REVIEW

Dyslipidemia and aortic valve disease

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Purpose of review
Degenerative aortic stenosis (AS) is one of the most prevalent heart valve diseases in the adult population. The understanding of AS pathophysiology and involved risk factors have recently undergone a great advance, with low-density lipoprotein cholesterol (LDL-C), lipoprotein (a) [Lp(a)] and other clinical conditions taking on a relevant role. Although little is known about the prevention of AS, we can progressively find more evidence of the possible use of drugs to control risk factors as tools that may delay the progression to severe AS and aortic valve replacement.

Recent findings
Several factors have shown to be solid predictors of the development of AS. Mendelian randomization and observational studies on risk factors specifically lipid factors, such as hypercholesterolemia, Lp(a), proprotein convertase subtilisin/kexin type 9 and hypertension have provided meaningful new information. The SAFEHEART study has significantly contributed to define the role of LDL-C and Lp(a) in AS.

Summary
In this review we discuss the interrelationship of dyslipidemia, especially hypercholesterolemia and Lp(a) in the development and prognosis of valvular AS. New imaging tools may contribute to its early detection. Future studies with proprotein convertase subtilisin/kexin type 9 inhibitors and specific therapies to lower Lp(a) might contribute to delay AS development.

Keywords
aortic valve replacement, familial hypercholesterolemia, low-density lipoprotein cholesterol, lipoprotein (a), valvular aortic stenosis

INTRODUCTION

Degenerative aortic valve stenosis (AS) is the most common acquired valvular heart disease in the adult population in the western communities. Its prevalence, due to the ageing of the population, is progressive and rapidly increasing, becoming a crucial problem on public health and healthcare resources. The prevalence of AS in patients 65 years or older ranges between 2% and 7% [1] and seems to have a similar prevalence in both genders. In a recent study it was evidenced that the burden of unknown AS in the elder general population in Spain is higher than expected; indeed, AS was present in 4.2% of studied population with an age-related dependency on its prevalence [2].

Nowadays, there is no treatment to prevent the development of AS. It goes unnoticed in many instances, and it is only treated in final stages, when it is severe and symptomatic, by means of transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (AVR). Such procedures are not free from complications and represent a burden in healthcare budgets [3]. In addition, if TAVR or AVR interventions are not performed at an appropriate time, severe AS can lead to increased morbidity and mortality. The benefit of an early treatment has been recently shown in asymptomatic patients with severe AS [4▪,5].

Aortic valve stenosis is a consequence of a complex disease with genetic and nongenetic risk factors. Among these, lipid factors such as low-density lipoprotein cholesterol (LDL-C) and lipoprotein (a) [Lp(a)] play an important causal association. The aim of this review is to provide an update on the recent knowledge concerning AS risk factors and its

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KEY POINTS

- LDL cholesterol and lipoprotein (a) are involved in the development of AS. The strongest scientific evidence comes from the observational studies of patients with familial hypercholesterolemia.
- Patients with familial hypercholesterolemia and elevated lipoprotein (a) have an increased risk for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic stenosis.
- In addition to LDL cholesterol and lipoprotein (a), there are other factors such as hypertension, proprotein convertase subtilisin/kexin type 9 (PCSK9) and triglycerides that can contribute to the development of AS.
- New treatments are opening a bright future for the prevention of AS and thus for reducing the need of aortic valve replacement interventions.

subsequent control to try to prevent or slow down the progression of severe AS.

PATHOPHYSIOLOGY AND RISK FACTORS (Fig. 1)

AS isan inflammatory and degenerative disease mainly caused by endothelial damage. It is a complex physiopathological process that implies lipid infiltration and oxidation, chronic inflammation, progressive fibrosis and calcification [6], ending up in the narrowing the aortic valve area to a critical point. The development of AS is related to atherosclerosis and share common risk factors, including age, hypertension and hypercholesterolaemia [6,7▪].

The risk factors associated to AS can be categorized in three types: Degenerative factors, hemodynamic factors and metabolic factors. In our recently published SAFEHEART long-term prospective cohort study, increasing age (a degenerative biological factor), hypertension (a hemodynamic factor) and elevated Lp(a) and Lp(a)-corrected LDL-C-years (two metabolic factors), were demonstrated to participate in the appearance of severe AS [8▪▪]. Furthermore, once deposited, causes a hemodynamic alteration locally, independent from hypertension that contributes to stenosis. In this review, we will focus on the metabolic component of the physiopathology of AS.

Regarding metabolic factors, Mendelian randomization data show that elevated LDL-C and Lp(a) both contribute to the development of AS [9–11]. The development of AS is well recognized to occur at early stages in patients with homozygous FH, a condition with extremely high levels of LDL-C [12]. But AS also occurs in patients with heterozygous familial hypercholesterolaemia (FH). In a large Mendelian randomization study, genetic predisposition to high LDL-C levels was associated with increased risk of aortic valve calcification and AS [9]. Furthermore, Mundal *et al.* reported that increased LDL-C due to FH increases the risk of severe AS and subsequent AVR [7▪]. Mendelian randomization data testify to causal roles of elevated LDL-C and Lp(a) in the development of AS [9,11]. Accordingly, these lipoproteins may conjointly contribute to the initiation and propagation phases.

It has been recently shown that genetically determined exposure to raised lipid levels, specifically LDL-C and triglycerides (TG), significantly increased the risk of AS. After adjustment for other

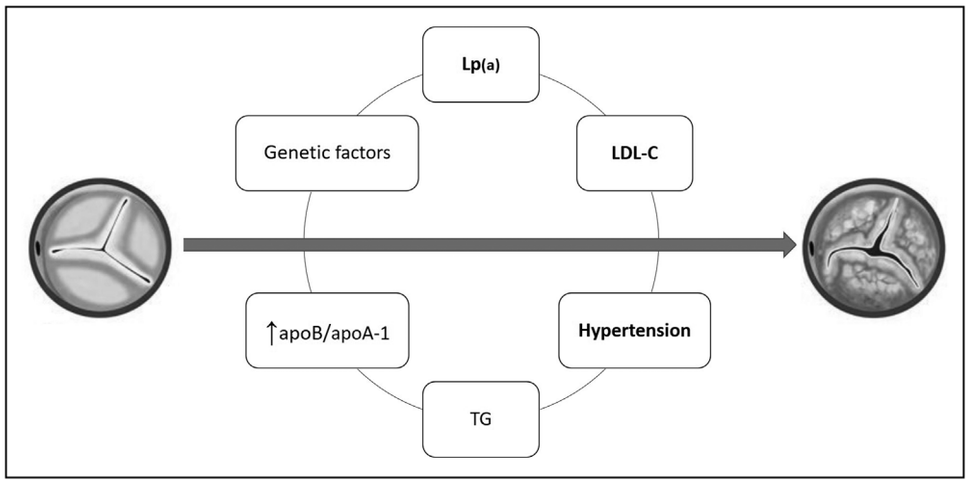

FIGURE 1. Risk factors for the development of AS. AS, aortic stenosis.

lipid parameters, the findings confirmed the causal association between LDL-C and AS. This study clearly demonstrated that lipids play a role in the aetiology of AS and it is a landmark to guide lipid-lowering strategies to reduce the incidence of AS [13▪▪].

There is also evidence suggesting a role for TG-rich lipoproteins and their remnants. Kaltoft *et al.* using Mendelian randomization and data from the Copenhagen General Population Study [14], found that higher TG and remnant cholesterol were observationally and genetically associated with increased risk of AS, providing the rationale for the role of elevated TG-rich remnant lipoproteins as potential drivers of AS, probably also involving inflammation. Supporting these findings a new study has shown that low levels of LDL-C are likely to prevent aortic aneurysm, AS and coronary artery disease although it may increase thromboembolic risk [15]. In other study from the Swedish Apolipoprotein MOrtality RISk (AMORIS) cohort an elevated apoB/apoA-1 ratio was associated with an increased incidence of AS [16].

A recent meta-analysis including 10 studies investigated the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition as a therapeutic strategy in calcific AS. The authors found that calcific AS was less prevalent in carriers of the PCSK9 R46L variant, associated with lower LDL-C and Lp(a) levels and a lower risk of calcific AS, compared with no carriers and that the PCSK9 expression was higher in the aortic valves of patients suffering from calcified AS compared with control patients. Furthermore, they found that PCSK9 neutralizing antibody significantly reduced calcium accumulation [17]. These findings highlight the potential role of PCSK9 inhibitors in the inhibition of AS development and support LDL-C reduction for optimal coronary disease reduction and potential slow-down of the progression of AS.

High Lp(a) concentrations found in 10–20% of the population have long been linked to increased risk of ischemic cardiovascular disease, including AS [18]. A major impact of Lp(a) per se on progression of AS has been supported by several studies. The mechanisms involved include valvular deposition of oxidized phospholipids, autotaxin mediated generation of phosphatidic acid, activation of the nuclear factor-kB inflammatory cascade, and calcification due to induction of alkaline phosphatase [19,20]. Faster progression of AS and need for AVR are directly dependent on elevated Lp(a) and specifically the particle content of oxidized phospholipids [19,21]. Furthermore, the crucial role of Lp(a) could explain the limited effectiveness of the cholesterol-lowering therapy on AS [22,23]. Statins and ezetimibe lower plasma levels of LDL-C but not Lp(a) and statins might actually increase Lp(a) [24]. Furthermore, LDL-C levels are not associated in some studies with the need for AVR due to AS; a potential explanation for this finding might be a low reduction of LDL-C by statins or that the estimated LDL-C contains about 20% of Lp(a)-cholesterol [25]. Consistent with this, in an exploratory analysis of the FOURIER trial, higher Lp(a) levels, but not Lp(a)-corrected LDL-C levels, were associated with a higher risk of cardiovascular events, including AVR [26▪,27]. PCSK9 inhibitors, theoretically, could constitute a new alternative to slow-down the development of AS probably by lowering Lp(a) and LDL-C levels [23]. PCSK9 inhibitors and specific therapies to reduce Lp(a) are required to address the residual risk attributed to atherosclerotic cardiovascular disease (ASCVD) and AS in FH [24,28]. Recently, profound reductions in Lp(a) levels have been achieved with apo(a) antisense therapy that targets hepatic apo(a) messenger ribonucleic acid (mRNA) and safely reduces Lp(a) concentrations by up to 92.4% in patients with and without established ASCVD, at least in shorter-term trials [29,30▪].

In the development of AS, no clear differences have been found in terms of gender. A recent study evaluated the impact of sex on the management and outcome of patients according to AS severity, with women representing 42% of the study cohort, and concluded that women had the same degree of AS severity than men [31].

PREDICTORS OF SEVERE AORTIC VALVE DISEASE IN FAMILIAL HYPERCHOLESTEROLEMIA

Undoubtedly, the FH patients have provided the highest evidence on the pathophysiology and risk factors for AS. Results obtained from our own research program with the SAFEHEART cohort and using a long-term follow-up period of a real-life cohort, showed the predictive factors for AVR in patients with heterozygous FH. The incidence rate of AVR was 4.36 times higher in patients with FH than in nonaffected relatives. In addition, the average incidence of AVR in patients with FH was 1.7 cases for 1000 patients-year compared with a corresponding incidence of 7.7-fold for ASCVD [32]. We showed that AS in FH was associated with sustained elevation in LDL-C levels, age, hypertension and elevated Lp(a) [8▪▪,33]. The results of our study may lead to a new paradigm for managing patients with FH centred on preventing the development of AS by targeting the total intensity and time of exposition to LDL-C, elevated Lp(a) and

hypertension more than waiting to the stenosis to be severe and requiring mechanical treatment. Thus, reduction in LDL-C and Lp(a) together with control of hypertension could retard the progression of AS in FH, but this needs testing in a clinical trial. Moreover, the prevalence of high Lp(a) is higher than 30% in FH patients, therefore its screening is recommended at least once in this population [34,35].

One aspect to take into account, closely related to what we are here discussing, is that the development of treatments might be a new window to explore how to stop or, at least, slow down the development of AS and it should go hand in hand with a strategy to the early detection of aortic valve disease, before it reaches the stage of severity [36]. For instance, it will be useful to determine at what age and with what periodicity should patients with FH have an echocardiogram done. We consider that the use of other imaging techniques, such as quantification of aortic valve calcium by computed tomography, should be reserved for patients in whom the detection and quantification of valvular calcification could be used to modify their prognosis estimation [37].

THERAPEUTIC STRATEGIES FOR PREVENTION AND TREATMENT OF AORTIC STENOSIS. ARE WE ABLE TO AVOID AORTIC VALVE REPLACEMENT? (Table 1)

Unfortunately,no effective medical therapy has been identified to prevent or slow down the progression of AS, and consequently AVR is the only effective treatment to improve symptoms or prognosis [27]. In addition, 40% of patients require concomitant coronary artery bypass grafting [37]. This finding is similar to our own finding obtained from the SAFEHEART study in which 46% of patients suffered from concomitant coronary heart disease and 34% underwent simultaneous AVR and coronary revascularization [8▪▪].

The treatment for hypercholesterolemia with statins and ezetimibe has not proven to reduce AS progression in the long term, although some benefit was observed in a subset of patients with mild AS and high pretreatment LDL-C levels [38,39]. Older patients with FH in prolonged statin treatment show a higher frequency of AS than controls. Independent risk factors for AS were age and LDL-C levels before treatment, whereas duration of statin treatment was not associated with AS. These results suggest that elderly patients with FH should be monitored for the presence of aortic disease and emphasize the importance of early lipid-lowering treatment in this high-risk population to prevent not only coronary disease, but also AS [40].

With the recently developed gene silencing technology new therapies may appear to stop or at least to delay the progression of AS [41▪]. Furthermore, preliminary studies have shown that PCSK9 inhibitors, statin/ezetimibe combination and Lp(a)-lowering agents are promising candidates in the prevention of AS progression. Focused management of increased levels of Lp(a) is a therapeutic option. Since PCSK9 is produced and secreted by aortic valves, PCSK9 inhibition could represent a therapeutic strategy for AS [17]. PCSK9 inhibitors and specific therapies that lower Lp(a) might be involved in the fight against the residual risk of ASCVD and AS. As discussed before, intense reductions in Lp(a) levels have been achieved with apo(a) antisense therapy that targets hepatic apo(a) mRNA and reduces Lp(a) concentrations in patients with and without established cardiovascular disease, at least in shorter-term follow-up [29,30▪]. Future studies should definitely assess the relationship between Lp(a) and rates of progression of AS and the response to specific Lp(a) lowering therapy [30▪], but we think that dedicated trials for AS with PCSK9 inhibitors and Lp(a)-lowering therapies are needed to test the hypothesis that AVR interventions can be either reduced or avoided with medical treatment. Finally, preclinical studies show that new oral anticoagulants may inhibit valvular inflammation and coagulation activation and might delay the rate of AS progression [42].

Although we await the outcomes of the new anti-Lp(a) ongoing randomized trials to provide final evidence of causality and to assess the potential clinical benefit of new potent Lp(a) lowering therapies, we must strictly control LDL-C levels and other hemodynamic risk factors such as hypertension which are associated with higher rates of mortality and ischemic coronary events in patients with AS.

Table 1. Efficacy of drugs to revert, stop or delay the progression of aortic stenosis

	Ineffective	Possibly effective
Statins	X	
Ezetimibe	X	
Statins-ezetimibe combinations		x
PCSK9 inhibitors		x
Lipoprotein(a)-lowering agents		x
New oral anticoagulants		x

CONCLUSION

AS is common and it is expected to rapidly increase in prevalence with the aging of the population. In addition to aging, clinical risk factors for the development of AS are similar to those for ASCVD and include hyperlipidaemia, increased Lp(a) and hypertension. Increased information about the pathophysiology and risk factors for the development of AS is rapidly increasing, largely thanks to the knowledge provided by patients with FH that have frequently elevated Lp(a) levels. This knowledge is the basis for the development of new treatments and imaging tools that would signify that AVR will not be the only solution to offer to our AS patients.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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