



The time for lipoprotein(a) based intervention has arrived: where will the light shine?

Stephen J. Nicholls^{1,2}, Adam J. Nelson¹

¹South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia; ²Department of Medicine, Monash University, Melbourne, Australia

Correspondence to: Stephen J. Nicholls, MBBS, PhD. South Australian Health and Medical Research Institute, PO Box 11060, Adelaide, SA 5001, Australia. Email: stephen.nicholls@sahmri.com.

Comment on: Verbeek R, Hoogeveen RM, Langsted A, *et al.* Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. *Eur Heart J* 2018;39:2589-96.

Submitted Oct 04, 2018. Accepted for publication Nov 02, 2018.

doi: 10.21037/jtd.2018.11.54

View this article at: <http://dx.doi.org/10.21037/jtd.2018.11.54>

For more than a quarter century, evidence has accumulated supporting the pivotal role of lowering levels of low-density lipoprotein cholesterol (LDL-C). The benefits of more intensive lipid lowering have been reflected in treatment guidelines and increasing use of high intensity statin therapy in patients at the highest risk of experiencing a cardiovascular event. In more recent years, we have observed incremental benefit from use of additional lipid lowering agents, beyond statins, which have further consolidated the LDL hypothesis in atherosclerotic cardiovascular disease. Yet, there remains a substantial residual risk of cardiovascular events, despite use of these agents and achieving lower LDL-C levels. This suggests that modifying additional targets may be required to achieve more effective reductions in cardiovascular risk.

From a lipid perspective, the search to develop effective strategies beyond LDL-C lowering has focused on two broad areas: high-density lipoproteins (HDL) and triglyceride rich lipoproteins (TRL). Despite convincing data of an inverse relationship between HDL-C and cardiovascular risk in population studies (1) and atheroprotective effects of HDL based interventions in animal studies (2), clinical trials of HDL raising therapies in contemporary clinical trials have proven to be disappointing (3-6). To date, no such agent has proven to substantially reduce cardiovascular events in statin-treated patients. Given the lack of association between genetic polymorphisms influencing HDL-C levels and cardiovascular risk, this is not necessarily surprising (7,8). It is of interest that ongoing efforts in the HDL therapeutic field

are focusing primarily on enhancing its functional quality as opposed to its quantity.

Triglyceride based therapeutics has presented a considerable challenge with regard to guiding therapies. Given the higher residual cardiovascular risk in statin-treated patients with hypertriglyceridemia, the conventional and guideline-based approach has advocated use of more intensive LDL-C lowering in this setting. While a number of therapies with triglyceride lowering properties have been demonstrated to reduce cardiovascular events (9), they typically have a multitude of functional properties and triglyceride lowering has not been demonstrated to associate with their benefit. Even with the observation that high dose omega-3 fatty acids confer cardiovascular benefit, this may result from effects beyond their triglyceride lowering (10). In contrast to HDL, genetic studies do implicate TRLs and factors that influence their metabolism in atherosclerotic disease (11). Accordingly, a new wave of therapeutics specifically targeting these remodelling factors have the chance to initiate a new phase of cardiovascular outcomes trials with triglyceride lowering being the primary focus.

Of all of the lipid species associated with cardiovascular disease, lipoprotein (a) [Lp(a)] has proven to be the most challenging. Once considered an elusive parameter measured in patients with premature coronary heart disease in the absence of conventional risk factors, accumulating insights into the role of Lp(a) in a broader range of atherosclerotic cardiovascular disease have brought into the forefront of attempts to reducing cardiovascular risk in

the post-statin era. Lp(a) comprises an LDL-like particle, with apoB covalently bound by a disulfide bond to apo(a), which bears considerable homology to plasminogen. Apo(a) contains a number of kringles, with upwards of 40 copies of KIV₂. This results in a range of isoforms, with more than 80% of individuals carrying two different sized isoforms. Preclinical studies have established that Lp(a) possess a number of functional activities that implicates its role in atherosclerotic cardiovascular disease. These include upregulation of inflammatory mediators (12), increase foam cell formation, plaque calcification, platelet hyperresponsiveness and reduced fibrinolytic activity (13). These properties suggest that Lp(a) plays a role at all stages of atherosclerosis from its early formation through to the consequences of plaque rupture.

Population studies have suggested that Lp(a) levels independently associate with cardiovascular risk (14). This is supported by genomic observations that implicate Lp(a) as a causal factor in both atherosclerotic disease (15) and calcific aortic valvular stenosis (16). These reports suggest that Lp(a) may have emerged from a factor of interest in patients, for whom no other factor seems to explain their premature cardiovascular disease, to a potential role in risk prediction and as a target for therapeutic modification (17). The ability to modify Lp(a) and subsequently cardiovascular risk will be the next step required to continue to advance the importance of Lp(a) in cardiovascular prevention. Lp(a) targeted therapeutics has proven to be challenging to date. Statins have no impact on Lp(a) levels (18). Agents that have been demonstrated to reduce Lp(a) levels (niacin, oestrogen) do not reduce cardiovascular events (4,19). Lp(a) apheresis presents an opportunity to treat patients with extremely high levels (20). The emergence of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors provides an additional option, by virtue of their ability to lower Lp(a) by approximately 30% (21). Given the robust LDL cholesterol lowering achieved with these agents, it will be difficult to truly elucidate to what degree Lp(a) lowering contributes to their benefits on progression of coronary atherosclerosis and cardiovascular events. More recently, apo(a) antisense therapy has been developed, with dose dependent lowering by up to 90% and a reassuring safety profile (22).

With the emergence of Lp(a) lowering therapies, there will be considerable interest in determining the optimal clinical setting to target these agents. Increasing use of Mendelian randomization may provide insights into the degree of Lp(a) lowering required to achieve effective

reductions in cardiovascular risk. While the Lp(a) reduction required for benefit may be considerable, this may be modified in the setting of additional cardiovascular risk factors. The question also arises to what degree intensive LDL cholesterol lowering may attenuate such benefits. Confusion in this area is supported by reports that Lp(a) continues to associate with cardiovascular risk in the setting of low LDL cholesterol levels in some reports (23), but not others (24). Additional work is required in this space to clarify whether Lp(a) continues to be an important risk factor in patients with low LDL cholesterol levels.

In a recent issue of the *European Heart Journal*, Verbeek and colleagues have attempted to address the relationship between Lp(a) and cardiovascular risk across a range of LDL cholesterol levels in asymptomatic individuals participating in the EPIC-Norfolk and Copenhagen City Heart Studies (25). Given that a proportion of LDL cholesterol is carried on Lp(a) particles, they calculated a corrected LDL cholesterol for each individual. The findings were of interest. Those patients with the highest Lp(a) levels demonstrated a greater risk of cardiovascular events at all corrected LDL cholesterol levels greater than 2.5 mmol/L, but not in individuals with lower levels of LDL cholesterol. The findings of this study continue to suggest that, even in the primary prevention setting, intensive LDL cholesterol lowering continues to be the major focus of efforts to reduce cardiovascular risk.

How such findings influence clinical development of novel Lp(a) therapies remains uncertain. Given that these agents are more likely to be evaluated in higher risk patients with established atherosclerotic cardiovascular disease, treatment guidelines will mandate maximally tolerated statin therapy and achieving low LDL cholesterol levels at baseline. However, many patients fail to achieve effective LDL cholesterol lowering despite such therapy. It is likely that these patients, with Lp(a) elevation in the presence or absence of additional cardiovascular risk factors, will form the cohort to ultimately test the hypothesis that Lp(a) lowering will result in cardiovascular protection. Such findings will be pivotal to determine whether Lp(a) will step and deliver as a pharmacological target or whether it will continue play a role as an occasionally tested risk factor. The time has arrived to answer the question.

Acknowledgements

None.

Footnote

Conflicts of Interest: SJ Nicholls has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx and Sanofi-Regeneron and is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron and Novo Nordisk. AJ Nelson has no conflicts of interest to declare.

References

- Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79:8-15.
- Nicholls SJ, Rye KA, Barter PJ. High-density lipoproteins as therapeutic targets. *Curr Opin Lipidol* 2005;16:345-9.
- Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;357:2109-22.
- AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-67.
- Lincoff AM, Nicholls SJ, Riesmeyer JS, et al. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med* 2017;376:1933-42.
- Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367:2089-99.
- Frikke-Schmidt R, Nordestgaard BG, Stene MC, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. *JAMA* 2008;299:2524-32.
- Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012;380:572-80.
- Ganda OP, Bhatt DL, Mason RP, et al. Unmet Need for Adjunctive Dyslipidemia Therapy in Hypertriglyceridemia Management. *J Am Coll Cardiol* 2018;72:330-43.
- Nicholls SJ, Lincoff AM, Bash D, et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. *Clin Cardiol* 2018;41:1281-8.
- Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 2013;45:1345-52.
- Haque NS, Zhang X, French DL, et al. CC chemokine I-309 is the principal monocyte chemoattractant induced by apolipoprotein(a) in human vascular endothelial cells. *Circulation* 2000;102:786-92.
- Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol* 2017;69:692-711.
- Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009;302:412-23.
- Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518-28.
- Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013;368:503-12.
- Nicholls SJ, Psaltis PJ. What role for lipoprotein(a) in clinical practice? *Lancet Diabetes Endocrinol* 2017;5:487-9.
- van Capelleveen JC, van der Valk FM, Stroes ES. Current therapies for lowering lipoprotein (a). *J Lipid Res* 2016;57:1612-8.
- HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;371:203-12.
- Roeseler E, Julius U, Heigl F, et al. Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization. *Arterioscler Thromb Vasc Biol* 2016;36:2019-27.
- Raal FJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol* 2014;63:1278-88.
- Tsimikas S, Viney NJ, Hughes SG, et al. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet* 2015;386:1472-83.
- Hippe DS, Phan BAP, Sun J, 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. *Arterioscler Thromb Vasc Biol* 2018;38:673-8.
24. Nicholls SJ, Tang WH, Scoffone H, et al. Lipoprotein(a) levels and long-term cardiovascular risk in the contemporary era of statin therapy. *J Lipid Res* 2010;51:3055-61.

25. Verbeek R, Hoogeveen RM, Langsted A, et al. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. *Eur Heart J* 2018;39:2589-96.

Cite this article as: Nicholls SJ, Nelson AJ. The time for lipoprotein(a) based intervention has arrived: where will the light shine? *J Thorac Dis* 2019;11(Suppl 3):S433-S436. doi: 10.21037/jtd.2018.11.54