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LIPOPROTEIN(A). UN FACTEUR DE RISQUE NÉGLIGÉ EN SUISSE?

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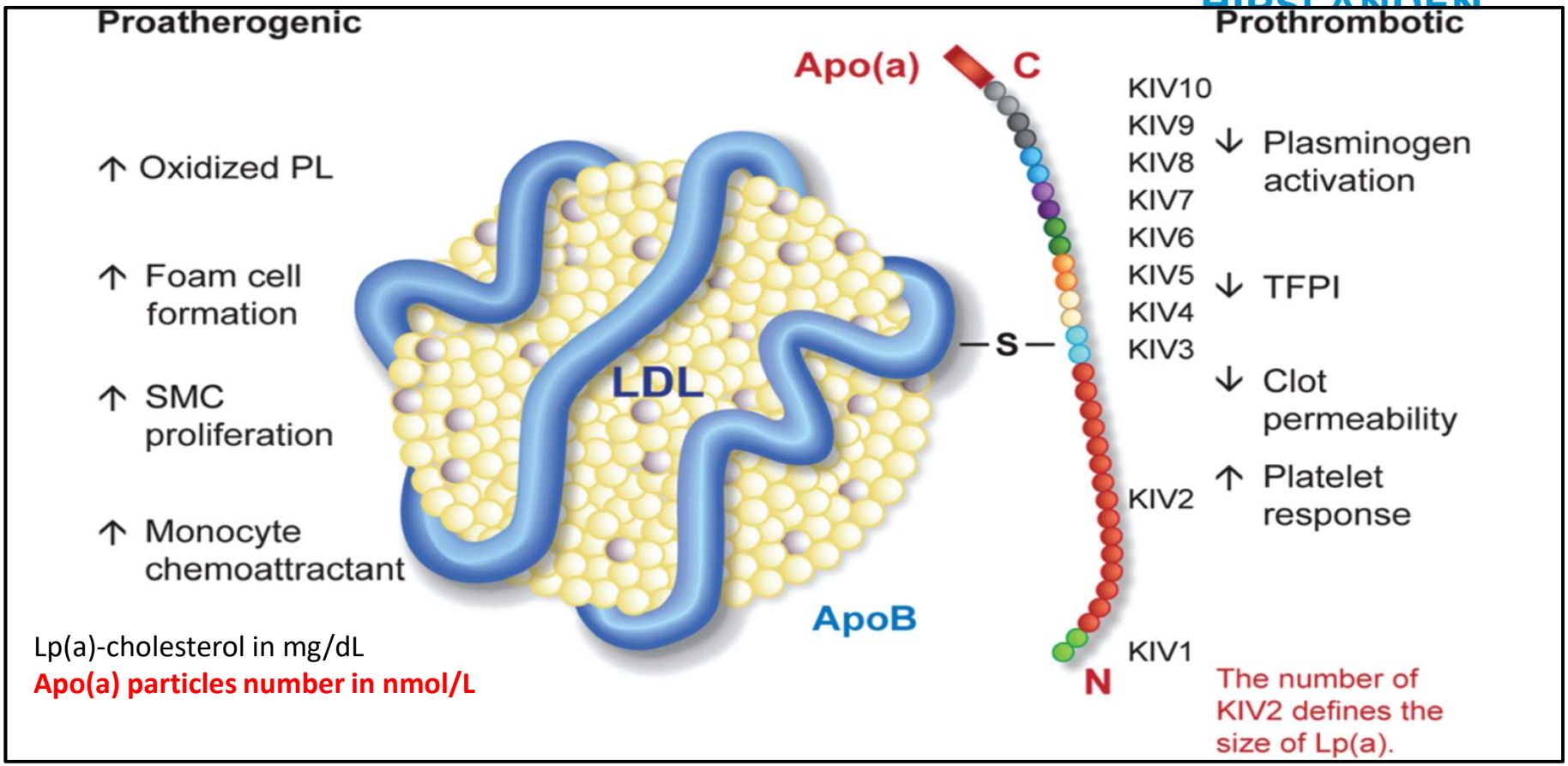
LINDE TILLEULS ACADEMY

Lipoprotein(a): the revenant

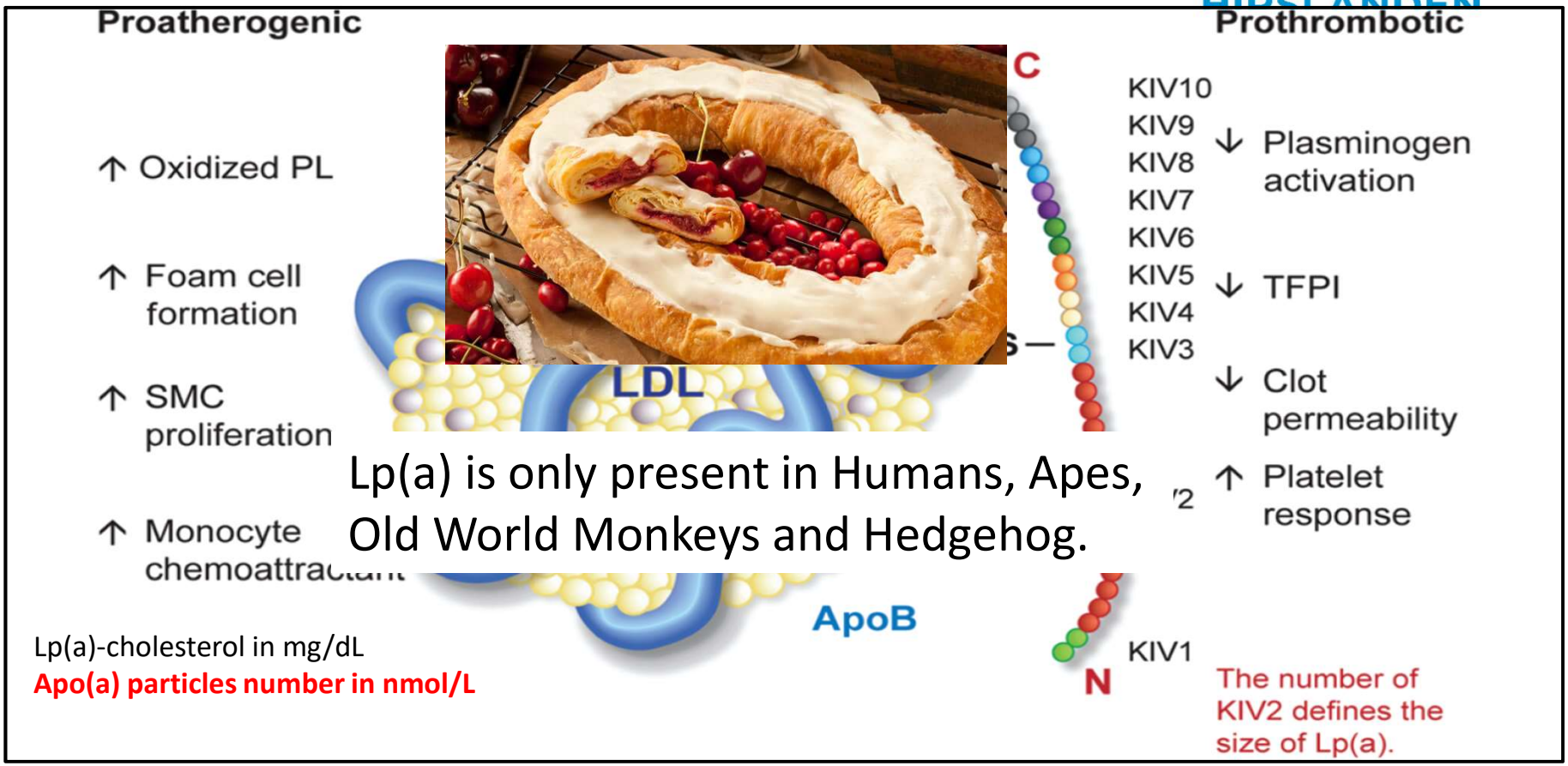


Lp(a)-cholesterol in mg/dL

Apo(a) particles number in nmol/L

Eur Heart J. 2017 May 21;38(20):1553-1560.

Lipoprotein(a): the revenant



Lp(a) is only present in Humans, Apes, Old World Monkeys and Hedgehog.

Eur Heart J. 2017 May 21;38(20):1553-1560.

Lp(a) distribution in the population

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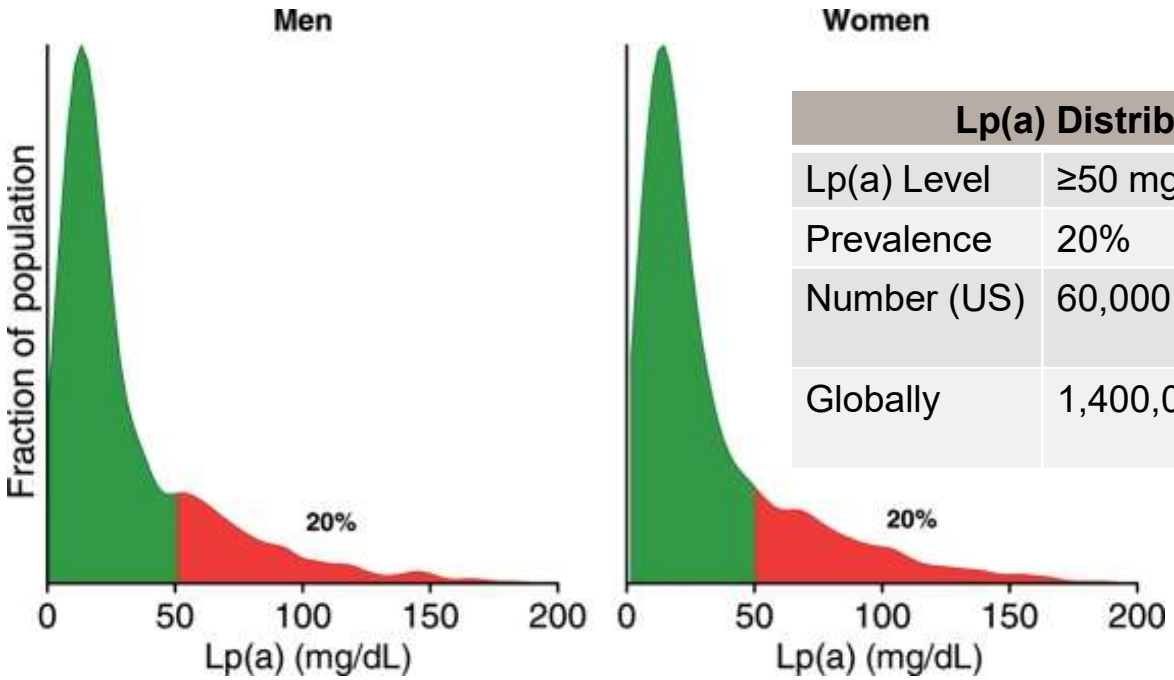

Lp(a) Distribution in general population			
Lp(a) Level	≥50 mg/dL	≥100 mg/dL	≥200 mg/dL
Prevalence	20%	5%	0.2%
Number (US)	60,000,000	15,000,000	600,000
Globally	1,400,000,000	350,000,000	14,000,000

Eur Heart J 2010 Dec; 31(23): 2844–2853.

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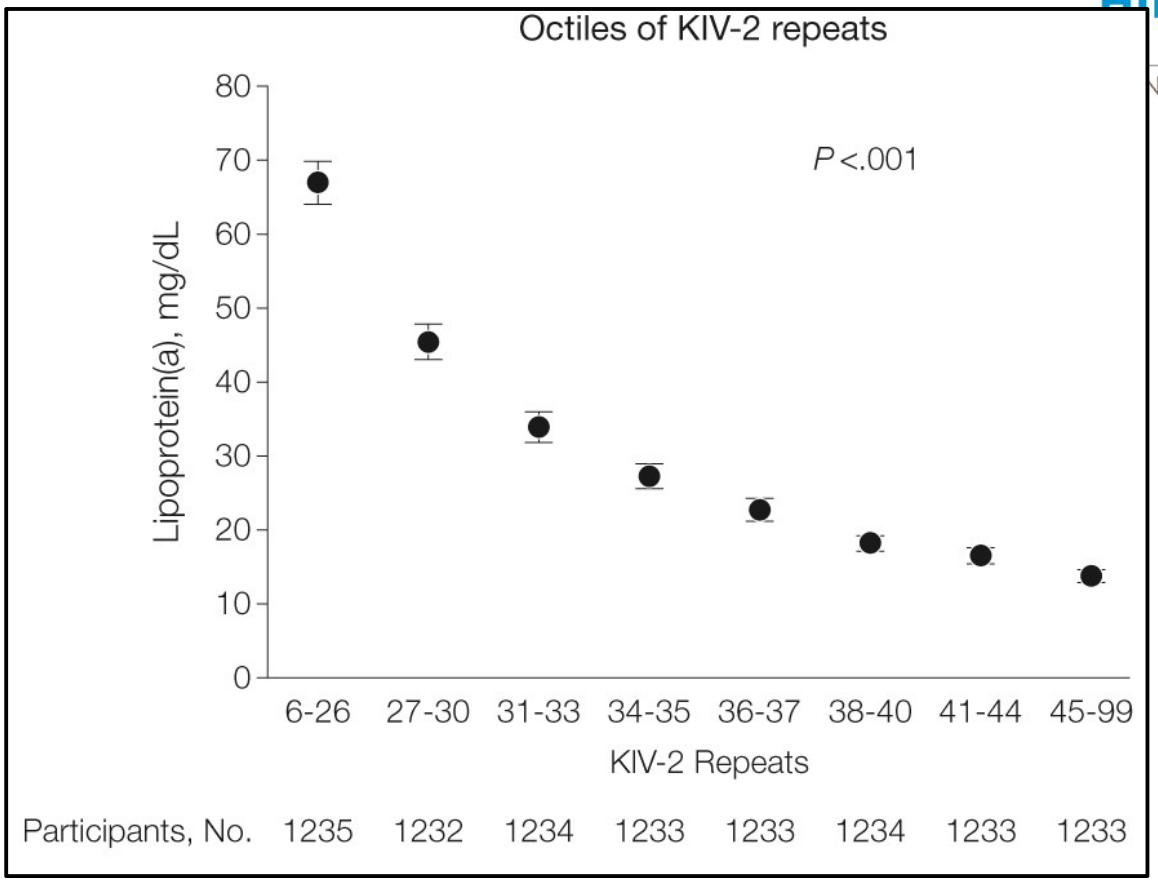
Genetically elevated Lp(a)



JAMA 2009 Jun 10;301(22):2331-9

Lipoprotein(a) and CV risk

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

CURRENT OPINION

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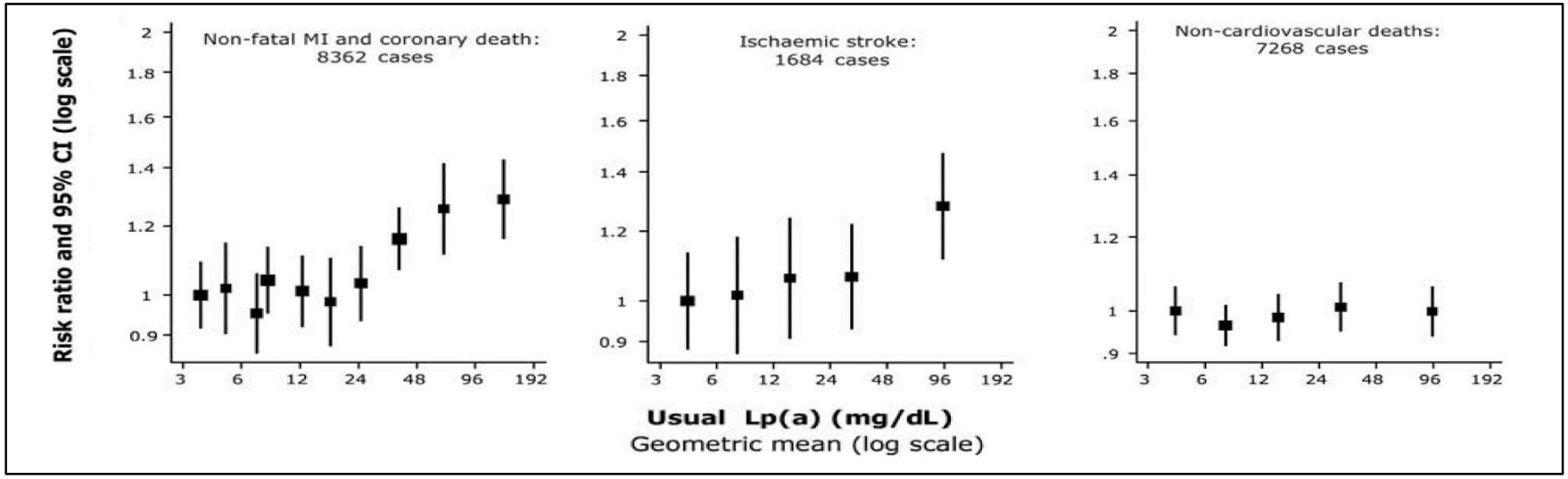
Lipoprotein(a) as a cardiovascular risk factor: current status

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[†]



Eur Heart J 2010;31:2844

Genetically elevated Lp(a) and risk of MI

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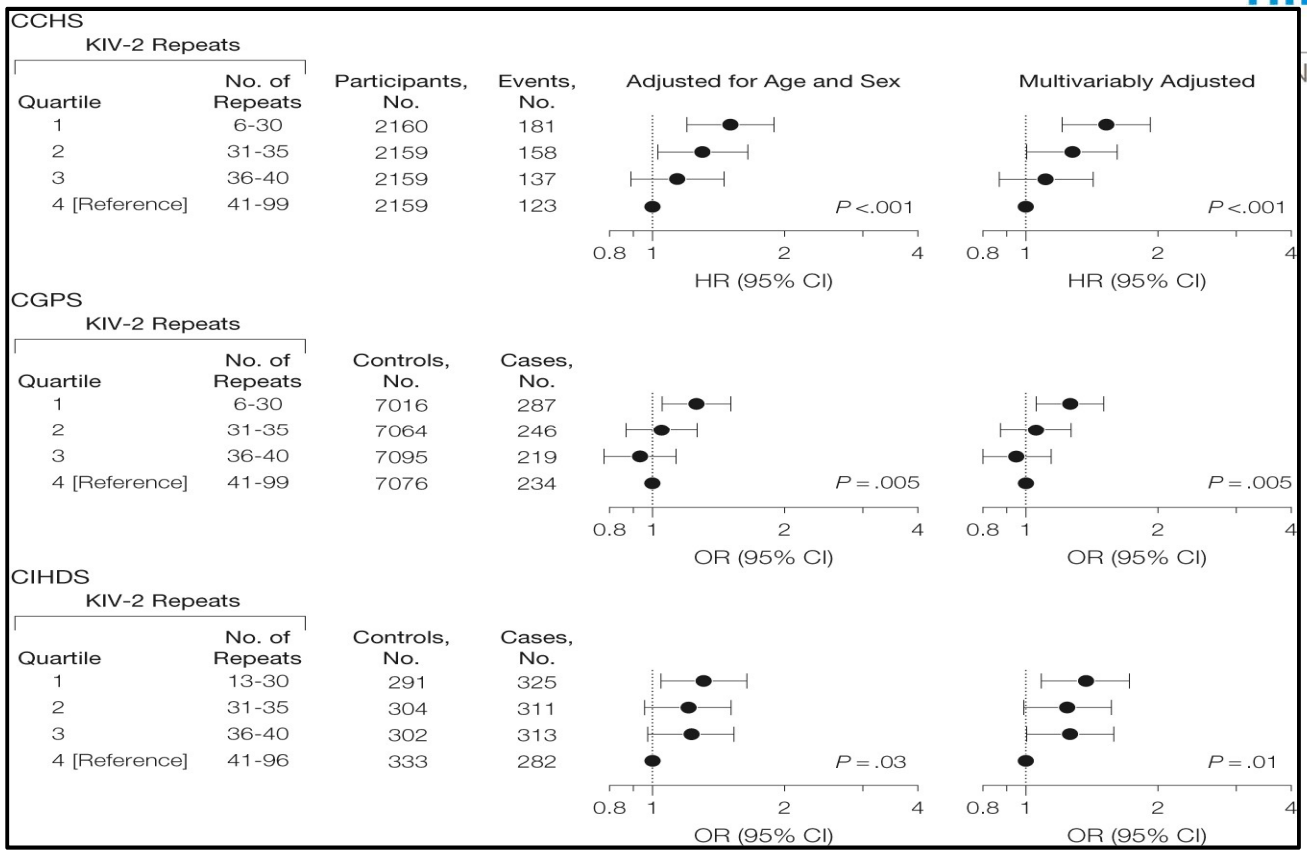
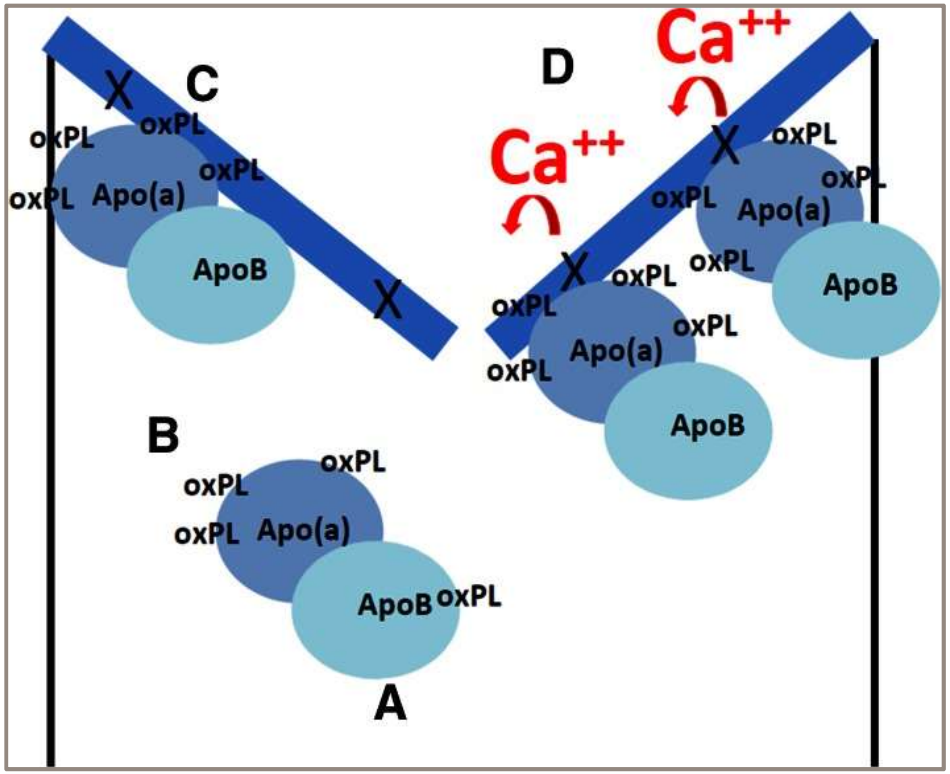


JAMA 2009 Jun 10;301(22):2331-9

LINDE TILLEULS ACADEMY

Lp(a) and aortic stenosis



J Lipid Res, 2016 Jun;57(6):917-924

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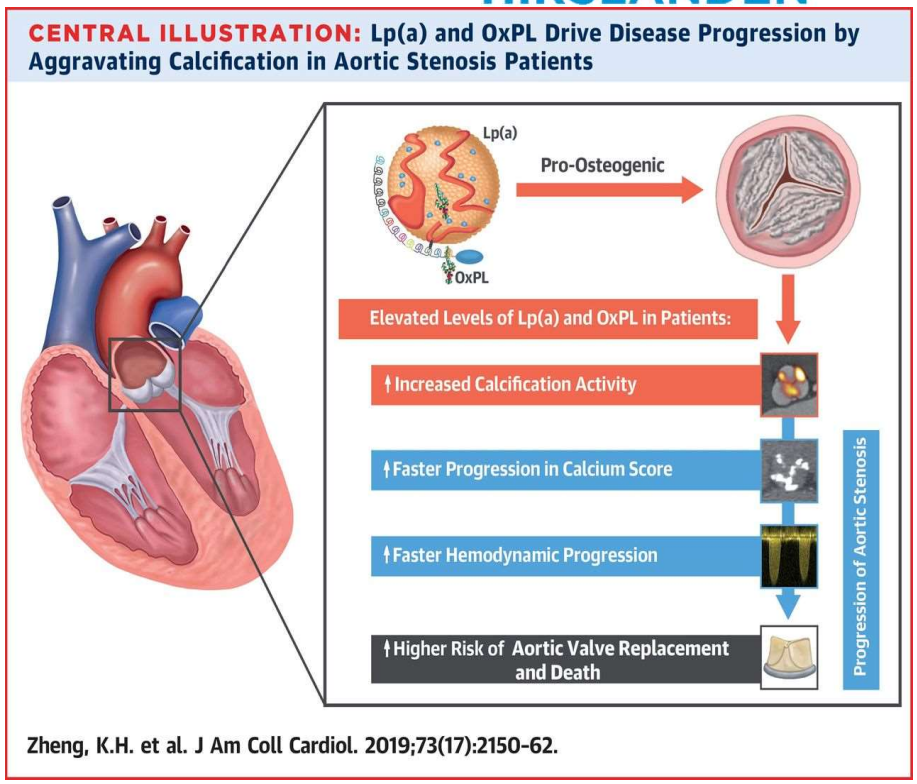

LINDE TILLEULS ACADEMY

Recommendations for lipid analysis

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.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Diagnosis of Familial Hypercholesterolemia

Dutch FH criterias

Lp(a) is not in the Dutch FH criteria

Feature	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men <55 years, females <60 years) OR First-degree relative with known LDL-C above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C above the 95th percentile for age and sex	2
Clinical history	
Premature coronary artery disease (men <55 years, females < 60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, females <60 years)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
LDL-C (mmol/L) – 8.5 or higher – 6.5 to 8.4 – 5.0 to 6.4 – 4.0 to 4.9	 8 5 3 1
DNA analysis: functional mutation in the *LDLR*, *APOB* or *PCSK9* gene	8
Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria: · **Definite FH = total score greater than 8** · **Probable FH = total score between 6 and 8** · **Possible FH = total score between 3 and 5** · **Unlikely FH = total score of less than 3**	

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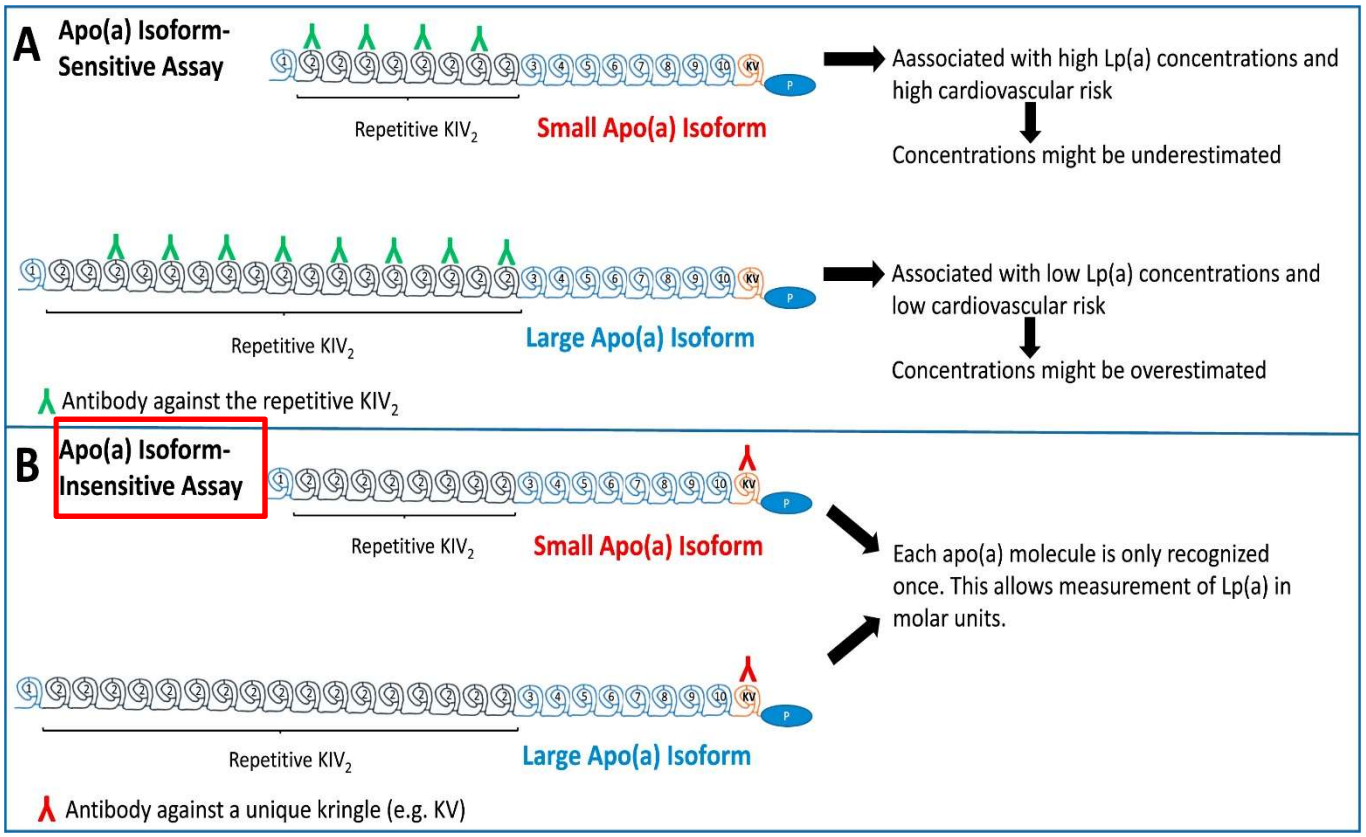
Lp(a) measurement



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Units: mg/dL

Units: nmol/L

Atherosclerosis 2019 Oct;289:181-183.

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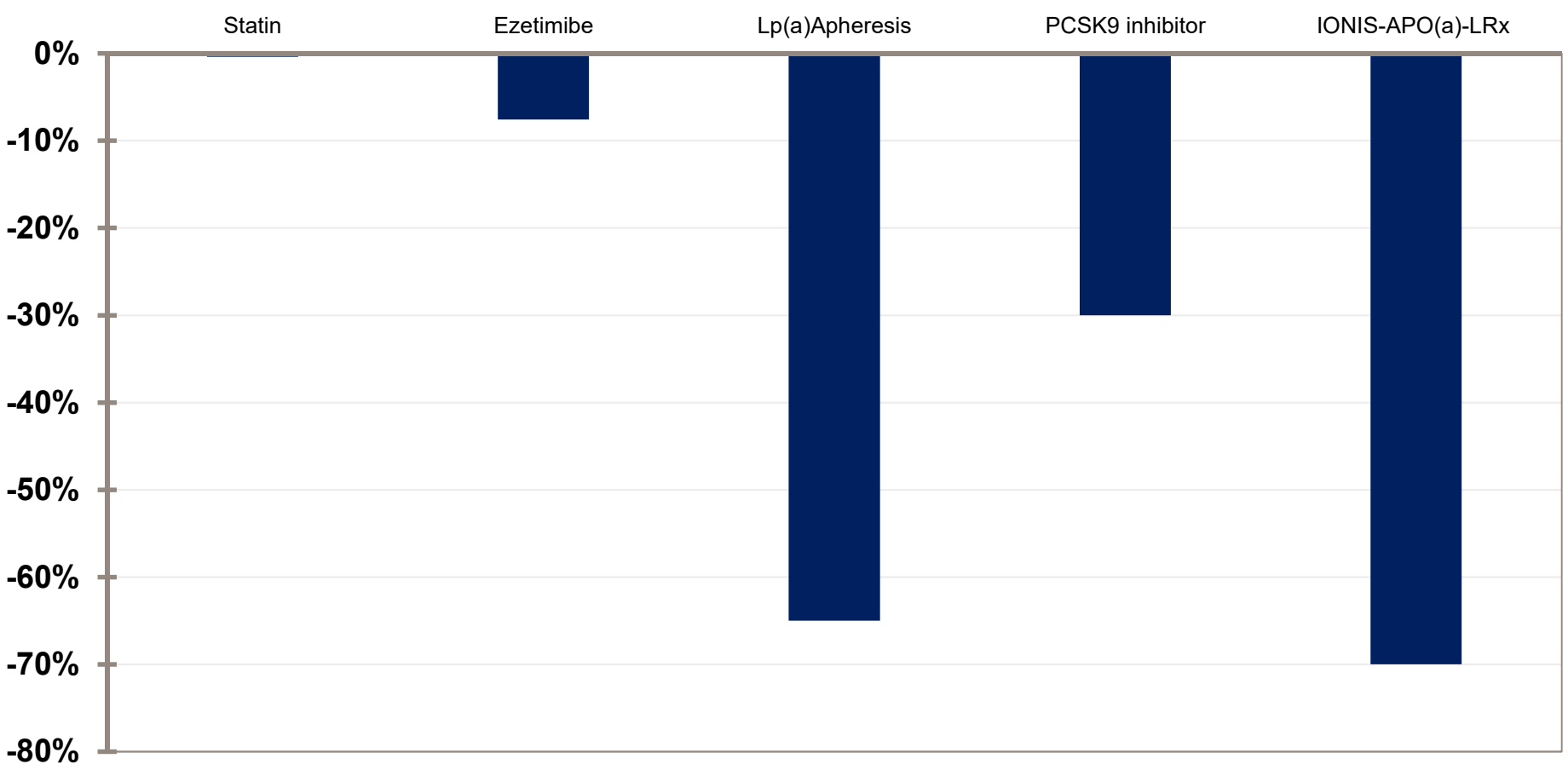
Lp(a) effect of lipid-lowering



Predicted Lp(a) reduction and CV outcome

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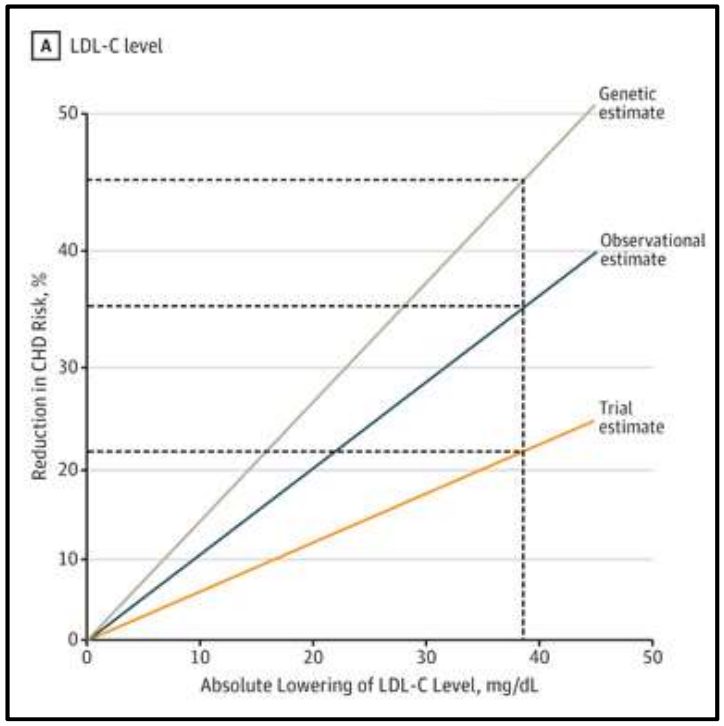
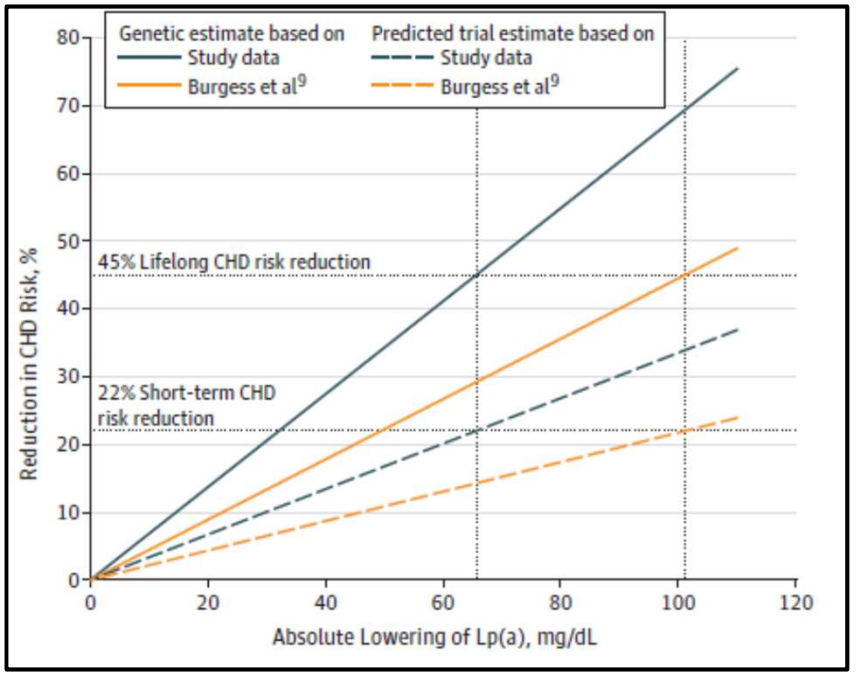
For each LDL-C reduction of **38.67 mg/dL** CHD risk reduction by 22%



For each Lp(a) reduction of **65.7-100 mg/dL** CHD risk reduction by 22%



JAMA Cardiol. 2018 Jul 1;3(7):619-627.

LINDE TILLEULS ACADEMY

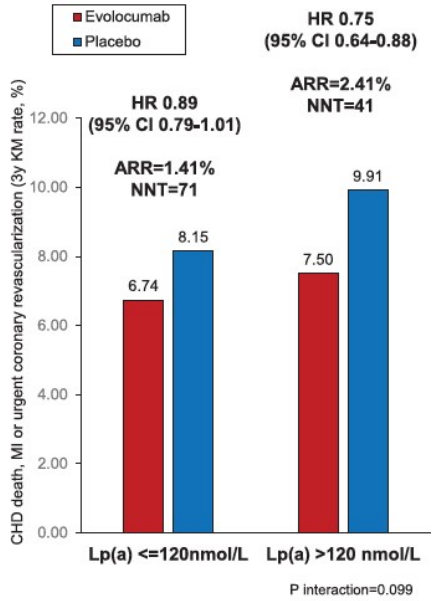
PCSK9 mAb (evolocumab)- Lp(a) and CV outcomes ?

Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

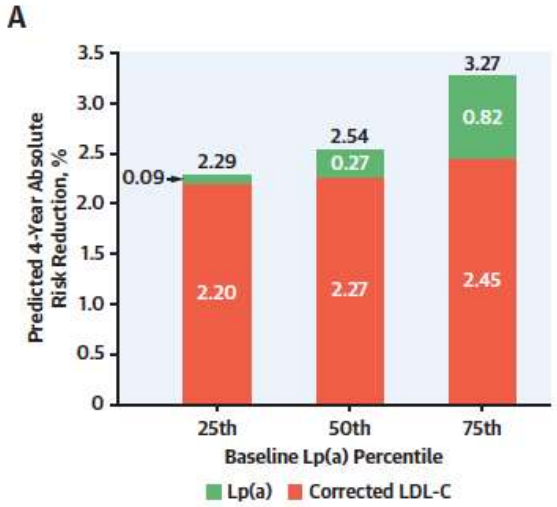
Insights From the FOURIER Trial



Circulation 2019;139:1483

ORIGINAL INVESTIGATIONS

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



JACC 2020;75:133

TILLEULS ACADEMY

Inclisiran and Lp(a)

Circulation

ORIGINAL RESEARCH ARTICLE

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Effect of an siRNA Therapeutic Targeting PCSK9 on Atherogenic Lipoproteins

Prespecified Secondary End Points in ORION 1

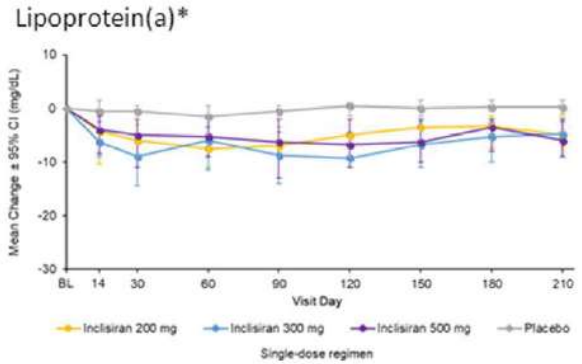
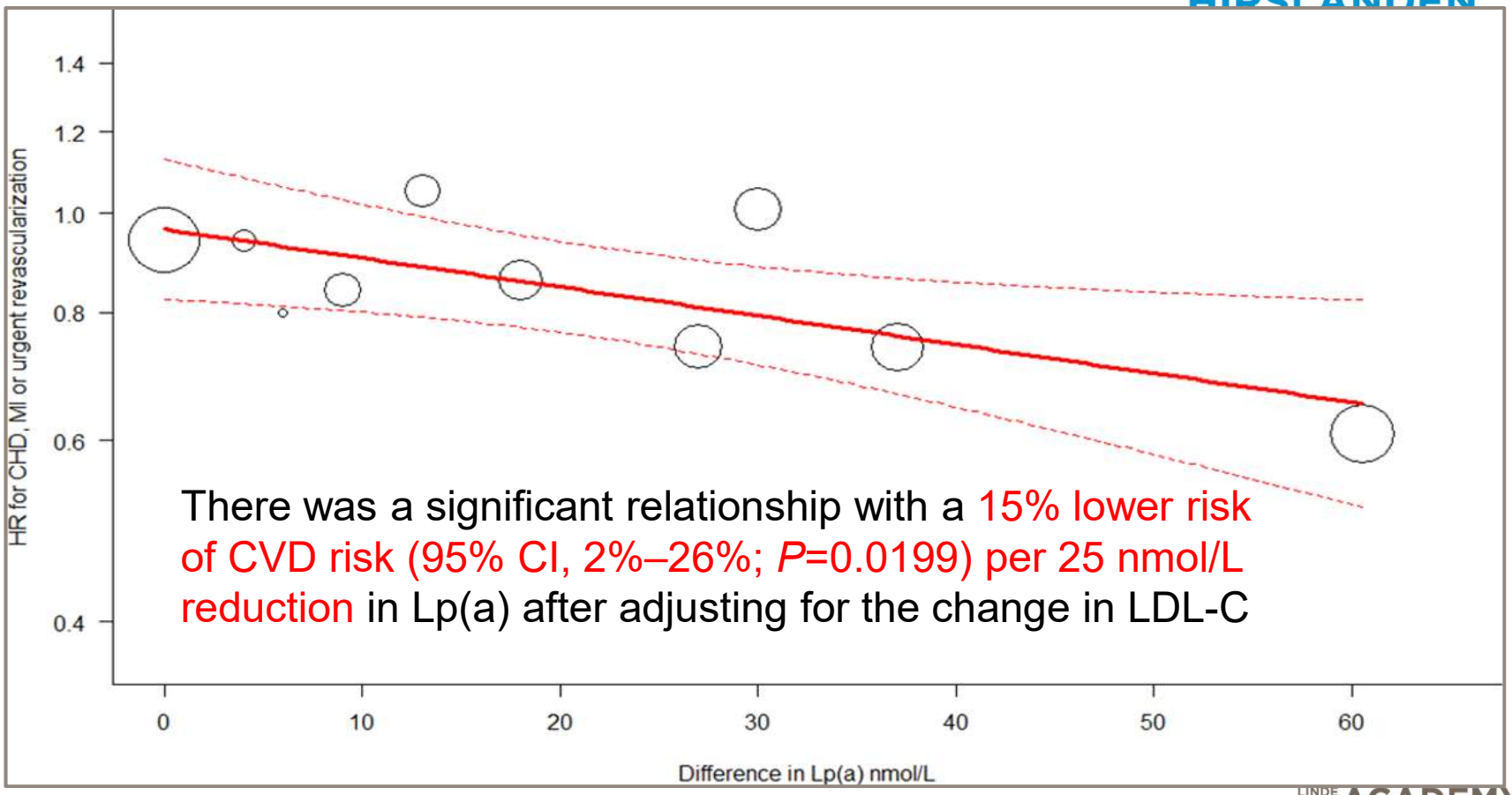


Table 2. Lipids and Lipoproteins at Baseline and Day 180*

	Single-Dose Groups				Double-Dose Groups			
	Placebo (n=64)	200 mg Inclisiran (n=60)	300 mg Inclisiran (n=60)	500 mg Inclisiran (n=60)	Placebo (n=61)	100 mg Inclisiran (n=59)	200 mg Inclisiran (n=60)	300 mg Inclisiran (n=59)
LDL-C								
Baseline	127.2 (52.31)	122.5 (34.73)	119.5 (41.56)	138.1 (46.05)	124.9 (44.20)	127.9 (47.85)	137.1 (70.98)	131.8 (58.51)
Day 180	127.8 (48.77)	87.7 (38.98)	75.2 (44.65)	82.4 (36.57)	124.1 (39.57)	82.9 (40.36)	82.0 (70.13)	67.6 (55.81)
Lp(a)								
Baseline	25.3 (8.5–122.0)	43.0 (11.0–127.0)	36.8 (18.8–147.0)	33.3 (10.8–151.5)	44.5 (12.0–146.0)	32.0 (11.5–134.0)	41.0 (9.8–140.5)	47.0 (11.0–160.5)
Day 180	22.0 (9.0–138.0)	29.5 (9.0–22.5)	31.5 (14.0–125.0)	19.5 (8.0–145.0)	52.0 (9.0–148.0)	29.0 (7.0–103.0)	32.0 (6.0–132.5)	36.0 (8.0–130.0)

Circulation 2018;138:1304

Lp(a) Reduction and outcomes in FOURIER trial



Circulation 2019 Mar 19;139(12):1483-1492

Lowering Lipoprotein(a) with apo(a)-antisense

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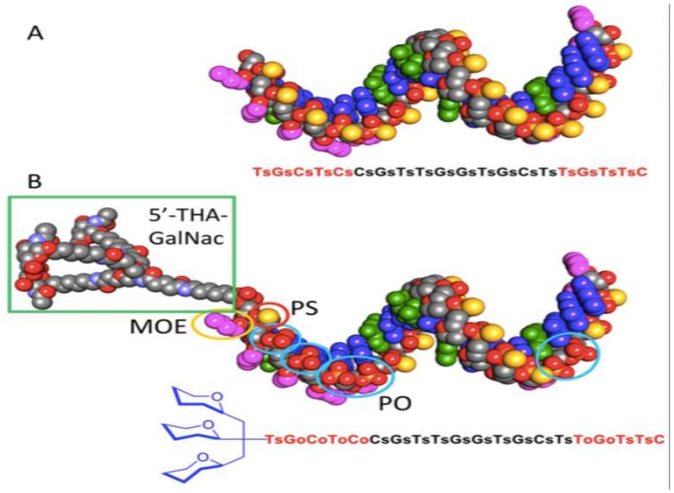
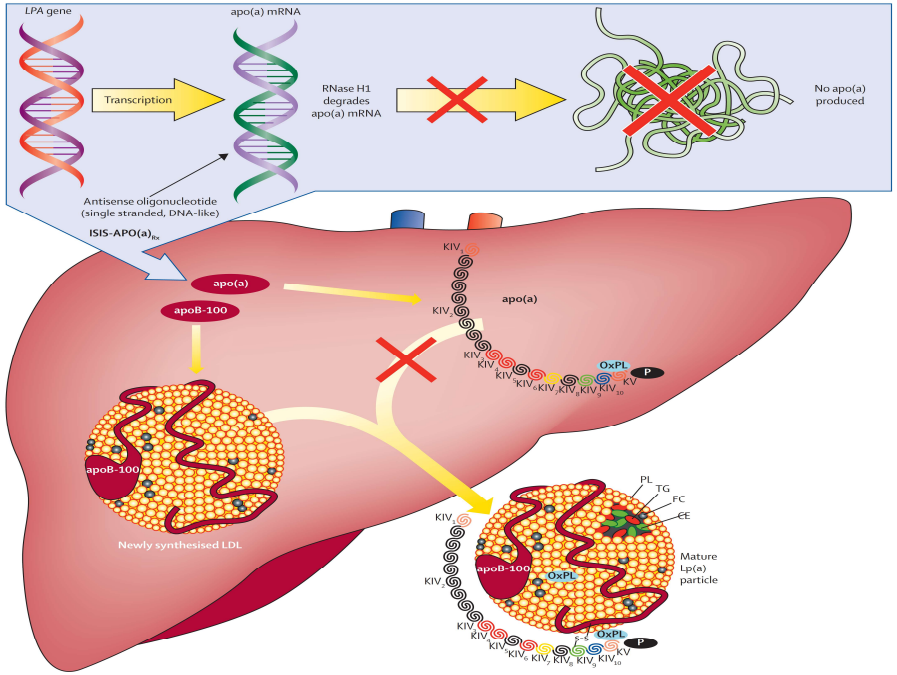
Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum

Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials

Nicholas J Viney, Julian C van Capelleveen, Richard S Geary, Shuting Xia, Joseph A Tami, Rosie Z Yu, Santica M Marcovina, Steven G Hughes, Mark J Graham, Rosanne M Crooke, Stanley T Crooke, Joseph L Witztum, Erik S Stroes, Sotirios Tsimikas





Lancet 2015;386:1472

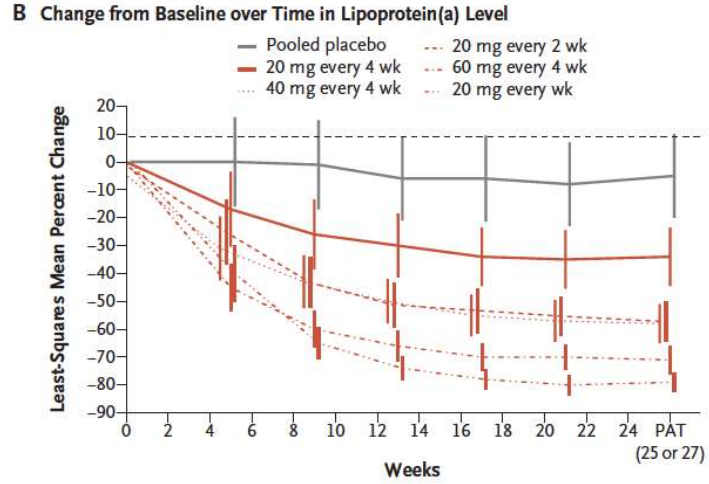
Lowering Lipoprotein(a) with apo(a)-antisense

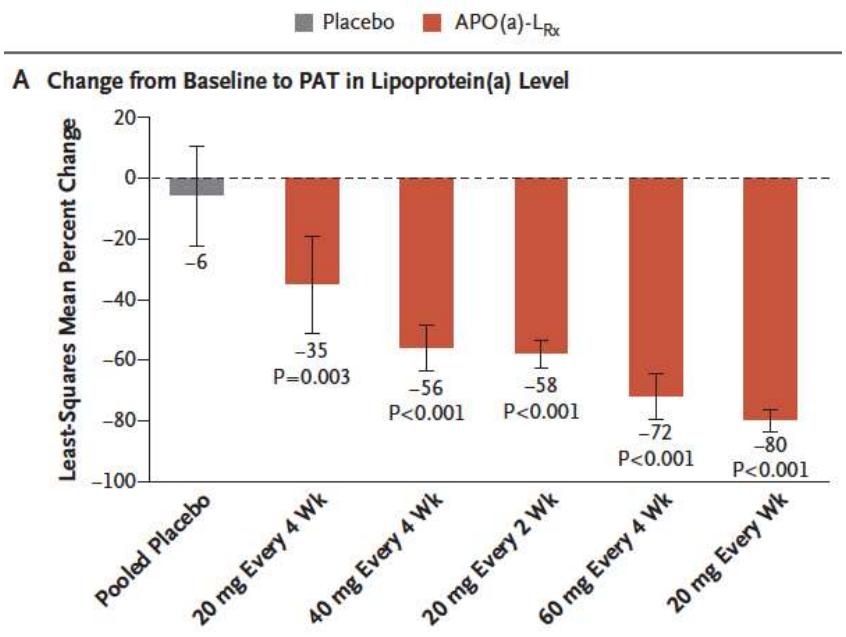
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

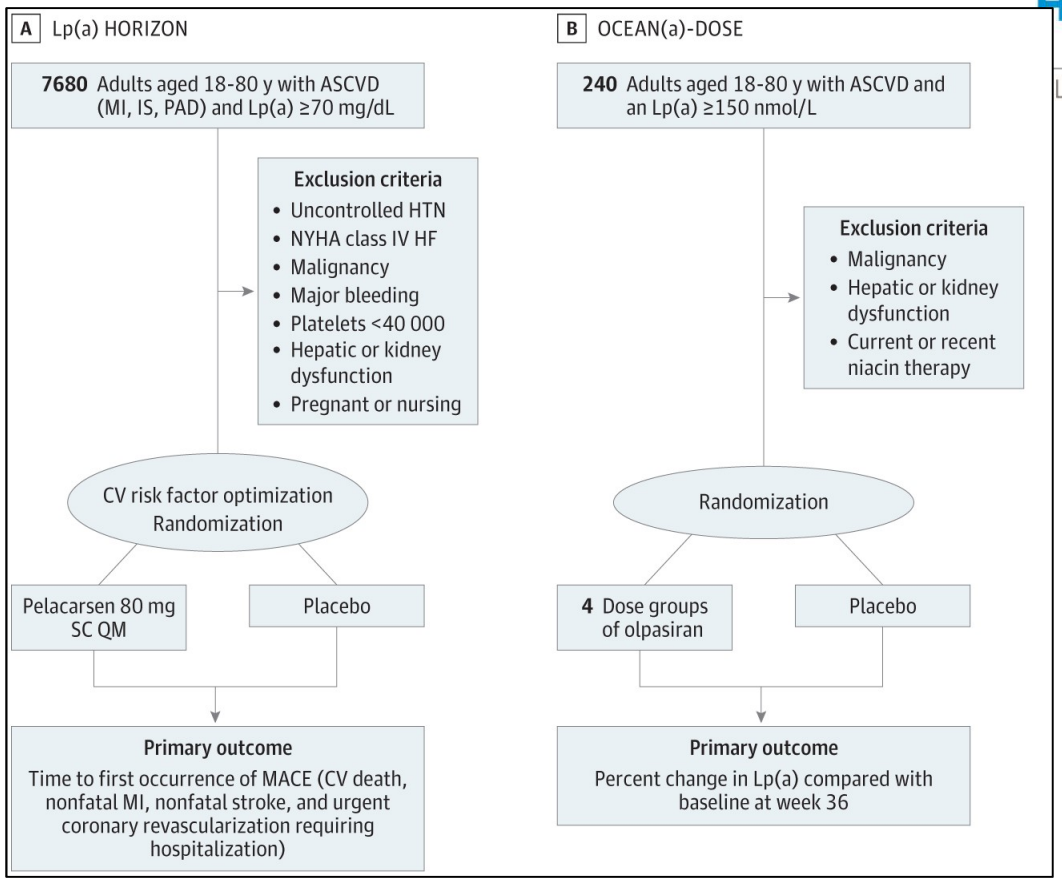
Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia, 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*





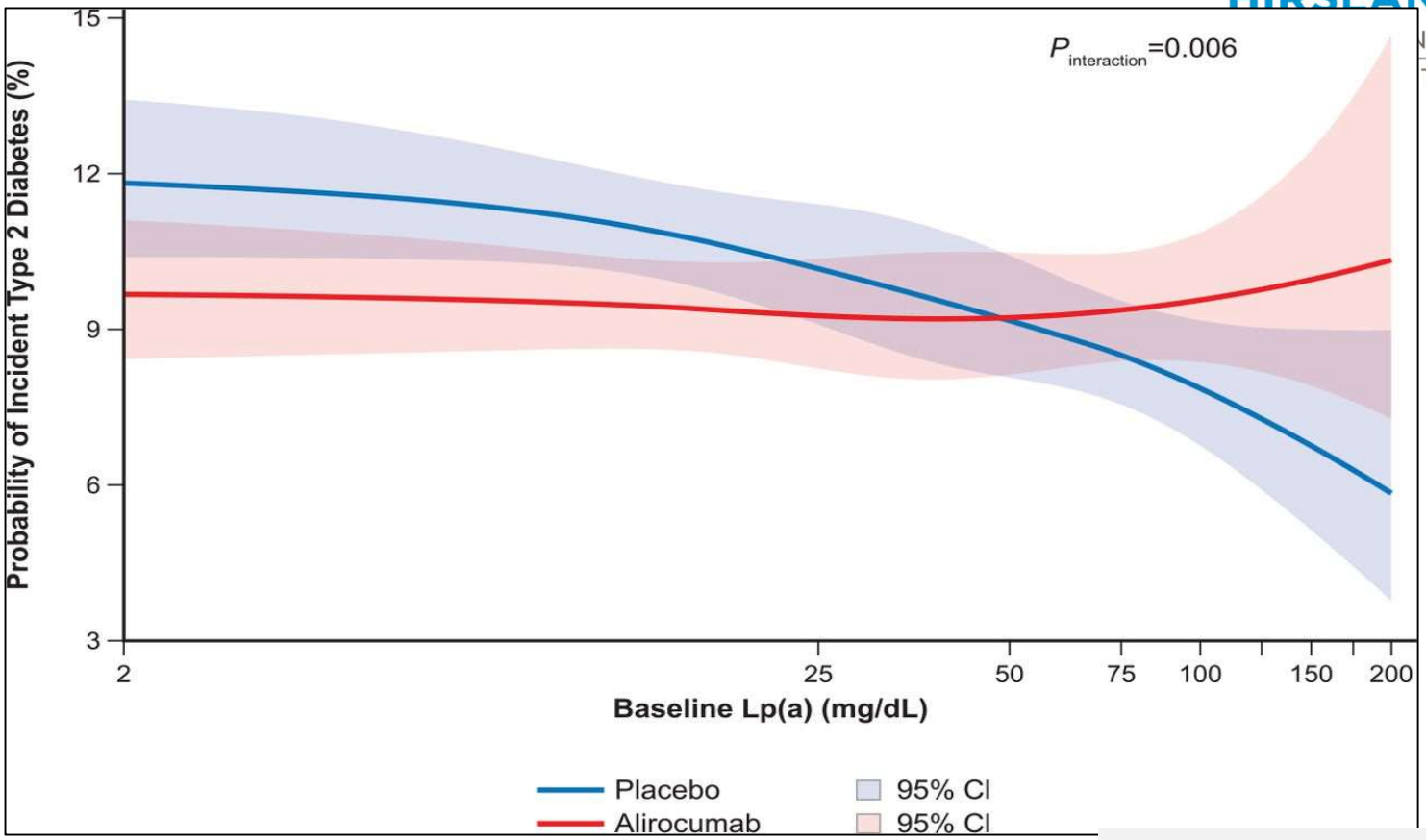
New Engl J Med 2020;382:244

Future trials with Lp(a)-lowering



JAMA Cardiol. Published online May 18, 2022. doi:10.1001/jamacardio.2022.0987

Safety of low Lp(a) Levels – Risk of new diabetes



Diabetes Care. 2021;44(5): 1219-1277

Conclusion

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- European guidelines recommend to measure Lp(a) at least once in each adult
- Observational and genetical data suggest that Lp(a) is a causal CVD risk factor
- Lp(a) > 180 mg/dL could be considered as a higher risk of CVD
- Currently no specific drugs are effective to reduce strongly Lp(a) levels (PCSK9i reduce Lp(a) by 30%)
- Antisense therapy lowering Lp(a) are currently tested in large CV trials

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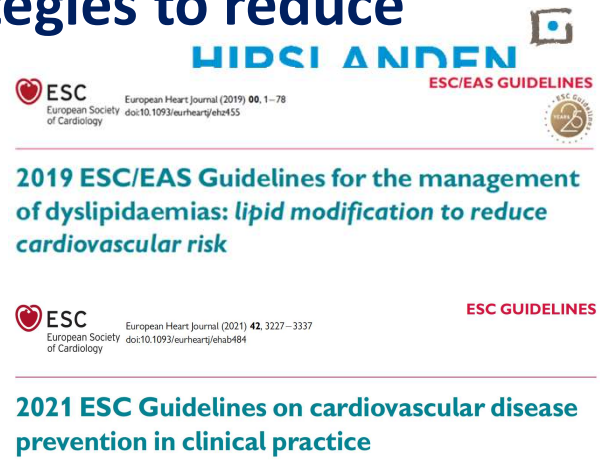
Merci pour votre attention

LINDE TILLEULS ACADEMY

The modern concept of lipid-lowering strategies to reduce cardiovascular diseases



Concept change I: More ambitious targets

Less "lipid-exposure" leads to prevention of lesion formation

Concept change II: Treat (much more) aggressively

From desirable target to "LDL-C elimination in the blood"

Concept change III: New powerful tools: Use lipid-lowering combination therapy

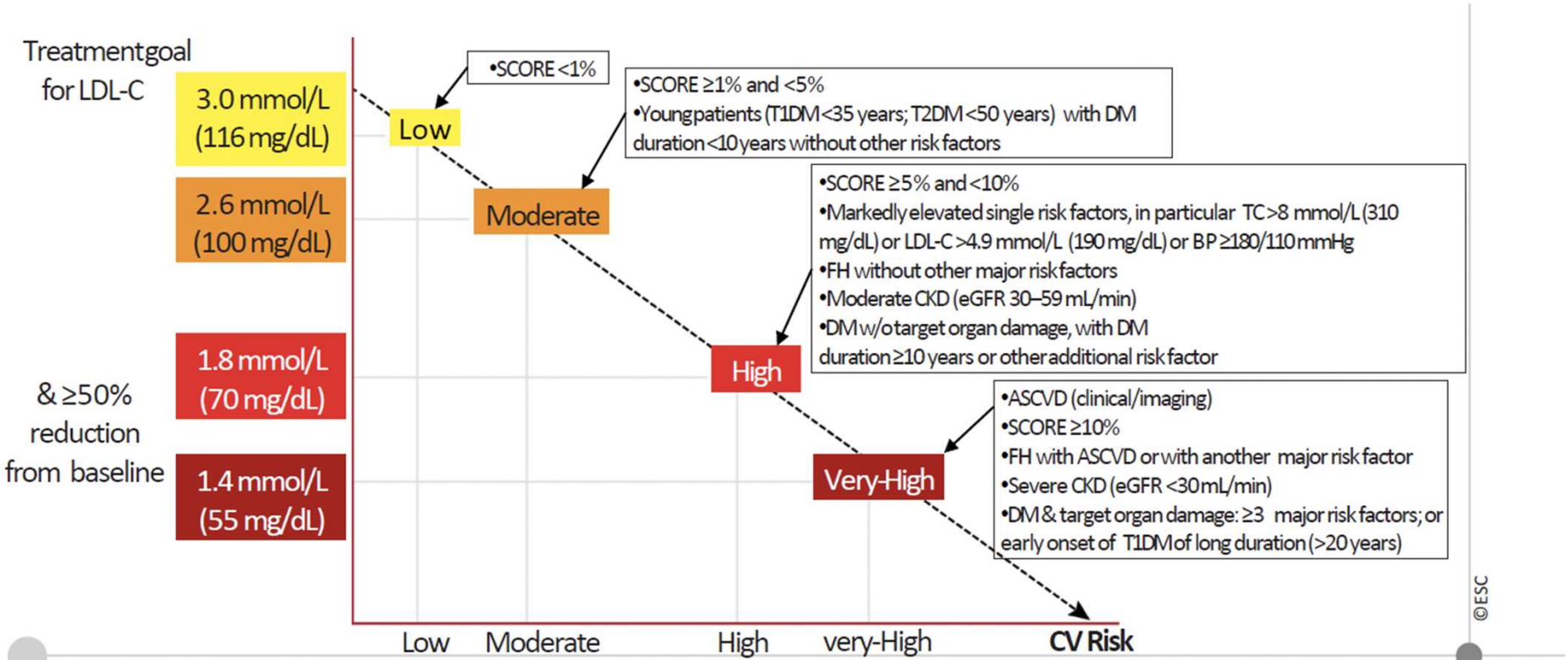
Statin +/- ezetimibe (+/- PCSK9mAb; inclisiran, bempedoic acid) induced LDL-C lowering reduces CV risk

Concept change IV: New powerful tools: New CV risk scores

SCORE2 and SCORE2-OP; Life-time CVD benefit and stepwise treatment-intensification approach

Treatment goals for LDL-C across categories of total cardiovascular disease risk

EAS ESC
European Society of Cardiology



www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Intensity of pharmacological LDL lowering

EAS ESC European Society

Intensity of lipid lowering treatment

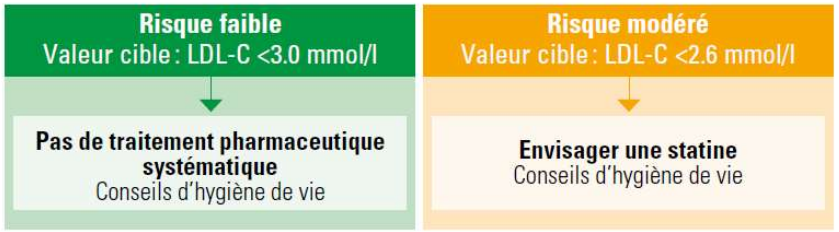
Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor **(Evolocumab, alirocumab, inclisiran and oral?)**	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%
Bempedoic Acid (ATP-Citrate Lyase Inhibitor) plus ezetimibe	≈35%

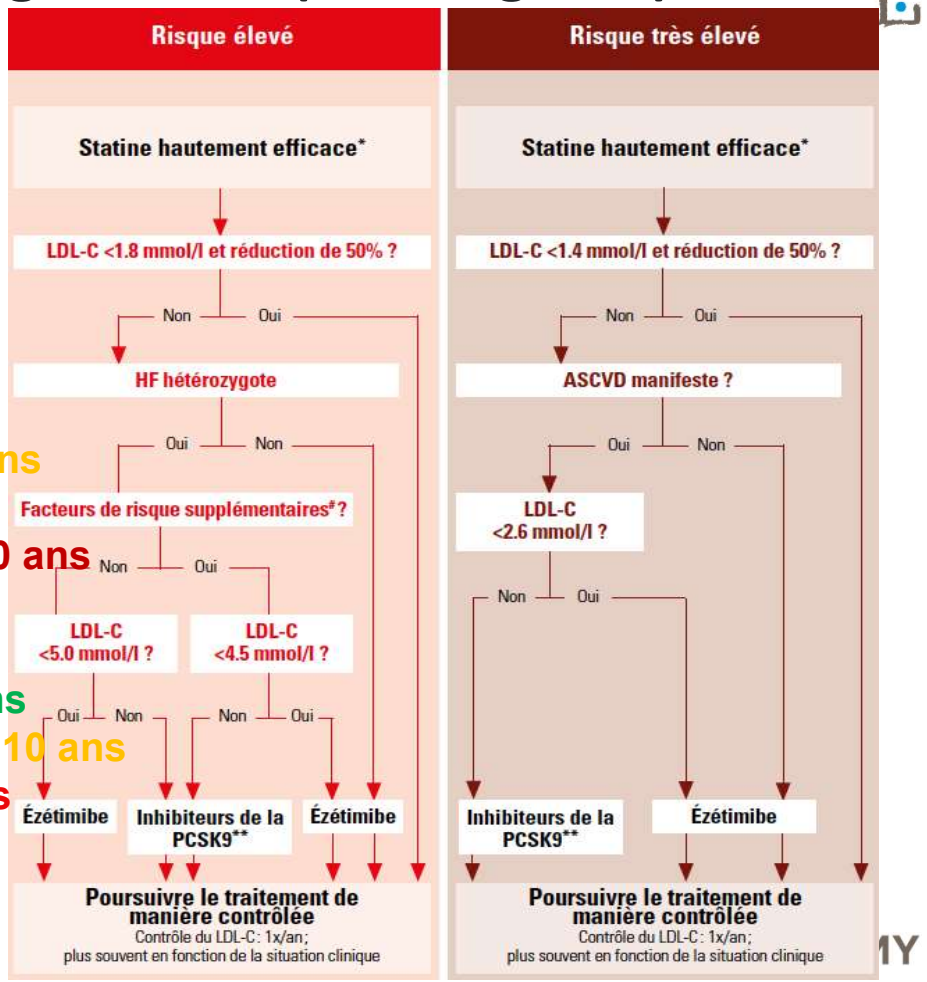
ANGPTL3 inhibition with evinacumab (Approved FDA and UE for HoFH)

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Swiss AGLA/GSLA lipid guidelines (www.agla.ch)





SCORE ESC (pays à bas risque):

Risque faible: < 1% risque décès CV sur 10 ans

Risque modéré: 1-5% risque décès CV sur 10 ans

Risque élevé: 5-9% risque décès CV sur 10 ans

Risque très élevé: ≥10% risque décès CV sur 10 ans

Score GSLA:

Risque faible: < 10% risque MCV total sur 10 ans

Risque modéré: 10%-20% risque MCV total sur 10 ans

Risque élevé: >20% risque MCV total sur 10 ans