

Lipoprotein (a): a promising target in the treatment of stenotic valvular diseases

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Introduction

The main findings of the study published by Hojo *et al.*¹ in this edition of the journal are (i) valvular heart disease (VHD), and particularly, aortic regurgitation (AR) and mitral regurgitation (MR) are highly prevalent in patients with peripheral vascular disease (PAD), and (ii) higher circulating levels of lipoprotein a (Lp(a)) are associated with increased risk of aortic (AS) and mitral (MS) valve stenosis. In this large series of 861 patients with PAD referred to Kitakanto Hospital in Japan, 43.6% had VHD at echocardiographic examination: 26.8% AR, 19.7% MR, 5.9% AS, 1.3% MS, and 9.4% tricuspid regurgitation (TR). Not surprisingly, older age was associated with increased prevalence of all types of VHD, except MS. Reduced glomerular filtration was associated with AR, MR, and AS. However, the most striking observation of this study¹ was that high levels of Lp(a) were independently associated with increased prevalence of stenotic valvular lesions but not of regurgitant lesions.

Fibrotic degeneration of the aortic valve cusps is, by far, the most frequent cause of AS.² Although rheumatic disease remains the most frequent aetiology of MS, degenerative disease may also occur in elderly people. All cases of MS documented in the series of Hojo *et al.*¹ were of non-rheumatic aetiology. Degenerative MS is characterized by calcification of the mitral annulus and of the leaflets (predominantly at their base). With ageing of the population, the prevalence of degenerative valvular stenosis (AS and/or MS) has increased exponentially.²

No pharmacological treatment is currently available to prevent the development or reduce the progression of AS or MS. Furthermore, in contrast to patients with rheumatic MS, those with degenerative MS have no commissural fusion and are thus not good candidates for percutaneous mitral commissurotomy. Hence, valve replacement is generally the sole option currently available for the treatment of severe symptomatic severe AS or MS.

The role of Lp(a) in the development of VHD

Previous studies suggest that AS is an actively regulated process that involves several pathways including lipid infiltration, retention and oxidation, inflammation, and fibrocalcific remodelling of the aortic valve.³ Although data from animal models, Mendelian randomization, and retrospective studies^{3,4} suggest that LDL-cholesterol could be an important initiator of AS, three randomized clinical trials (SALTIRE, SEAS, ASTRONOMER)^{5–7} failed to demonstrate any significant benefit of aggressive LDL-cholesterol-lowering therapy with statins and/or fibrates in patients with mild to moderate AS. On the other hand, recent studies reported that genetic variation in the LPA locus, mediated by Lp(a) levels, is associated with higher incidence of aortic sclerosis and AS in the general population.^{4,8,9} In a substudy of ASTRONOMER, Capoulade *et al.*¹⁰ also reported that elevated plasma level of Lp(a) is a powerful independent predictor of faster AS progression, particularly in the younger patients. In contrast to AS, there is relatively few published data on the pathophysiology of degenerative MS. In the present study, Hojo *et al.*¹ found that Lp(a) is associated not only with AS but also with MS. These findings would suggest that degenerative MS shares with AS some common causative factors, including Lp(a). However, the study of Hojo *et al.*¹ has some significant limitations including (i) the cross-sectional and retrospective nature of the study, which precludes the demonstration of a cause–effect relationship between Lp(a) and stenotic valvular lesions; and (ii) the very small number ($n = 11$) of patients with MS, which considerably limits the statistical power and thus the robustness of the multivariable analysis for MS. In the large study by Thanassoulis *et al.*,⁴ genetic variations in the LPA locus was not associated with mitral annulus calcification. However, this previous study did not examine the association with MS. Despite its inherent limitations, the study of Hojo *et al.*¹ provides further support to the concept that Lp(a) is a factor associated with the development of AS

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and, in addition, it raises the hypothesis that Lp(a) may also be involved in the pathogenesis of degenerative MS.

About 20% of the general population have elevated Lp(a), and there is now a large body of evidence in experimental and clinical studies supporting the role of Lp(a) in the development of coronary artery disease, PAD, and VHD.¹¹ Among lipoproteins, Lp(a) is the main carrier of oxidized phospholipids (OxPL) in the bloodstream. When OxPL accumulate in the vascular or valvular tissues, they are recognized by the immune system as danger-associated molecular patterns (DAMPs). The response of the immune system in trying to clear DAMPs is to generate inflammation, which then mediates atherogenicity. Furthermore, OxPL are transformed into lysophosphatidylcholine (LPC) by the lipoprotein-associated phospholipase A₂ (Lp-PLA₂) enzyme. In turn, LPC provides a substrate for the autotaxin enzyme, which produces lysophosphatidic acid (LPA).¹² Both LPC and LPA have been shown to promote the osteogenic differentiation and calcification of vascular and valvular cells. Hence, Lp(a) and associated OxPL could, through their pro-inflammatory, pro-atherogenic, and pro-calcifying properties, contribute to the development of both PAD and degenerative stenotic valvular lesions. On the other hand, these factors likely have little role in the pathogenesis of regurgitant valvular lesions, which involve more myxomatous degeneration rather than calcific degeneration. These findings may explain, at least in part, why in the study of Hojo *et al.*¹ Lp(a) was associated with AS and MS but not with AR, MR, or TR.

Lp(a)-lowering therapy in VHD

When analysed collectively, the findings reported in the literature, including the present study,^{1,4,8–10,13} support a role for Lp(a)/OxPL/LPC/LPA pathway in the development and progression of AS and thus provide an impetus for the realization of a randomized clinical trial of Lp(a)-lowering therapy in this population. However, the Lp(a) circulating levels are, in large part, determined genetically, and currently available drugs such as niacin only achieve minimal reduction in Lp(a) and have several important side effects. Recently, antisense oligonucleotide directed to Apolipoprotein A has been developed and has been shown to reduce Lp(a) levels by >80% with minimal side effects.¹⁴ PCSK9 inhibitors may also reduce Lp(a) by 20–30%. The next step is to test the efficacy of these new drugs to slow the progression of AS.

Conclusion

The study of Hojo *et al.*¹ provides further arguments to implement systematic screening of Lp(a) in patients with PAD and/or VHD and

to undertake randomized trials to assess the effect of Lp(a)-lowering therapy in patients with AS. This study also suggests that Lp(a) may also be involved in the development of degenerative MS, but further studies in larger series of patients are necessary to confirm this hypothesis and eventually consider a Lp(a)-lowering trial targeting this population.

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