Clinical *Standard*

CLINICAL STANDARD · VOL. 1 NO. 1 · 2026
DOI 10.68913/CS.2026.0004 · CC BY 4.0

CLINICAL REVIEW · GENERAL MEDICINE · CARDIOLOGY

Lipoprotein(a) as a treatable cardiovascular risk factor: measurement, risk thresholds and what the outcome trials mean for practice

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a genetically determined, low-density lipoprotein-like particle that raises the risk of myocardial infarction, large-artery ischaemic stroke and calcific aortic stenosis independently of LDL cholesterol. Roughly one adult in five has a concentration above 125 nmol/L (50 mg/dL), the threshold at which most guidance now labels risk as high. This review synthesises, for the general physician, what is settled and what remains open now that the first outcome trial of targeted Lp(a) lowering has reported. Mendelian randomisation and prospective cohorts, including the UK Biobank, the Copenhagen studies and the 30-year Women's Health Study, establish a continuous, causal and additive relation with cardiovascular events that persists at low achieved LDL cholesterol. Because concentration is stable, a single molar (nmol/L) measurement suffices for most adults, with repeat testing reserved for postmenopausal women and borderline values that would change a decision. Existing management is indirect: intensive LDL-cholesterol lowering, PCSK9 inhibitors (which lower Lp(a) by about a quarter), individualised aspirin decisions and lipoprotein apheresis for progressive disease. Antisense (pelacarsen) and small interfering RNA (olpasiran, lepodisiran, zerlasiran) agents and the oral inhibitor muvalaplin lower Lp(a) by 80% or more in phase 2 trials. However, on 4 September 2026 the first outcome trial, Lp(a)HORIZON (pelacarsen), was announced not to have met its primary endpoint; its full results and the small interfering RNA outcome trials are awaited. We propose explicit thresholds, an absolute-risk framing and a stepwise algorithm that can be applied now and refined as outcome data are published.

Keywords: lipoprotein(a) · cardiovascular risk · Mendelian randomisation · antisense oligonucleotide · small interfering RNA · lipoprotein apheresis · aspirin · risk stratification

Introduction

Lipoprotein(a) [Lp(a)] has moved from a curiosity of lipidology to a target with five late-stage drugs. The 2022 European Atherosclerosis Society (EAS) consensus concluded that genetic and epidemiological studies in hundreds of thousands of people support a causal and continuous association with cardiovascular outcomes across ethnicities, and that elevated Lp(a) remains a risk factor even at very low LDL cholesterol [1]. The 2024 National Lipid Association (NLA) update recommended measurement at least once in every adult, noting that about one person in five is affected yet measurement rates remain low [2]. Concentration is 70-90% heritable and largely unresponsive to lifestyle or statins [3].

For the general physician the difficulty is not whether Lp(a) matters but what to do with the result. Antisense and small interfering RNA (siRNA) agents and an oral assembly inhibitor lower Lp(a) by 80% or more, yet of the three outcome trials, Lp(a)HORIZON, OCEAN(a)-Outcomes and ACCLAIM-Lp(a) [4], the first to report, Lp(a)HORIZON, was announced on 4 September 2026 not to have reduced major cardiovascular events with pelacarsen [5]. This review sets out who to test and how, which thresholds to use, how to frame absolute risk, what current therapy achieves, and how to read the outcome trials when they report. We state plainly what the peer-reviewed literature contained on 7 September 2026, with trial status updated to 30 September 2026.

Search strategy

We searched PubMed through the NCBI E-utilities on 7 September 2026, combining "lipoprotein(a)" or "Lp(a)" with "Mendelian randomization", "UK Biobank",

"Copenhagen", "Women's Health Study", "assay", "aspirin", "apheresis", "PCSK9", "pelacarsen", "HORIZON", "olpasiran", "OCEAN(a)", "lepodisiran", "zerlasiran", "muvalaplin", "consensus" and "guideline". Genetic and cohort searches had no date limit; therapy searches covered 2019-2026, with a final check for cardiovascular outcome results from any Lp(a)-targeted agent. We prioritised randomised trials, Mendelian randomisation analyses, prospective cohorts above 10,000 participants, participant-level meta-analyses and society statements; narrative reviews were used only to document trial status. Every journal citation was verified against its PubMed record and numerical claims are taken from published abstracts. Because the first outcome result was released by the sponsor rather than in a journal, trial status was updated on 30 September 2026 from the sponsor announcement.

Biology in brief

Lp(a) is an LDL-like particle whose apolipoprotein B-100 is covalently bound to apolipoprotein(a), a plasminogen-like glycoprotein encoded by LPA. Concentration is set mainly by LPA variation: the number of kringle IV type 2 (KIV-2) repeats explained 21-27% of plasma variance in the Copenhagen cohorts, with mean levels falling from 56 to 15 mg/dL across quartiles of repeat number [6]. Two common variants, rs10455872 and rs3798220, carried odds ratios for coronary disease of 1.70 and 1.92, and the association disappeared after adjustment for Lp(a) concentration [7].

The particle carries oxidised phospholipids and is pro-inflammatory and pro-atherogenic [1]. Per particle it is markedly more harmful than LDL: in a UK Biobank apolipoprotein B-based genetic analysis, 50 nmol/L more Lp(a)-apoB carried an odds ratio for coronary disease of 1.28 against 1.04 for the same increment in LDL-apoB, an estimated 6.6-fold difference [8]. The LPA variant that raises coronary risk is also associated with aortic valve calcification (odds ratio 2.05 per allele) and incident aortic stenosis (hazard ratio 1.68 per allele) [9]. Current evidence does not support a role in venous thrombosis [1].

Who to test, how often and how to measure

Three bodies recommend universal once-in-a-lifetime testing: the EAS (at least once in adults, with cascade testing in familial hypercholesterolaemia or where there is a family or personal history of very high Lp(a) or premature disease) [1], the NLA [2] and the Canadian Cardiovascular Society, whose 2021 guideline made Lp(a) part of the initial lipid screen [10]. HEART UK in 2019 took a targeted approach: premature atherosclerotic disease in the patient or family, first-degree relatives with Lp(a) above 200 nmol/L, familial hypercholesterolaemia, calcific aortic stenosis and borderline 10-year risk [11]. The 2026 ACC/AHA multisociety dyslipidaemia guideline, replacing the 2018 cholesterol guideline, now also recommends measuring Lp(a) in all adults [12]. We favour universal testing.

One measurement is usually enough. In 16,017 UK Biobank participants the correlation between baseline and repeat molar concentration over a median of 4.4 years was 0.96, and the change added nothing to prediction beyond the follow-up value [13]. Women show an additional rise around the age of 50; levels were 27% higher after the menopause and 12% lower on hormone replacement in the Copenhagen General Population Study, which argues for a repeat in women over 50 whose earlier value was borderline [14]. Statins raise Lp(a) modestly (geometric mean ratio 1.11 against placebo in a participant-level meta-analysis of 5,256 patients) [15], so a value obtained on treatment is, if anything, an overestimate.

Assay choice matters more than repetition. Apolipoprotein(a) is polymorphic in size, so antibodies raised against the repetitive kringle structure make results isoform dependent, and conversion between mass (mg/dL) and molar (nmol/L) units is only approximate [16]. Laboratories should use isoform-insensitive assays traceable to the WHO/IFCC reference material and report in nmol/L. Practice lags: in a 2021 UK survey, 77% of laboratories offering the test referred it externally and only 3 of 60 respondents had fully adopted the HEART UK recommendations [17]. A newer complication is that assays measuring total apolipoprotein(a) understate the effect of drugs that block particle assembly: in the muvalaplin phase 2 trial the placebo-adjusted reduction was 85.8% with an intact-particle assay and 68.9% with a conventional assay [18]. When a decision hinges on the number, ask the laboratory what it measured and in which unit.

Cascade testing is justified by the inheritance. Among 61,715 Swedish first-degree relatives of 41,304 index patients, relatives of index cases in the 80th-95th and 95th-100th Lp(a) percentiles had hazard ratios for major cardiovascular events of 1.30 and 1.28, and concordance for an elevated level was 53% [19].

Risk thresholds and absolute-risk framing

Thresholds are conventions placed on a continuous gradient, and the gradient is linear: in 460,506 UK Biobank participants the hazard ratio for incident

atherosclerotic disease was 1.11 per 50 nmol/L with no inflection [20]. Ancestry changes the distribution but not the slope; medians were 19, 31, 75 and 16 nmol/L in white, South Asian, black and Chinese participants, whereas risk per 50 nmol/L was 1.11, 1.10 and 1.07 [20]. The same threshold should therefore apply to everyone.

The NLA categories are the most usable: below 75 nmol/L (30 mg/dL) low, 75-125 nmol/L intermediate, 125 nmol/L (50 mg/dL) or above high [2]. Higher bands carry qualitatively different implications. In the Copenhagen General Population Study, a level at or above the 91st percentile (about 147 nmol/L) carried hazard ratios for atherosclerotic disease of 1.61 and 1.57 in those with C-reactive protein below and at or above 2 mg/L [21]. For myocardial infarction, 180 mg/dL (389 nmol/L) conferred the same risk as genetically confirmed familial hypercholesterolaemia, and people with both traits had a hazard ratio of 14.0 [22]. In secondary prevention the adjusted rate ratios for recurrent events were 1.28 for 10-49 mg/dL, 1.44 for 50-99 mg/dL and 2.14 for 100 mg/dL or more, against absolute rates rising from 29 to 54 per 1,000 person-years [23].

Absolute risk is what patients act on. The highest Copenhagen 10-year risks were in men aged 70-79 with Lp(a) in the top decile and C-reactive protein at or above 2 mg/L: 34% for atherosclerotic disease, 19% for myocardial infarction and 13% for aortic stenosis, with 20%, 10% and 8% in women [21]. A relative hazard of 1.5 applied to a 3% baseline is a different proposition from the same hazard applied to 20%. We recommend recording Lp(a) alongside the estimated 10-year or lifetime risk rather than as a free-standing label (Table 1).

Table 1. Suggested interpretation of a single lipoprotein(a) result in adults

Concentration	Mass equivalent (approximate)	Interpretation	Action
<75 nmol/L	<30 mg/dL	Low	Standard care
75-124 nmol/L	30-49 mg/dL	Intermediate; 30-year risk raised in women above 30 mg/dL	Risk enhancer; tighten LDL-cholesterol target if other risk factors present
125-199 nmol/L	50-79 mg/dL	High; ≥125 nmol/L affects about one adult in five	Intensify LDL-cholesterol lowering; cascade test relatives
200-399 nmol/L	80-159 mg/dL	Very high; entry range of outcome trials	As above; PCSK9 inhibitor if LDL cholesterol above target; lipid clinic referral
≥400 nmol/L	≥160 mg/dL	Extreme; comparable to genetic familial hypercholesterolaemia	Lipid clinic; apheresis if progressive disease despite optimal therapy

Conversions are assay dependent [16]; bands follow the NLA categories [2] and the Copenhagen familial hypercholesterolaemia equivalence [22]. The Emerging Risk Factors Collaboration pooled 126,634 participants from 36 prospective studies: the association with coronary disease was continuous, risk ratio 1.13 per 3.5-fold higher usual concentration after adjustment for lipids and other risk factors, weaker for ischaemic stroke (1.10) and absent for non-vascular mortality [24]. Mendelian randomisation converts association into cause. In Copenhagen, genetically elevated Lp(a) carried a hazard ratio for myocardial infarction of 1.22 per doubling [6]. In 48,333 people with individual data and external validation in 189,539 more, 10 mg/dL lower genetically predicted Lp(a) was associated with 5.8% lower coronary risk, and a 101.5 mg/dL change carried the same association as 1 mmol/L (38.67 mg/dL) of LDL cholesterol [25]. A second analysis using a single-laboratory assay put the required reduction at 65.7 mg/dL and cautioned that assay standardisation changes the answer [26]. Both estimates are per unit of absolute, not percentage, reduction, which is why trial populations were selected for very high baseline levels. Genetic effects are consistent across ancestries and arterial territories. Combining the China Kadoorie Biobank with European data, each 100 nmol/L lower genetically predicted Lp(a) gave rate ratios of 0.78 for myocardial infarction and 0.80 for large-artery ischaemic stroke, but 0.94 for total ischaemic stroke, 0.99 for small-vessel stroke and 1.08 for intracerebral haemorrhage, with concordant effects in both ancestries [27]. The Women's Health Study extends the horizon. Among 27,939 initially healthy women followed for 30 years, with 3,662 first major events, the top versus bottom quintile of Lp(a) carried an adjusted hazard ratio of 1.33, alongside 1.70 for C-reactive protein and 1.36 for LDL cholesterol, each contributing independently [28]. A threshold analysis of the same cohort found that levels above 30 mg/dL (75th percentile) raised 30-year risk of major events and coronary disease, whereas associations with ischaemic stroke and cardiovascular death emerged above 120 mg/dL (99th percentile), with a hazard ratio for major events of 1.54 above 120 mg/dL versus below 10 mg/dL [29]. Lp(a) risk is additive to, not absorbed by, LDL-cholesterol lowering. In a participant-level meta-analysis of 27,658 patients in six statin trials, those with Lp(a) above 50 mg/dL had higher event rates in every quartile of achieved LDL cholesterol, with a hazard ratio of 1.38 even in the lowest quartile (3.1-77.0 mg/dL) and 1.90 when both were high [30]. No approved drug was designed to lower Lp(a), so management is indirect. The EAS and NLA both call for early, intensive risk-factor management scaled to global risk and Lp(a) level, primarily by reducing LDL cholesterol [1,2]: total atherogenic particle burden can be cut even if the Lp(a) fraction cannot. PCSK9 monoclonal antibodies lower Lp(a) by roughly a quarter. In FOURIER, evolocumab reduced Lp(a) by a median 26.9% at 48 weeks; patients with baseline Lp(a) above the median (37 nmol/L) had a 23% relative reduction in coronary death, myocardial infarction or urgent revascularisation (hazard ratio 0.77) against 7% below it (0.93; interaction P = 0.07), with three-year numbers needed to treat of 40 and 105 [31]. In ODYSSEY Outcomes, alirocumab lowered Lp(a) by a median 5.0 mg/dL and that reduction predicted lower event risk independently of the LDL-cholesterol change (hazard ratio 0.994 per 1 mg/dL) [32]. Among patients whose LDL cholesterol was already near 70 mg/dL on statin, alirocumab benefited only those with Lp(a) above the median of 13.7 mg/dL (hazard ratio 0.68 versus 1.11; interaction P = 0.017) [33]. Elevated Lp(a) should therefore lower the threshold for adding a PCSK9 inhibitor when LDL cholesterol is above target. A network meta-analysis of 51 trials placed evolocumab's Lp(a) effect at 31.6 percentage points against 98.9 for olpasiran 225 mg, with high heterogeneity and low certainty for several estimates [34]. Aspirin is the unresolved question. In ASPREE, 12,815 genotyped participants aged 70 or older showed an interaction between rs3798220-C carriage and aspirin (P = 0.049): carriers had a hazard ratio for major events of 1.90 on placebo and 0.54 on aspirin, an absolute reduction of 11.4 events per 1,000 person-years without significant excess bleeding [35]. In propensity-matched MESA participants, aspirin was associated with a hazard ratio for coronary events of 0.54 among those with Lp(a) above 50 mg/dL [36]. A 2026 meta-analysis of six studies and 6,628 adults found no significant reduction in major events (hazard ratio 0.60, 95% CI 0.31-1.17), a numerically higher bleeding hazard (1.24, 0.83-1.87) and an rs3798220 signal that did not survive sensitivity analysis [37]. Aspirin may be reasonable when Lp(a) is very high and bleeding risk is low, but it is not an evidence-based indication. Lipoprotein apheresis remains the only approved Lp(a)-specific treatment. The NLA cites a US indication for familial hypercholesterolaemia with documented coronary or peripheral disease and Lp(a) at or above 60 mg/dL (about 150 nmol/L) with LDL cholesterol at or above 100 mg/dL on maximal therapy [2]; the EAS reserves it for very high Lp(a) with progressive disease despite optimal management [1]. Evidence is observational and small: in 25 patients with isolated Lp(a) elevation treated for a mean of 7.1 years, median Lp(a) fell from 95.0 to 31.1 mg/dL and events from 0.87 to 0.24 per patient-year, a before-after comparison vulnerable to regression to the mean [38]. Its role will shrink. In Lp(a)FRONTIERS APHERESIS, 51 German patients on weekly apheresis were randomised to pelacarsen 80 mg monthly or placebo; pelacarsen cut the apheresis rate from 0.93 to 0.16 of scheduled sessions and lowered Lp(a) by a placebo-adjusted 72% at 52 weeks [39]. Safety of low Lp(a) has been examined in FOURIER: concentrations at or below 13 nmol/L were not associated with haemorrhagic stroke, serious bleeding, neurocognitive events, malignancy or atrial fibrillation, but lower Lp(a) was associated

with incident diabetes (hazard ratio 1.05 per 50 nmol/L lower), and evolocumab did not increase diabetes even in the top decile of baseline Lp(a) [40]. Five agents have reached late-stage development (Table 2). Pelacarsen, a hepatocyte-directed antisense oligonucleotide, produced mean reductions of 35% to 80% across regimens in 286 patients with established disease and Lp(a) of at least 150 nmol/L, injection-site reactions being the main adverse effect [41]. Lp(a)HORIZON randomised 8,323 patients with prior myocardial infarction, ischaemic stroke or symptomatic peripheral disease and Lp(a) of at least 70 mg/dL (about 149 nmol/L) to pelacarsen 80 mg monthly or placebo, with a minimum 2.5-year follow-up, an event-driven stop at 993 adjudicated primary events and a multiplicity-controlled analysis in the subgroup at or above 90 mg/dL [42]. On 4 September 2026 the sponsor announced that the trial had not met its primary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and urgent coronary revascularisation, although Lp(a) was lower with pelacarsen in a population receiving guideline-directed lipid-lowering and antihypertensive therapy; the magnitude of Lp(a) lowering, the effect estimate and the result in the 90 mg/dL subgroup had not been disclosed [5]. Olpasiran, an siRNA, produced placebo-adjusted reductions of 70.5% (10 mg), 97.4% (75 mg) and 101.1% (225 mg every 12 weeks) at 36 weeks in 281 patients with a median baseline of 260 nmol/L [43]. OCEAN(a)-Outcomes enrols patients with prior myocardial infarction or percutaneous intervention and Lp(a) of at least 200 nmol/L; in an observational cohort resembling that population, such patients had a 33% higher adjusted hazard of the composite coronary outcome over 12 years [44]. Lepodisiran, an extended-duration siRNA, lowered Lp(a) by a placebo-adjusted 93.9 percentage points from day 60 to 180 after 400 mg, and by 94.8 points from day 30 to 360 when redosed at day 180, in 320 participants with a median baseline of 254 nmol/L [45]; its outcome trial is ACCLAIM-Lp(a) [4]. Zerlasiran, dosed every 16 or 24 weeks, reduced time-averaged Lp(a) by 81-86% over 36 weeks in 178 patients [46]. Muvalaplin, an oral inhibitor of apolipoprotein(a)-apoB assembly, reduced intact Lp(a) by 85.8% at 240 mg daily over 12 weeks in 233 participants, with a 16.1% fall in apolipoprotein B and no change in C-reactive protein [18]; its phase 3 trial, MOVE-Lp(a), is under way [3].

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Evidence from genetics and cohorts

The Emerging Risk Factors Collaboration pooled 126,634 participants from 36 prospective studies: the association with coronary disease was continuous, risk ratio 1.13 per 3.5-fold higher usual concentration after adjustment for lipids and other risk factors, weaker for ischaemic stroke (1.10) and absent for non-vascular mortality [24]. Mendelian randomisation converts association into cause. In Copenhagen, genetically elevated Lp(a) carried a hazard ratio for myocardial infarction of 1.22 per doubling [6]. In 48,333 people with individual data and external validation in 189,539 more, 10 mg/dL lower genetically predicted Lp(a) was associated with 5.8% lower coronary risk, and a 101.5 mg/dL change carried the same association as 1 mmol/L (38.67 mg/dL) of LDL cholesterol [25]. A second analysis using a single-laboratory assay put the required reduction at 65.7 mg/dL and cautioned that assay standardisation changes the answer [26]. Both estimates are per unit of absolute, not percentage, reduction, which is why trial populations were selected for very high baseline levels.

Genetic effects are consistent across ancestries and arterial territories. Combining the China Kadoorie Biobank with European data, each 100 nmol/L lower genetically predicted Lp(a) gave rate ratios of 0.78 for myocardial infarction and 0.80 for large-artery ischaemic stroke, but 0.94 for total ischaemic stroke, 0.99 for small-vessel stroke and 1.08 for intracerebral haemorrhage, with concordant effects in both ancestries [27].

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Lp(a) risk is additive to, not absorbed by, LDL-cholesterol lowering. In a participant-level meta-analysis of 27,658 patients in six statin trials, those with Lp(a) above 50 mg/dL had higher event rates in every quartile of achieved LDL cholesterol, with a hazard ratio of 1.38 even in the lowest quartile (3.1-77.0 mg/dL) and 1.90 when both were high [30].

Current management: what can be done today

No approved drug was designed to lower Lp(a), so management is indirect. The EAS and NLA both call for early, intensive risk-factor management scaled to global risk and Lp(a) level, primarily by reducing LDL cholesterol [1,2]: total atherogenic particle burden can be cut even if the Lp(a) fraction cannot.

PCSK9 monoclonal antibodies lower Lp(a) by roughly a quarter. In FOURIER, evolocumab reduced Lp(a) by a median 26.9% at 48 weeks; patients with baseline Lp(a) above the median (37 nmol/L) had a 23% relative reduction in coronary death, myocardial infarction or urgent revascularisation (hazard ratio 0.77) against 7% below it (0.93; interaction P = 0.07), with three-year numbers needed to treat of 40 and 105 [31]. In ODYSSEY Outcomes, alirocumab lowered Lp(a) by a median 5.0 mg/dL and that reduction predicted lower event risk independently of the LDL-cholesterol change (hazard ratio 0.994 per 1 mg/dL) [32]. Among patients whose LDL cholesterol was already near 70 mg/dL on statin, alirocumab benefited only those with Lp(a) above the median of 13.7 mg/dL (hazard ratio 0.68 versus 1.11; interaction P = 0.017) [33]. Elevated Lp(a) should therefore lower the threshold for adding a PCSK9 inhibitor when LDL cholesterol is above target. A network meta-analysis of 51 trials placed evolocumab's Lp(a) effect at 31.6 percentage points against 98.9 for olpasiran 225 mg, with high heterogeneity and low certainty for several estimates [34].

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Lipoprotein apheresis remains the only approved Lp(a)-specific treatment. The NLA cites a US indication for familial hypercholesterolaemia with documented coronary or peripheral disease and Lp(a) at or above 60 mg/dL (about 150 nmol/L) with LDL cholesterol at or above 100 mg/dL on maximal therapy [2]; the EAS reserves it for very high Lp(a) with progressive disease despite optimal management [1]. Evidence is observational and small: in 25 patients with isolated Lp(a) elevation treated for a mean of 7.1 years, median Lp(a) fell from 95.0 to 31.1 mg/dL and events from 0.87 to 0.24 per patient-year, a before-after comparison vulnerable to regression to the mean [38]. Its role will shrink. In Lp(a)FRONTIERS APHERESIS, 51 German patients on weekly apheresis were randomised to pelacarsen 80 mg monthly or placebo; pelacarsen cut the apheresis rate from 0.93 to 0.16 of scheduled sessions and lowered Lp(a) by a placebo-adjusted 72% at 52 weeks [39].

Safety of low Lp(a) has been examined in FOURIER: concentrations at or below 13 nmol/L were not associated with haemorrhagic stroke, serious bleeding, neurocognitive events, malignancy or atrial fibrillation, but lower Lp(a) was associated with incident diabetes (hazard ratio 1.05 per 50 nmol/L lower), and evolocumab did not increase diabetes even in the top decile of baseline Lp(a) [40].

Targeted therapies and the outcome trials

Five agents have reached late-stage development (Table 2). Pelacarsen, a hepatocyte-directed antisense oligonucleotide, produced mean reductions of 35% to 80% across regimens in 286 patients with established disease and Lp(a) of at least 150 nmol/L, injection-site reactions being the main adverse effect [41]. Lp(a)HORIZON randomised 8,323 patients with prior myocardial infarction, ischaemic stroke or symptomatic peripheral disease and Lp(a) of at least 70 mg/dL (about 149 nmol/L) to pelacarsen 80 mg monthly or placebo, with a minimum 2.5-year follow-up, an event-driven stop at 993 adjudicated primary events and a multiplicity-controlled analysis in the subgroup at or above 90 mg/dL [42]. On 4 September 2026 the sponsor announced that the trial had not met its primary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and urgent coronary revascularisation, although Lp(a) was lower with pelacarsen in a population receiving guideline-directed lipid-lowering and antihypertensive therapy; the magnitude of Lp(a) lowering, the effect estimate and the result in the 90 mg/dL subgroup had not been disclosed [5].

Table 2. Lipoprotein(a)-targeted agents and their outcome trials, status on 30 September 2026

Agent (class)	Phase 2 Lp(a) reduction, population	Outcome trial, entry criteria	Outcome results
Pelacarsen (antisense)	35-80% by regimen; 286 patients, ≥150 nmol/L [41]	Lp(a)HORIZON: 8,323 patients, prior MI, stroke or PAD, ≥70 mg/dL; 993 events [42]	Topline 4 Sep 2026: primary endpoint not met; full data not yet presented [5]
Olpasiran (siRNA)	97-101% at ≥75 mg every 12 weeks; 281 patients, >150 nmol/L [43]	OCEAN(a)-Outcomes: prior MI or PCI, ≥200 nmol/L [44]	None [4]
Lepodisiran (siRNA)	94% at 400 mg, sustained to day 360 with redosing; 320 participants [45]	ACCLAIM-Lp(a) [4]	None [4]
Zerlasiran (siRNA)	81-86% time-averaged over 36 weeks; 178 patients, ≥125 nmol/L [46]	No outcome trial described	None
Muvalaplin (oral assembly inhibitor)	86% (intact assay) at 240 mg daily; 233 participants, ≥175 nmol/L [18]	MOVE-Lp(a) [3]	None

MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; siRNA, small interfering RNA. What the literature holds. On 7 September 2026, PubMed contained no primary results paper from any cardiovascular outcome trial of an Lp(a)-targeted agent; searches for each agent returned only phase 1-2 trials, design papers and reviews [3,4]. The first outcome result arrived instead as a sponsor announcement: Lp(a)HORIZON did not reduce major cardiovascular events with pelacarsen [5]. Until the full data are published, the effect estimate and its confidence interval, the achieved Lp(a) reduction and the subgroup results are unknown. The first direct test of Lp(a) lowering in secondary prevention, on top of guideline-directed therapy, was therefore negative for its primary endpoint; OCEAN(a)-Outcomes and ACCLAIM-Lp(a), which use more potent siRNA agents and, in OCEAN(a), a higher entry threshold, have not reported [4]. Any claim that Lp(a) lowering prevents events remains an inference from genetics and from the PCSK9 analyses, not a demonstrated result, and the apheresis-sparing trial shows that pelacarsen replaces a burdensome procedure, not that it prevents infarction [39]. How to read the trials. Three features will decide what Lp(a)HORIZON and its successors mean. First, baseline: HORIZON's entry level of 70 mg/dL and OCEAN(a)'s of 200 nmol/L mean the results apply to roughly the top decile, and a positive trial there will not by itself justify treating 130 nmol/L. Second, absolute reduction: genetic estimates suggest 66-100 mg/dL of lowering is needed to match 1 mmol/L of LDL cholesterol [25,26], so 80% lowering from a baseline of 80 mg/dL delivers about 64 mg/dL, at the lower edge of that range. Third, HORIZON's pre-specified subgroup at or above 90 mg/dL, built with multiplicity control because effect may scale with baseline [42]. The topline announcement did not report this subgroup [5]. A neutral overall result with a positive high-baseline subgroup would be consistent with the genetics rather than a refutation of them; a neutral result in both would weaken the case that lowering Lp(a) by this mechanism and magnitude prevents events within the trial period. Step 1: measure Lp(a) once at the first lipid profile, in nmol/L, and record it permanently. Step 2: interpret against Table 1 and global risk; below 75 nmol/L, standard care. Step 3: at 75-124 nmol/L, count Lp(a) as a risk enhancer that tips borderline statin decisions and lowers the LDL-cholesterol target in those with other risk factors. Step 4: at 125 nmol/L or above, treat as high risk irrespective of the score; set the LDL-cholesterol target of the next-higher risk category, address blood pressure, smoking and glycaemia, and offer testing to first-degree relatives. Step 5: at 200 nmol/L or above, or at any high level with established disease, add a PCSK9 inhibitor if LDL cholesterol remains above target on statin and ezetimibe, refer to a lipid clinic and discuss trial enrolment. Step 6: reserve apheresis for progressive disease despite optimal therapy. Step 7: do not start aspirin for Lp(a) alone in primary prevention. Step 8: repeat the measurement only in women after the menopause, when a borderline value would change a decision, or after starting an Lp(a)-lowering drug. Measure Lp(a) at least once in every adult with a molar, isoform-insensitive assay, and do not routinely repeat it (High certainty for the risk association and measurement stability; Moderate for universal over targeted testing) [1,2,13]. Use 125 nmol/L (50 mg/dL) as the threshold for high risk and 75 nmol/L as the lower bound of intermediate risk, applied identically across ancestries (Moderate certainty) [2,20]. At or above 125 nmol/L, intensify LDL-cholesterol lowering to the target of the next-higher risk category and prefer a PCSK9 inhibitor when LDL cholesterol stays above target on oral therapy (Moderate certainty, from pre-specified and post hoc trial analyses) [31-33]. Offer cascade testing to first-degree relatives of anyone with Lp(a) at or above the 80th percentile (Moderate certainty) [19]. Do not prescribe aspirin for elevated Lp(a) alone in primary prevention; individualise when Lp(a) is very high and bleeding risk is low (Low certainty) [35-37]. Consider lipoprotein apheresis only for very high Lp(a) with progressive disease despite optimal therapy (Very low certainty for event reduction; High certainty that pelacarsen can replace it) [38,39]. Do not use Lp(a)-targeted antisense, RNA or oral therapies outside trials: the first outcome trial, of pelacarsen, did not meet its primary endpoint, and the siRNA outcome trials have not reported (Very low certainty for clinical benefit) [4,5]. Lp(a) is the one major lipid risk factor for which the genetics are settled and the therapeutics are not. Measurement changes management now: it reclassifies risk over a 30-year horizon, sharpens LDL-cholesterol targets, guides PCSK9-inhibitor use and identifies families. What it cannot yet do is justify a specific Lp(a)-lowering drug: the first outcome trial, Lp(a)HORIZON, did not meet its primary endpoint, and OCEAN(a)-Outcomes and ACCLAIM-Lp(a) have yet to report. As full results appear, the questions to ask are who was enrolled, how much absolute lowering was achieved and whether benefit tracked baseline concentration. Until then, the thresholds and algorithm proposed here let general physicians act on a result most of their patients have never had measured.

Olpasiran, an siRNA, produced placebo-adjusted reductions of 70.5% (10 mg), 97.4% (75 mg) and 101.1% (225 mg every 12 weeks) at 36 weeks in 281 patients with a median baseline of 260 nmol/L [43]. OCEAN(a)-Outcomes enrols patients with prior myocardial infarction or percutaneous intervention and Lp(a) of at least 200 nmol/L; in an observational cohort resembling that population, such patients had a 33% higher adjusted hazard of the composite coronary outcome over 12 years [44]. Lepodisiran, an extended-duration siRNA, lowered Lp(a) by a placebo-adjusted 93.9 percentage points from day 60 to 180 after 400 mg, and by 94.8 points from day 30 to 360 when redosed at day 180, in 320 participants with a median baseline of 254 nmol/L [45]; its outcome trial is ACCLAIM-Lp(a) [4]. Zerlasiran, dosed every 16 or 24 weeks, reduced time-averaged Lp(a) by 81-86% over 36 weeks in 178 patients [46]. Muvalaplin, an oral inhibitor of apolipoprotein(a)-apoB assembly, reduced intact Lp(a) by 85.8% at 240 mg daily over 12 weeks in 233 participants, with a 16.1% fall in apolipoprotein B and no change in C-reactive protein [18]; its phase 3 trial, MOVE-Lp(a), is under way [3].

Table 2. Lipoprotein(a)-targeted agents and their outcome trials, status on 30 September 2026

MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; siRNA, small interfering RNA.

What the literature holds. On 7 September 2026, PubMed contained no primary results paper from any cardiovascular outcome trial of an Lp(a)-targeted agent; searches for each agent returned only phase 1-2 trials, design papers and reviews [3,4]. The first outcome result arrived instead as a sponsor announcement: Lp(a)HORIZON did not reduce major cardiovascular events with pelacarsen [5]. Until the full data are published, the effect estimate and its confidence interval, the achieved Lp(a) reduction and the subgroup results are unknown. The first direct test of Lp(a) lowering in secondary prevention, on top of guideline-directed therapy, was therefore negative for its primary endpoint; OCEAN(a)-Outcomes and ACCLAIM-Lp(a), which use more potent siRNA agents and, in OCEAN(a), a higher entry threshold, have not reported [4]. Any claim that Lp(a) lowering prevents events remains an inference from genetics and from the PCSK9 analyses, not a demonstrated result, and the apheresis-sparing trial shows that pelacarsen replaces a burdensome procedure, not that it prevents infarction [39].

How to read the trials. Three features will decide what Lp(a)HORIZON and its successors mean. First, baseline: HORIZON's entry level of 70 mg/dL and OCEAN(a)'s of 200 nmol/L mean the results apply to roughly the top decile, and a positive trial there will not by itself justify treating 130 nmol/L. Second, absolute reduction: genetic estimates suggest 66-100 mg/dL of lowering is needed to match 1 mmol/L of LDL cholesterol [25,26], so 80% lowering from a baseline of 80 mg/dL delivers about 64 mg/dL, at the lower edge of that range. Third, HORIZON's pre-specified subgroup at or above 90 mg/dL, built with multiplicity control because effect may scale with baseline [42]. The topline announcement did not report this subgroup [5]. A neutral overall result with a positive high-baseline subgroup would be consistent with the genetics rather than a refutation of them; a neutral result in both would weaken the case that lowering Lp(a) by this mechanism and magnitude prevents events within the trial period.

A practical algorithm for the general physician

Step 1: measure Lp(a) once at the first lipid profile, in nmol/L, and record it permanently. Step 2: interpret against Table 1 and global risk; below 75 nmol/L, standard care. Step 3: at 75-124 nmol/L, count Lp(a) as a risk enhancer that tips borderline statin decisions and lowers the LDL-cholesterol target in those with other risk factors. Step 4: at 125 nmol/L or above, treat as high risk irrespective of the score; set the LDL-cholesterol target of the next-higher risk category, address blood pressure, smoking and glycaemia, and offer testing to first-degree relatives. Step 5: at 200 nmol/L or above, or at any high level with established disease, add a PCSK9 inhibitor if LDL cholesterol remains above target on statin and ezetimibe, refer to a lipid clinic and discuss trial enrolment. Step 6: reserve apheresis for progressive disease despite optimal therapy. Step 7: do not start aspirin for Lp(a) alone in primary prevention. Step 8: repeat the measurement only in women after the menopause, when a borderline value would change a decision, or after starting an Lp(a)-lowering drug.

Practice recommendations

Measure Lp(a) at least once in every adult with a molar, isoform-insensitive assay, and do not routinely repeat it (High certainty for the risk association and measurement stability; Moderate for universal over targeted testing) [1,2,13].

Use 125 nmol/L (50 mg/dL) as the threshold for high risk and 75 nmol/L as the lower bound of intermediate

risk, applied identically across ancestries (Moderate certainty) [2,20].

At or above 125 nmol/L, intensify LDL-cholesterol lowering to the target of the next-higher risk category and prefer a PCSK9 inhibitor when LDL cholesterol stays above target on oral therapy (Moderate certainty, from pre-specified and post hoc trial analyses) [31-33].

Offer cascade testing to first-degree relatives of anyone with Lp(a) at or above the 80th percentile (Moderate certainty) [19].

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Consider lipoprotein apheresis only for very high Lp(a) with progressive disease despite optimal therapy (Very low certainty for event reduction; High certainty that pelacarsen can replace it) [38,39].

Do not use Lp(a)-targeted antisense, RNA or oral therapies outside trials: the first outcome trial, of pelacarsen, did not meet its primary endpoint, and the siRNA outcome trials have not reported (Very low certainty for clinical benefit) [4,5].

Conclusion

Lp(a) is the one major lipid risk factor for which the genetics are settled and the therapeutics are not. Measurement changes management now: it reclassifies risk over a 30-year horizon, sharpens LDL-cholesterol targets, guides PCSK9-inhibitor use and identifies families. What it cannot yet do is justify a specific Lp(a)-lowering drug: the first outcome trial, Lp(a)HORIZON, did not meet its primary endpoint, and OCEAN(a)-Outcomes and ACCLAIM-Lp(a) have yet to report. As full results appear, the questions to ask are who was enrolled, how much absolute lowering was achieved and whether benefit tracked baseline concentration. Until then, the thresholds and algorithm proposed here let general physicians act on a result most of their patients have never had measured.

DECLARATIONS

Author contributions

Both authors contributed to the conception of the review, the literature review, drafting and critical revision of the manuscript. Both authors approved the final version and agree to be accountable for all aspects of the work.

Acknowledgements

None.

Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Ethical approval

Not applicable; this review is based on published literature and public announcements and involved no human participants or patient data.

Data availability

No new data were generated or analysed; all sources are cited in the reference list.

Use of AI tools

The literature search, reference verification, first draft and the trial-status update of 30 September 2026 were prepared with AI assistance (Claude, Anthropic) using PubMed E-utilities and web sources; the authors reviewed and edited the text, verified its content and take full responsibility for it.

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Received 02 September 2026 **Accepted** 07 October 2026 **Published** 07 October 2026
Citation Engy Nasser Dongol, Asmaa Bahaaeldin Soliman. Lipoprotein(a) as a treatable cardiovascular risk factor: measurement, risk thresholds and what the outcome trials mean for practice. Clinical Standard. 2026;1(1). doi:10.68913/cs.2026.0004
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