Lipoprotein (a). History and significance of Lp(a) discoveries.

Mechanisms of cardiovascular risk related to Lp (a).

Lp (a), Lipoprotein (a) structure.

Genetic influences. Association of Lipoprotein(a) concentration and apo (a) isoform size in different ethnic groups.

Non-genetic influences on Lipoprotein (a) concentration.

Lipoprotein (a) and immunopathology.

Lipoprotein (a) determination. Test selection.

Lipoprotein (a) determination. Guidelines and recommendations.

Lipoprotein (a) therapy. Current medications.

Lipoprotein (a) therapy. Emerging medications.

Lipoprotein (a)

History and significance of Lp(a) discoveries.

Mechanisms

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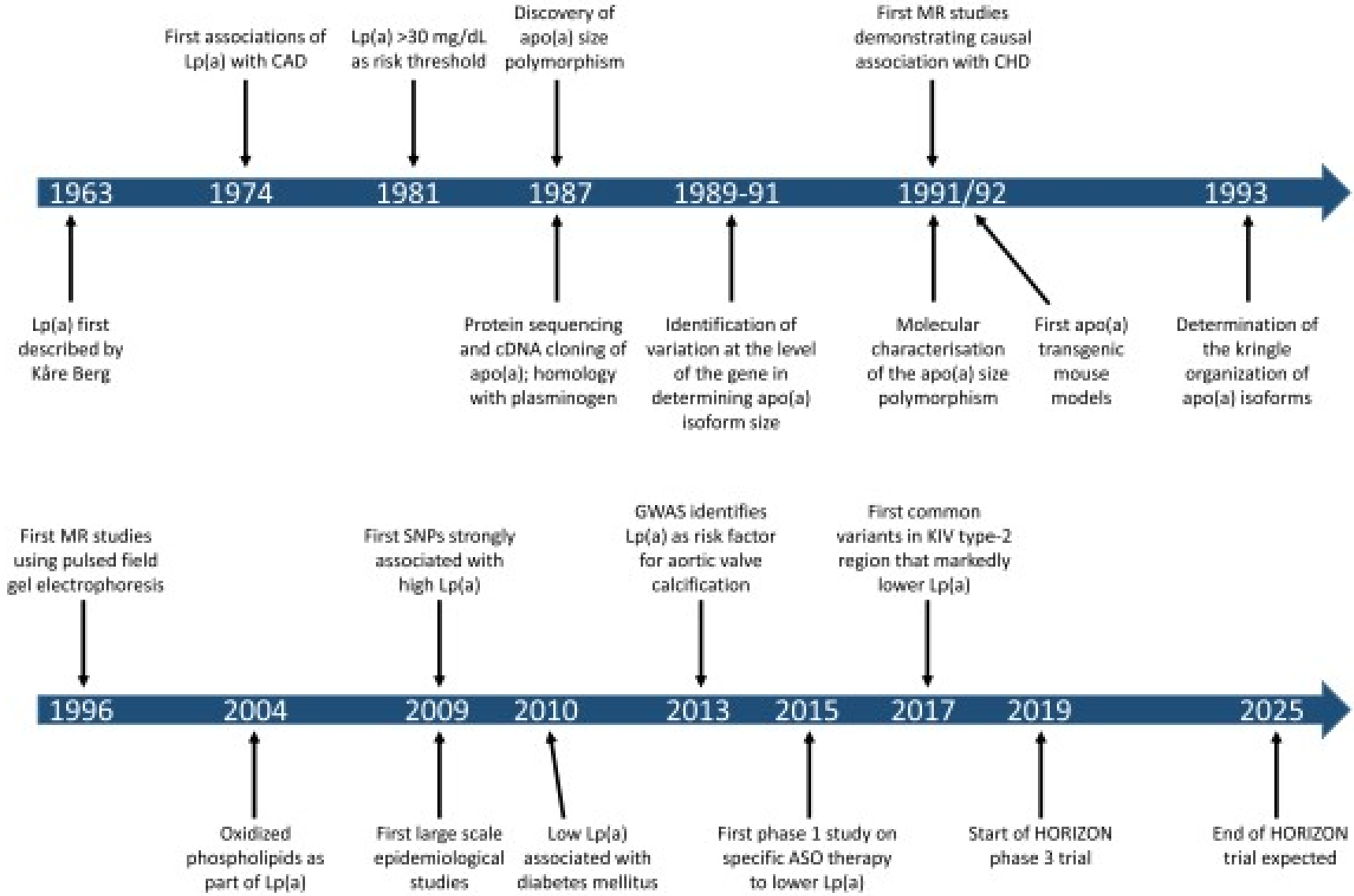
History and significance of Lp(a) discoveries



Atherosclerosis 349 (2022) 1–6

Lipoprotein (a)

Mechanisms of cardiovascular risk related to Lp (a)

Lp (a).

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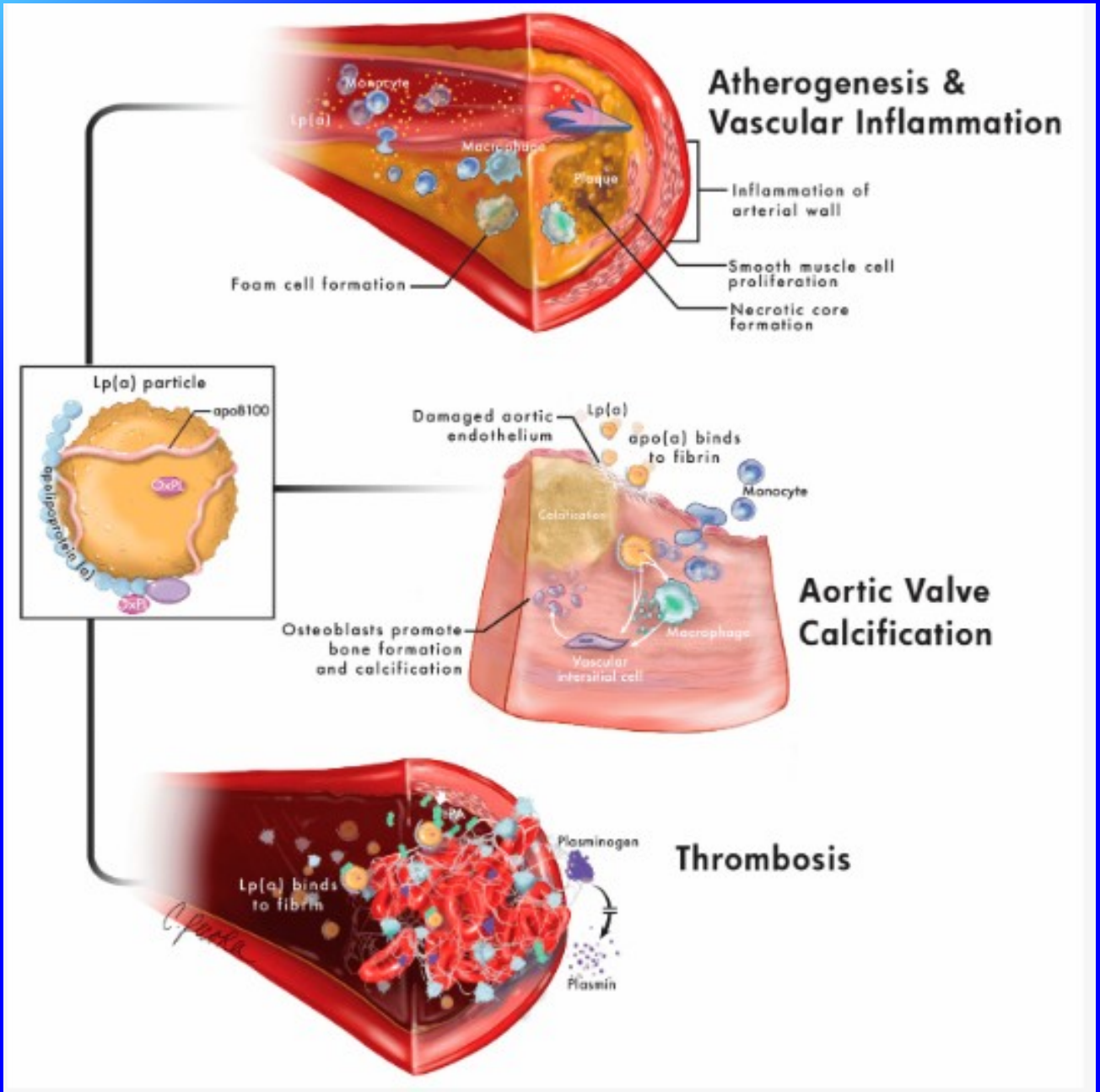
Mechanisms of cardiovascular risk related to Lp (a).



Lipoprotein(a) and its individual components are associated with cardiovascular disease through multiple overlapping mechanisms.

Lp (a) is composed of apolipoproteinB100 (apoB100) and apolipoprotein (a) (apo (a)), both of which contain oxidized phospholipids (OxPL). The apoB100 contributes to atherogenesis through similar mechanisms as low-density lipoprotein (LDL), including vessel wall binding, smooth muscle cell proliferation, foam cell formation and necrotic core formation.

OxPL contribute to vascular inflammation through increased transmigration and cytokine production by monocytes as well as upregulation of inflammatory genes.

Lp(a) contributes to aortic valve calcification as apo(a) binds to fibrin on injured aortic endothelium, and OxPL promote calcification and bone formation via vascular interstitial cells and upregulation of reactive oxygen species and pro-inflammatory cytokines in macrophages.

Finally, apo (a) contributes to thrombosis by inhibiting fibrinolysis through competitive inhibition of tissue plasminogen activator (tPA) activation of plasminogen to plasmin and plasminogen binding to fibrin as well as promoting increased platelet activity.

J. Clin. Med. 2022, *11*(20), 6040

Lipoprotein (a)

Mechanism

Lp (a), Lipoprotein (a) structure

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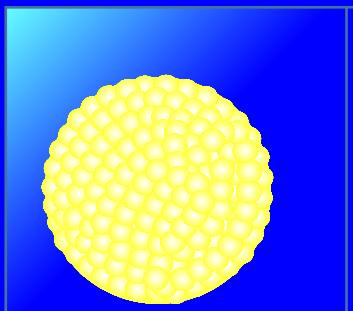
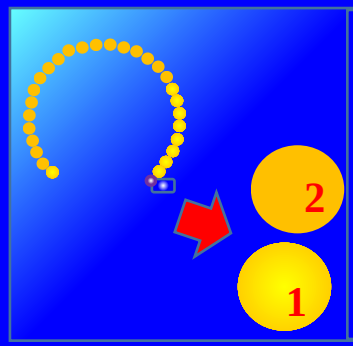
Lp (a), Lipoprotein (a) structure



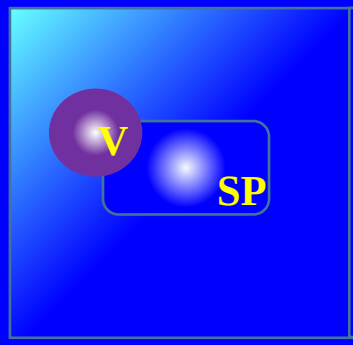
Low Density Lipoprotein
LDL

Apo B100 glycoprotein



Apo (a) lipoprotein

10 different types of kringle IV (KIV) repeats, from 1 to 10



V - plasminogen kringle 5

SP - serin proteinase

Journal of Lipid Research 2016. 56: 1339–1359.

SMALL
apo (a) isoform

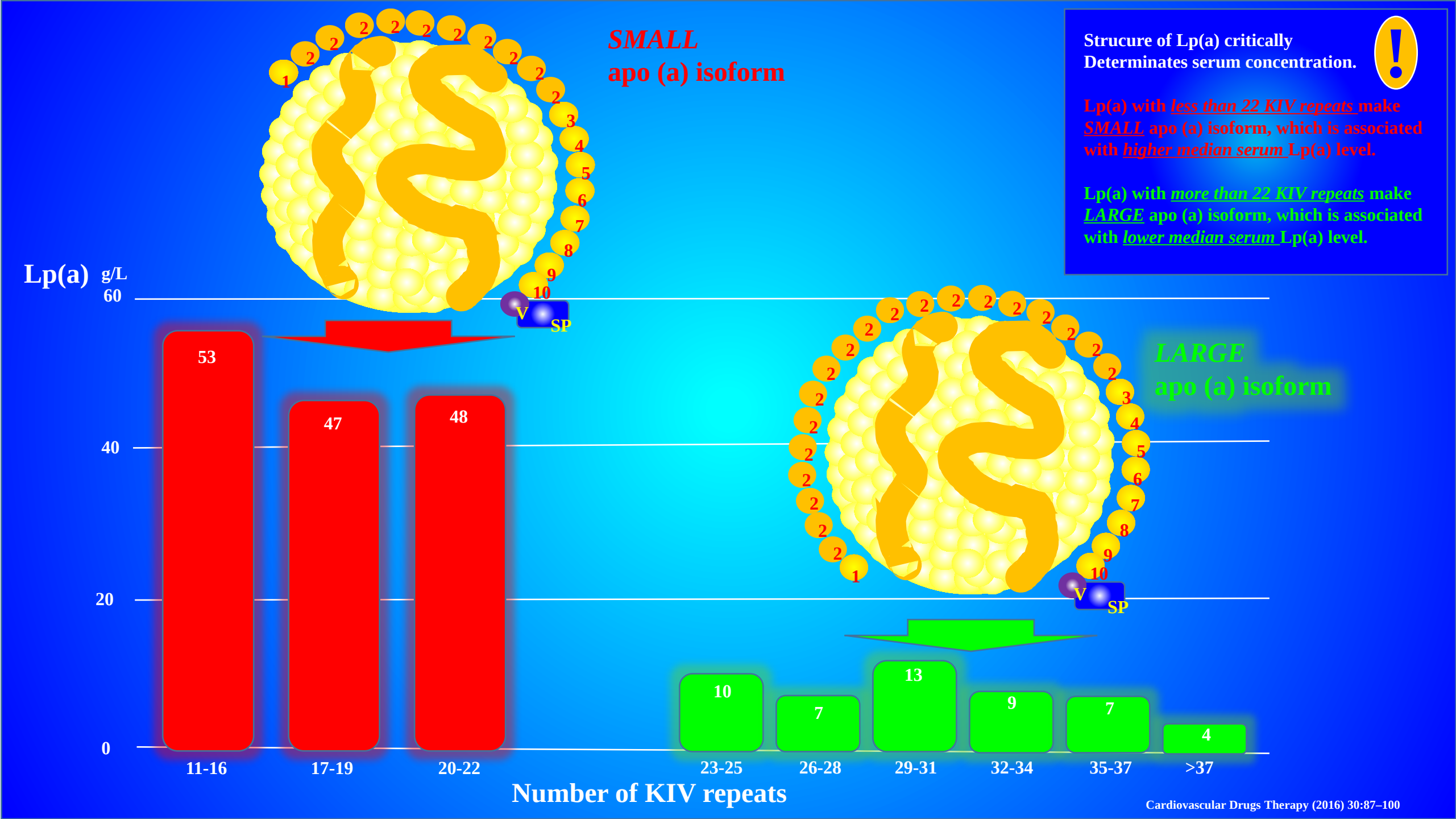
According to the KIV repeats there are two isoforms of Lp(a).

SMALL isforom has less than 22 KIV repeats af apo(a).

SMALL isforom has more than 22 KIV repeats af apo(a).

LARGE
apo (a) isoform

Cardiovascular Drugs Therapy (2016) 30:87–100


SMALL
apo (a) isoform
Strucure of Lp(a) critically
Determinates serum concentration.
Lp(a) with less than 22 KIV repeats make SMALL apo (a) isoform, which is associated with higher median serum Lp(a) level.
Lp(a) with more than 22 KIV repeats make LARGE apo (a) isoform, which is associated with lower median serum Lp(a) level.
LARGE
apo (a) isoform
V
SP
Lp(a) g/L
60
40
20
0
53
47
48
10
7
13
9
7
4
11-16
17-19
20-22
23-25
26-28
29-31
32-34
35-37
>37
Number of KIV repeats
Cardiovascular Drugs Therapy (2016) 30:87–100

Lipoprotein (a)

Mechanism

Lp (a)

Genetic influences

Non-genetic influences on Lipoprotein (a) concentration.

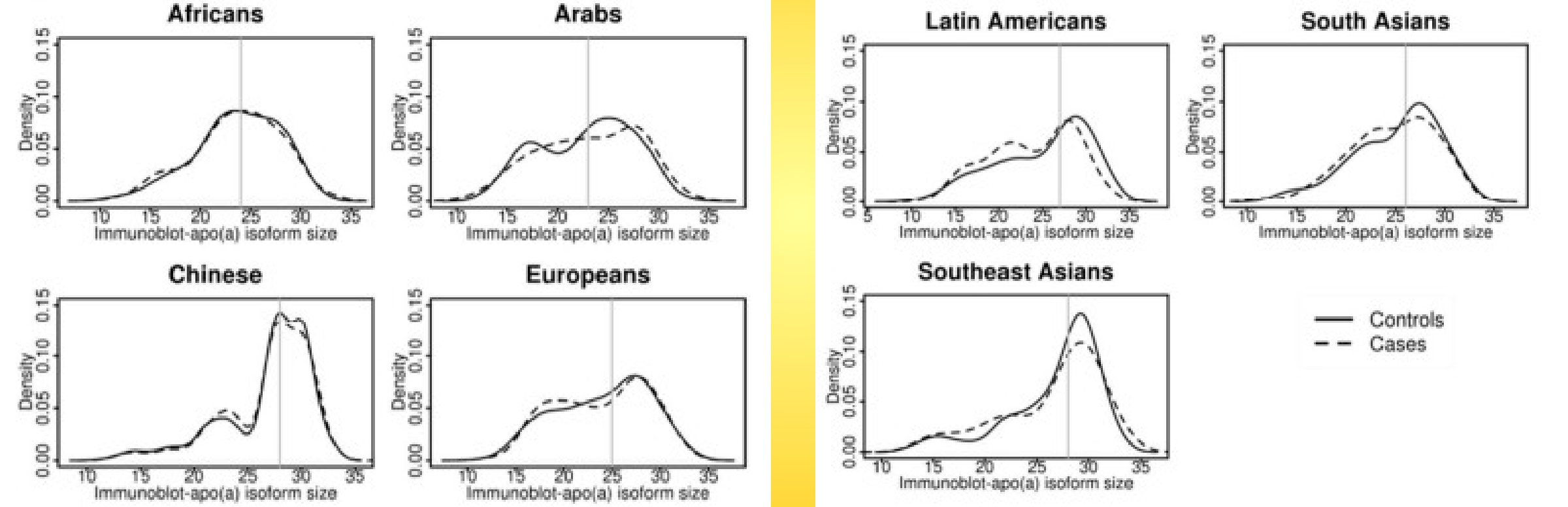
Lipoprotein (a) and immunopathology.

Lipoprotein (a) determination. Test selection.

Association of Lipoprotein(a) concentration and apo (a) isoform size in different ethnic groups

Genetic influences.
Lipoprotein(a) concentration in different ethnic groups.

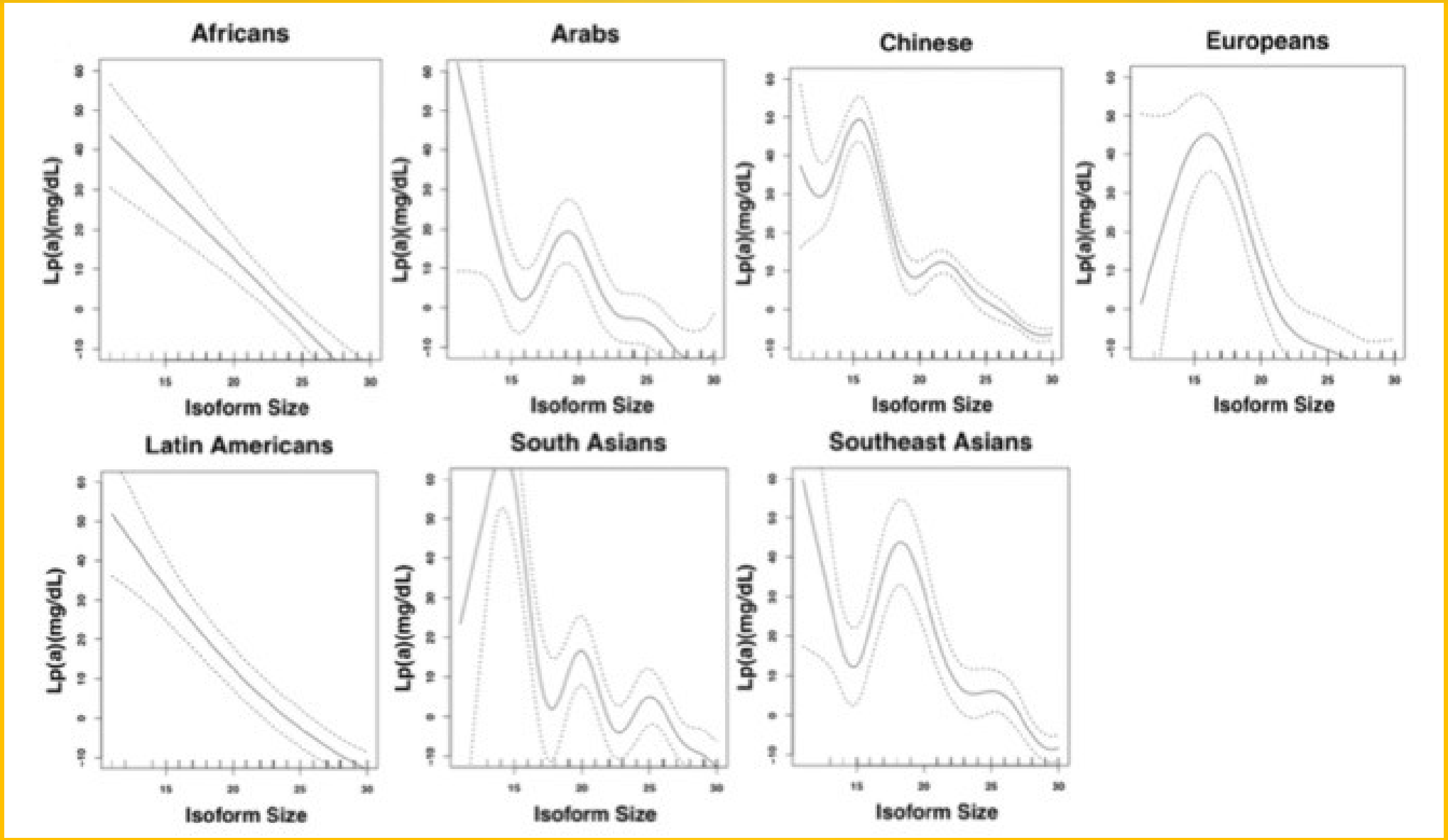
Different ethnic groups demonstrate different group-specific Lp(a) isoform sizes, as well as median Lp(a) serum concentration.
Difference also exist between cardiovascular patients from different ethnic groups.



Differences in Lp(a) concentrations between ethnic groups. Shown are isoform sizes between the seven ethnic groups tested.
Dashed lines represent MI cases, solid lines represent controls, and vertical lines represent the medians.

Circulation. 2019; 139:1472–1482

Genetic influences.
Association of Lipoprotein(a) concentration and apo (a) isoform size in different ethnic groups (Interheart study).



Circulation. 2019; 139:1472–1482

Lipoprotein (a)

Mechanism

Lp (a)

Genetic influences. Association of Lipoprotein(a) concentration and apo (a) isoform size in different ethnic groups.

Non-genetic influences on Lipoprotein (a) concentration

Lipoprotein (a) and immunopathology.

Lipoprotein (a) determination. Test selection.

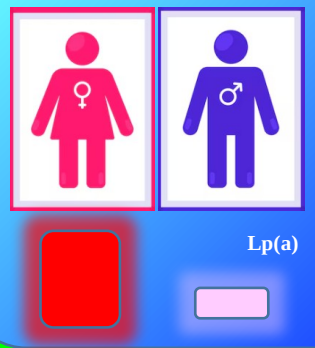
Non-genetic influences on Lipoprotein(a) concentration.

Diet and Lp (a) levels

Dietary reduction of saturated fatty acids (SFA) increases Lp(a) concentration.
Dietary SFA reduction consistently decreased LDL-C, resulting in an opposite pattern compared to Lp(a). As pro-inflammatory and pro-atherogenic OxPLs may shuttle between Lp(a) and LDL-C particles, dietary SFA reduction could induce pro-inflammatory status.
Studies found no association between alcohol consumption and Lp(a) level .

Physical activity, exercise, cardiorespiratory fitness and Lp (a)

Intensive exercise training, increases in exercise or cardiorespiratory fitness **have no or minimal impact on Lp(a) concentration**, while significantly influencing concentrations of other lipids and lipoproteins.
However, results of some studies, particularly those in younger or diabetic populations, deviate from this and suggest a possible Lp(a)- modulating effect by a prolonged high-level exercise training, aerobic exercise or low-intensity resistance training.

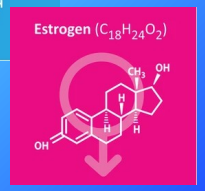


GENDER-specific differences and Lp (a)

Lp(a) levels are higher in females than males.
Among children and adolescents, Lp(a) levels were significantly higher in girls than in boys for both Blacks and Whites. In a group of more than 460,000 UK Biobank participants, Lp(a) levels were elevated in women /men and in individuals who had established CVD at the time of enrollment. While Lp(a) level predicted incident CVD in both men and women, it was a stronger risk factor for CVD among those without diabetes mellitus than with diabetes mellitus..

Atherosclerosis 349 (2022) 53–62

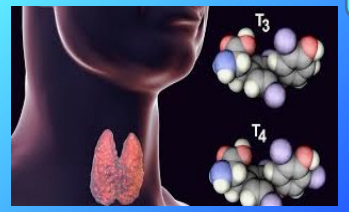
Non-genetic influences on Lipoprotein(a) concentration.



Sex hormones and Lp (a)

Among men with CAD, **Lp(a) levels were negatively associated with free testosterone**, but not with DHEA-S.
Administration of testosterone significantly reduced Lp(a) levels in healthy men, but not in healthy postmenopausal women, hypogonadal men or oophorectomized women.
Oral estrogen resulted in a greater reduction in Lp(a) concentrations than transdermal estrogen, whereas there was no significant difference comparing continuous versus cyclic HRT, conventional with low-dose estrogen, or estrogen monotherapy with estrogen combined with progestogen.

Thyroid hormones and Lp (a)



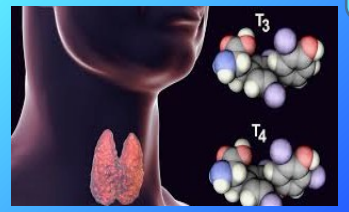
Lp(a) levels are decreased in hyperthyroidism and **increased in hypothyroidism.**
Levothyroxine therapy in clinical and subclinical hypothyroidism significantly decreased Lp(a).
Lp(a) levels are elevated in patients with clinical or subclinical hypothyroidism compared to healthy controls.

Non-genetic influences on Lipoprotein(a) concentration.

Renal diseases and Lp (a)

Chronic Kidney Diseases (CKD) patients demonstrated increase in Lp(a) levels, but only in part with large size apo (a) isoforms. Continuous ambulatory peritoneal dialysis patients demonstrated elevated Lp(a) levels regardless of apo(a) sizes. Nephrotic syndrome patients demonstrated increased Lp(a) levels both in diabetic and non-diabetic form. Decrease in Lp(a) levels was seen in non-diabetic NS patients following remission of the syndrome with immunosuppressive therapy.

Liver diseases and Lp (a)



Hepatocellular damage is associated with reduced Lp (a) levels, where the decrease in levels is in parallel with the disease progression. Patients with liver cirrhosis and hepatitis exhibited lower Lp(a) levels. A significant increase in Lp(a) levels was seen in chronic active HCV patients with a complete response to a 6-month interferon treatment. Studies in patients with nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) have shown variable results with regard to Lp(a).

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Lipoprotein (a)

Mechanism

Lp (a)

Genetic influences. Association of Lipoprotein(a) concentration and apo (a) isoform size in different ethnic groups.

Non-genetic influences on Lipoprotein (a) concentration.

Lipoprotein (a) and immunopathology

Lipoprotein (a) determination. Test selection.

Lipoprotein(a) and immunopathology.

1. Modulation of platelet aggregation (αIIbβ3) and reduction in fibrinolysis (αMβ2 , αv β3 , NFκB, PKC)

1.0. Thrombosis
1.1. Platelet Aggregation.
1.2. Tissue Factor Pathway.
1.3. Impairment of Plasminogen Activation.
1.4. Inhibition of TGFβ Activation.

2. Recruitment of inflammatory cells (αMβ2 , E-selectin,ICAM-1, VCAM-1, IL-1β, IL-8, PKC)

2.0. Inflammatory Cell Recruitment and Adhesion
2.1. Transportation of Oxidised Phospholipids.
2.2. Induction of Inflammatory Cytokines.
2.3. Chemoattraction.

3. Induction of vascular remodelling (αv β3 , Ca 2+ ,MAPK, RhoA, ROS)

3.0. Vascular Remodelling
3.1. Proliferation of Smooth Muscle Cells.
3.2. Proliferation of Endothelial Cells.
3.3. Migration of Smooth Muscle and Endothelial Cells.

Cholesterol, Volume 2012, Article ID 923289

Lipoprotein (a)

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Lipoprotein (a) determination

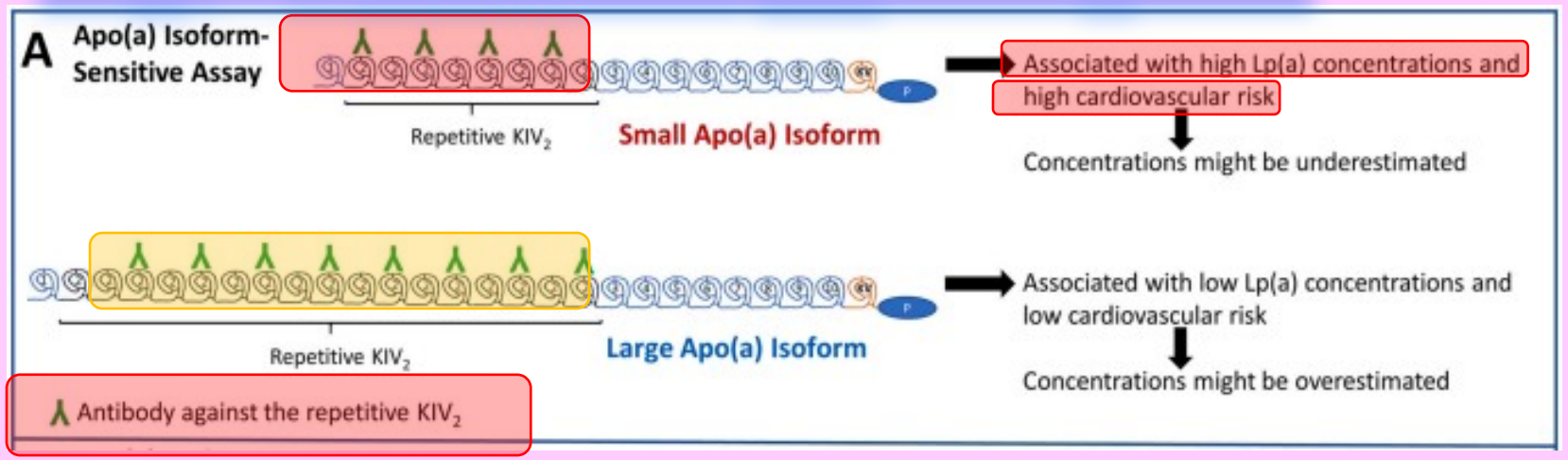
Lipoprotein (a) determination. Guidelines and recomm

Test selection

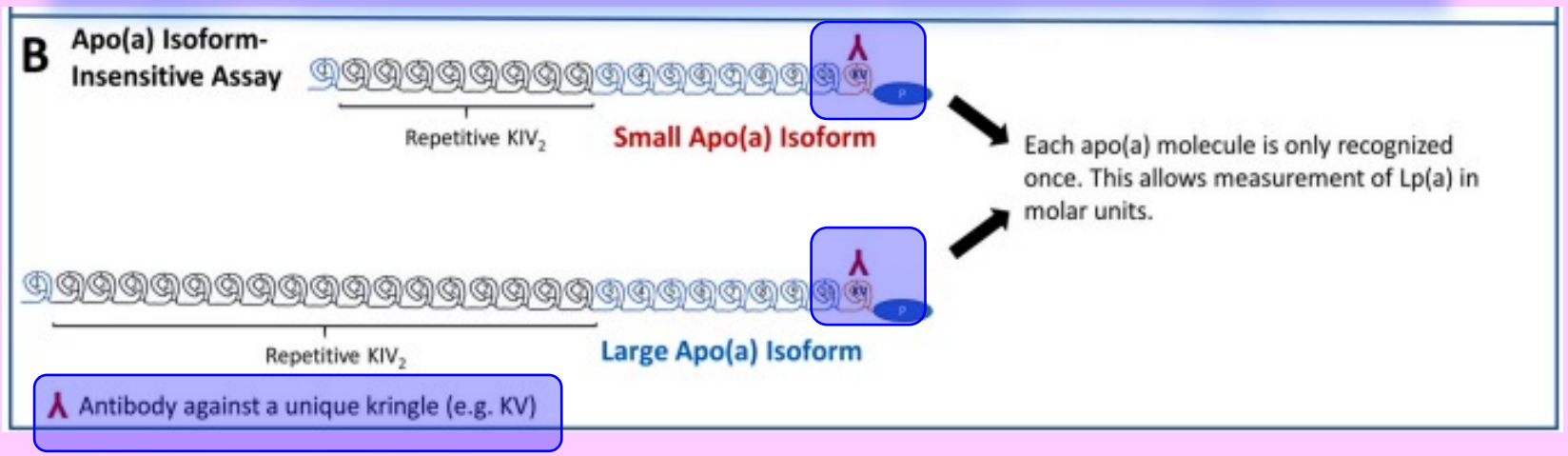
Lipoprotein (a) therapy.

Lipoprotein(a) determination. Test selection.

Principle of test that *enables discrimination* of Apo (a) levels according to isoform.



Principle of test that *does not enable discrimination* of Apo (a) levels according to isoform.



Only tests that use antibodies against repetitive KIV2 enable discrimination between LARGE and SMALL isoforms Apo (a) levels.

Increased levels of SMALL Apo(a) Isoforms are associated with high cardiovascular risk!

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Lipoprotein (a)

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Lp (a)

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Lipoprotein (a) determination. Test selection.

Lipoprotein (a) determination
Guidelines and recommendations

Lipoprotein (a) determination. Guidelines and recommendations.

Study	When to measure Lp(a)	Threshold of Lp(a)
2018 ACC/AHA Cholesterol Guidelines	Family history of premature ASCVD or personal history of ASCVD	Lp(a) ≥ 50 mg/ dL or 125 nmol/L
2019 NLA Scientific Statement on Use of Lp(a) in Clinical Practice	1) individuals with a family history of first-degree relatives with premature ASCVD), 2) individuals with premature ASCVD in absence of traditional risk factors, 3) primary severe hypercholesterolemia or suspected FH, 4) individuals at very-high-risk of ASCVD to better define those who are more likely to benefit from PCSK9 inhibitor therapy.	Lp(a) ≥ 50 mg/ dL or 100 nmol/L
2019 ESC/EAS Guidelines for Management of Dyslipidemias	1) 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 FH 2) 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	Lp(a) ≥ 180 mg/ dL or 430 nmol/L
2019 HEART UK Consensus Statement on Lp(a)	1) Personal or family history of premature atherosclerotic CV disease, first degree relatives, 2) with raised serum Lp(a) levels (> 200 nmol/l), familial hypercholesterolemia or other genetic dyslipidemias, 3) calcified aortic valve stenosis, 4) a borderline increased (but < 15%) 10 year risk of CV event.	Lp(a) ≥ 200 - 400 nmol/L
2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia	Once in patient's lifetime, with initial screening.	Lp(a) ≥ 50 mg/ dL or 100 nmol/L

American Journal of Preventive Cardiology 18 (2024) 100641

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Lipoprotein (a) therapy

Current medications

Lipoprotein (a) therapy. Current medications.

Medication / procedure	Effects	End result
Statins	Conflicting findings, increase, decrease, no effects	non significant
Ezetimibe	No effects on serum Lp(a) level	non significant
Niacin	Contraversial	0-40% Lp(a) reduction
PCSK9i	Proprotein convertase subtilisin / kexin type 9 inhibitors decrease Lp(a)	20-25% Lp(a) reduction
Bempedoic acid	ATP citrate lyase inhibitor does not reduce Lp(a) level	non significant
Antiplatelet agents	Aspirin (100 mg) in persons that carry rs3798220-C gene variant, Lp(a) reduction	primary prevention
Lipoprotein apheresis	Variable Lp(a) reduction	30-68% Lp(a) reduction
CETP	Cholesteryl ester transfer protein (torcetrapib, dalcetrapib, evacetrapib)	20-40% Lp(a) reduction
Thyroid hormone analogue	Eprotirome, Lp(a) reduction	7-32% Lp(a) reduction

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Lipoprotein (a) therapy
Emerging medications

Lipoprotein (a) therapy. Emerging medications.

Medication / procedure	Mechanisms / Effects	End result
Antisense oligonucleotides	***Pelacarsen*** **Bind apo(a) mRNAP, preventing translation and production of Lp(a)**	**35-80% Lp(a) reduction**
Small interfering RNA	***Olpasiran, SLN360, LY3819469*** **RNA induced silencing complex (RISC) mediated degradation of apo(a) mRNA preventing translation of protein and subsequent production**	**70-100% Lp(a) reduction**
Oral agents	***Muvalaplin*** **Disrupts noncovalent interaction between apo(a) and apoB100, preventing disulfide bond and Lp(a) formation**	**63-65% reduction**

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