Statin therapy of calcific aortic stenosis: hype or hope?

Volker Liebe, Martina Brueckmann, Martin Borggreffe, and Jens J. Kaden*

First Department of Medicine (Cardiology), University Hospital Mannheim, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany

Received 12 October 2005; revised 17 November 2005; accepted 1 December 2005; online publish-ahead-of-print 6 January 2006

KEYWORDS
Aortic valve stenosis; Calcification; Inflammation; HMG-CoA reductase inhibitors; Risk factors; Atherosclerosis

Calcific aortic stenosis, with a prevalence of 3–9%, is the most frequent heart valve disease and the main cause for valve replacement in patients over 60 years of age. Once thought to be caused by a passive calcium precipitate within the aortic valve leaflets, there is now increasing evidence that development and progression of calcific aortic valve disease may be triggered by underlying genetic and cardiovascular risk factors, and is regulated by an active cellular process involving inflammatory pathways.

Targeted drug therapy to prevent the progression of calcific aortic valve disease should ideally be based on the knowledge of risk factors and the molecular pathogenesis of the disease. Conflicting data exists on the potency of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e. statins) to influence both risk factors and inflammatory pathways by lowering lipid levels and exerting anti-inflammatory properties, respectively.

In this review, various aspects of the molecular pathogenesis of calcific aortic stenosis will be summarized and connected with recent experimental and clinical studies that address the potential benefit of the targeted drug therapy by statins in order to prevent the progression of the disease.

Introduction

Sclerotic changes of the aortic valve are common in the elderly. The prevalence of aortic valve sclerosis rises age-dependently, amounting up to 57% in octogenarians. It is considered that aortic valve sclerosis leads to valvular stenosis. The natural history of aortic stenosis includes a latency period followed by a more or less pronounced progression. Calcific aortic stenosis is the most common heart valve disease in industrialized countries and the main indication for surgical valve replacement in patients over 60 years of age. Currently, no medical therapies are approved for the prevention or treatment of this disease.

In this review, various aspects of the molecular pathogenesis of calcific aortic stenosis will be summarized (see also overview in Cowell et al.) and connected with experimental and clinical studies that were initiated to address the potential benefit of targeted drug therapy with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e. statins) in order to prevent the progression of the disease.

Risk factors and inflammation in the pathogenesis of calcific aortic valve stenosis

Histopathologically, sclerosis of the aortic valve is defined as a fibrous thickening and calcification of the valve cusps. Despite the high prevalence of this condition, the molecular mechanisms of the disease development and progression are not fully understood. According to traditional thinking, development and progression of calcific aortic valve disease results from passive calcium deposition within the aortic valve leaflets. Contemporarily, there is increasing evidence that the condition is regulated by an active cellular process, including an active and complex role for inflammation. Several, in part, population-based longitudinal studies found cardiovascular risk factors such as hypercholesterolaemia to have an impact on the development of degenerative aortic valve stenosis (overview in Rossebø and Pedersen). Studies by Otto et al. described an 'early lesion' that had much in common with the early lesion in atherosclerotic plaques, proposing the hypothesis of calcific aortic stenosis to be an atherosclerotic disease. The accumulation of T-lymphocytes in stenotic valves indicates that calcific aortic stenosis might be based on a chronic inflammatory process. Furthermore, genetic polymorphisms may have an impact on the development or degree of the calcification of stenotic aortic valves. Taken together, underlying genetic and cardiovascular risk factors are likely to contribute to the histologically demonstrated valvular macrophage and T-lymphocyte infiltration. Once resident in the valve, leukocytes can induce an inflammatory tissue milieu followed by an activation of myofibroblasts and increased cell proliferation by release of pro-inflammatory cytokines, such as interleukin (IL)-1β and tumour necrosis factor (TNF)-α. In addition, expression and activation of matrix metalloproteinases promotes the profound conversion of the valvular tissue. It has also been proposed that aortic valve calcification is an
actively regulated process that involves mechanisms of bone development.3-16 With TNF-α mediating the formation of an osteoblast-like phenotype of local myofibroblasts in stenotic aortic valves,4-21 development of aortic valve calcification may also be based on an inflammatory mechanism. Recent studies also suggest neoangiogenesis to be involved in the pathogenesis of non-rheumatic aortic valve stenosis.8,22-24 The present consideration of the pathogenesis of calcific aortic stenosis are summarized in the form of diagram in Figure 1.

Rationale for therapy with statins

Landmark clinical trials have demonstrated that statins reduce mortality in patients with atherosclerotic diseases, primarily by reducing LDL cholesterol serum levels.25-27 HMG-CoA reductase inhibitors have mechanisms of action that expand their effects beyond cholesterol lowering, and it has been suggested that these primarily anti-inflammatory mechanisms contribute to the positive results of the clinical trials.28 However, the degree to which certain clinical benefits of statins derive from such direct anti-inflammatory effects remain controversial. A clinical marker of inflammation is C-reactive protein, which is produced by the liver in response to pro-inflammatory stimuli. C-reactive protein has been suggested to contribute to the development of atherosclerosis.29 It was also increased in patients with degenerative aortic valvular stenosis.30 Statin therapy can significantly reduce serum C-reactive protein levels in primary and secondary prevention populations in a largely LDL-independent manner.31 Most recently, it has been shown that patients with low C-reactive protein levels after statin therapy have better clinical outcomes than those with higher C-reactive protein levels, regardless of the resultant level of LDL cholesterol.32 These studies suggest that statins are effective in decreasing systemic and vascular inflammation, at least in part, independently from their cholesterol-lowering capacity.

Mechanism of action of statins

Statins inhibit HMG-CoA reductase, the rate-limiting microsomal enzyme in cholesterol biosynthesis (Figure 2). The metabolic step, controlled by the enzyme, is the conversion of HMG-CoA to mevalonate, eventually resulting in a decline of plasma LDL.39 Lipid-lowering independent pleiotropic statin effects are believed to be based primarily on blocking the synthesis of important isoprenoid intermediates of the cholesterol biosynthetic pathway such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. By serving as...
lipid attachments, these intermediates control the localization and function of a variety of intracellular signalling molecules, especially the Rho family of small GTP-binding proteins, that play a crucial role in cytoskeletal remodelling, membrane trafficking, transcriptional activation, and cell growth control. Statins diminish the formation of isoprenylated and geranylgeranylated proteins through the mevalonate pathway, and provision of exogenous geranylgeranyl or farnesyl pyrophosphate can reverse many statin-mediated anti-inflammatory functions. As an additional mechanism of action, statins were shown to inhibit the de-stabilizing effects of mevalonate on nitric oxide synthase-mRNA in human endothelial cells (ECs), leading to enhanced synthesis and function of this enzyme.

Inflammation as a therapeutic target of statins in valve calcification

In vitro studies uniformly support anti-inflammatory roles of statins. Administration of these agents to cultured cells assumed to participate in atherosclerosis or valve calcification, diminishes pro-inflammatory functions implicated in the development of these states. In vitro, statins have been shown to decrease the expression of pro-inflammatory cytokines like TNF-α and IL-1β in ECs, macrophages, and to inhibit proliferation of smooth muscle cells (SMCs) via inhibition of Rho geranylgeranylation, respectively. Inhibition of HMG-CoA reductase reduced the synthesis of the chemokine macrophage chemoattractant protein (MCP)-1 and inhibited secretion of several matrix metalloproteinases (MMP-1, -2, -3, -9) from both SMCs and foam cell macrophages mediated by the inhibition of prenylation. Possible mechanisms include the downregulation of the activation of nuclear factor (NF)-κB, activator protein (AP)-1, and hypoxia-inducible factor-1α in cultured human endothelial and vascular SMCs. The activation of NF-κB regulates the expression of genes involved in mediating cellular migration, providing inflammation, and controlling the balance between cell proliferation and apoptosis.

Rho-like GTPases have been implicated in the activation of NF-κB. Genes regulated by the transcription factor AP-1 include MMPs, cytokines, chemokines, adhesion molecules, inducible nitric oxide synthase, and cell cycle proteins, respectively. Effects of statins on AP-1 DNA binding may be mediated by inhibited prenylation of the small GTP protein Ras or Rho. Thus, several lines of evidence suggest that anti-inflammatory effects of statins are mediated by non-sterol mevalonate-derived compounds. In addition, new mechanisms by which statins may modulate immune response have been described recently. Statins inhibit the interferon-γ-induced expression of class II major histocompatibility complexes (MHCII) on antigen presenting cells. Moreover, statins are able to selectively block the β2 integrin leukocyte function antigen-1 (LFA-1), thereby decreasing lymphocyte adhesion and impairing T-cell co-stimulation unrelated to the inhibition of HMG-CoA reductase. It has also been shown that statins decrease T-cell proliferation, probably via direct engagement of the T-cell receptor independently of MHCIII and LFA-1.

Several in vitro studies demonstrated a beneficial statin effect by preventing the progression of cardiovascular calcification: statins, as well as a specific inhibitor of Rho kinase, inhibited calcification of human vascular SMCs induced by inflammatory mediators. Similarly, statins inhibited calcification of aortic valve myofibroblasts by inhibiting the cholesterol synthetic pathway independent of protein prenylation.

In conclusion, administration of statins may be able to tackle several inflammatory pathways leading to valve calcification, including leukocyte/endothelial interaction, accumulation of inflammatory cells, migration to subendothelial sites of inflammation, and proliferation of SMCs.

Animal models

Several experimental models have been developed to understand the progression of calcific aortic stenosis. Recently, apolipoprotein E-deficient mice have been shown to display aortic valve sclerosis similar to that observed in human beings. Beneficial statin effects have been demonstrated in experimental settings using hypercholesterolaemic rabbits. Rajamannan et al. were able to induce valvular atherosclerotic changes and early bone matrix protein expression. Administration of the HMG-CoA reductase inhibitor atorvastatin reduced gene expression of osteoblast markers, including the bone matrix protein osteopontin, the essential osteoblastic transcription factor Cbfa-1, and the calcification-modulating enzyme alkaline phosphatase. However, C-reactive protein levels as markers of subclinical inflammation were not significantly lowered by statins in this model. In addition to its lipid-lowering effect, atorvastatin inhibited aortic valve calcification in the rabbit model. Although these data may provide an interesting perspective, the animal models will have to be optimized, and further evaluation is needed. Most notably, hyperlipidaemia alone is not sufficient to induce haemodynamically significant calcific aortic stenosis in the rabbit, as demonstrated by echocardiography.

Clinical studies and further directions of research

In an observational cross-sectional study, statin therapy was associated with reduced serum levels of vascular cellular adhesion molecules (VCAM) in patients with aortic stenosis, indicating a potential anti-inflammatory effect. Consistent findings in retrospective studies demonstrated a reduced progression rate of valve calcification of native and bio-prosthetic aortic valves in subjects treated with statins. Comparable results were obtained in the prospective, population-based study of Bellamy et al. Novaro et al. showed a reduced progression of aortic stenosis in statin-treated patients as assessed by a decrease in the peak gradient. Shavelle et al. also evaluated the effects of statin treatment on the degree of aortic valve calcification as measured by electron-beam computed tomography. In 211 patients with varying degrees of aortic stenosis, Rosenhek et al. demonstrated a significantly lower rate of disease progression in those treated with a statin when compared with those without statin therapy. The rate of disease progression was linked to LDL cholesterol serum levels in only two studies comprising 284 patients, whereas the other studies failed to demonstrate such a relationship.

The initial hopes placed in statin therapy were dampened recently, when the results of a prospective, randomized
controlled trial were reported by the SALTIRE investigators.\textsuperscript{72} In this study, with a mean follow-up of 25 months, a total of 155 patients with calcific aortic stenosis were assigned to receive either placebo or high-dose statin therapy (80 mg of atorvastatin daily). Patients who were already on statin therapy or were presumed to derive a potential benefit from statin therapy because of a pre-existing condition were excluded from the SALTIRE trial. Progression of aortic valve stenosis was assessed by echocardiography, and computed tomography was applied to examine valve calcification. As a result, intensive statin therapy did neither halt the progression of calcific aortic stenosis nor induced its regression.\textsuperscript{72} As pointed out by Rosenhek in the corresponding editorial, ‘in the retrospective trials, statin therapy was indicated for the treatment of hyperlipidaemia, whereas in the prospective trial, patients in whom statins were indicated for the treatment of hyperlipidaemia were excluded.’\textsuperscript{73} Overall statin treatment periods were longer in the retrospective studies, and there was a rather low prevalence of coronary artery disease in the trial. Thus, the selected patient group in the study may not completely reflect patients seen in the ‘real world’. As atherosclerosis is frequently associated with calcific aortic stenosis, statin therapy might influence the pathogenesis of calcification by reducing systemic inflammation in this patient group. Also, ‘pure’ calcific aortic stenosis without any atherosclerotic comorbidity is rare and might be based on other pathogenetic mechanisms than aortic stenosis accompanied by atherosclerosis.

In summary, the SALTIRE data have added importantly to our knowledge and slow down the initial expectations towards statin therapy. However, trial populations as well as treatment periods may influence the outcome. Furthermore, the pathogenesis of calcific aortic stenosis has not yet been resolved satisfactorily. Therefore, no final conclusion on the effect of statin therapy on the disease progression can be drawn presently. Meanwhile, the results of the ongoing large randomized clinical trials, e.g. the Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin (ASTRONOMER) study and the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, are awaited.\textsuperscript{74}

Further research should concentrate on the basic mechanisms involved in the pathogenesis of the disease. As more specific and effective therapies are warranted, the development of well characterized experimental models is critical to tackle pathways susceptible to medical therapy and to define the timing of therapy. Potential targets could include proximal triggers such as central signalling hubs in inflammation, and distal effectors such as mechanisms of bone-like transdifferentiation and tissue calcification. In addition, further studies of presumably predisposing genetic pathways may help identify other preventative and pharmacological approaches to slow the progression of this disease.

In summary, the concept of medical therapy of calcific aortic stenosis remains debated. Although, a major recent study showed no benefit of statin therapy, there is still hope that the disease may not represent an irrevocable destiny. The results of the ongoing trials are awaited eagerly. Meanwhile, patients with calcific aortic stenosis should be managed according to national and international clinical guidelines.\textsuperscript{75}

Conflict of interest: none declared.

References


Statin therapy of calcific aortic stenosis


Clinical vignette

doi:10.1093/eurheartj/ehi538

‘Hissing snake’ left ventricle thrombotic phase of hypereosinophilic endomyocardial disease

Maurizio Pieroni, Cristina Chimenti, and Andrea Frustaci*

Cardiology Department, Catholic University, Largo A. Gemelli 8, 00168 Rome, Italy

*Corresponding author. E-mail address: biocard@rm.unicatt.it

A 33-year-old girl with chronic allergic state and history of a recent travel in South-East Asiatic countries was admitted because of acute heart failure with pulmonary oedema. ECG revealed sinus tachycardia with diffuse T-wave abnormalities, whereas two-dimensional echocardiography in apical four-chamber view showed thickening of the mid-apical portion of left ventricular (LV) walls with almost complete apex obliteration and a restrictive LV filling pattern. Laboratory tests showed remarkable hypereosinophilia with cationic protein elevation. Cardiac catheterization revealed a marked increase in LV end-diastolic pressure and angiography showed obliteration of the LV apex by a mass centrally infiltrated by contrast medium (Panel A and Movie) resembling the shape of a snake head with forked tongue (Panel B). Multiple LV endomyocardial biopsies showed the presence of extensive eosinophil-rich endocardial thrombi (Panel C) with inner areas of organization (arrows), suggesting the thrombotic phase of an eosinophilic endomyocardial disease. Combination of steroids and anticoagulant therapy provided a rapid and significant improvement of clinical and echocardiographic picture. Hypereosinophilia, whatever its origin, causes a severe endomyocardial damage with endocardial thrombotic apposition when eosinophil degranulation with release of the cationic protein and factor X activation occurs.

End-diastolic frame from LV angiography (30° right anterior oblique view) (Panel A) showing significant obliteration of ventricular apex by a mass centrally infiltrated by contrast medium, resembling the shape of a snake head with forked tongue (Panel B). LV endomyocardial biopsy (Panel C) showed an extensive eosinophil-rich thrombus with inner areas of organization (arrows). (Masson’s trichrome, 40X).

Movie. LV angiography (30° right anterior oblique view) showing massive obliteration of ventricular apex by a huge mass centrally infiltrated by contrast medium, resembling the shape of a hissing snake with a forked tongue. For the movie, see online supplementary material available at *European Heart Journal* online.