ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
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ΙΔΡΥΘΕΝ ΤΟ 1837
ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΑΘΗΝΩΝ

ΠΜΣ: Καρδιομεταβολική Ιατρική
Ο ρόλος της Lp(a) στην Αθηρωμάτωση. Θεραπευτικές Προσεγγίσεις

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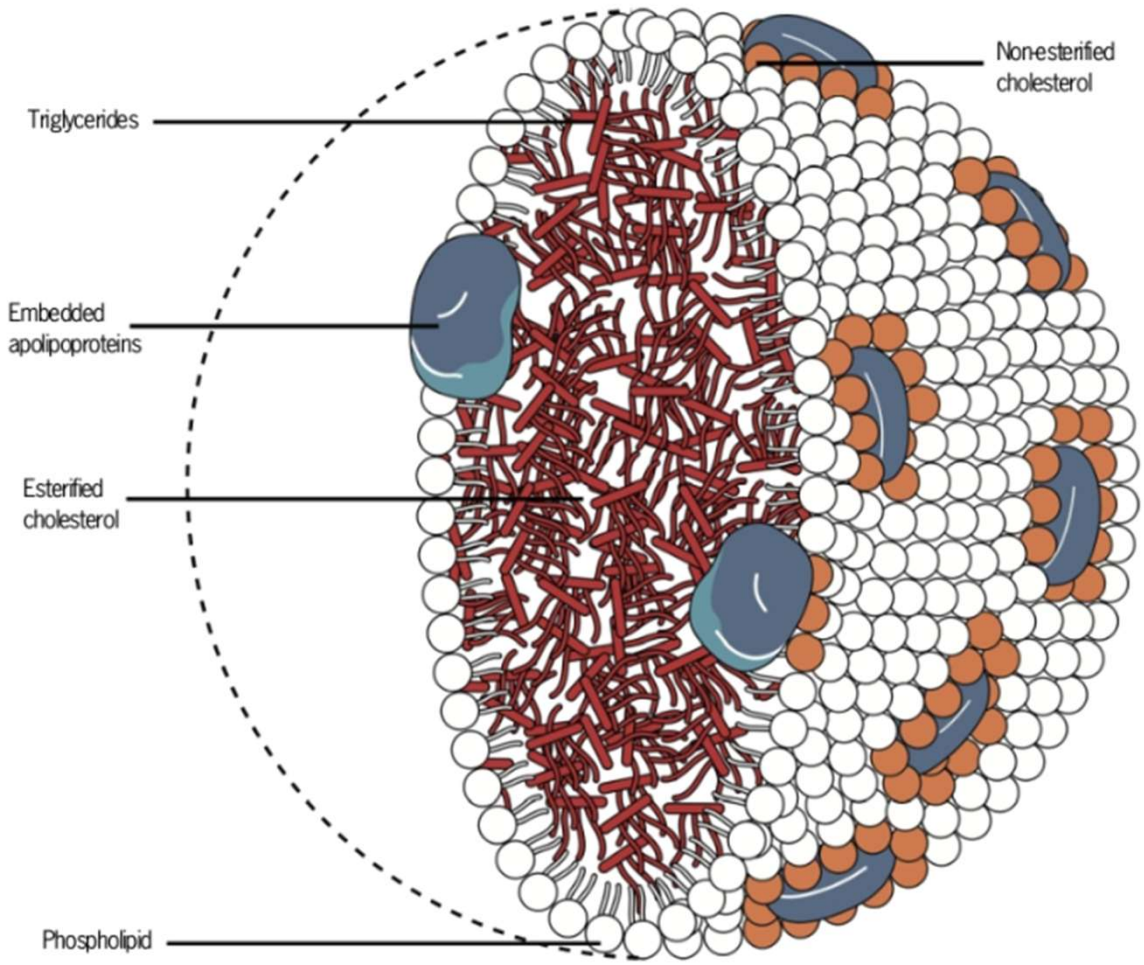
ΠΓΝ ΑΤΤΙΚΟΝ

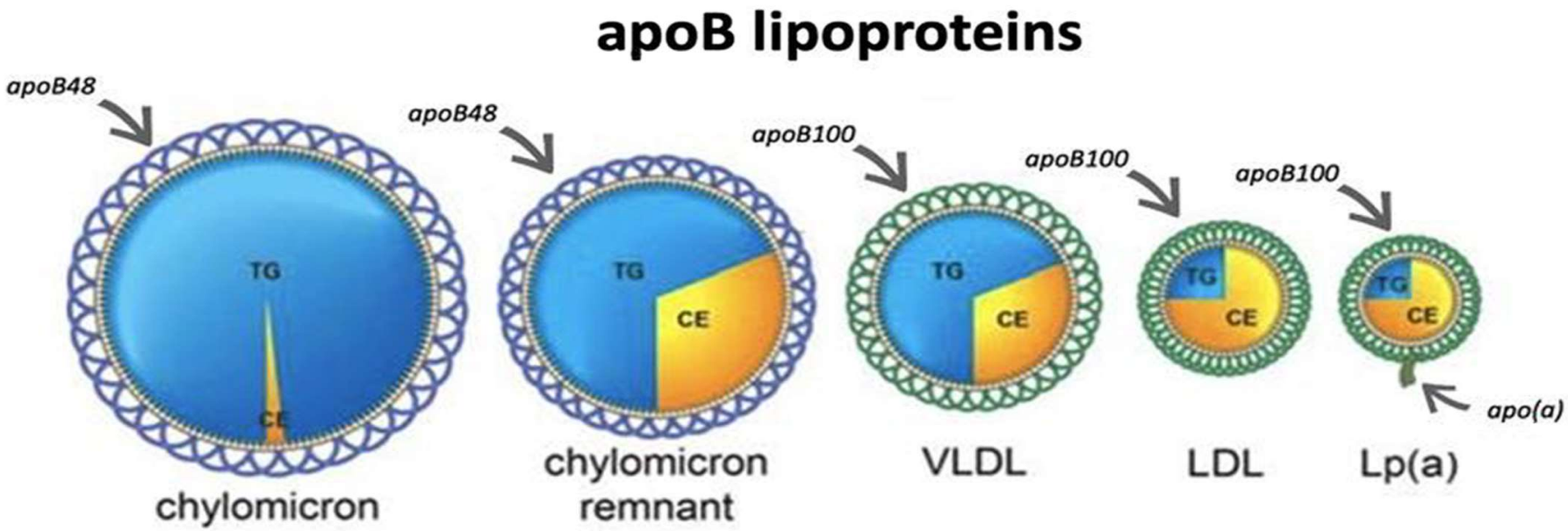


Surface	Free cholesterol (non-esterified) Phospholipid (e.g. lecithin) Apolipoproteins (non-exchangeable and exchangeable) Fat-soluble antioxidants and vitamins
Core	Cholesterol esters (fatty acyl cholesterol) Triglyceride (triacylglycerols) Fat-soluble antioxidants and vitamins

Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid deposition, steroid hormone production and bile acid formation.

Lipoproteins consist of esterified and unesterified cholesterol, TGs, phospholipids and protein components named apolipoproteins that act as structural components, ligands for cellular receptor binding and enzyme activators or inhibitors.

There are six major lipoproteins in blood: chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL; Lp(a), and HDL.

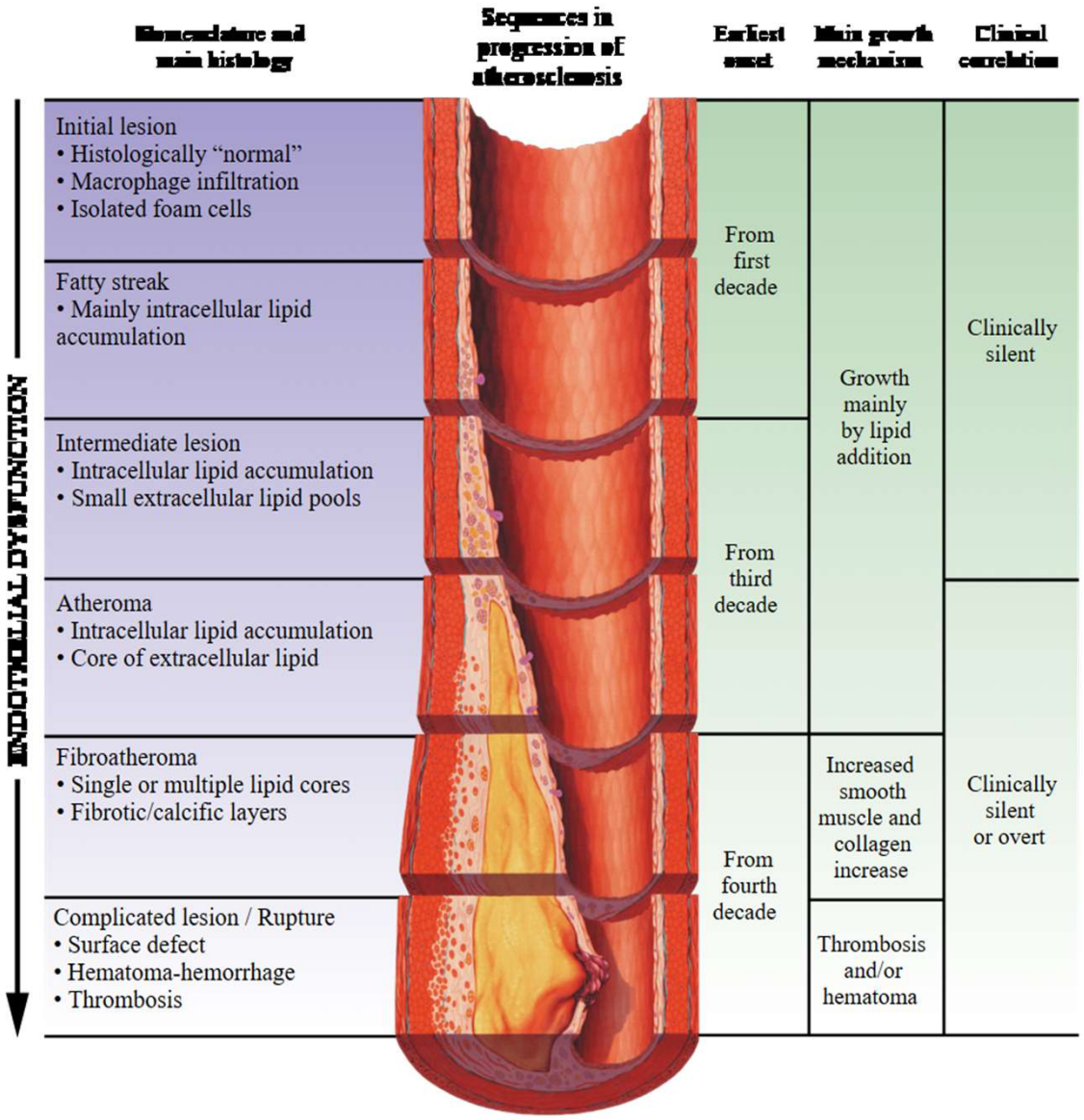


One molecule of apo B_{48} encircles each chylomicron and chylomicron remnant particle. The chylomicron remnant particle contains less TG but the same amount of cholesterol as the intact chylomicron particle. The difference in TG mass represents the mass of TG delivered to adipose tissue and skeletal muscle. One molecule of apo B_{100} encircles VLDL, LDL, and Lp(a) particles. Lp(a) particles are an LDL particle to which a molecule of apo(a) has been attached. One molecule of apo B_{48} encircles a chylomicron or chylomicron remnant particle.

apoB indicates apolipoprotein B; CE, cholesteryl ester; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TG, triglycerides; and VLDL, very low-density lipoprotein.

All ApoB-containing lipoproteins <70 nm in diameter, including smaller TG-rich lipoproteins and their remnant particles, can cross the endothelial barrier, especially in the presence of endothelial dysfunction, where they can become trapped after interaction with extracellular structures such as proteoglycan. Because atherosclerotic Plaques grow over time as additional ApoB-containing lipoprotein particles are retained, the size of the total atherosclerotic plaque burden is likely to be determined by both the concentration of circulating LDL-C and other ApoB-containing lipoproteins, and by the total duration of exposure to these lipoproteins.

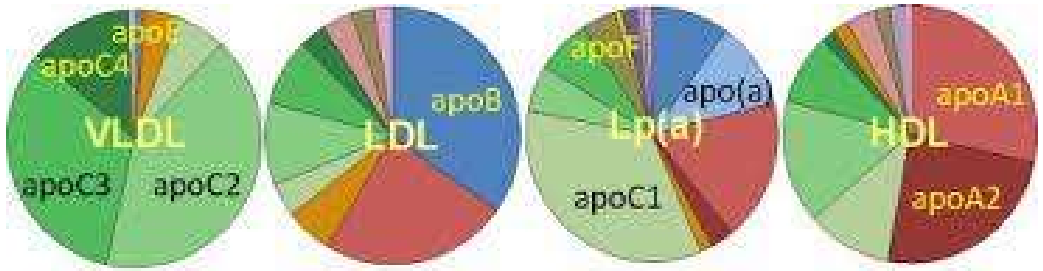
Therefore, total atherosclerotic plaque burden is likely to be proportional to the cumulative exposure to these lipoproteins.



Physical and chemical characteristics of human plasma lipoproteins

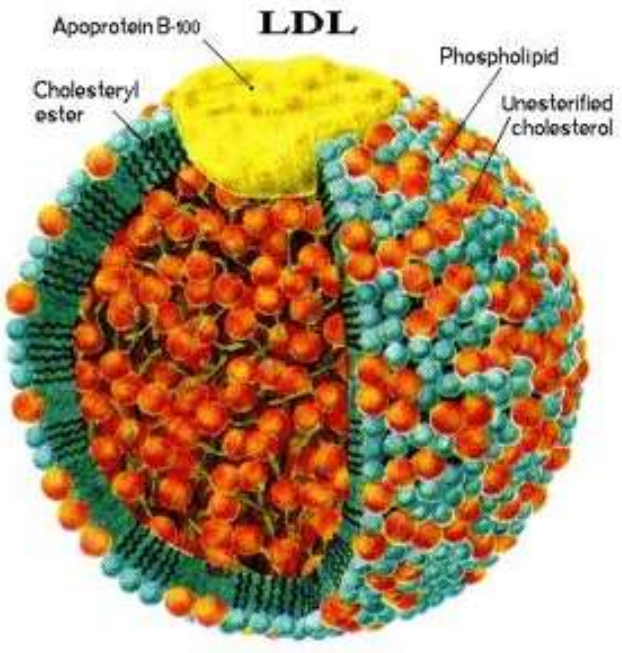
	Density (g/mL)	Diameter (nm)	TGs (%)	Cholesteryl esters (%)	PLs (%)	Cholesterol (%)	Apolipoproteins	
							Major	Others
Chylomicrons	<0.95	80–100	90–95	2–4	2–6	1	ApoB-48	ApoA-I, A-II, A-IV, A-V
VLDL	0.95–1.006	30–80	50–65	8–14	12–16	4–7	ApoB-100	ApoA-I, C-II, C-III, E, A-V
IDL	1.006–1.019	25–30	25–40	20–35	16–24	7–11	ApoB-100	ApoC-II, C-III, E
LDL	1.019–1.063	20–25	4–6	34–35	22–26	6–15	ApoB-100	
HDL	1.063–1.210	8–13	7	10–20	55	5	ApoA-I	ApoA-II, C-III, E, M
Lp(a)	1.006–1.125	25–30	4–8	35–46	17–24	6–9	Apo(a)	ApoB-100

Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PLs = phospholipids; TGs = triglycerides; VLDL = very low-density lipoprotein.



Frequencies of lipoprotein-associated proteins on different particle classes

- Plasma LDL-C is a measure of the cholesterol mass carried by LDL particles, by far the most numerous of the ApoB-containing lipoproteins and is an estimate of the concentration of circulating LDL.
- Mendelian randomization studies, and RCTs have consistently demonstrated a log-linear relationship between the absolute changes in plasma LDL-C and the risk of ASCVD.
- LDL-C is causally associated with the risk of ASCVD, and that lowering LDL-C reduces the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C.
- **The effect of LDL-C on the risk of ASCVD appears to be determined by both the absolute magnitude and the total duration of exposure to LDL-C.**



The clinical benefit of therapies that lower LDL-C by reducing LDL particle mass will be proportional to the absolute reduction in LDL-C, because—on average—the reduction in LDL-C and LDL particles will be concordant.
In contrast, the clinical benefit of therapies that lower LDL-C by a mechanism that may dramatically modify their composition may not be proportional to the observed absolute reduction in LDL-C, but instead would be expected to be proportional to the absolute change in LDL particle concentration as measured by a reduction in ApoB.

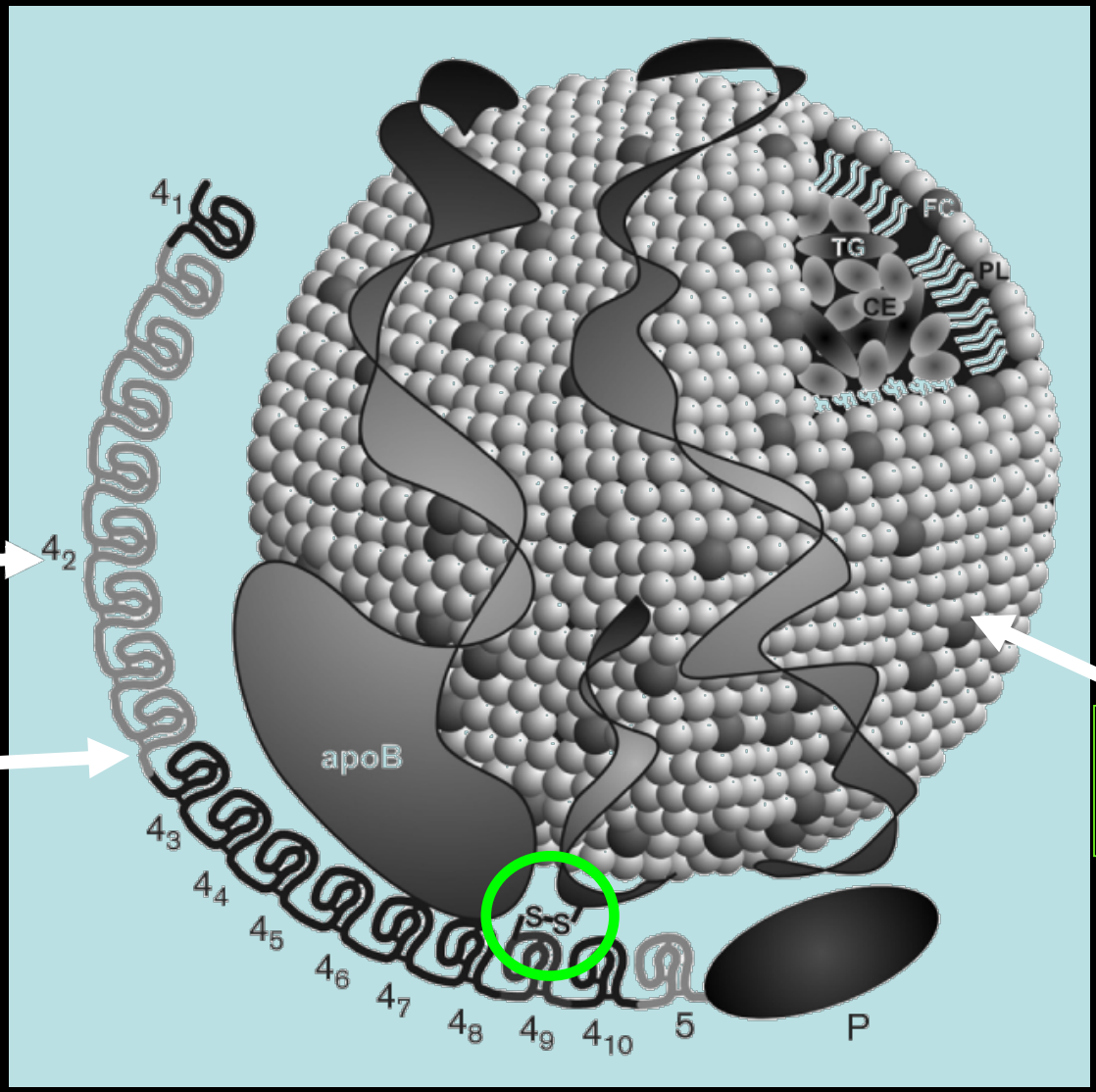
Lp(a) is an LDL particle with an Apo(a) moiety covalently bound to its ApoB component.
It is <70 nm in diameter and can freely flux across the endothelial barrier, where it can become—similarly to LDL—retained within the arterial wall and thus may increase the risk of ASCVD.
Pro-atherogenic effects of Lp(a) have also been attributed to pro-coagulant effects as Lp(a) has a similar structure to plasminogen, and it has pro-inflammatory effects most likely related to the oxidized phospholipid load carried by Lp(a).

Higher plasma Lp(a) concentrations are associated with an increased risk of ASCVD, but it appears to be a much weaker risk factor for most people than LDL-C.
In contrast, Mendelian randomization studies have consistently demonstrated that lifelong exposure to higher Lp(a) levels is strongly and causally associated with an increased risk of ASCVD.

While randomized trials evaluating therapies that lower Lp(a) by 20-30% (including niacin and CETP inhibitors) have not provided evidence that lowering Lp(a) reduces the risk of ASCVD beyond that which would be expected from the observed reduction in ApoB-containing lipoproteins, recent data with PCSK9 inhibitors have suggested a possible role for Lp(a) lowering in reducing CV risk.

This conflicting evidence appears to have been reconciled by a recent Mendelian randomization study that showed that the causal effect of Lp(a) on the risk of ASCVD is proportional to the absolute change in plasma Lp(a) levels. Importantly, this study also suggested that people with extremely high Lp(a) levels >180 mg/ dL (>430 nmol/L) may have an increased lifetime risk of ASCVD similar to that of people with heterozygous FH (HeFH). Because about 90% of a person's Lp(a) level is inherited, extremely elevated Lp(a) may represent a new inherited lipid disorder that is associated with extremely high lifetime risk of ASCVD and is twofold more prevalent than HeFH.[77] However, this study[77] and another based on the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial[78] have shown that large absolute changes in Lp(a) may be needed to produce a clinically meaningful reduction in the risk of ASCVD events.

Lipoprotein(a) particle structure

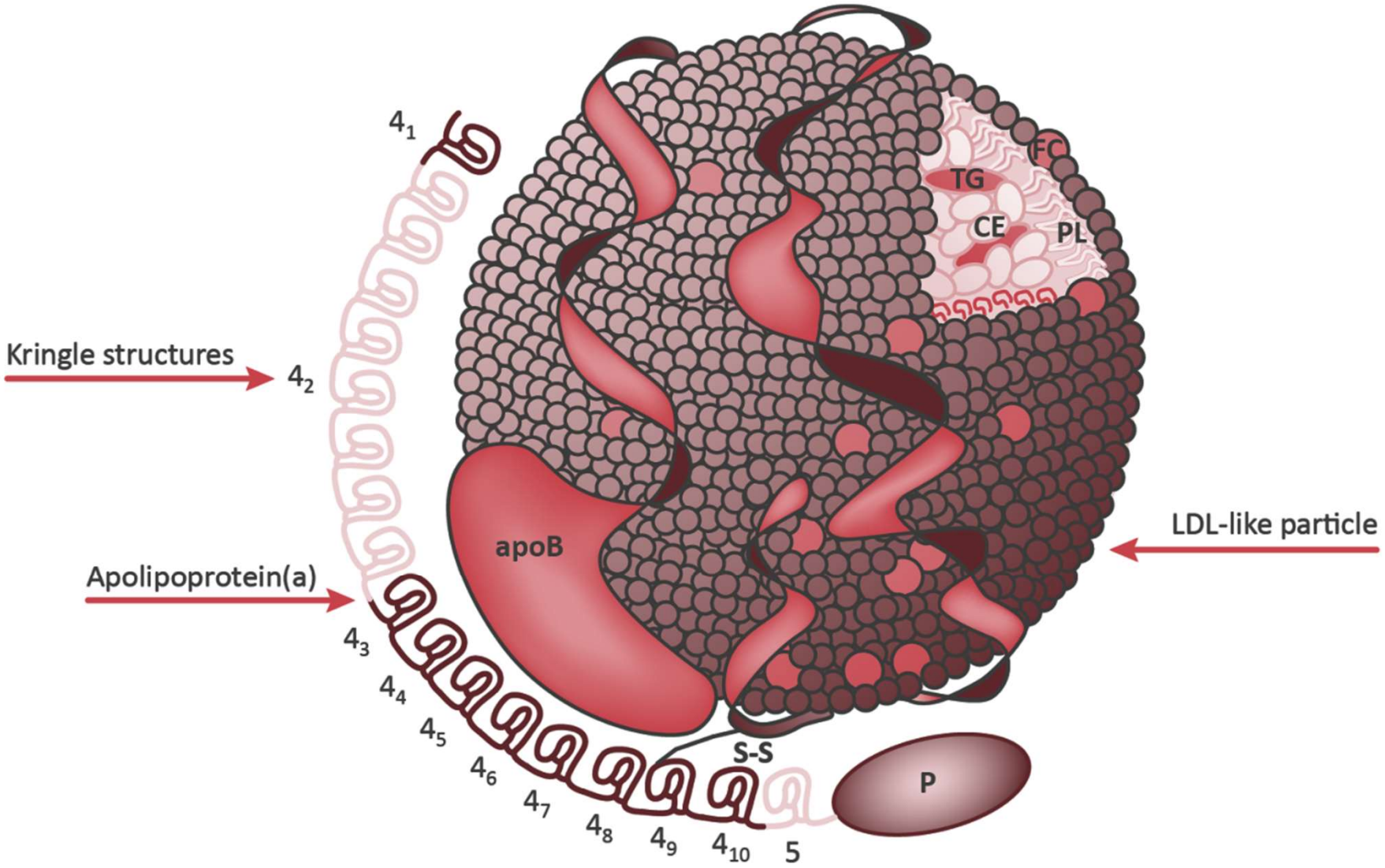


Kringle structures

Apolipoprotein(a)

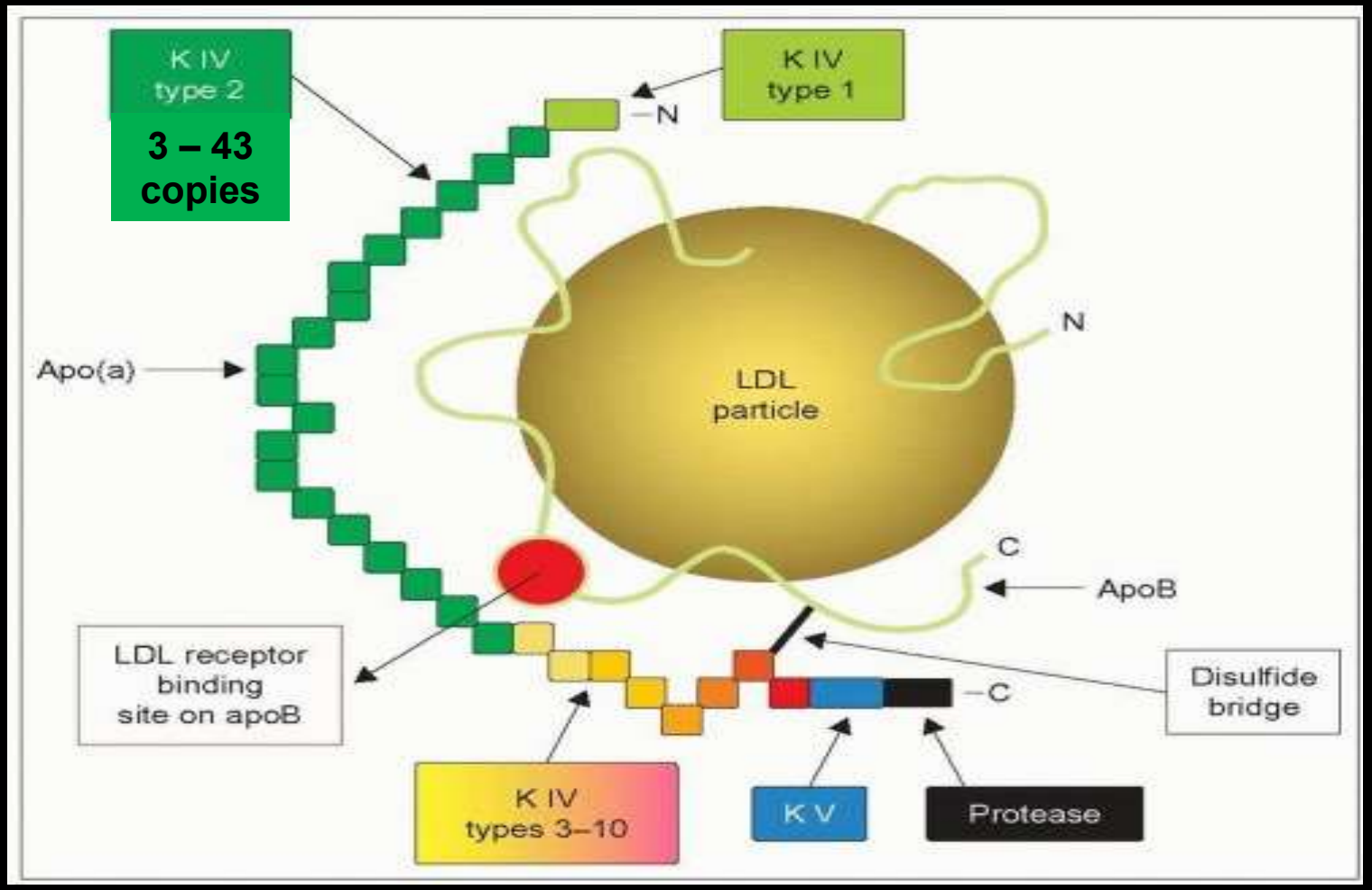
LDL-like particle

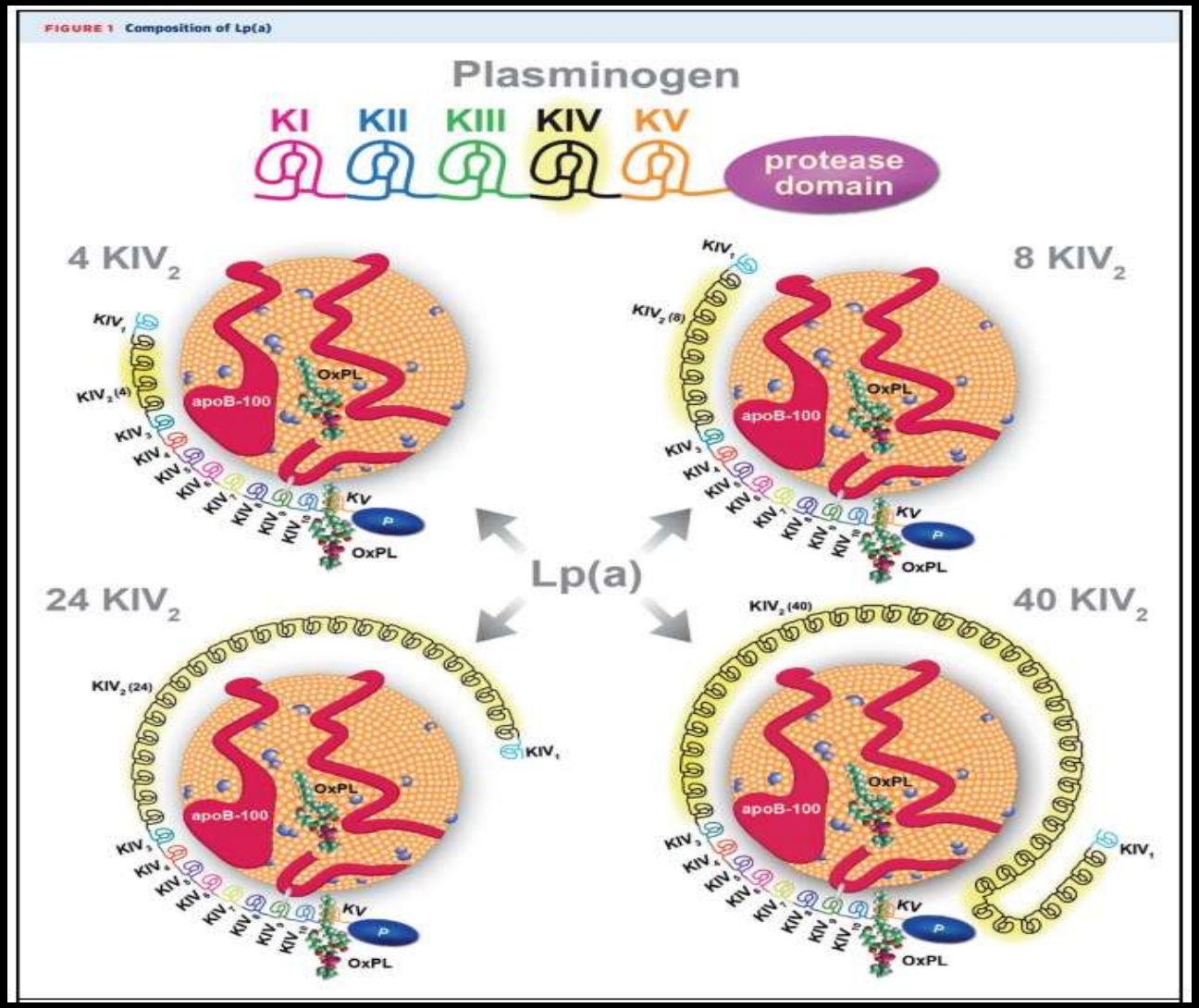
Koschinsky et al.,
Curr Opin Lipidol, 2004



Adapted from Kronenberg, Handbook Exp Pharmacol, 2021; Kamstrup et al, 2009

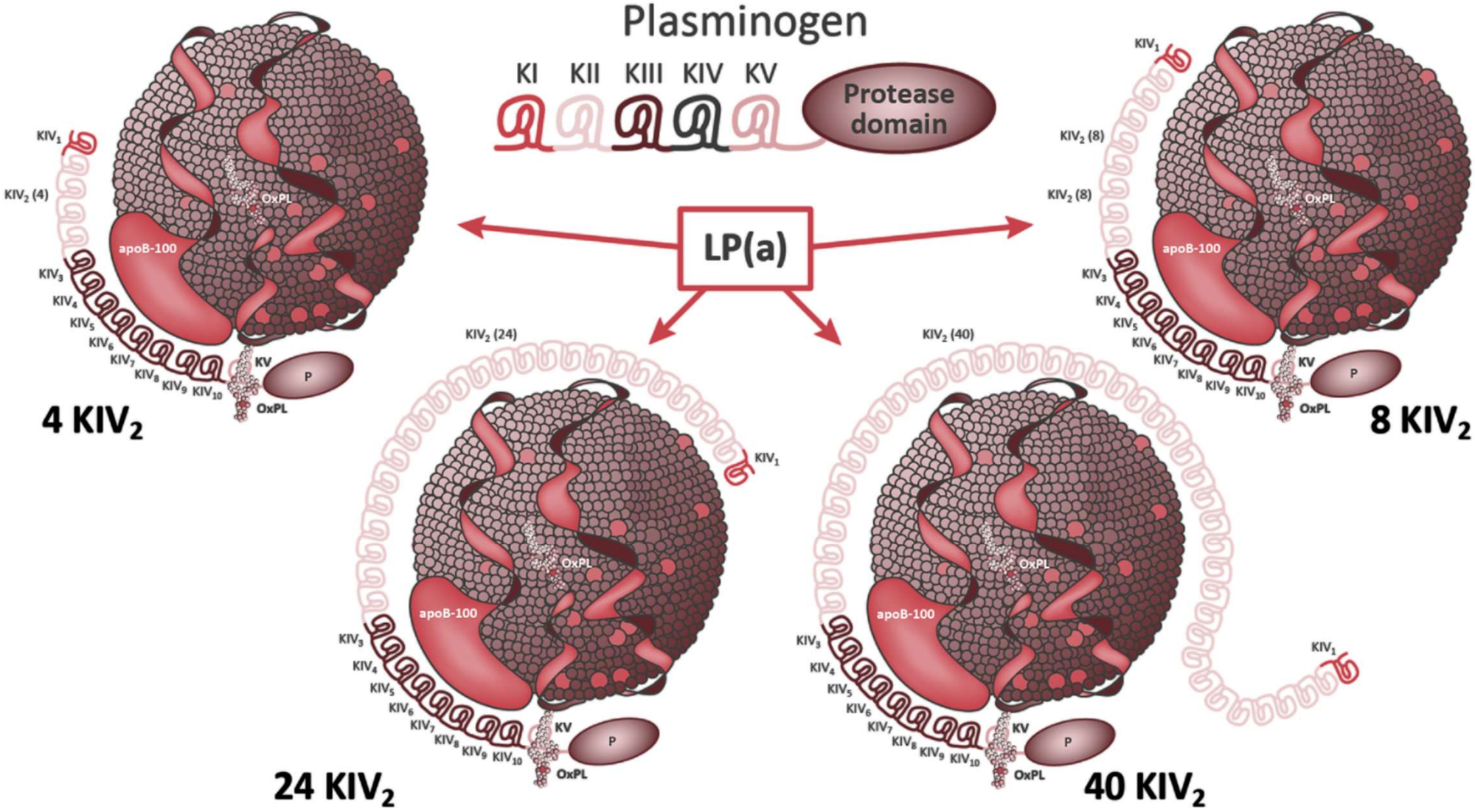
Apolipoprotein (a) and Lipoprotein Lp(a)





Particle size heterogeneity of Lipoprotein (a)

Tsimikas et al, JACC, 2017, 69: 692



Adapted from Tsimikas, S. (2017). A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *Journal of the American College of Cardiology*, *69*(6), 692-711. https://doi.org/10.1016/j.jacc.2016.11.042

Quantitation of Lp(a)

• Lp(a) is measured either in mass units (mg/dL) or in molar units (nmol/L), which causes major confusion in clinical practice.

• Measurements in molar terms are desirable but not easy to accomplish.

• The repetitive kringle IV (KIV) repeat structure of apolipoprotein(a) is the basic source of measurement problems.

• Polyclonal antibodies are widely used in clinical routine assays, and recognize with high likelihood the repetitive KIV structure of apolipoprotein(a).

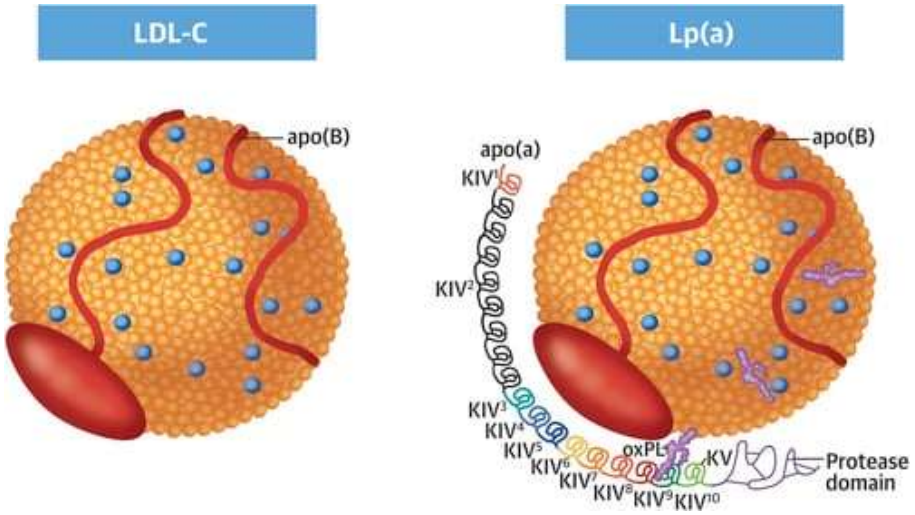
• Consequently, concentrations of Lp(a) with a large number of KIV repeats might be overestimated and those with a small number of KIV repeats might be underestimated.

• The selection of the calibrators and their isoform sizes is of key importance and might improve the measurement performance of an Lp(a) assay.

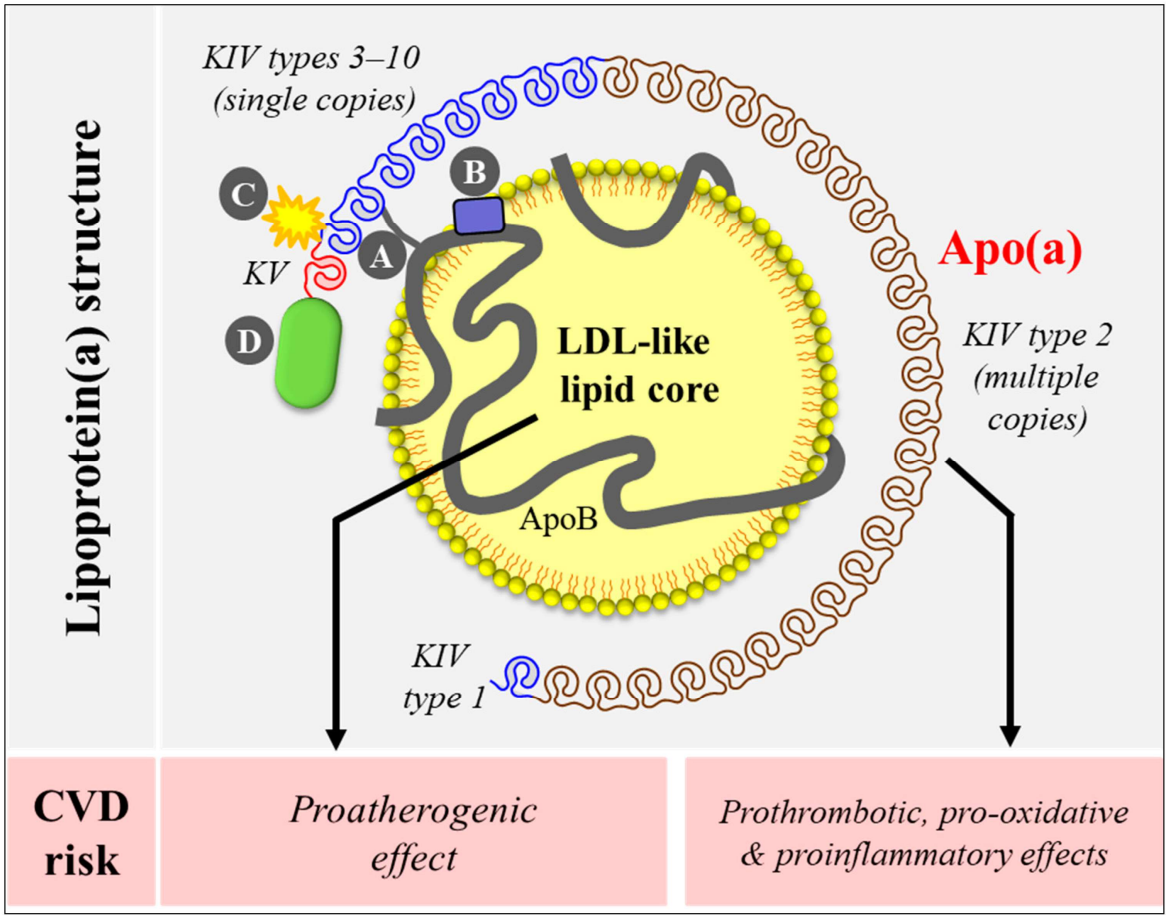
• Major efforts to better standardize Lp(a) measurements are under way.

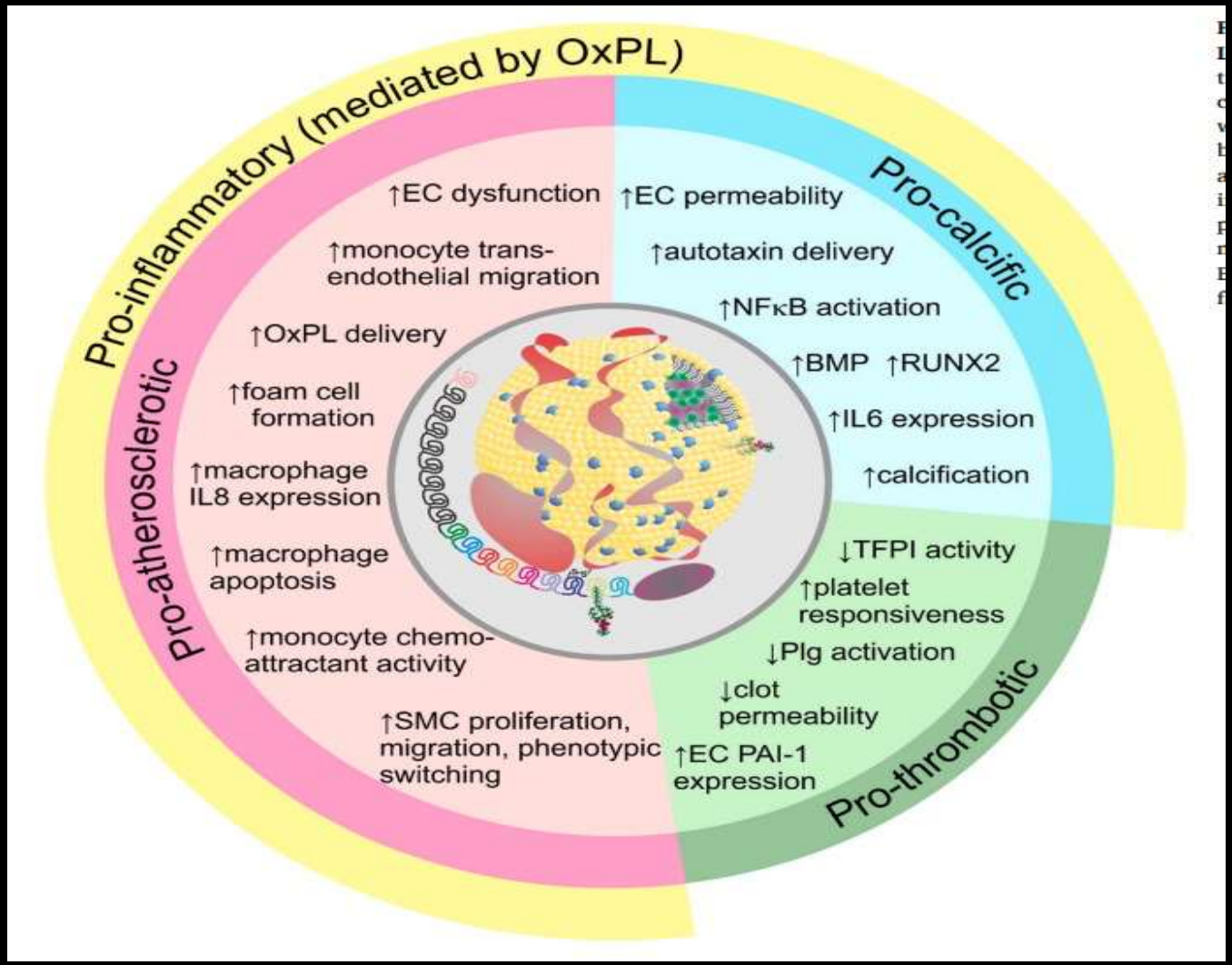
• Lp(a) assays are not yet perfect, but most are sufficient for risk stratification of patients.

Kronenberg, Atherosclerosis, 2022



Measurement of Lp(a) should be considered at least once in each person's lifetime, if available, to identify people who have inherited an extremely elevated level of Lp(a) >_180 mg/dL (>_430 nmol/L) and therefore have a very high lifetime risk of ASCVD that is approximately equivalent to the risk associated with HeFH. In addition, this strategy can identify people with less-extreme Lp(a) elevations who may be at a higher risk of ASCVD, which is not reflected by the SCORE system, or by other lipid or lipoprotein measurements. Measurement of Lp(a) has been shown to provide clinically significant improved risk reclassification under certain conditions, and therefore should be considered in patients who have an estimated 10-year risk of ASCVD that is close to the threshold between high and moderate risk





Potential pathogenic mechanisms of Lp(a)

Koschinsky et al, Pharmacological Res, 2023

Pro-atherogenic properties	Prothrombotic properties
↑ Oxidized phospholipids ↑ Foam cell formation ↑ Endothelial dysfunction ↑ Smooth muscle cell proliferation ↑ Chemoattraction of monocytes ↑ Inflammation of the arterial wall	↓ Plasminogen activation ↓ Fibrinolysis ↓ Tissue factor pathway inhibitor ↓ Clot permeability ↑ Platelet response

What is Lp(a)?

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein consisting of an LDL-like particle in which apolipoprotein B100 (apoB100) is covalently linked to the plasminogen-like protein, apolipoprotein(a) (apo(a)).

As apo(a) occurs in many different sizes, with more than 40 different isoforms, Lp(a) particles also occur in more than 40 different sizes – uniquely amongst circulating proteins. Over 80% of people carry two different sized apo(a) isoforms, each inherited from one parent; typically, the smallest form predominates in plasma.

Lp(a) is produced mainly in the liver, and is thought to play a role in wound healing though, as some people have undetectable levels, its physiological significance is uncertain.[1]

- Lp(a) is less than 70 nm in diameter and can pass freely across the endothelial barrier and remain within the arterial wall, as a result of strong interactions with extracellular matrix components within the arterial wall. It has a range of pathological properties, including atherogenic, thrombogenic and pro-inflammatory effects.

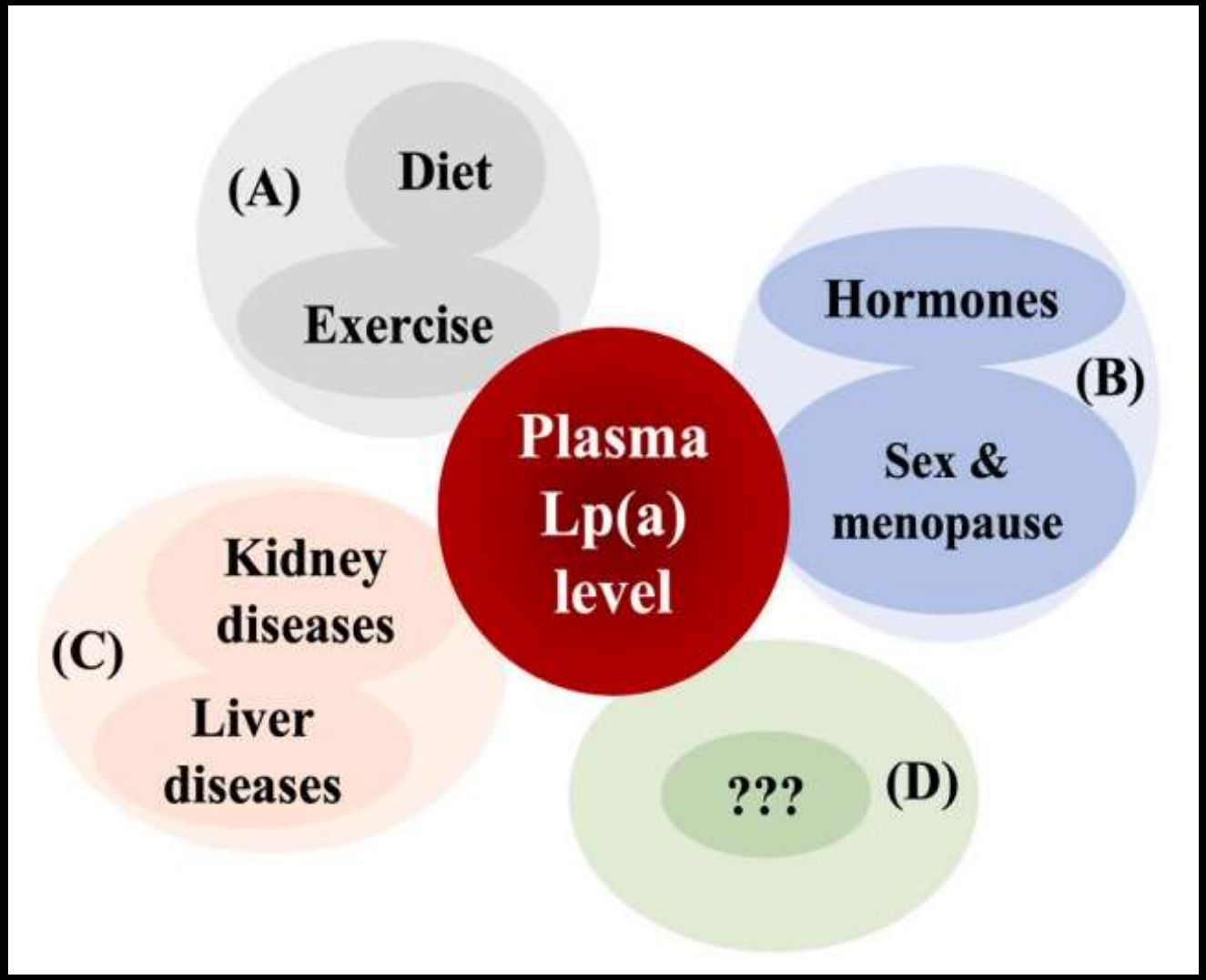
Lp(a) concentration is determined mainly by genetic factors, with the *LPA* gene fully expressed by the age of two years. Adult levels are generally reached by the age of five years, though they may increase into adulthood. The Kringle-IV (K-IV) repeat polymorphism is responsible for approximately 30-70% of the variability in Lp(a) concentration. Expression of fewer than 23 K-IV repeats is characterized by small apoA isoforms, and these are associated with raised Lp(a) concentration compared with large apoA isoforms.

Non-genetic factors may also affect Lp(a) levels:

•Factors that may increase Lp(a) levels: high carbohydrate diet, hypothyroidism, pregnancy, chronic kidney disease, severe inflammatory conditions, fine particle air pollution

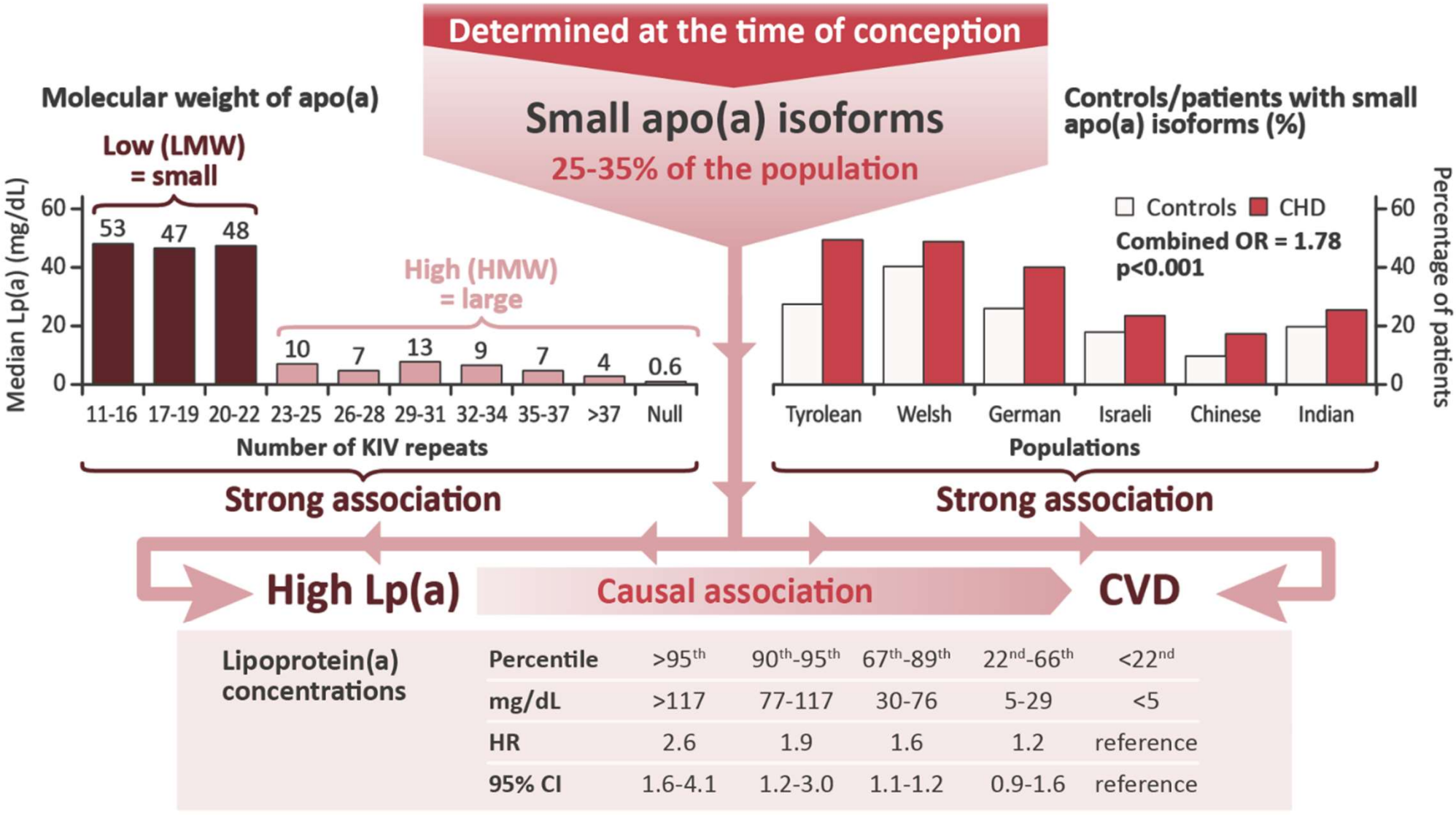
•Factors that may decrease Lp(a) levels: low carbohydrate diet, hyperthyroidism, postmenopausal hormone replacement therapy, hepatic impairment (depending on cause), sepsis, severe burns, tocilizumab (interleukin 6 inhibitor)

Sex and ethnicity also affect Lp(a) levels, with typical concentrations approximately 5-10% higher in women than men, and higher in black and South Asian populations than white and Chinese populations. In women, Lp(a) levels tend to increase at the menopause.



Non-genetic factors influencing Lp(a) levels

Enkhmaa et al, Atherosclerosis, 2022



Lipoprotein(a) concentrations	Percentile	>95th	90th-95th	67th-89th	22nd-66th	<22nd
	mg/dL	>117	77-117	30-76	5-29	<5
	HR	2.6	1.9	1.6	1.2	reference
	95% CI	1.6-4.1	1.2-3.0	1.1-1.2	0.9-1.6	reference

Adapted from Kronenberg, Handbook Exp Pharmacol, 2021; Kamstrup et al, 2009

Lp(a) measurement

•An Lp(a) concentration of ⩾50 mg/dL (⩾100/125 nmol/L) is widely considered to be elevated

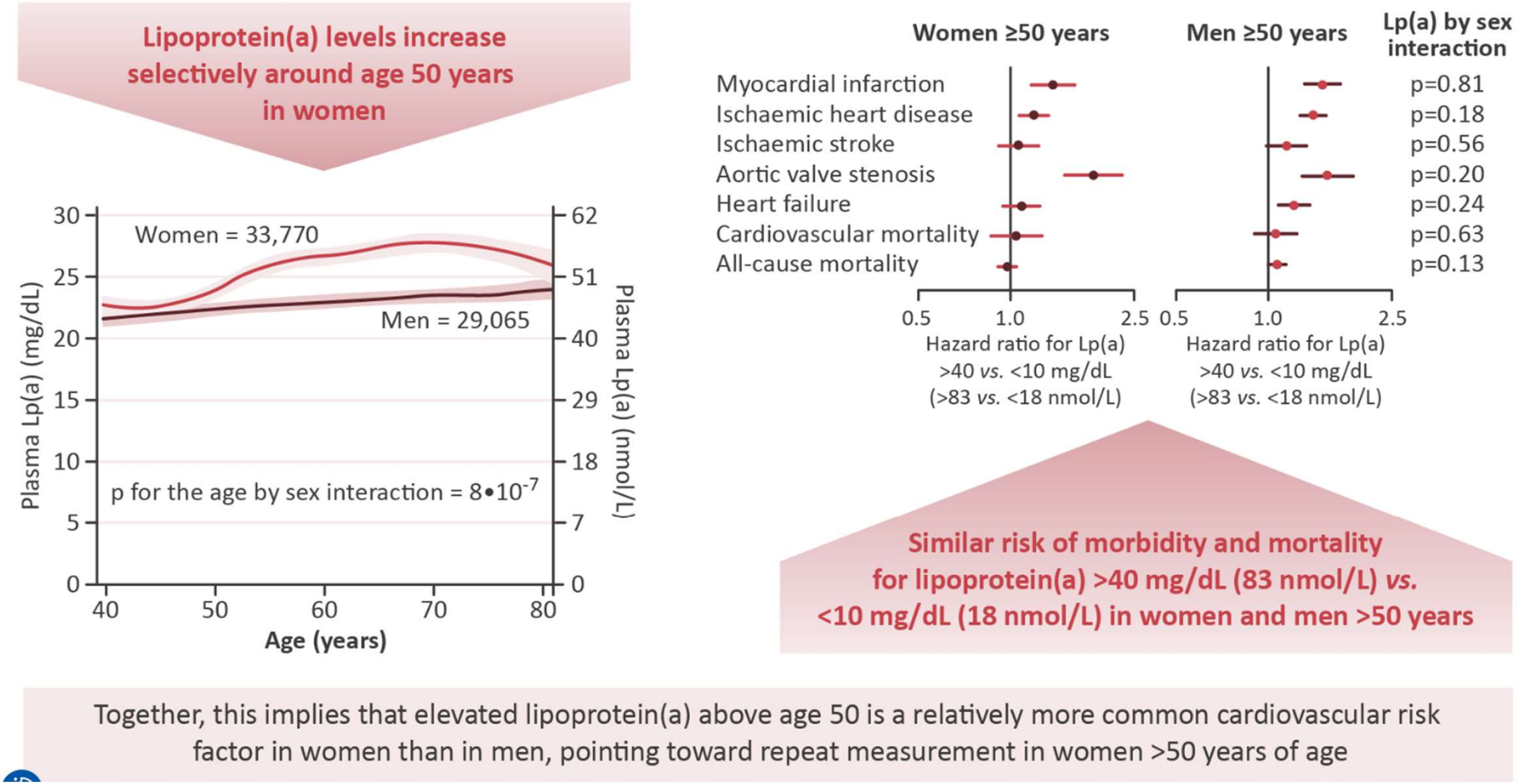
•Most currently available Lp(a) assays can be used for cardiovascular (CV) risk stratification

•International guidelines recommend Lp(a) measurement at least once in adult life

Lp(a) level is measured as the number of Lp(a) particles (nmol/L) or as Lp(a) mass concentration (mg/dL). Measurement of particle number is now the preferred method, and conversion between mg/dL and nmol/L is inaccurate because the molar to mass ratio is not constant between individuals due to major variation in apo(a) size. If Lp(a) measurement cannot be carried out in molar units, the results should be reported in the units in which the assay is calibrated.

The European Atherosclerosis Society (EAS) advises that laboratories should use an Lp(a) assay that is insensitive to apo(a) isoforms and traceable to official reference materials.[3] Ideally, the assay should use an antibody directed to a unique, non-repetitive epitope in apo(a). However, most assays currently available can be used for CV risk stratification.

Lp(a) concentration ranges from <0.1 mg/dL to >300 mg/dL (<0.2–750 nmol/L).



Adapted from Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: The Copenhagen General Population Study.4 Atherosclerosis. 2022 Aug;355:76-82

An Lp(a) concentration of ⩾50 mg/dL (⩾100/125 nmol/L) is widely considered to be elevated. The European Atherosclerosis Society (EAS) has proposed cut-offs indicating increased cardiovascular (CV) risk:[3]

•Lp(a) <30 mg/dL (<75 nmol/L) rules out risk

•Lp(a) >50 mg/dL (>125 nmol/L) rules in risk

•Lp(a) 30-50 mg/dL (75-125 nmol/l) – a 'grey zone' relevant when considering Lp(a)-attributable risk in the presence of other risk factors and in risk stratification

There is general agreement that Lp(a) should be measured at least once in adult life.

The European Atherosclerosis Society (EAS) Lp(a) consensus statement (2022) recommends Lp(a) testing at least once in adults (preferably in the first lipid profile) to identify those with high CV risk.[3] It also recommends Lp(a) measurement in younger people with a history of ischaemic stroke or a family history of premature atherosclerotic cardiovascular disease (ASCVD) or high Lp(a) and no other identifiable risk factors.[1]

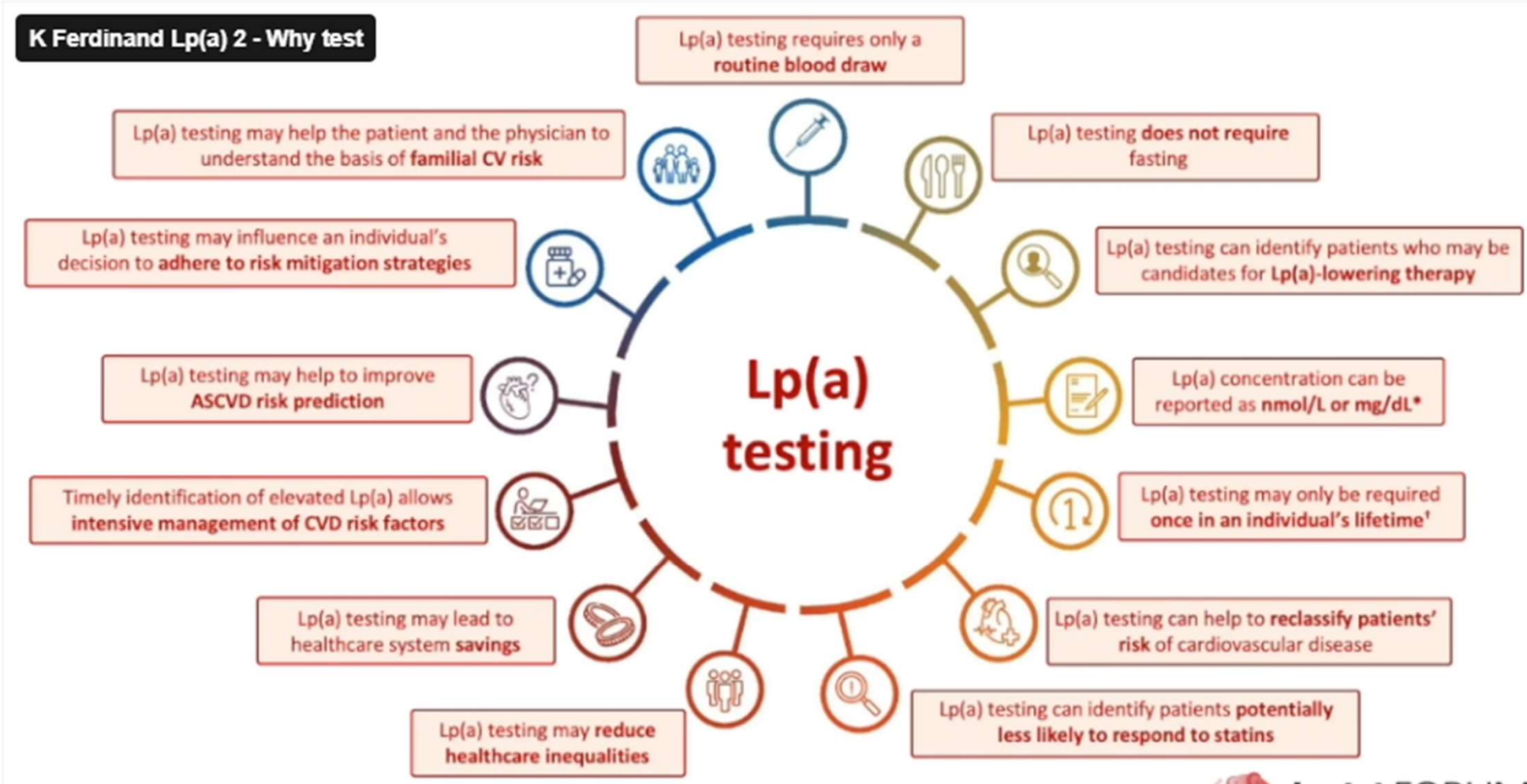
The Canadian Cardiovascular Society (CCS) dyslipidaemia guidelines (2021) recommend Lp(a) testing once in a patient's lifetime, as part of initial lipid screening to assess cardiovascular risk.[5]

The European Society of Cardiology (ESC)/EAS dyslipidaemia guidelines (2019) recommend Lp(a) testing at least once in a person's lifetime to identify people who have inherited an extremely elevated level of Lp(a) >180 mg/dL (>430 nmol/L) or people with less-extreme elevation who may be at a higher risk of ASCVD, which is not reflected by the SCORE system, or by other lipid or lipoprotein measurements[6]

The National Lipid Association (NLA) scientific statement (2019) recommends Lp(a) testing i) in adults with premature ASCVD or first degree relatives with ASCVD or with LDL-C >190 mg/dL, or suspected FH; ii) to aid prescribing in those aged 40-75 years with borderline (5%-7.4%) 10-year ASCVD risk; iii) to identify a possible cause for less than expected LDL-C reduction with LDL-C-lowering therapy; iv) in cascade screening of family members with severe hypercholesterolemia; v) to identify those at risk for progressive valvular aortic stenosis[7]

American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines (2018) recommend relative indications for Lp(a) testing in individuals with a family history of premature ASCVD or a personal history of ASCVD not explained by major risk factors.[8]

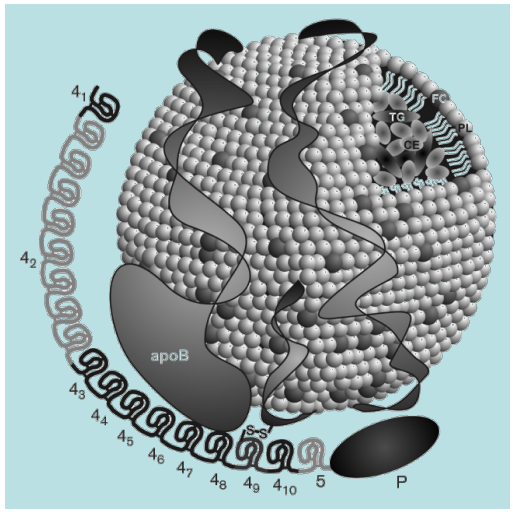
Why test Lp(a)?



Source: Ciffone N, McNeal CJ, McGowan MP, Ferdinand KC. Lipoprotein(a): An important piece of the ASCVD risk factor puzzle across diverse populations. Am Heart J Plus. 2023 Nov 24;38:100350. doi: 10.1016/j.ahjo.2023.100350. PMID: 38510747; PMCID: PMC10945898.

Lp(a) and cardiovascular disease

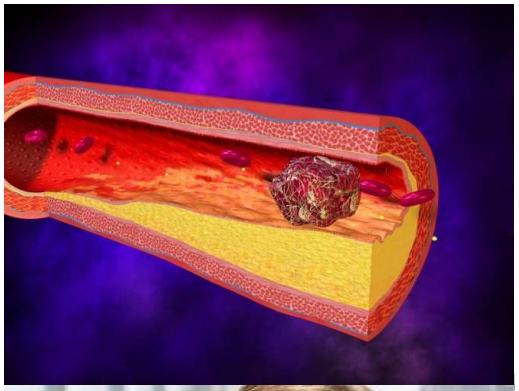
- Lp(a) is an independent risk factor for atherosclerotic cardiovascular disease (ASCVD), and elevated levels are associated with increased risk of
- coronary heart disease (CHD),
- ischaemic stroke,
- peripheral artery disease (PAD),
- heart failure,
- aortic valve stenosis (AVS), and
- mitral valve stenosis.



KIV-2↓
Lp(a)↑

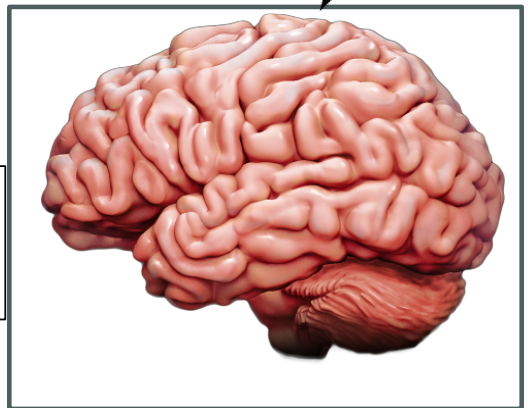
Lp(a)↑

Atherosclerotic stenosis

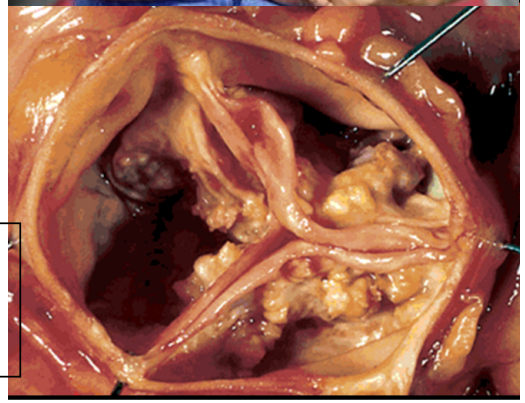


Myocardial infarction

Ischemic stroke



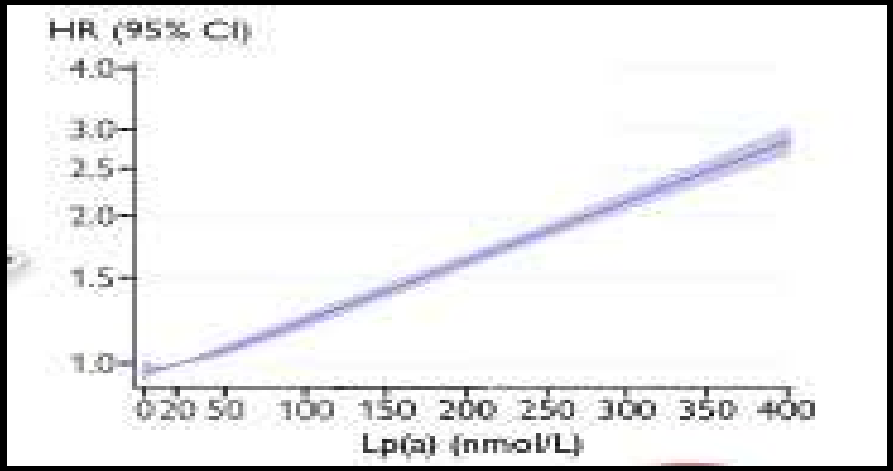
Aortic stenosis



Lp(a) and cardiovascular disease

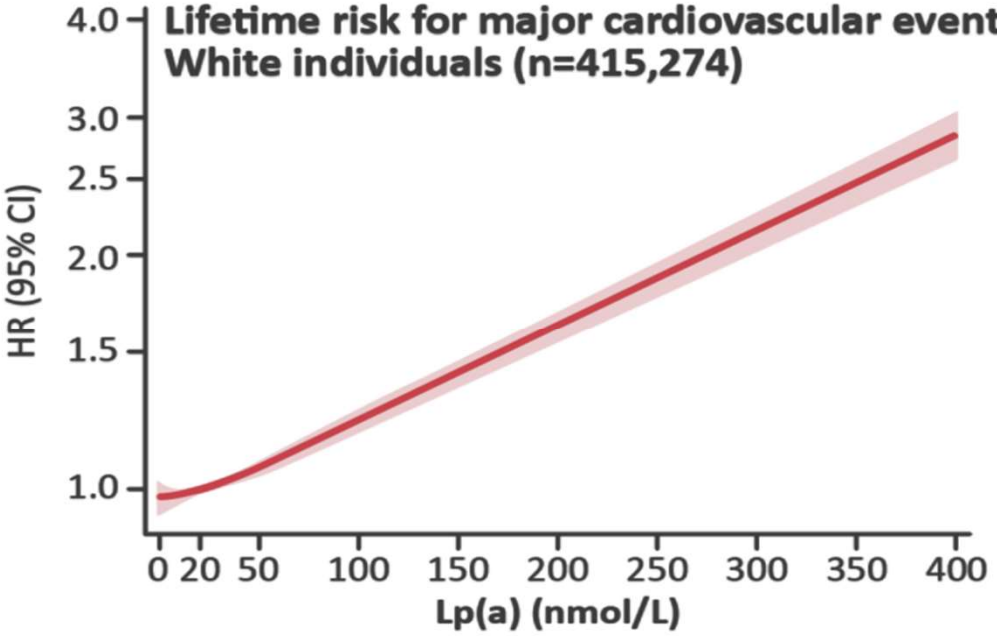
- Diabetic retinopathy may also be linked to elevated Lp(a).
- elevated Lp(a) does not appear to be a risk factor for venous thrombosis.
- Genetic variants associated with high Lp(a) are more common in patients with CV events. In contrast, rare loss-of-function variants and very common splice site variants within the K-IV Type-2 region that are associated with marked decreases in Lp(a), protect against CV events.
- Results of a recent Mendelian randomization study showed that the atherogenicity of Lp(a) was approximately six times higher than that of LDL on a per particle basis.

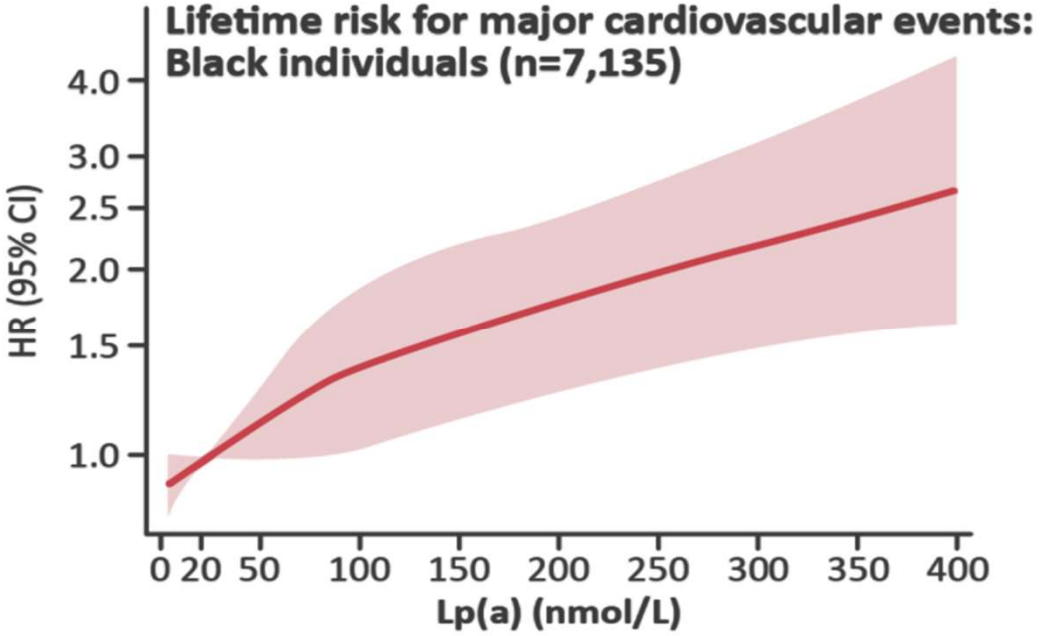
Causal continuous association between Lp(a) levels and ASCVD



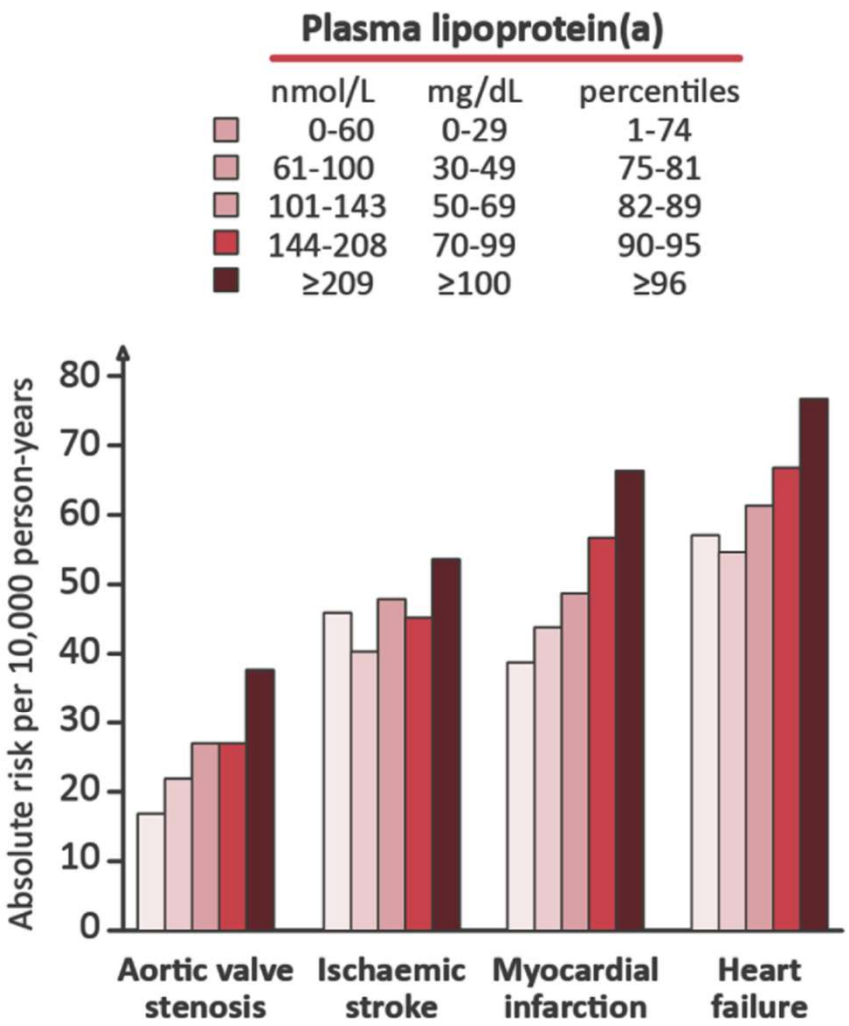
Kronenberg et al, Eur Heart J, 2022

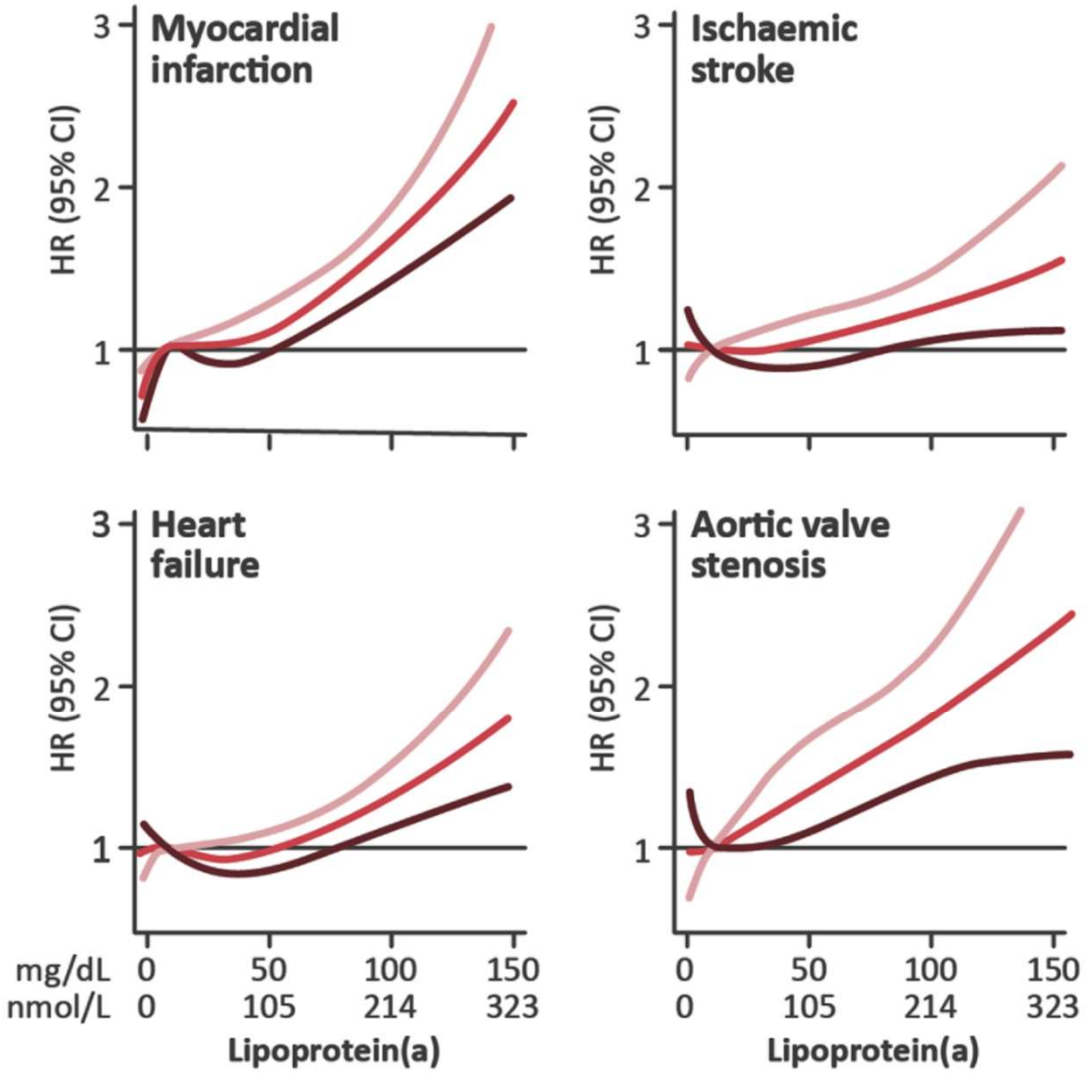
UK Biobank data have demonstrated the relationship between Lp(a) and lifetime risk of cardiovascular events in white and black individuals.





Adapted from Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, 2022





Adapted from Kronenberg et al, Eur Heart J, 2022

Elevated Lp(a) levels are associated with higher risk of all-cause mortality and death from CV disease (CVD) in the general population and in patients with CVD. In primary prevention, Lp(a) levels above the 75th percentile increased the risk for myocardial infarction (MI) and AVS, and levels above the 90th percentile increased heart failure risk. The risk for CV mortality and ischaemic stroke increased with Lp(a) levels above the 95th percentile.

•In the Copenhagen Heart Study, the hazard ratio (HR) for myocardial infarction (MI) was 1.7 in individuals with an Lp(a) concentration of 30-76 mg/dL (75-190 mmol/l) at 17 years follow up, and 2.7 in those with an Lp(a) level >117 mg/dL (292.5 mmol/L).

•In the INTERHEART study, an Lp(a) concentration >50 mg/dL (125 mmol/L) was associated with an increased risk of MI (odds ratio, 1.48; 95% confidence interval [CI], 1.43-1.67, p<0.001), independent of established CVD risk factors including diabetes mellitus, smoking, and high blood pressure.[6]

In secondary prevention, Lp(a) levels >80th percentile were significantly predictive of recurrent events in statin-treated patients with coronary artery disease (odds ratio [OR]): 1.40, 95% confidence interval (CI): 1.15 – 1.71] but not when baseline LDL-C was <130 mg/dL (<3.4 mmol/l).

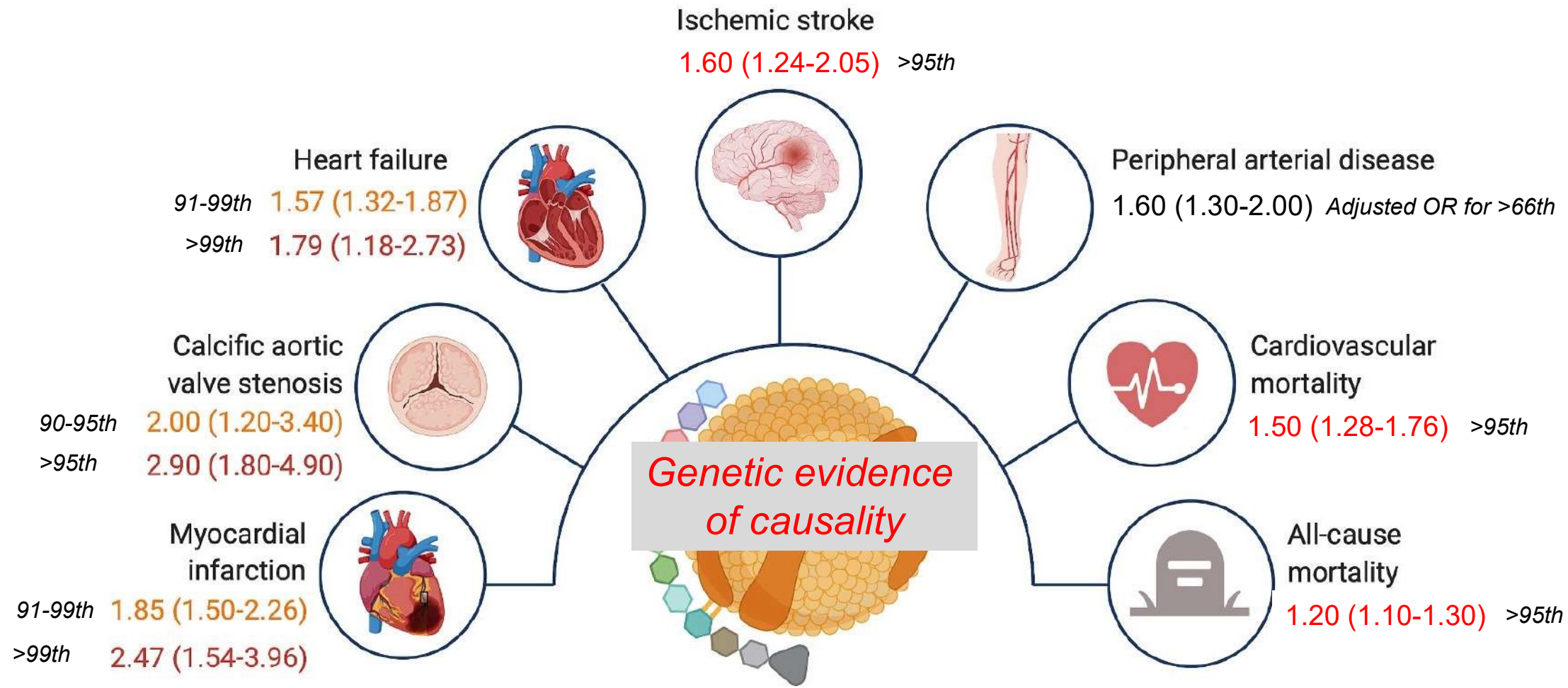
•Copenhagen General Population Study data in patients with a history of ASCVD, followed up over a median of five years showed adjusted major adverse CV event (MACE) incidence rate ratios of 1.28, 1.44 and 2.14 for Lp(a) levels of 10-49 mg/dL (18-104 nmol/L), 50 to 99 mg/dL (105-213 nmol/L), and ⩾100 mg/dL (⩾214 nmol/L) respectively, compared to Lp(a) <10mg dL.

•In the FOURIER and ODYSSEY OUTCOMES trials, high Lp(a) was associated with an increased risk of recurrent CV events in patients with established CV disease irrespective of LDL cholesterol.

In children, an Lp(a) >30 mg/dL (>75 nmol/L) is associated with increased risk of (recurrent) arterial ischaemic stroke. Elevated Lp(a) in adolescence is a risk factor for ASCVD in adulthood.

High Lp(a) and risk of CVD, CAVS, and mortality in the Copenhagen studies

Adjusted hazard ratios for high and extreme high Lp(a) levels (percentiles)



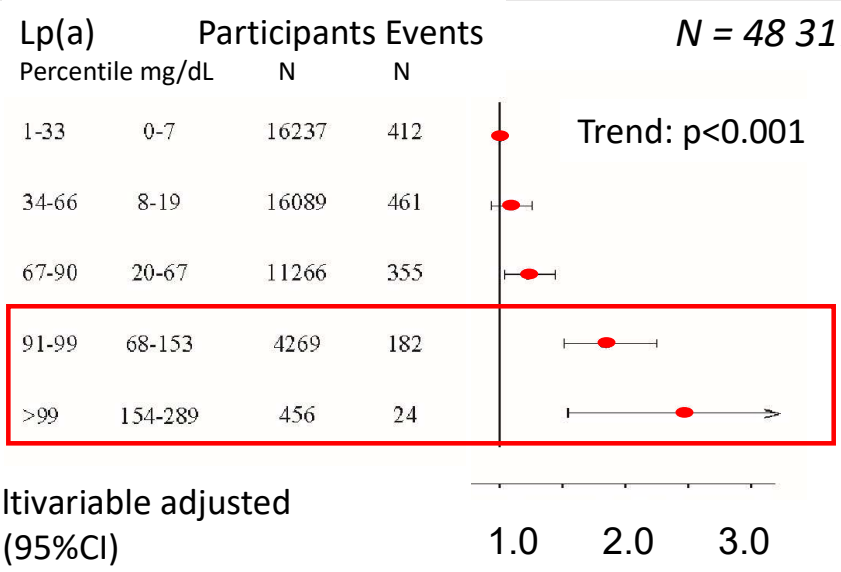
Arsenault BJ and Kamstrup PR. *Atherosclerosis*. 2022;349:7-16

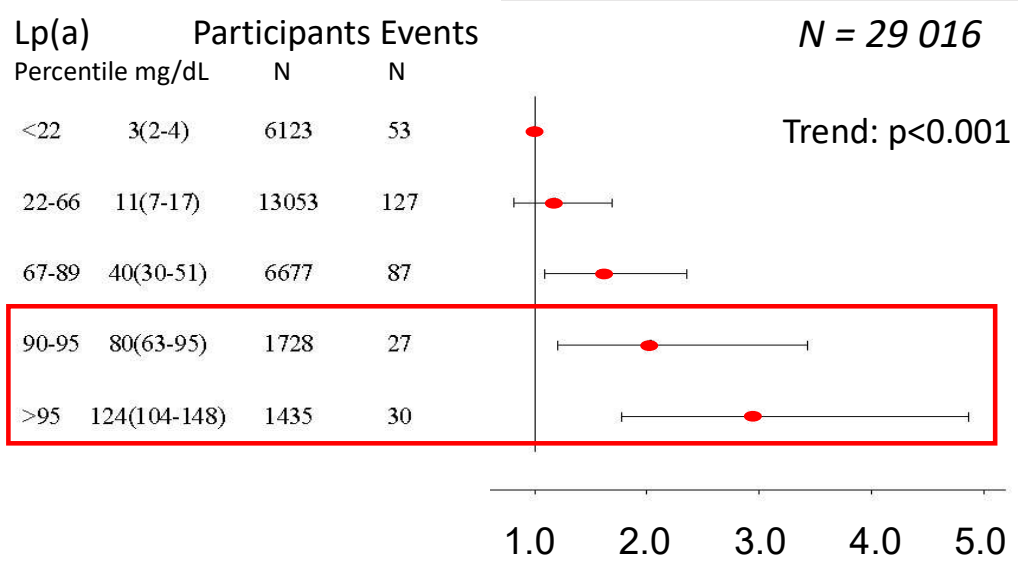
High and extreme high Lp(a) and risk of MI and CAVS

Myocardial infarction

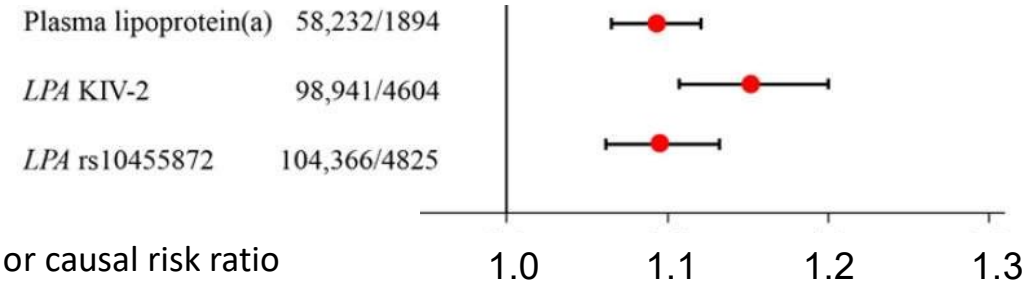
Calcific Aortic Valve Stenosis

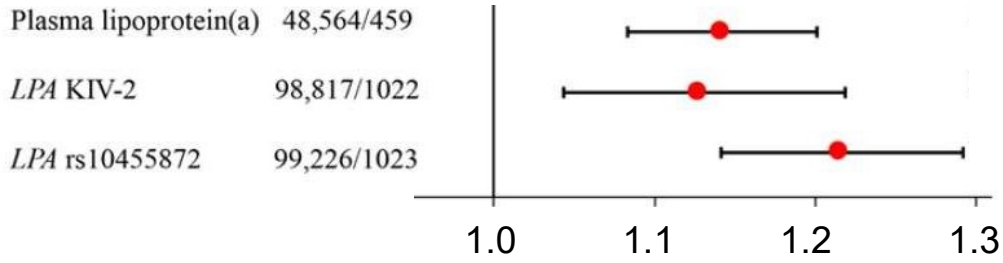
Lp(a) >90th percentile predicts 2-3 fold ↑ risk of MI & AVS:



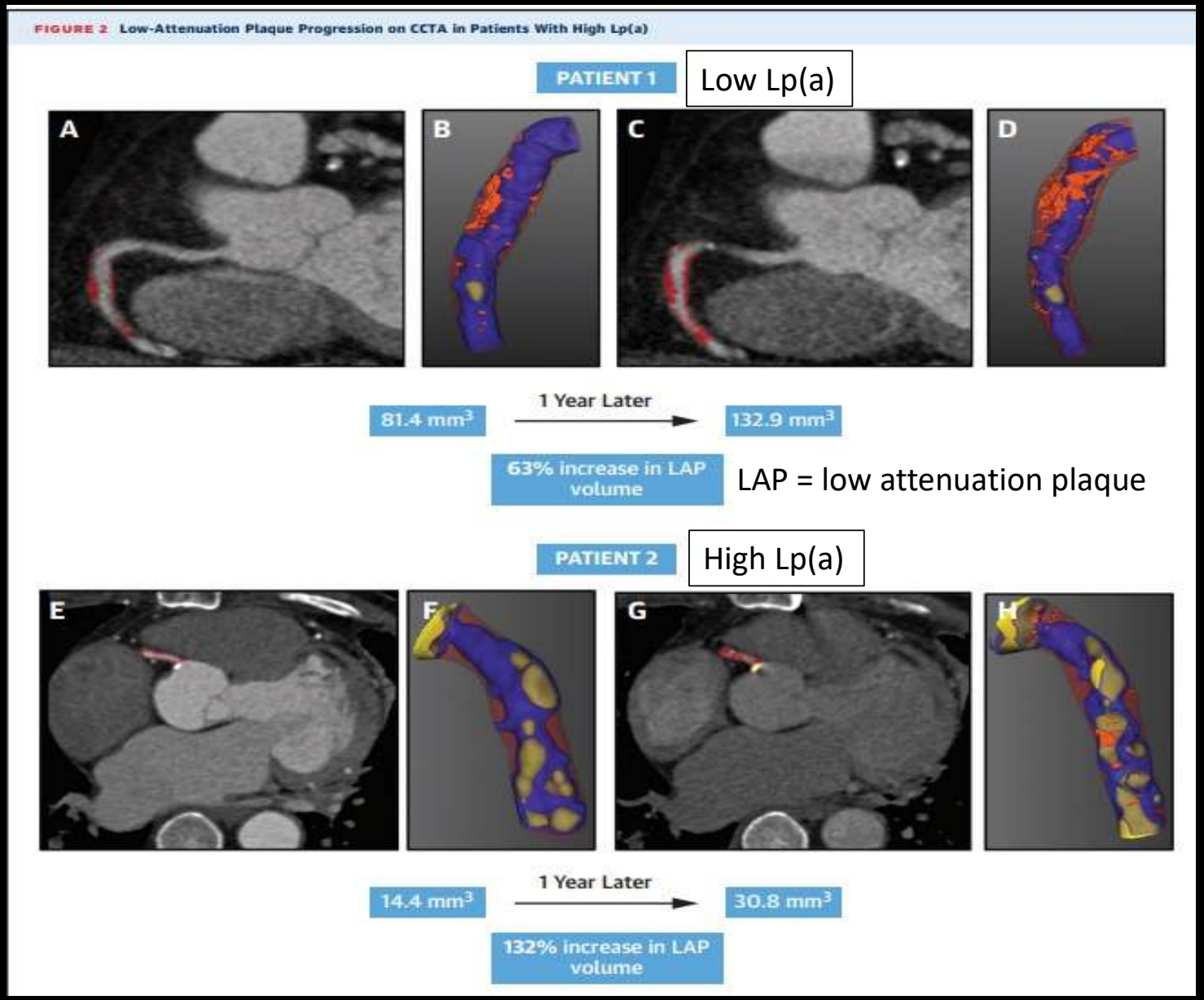


Genetic evidence of causality:





Kamstrup PR et al. J Am Coll Cardiol 2014;63:470-7, Kamstrup PR et al. JACC Heart Fail. 2016;4:78–87, Nordestgaard BG et al. J. Lipid Res. 2016. 57: 1953–75.



Lp(a) = 82 mg/dL

Coronary plaque progression detected by CTA : comparison of low and high Lp(a) levels

Lp(a) = 152 mg/dL

Kaiser et al, JACC, 2022, 79:223

Lp(a) and current lipid lowering therapies

- ✓ There are currently no approved lipid lowering therapies that specifically target Lp(a). Although there have been no randomized controlled trials (RCTs) showing that lowering Lp(a) improves cardiovascular (CV) outcomes, PCSK9 inhibitor outcome trials have provided initial data indicating that even small reductions in Lp(a) in secondary prevention can reduce event rates. Studies with Lp(a) apheresis are not inconsistent with this finding but RCTs have not been carried out to confirm this.

- ✓ For individuals with elevated Lp(a), the European Atherosclerosis Society (EAS) consensus statement recommends early, intensive management of other risk factors, aligned with European and North American guidelines. These include LDL-C, blood pressure, glucose, and lifestyle factors.

Lipid lowering therapies

PCSK9 inhibitors

Some PCSK9 inhibitors have been shown to reduce Lp(a) by 20-30%, and CV risk reduction with PCSK9 inhibitors is greater in individuals with higher baseline Lp(a) levels than in those with lower baseline levels.[1]

Lp(a) apheresis

Lp(a) apheresis reduces Lp(a) levels acutely by 60-75%, though patients are likely to experience rebound increases between sessions, resulting in a mean interval Lp(a) reduction of 25-40%, depending on treatment frequency and baseline Lp(a). Although apheresis is expensive and time-consuming, it is associated with few side effects. The EAS recommends that it can be considered in patients with very high Lp(a) and progressive CV disease despite optimal risk factor management.

Statins

Statins may slightly increase Lp(a) levels, but their beneficial effects on CV outcomes associated with their LDL-C-lowering effects mean that they should not be discontinued in patients with raised Lp(a).

Niacin

Niacin reduces Lp(a) by approximately 30–40%, depending on dose, but only by 18% in those with the highest Lp(a) levels. The mechanism is thought to be via a reduction in apoA production, but CV outcomes studies failed to show any additional benefit when niacin was added to statins.

Ezetimibe

The effect of ezetimibe on Lp(a) is unclear, as studies have shown variable effects, and the possible mechanism of action is also unclear.

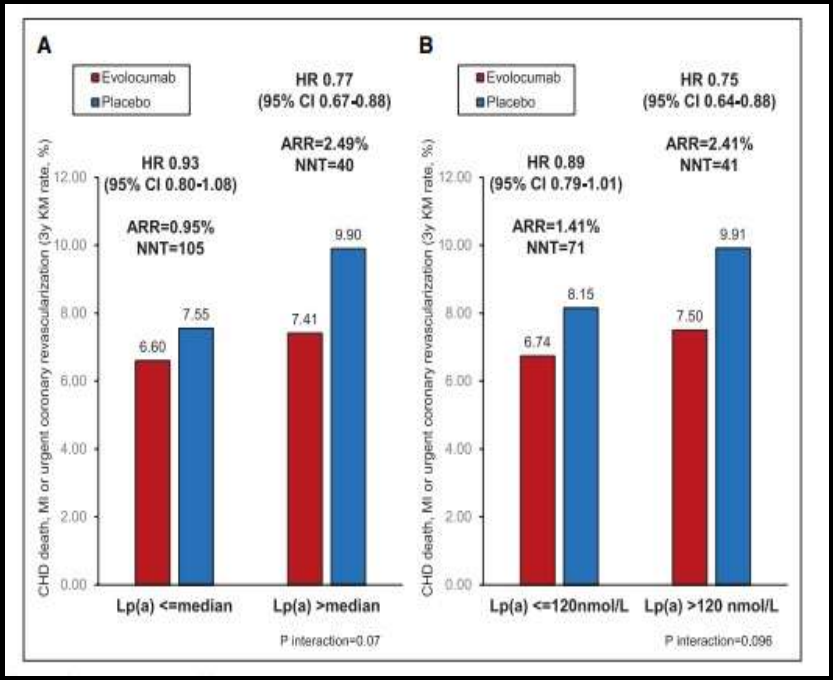
Targeted Lp(a) therapies

Ongoing Phase 3 and other trials are underway for the development of therapies targeted at Lp(a) involving injectable **antisense oligonucleotides** (ASOs) and **small interfering RNAs (siRNAs)**, and an oral **small molecule** inhibitor.

PCSK9 MABi's markedly lowered plasma Lp(a) levels with reduction in MACE

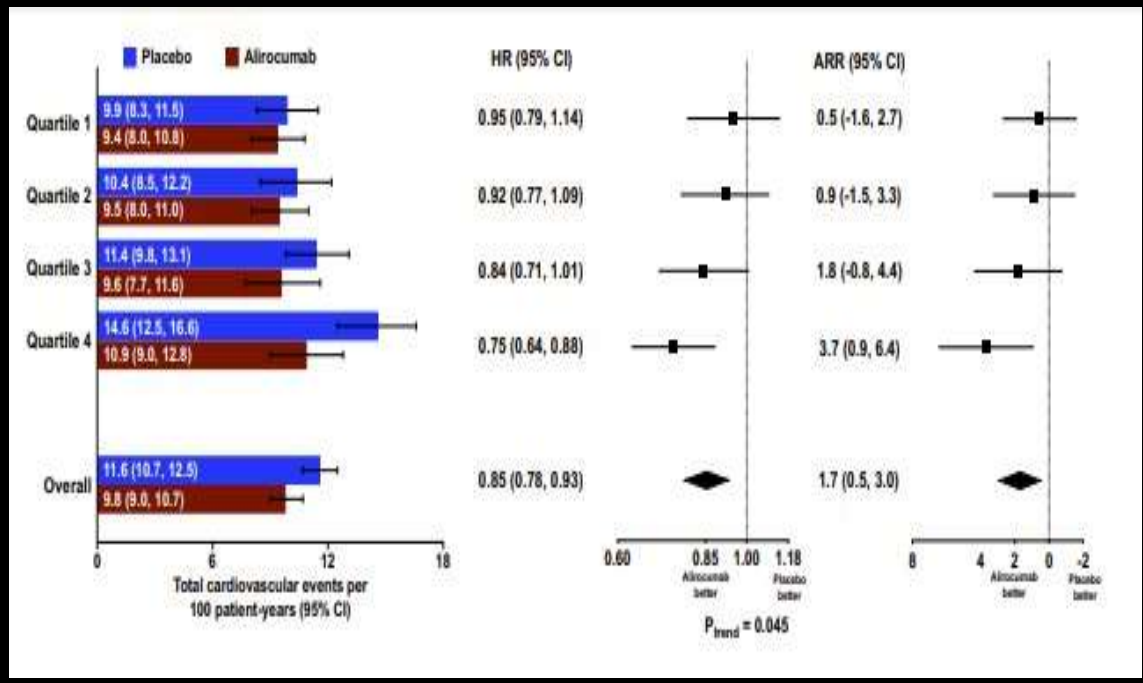
Greater clinical benefit from PCSK9 MABi treatment at higher Lp(a) levels

FOURIER trial



Reduction in total nonfatal CV events and death with PCSK9 MABi independent of LDL-C lowering

ODYSSEY OUTCOMES trial



O'Donoghue et al, Circulation, 2019
Szarek et al, Eur Heart J, 2020

Antisense Oligonucleotides

Pelacarsen	• A multicenter trial assessing the impact of Lp(a) lowering with pelacarsen (TQJ230) on the progression of calcific aortic valve stenosis (Lp(a)FRONTIERS CAVS) (NCT05646381) • Assessing the impact of Lp(a) lowering with pelacarsen (YQJ330) on major cardiovascular events in patients with CVD (Lp(a)HORIZON) (NCT04023552)als • Phase 2 study of pelacarsen (ISIS 681257; AKCEA-APO(a)-LRx) in participants with hyperlipoproteinemia(a) and cardiovascular disease

Small Interfering RNAs (siRNAs)

Lepodisiran	• A study to investigate the effect of lepodisiran on the reduction of major adverse cardiovascular events in adults with elevated lipoprotein(a) (ACCLAIM-Lp(a)) (NCT06292013)ed Trials • A study of lepodisiran (LY3819469) in healthy volunteers (NCT04914546) • A study of lepodisiran (LY3819469) in participants with elevated Lp(a) (ALPACA, NCT055565742)
Olpasiran	• Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction(OCEAN(a)) – Outcomes Trial (OCEAN(a)–OUTCOMES) (NCT05581303)eted Trials • Olpasiran trials of Cardiovascular Events lipoproteiN(a) reduction – Dose Finding Study (OCEAN(a)-DOSE) (NCT04270760)
Zerlasiran	• Evaluate SLN360 in participants with elevated Lp(a) at high risk of atherosclerotic cardiovascular disease events (ALPACAR-360, NCT05537571) • Study to investigate safety, tolerability, PK and PD response of SLN360 in subjects with elevated lipoprotein(a) (APOLLO) (NCT0406602)

Small Molecules

Muvalaplin	• A study of LY3473329 in healthy volunteers (NCT04472676) • A study of LY3473329 in adult participants with elevated lipoprotein(a) at high risk for cardiovascular events (KRAKEN) (NCT05563246)

🧬 RNA-Based Therapies

1. Pelacarsen (Antisense Oligonucleotide)

•**Mechanism**: Targets the mRNA of apolipoprotein(a), reducing Lp(a) production in the liver.
•**Efficacy**: Phase 2 trials demonstrated an approximate 80% reduction in Lp(a) levels.
•**Current Status**: Undergoing the **Lp(a)HORIZON** Phase 3 trial to assess its impact on major adverse cardiovascular events in patients with elevated Lp(a) and established cardiovascular disease.

2. Lepodisiran (Small Interfering RNA - siRNA)

•**Mechanism**: Utilizes siRNA to silence the gene responsible for apolipoprotein(a) production.
•**Efficacy**: In the Phase 2 **ALPACA** trial, a single 400 mg dose reduced Lp(a) levels by 93.9% between days 60 and 180.
•**Current Status**: Phase 3 trials are in progress to evaluate long-term cardiovascular outcomes.

3. Olpasiran (siRNA)

•**Mechanism**: Employs siRNA to inhibit apolipoprotein(a) synthesis.
•**Efficacy**: Phase 2 studies reported up to a 97% reduction in Lp(a) levels with quarterly dosing.
•**Current Status**: Currently in Phase 3 trials to determine its effect on cardiovascular events

🧪 PCSK9 Inhibitors

Alirocumab and Evolocumab

- **Mechanism**: Monoclonal antibodies that inhibit PCSK9, leading to increased clearance of LDL particles and modest reductions in Lp(a).
- **Efficacy**: Studies have shown approximately a 25-30% decrease in Lp(a) levels.
- **Current Status**: Approved for lowering LDL cholesterol; their specific impact on Lp(a)-related cardiovascular risk is still under investigation.

While these therapies show promise in significantly reducing Lp(a) levels, ongoing Phase 3 trials aim to establish whether such reductions translate into decreased cardiovascular events. No treatments are currently approved specifically for lowering Lp(a), but advancements in RNA-based therapies may soon offer targeted options.

Ο ρόλος της Lp(a) στην Αθηρωμάτωση

- ✓Η Lp(a) είναι μια σωματιδιακή λιποπρωτεΐνη που μοιάζει με την LDL, αλλά φέρει επιπλέον ένα μόριο απολιποπρωτεΐνης (a), το οποίο της προσδίδει ιδιαίτερες ιδιότητες:
- ✓Αθηρογόνος δράση: Διεισδύει στο τοίχωμα των αρτηριών και συμβάλλει στη δημιουργία της αθηρωματικής πλάκας.
- ✓Θρομβογόνος δράση: Η απολιποπρωτεΐνη (a) είναι δομικά παρόμοια με την πλασμινογόνο και ανταγωνίζεται την ινωδόλυση, αυξάνοντας τον κίνδυνο θρόμβωσης.
- ✓Προφλεγμονώδης δράση: Συμβάλλει στην ενεργοποίηση φλεγμονωδών διεργασιών στο αγγειακό ενδοθήλιο.

Κλινική σημασία Lp(a)

Υψηλά επίπεδα Lp(a) (>50 mg/dL ή >125 nmol/L) συνδέονται με:

- Αύξηση του κινδύνου για στεφανιαία νόσο.
- Αορτική στένωση.
- Εγκεφαλικά επεισόδια, κυρίως ισχαιμικά.

Θεραπευτικές Προσεγγίσεις (1)

Διατροφή & τρόπος ζωής

- Η Lp(a) επηρεάζεται ελάχιστα από τις αλλαγές στον τρόπο ζωής.
- Ωστόσο, η υγιεινή διατροφή και η σωματική άσκηση είναι σημαντικές για τη μείωση του συνολικού καρδιαγγειακού κινδύνου.

Θεραπευτικές Προσεγγίσεις (2)

2. Φαρμακευτικές επιλογές (τρέχουσες και υπό μελέτη)

✔ **Νιασίνη (νικοτινικό οξύ)**

- Μειώνει την Lp(a) κατά 20–30%.
- Περιορισμένη χρήση λόγω παρενεργειών (π.χ. εξάψεις, ηπατοτοξικότητα).
- Δεν απέδειξε μείωση των καρδιαγγειακών συμβαμάτων σε μεγάλες μελέτες.

✔ **PCSK9 Αναστολείς (π.χ. evolocumab, alirocumab)**

- Μείωση Lp(a) κατά ~20–30%.
- Αποτελεσματικοί και στην LDL-C.
- Οφέλη σε ασθενείς με υψηλό καρδιαγγειακό κίνδυνο.

Θεραπευτικές Προσεγγίσεις (3)

✔ **Αντισώματα κατά της Lp(a) / RNA-στοχευμένες θεραπείες (υπό ανάπτυξη)**

- **Antisense oligonucleotides (ASOs)** και **siRNA** έναντι του mRNA της απολιποπρωτεΐνης (a).
- Μπορούν να μειώσουν την Lp(a) κατά >80%.
- Π.χ. το **pelacarsen** (ASO) βρίσκεται σε φάση 3 κλινικών δοκιμών.
- Ελπιδοφόρες στρατηγικές, ειδικά για ασθενείς με πολύ υψηλή Lp(a) και τεκμηριωμένη καρδιαγγειακή νόσο.

✔ **Lipoprotein apheresis**

- Ειδική διαδικασία που απομακρύνει Lp(a) από το αίμα.
- Εφαρμόζεται κυρίως σε ασθενείς με οικογενή υπερλιπιδαιμία και σοβαρή καρδιαγγειακή νόσο.