

Aortic stenosis: new pathophysiological mechanisms and future perspectives for pharmacological therapy

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Aortic stenosis (AS) is the most common form of valve disease in the world and a rapidly increasing public health burden (especially in the elderly). AS occurs in almost 10% of adults over the age of 80 years, with a mortality about 50% at 2 years, unless valvular stenosis is relieved by intervention (aortic valve replacement or transcatheter aortic valve implantation).

In a recent study on AS patients, Lis et al.¹ used an attractive “double-assessment” methodology. Firstly, an indirect assessment was based on the measurement of biomarkers in serum before valve replacement, and secondly, excised valves were evaluated in a pathomorphological examination. The preoperative low concentration of osteoprotegerin (OPG) in plasma was associated with the presence of intravalvular osteoclastic differentiation in a histopathologic analysis in excised valves.¹ From the clinical point of view, this observation is important because plasma OPG levels (in preoperative measurement) are related to postoperative outcome.² Accordingly, patients with low OPG levels have a more favorable outcome in the postoperative follow-up in comparison with patients with high OPG levels, which may help identify individuals with poor improvement of symptoms during long-term follow-up after aortic valve replacement.²

In a preoperative echocardiographic examination, high OPG levels were associated with pathological left ventricular and left atrial remodeling.² In line with the results by Ueland et al.,³ high OPG levels were associated with all-cause mortality in patients with symptomatic AS in the analysis of combined follow-up (including both patients with and without valve replacement), even after adjustment for conventional risk markers. The strongest association was obtained by using a combination of high levels of both OPG and N-terminal pro-B-type natriuretic peptide. The authors³ have suggested that these markers may

reflect distinct pathways in the development and progression of AS.

The inflammation/calcification/ossification processes have been extensively monitored by various biomarkers⁴ indicating dysregulated mechanisms responsible for aortic valve damage. However, targeted medical therapies capable of modifying disease progression are not available yet.

AS can be divided into 2 distinct stages: an early initiation phase, dominated by valvular lipid deposition, injury, and inflammation, and a later propagation phase, where procalcific and pro-osteogenic factors take over and ultimately drive disease progression.⁵

The link between lipid, inflammation, and calcification in these early stages and the pathological similarities with atherosclerosis led to the hypothesis that treatment with statins might be beneficial in AS patients. This was supported by human data (RAAVE study)⁶ and experimental studies in hypercholesterolemic animal models,⁷ demonstrating that lipid deposition and oxidative stress precede the conversion of valvular interstitial cells to those with an osteoblastic phenotype, and that this process is inhibited by statins. However, when statins were prospectively tested in randomized controlled trials (SALTIRE,⁸ AS-TRONOMER,⁹ and SEAS¹⁰), each demonstrated a failure of this therapy to halt or retard AS progression. This observation has led researchers to analyze again the pathophysiology of AS underlying AS and to the observation that although inflammation and lipid deposition may be important in provoking or establishing the disease (the initiation phase), the later stages are characterized instead by a self-perpetuating cycle of calcium formation, resulting in valvular injury (the propagation phase). Indeed, once this propagation phase has become established, disease progression is governed neither by inflammation nor by lipid deposition, but rather by the relentless

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accumulation of calcium in the valve leaflets. This may explain the failure of statins to modify AS progression, which commonly presents beyond the initiation phase (SALTIRE,⁸ ASTRONOMER,⁹ and SEAS¹⁰ studies). Statin therapy did not modify progression in moderate to severe AS, but in early stage (aortic sclerosis or mild AS), statins reduced the plasma level of biomarkers of calcification and ossification.¹¹ It is important because AS is a pathological process with similarities to skeletal bone formation.⁵

As our understanding of the pathophysiology of AS has improved, the key role that calcification plays in driving disease progression has led us away from targeting inflammation and lipid deposition and toward pharmacotherapies capable of directly preventing valve calcification. The close association between disorders of skeletal bone metabolism and increased calcification in the vasculature offers a potential starting point. A growing body of preclinical and clinical findings indicates that treatments for osteoporosis, such as bisphosphonates and denosumab, can reduce vascular calcification and that these agents hold considerable promise as protective pharmacotherapies for AS.

Bisphosphonates (widely used for the treatment of osteoporosis) are inhibitors of osteoclast-mediated bone resorption. Importantly, bisphosphonates also have cardiovascular effects, demonstrating a consistent reduction in calcification both of the vasculature and the aortic valve. They reduce the production of interleukin (IL) 1 β , IL-6, and tumor necrosis factor α (key inflammatory cytokines implicated in the early stages of AS) and inhibit the secretion of matrix metalloproteinases 2 and 9, which remodel the valve as AS progresses. Moreover, nitrogen-containing bisphosphonates operate as inorganic pyrophosphate analogs, which have significant anticalcific properties in the vasculature. Additionally, bisphosphonates attenuate the differentiation of aortic valve myofibroblasts into cells with an osteogenic phenotype, the key step in triggering the propagation phase of AS. A recent study¹² indicated that bisphosphonate treatment was associated with less valvular and vascular calcification in older women. Other studies appear to support these findings with a beneficial effect of bisphosphonates on echocardiographic measures of AS progression.¹³⁻¹⁵ The true independent effect of bisphosphonates in AS will only be proven after a randomized controlled trial.

As concerns the other mechanisms, the OPG/RANK/RANKL system appears to play a pivotal role in aortic valve calcification and may provide an explanation for the link between osteoporosis and increased vascular calcification. Therefore, it represents an attractive therapeutic target for reducing vascular/valvular calcification. Denosumab is a human monoclonal antibody to RANKL that prevents its binding to RANK. In a murine model of osteoporosis, denosumab has effectively reduced aortic calcification.¹⁶

Bisphosphonates and denosumab hold promise as novel treatments for AS and are currently being investigated in an ongoing randomized controlled trial, SALTIRE II.¹⁷ The ability of lipoprotein(a)-lowering treatment to modify AS progression is likely to form the basis of a future clinical trial.

Summarizing, recent insights into the pathophysiology of AS have documented that although lipid and inflammation may be important in establishing the disease (initiation phase), it is the self-perpetuating processes of calcification that are predominantly responsible for driving disease progression (propagation phase). Despite the early enthusiasm that statins may slow the progression of AS, recent large clinical trials did not consistently demonstrate a decrease in the progression of AS. However, it is possible that statins may have a benefit in early stage of the disease process, where inflammation (and not calcification) is the predominant process. Positron emission tomography using ¹⁸F-fluorodeoxyglucose and ¹⁸F-sodium fluoride can visualize the relative contributions of valvular calcification and inflammation in AS, and thus this attractive method might be useful in providing the answer as to whether pharmacotherapeutic interventions at the earlier stages of AS would be more effective in slowing the progression of the disease.

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