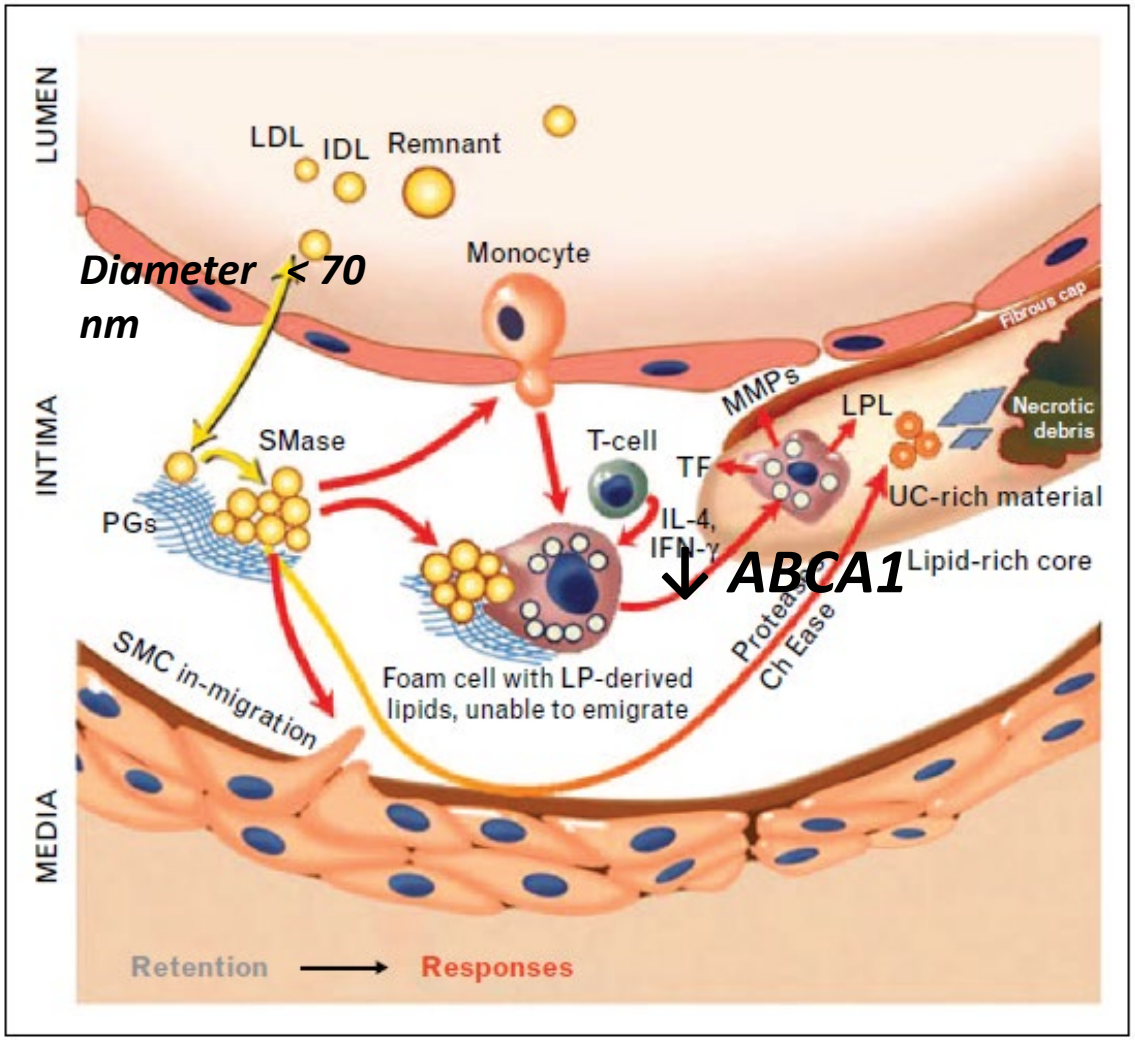
Interstitial fluid lipoproteins


ENDOCRINE SOCIETY

Elevated lipoprotein(a) levels lower ABCA1 cholesterol efflux capacity

1°

2°



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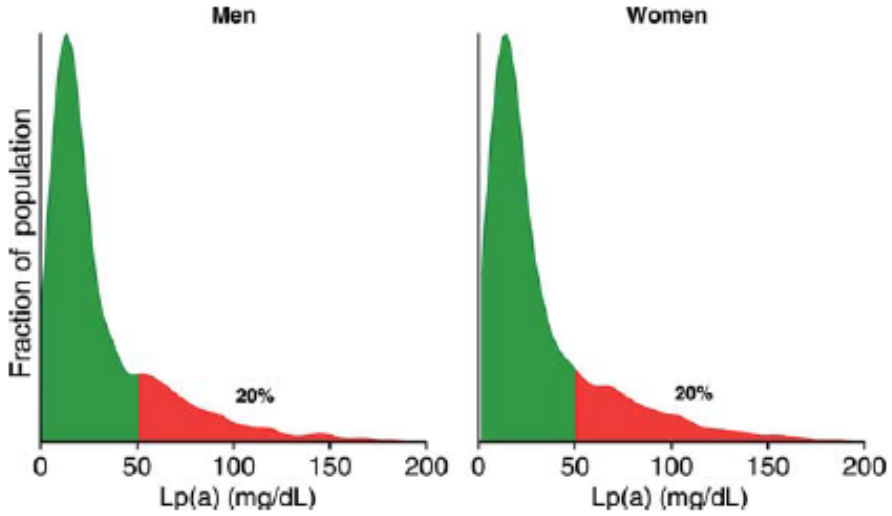

Figure 2 Typical distributions of lipoprotein(a) levels in the general population. These graphs are based on non-fasting fresh serum samples from ~3000 men and 3000 women from the Copenhagen General Population Study collected from 2003 through 2004.[2] Green colour indicates levels below the 80th percentile, whereas red colour indicates levels above the 80th percentile.

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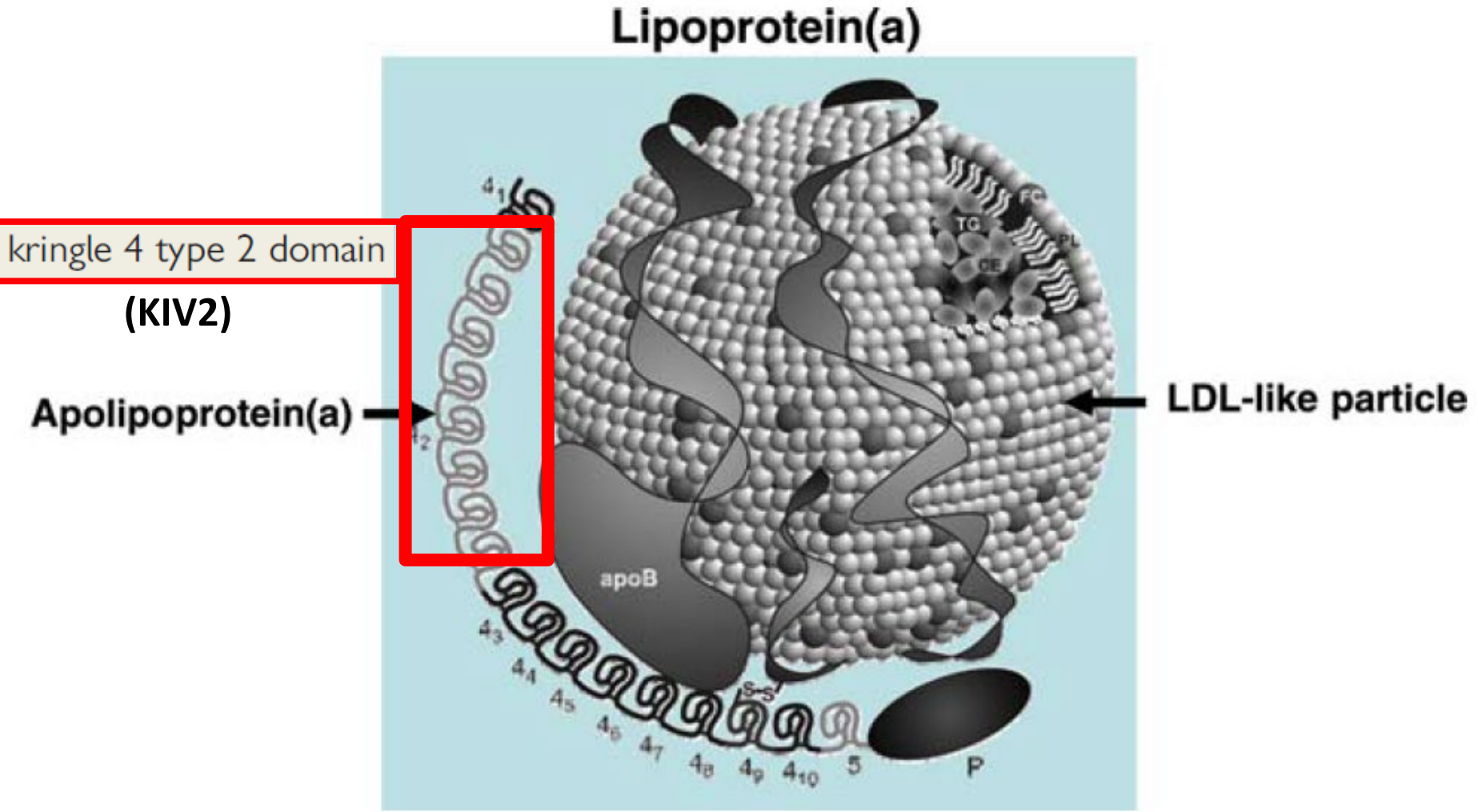

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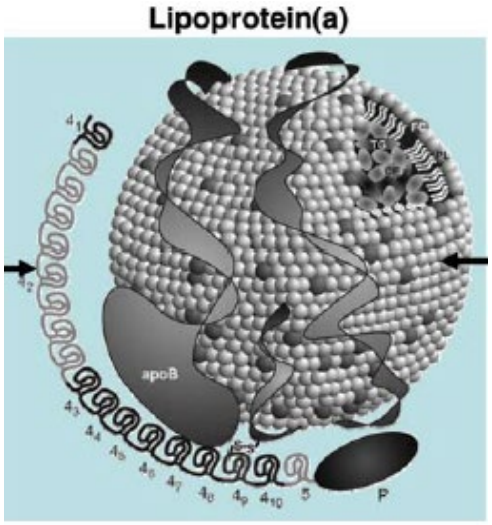

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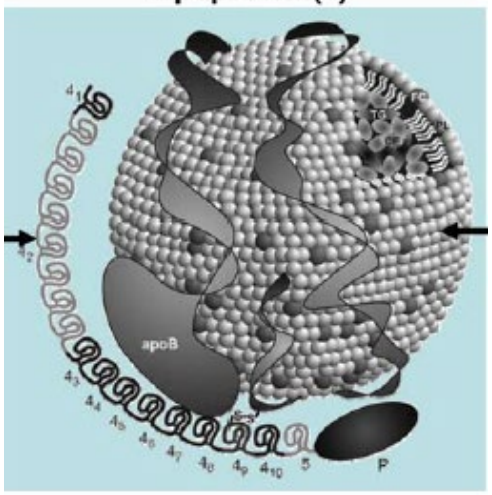

Lp(a) levels

KIV2 polymorphism

ASCVD

CAD

STROKE

PAD

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ORIGINAL CONTRIBUTION

Genetically Elevated Lipoprotein(a) and Increased Risk of Myocardial Infarction

Pia R. Kamstrup, MD, PhD *JAMA. 2009;301(22):2331-2339*

Cross-sectional **Prospective** **Case-control**

Table 1. Basic Characteristics of Participants (White Individuals of Danish Descent) in the 3 Studies

	CCHS	CGPS	CIHDS
Total, No.	8637	29 388	2461
Women, No. (%)	5302 (61)	15 260 (52)	566 (23)
Age, mean (SD), y	55 (17)	59 (13)	60 (10)
Diabetes mellitus, No. (%)	311 (4)	1346 (5)	242 (10)

Abbreviations: CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CIHDS, Copenhagen Ischemic Heart Disease Study.

Kringle IV Type 2 Quartile

First (6-30 Repeats)	Second (31-35 Repeats)	Third (36-40 Repeats)	Fourth (41-99 Repeats)

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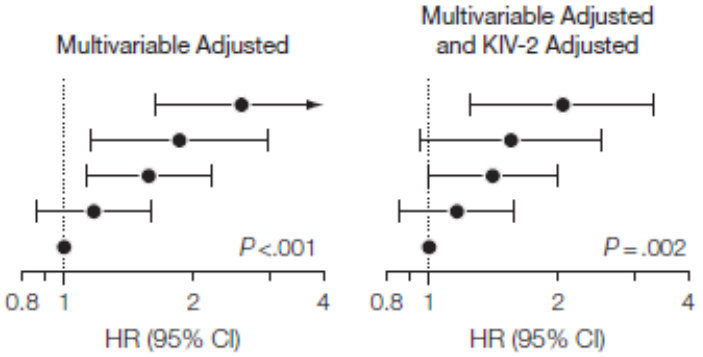
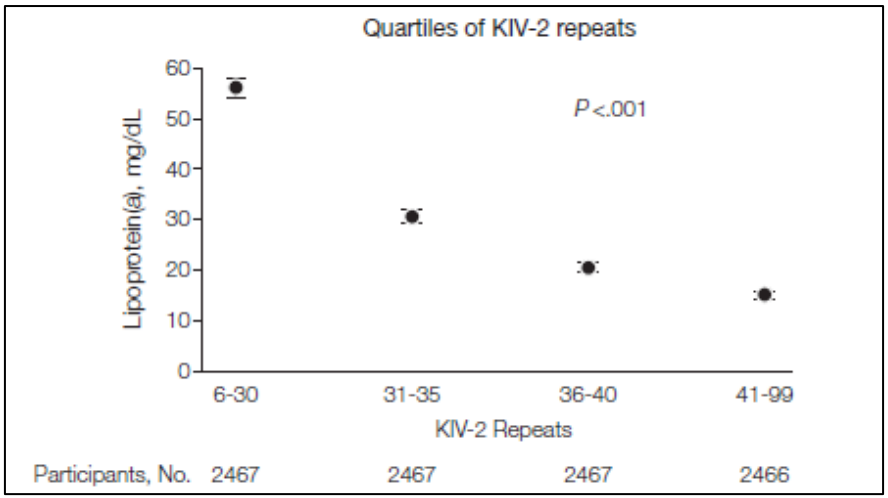
ORIGINAL CONTRIBUTION

Genetically Elevated Lipoprotein(a) and Increased Risk of Myocardial Infarction

Figure 1. Risk of Myocardial Infarction by Extreme Levels of Lipoprotein(a) in the General Population

Lipoprotein(a) Percentile	mg/dL	Participants, No.	Events, No.
>95th	>117	376	46
90th-95th	77-117	450	46
67th-89th	30-76	1731	155
22nd-66th	5-29	3385	241
<22nd [Reference]	<5	1582	104





Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

ORIGINAL CONTRIBUTION

Genetically Elevated Lipoprotein(a) and Increased Risk of Myocardial Infarction

Figure 3. Risk of Myocardial Infarction by Quartiles of Apolipoprotein(a) KIV-2 Repeats in the CCHS, CGPS, and CIHDS

CCHS

KIV-2 Repeats: Quartile	No. of Repeats	Participants, No.	Events, No.
1	6-30	2160	181
2	31-35	2159	158
3	36-40	2159	137
4 [Reference]	41-99	2159	123

Adjusted for Age and Sex: $P<.001$; 0.8 1 2 4; HR (95% CI)

Multivariably Adjusted: $P<.001$; 0.8 1 2 4; HR (95% CI)

CGPS

KIV-2 Repeats: Quartile	No. of Repeats	Controls, No.	Cases, No.
1	6-30	7016	287
2	31-35	7064	246
3	36-40	7095	219
4 [Reference]	41-99	7076	234

$P=.005$; 0.8 1 2 4; OR (95% CI)

$P=.005$; 0.8 1 2 4; OR (95% CI)

CIHDS

KIV-2 Repeats: Quartile	No. of Repeats	Controls, No.	Cases, No.
1	13-30	291	325
2	31-35	304	311
3	36-40	302	313
4 [Reference]	41-96	333	282

$P=.03$; 0.8 1 2 4; OR (95% CI)

$P=.01$; 0.8 1 2 4; OR (95% CI)

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

COMMENTARY

Lipoprotein(a) and Diabetes

An update

STEVEN M. HAFFNER, MD

Association Between Serum Lipoprotein(a) and Diabetic Retinopathy in Han Chinese Patients With Type 2 Diabetes

Atherosclerosis 282 (2019) 52–56

Contents lists available at ScienceDirect

Atherosclerosis

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

Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: The Atherosclerosis Risk in Communities study

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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

Elevated lipoprotein (a) levels are associated with the presence and severity of coronary artery disease in patients with type 2 diabetes mellitus

ORIGINAL ARTICLE

Lipoprotein(a) concentrations in patients with type 2 diabetes mellitus without cardiovascular disease: relationship to metabolic parameters and diabetic complications

SHORT REPORT

Independent Correlation Between Plasma Lipoprotein(a) and Angiographic Coronary Artery Disease in NIDDM

International Journal of Cardiology 108 (2006) 354–358

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Lipoprotein(a), apolipoprotein(a) polymorphism and coronary atherosclerosis severity in type 2 diabetic patients

Serum Lipoprotein(a) in Patients With Diabetes Mellitus

Assessment of Asymptomatic Coronary Artery Disease in Apparently Uncomplicated Type 2 Diabetic Patients

A role for lipoprotein(a) and apolipoprotein(a) polymorphism

Journal of Diabetes and Its Complications 17 (2003) 135–140

Diabetes and its Complications

Lipoprotein(a), apolipoprotein(a) polymorphism and restenosis after intracoronary stent placement in Type 2 diabetic patients

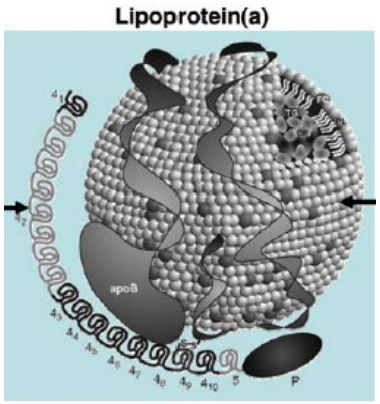
Impact of Lipoprotein(a) on Long-term Outcomes in Patients With Diabetes Mellitus Who Underwent Percutaneous Coronary Intervention

European Heart Journal (2012) 33, 325–334
doi:10.1093/eurheartj/ehr350

CLINICAL RESEARCH
Prevention and epidemiology

Genetic variants, plasma lipoprotein(a) levels, and risk of cardiovascular morbidity and mortality among two prospective cohorts of type 2 diabetes

The Association Between Circulating Lipoprotein(a) and Type 2 Diabetes: Is It Causal?



Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Atherosclerosis 282 (2019) 52–56

Contents lists available at ScienceDirect

Atherosclerosis

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

Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: The Atherosclerosis Risk in Communities study

Anum Saeed[a], Wensheng Sun[a], Anandita Agarwala[b], Salim S. Virani[a,c], Vijay Nambi[a,c], Josef Coresh[d], Elizabeth Selvin[d], Eric Boerwinkle[e], Peter H. Jones[a,f], Christie M. Ballantyne[a], Ron C. Hoogeveen[a,*]

Table 3A

Association of Lp(a) levels with risk of incident ASCVD events in Caucasians with diabetes, prediabetes.

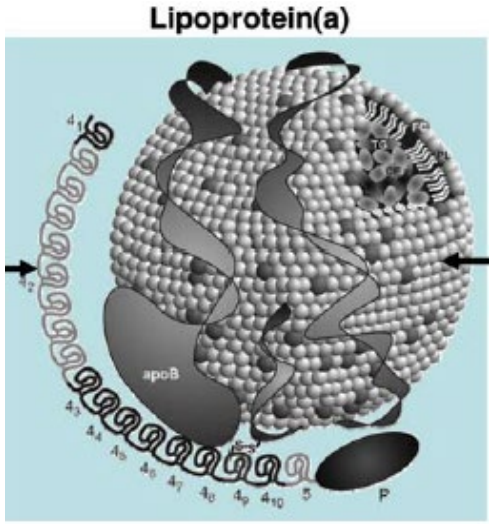
		Lp(a) categories, mg/dL (percentiles)					*p*-trend
		≤10	> 10–20	> 20–30	> 30– < 50	≥50	
		(0–13)	(13–30)	(30–47)	(47–71)	(71–100)	
Diabetes (n = 981)	Model 1	Ref	0.94 (0.66–1.34)	0.91 (0.52–1.60)	1.20 (0.81–1.78)	1.59 (1.18–2.16)	0.028
	Model 2	Ref	0.94 (0.66–1.34)	0.90 (0.51–1.58)	1.21 (0.81–1.80)	1.59 (1.18–2.15)	0.028
	Events/Popn	175/577 (30.33)	37/133 (27.82)	13/50 (26.00)	29/84 (34.52)	59/137 (43.07)	0.010
Prediabetes (n = 2800)	Model 1	Ref	1.06 (0.83–1.34)	1.39 (1.00–1.92)	1.20 (0.88–1.63)	1.40 (1.09–1.80)	0.046
	Model 2	Ref	1.06 (0.83–1.34)	1.37 (0.99–1.90)	1.20 (0.88–1.63)	1.40 (1.09–1.81)	0.048
	Events/Popn	255/1472 (17.32)	94/523 (17.97)	42/187 (22.46)	49/237 (20.68)	83/381 (21.78)	0.017

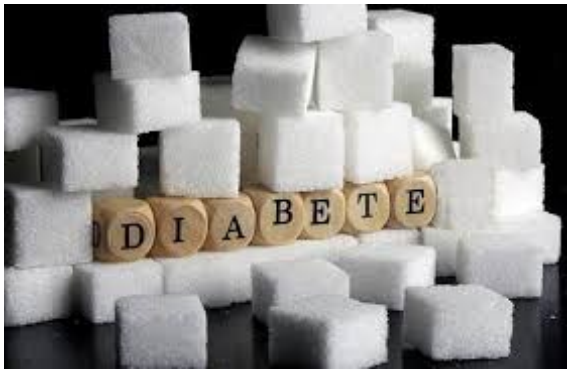
Table 1

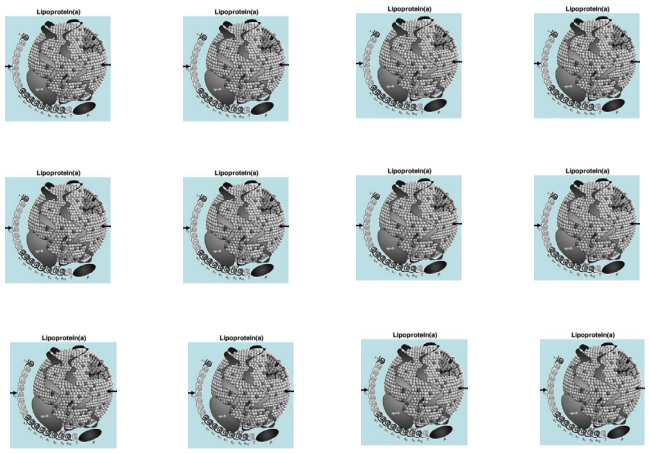
Baseline characteristics and incident atherosclerotic cardiovascular disease events across glycemic subgroups.

	Diabetes (N = 1543)	Prediabetes (N = 3615)	Normal fasting glucose (N = 4713)	*p*-trend
Lp(a), mg/dL	14.3 (4.7, 40.7)	12.4 (5.0, 35.6)	13.0 (5.3, 39.6)	0.765

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?







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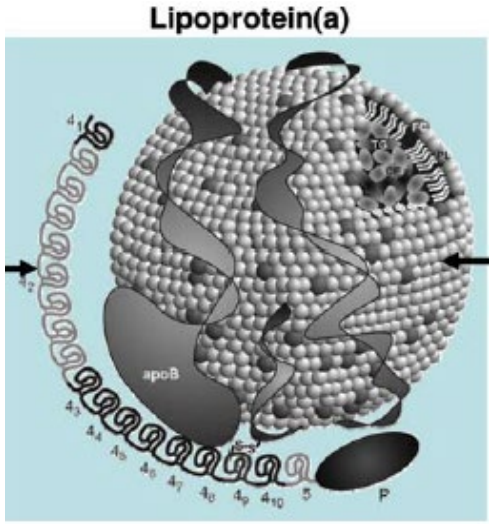
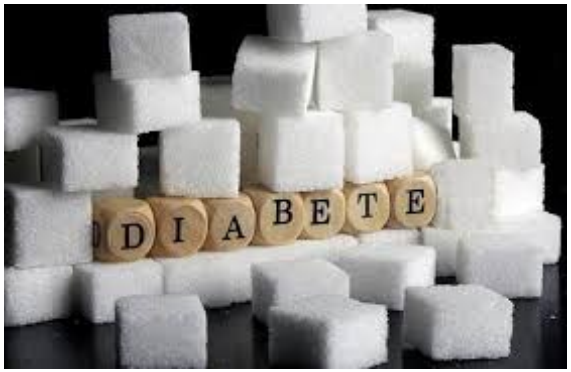
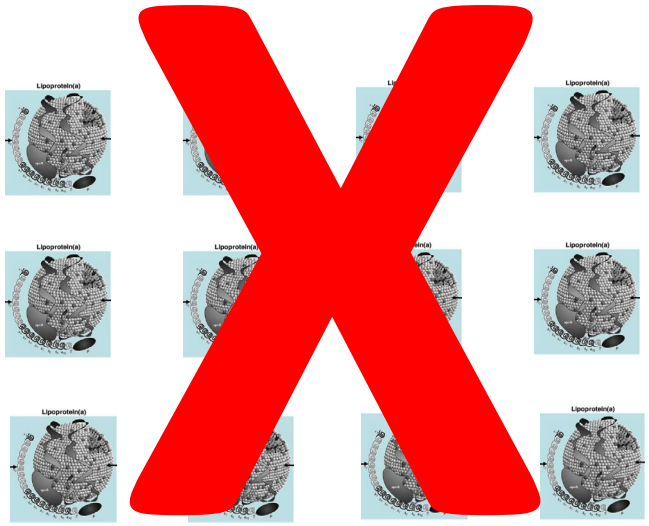
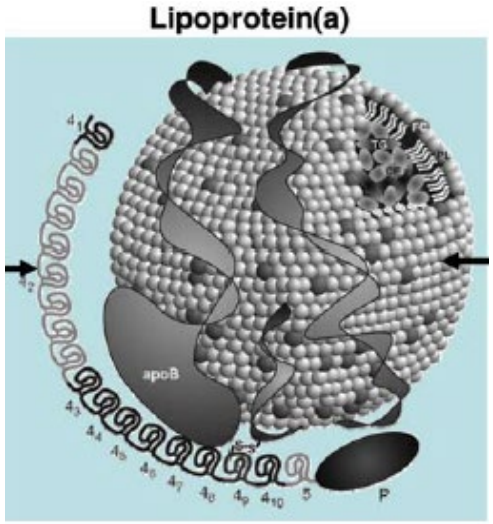
Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

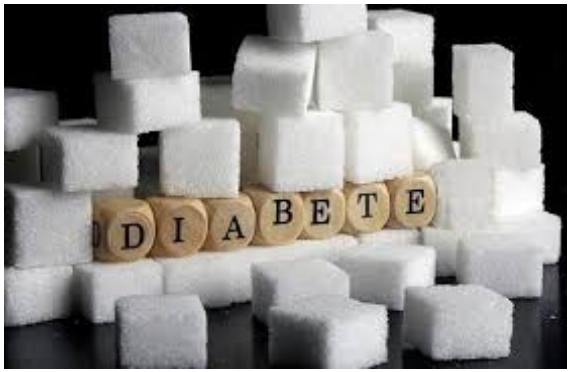


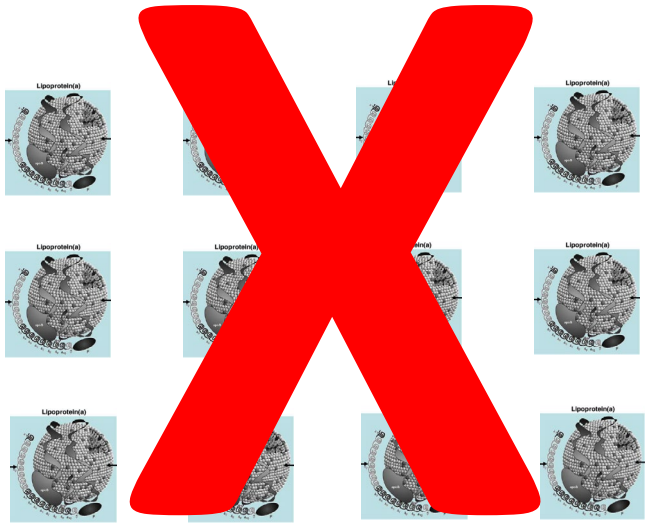




Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?







Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Journal of Diabetes and Its Complications 29 (2015) 1165–1170

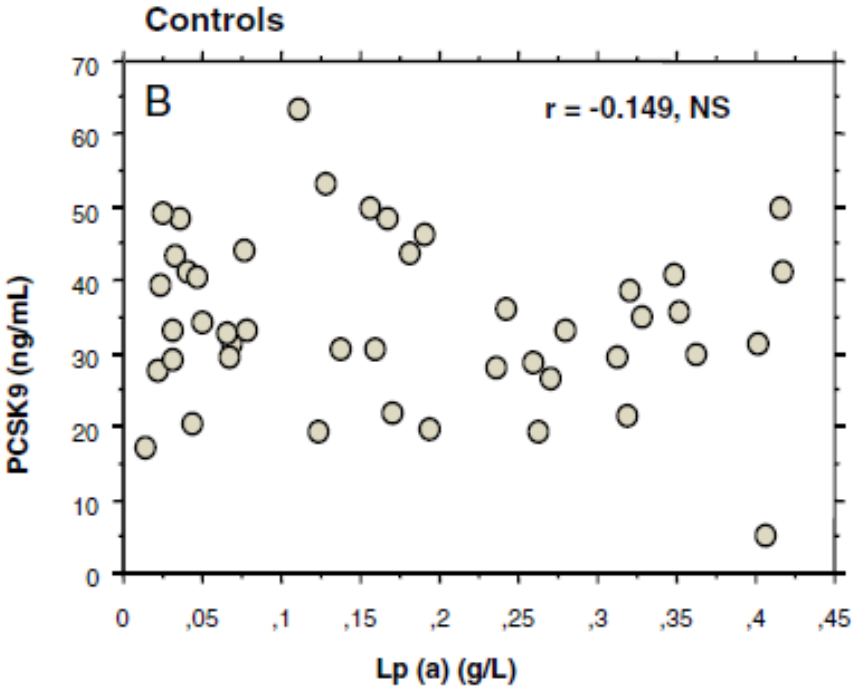
Contents lists available at ScienceDirect

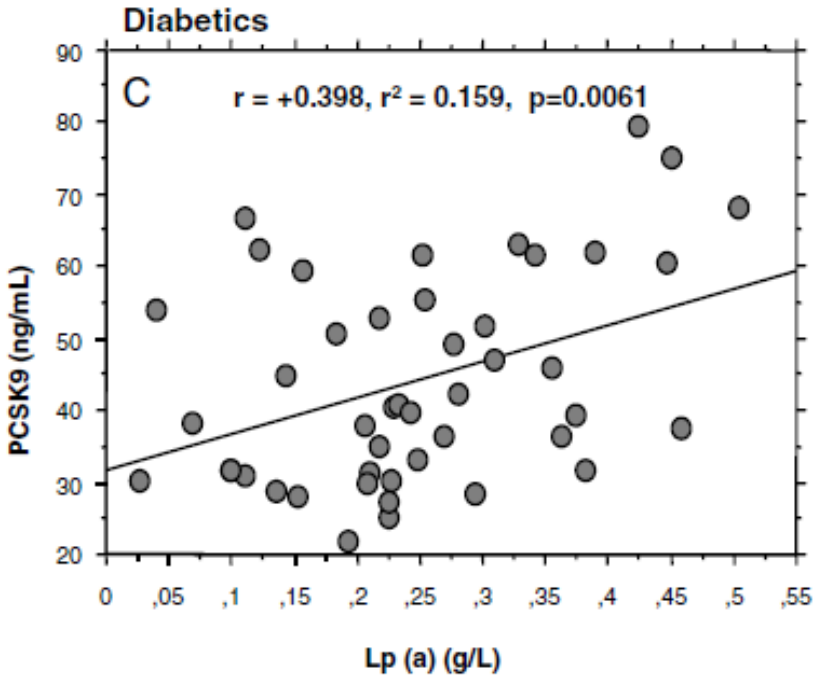
Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

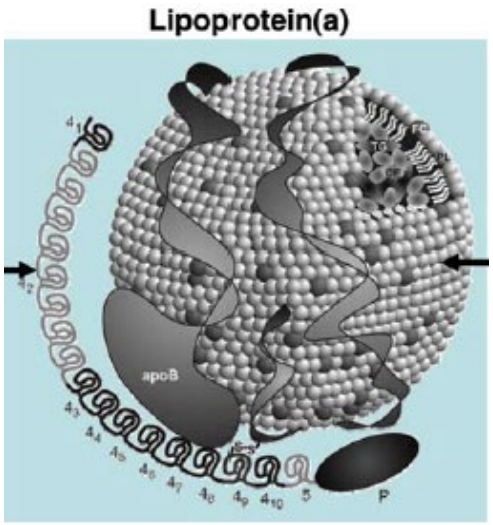
Plasma proprotein convertase subtilisin/kexin type 9 is associated with Lp(a) in type 2 diabetic patients

Ymène Nekaies [a], Bruno Baudin [b], Sami Kelbousi [c], Mohsen Sakly [a], Nebil Attia [a,*]





Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?



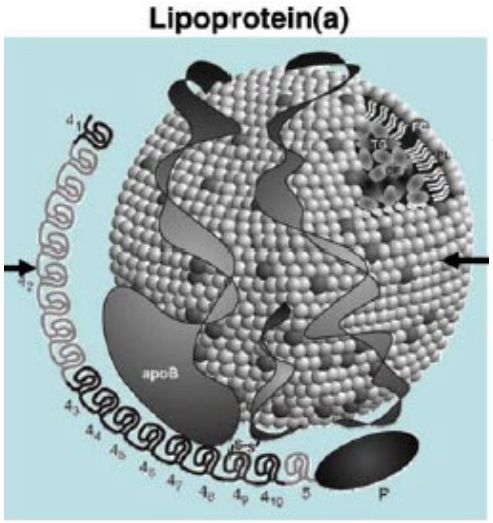
ASCVD

CAD

STROKE

PAD

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?



PCSK9

ASCVD

CAD

STROKE

PAD

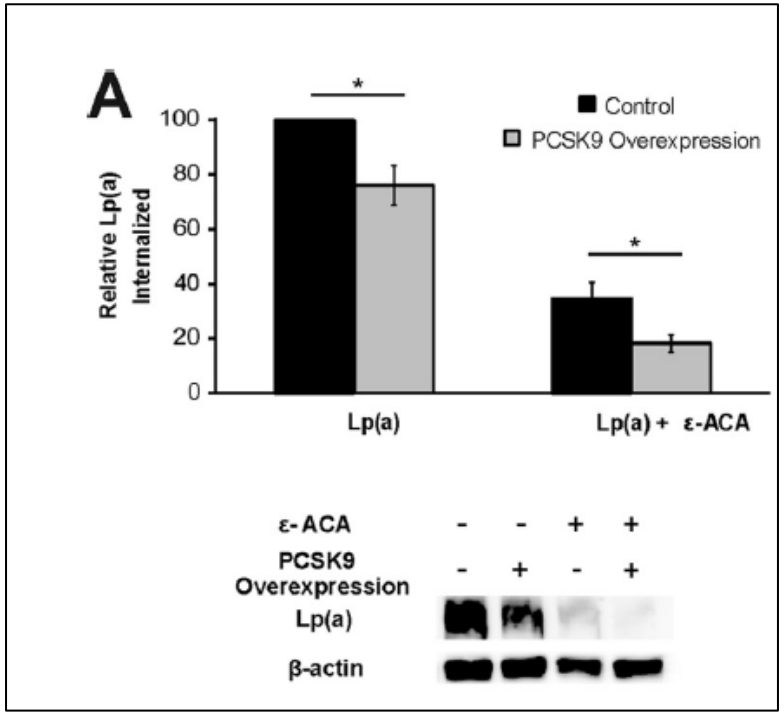
Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 290, NO. 18, pp. 11649–11662, May 1, 2015

Lipoprotein(a) Catabolism Is Regulated by Proprotein Convertase Subtilisin/Kexin Type 9 through the Low Density Lipoprotein Receptor*

Received for publication, September 14, 2014, and in revised form, February 21, 2015 Published, JBC Papers in Press, March 16, 2015, DOI 10.1074/jbc.M114.611988

Rocco Romagnuolo[‡], Corey A. Scipione[‡], Michael B. Boffa[‡], Santica M. Marcovina[§], Nabil G. Seidah[¶], and Marlys L. Koschinsky[‡†]



Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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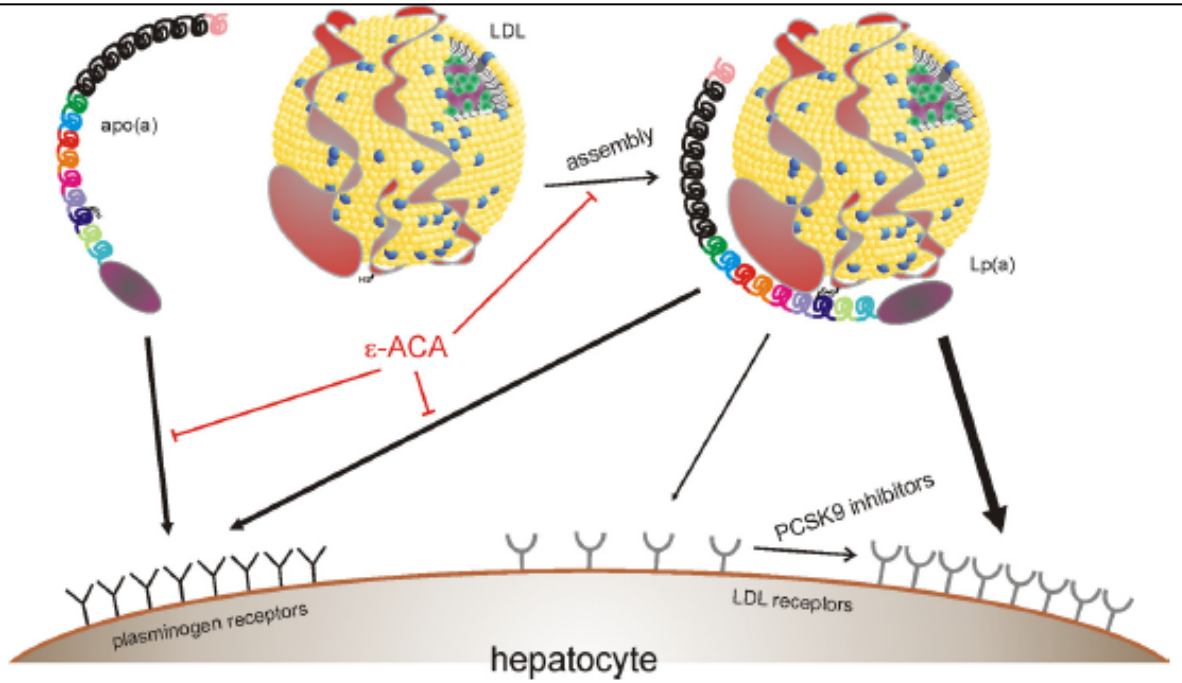
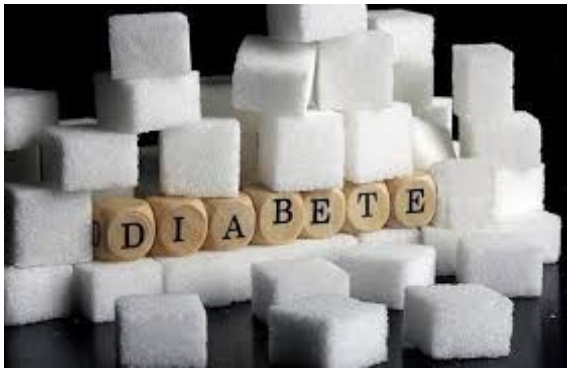


FIGURE 7. **Model for receptor-mediated catabolism of apo(a) and Lp(a).** Apo(a) and apoB-containing lipoproteins are independently secreted from hepatocytes and form a non-covalent, and subsequently covalent, complex as Lp(a). Apo(a) can be internalized by plasminogen receptors, and the apo(a) component of Lp(a) mediates clearance of the particle by plasminogen receptors. Apo(a) can only be internalized by the LDL receptor when in a complex with LDL. ϵ-ACA can inhibit binding of apo(a) or Lp(a) to plasminogen receptors as well as Lp(a) assembly, the latter through inhibition of non-covalent interactions between apo(a) and apoB-100. However, ϵ-ACA cannot prevent binding of pre-formed Lp(a) to the LDL receptor. In the presence of inhibitors of PCSK9, there is a substantial increase in DL receptor number such that clearance of Lp(a) through this route is of a much greater magnitude.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

PCSK9



Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

ORIGINAL ARTICLE
Endocrine Research

Genetic and Metabolic Determinants of Plasma PCSK9 Levels

Susan G. Lakoski, Thomas A. Lagace, Jonathan C. Cohen, Jay D. Horton, and Helen H. Hobbs

Donald W. Reynolds Cardiovascular Clinical Research Center, Departments of Internal Medicine (S.G.L., J.C.C., J.D.H., H.H.H.) and Molecular Genetics (T.A.L., J.D.H., H.H.H.), and the Howard Hughes Medical Institute (H.H.H.), University of Texas Southwestern Medical Center, Dallas, Texas 75390-9046

Received: 12 September 2016 | Revised: 24 October 2016 | Accepted: 27 October 2016
DOI 10.1111/dom.12819

BRIEF REPORT

WILEY

Glycaemic control influences the relationship between plasma PCSK9 and LDL cholesterol in type 1 diabetes

Stéphanie Laugier-Robiolle MD[1] | Bruno Vergès MD, PhD[2] | Maëlle Le Bras MD[3] | Elise Gand MD[1] | Benjamin Bouillet MD, PhD[2] | Pierre-Jean Saulnier MD, PhD[4] | Cédric Le May PhD[5] | Matthieu Pichelin PharmD[6] | Richard Maréchaud MD[1] | Jean-Michel Petit MD, PhD[2] | Samy Hadjadj MD, PhD[1,4,7] | Bertrand Cariou MD, PhD[6]

Endocrine (2016) 54:588–601
DOI 10.1007/s12020-016-0939-0

REVIEW

Proprotein convertase subtilisin/kexin type 9 (PCSK9) and metabolic syndrome: insights on insulin resistance, inflammation, and atherogenic dyslipidemia

Nicola Ferri[1] · Massimiliano Ruscica[2]

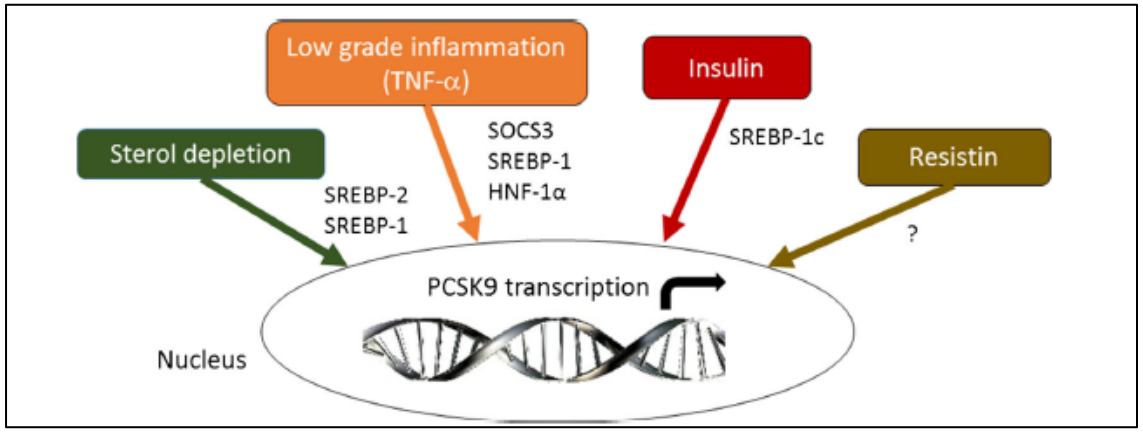
Received: 1 April 2016 | Revised: 2 November 2016 | Accepted: 22 November 2016
DOI: 10.1111/pedi.12490

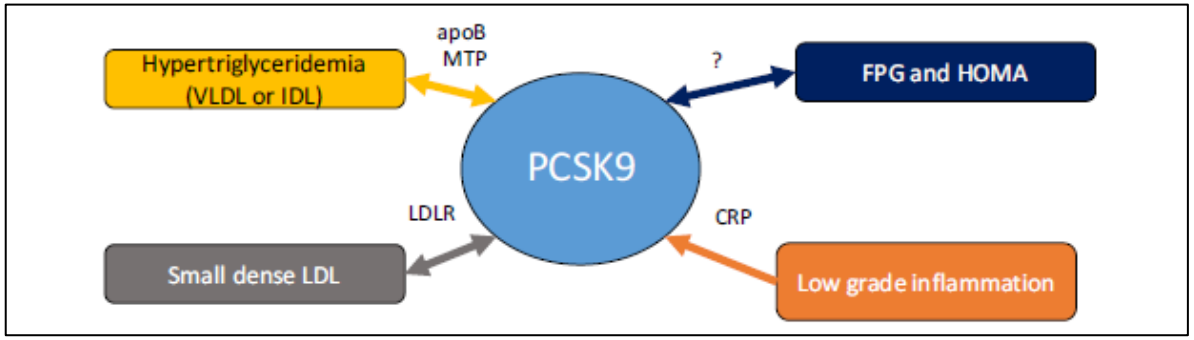
WILEY

ORIGINAL ARTICLE

Obesity and type 2 diabetes are associated with elevated PCSK9 levels in young women

Amy E. Levenson[1] | Amy S. Shah[2] | Philip R. Khoury[3] | Thomas R. Kimball[3] | Elaine M. Urbina[3] | Sarah D. de Ferranti[4] | David M. Maahs[5] | Lawrence M. Dolan[2] | R. Paul Wadwa[5] | Sudha B. Biddinger[1]





Agenda

- Diabetic dyslipidemia
- Role of Lp(a) in diabetic patients
- Target and Therapies of Lp(a)

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

European Heart Journal (2010) 31, 2844–2853
doi:10.1093/eurheartj/ehq386

CURRENT OPINION

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

Børge G. Nordestgaard[1]*, M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Amarenco[8], Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], Petri T. Kovanen[12], Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zeljko Reiner[15], Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg-Hansen[18], for the European Atherosclerosis Society Consensus Panel†

Journal of Clinical Lipidology (2019) 13, 374–392

Journal of Clinical Lipidology

Scientific Statement

Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association

Don P. Wilson, MD*, Terry A. Jacobson, MD, Peter H. Jones, MD, Marlys L. Koschinsky, PhD, Catherine J. McNeal, MD, PhD, Børge G. Nordestgaard, MD, DMSc, Carl E. Orringer, MD

↑ Lp(a) levels

- **1° goal → LDL reduction**
- **2° goal → Lp(a) levels < 50 mg/dL (+++ ASCVD)**

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Table 3 New recommendations, and new and revised concepts

Lipid analyses for CVD risk estimation
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.

ASCVD Risk

Lp(a) levels > 180 mg/dL = HeFH

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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doi:10.1093/eurheartj/ehq386

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Check for updates

↑ Lp(a) levels

- 1° goal → LDL reduction

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Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

- **EPA/DHA / Bile acid sequestrants / Nutraceuticals / fibrates**
- **Niacin/Hormone replacement therapy (HRT)**
- **Statins**
- **Ezetimibe**
- **PCSK9 inhibitors**
- **Lomitapide**
- **Apheresis**

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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III. Treatment

Summary Table of Recommendations†	Class of Rec (strength)	Levels of Evidence
6. Niacin, which lowers Lp(a) concentration, **is not recommended** to reduce ASCVD risk in patients receiving moderate- to high-intensity statins +/− ezetimibe and an on-treatment LDL-C <80 mg/dL.[54,72]	III (harm)	A
7. HRT with estrogen and progesterone, which lowers Lp(a) concentration, **is not recommended** in perimenopausal/postmenopausal women to reduce ASCVD risk.[68,118]	III (harm)	B-R

- ~~Niacin~~/~~Hormone replacement therapy (HRT)~~

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

- EPA/DHA / Bile acid sequestrants / Nutraceuticals / fibrates
- Niacin/Hormone replacement therapy (HRT)
- **Statins**
- Ezetimibe
- PCSK9 inhibitors
- Lomitapide
- Apheresis

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Atherosclerosis 291 (2019) 27–33
Contents lists available at ScienceDirect
Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis

Baseline and on-statin treatment lipoprotein(a) levels for predicting cardiovascular events in patients with familial hypercholesterolemia

Ye-Xuan Cao, Jing-Lu Jin, Yuan-Lin Guo, Di Sun, Hui-Hui Liu, Na-Qiong Wu, Rui-Xia Xu, Cheng-Gang Zhu, Geng Liu, Qian Dong, Jing Sun, Jian-Jun Li

Available online at www.annclinlabsci.org
Annals of Clinical & Laboratory Science, vol. 36, no.3, 2006 353

Brief Communication:
Plasma Lipoprotein(a) Levels and LDL-Cholesterol Lowering Response to Statin Therapy in Patients with Heterozygous Familial Hypercholesterolemia

Atherosclerosis 289 (2019) 201–205
Contents lists available at ScienceDirect
Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis

Statin treatment increases lipoprotein(a) levels in subjects with low molecular weight apolipoprotein(a) phenotype

Reyhana Yahya, Kirsten Berk, Adrie Verhoeven, Sven Bos, Leonie van der Zee, Jeanette Touw, Gertraud Erhart, Florian Kronenberg, Reinier Timman, Eric Sijbrands, Jeanine Roeters van Lennep, Monique Mulder

Eur J Clin Pharmacol (1992) 43: 369–373
European Journal of Clinical Pharmacology

Changes in Lp(a) lipoprotein levels during the treatment of hypercholesterolaemia with simvastatin

L. Slunga, O. Johnson, and G. H. Dahlén

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ATHEROSCLEROSIS
Atherosclerosis 164 (2002) 305–311
www.elsevier.com/locate/atherosclerosis

Atorvastatin lowers lipoprotein(a) but not apolipoprotein(a) fragment levels in hypercholesterolemic subjects at high cardiovascular risk

HMG CoA Reductase Inhibitors Lower LDL Cholesterol Without Reducing Lp(a) Levels

Gerhard M. Kostner, PhD, Dov Gavish, MD, Beate Leopold, PhD, Klaus Bolzano, PhD, Moshe S. Weintraub, MD, and Jan L. Breslow, MD

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association

Lipoprotein(a) Concentrations, Rosuvastatin Therapy, and Residual Vascular Risk: An Analysis From the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin)

Amit V. Khera, Brendan M. Everett, Michael P. Caulfield, Feras M. Hantash, Jay Wohlgemuth, Paul M Ridker and Samia Mora

Articles

Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials

Peter Willeit, Paul M Ridker, Paul J Nestel, John Simes, Andrew M Tonkin, Terje R Pedersen, Gregory G Schwartz, Anders G Olsson, Helen M Colhoun, Florian Kronenberg, Christiane Drechsler, Christoph Wanner, Samia Mora, Anastasia Lesogor, Sotirios Tsimikas

ESC European Society of Cardiology
European Heart Journal (2019) 0, 1–10
doi:10.1093/eurheartj/ehz310
CLINICAL RESEARCH
Lipids

Statin therapy increases lipoprotein(a) levels

Sotirios Tsimikas [1]*, Philip L.S.M. Gordts[2,3]*, Chelsea Nora[2,3], Calvin Yeang[1], and Joseph L. Witztum [3]

Statins → no Lpa reduction

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Journal of Clinical Lipidology (2019) 13, 374–392

Journal of Clinical Lipidology

Scientific Statement

Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association

Don P. Wilson, MD*, Terry A. Jacobson, MD, Peter H. Jones, MD, Marlys L. Koschinsky, PhD, Catherine J. McNeal, MD, PhD, Børge G. Nordestgaard, MD, DMSc, Carl E. Orringer, MD

Summary Table of Recommendations†	Class of Rec (strength)	Levels of Evidence
III. Treatment		
1. In adults aged 40-75 y with a 10-y ASCVD risk of 7.5%–19.9%, the finding of an Lp(a) ≥50 mg/dL or ≥100 nmol/L **is reasonable** to be used as a risk-enhancing factor to favor initiation of a moderate- or high-intensity statin in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[26,36]	IIa	B-NR
2. In high-risk* or very-high-risk** patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L, it **is reasonable** to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.[21,50,53]	IIa	A

Statins

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

- EPA/DHA / Bile acid sequestrants / Nutraceuticals / fibrates
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- Statins
- **Ezetimibe**
- PCSK9 inhibitors
- Lomitapide
- Apheresis

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

SCIENTIFIC REPORTS

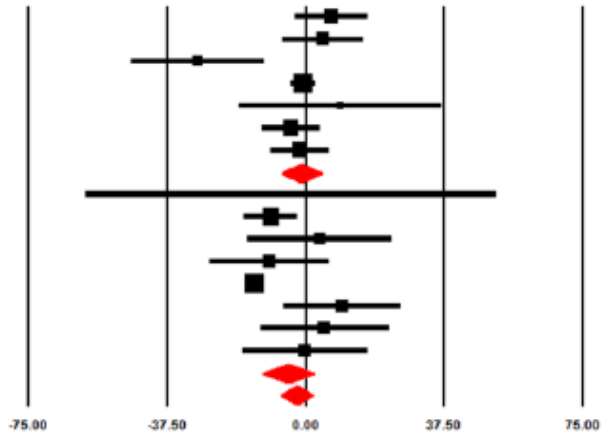
OPEN

Received: 30 April 2018
Accepted: 6 November 2018
Published online: 14 December 2018

Impact of ezetimibe on plasma lipoprotein(a) concentrations as monotherapy or in combination with statins: a systematic review and meta-analysis of randomized controlled trials

Amirhossein Sahebkar[1,2,3], Luis E. Simental-Mendía[4], Matteo Pirro[5], Maciej Banach[6,7], Gerald F. Watts[8,9], Cesare Sirotri[10], Khalid Al-Rasadi[11] & Stephen L. Atkin[12]

Group by Treatment mode	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Combination therapy	Kerzner et al., 2003b	7.000	4.921	24.216	-2.645	16.645	1.422	0.155
Combination therapy	Melani et al., 2003b	4.900	5.513	30.397	-5.906	15.706	0.889	0.374
Combination therapy	Moutzouri et al., 2012	-29.030	9.039	81.698	-46.745	-11.315	-3.212	0.001
Combination therapy	Sacougos et al., 2007	-0.579	1.642	2.696	-3.788	2.648	-0.347	0.728
Combination therapy	Ballantyne et al., 2003b	9.509	13.931	194.072	-17.804	36.804	0.682	0.495
Combination therapy	Davidson et al., 2002b	-3.809	4.027	16.213	-11.692	4.092	-0.944	0.345
Combination therapy	Goldberg et al., 2004b	-1.300	3.948	15.587	-9.038	6.438	-0.329	0.742
Combination therapy		-1.043	2.705	7.315	-6.344	4.258	-0.386	0.700
Monotherapy	Ballantyne et al., 2003a	-3.709	28.233	797.102	-59.036	51.636	-0.131	0.896
Monotherapy	Knopp et al., 2003	-9.260	3.637	13.230	-16.389	-2.131	-2.546	0.011
Monotherapy	Melani et al., 2003a	4.100	9.828	96.580	-15.162	23.362	0.417	0.677
Monotherapy	Davidson et al., 2002a	-9.609	8.159	66.421	-25.573	6.373	-1.178	0.239
Monotherapy	Dujovne et al., 2002	-13.499	0.324	0.105	-14.135	-12.865	-41.639	0.000
Monotherapy	Geiss et al., 2005	10.000	8.062	65.000	-5.802	25.802	1.240	0.215
Monotherapy	Goldberg et al., 2004a	5.209	8.802	77.470	-12.051	22.451	0.591	0.555
Monotherapy	Kerzner et al., 2003a	0.000	8.514	72.485	-16.687	16.687	0.000	1.000
Monotherapy		-4.641	3.515	12.355	-11.530	2.248	-1.320	0.187
Overall		-2.381	2.143	4.595	-6.582	1.820	-1.111	0.267



Ezetimibe ~~+~~ X no Lpa reduction

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Journal of Clinical Lipidology (2019) 13, 374–392

Journal of Clinical Lipidology

Scientific Statement

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Summary Table of Recommendations†	Class of Rec (strength)	Levels of Evidence
3. In very-high-risk** patients, taking a maximally tolerated statin with Lp(a) ≥50 mg/dL or ≥100 nmol/L, the addition of ezetimibe **is reasonable** in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[117]		
4. In high-risk* patients taking a maximally tolerated statin, with Lp(a) ≥50 mg/dL or ≥100 nmol/L, the addition of ezetimibe **may be reasonable** in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[117]		

Ezetimibe ✓

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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- Lomitapide
- Apheresis

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 290, NO. 18, pp. 11649–11662, May 1, 2015

Lipoprotein(a) Catabolism Is Regulated by Proprotein Convertase Subtilisin/Kexin Type 9 through the Low Density Lipoprotein Receptor*

Received for publication, September 14, 2014, and in revised form, February 21, 2015 Published, JBC Papers in Press, March 16, 2015, DOI 10.1074/jbc.M114.611988

Rocco Romagnuolo[‡], Corey A. Scipione[‡], Michael B. Boffa[‡], Santica M. Marcovina[§], Nabil G. Seidah[¶], and Marlys L. Koschinsky[‡‖]

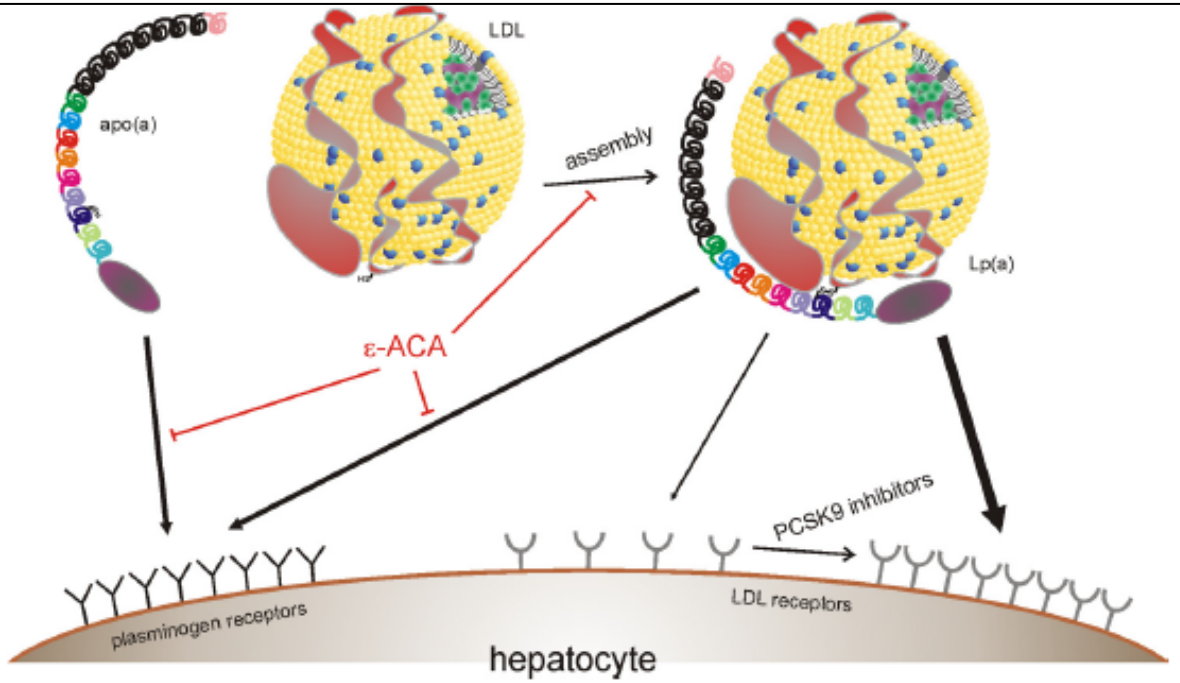


FIGURE 7. **Model for receptor-mediated catabolism of apo(a) and Lp(a).** Apo(a) and apoB-containing lipoproteins are independently secreted from hepatocytes and form a non-covalent, and subsequently covalent, complex as Lp(a). Apo(a) can be internalized by plasminogen receptors, and the apo(a) component of Lp(a) mediates clearance of the particle by plasminogen receptors. Apo(a) can only be internalized by the LDL receptor when in a complex with LDL. ϵ-ACA can inhibit binding of apo(a) or Lp(a) to plasminogen receptors as well as Lp(a) assembly, the latter through inhibition of non-covalent interactions between apo(a) and apoB-100. However, ϵ-ACA cannot prevent binding of pre-formed Lp(a) to the LDL receptor. In the presence of inhibitors of PCSK9, there is a substantial increase in DL receptor number such that clearance of Lp(a) through this route is of a much greater magnitude.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 2, 2020

ORIGINAL INVESTIGATIONS

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome

Vera A. Bittner, MD, MSPH,[a] Michael Szarek, PhD,[b] Philip E. Aylward, BM, BCh, PhD,[c] Deepak L. Bhatt, MD, MPH,[d] Rafael Diaz, MD,[e] Jay M. Edelberg, MD, PhD,[f] Zlatko Fras, MD,[g,h] Shaun G. Goodman, MD,[i,j] Sigrun Halvorsen, MD,[k,l] Corinne Hanotin, MD,[m] Robert A. Harrington, MD,[n] J. Wouter Jukema, MD, PhD,[o] Virginie Loizeau, MS,[m] Patrick M. Moriarty, MD,[p] Angèle Moryusef, MD,[f] Robert Pordy, MD,[q] Matthew T. Roe, MD, MHS,[r,s] Peter Sinnaeve, MD,[t,u] Sotirios Tsimikas, MD,[v] Robert Vogel, MD,[w] Harvey D. White, DSc,[x] Doron Zahger, MD,[y] Andreas M. Zeiher, MD,[z] Ph. Gabriel Steg, MD,[aa,bb] Gregory G. Schwartz, MD, PhD,[w] for the ODYSSEY OUTCOMES Committees and Investigators

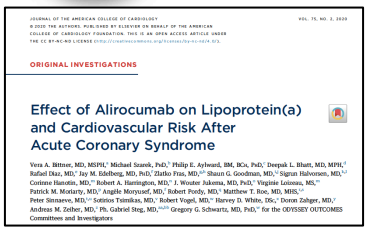
Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

Insights From the FOURIER Trial

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?



ORIGINAL INVESTIGATIONS

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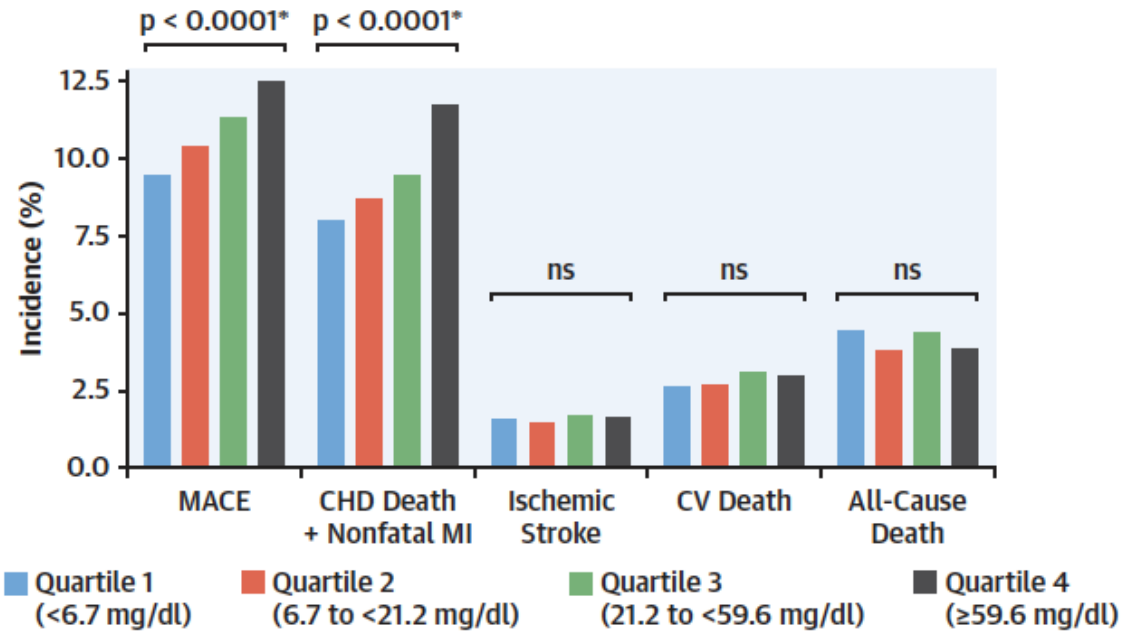
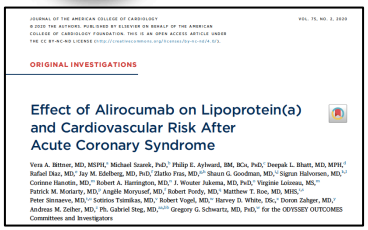
FIGURE 1 Baseline Lipoprotein(a) Quartile as a Predictor of Events in the Placebo Group



Incidence of major adverse cardiovascular events (MACE) and secondary endpoints are shown by baseline lipoprotein(a) quartiles for the placebo group. MACE and coronary heart disease (CHD) death and nonfatal myocardial infarction (MI) incidence were greater at higher lipoprotein(a) levels. There were no significant relationships between lipoprotein(a) quartile and ischemic stroke, cardiovascular (CV) death, or all-cause death. *$p < 0.0001$ for linear trend across quartiles in unadjusted Cox proportional hazards model for MACE and coronary heart disease death and nonfatal myocardial infarction. $p > 0.05$ for other endpoints.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 2, 2020

ORIGINAL INVESTIGATIONS

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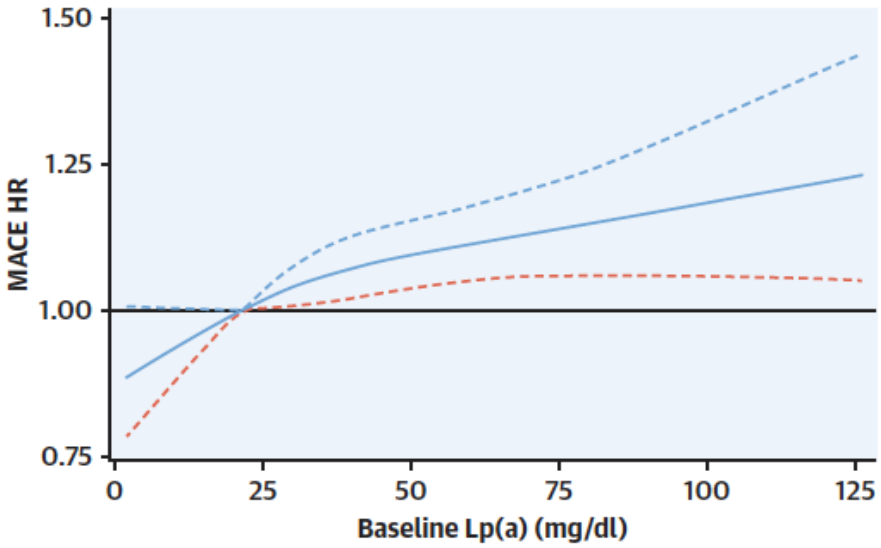
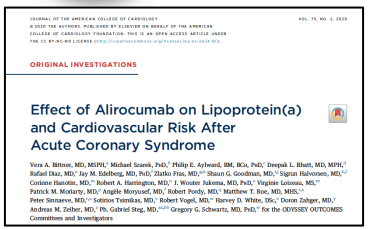
FIGURE 2 Spline Analysis of Continuous Baseline Lipoprotein(a) and the Primary Endpoint Hazard Ratio (MACE) in the Placebo Group



Hazard ratio (HR) set to 1.00 at the overall baseline median (21.2 mg/dl) concentration of lipoprotein(a). $p < 0.0001$ for spline effect. This reflects spline of degree 3 (piecewise cubic curve) with natural cubic basis and 3 knots, located at overall 25th percentile (6.7 mg/dl), median (21.2 mg/dl), and 75th percentile (59.6 mg/dl). The p value for spline effect is based on the score test. The **blue dotted line** indicates the upper bound of 95% confidence intervals (CIs) and the **red dotted line** indicates the lower bound of 95% CIs. Lp(a) = lipoprotein(a); other abbreviation as in Figure 1.



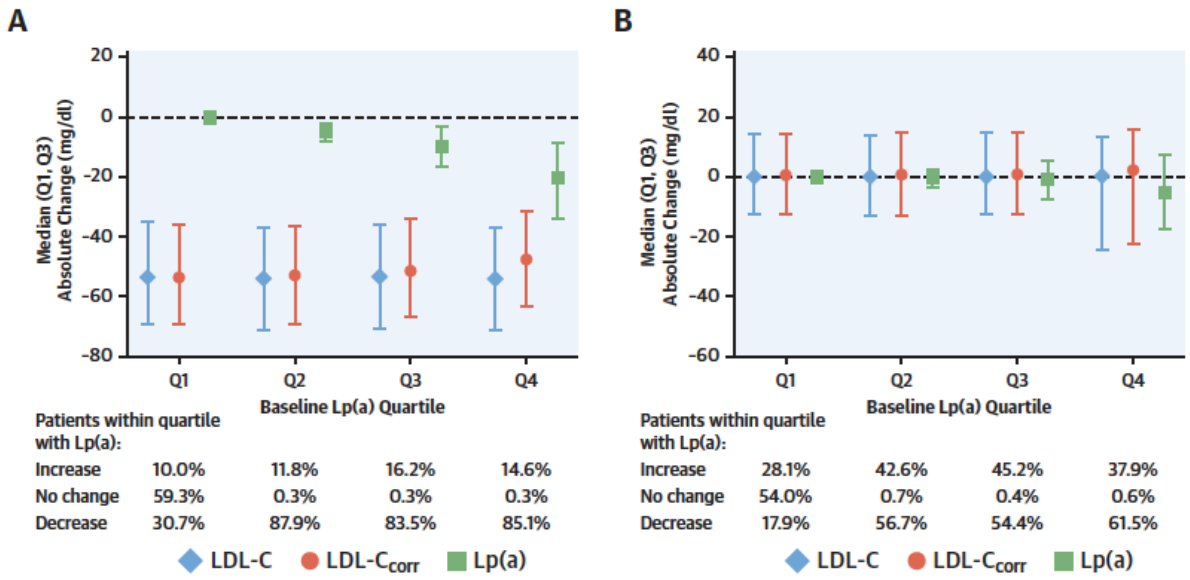
ORIGINAL INVESTIGATIONS

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

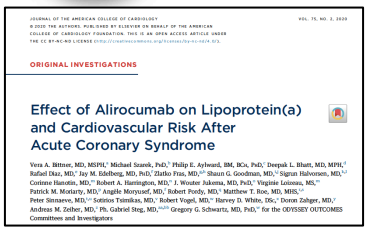
week 16 (48)
Lp(a) -23%

FIGURE 4 Absolute Change From Baseline to Month 4 in LDL-C, LDL-C_{corr}, and Lipoprotein(a) Levels



Absolute change from baseline to month 4 in low-density lipoprotein cholesterol (LDL-C), low-density lipoprotein cholesterol corrected for cholesterol content in lipoprotein(a) (LDL-C_{corr}), and lipoprotein(a) levels by baseline lipoprotein(a) quartile in **(A)** alirocumab group and **(B)** placebo group. Medians and interquartile ranges of absolute changes from baseline to month 4 are shown stratified by baseline lipoprotein(a) quartile for 3 lipid parameters: LDL-C **(blue)**, LDL-C_{corr} **(red)**, and lipoprotein(a) **(green)**. The percentages below the x-axis summarize the percent of patients within each baseline lipoprotein(a) quartile with an increase, no change, or decrease in lipoprotein(a) from baseline to month 4. Q = quartile.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 2, 2020

ORIGINAL INVESTIGATIONS

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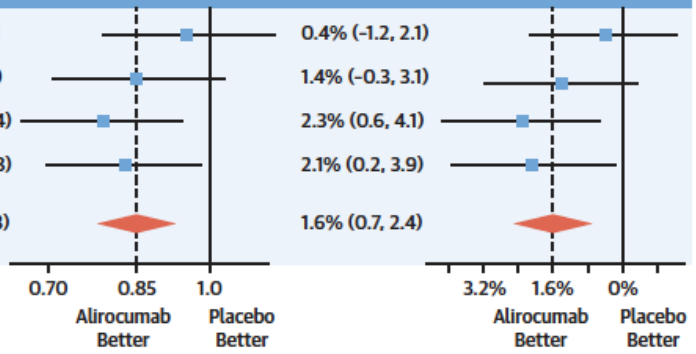
FIGURE 3 Relative and Absolute Treatment Effect on MACE by Baseline Lipoprotein(a) Quartile

Subgroup	MACE Incidence: Alirocumab n/N (%)	MACE Incidence: Placebo n/N (%)	HR (95% CI) ($p_{interaction}$ = 0.55)	Absolute Risk Reduction (95% CI) ($p_{interaction}$ = 0.0011)
Quartile 1	211/2,327 (9.1)	228/2,403 (9.5)	0.95 (0.79, 1.15)	0.4% (-1.2, 2.1)
Quartile 2	219/2,438 (9.0)	239/2,293 (10.4)	0.85 (0.71, 1.03)	1.4% (-0.3, 3.1)
Quartile 3	212/2,356 (9.0)	269/2,373 (11.3)	0.79 (0.66, 0.94)	2.3% (0.6, 4.1)
Quartile 4	261/2,341 (11.2)	316/2,393 (13.2)	0.83 (0.70, 0.98)	2.1% (0.2, 3.9)
Overall	903/9,462 (9.5)	1,052/9,462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7, 2.4)



Incidence of MACE is shown for the alirocumab and placebo groups stratified by baseline quartile of lipoprotein(a) and for the overall population. The Forest plots depict relative and absolute risk reduction with alirocumab compared with placebo. For relative risk reduction, there was no significant interaction by baseline lipoprotein(a) quartile, but absolute treatment effect was significantly greater in the 2 highest lipoprotein(a) quartiles. Abbreviations as in Figures 1 and 2.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Circulation

ORIGINAL RESEARCH ARTICLE

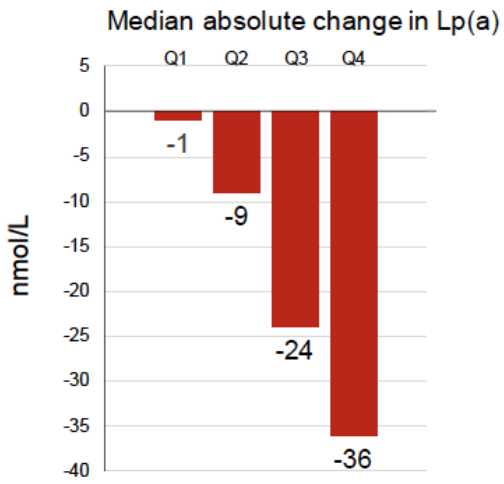
Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk
Insights From the FOURIER Trial

week 48
Lp(a) -26.9%

O'Donoghue ML et al., Lp(a), PCSK9 Inhibition and CV Risk

Supplemental Figure 4:

A/



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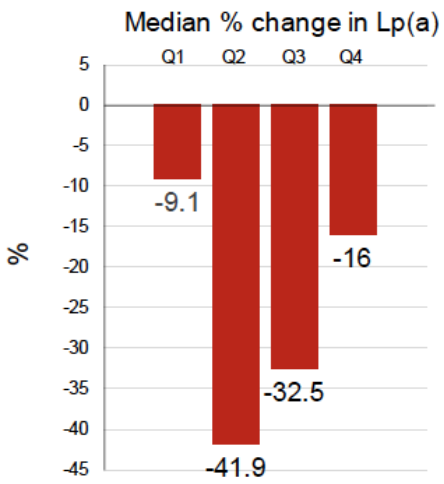

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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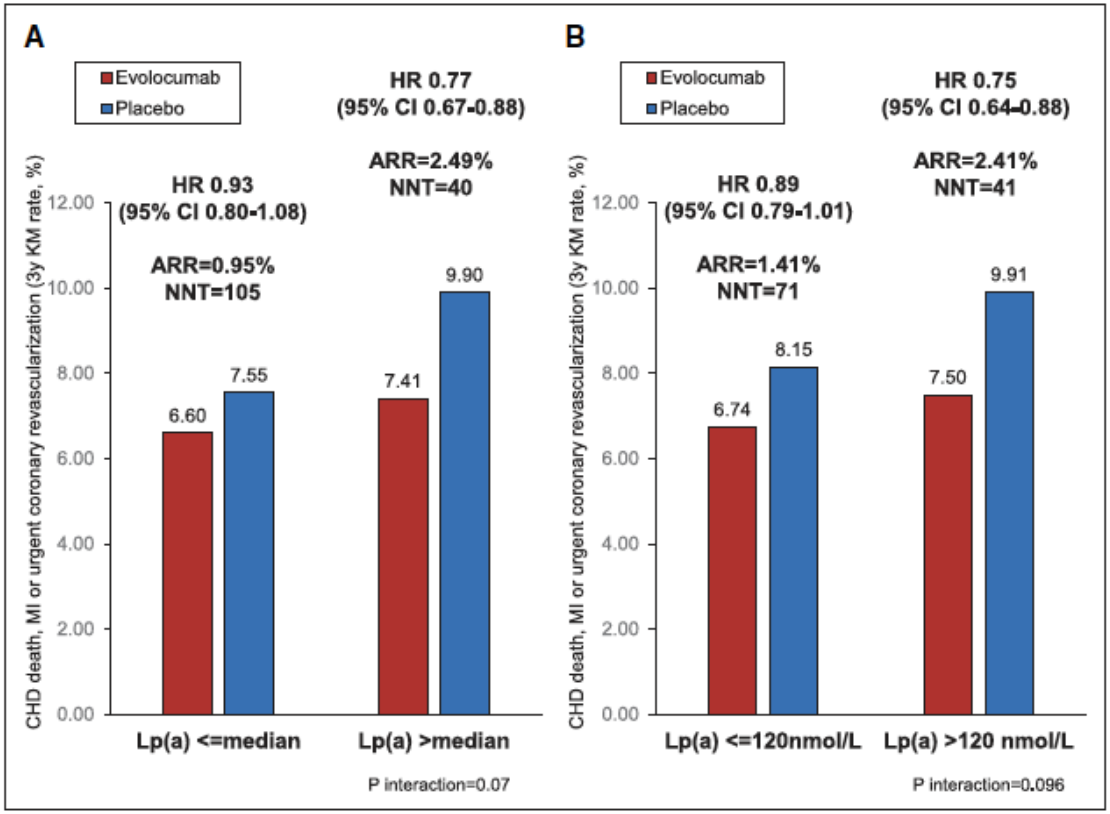


Figure 1. The efficacy of evolocumab by Lp(a) concentration.

The efficacy of evolocumab vs placebo stratified by baseline Lp(a) concentration split at the median (**A**) and split at 120 nmol/L (50 mg/dL) for reducing CHD death, MI, or urgent coronary revascularization (**B**). ARR indicates absolute risk reduction; CHD, coronary heart disease; KM, Kaplan–Meier; Lp(a), lipoprotein(a); MI, myocardial infarction; and NNT, number needed to treat.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

Insights From the FOURIER Trial

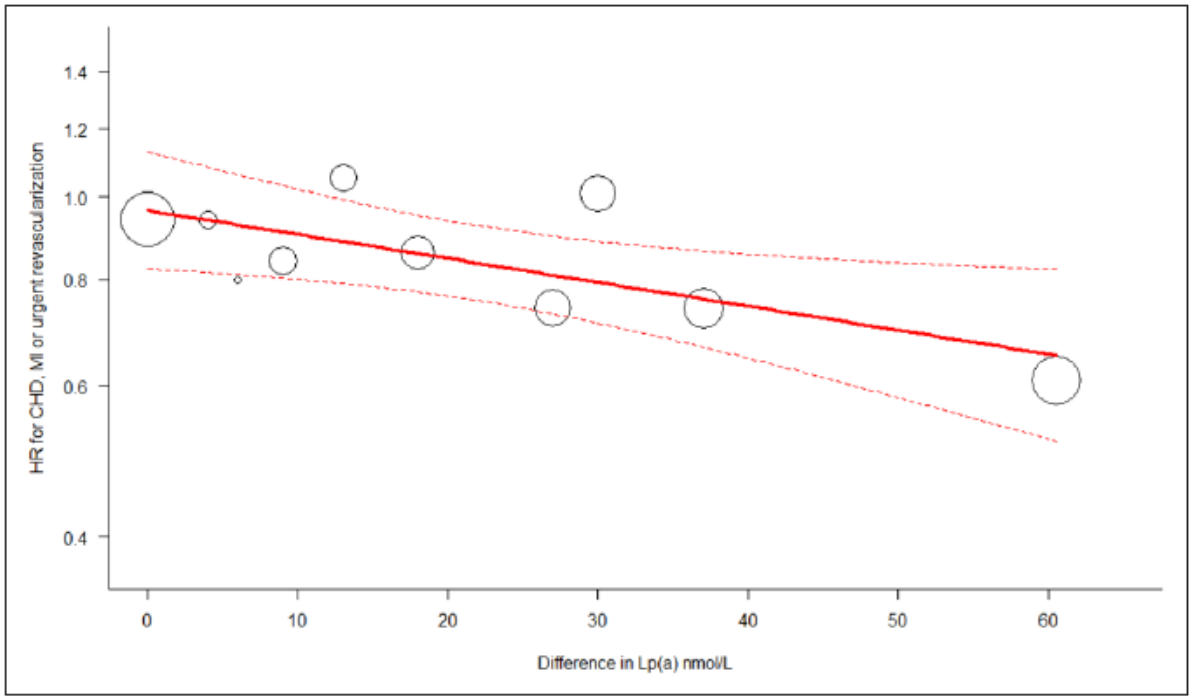


Figure 2. Treatment effect on major coronary events per unit decrease in Lp(a).
Patients were stratified into deciles on the basis of baseline Lp(a), and the difference in Lp(a) and LDL-C at 48 weeks between the evolocumab and placebo arms was calculated within each decile. The hazard ratio (HR) for major coronary events with evolocumab vs placebo was also calculated within each decile. Weighted least-square linear regression was then performed on the log-transformed HR to examine the association between the treatment effect on major coronary events and per unit decrease in Lp(a), adjusting for differences in LDL-C. There was a significant relationship with a 15% lower risk (95% CI, 2%–26%; *P*=0.0199) per 25 nmol/L reduction in Lp(a) after adjusting for the change in LDL-C (model accounts for 57% of total variability of clinical benefit). Red dotted lines represent 95% CIs. CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); and MI, myocardial infarction.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 2, 2020

ORIGINAL INVESTIGATIONS

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome

Vera A. Bittner, MD, MSPH,[a] Michael Szarek, PhD,[b] Philip E. Aylward, BM, BCh, PhD,[c] Deepak L. Bhatt, MD, MPH,[d] Rafael Diaz, MD,[e] Jay M. Edelberg, MD, PhD,[f] Zlatko Fras, MD,[g,h] Shaun G. Goodman, MD,[i,j] Sigrun Halvorsen, MD,[k,l] Corinne Hanotin, MD,[m] Robert A. Harrington, MD,[n] J. Wouter Jukema, MD, PhD,[o] Virginie Loizeau, MS,[m] Patrick M. Moriarty, MD,[p] Angèle Moryusef, MD,[f] Robert Pordy, MD,[q] Matthew T. Roe, MD, MHS,[r,s] Peter Sinnaeve, MD,[t,u] Sotirios Tsimikas, MD,[v] Robert Vogel, MD,[w] Harvey D. White, DSc,[x] Doron Zahger, MD,[y] Andreas M. Zeiher, MD,[z] Ph. Gabriel Steg, MD,[aa,bb] Gregory G. Schwartz, MD, PhD,[w] for the ODYSSEY OUTCOMES Committees and Investigators

Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

Insights From the FOURIER Trial

PCSK9i → 25% Lpa reduction

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Journal of Clinical Lipidology (2019) 13, 374–392

Journal of Clinical Lipidology

Scientific Statement

Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association

Don P. Wilson, MD*, Terry A. Jacobson, MD, Peter H. Jones, MD, Marlys L. Koschinsky, PhD, Catherine J. McNeal, MD, PhD, Børge G. Nordestgaard, MD, DMSc, Carl E. Orringer, MD

Summary Table of Recommendations†	Class of Rec (strength)	Levels of Evidence
III. Treatment		
5. In very-high-risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL) and an Lp(a) of ≥50 mg/dL or ≥100 nmol/L, the addition of a PCSK9 inhibitor **is reasonable.** [74,99,106,116]		

PCSK9i

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

- EPA/DHA / Bile acid sequestrants / Nutraceuticals / fibrates
- Niacin/Hormone replacement therapy (HRT)
- Statins
- Ezetimibe
- PCSK9 inhibitors
- **Lomitapide**
- Apheresis

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Journal of Clinical Lipidology (2016) 10, 273–282
Journal of Clinical Lipidology

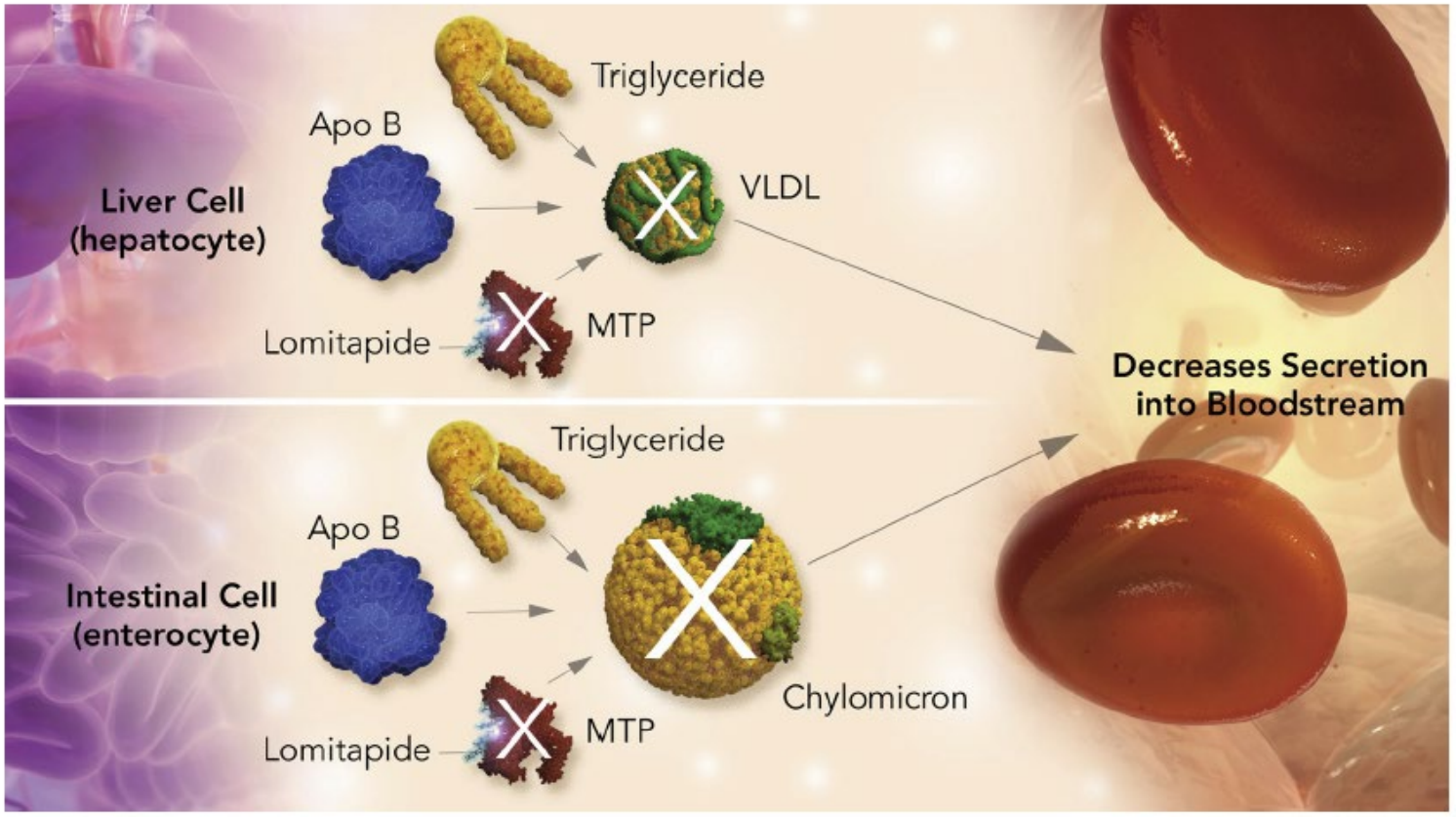
LOWER, a registry of lomitapide-treated patients with homozygous familial hypercholesterolemia: Rationale and design

Dirk J. Blom, MD, PhD*, Zahi A. Fayad, BSEE, MSE, PhD, John J. P. Kastelein, MD, PhD, Dominique Larrey, MD, PhD, Lukas Makris, BS, MS, PhD, Charles Schwamlein, MD, MPH, LeAnne Bloeden, BS, MS, RD, James Underberg, MS, MD, on behalf of the LOWER investigators

Adv Ther
DOI 10.1007/s12325-017-0531-x
ORIGINAL RESEARCH

Efficacy of Lomitapide in the Treatment of Familial Homozygous Hypercholesterolemia: Results of a Real-World Clinical Experience in Italy

Laura D'Erasmo · Angelo Baldassare Cefalù · Davide Noto · Antonina Giammanco · Maurizio Averna · Paolo Pintus · Paolo Medde · Giovanni Battista Vigna · Cesare Sirtori · Laura Calabresi · Chiara Pavanello · Marco Bucci · Carlo Sabbà · Patrizia Suppressa · Francesco Natale · Paolo Calabrò · Tiziana Sampietro · Federico Bigazzi · Francesco Sbrana · Katia Bonomo · Fulvio Sileo · Marcello Arca



Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study

Marina Cuchel, Emma A Meagher, Hendrik du Toit Theron, Dirk J Blom, A David Marais, Robert A Hegele, Maurizio R Averna, Cesare R Sirtori, Prediman K Shah, Daniel Gaudet, Claudia Stefanutti, Giovanni B Vigna, Anna M E Du Plessis, Kathleen J Propert, William J Sasiela, LeAnne T Blankon, Daniel J Rader, for the Phase 3 HoFH Lomitapide Study investigators

	Baseline (n=29)	Week 26 (n=23)		
		Concentrations	Change from baseline (%)	p value†
Total cholesterol, mmol/L	11·1 (3·5)	6·1 (2·9)	−46% (−56 to −35)	<0·0001
LDL cholesterol, mmol/L	8·7 (2·9)	4·3 (2·5)	−50% (−62 to −39)	<0·0001
VLDL cholesterol, mmol/L	0·5 (0·3)	0·3 (0·3)	−45% (−61 to −29)	<0·0001
Non-HDL cholesterol, mmol/L	10·0 (3·4)	5·1 (2·8)	−50% (−61 to −39)	<0·0001
Triglycerides, mmol/L	1·0 (0·4 to 2·9)	0·5 (0·1 to 1·7)	−45% (−61 to −29)	<0·0001
ApoB, g/L	2·6 (0·8)	1·3 (0·7)	−49% (−60 to −38)	<0·0001
Lipoprotein (a), µmol/L	2·4 (0·6 to 2·1)	1·7 (0·3 to 7·1)	−15% (−30 to 0·9)	0·0003
HDL cholesterol, mmol/L	1·1 (0·3)	1·0 (0·4)	−12% (−20 to −4)	0·0001
ApoA-I, g/L	1·2 (0·3)	1·0 (0·2)	−14% (−17 to −4)	0·0003

Lomitapide → 20% Lpa reduction

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

- EPA/DHA / Bile acid sequestrants / Nutraceuticals / fibrates
- Niacin/Hormone replacement therapy (HRT)
- Statins
- Ezetimibe
- PCSK9 inhibitors
- Lomitapide
- **Apheresis**

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Journal of Clinical Lipidology (2019) 13, 894–900

Journal of Clinical Lipidology

Original Articles

Lipoprotein apheresis for lipoprotein(a) and cardiovascular disease

Patrick M. Moriarty, MD*, Jessica V. Gray, BA, Lauryn K. Gorby, BS

Atherosclerosis Supplements 40 (2019) 1–7

Contents lists available at ScienceDirect

Atherosclerosis Supplements

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

Actual situation of lipoprotein apheresis in patients with elevated lipoprotein(a) levels

Ulrich Julius*, Sergey Tselmin, Ulrike Schatz, Sabine Fischer, Andreas L. Birkenfeld, Stefan R. Bornstein

Lipoaferesi → 20% Lpa reduction

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

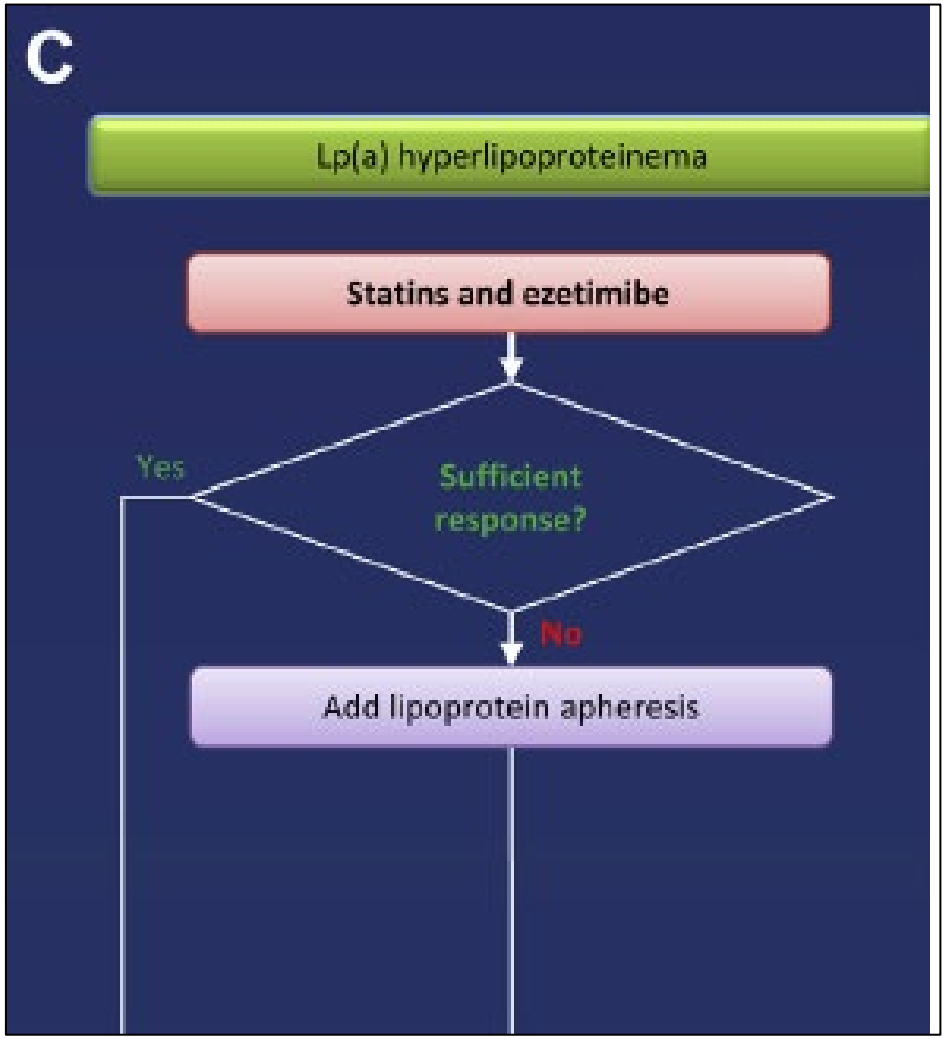
Journal of Clinical Lipidology (2017) 11, 858–871

Journal of Clinical Lipidology

Review Articles

Toward an international consensus—Integrating lipoprotein apheresis and new lipid-lowering drugs

Claudia Stefanutti, MD, PhD*, Ulrich Julius, MD,
Gerald F. Watts, MD, PhD, DSc, FRACP, FRCP (Lond),
Mariko Harada-Shiba, MD, PhD, Maria Cossu, MD,
Volker J. Schettler, MD, Priv Doz, Giustina De Silvestro, MD,
Handrean Soran, MD, FRCP, MSc, MRCP, MBChB,
Jeanine Roeters Van Lennep, MD, PhD, Livia Pisciotta, MD, PhD,
Hans U. Klör, MD, Kurt Widhalm, MD,
Patrick M. Moriarty, MD, PhD, FACC, FACP, and the MIGHTY MEDIC Multinational Society



Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia, M.S., Jonathan Guerriero, M.B.A., Nicholas J. Viney, B.Sc., Louis O'Dea, M.B., B.Ch., B.A.O., and Joseph L. Witztum, M.D., for the AKCEA-APO(a)-L_{Rx} Study Investigators*

APO(a)-L_{Rx}

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

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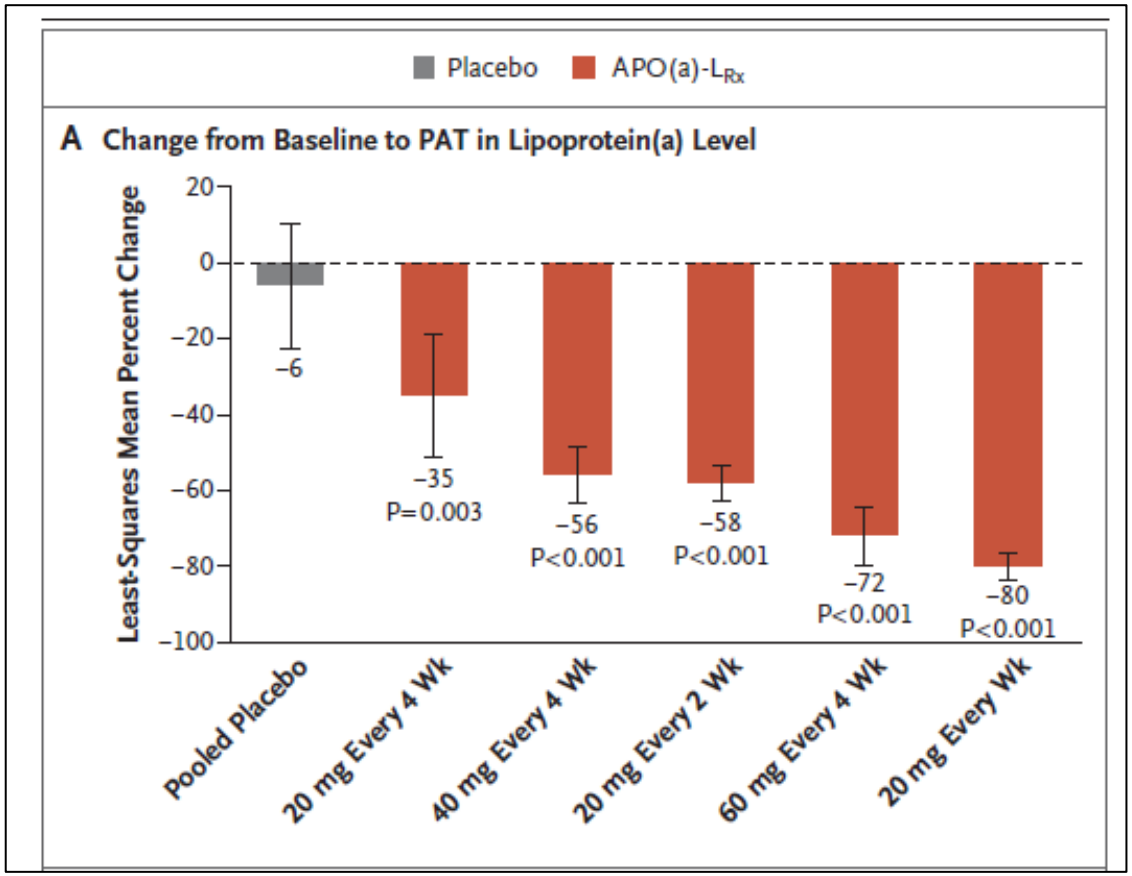

CASI CLINICO

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Man
60 years
No illness reported
Son affected by heterozygous familial hypercholesterolemia
Pre-treatment lipid values:
CT 375 mg/dL
HDL 46 mg/dL
TG 95 mg/dL
LDL 310 mg/dL
No data on apolipoprotein

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Visit 25/07/2019

Lipid lowering therapy:

Simvastatin 40 mg/Ezetimibe 10 mg

CT 201

HDL 43

TG 92

LDL 140 mg/dL

Planel:

Day Hospital 09/09/19

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

09/09/19:

NO DAY HOSPITAL

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

LIPID inCode

Genetic report

Sample nº: 70058805
Your reference: ITA CT 01 226

Barcelona,
22 November 2019

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Result of the genetic diagnosis

Familial Hypercholesterolemia: POSITIVE

Detected the variant c.1207_1209del, p.(Phe403del), of the gene *LDLR* (NM_000527.4) in heterozygosis, classified as LIKELY PATHOGENIC regarding Familial Hypercholesterolemia.

Autosomal Recessive Hypercholesterolemia: NEGATIVE

The genetic analysis has not identified any clinically significant variant in the *LDLRAP1* gene.

Lysosomal Acid Lipase Deficiency: NEGATIVE

The genetic analysis has not identified any clinically significant variant in the *LIPA* gene.

Clinical management of patient with dyslipidemia

Genetic variants associated with response to statins:

The genotypes of the variants analysed do not imply a response to statins in this subject different from that of the general population.

Genetic variants associated with elevated plasma levels of Lp(a):

Identified the variant rs10455872 of the *LPA* gene in homozygosis; its presence is associated with elevated plasma Lp(a) levels, an independent marker of cardiovascular risk; consider determining the levels of this lipoprotein in your patient.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE E DI ALTA SPECIALIZZAZIONE
CATANIA

Direttore:

Ambulatorio Prelievi: 095-7594411

Presa in carico: 10/12/2019 Ore: 12:07

Id.:00026380

Sig. [redacted]

Routine

Data Nascita: 10/11/1962 Età: 57 Anni
Sesso M

Provenienza: NESIMA MEDICINA 02210101

Richiesta: **12100034** **10/12/2019** Ore: 12:10

Esame	*Esito*		*U.M.*	*Intervalli Riferimento*
MARCATORI DI TROMBOFILIA				
Lipoproteina (a)	**254**		mg/dl	< 30
PROTEINE SPECIFICHE				
Apolipoproteina A-I	**103**	<	mg/dl	115.0 - 220.0
Apolipoproteina B	**108**		mg/dl	60.0 - 160.0
Apo B/Apo A-I	**1.05**	>		0.35 - 1.00

Referto Completo

Il Direttore

CASO CLINICO 2

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Man
57 years
History of MI
Type 2 diabetes
Treatment: Metformin - no lipid lowering therapy
Day Hospital
Pre-treatment lipid values:
CT 311mg/dL
HDL 49 mg/dL
TG 115 mg/dL
LDL 239 mg/dL
ApoB 151 mg/dL
ApoAI 118 mg/dL
Lp(a) 154 mg/dL

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

LIPID inCode

Genetic report

Sample nº: 70058800
Your reference: ITA CT 01 221

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

Result of the genetic diagnosis

Familial Hypercholesterolemia: INCONCLUSIVE

Detected the variant c.2014G>A, p.(Val672Met), of the gene *PCSK9* (NM_174936.3) in heterozygosis, classified as of UNCERTAIN CLINICAL SIGNIFICANCE regarding Familial Hypercholesterolemia.

Autosomal Recessive Hypercholesterolemia: NEGATIVE

The genetic analysis has not identified any clinically significant variant in the *LDLRAP1* gene.

Lysosomal Acid Lipase Deficiency: NEGATIVE

The genetic analysis has not identified any clinically significant variant in the *LIPA* gene.

Genetic variants associated with elevated plasma levels of Lp(a):

No variants associated with elevated plasma Lp(a) levels have been identified.

Lpa e rischio cardiovascolare: è importante ridurla, con quali farmaci?

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 290, NO. 18, pp. 11649–11662, May 1, 2015

Lipoprotein(a) Catabolism Is Regulated by Proprotein Convertase Subtilisin/Kexin Type 9 through the Low Density Lipoprotein Receptor*

Received for publication, September 14, 2014, and in revised form, February 21, 2015 Published, JBC Papers in Press, March 16, 2015, DOI 10.1074/jbc.M114.611988

Rocco Romagnuolo[‡], Corey A. Scipione[‡], Michael B. Boffa[‡], Santica M. Marcovina[§], Nabil G. Seidah[¶], and Marlys L. Koschinsky[‡‖]

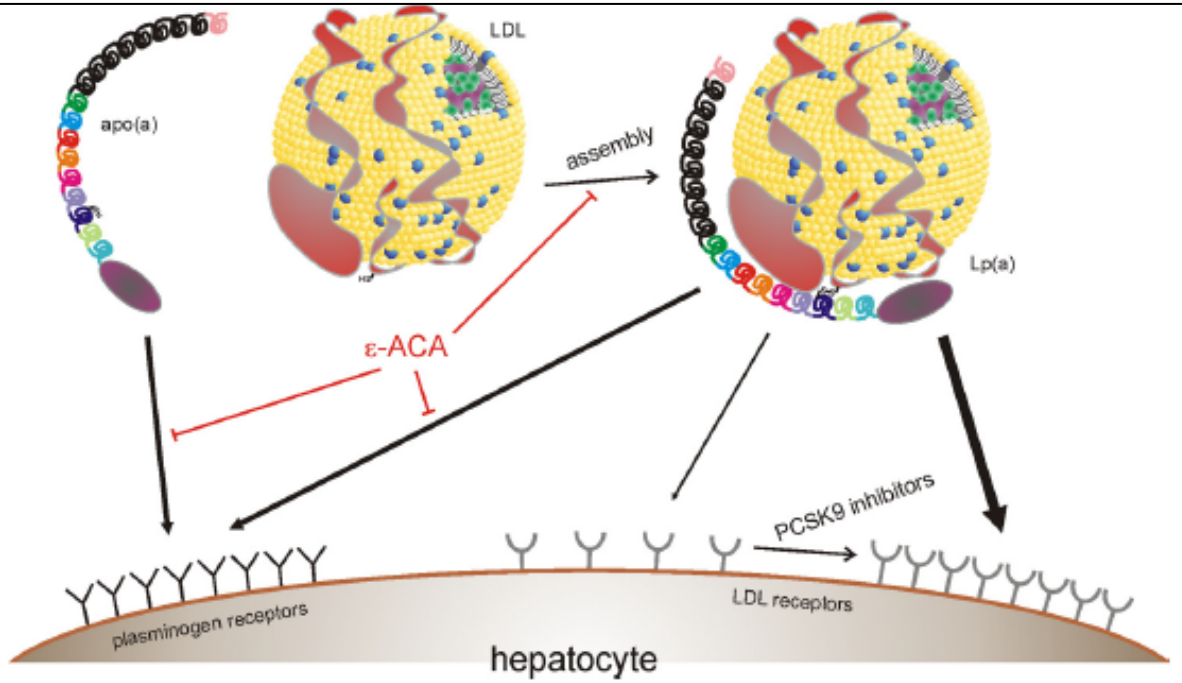

FIGURE 7. **Model for receptor-mediated catabolism of apo(a) and Lp(a).** Apo(a) and apoB-containing lipoproteins are independently secreted from hepatocytes and form a non-covalent, and subsequently covalent, complex as Lp(a). Apo(a) can be internalized by plasminogen receptors, and the apo(a) component of Lp(a) mediates clearance of the particle by plasminogen receptors. Apo(a) can only be internalized by the LDL receptor when in a complex with LDL. ϵ-ACA can inhibit binding of apo(a) or Lp(a) to plasminogen receptors as well as Lp(a) assembly, the latter through inhibition of non-covalent interactions between apo(a) and apoB-100. However, ϵ-ACA cannot prevent binding of pre-formed Lp(a) to the LDL receptor. In the presence of inhibitors of PCSK9, there is a substantial increase in DL receptor number such that clearance of Lp(a) through this route is of a much greater magnitude.

Conclusion

- Lp(a) is a causal cardiovascular risk factor as well as LDL cholesterol

- Type 2 diabetes may exhibite an impaired cross-talk of Lp(a) and PCSK9 plasma levels

- APO (a)-Lrx (ASO) may be a novel necessary therapy for Lp(a) reduction