DELIVERING SCIENCE SUPPORTING HEALTHCARE

NHS
North West
London Pathology

GP Study Webinar

Lipoprotein(a): cardiovascular risk factor and future therapeutic target

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Consultant in Metabolic Medicine, North West London Pathology

March 16th 2022

Patient focused Collaborative Expert Caring

Learning objectives

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- What is lipoprotein(a)?
- What causes raised lipoprotein(a)?
- When is it useful to measure it?
- What do I do if it's raised?
- What are the future prospects for lipoprotein(a) treatment?

Take home messages

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- Lp(a) is a pro-atherogenic and pro-thrombotic lipoprotein that increases CV risk independently of traditional risk factors

- Lp(a) has a strong genetic inheritance pattern

- Current management of Lp(a) is centred on intensive manage other modifiable CV risk factors (and sometimes aspirin)
- New Lp(a)-lowering treatments are on the horizon…

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Atherosclerosis

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

Review article

HEART UK consensus statement on Lipoprotein(a): A call to action

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High lipoprotein (a)

Join our free webinar: Thursday 24th March 2022

Other cholesterol conditions

- High HDL Cholesterol
- Metabolic syndrome
- Polygenic hypercholesterolaemia
- Rarer genetic conditions
- Secondary hyperlipidaemia
- Severe polygenic hypercholesterolaemia
- Sitosterolaemia
- Familial combined hyperlipidaemia (FCH)
- Familial hypertriglyceridaemia
- Low HDL cholesterol

HEART UK website

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What is lipoprotein(a)?

Lp(a) structure – "LDL + plasminogen"

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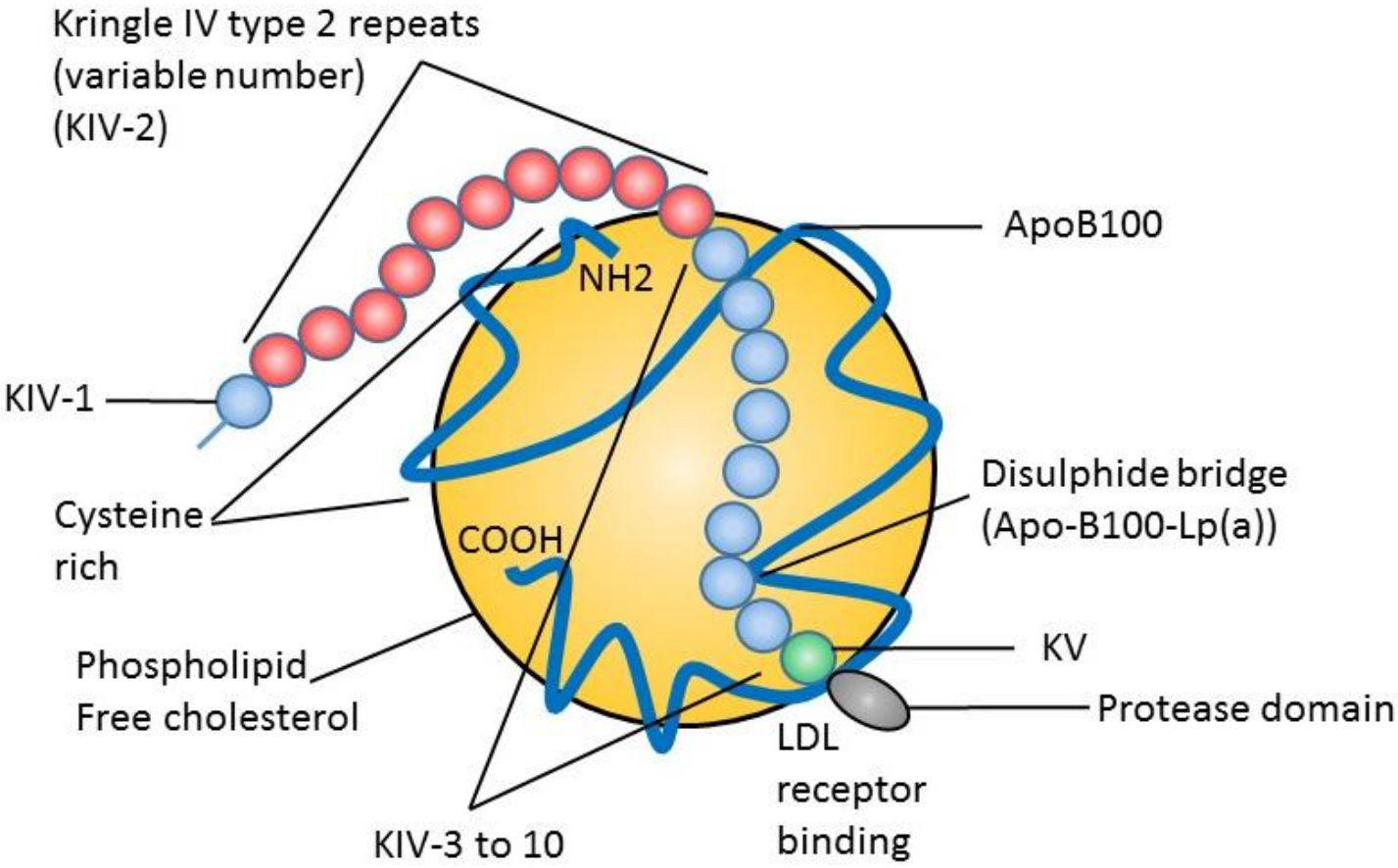

ApoB100 part resembles LDL - **atherogenic**
Kringle IV repeats resemble plasminogen - **prothrombotic**

Lp(a) Pathophysiology

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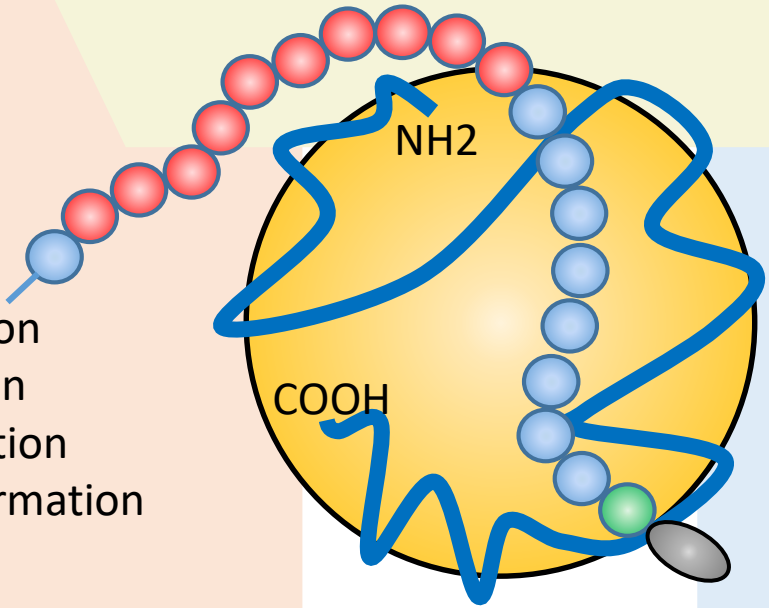
Pro-inflammatory
↑ oxidised phospholipids
↑ monocyte trafficking
↑ monocyte cytokine release



Proatherogenic
↑ arterial infiltration
↑ SMC proliferation
↑ foam cell formation
↑ necrotic core formation

Prothrombotic
↓ plasminogen activation
↓ fibrin degradation
↑ platelet aggregation

Lp(a) population distribution

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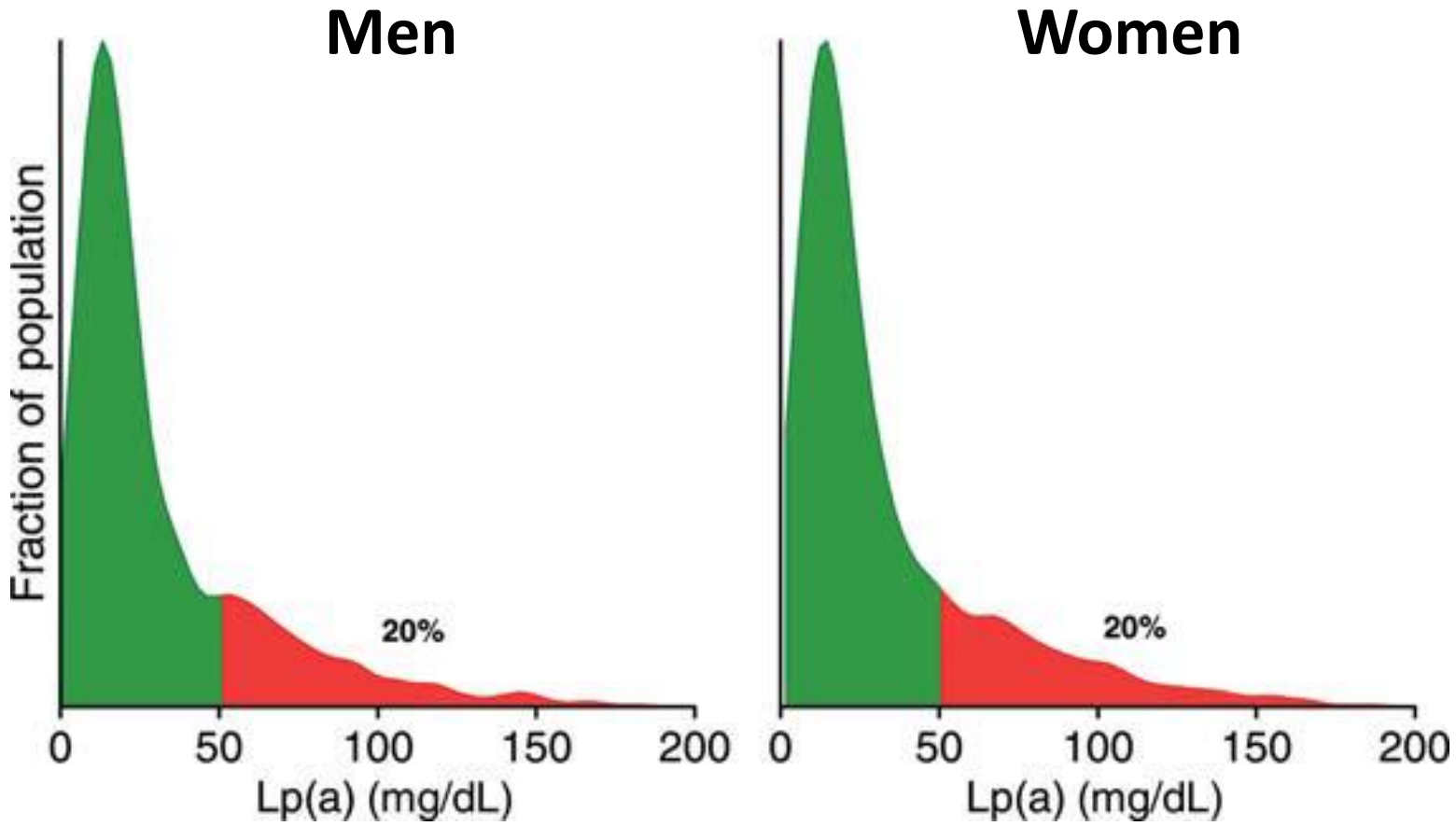

Note that Lp(a) measurement units have changed!

Kamstrup JAMA 2009

Lp(a) and CV risk – epidemiological and genetic evidence

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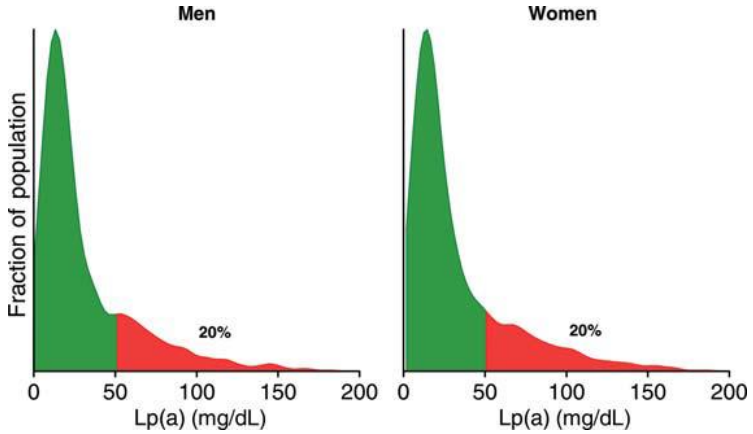

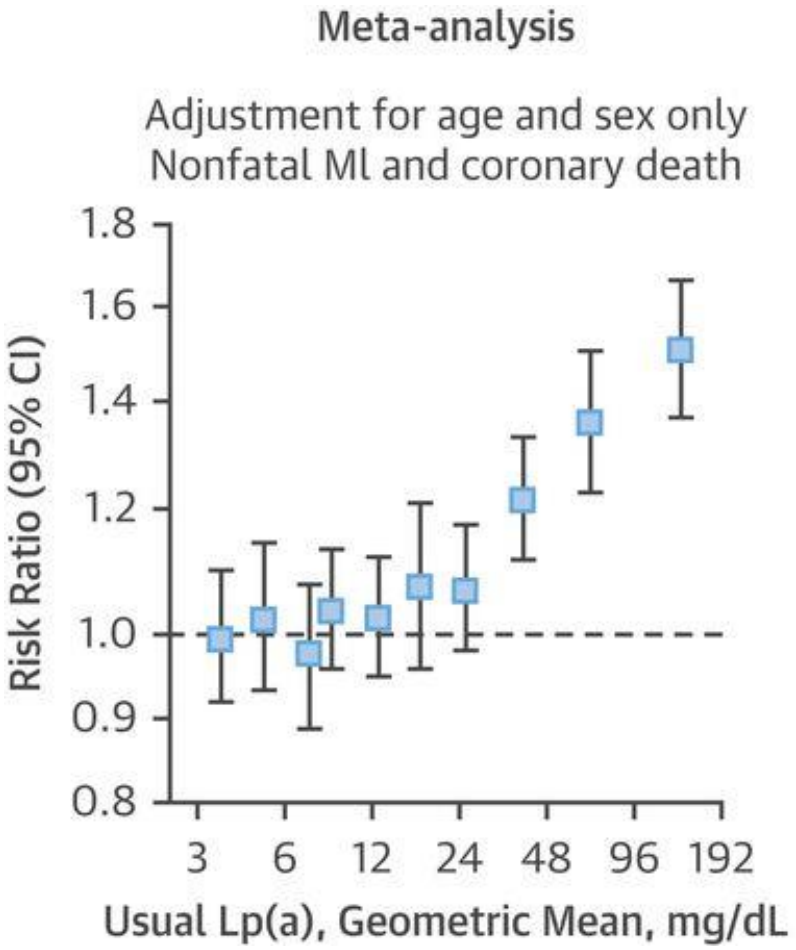

ERF Collab JAMA 2009

Lp(a) and CV risk – epidemiological and genetic evidence

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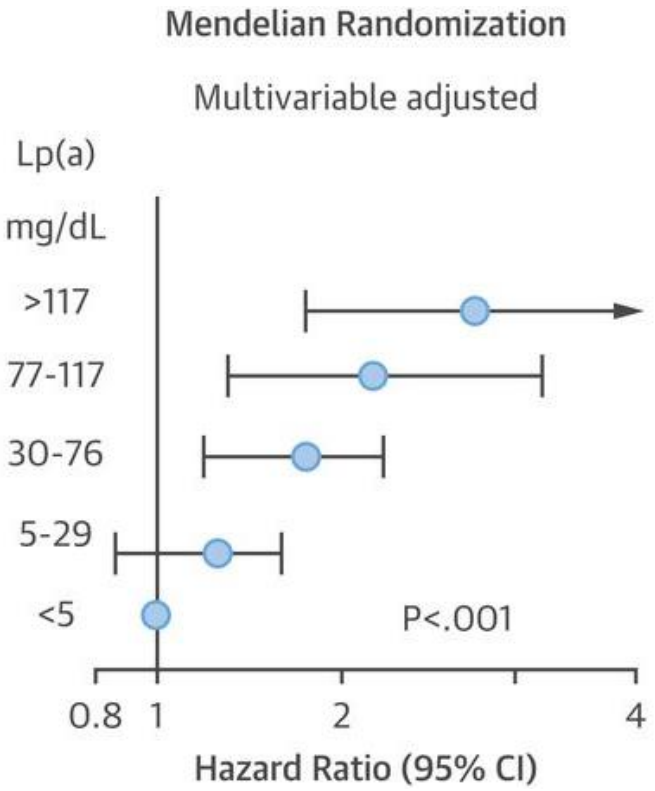
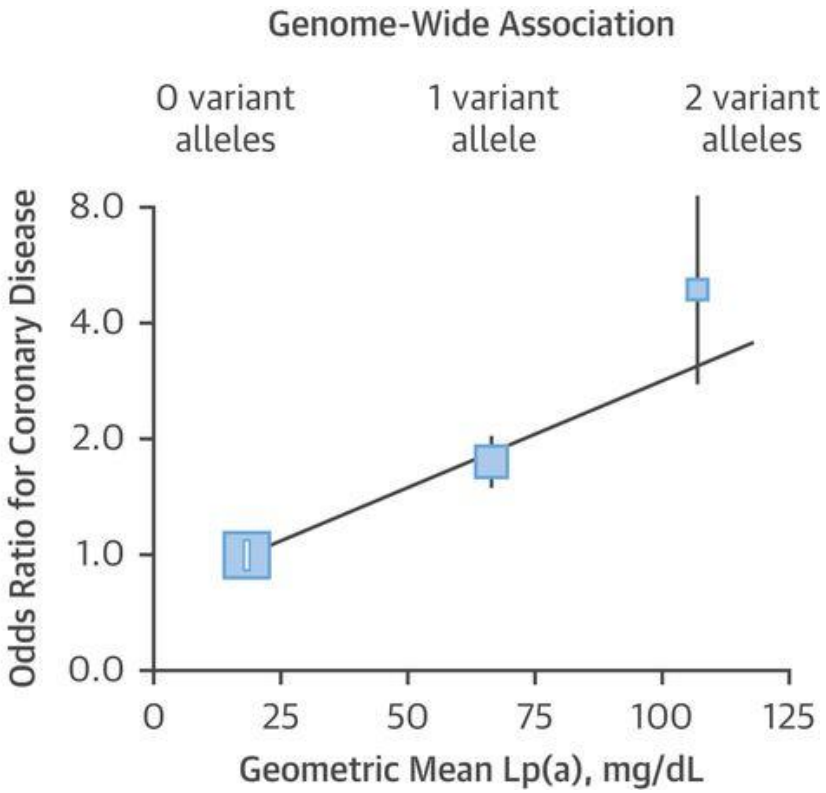


Kamstrup JAMA 2009



Clarke NEJM 2009

Lp(a) and graded risk

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Lp(a) level nmol/l[a]	Lp(a) level approx. in mg/dl[b]	Percentile of general population[12]	Impact on CV risk
32-90	18-40	67-80th	Minor
90-200	40-90	80-95th	Moderate
200-400	90-180	95-99.8th	High
>400	>180	>99.8th	Very High

*Percentile cutpoints in nmol/l and mg/dl for Lp(a) values derived from 13900 participants (Nov. 2015 to June 2017) in the on-going Copenhagen General Population Study. Measurements were performed with the Roche assay on a Cobas platform (unpublished data, courtesy of P. Kamstrup and B. Nordestgaard).

HEART UK, Atherosclerosis 2019

Lp(a) is also a risk factor for calcific aortic valve stenosis

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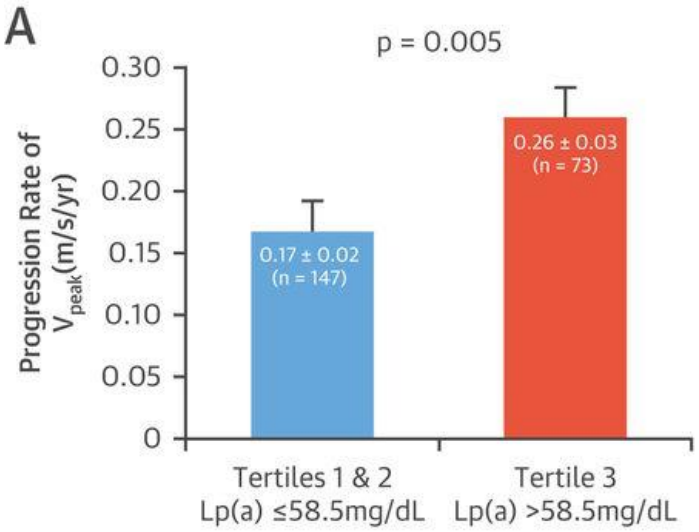

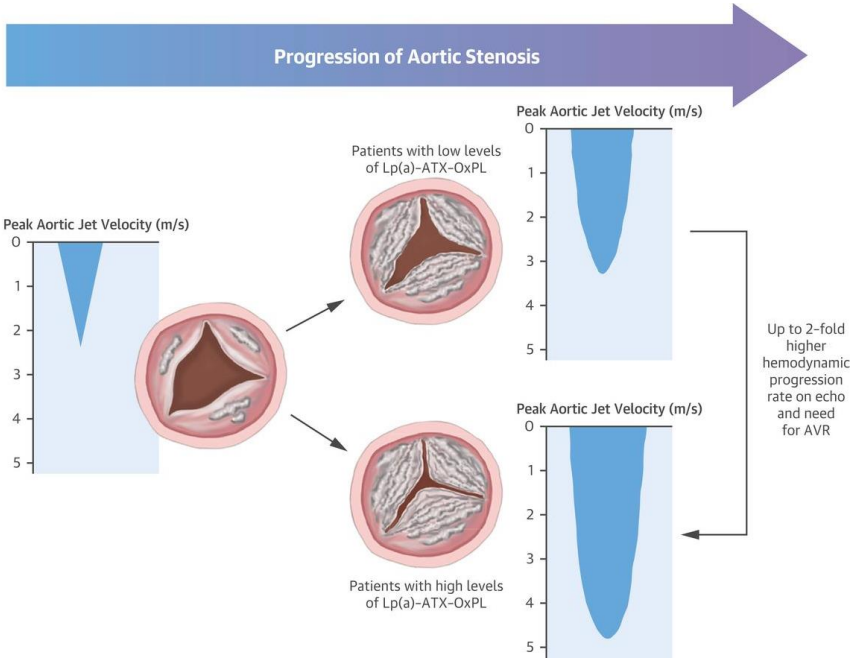

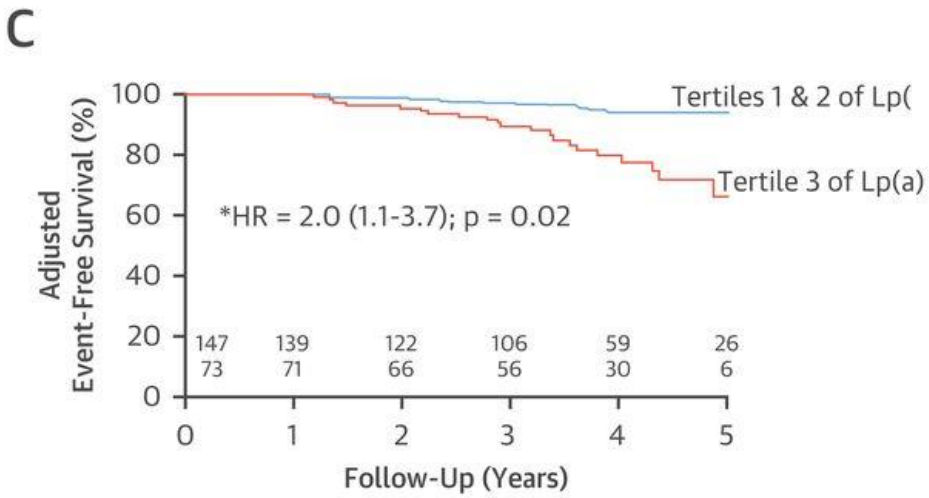

Capoulade JACC 2015, Tsimikas JACC 2018

Take home messages

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- Lp(a) is a pro-atherogenic and pro-thrombotic lipoprotein that increases CV risk independently of traditional risk factors

- Lp(a) has a strong genetic inheritance pattern

- Current management of Lp(a) is centred on intensive manage other modifiable CV risk factors (and sometimes aspirin)
- New Lp(a)-lowering treatments are on the horizon…

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What causes raised lp(a) - mainly genetics

LPA genetic variation controls Lp(a) levels

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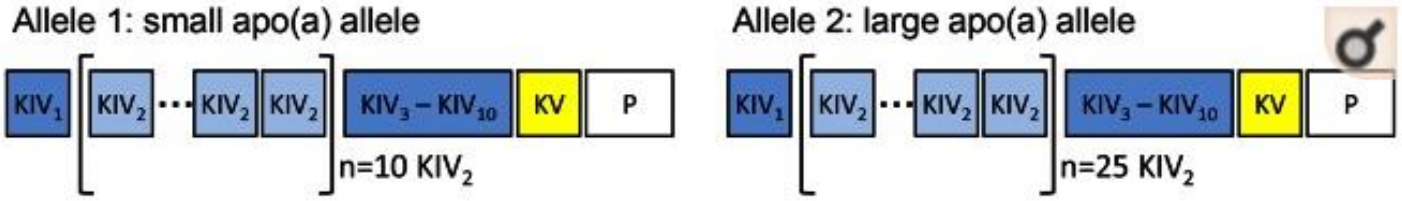
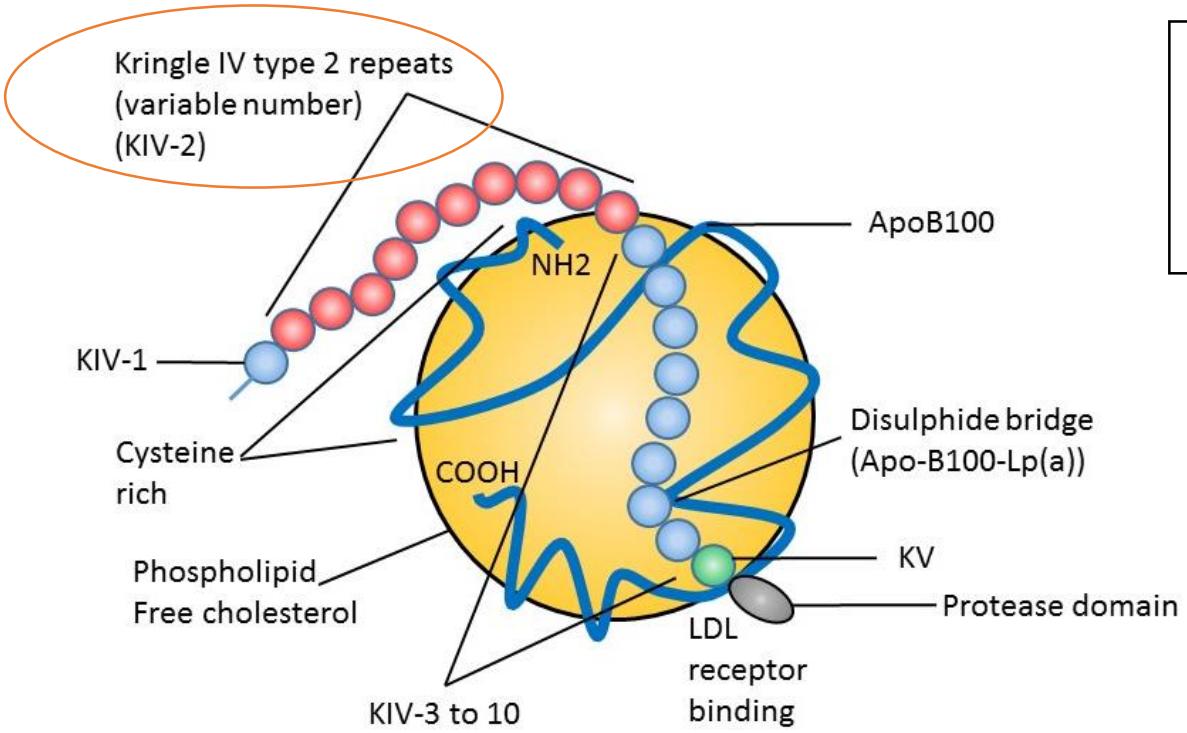
LPA gene





More KIV repeats:

- Slower hepatic synthesis
- **Fewer, larger particles**
- Reduced CV risk

LPA genetic variation controls Lp(a) levels

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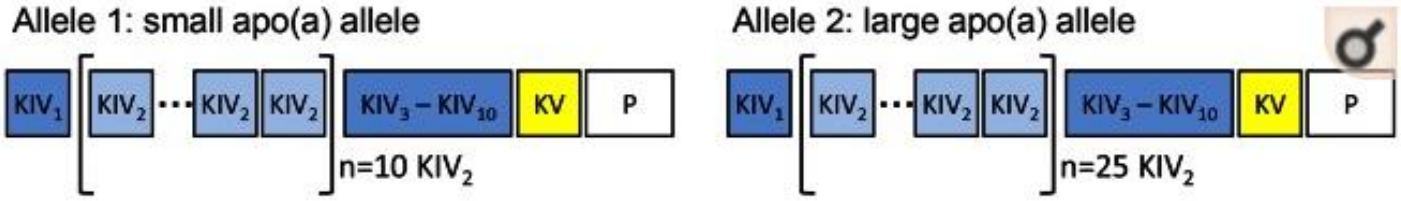
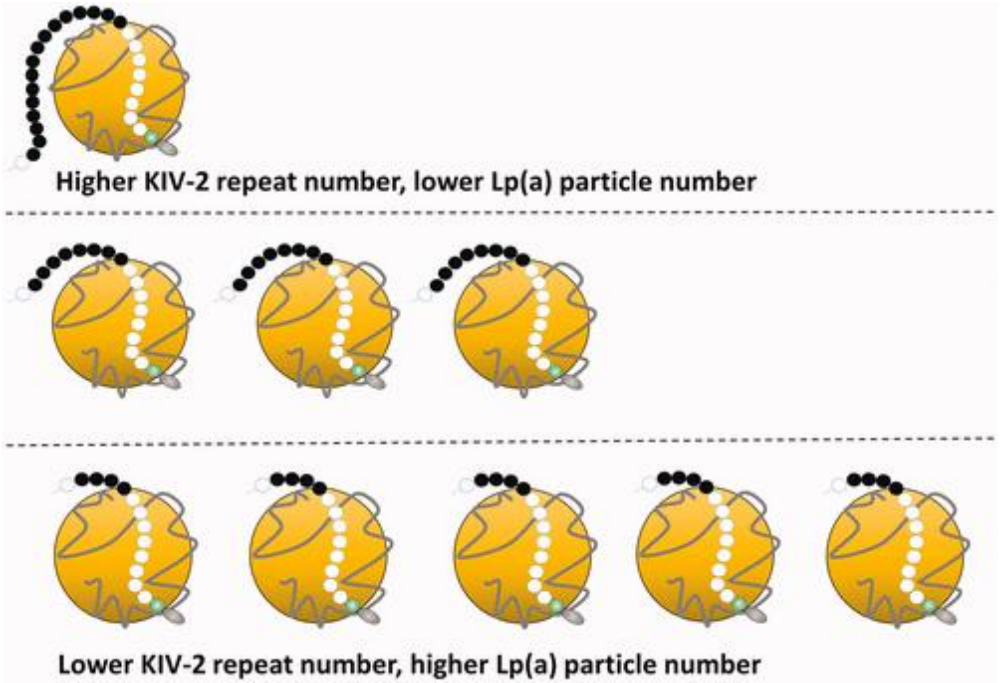
LPA gene





More KIV repeats:

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Combined influence of both parental alleles: co-dominant inheritance pattern

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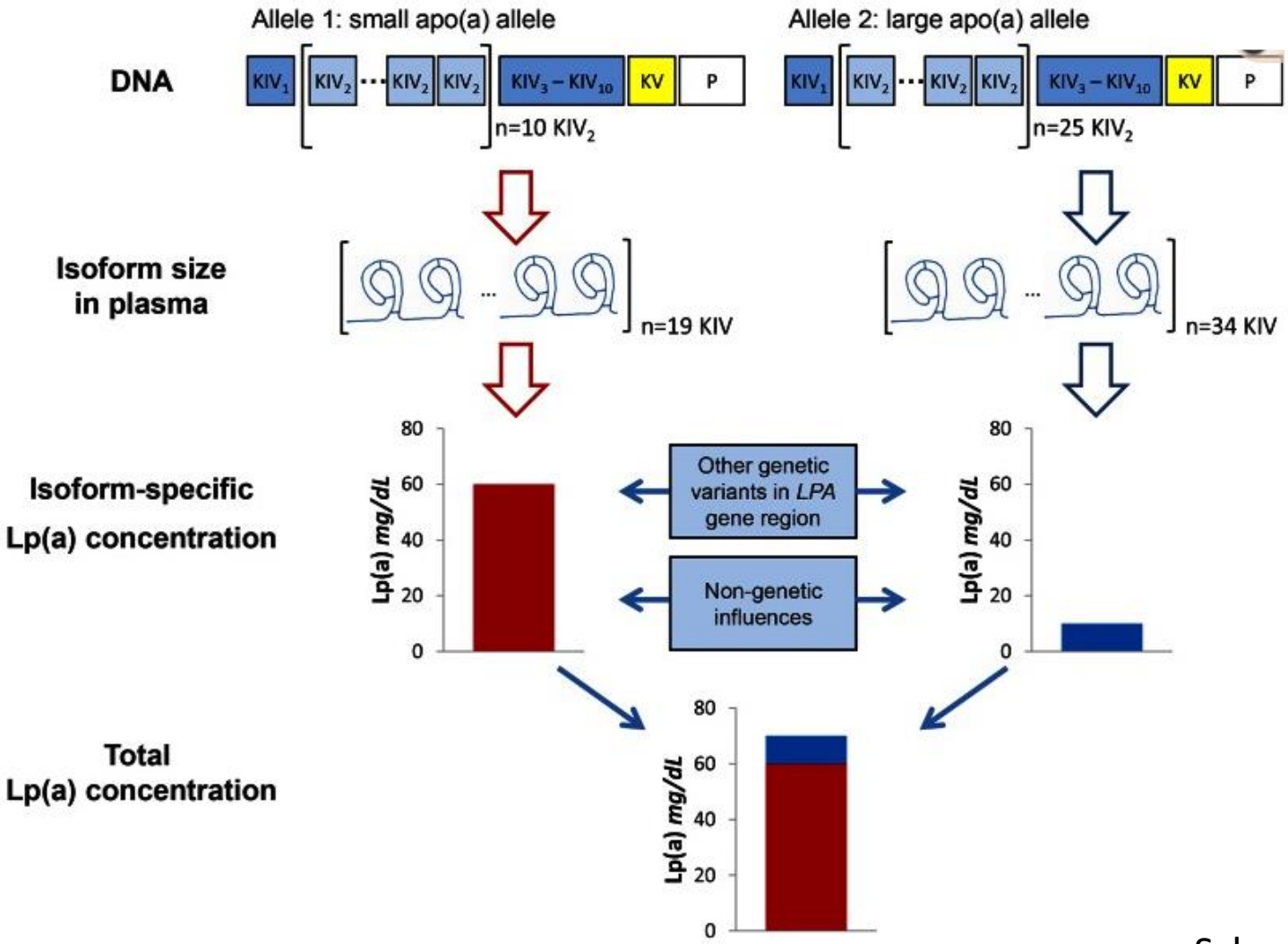

Schmidt JLR 2016

Measurement issues

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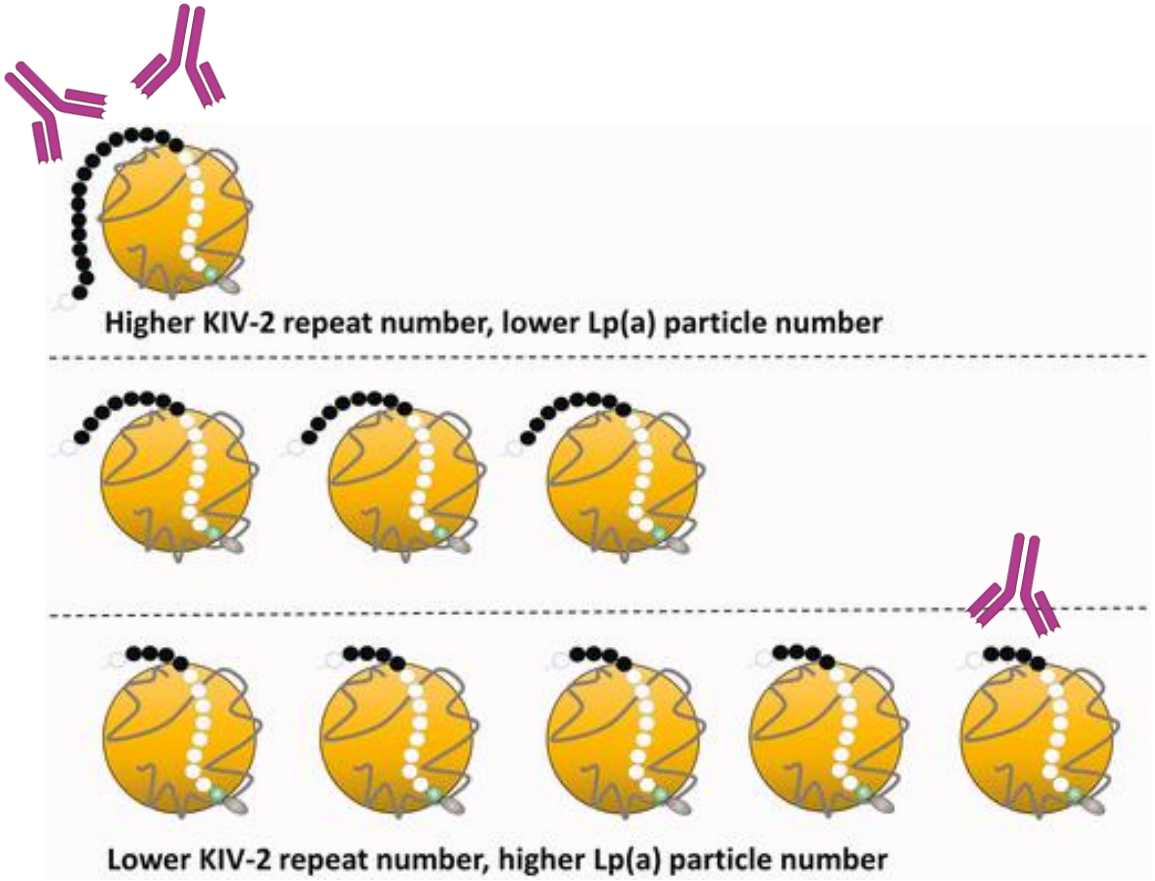

Larger isoforms could cause ***overestimation*** of Lp(a) concentration

However, the assay used at NWLP is considered ***isoform-insensitive*** and provides a true estimate of "concentration" or "particle number"

Is there an impact of genetic ancestry, ethnicity, or race?

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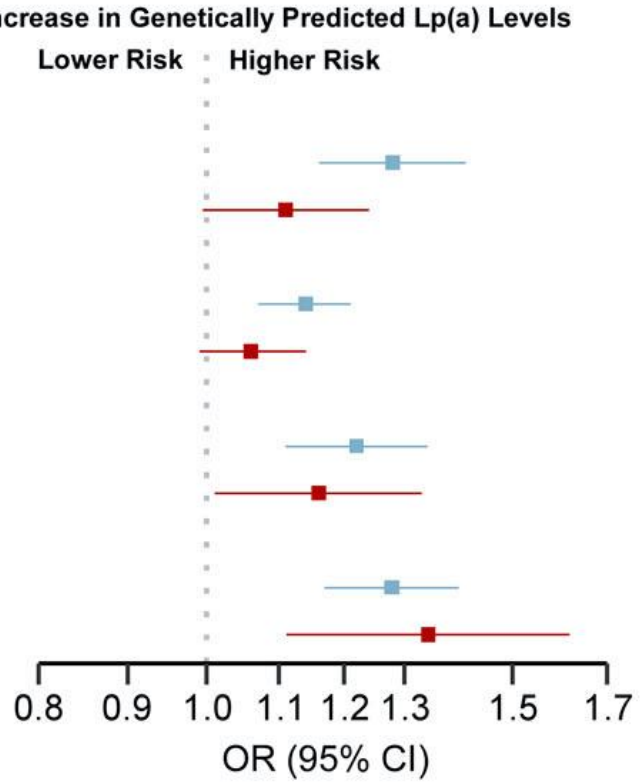
A

ASCVD type, Ancestry	*P*-value	OR (95% CI)
Coronary Heart Disease		
European Ancestry	1.51E-06	1.28 (1.16-1.41)
African Ancestry	0.056	1.11 (0.99-1.24)
Cerebrovascular Disease		
European Ancestry	2.37E-05	1.14 (1.07-1.21)
African Ancestry	0.112	1.06 (0.99-1.14)
Peripheral Artery Disease		
European Ancestry	2.97E-05	1.22 (1.11-1.34)
African Ancestry	0.034	1.16 (1.01-1.33)
Abdominal Aortic Aneurysm		
European Ancestry	6.24E-08	1.28 (1.17-1.40)
African Ancestry*	2.18E-03	1.34 (1.11-1.62)



Satterfield 2021

Lp(a) association with CVD is less strong in Black or African ancestry people than in people of South Asian, East Asian or European ancestry

Secondary causes of (or contributors to) raised Lp(a)

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- 70-90% genetically determined
- Menopause (moderate effect)
- Kidney disease including nephrotic syndrome
- Uncontrolled hypothyroidism
  - Not sub-clinical hypothyroidism

Do drugs affect Lp(a) levels?

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- Statins and ezetimibe – no! (not much anyway – possible slight increase with statins?)

- Anti-PCSK9 drugs – monoclonal antibodies (Evolocumab, Alirocumab) and Inclisiran – 15-20% reduction – but not licensed for this specifically

- Oestrogen replacement therapy – moderate effect
- Thyroxine

Take home messages

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- New Lp(a)-lowering treatments are on the horizon…

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When should Lp(a) be measured?

HEART UK recommendations on when to measure:

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Serum lipoprotein(a) levels should be measured in those with:

1) a personal or family history of premature atherosclerotic cardiovascular disease (<60 years of age)

2) first degree relatives with raised Lp(a) levels (>200 nmol/l)

3) familial hypercholesterolaemia (FH) and other genetic dyslipidaemias

4) calcific aortic valve stenosis

5) a borderline increased (but <15%) 10-year risk of a cardiovascular event as per NICE CG181 and Joint British Societies' guidelines.

HEART UK, Atherosclerosis 2019

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What do I do if lp(a) is raised?

Treatment of Lp(a)

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Conventional

- Niacin
- Reducing residual risk
- PCSK9i
- Aspirin

Novel

- Mipomersen
- Anacetrapib
- Antisense oligos ....

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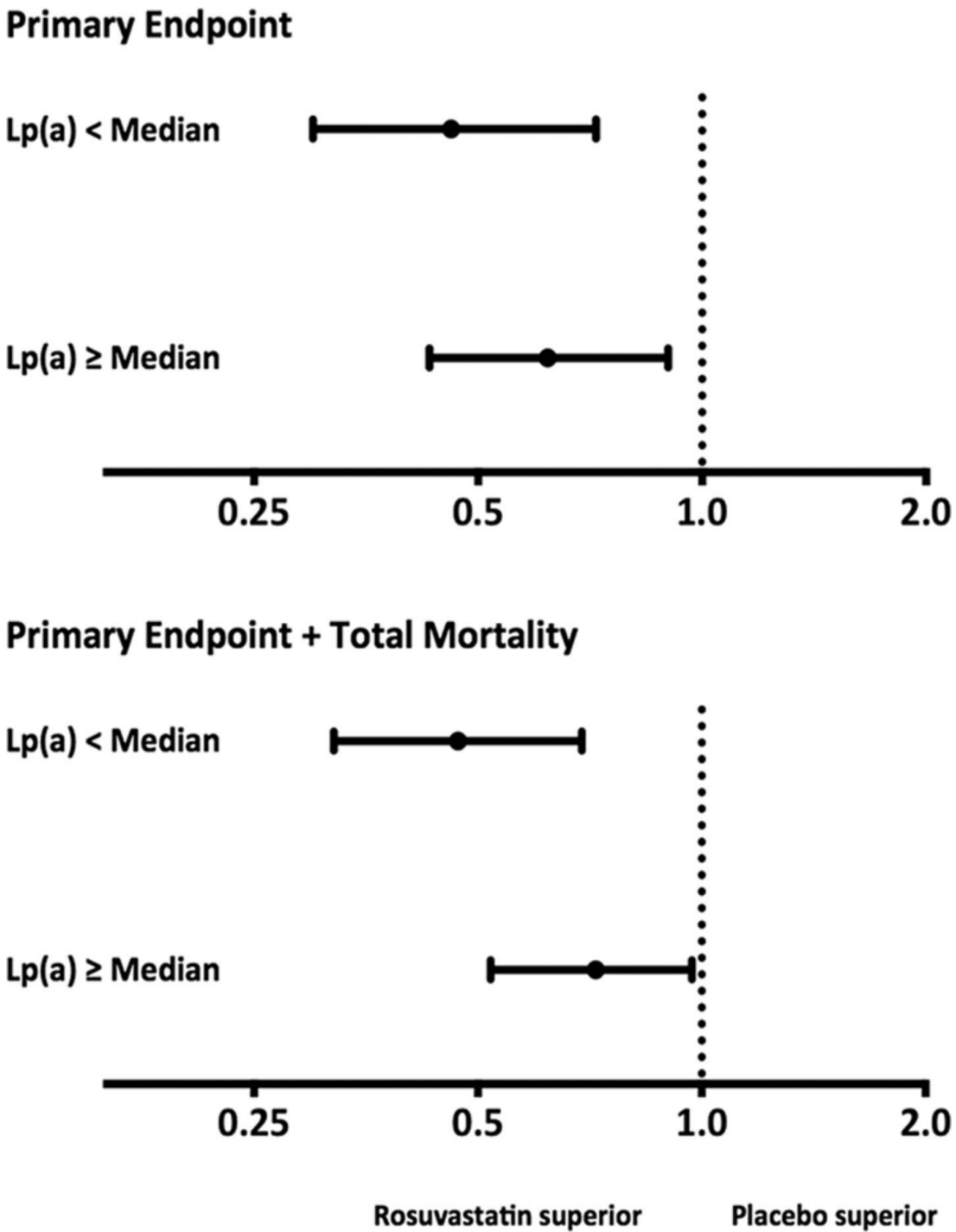

High intensity statin reduces CVD events in people with low and high Lp(a)

JUPITER, Rosuva 40
Khera Circulation 2013

Aspirin reduces CVD risk in women with genetically determine high Lp(a)

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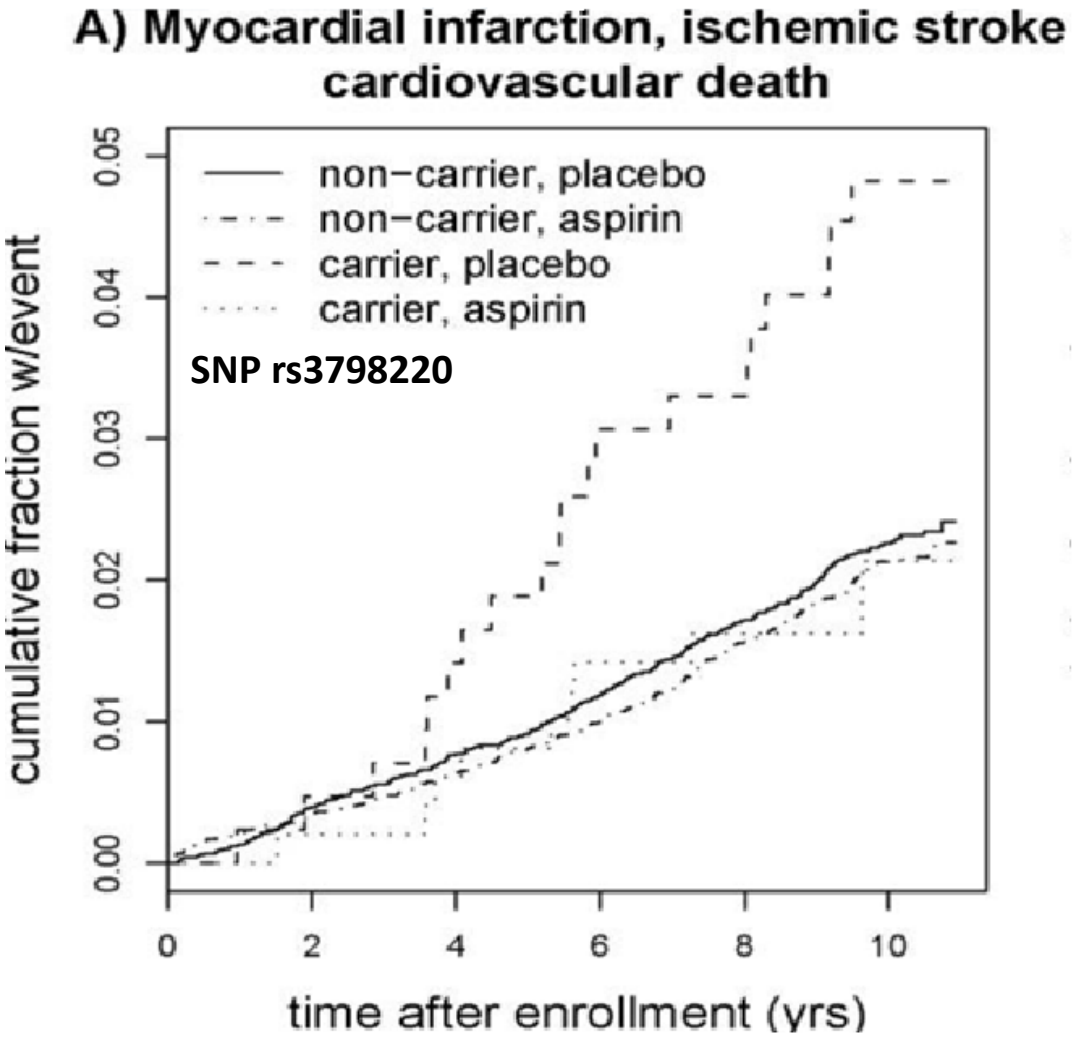

Chasman Atherosclerosis 2009

PCSK9 inhibition

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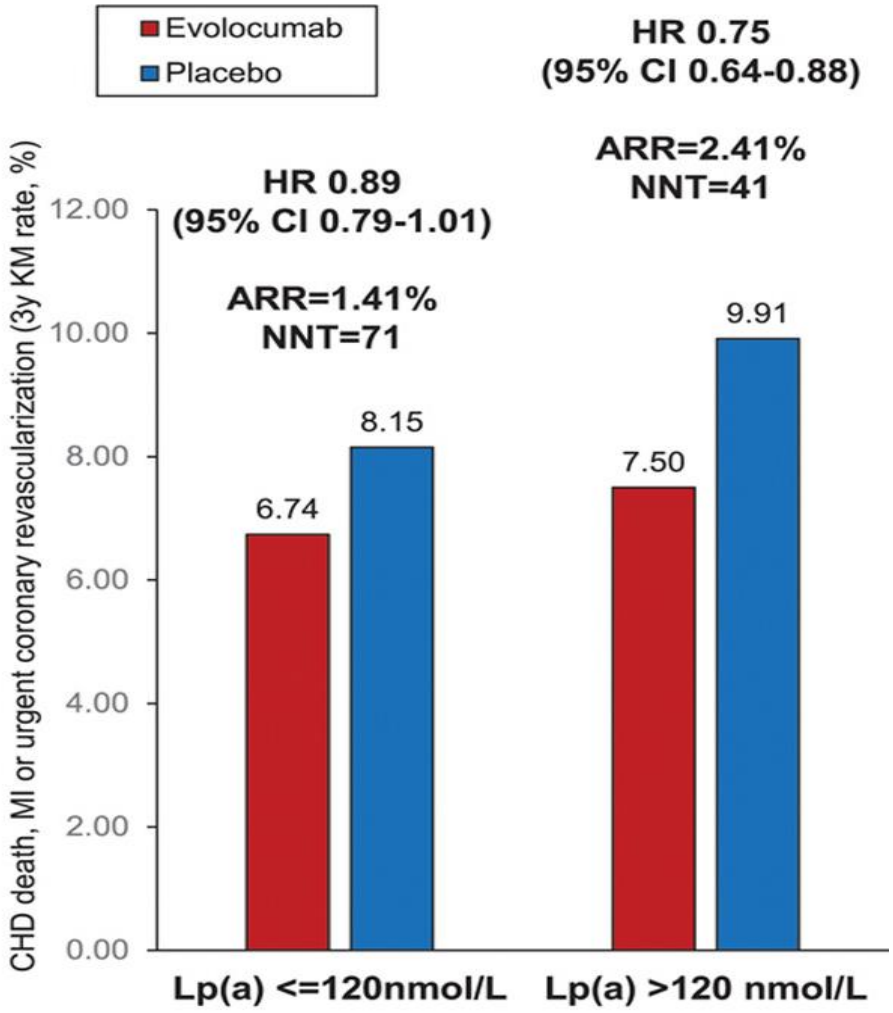

- Anti-PCSK9 monoclonal antibodies (Evolocumab, Alirocumab) and Inclisiran reduce Lp(a) by 15-20%
- PCSK9 therapy reduces CVD risk in people with high or low Lp(a)

O'Donoghue Circulation 2019

Antisense Oligonucleotides

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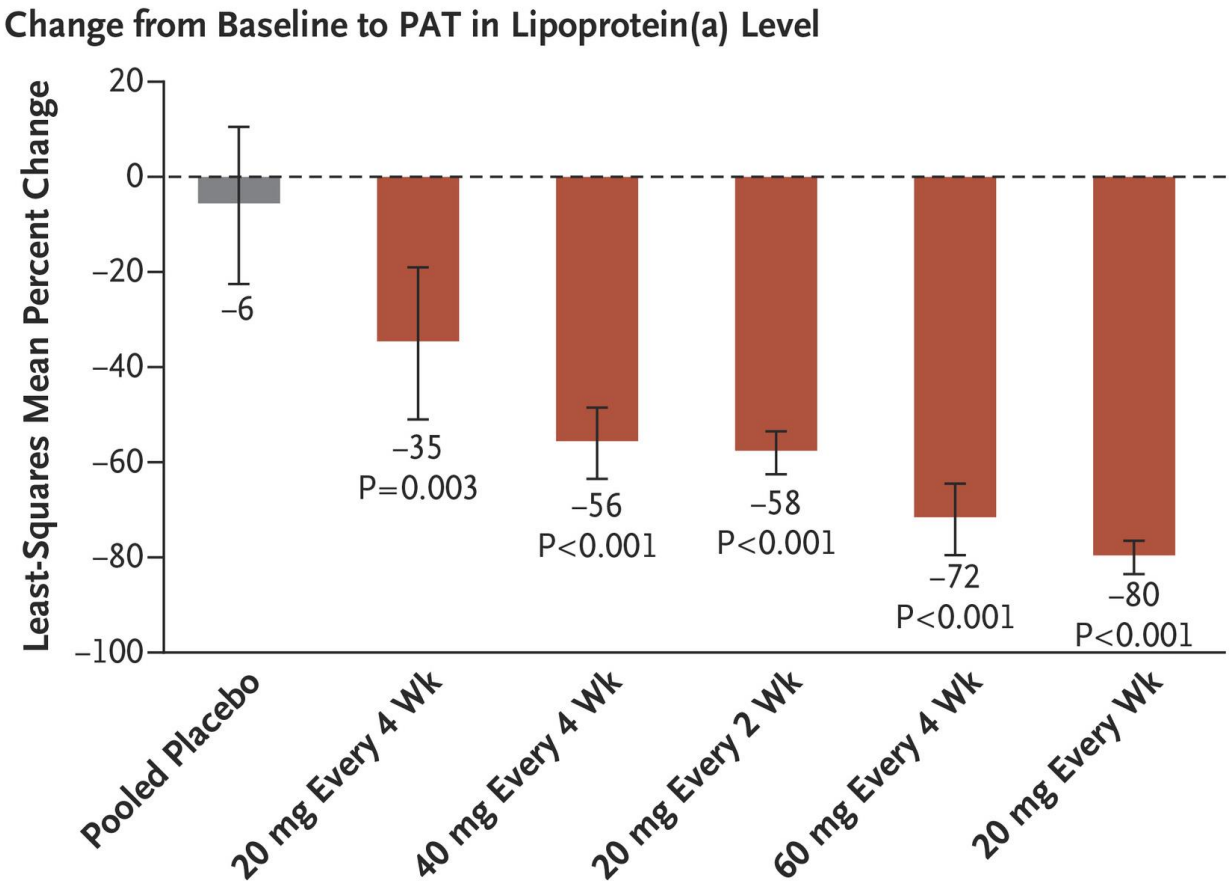

Tsimikas NEJM 2020

The Phase 3 HORIZON trial is investigating anti-apo(a) antisense oligonucleotides on cardiovascular outcomes. Expected to complete in 2024

Should all patients with high Lp(a) be referred to local lipid clinic?

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(If you measure it)

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- At present, specific Lp(a)-lowering treatments are not available

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- In my view, if Lp(a) measured in primary care in patient categories listed above, and initial management of modifiable risk factors has been initiated, it would be reasonable to refer patients with at least moderately elevated Lp(a)

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Acknowledgements

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- Jaimini Cegla and Lipid Clinic colleagues
- NWLP scientific colleagues

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Questions?