State of the Art Paper

Medical Therapy for Rheumatic Heart Disease: Is it time to be Proactive rather than Reactive?

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Abstract

Rheumatic Heart Disease (RHD) is well known to be an active inflammatory process which develops progressive calcification and leaflet thickening over time. The potential for statin therapy in slowing the progression of valvular heart disease is still controversial. Retrospective studies have shown that medical therapy is beneficial for patients with calcific aortic stenosis and recently for rheumatic valve disease. However, the prospective randomized clinical trials have been negative to date. This article discusses the epidemiologic risk factors, basic science, retrospective and prospective studies in valvular heart disease and a future clinical trial to target RHD with statin therapy to slow the progression of this disease. Recent epidemiological studies have revealed the risk factors associated with valvular disease include male gender, smoking, hypertension and elevated serum cholesterol and are similar to the risk factors for vascular atherosclerosis. An increasing number of models of experimental hypercholesterolemia demonstrate features of atherosclerosis in the aortic valve (AV), which are similar to the early stages of vascular atherosclerotic lesions. Calcification, the end stage process of the disease, must be understood as a prognostic indicator in the modification of this cellular process before it is too late. This is important in calcific aortic stenosis as well as in rheumatic valve disease. There are a growing number of studies that describe similar pathophysiologic molecular markers in the development of rheumatic valve disease as in calcific aortic stenosis. In summary, these findings suggest that medical therapies may have a potential role in patients in the early stages of this disease process to slow the progression of RHD affecting the valves. This review will summarize the potential for statin therapy for this patient population.

Keywords: *Valvular Heart Disease, Lipids, Pathophysiology, Clinical Trials*

INTRODUCTION

Rheumatic heart pathology is a major cause of valvular heart disease in the world. Aggressive approaches for the treatment of penicillin-sensitive group A b-hemolytic streptococcus have changed the epidemiology of this disease throughout the world. A study by Carapentis et al estimated that up to 15.6 million people are affected by RHD worldwide[1]. Each year there are approximately 470,000 new cases diagnosed and 233,000 deaths attributed to RHD[2]. In recent

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echocardiographic studies, the prevalence of aortic valve (AV) disease is 5% and 24% in developing countries. The epidemiology of the disease has had a long and important history dating back to 1706; in an autopsy study conducted by Lancisi[5] when there was a major epidemic of sudden cardiac deaths, the original observations of the pathologic lesions were similar to what later were discovered to be rheumatic heart lesions. The impression that RHD is present only in developing countries is not valid and the concept that it is a worldwide problem requires a paradigm shift. In 2009, current changes in socio-economic trends, the role of the world-wide internet in the dissemination of health care information and access to health care in the future may again change our understanding of the prevalence of this disease and magnitude of the problem.

During epidemics over a half century ago, as many as 3% of untreated acute streptococcal sore throats were followed by rheumatic fever; in endemic infections, the incidence of rheumatic fever is substantially less[6]. Physicians throughout the world, in areas that have a higher incidence of this disease or the future potential for an increase in the presentation of this disease, will need to take these issues into consideration for the future approach towards treating these patients. This article will discuss the current treatments, the pathogenesis, similarities between rheumatic mitral stenosis (MS) which are parallel to those of calcific aortic stenosis (AS) and the potential for medical therapy for secondary prevention of RHD.

Current Medical Therapy for the Treatment of Rheumatic Fever

The current guidelines for the Prevention of Rheumatic Fever and Diagnosis of Acute Streptococcal Pharyngitis was recently summarized in the most recent American Heart Association Scientific Statement[7]. This paper outlines the specific approaches based on the evidence in the literature of the diagnosis of streptococcal infections, the use of throat cultures, antigen and antibody tests and recommended treatment schedules for primary and secondary prevention of Rheumatic Fever. The most common cardiac manifestations of rheumatic heart disease is MS followed by involvement of the AV, either a stenotic or a regurgitant lesion. MS in these patients is a slow and progressive development, usually over decades, although in certain areas of the world, the stenosis can accelerate in part due to recurrent episodes of rheumatic carditis. Over time, any decrease in stroke volume can cause a further reflex tachycardia, all of which contribute to an elevated left atrial pressure. The onset of atrial fibrillation (AF) secondary to the stenosis, may precipitate acute pulmonary edema.

Careful echocardiographic evaluation of the mitral valve (MV) gradient, valve area, and pulmonary pressures is necessary to appropriately evaluate this patient population[8].

The only medical therapies indicated for these patients are secondary prevention of repeat carditis[7] and prevention of infective endocarditis[7], and for the symptomatic patient is beta blockade. The judicious use of diuretics is appropriate if there is pulmonary congestion. Anticoagulants should probably be given if the patient is on bed rest and should certainly be administered in the setting of AF[8]. Balloon valvuloplasty is performed if the valve anatomy is favorable and there is no significant mitral regurgitation (MR)[9]. Rarer still, surgical valvotomy and or valve replacement may be performed when indicated. Table 1 and 2 show the current standards for the duration and treatment options for secondary Rheumatic Fever Prophylaxis.

Atherosclerotic Risk Factors for Valvular Heart Disease

Recent epidemiologic studies have demonstrated that aortic valve disease and mitral annular calcification (MAC) have similar associated risk factors like vascular atherosclerosis, including smoking, male gender, body mass index, hypertension, elevated lipid and inflammatory markers, metabolic syndrome and renal failure[10-27]. For years this disease process was thought to be due to a degenerative phenomenon by which calcium attaches to the surface of the aortic valve leaflet and mitral annulus. Recently, Yimaz and colleagues[28] determined that lipids are also associated with severe MS as defined by Wilkins score[9] (Table 3). Understanding the observation that calcification, as the critical end-stage process which causes progression to severe stenosis and leads to poor outcomes in both rheumatic mitral disease[9] and calcific AS[29], is becoming important in the results of the randomized trials for treating valvular heart disease with medical therapy. Calcification in rheumatic MS is also a key determinant in the outcome in patients with severe MS. Over the past decade, there have been a growing number of studies in human disease tissues which are defining the molecular markers in calcific and rheumatic valve disease. In addition, there are a growing number of retrospective and prospective studies testing the hypothesis that atherosclerotic calcific AS may be targeted with medical therapy. These risk factors provide the foundation for future clinical trials testing medical

Table 1. Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)[7]

Agent	Dose	Mode	Rating
Benzathine penicillin G	600 000 U for children ≤27 kg (60 lb), 1 200 000 U for those >27 kg (60 lb) every 4 wk*	Intramuscular	IA
Penicillin V	250 mg twice daily	Oral	IB
Sulfadiazine	0.5 g once daily for patients ≤27 kg (60 lb), 1.0 g once daily for patients >27 kg (60 lb)	Oral	IB
For individuals allergic to penicillin and sulfadiazine			
Macrolide or azalide	Variable	Oral	IC

Rating indicates classification of recommendation and LOE (eg, IA indicates class I, LOE A).
*In high-risk situations, administration every 3 weeks is justified and recommended.

therapies in the development of RHD.

Rheumatic Valvular Heart Disease: Cellular Biology

The hallmark of valve disease is calcification which for years was thought to be due to a passive process, but currently is defined as a bone formation process. In 1924, Dr. Carey Coombs wrote the first systematic textbook on rheumatic heart disease describing the inflammatory lesion in the rheumatic valve leaflet and the presence of new vessels developing within the valve[30]. Since 1924, there have been a number of studies further demonstrating the histopathology of this disease with correlations of the degree of rheumatic activity which include the presence of Aschoff bodies, nonspecific edema and leukocyte infiltration[31]. Despite the high prevalence, increased morbidity and well described histopathologic findings of this disease, little is known regarding the cellular mechanisms responsible for calcification in these valves. Recently, studies have demonstrated that calcification in non-rheumatic, "degenerative" stenotic AV removed at the time of surgical valve replacement is associated with an osteoblast like phenotype[32,33]. Figure 1[34], shows the histologic features of angiogenesis, inflammation and bone formation within a rheumatic valve explanted at surgical valve replacement. Special stains for masson trichrome stains are shown in Figure 1, Panels A1 and A2, demonstrate a marked inflammatory cellular infiltrate within the rheumatic valve lesions. Furthermore, there were multiple areas of new vessels forming (see arrows) within the valve lesions. Osteoblast Bone Marker: Figure 1, Panel B1 and B2, is the immunohistochemistry for osteocalcin a bone matrix protein important in osteoblast mineralization. MicroCT: A 3-dimensional analysis of the calcified rheumatic valve by microCT which reveals the depth and extent of calcification within the valve. Figure 1, Panel C1 and C2, shows the 3-dimensional reconstructed slice of the calcified valve lesion demonstrating the complex distribution of mineral within each leaflet. The soft tissue of the valve leaflet is the lighter blue area surrounding the areas of calcification.

Furthermore, there is a growing number of experimental models of calcific AS which demonstrate primarily that lipids[35-41], diabetes[41] and renal failure[42] are important in the development of this disease. Early studies have demonstrated that cholesterol[38], and Vitamin D[37] can induce early stenosis of the valve[37] as documented by echocardiographic measurements. Chronic experimental hypercholesterolemia models develop AV atherosclerosis and eventual calcification secondary to myofibroblast differentiation, which provide further direction for the understanding of the initiating events in the disease development[35 ,36-40,43-47,48 ,49,50]. Similar to vascular atherosclerosis these events are potential cellular targets for pharmacologic agents to slow this disease process. HMG CoA Reductase agents, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) provide an interesting approach for targeting in this disease. A number of experimental studies have tested the effects of statins and ARBs *in vivo* and *in vitro*[35,49,51-55]. The results from these experimental studies demonstrate *in vivo* and *in vitro* reduction in the atherosclerotic bone forming lesion[53,51,56].

Calcification: Important Prognostic Marker of Valvular Heart Disease

The presence of calcification is responsible for valve stenosis and for disease progression. Calcification is also an important marker in the development of MS in terms of clinical indications for balloon valvuloplasty[9]. From recent studies,

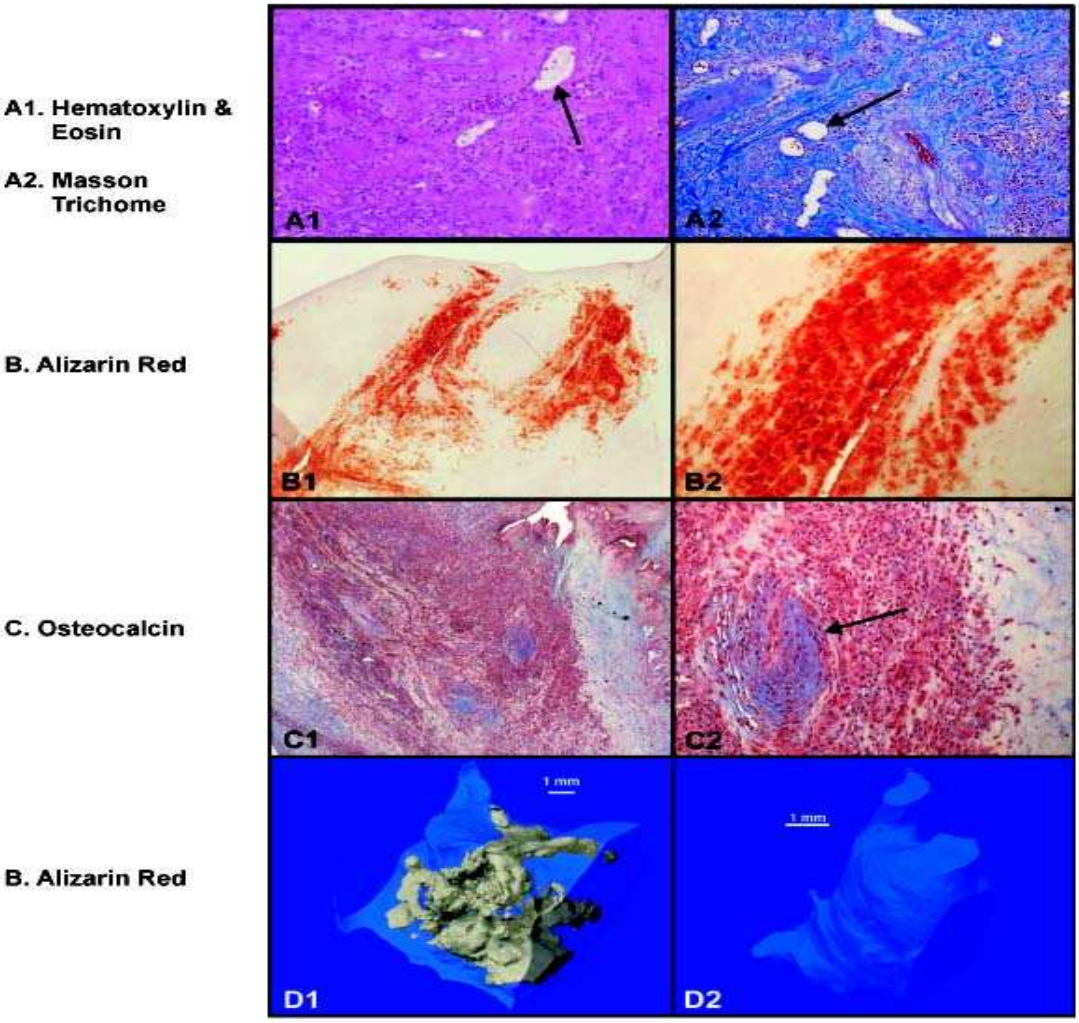

Figure 1. Identification of Neoangiogenesis and Bone Matrix Markers in Calcified Human Rheumatic Valves[34].

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Panel A1 Hematoxylin and Eosin Stain of a calcified Rheumatic valve. The arrow point to the new vessels. (10X mag.)
Panel A2 Masson Trichrome Stain. The arrow point to the new vessels. (10X mag.)
Panel B1 Alizarin Red Stain. (10X mag.)
Panel B2 Alizarin Red Stain. (40X mag.)
Panel C1 Osteocalcin Immunostain (10X mag.).
Panel C2 Osteocalcin Immunostain. The arrow point to the myofibroblast staining cells. (40X mag.).
Panel D1 MicroCT 3-dimensional reconstruction of the calcified rheumatic valve.
Panel D2 MicroCT 3-dimensional reconstruction of the uncalcified degenerative mitral valve.

Table 2. Duration of Secondary Rheumatic Fever Prophylaxis[7]

Category	Duration After Last Attack	Rating
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis	IC
Rheumatic fever with carditis but no residual heart disease (no valvular disease*)	10 years or until 21 years of age (whichever is longer)	IC
Rheumatic fever without carditis	5 years of until 21 years of age (whichever is longer)	IC

Rating indicates classification of recommendation and LOE (eg, IC indicates class I, LOE C).

*Clinical or echocardiographic evidence.

it is evident that the active and progressive disease process of AS is more appropriately described as "Calcific aortic stenosis" and not by the term "Degenerative aortic stenosis". In advanced stages, the detection of calcification is no longer limited to histopathological studies and is detectable macroscopically when assessing a surgically explanted valve. The stenotic AV is characterized by thickened and calcified cusps that ultimately impair systolic opening of the valve and result in a reduced leaflet motion. *In vivo*, the extent of calcification can be assessed semi-quantitatively by echocardiography or quantitatively by electron beam computed tomography. Echocardiography demonstrates the extent of calcification which is best assessed in a parasternal short axis view at the level of the AV. For clinical use in calcific AS, investigators have developed a similar system, the Rosenhek score[57] to describe the extent of AV calcification by echocardiography: 1- no calcification, 2- mildly calcified (isolated, small spots), 3- moderately calcified (multiple bigger spots), 4- severely calcified (extensive thickening/calcification of all cusps).

Calcification and disease progression

Calcification, the end stage process of the disease, must be understood as a prognostic indicator in the modification of this cellular process before it is too late. This is important in calcific AS as well as in rheumatic valve disease. Peak aortic jet velocity, a marker of disease severity, is a predictor of outcome in asymptomatic patients with AS[58]. The presence of a moderately or severely calcified AV is a predictor of rapid hemodynamic progression with progression rates of 0.35±0.31 m/s/yr as compared to 0.16±0.19 m/s/yr ($p < 0.0005$) in the absence of significant calcification[59]. In particular, the patients being in the highest tercile of AV calcification at baseline seem to experience the most significant progression of calcification. Similar findings have been published in rheumatic mitral disease[60] in terms of optimal results in patients undergoing balloon valvuloplasty for rheumatic mitral stenosis.

Lessons Learned from the Human Clinical Trials in Valvular Heart Disease

There are a number of retrospective and prospective studies measuring the progression of AS while on medical therapy as compared to patients with AS not on medical therapy. The retrospective studies to date have all demonstrated that the use of statins in AV disease slows the progression of calcification as assessed by echocardiography[12,43,61-63] and by computed tomography[26,64,65]. The studies provide the foundation for the future prospective clinical trials in calcific AS. The most recent study by Antonini-Cantorin and colleagues[66] (Data in Press, provided from the authors for this review) is the first to analyze the possible effect of statin treatment in rheumatic valve disease. The current therapy as outlined earlier in this paper, is the therapy to prevent acute attacks of rheumatic fever but there is no specific treatment aimed to prevent progressive valve calcification-osteoblastogenesis.

The authors[66] developed a hypothesis based on the growing evidence that inflammation may be responsible for the development of RHD similar to that of AV disease. The risk factor studies are emerging showing similar inflammatory markers for AV disease are also associated with RHD[67].

Table 3: Grading of Mitral Valve Characteristics from the Echocardiographic Examination[9]

Grade	Mobility	Subvalvar thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4-5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one third of the chordal length	mid-leaflets normal, considerable thickening of margins (5-8 mm)	Scattered areas of brightness
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5-8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8-10 mm)	Extensive brightness throughout much of he leaflet tissue

The total echocardiographic score was derived from an analysis of mitral leaflet mobility, valvar and subvalvar thickening, and calcification which were graded from 0 to 4 according to the above criteria. This gave a total score of 0 to 16

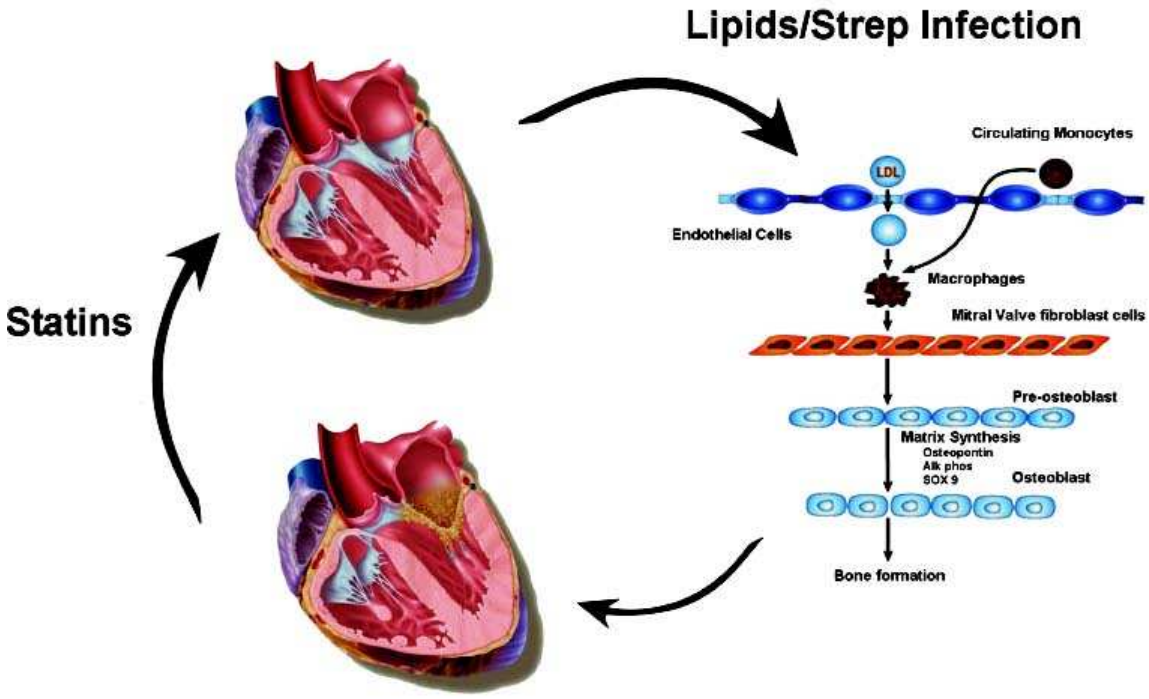

Figure 2. *Cell Signaling Events involved in the Development of Rheumatic Valve Disease and the potential for medical therapy.*

Table 4. List Prospective Clinical Studies Testing Medical Therapy in Aortic Valve Disease.

Trial/University	*Locations*	*Hypothesis*	*Medication*
SALTIRE NEJM, 2005	Edinburgh, Scotland	The Scottish Aortic Stenosis and Lipid Lowering Trail, Impact on Regression	Atorvastatin
RAAVE JACC, 2007	Porto, Portugal	Rosuvastatin Affecting Aortic Valve Endothelium	Rosuvastatin
ASTRONOMER	Multicenter, Canadian	The Aortic Stenosis Progression Observation: Measuring the Effect of Rosuvastatin	Rosuvastatin
SEAS NEJM, 2008	Multicenter, European	The Simvastatin and Ezetimide in Aortic Stenosis Study	Simvastatin and Ezetimide
University of Leipzig	Leipzig, Germany	Statin Therapy in Asymptomatic Mild to Moderate Aortic Stenosis	Fluvastatin
Odense University Hospital	Odense, Denmark	Effect of Angiotensin II Receptor Blockers Remodeling (ARB) on Left Ventricular Reverse After Aortic Valve Replacement in Severe Valvular Aortic Stenosis	Candesartan
ACCESS	Rigshospitalet, Copenhagen, Denmark	Acute Hemodynamic Effects of Treatment With ACE-Inhibitors in Patients With Symptomatic Aortic Stenosis AVA<1.0	Captopril and Trandolapril
AORTICA Group	Salamanca, Spain	Randomized Study to Evaluate the Efficacy of Fluvastatin on Inflammatory Markers in Patients with Aortic Stenosis	Fluvastatin
STOP-AS	Cleveland, Ohio	STOP Aortic Stenosis	Atorvastatin
TASS American Journal of Cardiology, 2008	Innsubruck, Austria	Prognosis and Risk Factors in Patients With Asymptomatic Aortic Stenosis and Their Modulation by *Atorvastatin* (20 mg)	Atorvastatin
Genetic Database/Scripps	La Jolla, CA	Genomic Investigation of CV Disease	none
ROCK-AS /Helsinki University	Helsinki,Finland	The potential of Rosuvastatin and Candesartan to Retard the Progression of Aortic Stenosis	Rosuvastatin and Candesartan
Charles University	Czech, Republic	Risk Factors Associated with Calcification of the Aortic Valve	none
GENERAC/ Assistance Publique-Hopitaux de Paris	Paris, France	Genetic or Aortic Valve Stenosis- Clinical and Therapeutic Implications	none
Assistance Publique-Hopitaux de Paris	Paris,France	Genetic or Aortic Valve Stenosis- Clinical and Therapeutic Implications	none
National Center for Research Resources	NCRR	Vitamin D Metabolism and Williams Syndrome	1,25(OH)2D3(Vitamin D)

Galente et al[68] and Skowasch et al[69] have previously demonstrated that elevated high senstivity C-reactive protein (hsCRP) is associated with the disease process of calcific AS. The authors[70] hypothesized that statins would have a beneficial effect in rheumatic AS similar to the results of the previously described studies. The patient populations for comparison were very similar with respect to age, gender, prevalence of hypertension, diabetes mellitus, coronary artery disease and baseline echocardiographic parameters of AS severity[66]. Then they identified whether the patients were taking statins or not. They found the prevalence of hypercholesteremia was higher in the statin treated group as expected. The investigators found a significant difference between the groups regarding the annual changes in peak aortic velocity and overall change in velocity between the baseline and the last follow-up. In addition there was a faster rate of progression in the untreated patients with a higher frequency that in the statin-treated patients[66]. This is the first retrospective study to demonstrate that statins slow progression in rheumatic valve disease.

In the first randomized prospective, double-blind, placebo-controlled study- The Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) that tested the effects of statins in AV disease[71], patients with calcific AS were randomly assigned to receive either 80 mg of atorvastatin daily or a matched placebo. The authors concluded that intensive lipid-lowering therapy does not halt the progression of calcific AS or induce its regression. One potential reason for the negative results is the study design were that of patients being treated with atorvastatin, who received the therapy late in the course of the disease process. Experimental data show that, earlier the statin therapy is initiated in the disease process, greater is the potential for slowing the

progression of this disease[35,49]. The Simvastatin and Ezetimide in Aortic Stenosis (SEAS) trial was recently published and again was a negative study testing the effects of Simvastatin plus Ezitimide in a randomized control methodology for the slowing of progression of AS[72]. The SEAS study initiated therapy earlier in the disease process but again was a negative study and the progression of AS was not slowed.

Currently, there are eleven prospective clinical trials testing the effects of statins, ACE inhibitors and ARBs in aortic valve disease (Table 4). There are also five prospective trials testing genetics and risk factors associated with calcific aortic stenosis. The first study is RAAVE (Rosuvasatin Affecting Aortic Valve Endothelium), from Porto Portugal, which determined that early treatment with a statin is more efficacious in the prevention of progression of aortic valve stenosis than late treatment

It is important to question why SEAS and SALTIRE were negative. Possible reasons can be derived from other retrospective statin trial results[12,61-64]. The retrospective studies included patients with hypercholesterolemia already on statin therapy and demonstrated slowing of disease progression with medication as compared to patients with normal cholesterol levels. This was true for all studies except the retrospective study by Bellamy et al, which had patients without elevated lipids[61]. The results of this study represent the potential for the pleiotropic non-lipid lowering effects of statins. Another probable reason is that although vascular atherosclerosis and valvular calcification have similar initiating events they have different biologic endpoints.

Summary

in an open label treatment protocol[73]. The RAAVE trial, prospective treatment of AS with Rosuvastatin targeting serum LDL slowed progression of hemodynamic measurements documented by echocardiography; it also showed improved inflammatory biomarkers. The study's aim was to assess Rosuvastatin on the hemodynamic progression and inflammatory markers of AS by treating LDL in patients with AS according to the NCEP-ATPIII guidelines for one year. Prospective treatment of moderate AS with Rosuvastatin targeting serum LDL slowed progression of AV peak velocity and improved inflammatory biomarkers providing the first clinical evidence for targeted therapy in asymptomatic patients with moderate to severe AS[73].

SALTIRE and SEAS trials were designed according to the classical clinical trial methodology. The primary outcome tested in SALTIRE and RAAVE trials was the progression of AS and the secondary outcome was the cardiovascular events. The primary endpoint for the SEAS trial was the cardiovascular events including time for AV replacement and the secondary endpoint is the slowing of progression of AS. These two end-points are important in performing clinical trials with statins in order to measure the progression of vascular events and in the heart valve. To date, the effects of statins on AV progression has only been proven in the RAAVE study and also in the retrospective studies[12,61-64]. The question that remains is: why was the well established vascular clinical trial design not successful in for the SALTIRE and the SEAS trials for outcomes in patients with AS? There are two possible reasons. Patients in the RAAVE trial patients with elevated lipids received therapy with a statin and patients with normal LDL levels did not get a statin. In the control group AS progressed in line with the published data for the natural history for this disease[74].

For the past 40 years, antibiotic therapy, catheter hemodynamics, echocardiography and timing of balloon valvuloplasty and surgery have evolved as the diagnostic and therapeutic approaches for severe MS. Studies during the past decade that employed experimental models and *ex vivo* analysis, have shown that the rheumatic mitral valve has an active cellular biology. Three main processes appear to play roles in the progression of MS: recurrent episodes of carditis, traditional cardiovascular risk factors and cellular signaling pathways to differentiate the valve into the osteoblast phenotype. The future management of the rheumatic disease process will incorporate the understanding of these different mechanisms for future medical therapy of this disease. If the physician can define the traditional risk factors in patients with rheumatic valve disease, targeting those risk factors may slow progression of the lesion.

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