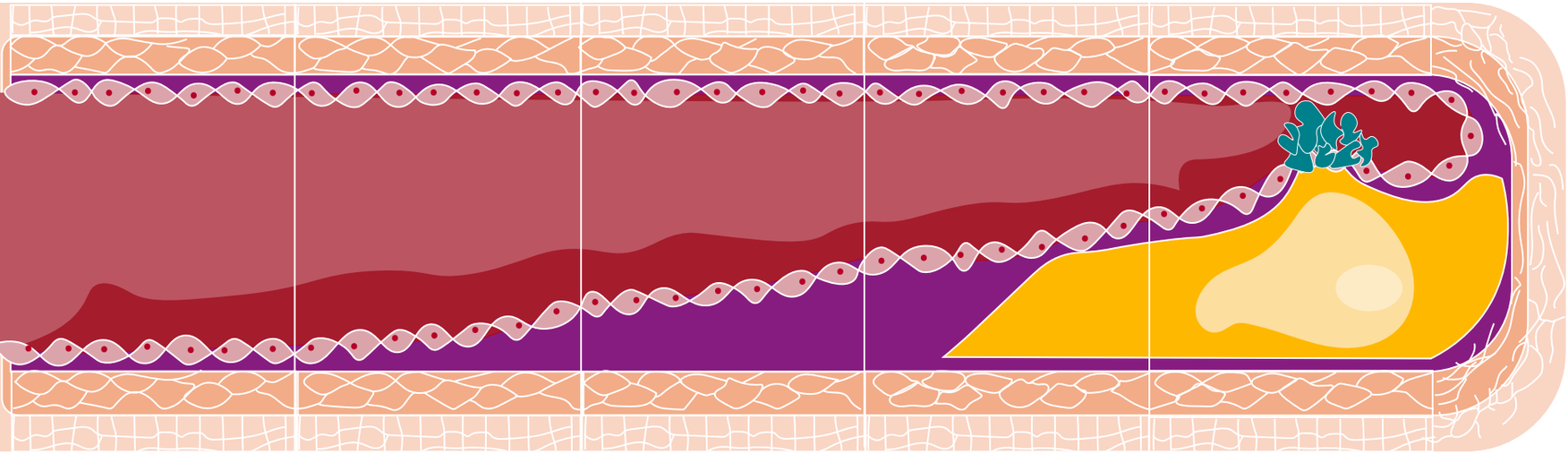
Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Kronenberg, F et al. *Eur Heart J* 2022;43(39):3925–3946

Background

Evidence supports a strong association between elevated lipoprotein(a) (Lp[a]), an apoB-containing lipoprotein, and cardiovascular outcomes[1]



Adapted[2]

To clarify the role of Lp(a) testing in practice, the 2022 European Atherosclerosis Society Consensus Statement[1] provided an updated summary of evidence and clinical guidance on testing and treating elevated Lp(a)

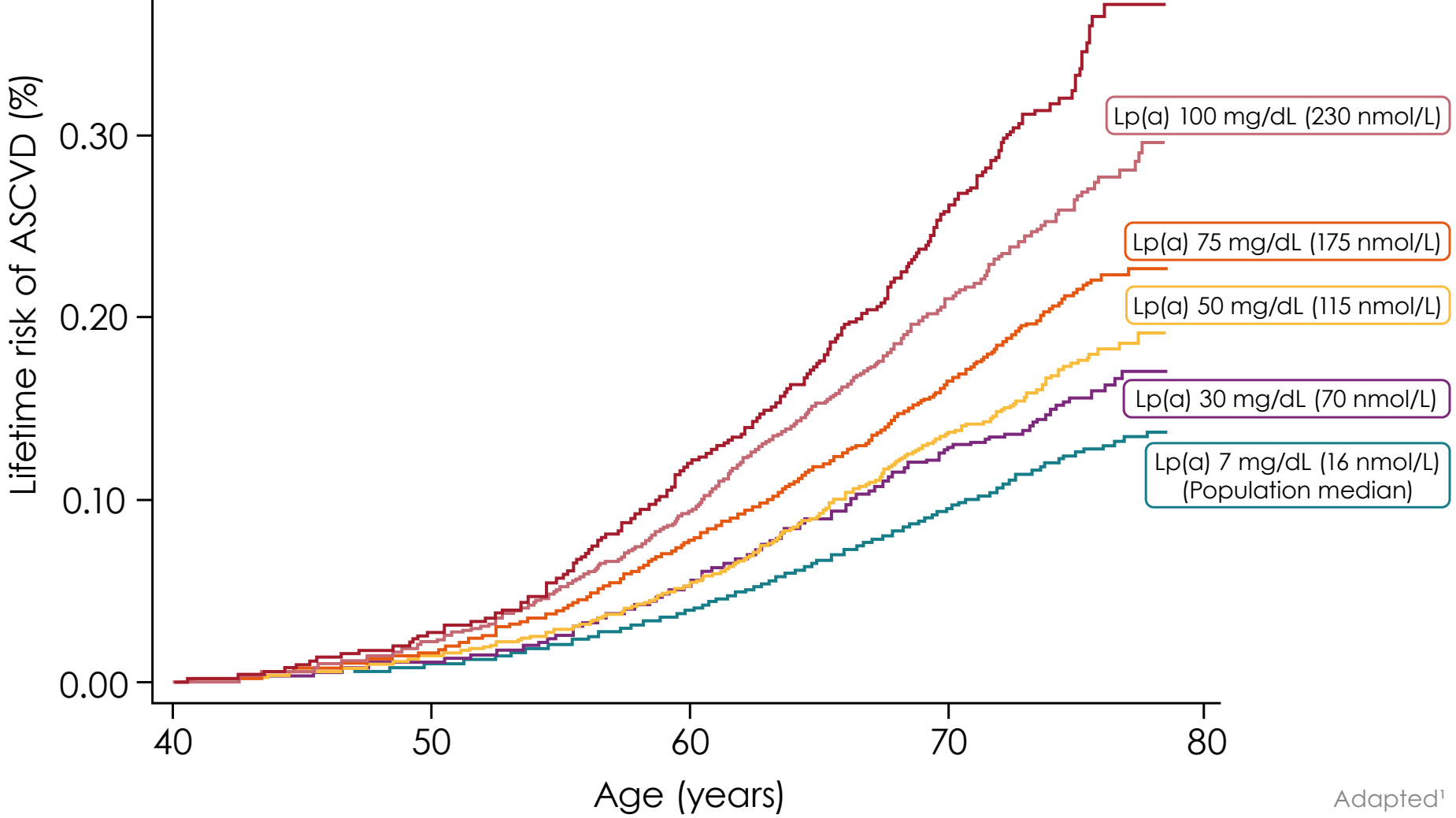
A strong causal and continuous association between Lp(a) and cardiovascular outcomes

Observational and genetic evidence demonstrates high Lp(a) concentration is causal for ASCVD, AVS, and CV and all-cause mortality in men and women, across ethnic groups[1]

Lifetime risk for major CV events associated with increasing Lp(a) concentrations[1]*

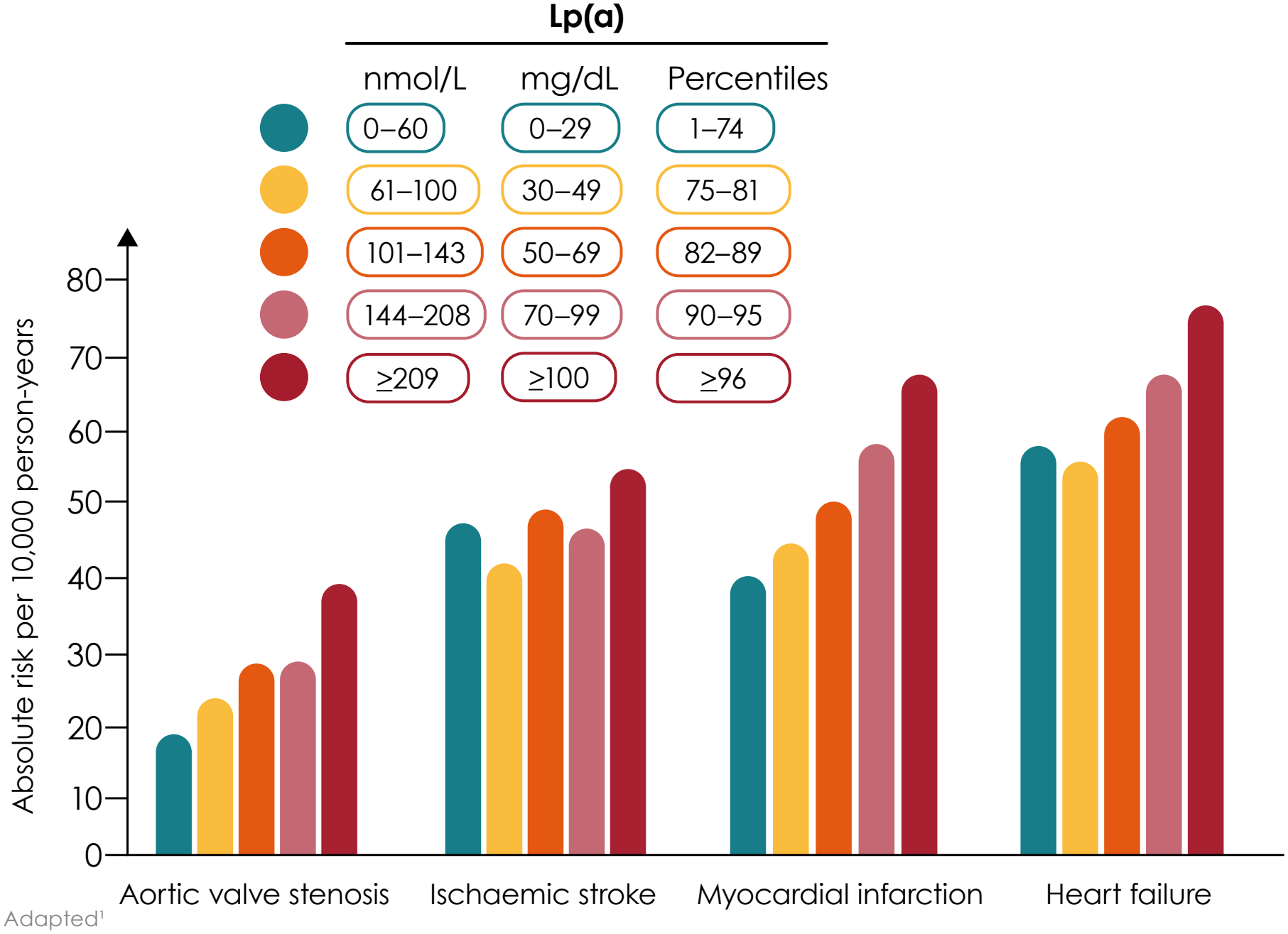
0.40

Lp(a) 150 mg/dL (350 nmol/L)



Adapted[1]

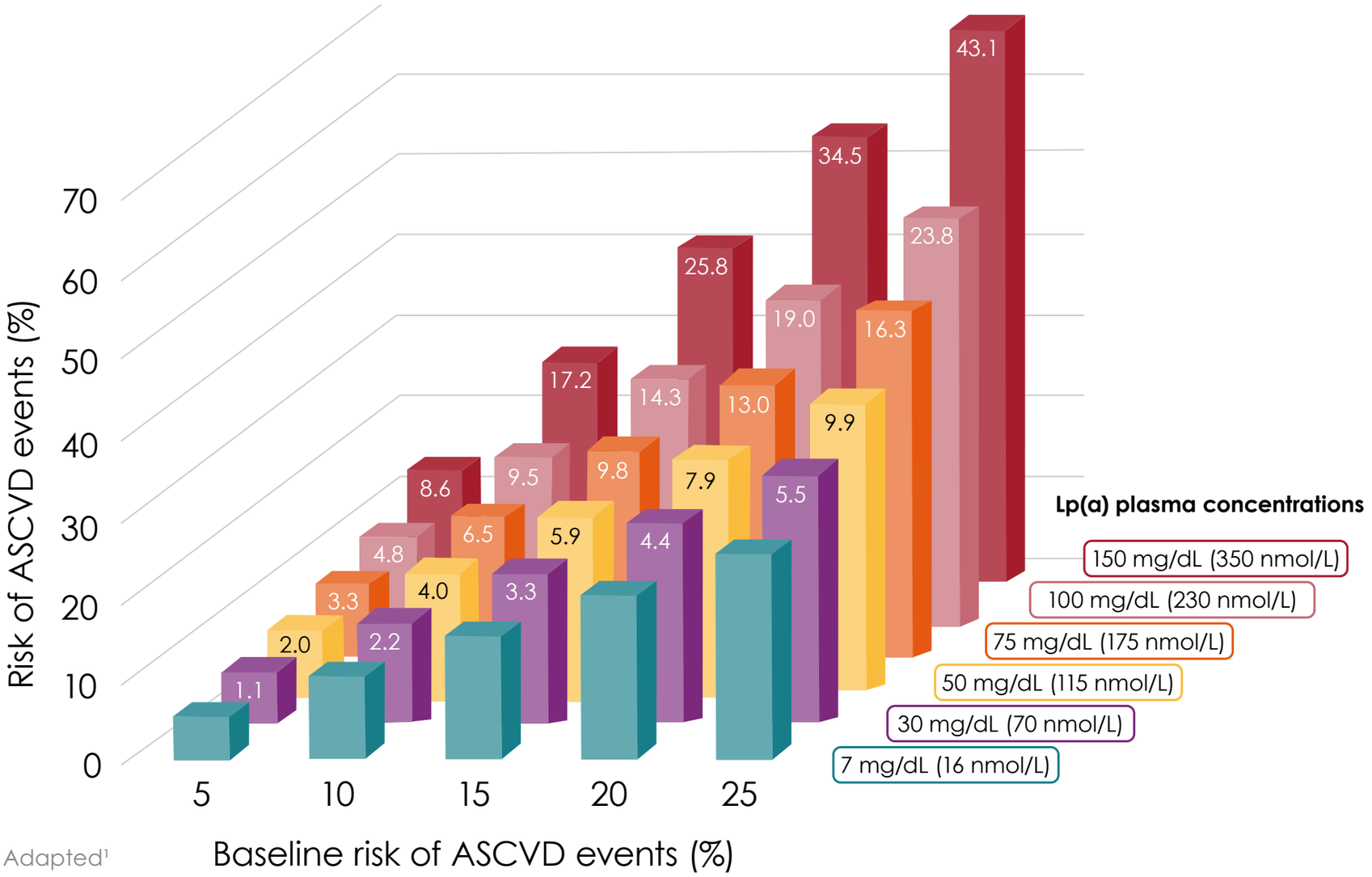
Absolute and relative risks of CV outcomes as a function of increasing Lp(a) concentrations[†]



Adapted[1]

"Lp(a) is a new risk factor for aortic valve stenosis"
– Kronenberg et al. 2022[1]

Estimated remaining lifetime risk of a major CV event versus Lp(a) concentration‡



Adapted[1]

In the graph above:

Green bars show categories of estimated lifetime risk at baseline (5%, 10%, 15%, 20%, and 25%)[1]

Within each baseline risk category, participants were then further divided into categories defined by baseline measured Lp(a) concentration[1]

The numbers on each bar show the estimated incremental increase in absolute risk caused by higher Lp(a) concentrations from 30 to 150 mg/dL (70 to 350 nmol/L), over baseline[1]

The magnitude of ASCVD risk is informed by Lp(a) levels and baseline ASCVD risk

Irrespective of absolute risk of ASCVD at baseline, an Lp(a) level of 100 mg/dL (~250 nmol/L) confers ~double the risk of ASCVD[1]

For individuals at higher baseline risk, the magnitude of absolute increase in ASCVD risk is greater than those with a lower baseline risk (e.g., from 20–40% risk versus 5–10% risk, respectively)[1]

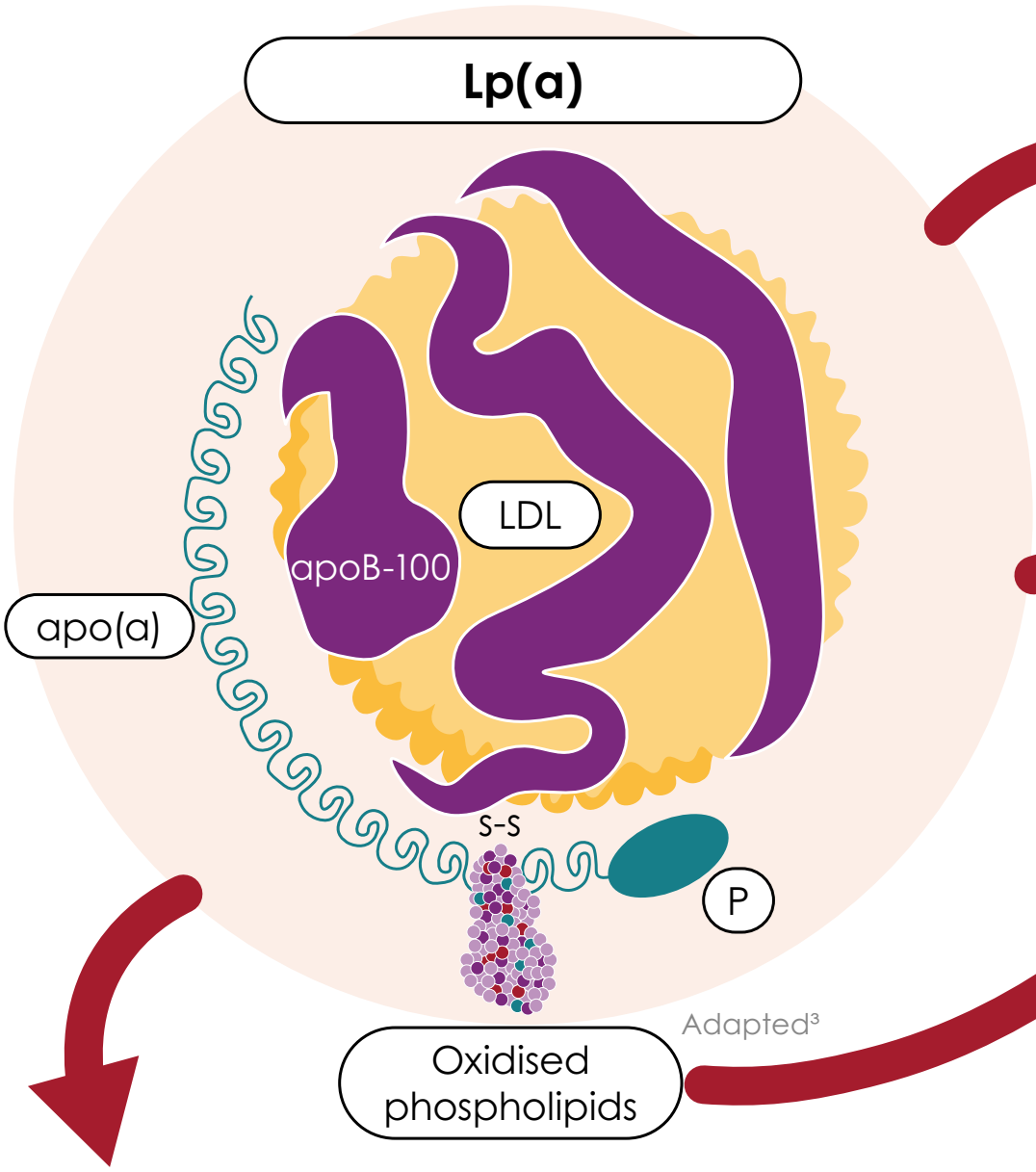
Failure to consider a person's Lp(a) level can lead to a substantial underestimate of their absolute risk of a major CV event[1]

Other findings:

Elevated Lp(a) remains a risk factor even at very low levels of LDL-C

Current evidence does not support Lp(a) as a risk factor for venous thrombotic events

Potential pathogenic mechanisms of Lp(a)



Pro-atherosclerotic[1]

Pro-inflammatory[1]

High Lp(a)
Induces expression of inflammatory and calcification genes in vascular and valvular cells[1]

Associated with incidence and progression of AVS[1]

A potential role for Lp(a) in the thrombotic process remains uncertain[1]

Elevated Lp(a) is not associated with venous thrombosis[1]

2022 European Atherosclerosis Society Consensus Statement
Guidance for clinical practice

Lp(a) testing – who to test, and when?

- Lp(a) should be measured at least once in adults to identify those with high cardiovascular risk[1]
- Lp(a) screening is also recommended for youth with a history of ischaemic stroke or family history of premature ASCVD or high Lp(a) and no other identifiable risk factors[1]

Cascade testing for high Lp(a) is recommended in settings of:[1]

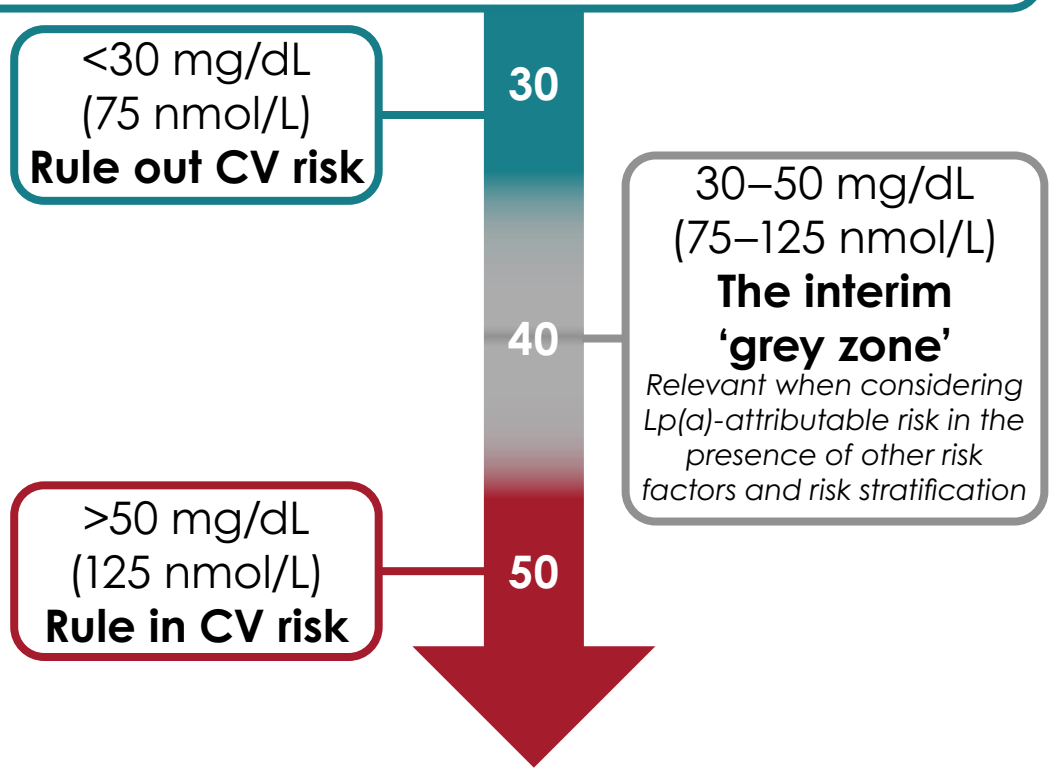
Familial hypercholesterolaemia

Family history of very high Lp(a)

Personal or family history of ASCVD

How Lp(a) test results can inform CV risk

Rather than absolute values, the consensus panel suggested use of risk thresholds with grey zones[1]



- Very high Lp(a) levels (>180 mg/dL or >430 nmol/L) indicate a lifetime ASCVD risk equivalent to untreated heterozygous familial hypercholesterolaemia[1]
- A high Lp(a) concentration should be interpreted in the context of other risk factors and absolute global CV risk[1]

Recommendations to manage elevated Lp(a)

Early, intensive management of other risk factors for individuals with elevated Lp(a) levels is recommended, in the absence of approved specific Lp(a)-lowering drugs[1]

Investigational drugs in development

Specific Lp(a)-lowering therapies are being investigated in Phase 2/3 clinical trials[1]

Outcomes of these trials are critical to confirm clinical benefit of specific Lp(a)-lowering for CV disease and AVS[1]

Personalised management of the following is recommended to reduce ASCVD risk, considering baseline CV risk and the untreated Lp(a) level:[1]

LDL-C

Blood pressure

Glucose

Lifestyle factors

Abbreviations: apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AVS, aortic valve stenosis; CV, cardiovascular; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

Footnotes: *Among men of European ancestry in the UK Biobank (results were similar for women but with lower absolute event rates)[1].

†Based on data from 70,286 white individuals in the Copenhagen General Population Study with a median 7.4 years of follow-up[1].

‡Shows the estimated remaining lifetime risk of a major CV event among 415,274 participants of European ancestry in the UK Biobank for whom measured Lp(a) values were available[1]. Major CV event was a composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or coronary revascularisation[1].

References: 1. Kronenberg, F et al. Eur Heart J 2022;43(39):3925–3946. **2.** Soppert J, et al. Adv Drug Delivery Rev 2020;159:4-33. **3.** Likozar A, et al. Ann Med. 2020;52(5):162-177.

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