Lipoprotein(a): The Science Behind the Risk Factor

Keywords: Lipoprotein(a), cardiology, atherosclerotic cardiovascular disease, cardiovascular risk.

In recent decades, lipoprotein(a) [Lp(a)] has emerged as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. Its measurement has since been incorporated into cardiovascular guidelines globally [2-4].

To facilitate understanding of the clinical utility of Lp(a) and its association with cardiovascular risk, Roche Diagnostics hosted a webinar on 1 November 2023. The webinar featured presentations from Prof Steven Nicholls, Program Director at Victorian Heart Hospital, A/Prof David Sullivan, Clinical Associate Professor at Sydney Medical School, University of Sydney, and A/Prof Karam Kostner, Director of Cardiology at Mater Hospital in Sydney.

Lipoprotein(a) is prominently associated with risk of cardiovascular disease

> "Elevated Lp(a) is an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD)" — ***Australian Atherosclerosis Society***

The higher an individual's Lp(a) levels, the higher their risk of early cardiovascular disease (CVD), myocardial infarction and coronary death [1, 5, 6]. Approximately 30-50% of individuals with familial hypercholesterolaemia (FH) are also found to have elevated Lp(a) levels [7]. The CVD risk conferred by Lp(a) elevation persists across ethnic groups, despite racial variation in Lp(a) levels [8].

Various studies have investigated the association between CVD risk and LP(a). Mendelian randomisation has demonstrated the causal role of Lp(a) in ASCVD and the subsequent usefulness of Lp(a) as a target for cardiovascular (CV) therapies [9]. Recent large randomised controlled trials for lipid lowering therapies, such as the AIM-HIGH [10] and JUPITER studies [11], have also found an association between elevated Lp(a) levels and residual CVD risk [12]. Data from genomic studies not only indicate the CV risks associated with Lp(a) but indicate that Lp(a) lowering can reduce CVD risk [9]. However, Prof Nichols indicated that this requires confirmation through clinical outcome studies, which "becomes important for the design of clinical trials moving forward".

The importance of lipoprotein(a) measurement for personalised treatment

Elevated p(a) is highly prevalent. Approximately 20% of the global population have elevated Lp(a) levels [13]. This, alongside its association with CVD risk, signifies the potential clinical utility of Lp(a), and the subsequent importance of Lp(a) measurement [2-4].

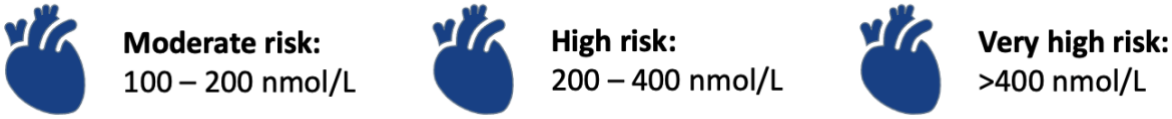
However, the high structural variability of Lp(a) complicates its measurement. Historical assays based on mass would subsequently miscalculate the amount of Lp(a). Because of this, modern size-calibrated polyclonal immunoassays calculate Lp(a) concentrations in molar

units instead of mass units [13, 14]. Consensus statements from both the European [2] and Australian Atherosclerosis Society [3] recommend the measurement of Lp(a) with a size independent assay, in molar units.

> "Circulating Lp(a) concentrations should be estimated using an apo(a)-isoform independent assay that employs appropriate calibrators and reports the results in molar units (nmol/L)." — ***Australian Atherosclerosis Society***

The Australian Atherosclerosis Society recommends selective screening strategies be implemented when measuring Lp(a). Lp(a) should be measured in all patients with premature ASCVD and those considered to be at intermediate-high risk of ASCVD [3, 15]. A/Prof Kostner explained that the elevation of Lp(a) can then be used to assess and stratify the patient's CVD risk leading to initiation or intensification of preventative treatment [3].

Risk stratification with Lp(a) measurement



Lp(a) testing in clinical practice has the potential to recharacterize the risk, and therefore optimise treatment, of up to 40% of conventionally classified intermediate-risk patients, as noted by Prof Nicholls [16]. For intensive treatment of patients with Lp(a) correlating to a high CVD risk, A/Prof Kostner particularly recommended aggressive reduction of low-density lipoprotein with statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

For the clinical utility of Lp(a) to be seen in practice, widespread access to Lp(a) testing is needed.

Current and emerging therapies for the management of elevated lipoprotein(a)
Therapies that lower Lp(a) are currently used in clinical practice [17, 18].

Current approaches to lowering of Lp(a)

Nicotinic acid	• 20-30% reduction of Lp(a) • Difficult to tolerate due to side effects • Not widely available.
PCSK9 inhibitors	• 14-30% reduction of Lp(a)
Apheresis	• Uncommonly used in FH patients. • 70% ± 10% reduction of Lp(a) • Not widely available

In large clinical outcome trials of PCSK9 inhibitors such as alirocumab, Lp(a) lowering appears to correlate to a reduction of CV risk [19]. "This leads to thoughts about new

therapies coming down the line, which have been specifically designed to directly target Lp(a)" Prof Nicholls said.

Emerging therapies primarily target Lp(a) production in the liver by targeting Lp(a) RNA. These include antisense RNA therapy, which reduced Lp(a) by75-80%, RNA interference therapy which reduces Lp(a) by approximately 90%, and RNA silence therapies such as olpasiran [20-22] which can reduce Lp(a) by approximately 98%. Oral treatments are also in development. Muvalaplin is a small molecule Lp(a) inhibitor that prevents binding between the apolipoproteins in Lp(a), reducing levels by 65%. Cholesterylester transfer protein (CETP) inhibitors such as obicetrapib [23, 24] can also reduce Lp(a) by 30-50%. Gene editing is also emerging as an approach to treating low density lipoprotein cholesterol, with non-human primate data showing promising results [25]. This may be utilised in the future to target the Lp(a) gene, Prof Nicholls noted.

A/Prof Kostner noted that, aside from infusion related reactions, therapies targeting Lp(a) appear to be well tolerated. "Mendelian randomisation can predict if a therapy will have side effects." A/Prof Sullivan explained. He said that, as Lp(a) is not widely distributed in nature, it is expected that lowering it would have few side effects.

These emerging therapies require evaluation in CV outcome trials to determine any reduction in CV risk, directly related to a reduction in Lp(a). With further evidence, practice will evolve from therapies that have a limited effect on Lp(a), to much more effective oral small-molecule or injectable treatments, Prof Nicholls concluded.

Future considerations for the clinical utility of lipoprotein(a)

Lp(a) is a highly important area for development in CVD. "Lp(a) is the first independent CVD risk factor within the last two or three decades and is exemplar of precision medicine via mendelian randomisation," A/Prof Sullivan highlighted.

As emphasised by Prof Nicholls, future management of CVD will depend on evidence from large clinical outcome trials, and effective biomarkers to identify prominent risk factors such as Lp(a), to allow personalised treatment. Investigation of Lp(a) in clinical outcomes trials is vital for important considerations, such as: what a clinical meaningful reduction of Lp(a) is; why Lp(a) is produced in the body; and subsequently, if there are any long-term consequences of Lp(a) lowering agents. A/Prof Sullivan emphasised that, until Lp(a) lowering agents are proven to be safe and effective, Lp(a) must be regarded as an important means of nuancing risk in the intermediate category of ASCVD. A/Prof Sullivan said. "We should not think about other biomarkers until we have done a good job sorting out Lp(a). It may do just about everything we need."

To learn more about lipoprotein(a), watch the full webinar with Prof Nicholls, A/Prof Sullivan and A/Prof Kostner.

References

[1] B. G. Nordestgaard and A. Langsted, "Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology," *Journal of Lipid Research,* vol. 57, no. 11, pp. 1953-1975, 2016, doi: 10.1194/jlr.R071233.

[2] F. Kronenberg *et al.*, "Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement " *European Heart Journal,* vol. 43, no. 39, pp. 3925-3946, 2022, doi: 10.1093/eurheartj/ehac361.

[3] N. C. Ward *et al.*, "Australian Atherosclerosis Society Position Statement on Lipoprotein(a): Clinical and Implementation Recommendations," *Heart, Lung and Circulation,* vol. 32, no. 3, pp. 287-296, 2023, doi: 10.1016/j.hlc.2022.11.015.

[4] F. Mach *et al.*, "2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)," *European Heart Journal,* vol. 41, no. 1, pp. 111-188, 2019, doi: 10.1093/eurheartj/ehz455.

[5] C. Emerging Risk Factors *et al.*, "Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality," *JAMA,* vol. 302, no. 4, pp. 412-23, Jul 22 2009, doi: 10.1001/jama.2009.1063.

[6] P. R. Kamstrup, A. Tybjaerg-Hansen, R. Steffensen, and B. G. Nordestgaard, "Genetically elevated lipoprotein(a) and increased risk of myocardial infarction," (in eng), *Jama,* vol. 301, no. 22, pp. 2331-9, Jun 10 2009, doi: 10.1001/jama.2009.801.

[7] A. Vuorio, G. F. Watts, W. J. Schneider, S. Tsimikas, and P. T. Kovanen, "Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities," *Journal of Internal Medicine,* vol. 287, no. 1, pp. 2-18, 2020, doi: https://doi.org/10.1111/joim.12981.

[8] G. Reyes-Soffer, "The impact of race and ethnicity on lipoprotein(a) levels and cardiovascular risk," (in eng), *Curr Opin Lipidol,* vol. 32, no. 3, pp. 163-166, Jun 1 2021, doi: 10.1097/mol.0000000000000753.

[9] S. Burgess *et al.*, "Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis," *JAMA Cardiology,* vol. 3, no. 7, pp. 619-627, 2018, doi: 10.1001/jamacardio.2018.1470.

[10] D. S. Hippe *et al.*, "Lp(a) (Lipoprotein(a)) Levels Predict Progression of Carotid Atherosclerosis in Subjects With Atherosclerotic Cardiovascular Disease on Intensive Lipid Therapy: An Analysis of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) Carotid Magnetic Resonance Imaging Substudy-Brief Report," (in eng), *Arterioscler Thromb Vasc Biol,* vol. 38, no. 3, pp. 673-678, Mar 2018, doi: 10.1161/atvbaha.117.310368.

[11] L. M. de Boer *et al.*, "Statin therapy and lipoprotein(a) levels: a systematic review and meta-analysis," *European Journal of Preventive Cardiology,* vol. 29, no. 5, pp. 779-792, 2021, doi: 10.1093/eurjpc/zwab171.

[12] S. Tsimikas, "A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies," (in eng), *J Am Coll Cardiol,* vol. 69, no. 6, pp. 692-711, Feb 14 2017, doi: 10.1016/j.jacc.2016.11.042.

[13] P. R. Kamstrup, "Lipoprotein(a) and Cardiovascular Disease," *Clinical Chemistry,* vol. 67, no. 1, pp. 154-166, 2020, doi: 10.1093/clinchem/hvaa247.

[14] J. J. Albers, S. M. Marcovina, and M. S. Lodge, "The unique lipoprotein(a): properties and immunochemical measurement," *Clinical Chemistry,* vol. 36, no. 12, pp. 2019-2026, 1990, doi: 10.1093/clinchem/36.12.2019.

[15] K. M. Kostner, W. März, and G. M. Kostner, "When should we measure lipoprotein (a)?," (in eng), *Eur Heart J,* vol. 34, no. 42, pp. 3268-76, Nov 2013, doi: 10.1093/eurheartj/eht053.
[16] A. Saeed, S. Kinoush, and S. S. Virani, "Lipoprotein (a): Recent Updates on a Unique Lipoprotein," (in eng), *Curr Atheroscler Rep,* vol. 23, no. 8, p. 41, Jun 19 2021, doi: 10.1007/s11883-021-00940-5.
[17] W. E. Boden, M. S. Sidhu, and P. P. Toth, "The Therapeutic Role of Niacin in Dyslipidemia Management," *Journal of Cardiovascular Pharmacology and Therapeutics,* vol. 19, no. 2, pp. 141-158, 2014, doi: 10.1177/1074248413514481.
[18] J. C. van Capelleveen, F. M. van der Valk, and E. S. Stroes, "Current therapies for lowering lipoprotein (a)," (in eng), *J Lipid Res,* vol. 57, no. 9, pp. 1612-8, Sep 2016, doi: 10.1194/jlr.R053066.
[19] V. A. Bittner *et al.*, "Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome," (in eng), *J Am Coll Cardiol,* vol. 75, no. 2, pp. 133-144, Jan 21 2020, doi: 10.1016/j.jacc.2019.10.057.
[20] M. L. O'Donoghue *et al.*, "Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease," *New England Journal of Medicine,* vol. 387, no. 20, pp. 1855-1864, 2022, doi: 10.1056/NEJMoa2211023.
[21] S. Tsimikas *et al.*, "Lipoprotein(a) Reduction in Persons with Cardiovascular Disease," *New England Journal of Medicine,* vol. 382, no. 3, pp. 244-255, 2020, doi: 10.1056/NEJMoa1905239.
[22] S. E. Nissen *et al.*, "Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Lipoprotein(a) Levels," *JAMA,* vol. 327, no. 17, pp. 1679-1687, 2022, doi: 10.1001/jama.2022.5050.
[23] S. J. Nicholls *et al.*, "Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial," (in eng), *Jama,* vol. 330, no. 11, pp. 1042-1053, Sep 19 2023, doi: 10.1001/jama.2023.16503.
[24] S. J. Nicholls *et al.*, "Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial," *Nature Medicine,* vol. 28, no. 8, pp. 1672-1678, 2022/08/01 2022, doi: 10.1038/s41591-022-01936-7.
[25] R. G. Lee *et al.*, "Efficacy and Safety of an Investigational Single-Course CRISPR Base-Editing Therapy Targeting PCSK9 in Nonhuman Primate and Mouse Models," (in eng), *Circulation,* vol. 147, no. 3, pp. 242-253, Jan 17 2023, doi: 10.1161/circulationaha.122.062132.