Opinion Paper

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in aortic stenosis - Is this the light at the end of the tunnel for patients with aortic stenosis?

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A B S T R A C T

The exploratory analysis of FOURIER trial has offered a ray of hope for patients with nonrheumatic aortic stenosis (AS). At present, the only definitive treatment of severe AS is aortic valve replacement (AVR). Despite transaortic valvular replacement revolutionizing the treatment of AS, it still remains a progressive condition, with no disease-modifying pharmacotherapy. Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, eplerenone, nitrates and statins all have been tried previously but failed to slow down the progression of aortic stenosis. Recently, there has been an emerging role of lipoprotein A [Lp(a)] in the pathogenesis of AS. This raises the possibility that long-term therapy with specific emphasis on Lp(a) reduction may reduce or slow the progression of AS.

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1. Introduction

Based on population based recent echocardiographic studies, the prevalence of calcific aortic stenosis is 1%–2% in persons aged 65 and above and 12% among persons 75 and above. In populations older than 75, 3.4% have severe AS.1 The prevalence of aortic valve sclerosis alone, seen as irregular thickening or calcification of the leaflets, ranges from 9% in populations with a mean age of 54 years to 42% in populations with a mean age of 81 years. The annual rate of progression from aortic sclerosis to AS is 1.8%–1.9%.2 As the world and Indian population in particular grows older, the prevalence of AS is expected to increase two to three fold in the near future. Calcific degenerative aortic valve disease (58.1–65%) is the most common cause of AS in India followed by congenital bicuspid, unicuspid or tricuspid valve (25–33.9%) rheumatic heart disease (1.1–2.9%), and familial hypercholesterolemia.3,4

2. Pathogenesis of nonrheumatic AS

The pathophysiology of AS involves multiple molecular, cellular, and tissue-level processes and is similar to vascular atherosclerosis (Fig. 1). AS is associated with similar epidemiologic risk factors as cardiovascular diseases including smoking, hypertension and hypercholesterolemia, and treating or preventing these risk factors may reduce the risk of developing AS. The precursor of AS is aortic sclerosis, and it is independently associated with an increased risk of myocardial infarction and cardiovascular all-cause mortality, even in the absence of AS.5 The mechanical stress on an otherwise normal valve has traditionally been considered to cause calcific AS. Pathogenesis includes three main steps-valvular lipid deposition into intima cusps, subsequent lipid oxidation and inflammation followed by a cycle of progressive valve calcification.

The first step in aortic sclerosis is a damaged endothelium in an at-risk valve leading to lipid infiltration, specifically low-density lipoprotein (LDL) and lipoprotein(a) [Lp(a)], which triggers the recruitment of inflammatory cells into the aortic valve. Production of reactive oxygen species (ROS) by uncoupled nitric oxide synthase (NOS) leads to increased lipid oxidation and intense secretion of cytokines such as Interleukin 6.6 A hypercholesterolemic diet and higher levels of oxidized LDL contribute to leaflet thickening, macrophage infiltration, and fibro calcification. Enzymes transported in the aortic valve by LDL and Lp[a] such as lipoprotein-associated phospholipase A2 (Lp-PLA2) and ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), also known as autotoxin (ATX), produce lyso phosphaticid derivatives. ATX, which is also secreted by valve interstitial cells (VIC), transforms...
lysophosphatidylcholine (lysoPC) into lysophosphatidic acid (lysoPA). LysoPA and the receptor activator of nuclear factor-
phatase/phosphodiesterase 2 (ENPP2), also known as autotoxin (ATX), produce lysophospholipid derivatives. ATX, which is also secreted by valve interstitial cells (VIC), transforms
such as Interleukin-6 (IL-6). Enzymes transported in the aortic valve by LDL and Lp[a] such as lipoprotein-associated phospholipase A2 (Lp-PLA2) and ectonucleotide pyrophos-
ligand (RANKL) promote the osteogenic transition of VIC. 8

3. Role of Lp(a) in AS

‘Kaare Berg’ in 1963 discovered the Lp(a), and elevated Lp(a) levels were considered a cardiovascular risk factor.13,14 There are multiple proposed mechanisms by which Lp(a) can lead to AS. Lp(a) consists of LDL bonded with apo (a) and in the blood stream, it attaches to aortic valve, just like LDL cholesterol to coronary ar-
terries. The progressive accumulation leads to AS through the mechanism as discussed above. Other mechanism is due to simi-
larity of apo (a) with plasminogen. Plasminogen is the zymogen of plasmin, the major enzyme that degrades fibrin clots. By competing with plasminogen, it promotes thrombosis at aortic valve. Physi-
ologically, Lp(a) accumulates at wound healing sites.15 The mechanical stress at aortic valve causes subclinical injury and promotes accumulation of Lp(a) and LDL cholesterol and leads to AS.

4. Role of PCSK9 in AS

PCSK9 is primarily expressed in the liver, is a crucial protein in lipid metabolism as it degrades the LDL receptor. There can be a direct or indirect association between PCSK9 levels and AS. The PCSK9R 46L loss-of-function mutation has been associated with lower levels of Lp(a) and LDL cholesterol, and reduced risk of aortic valve stenosis and myocardial infarction.16 The expression of PCSK9 in the aortic valves hypothesized the independent association of PCSK9 with AS, as reported in small human and animal studies.17,18

5. Strategies for prevention of progression of AS

Given the correlation between hypercholesterolemia and AS, statins were hypothesized to reduce the incidence of calcific AS.19–22 Indeed, the first prospective study by Moura et al, comparing rosuvastatin 20 mg/day to placebo daily in 121 asymptomatic patients with moderate to severe AS followed up for a mean of 73 ± 24 weeks, the change in aortic valve area and the increase in aortic valve velocity were less in the rosuvastatin group.19 However, the initial enthusiasm was curbed following dedicated randomized controlled trials comparing high intensity statin therapy with AS progression. One possible explanation is that low-density lipoprotein cholesterol (LDL-C) is not the principal lipid mediator of calcific AS, and Lp(a) may be more centrally implicated in the pathogenesis of AS than LDL-C. Table 1 summa-
rizes the studies of statins in delaying the progression of AS.

The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial23 was a randomized, double blinded, placebo-controlled trial of evolocu-
mab (PCSK9 antibody) (either 140 mg every 2 weeks or 420 mg
of apolipoprotein(a) inhibitor, reduces Lp(a) levels significantly. However, the FOURIER trial enrolled only known atherosclerotic cardiovascular disease patients, and the results may not be applicable to the general population. Secondly, this was a post hoc analysis of the Fourier trial, with unknown baseline prevalence and severity of AS. Hence, the initial excitement must be tempered in view of important limitations of this study. Firstly, this was a single center experience.

Table 1
Clinical studies of role of statins in delaying the progression of Aortic stenosis.

| Author (Study) | Design of Study, Study population | Results | Interpretation |
|---------------|-----------------------------------|---------|----------------|
| Moura et al. | Open-label, prospective study of rosuvastatin 80 mg daily (n = 61) versus placebo daily (n = 60). Population with asymptomatic moderate to severe aortic stenosis (aortic valve area ≥ 1.0 cm²) | Significant decrease in change in aortic valve area and aortic valve velocity in patients treated with rosuvastatin 20 mg daily when compared with placebo | First prospective study showing potential benefits of statin in slowing the hemodynamic progression of AS |
| Cowell et al. | Randomized control trial of 80 mg of atorvastatin daily (n = 77) versus placebo (n = 78). Population aged >18 years with aortic stenosis, aortic-jet velocity of at least 2.5 m/s, and aortic valve calcification on echocardiography | No significant difference in change in aortic-jet velocity by Doppler echocardiography and change in aortic valve calcium score by helical computed tomography | Intensive lipid-lowering therapy does not halt the progression of calcific AS or induce its regression |
| Rosseba et al. | Randomized controlled trial of 40 mg of simvastatin plus 10 mg of ezetimibe daily (n = 943) versus placebo daily (n = 929). Population with mild-to-moderate, asymptomatic aortic stenosis | No significant difference in primary and secondary outcomes in aortic-valve-related events. No significant difference in peak aortic-jet velocity between two groups. | No reduction in events related to AS |
| Chan et al. | Randomised control trial of rosuvastatin 40 mg daily (n = 134) versus placebo (n = 135). Population with mild to moderate AS | No significant difference in increase in the peak AS gradient between rosuvastatin and placebo. | Rosuvastatin should not be used for the sole purpose of reducing the progression of AS. |

(monthly) or matching placebo as subcutaneous injections in patients with known atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per decilitre or higher who were receiving statin therapy. The results reported a reduction in LDL-C by 58% from baseline by evolocumab, as compared with placebo. Bergmark et al. performed the exploratory analysis of the trial. The primary outcome was AS events, which were new or worsening AS or aortic valve replacement. After a median follow up of 2.2 years, the primary events occurred in 63 patients. The results reported that the elevated Lp(a) levels were associated with higher rates of AS events (adjusted hazards ratio [aHR], 1.55 [95% CI, 1.17–2.05] per SD; p = .002), including AVR (aHR, 2.22 [95% CI, 1.38–3.58] per SD; P = .001), and no significant association between the corrected LDL cholesterol levels and AS events (aHR, 1.23 [95% CI, 0.93–1.61] per SD; P = .14). Therefore, a significant association between week-12 Lp(a) concentration and AS events, especially AVR. Patients assigned to receive evolocumab had numerically lower incidence of AS events (0.27% [95% CI, 0.17%–0.44%]) than patients assigned to receive placebo (0.41% [95% CI, 0.28%–0.59%]). The benefit of evolocumab was seen after 1 year of treatment. The overall HR for AS events with evolocumab was 0.48 (95% CI, 0.25–0.93) beyond one year of treatment. The conclusion of the post hoc analysis was that it was the higher Lp(a) levels, and not Lp(a)-corrected LDL cholesterol levels, which correlated significantly with a higher risk of subsequent AS events, including AVR. The higher reduction of Lp(a) levels with PCSK9 might explain the benefit in AS. However, the initial excitement must be tempered in view of important limitations of this study. Firstly, this was a post hoc analysis of the Fourier trial, with unknown baseline prevalence and severity of AS. Secondly, the FOURIER trial enrolled only known atherosclerotic cardiovascular disease patients, and the results may not be applicable to the general population.

Other novel therapies such as ISIS-APO(a)Rx, a hepatic synthesis of apolipoprotein(a) inhibitor, reduces Lp(a) levels significantly. Niacin, antisense-specific Lp(a) inhibitors and recombinant apolipoprotein A-1 Milano, an anti-inflammatory molecule that reverses cholesterol transport are also promising alternatives. Use of bisphosphonates, calcitonin, and estrogen receptor modulators for the treatment of osteoporosis has also shown a strong and independent association with decreased progression of AS. Furthermore, therapies like Taladafli, Ataciguat, vitamin K2 and Phytine are currently being evaluated for their efficacy on long term benefits in AS patients. Precision medicine which involves standard clinical evaluation along with synthesis of data, imaging, or laboratory tests and genomics is the future in the management of AS patients.

6. Conclusion
Clinical and experimental studies aimed at finding therapeutic targets have failed to alter the natural course of AS in humans in the past. Nonetheless, PCSK9 inhibitors might be beneficial in decelerating the progression of the AS along with investigational chemical therapies but one must bear in mind that these findings require validation in dedicated randomized control trials and can only be considered as hypothesis-generating at present.

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Declaration of competing interest
We have no conflicts of interests.

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