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Review

Degeneration of native and tissue prosthetic valve in aortic position: Do statins play an effective role in prevention?

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Abstract

Degenerative aortic valve stenosis is a common disease in western countries. When it becomes severe, it confers significant morbidity and mortality. Aortic stenosis has been recognized as a complex inflammatory and highly regulated process with histological and immunochemical similarities with the process of atherosclerosis. Hypertension, smoking and diabetes mellitus have consistently been linked to the development of aortic stenosis. Endothelial injury or other processes that contribute to coronary disease may play a role in calcific aortic stenosis. Several observational studies suggests that the key factors of aortic stenosis are lipoproteins and that medical therapies with cholesterol lowering drugs may retard its progression. Similarly, it has been suggested that the process of degeneration of the tissue heart valve has been associated with the same risk factors of atherosclerosis and shares many histological and molecular characteristics. Assuming all this concept, and evaluating the results of a retrospective study it has been suggested to use statin also as medical therapy able to prevent tissue valve degeneration. Randomized controlled clinical trials will be needed to demonstrate the role of lipid intervention to prevent the progression of aortic stenosis and the degeneration of tissue heart valves.

Keywords: Aortic stenosis; Statins; Tissue valve degeneration

1. Calcific aortic valve disease

1.1. Epidemiology, historical perspective

Degenerative valvular aortic stenosis is the most common cause of aortic valve disease in the so-called developed countries [1]. It is associated with significant mortality and morbidity. It has been recently shown that its prevalence increases with advancing age; the Helsinki Ageing Study [2] found a prevalence of 2.9% of critical aortic stenosis using echocardiography (aortic valve area ≤ 0.8 cm^2) in the age group of 75–86 years and a prevalence of 4.8% of moderate aortic stenosis (aortic valve area $\geq 0.8 \leq 1.2$ cm^2) in the same age group. The presence of calcification is even more frequent; in the age group 55–86 years, 53% of individuals had some degree of calcification. In the age group 55–71 years, 27% had some degree of calcification compared with 75% in individuals aged 85–86 years [3,4]. The prevalence of this pathology has been increasing over the past 30 years because of the increasing median lifespan of the population.

Pathologically, progressive aortic stenosis may induce left ventricular hypertrophy, left ventricular diastolic and systolic dysfunction, congestive heart failure, angina, arrhythmias and syncope. Recent studies have demonstrated an association between atherosclerosis, including its risk factors, and aortic valve disease.

Historically, calcific aortic stenosis was thought to result from aging and "wear and tear" of the aortic valve [5,6]. Hence it was designated "degenerative" or "senile-type" according with the idea of a passive accumulation of calcium binding to the aortic surface of the valve leaflet. This perception is changing. Over the last decades, a growing

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understanding of the risk factors for calcific aortic stenosis and of its histologic characteristics have led to new insights into how it develops. Investigators have found histologic similarities between the lesion of aortic stenosis and atheromatous coronary artery disease [7,8] and have established an association between traditional atherosclerotic risk factors and the development of calcific aortic valve disease [3,9–16].

Actual data indicate aortic stenosis is an active disease with a distinctive histological appearance and variable disease progression, which suggests this disease may be amenable to medical therapy to prevent or slow down its progression.

In 1854 William Stokes described in his masterpiece, *The diseases of the heart and the aorta*, specific physio-pathological observations of calcific aortic valve disease, including the following: "an extreme ossific growth along the valve surrounding the ventricle, at which the valves are often destroyed", and "an atheromatous deposit on the ventricular surface of the valve which is often seen in the context of fatty degeneration of the heart" [17]. The debate over the pathogenesis of non-rheumatic calcific aortic stenosis found another important step in the 1904 when Mönckeberg published his first description of the dystrophic calcification of the aortic valve [18].

The hypothesis at the base of the dystrophy theory was the conventionally accepted, that with age, repeated mechanical stimuli and haemodynamic forces lead to leaflet injury and dystrophic calcification [5,6]. However age alone could not completely explain the pathology of the aortic valve degeneration, because many elderly people do not develop aortic stenosis [13].

1.2. Atherosclerotic risk factors and aortic valve calcification

Over the last decade new studies, in particularly from Otto et al. [7] and O'Brien et al. [8] have linked the development and progression of calcific aortic valve disease to various traditional risk factors for atherosclerosis. They found that the early lesions of the aortic stenosis are microscopically similar to the atheroma.

Many observational studies, evaluating large numbers of patients have repetitively found that aortic valve stenosis is associated with dyslipidemia (Table 1). In particular, elevated levels of total cholesterol [9,10,12,13,19–22], low-density lipoprotein cholesterol (LDL) [4,16] elevated levels of triglycerides [11,16] and conversely low levels of high-density lipoprotein (HDL) cholesterol have been observed. Moreover, Steward et al. [4] and Gotoh et al. [13] have evidenced that serum concentration of lipoprotein (a) closely correlate with the presence of aortic stenosis, independently from LDL levels. Supporting the role of lipids in the development of aortic stenosis is the observation of Sprecher [23] and of Rallidis [24] that homozygous familial hypercholesterolemic patients produce a particularly severe form of aortic stenosis at an early age. In this specific condition extremely high low density lipoprotein cholesterol (LDL-c) concentrations are seen without the other traditional risk factors for coronary artery disease.

Table 1
Clinical risk factors predicting aortic valve stenosis progression

Clinical factor	Supporting studies
Older age	[3,4,12,13,21,45]
Male gender	[4,11,47]
Obesity	[12]
Hypertension	[3,4,10,21]
Hypercholesterolemia	[4,11,13,47–49]
Higher body mass index	[12,50]
Smoking	[4,11,25,48–50]
Elevated LDL	[11,48–50]
Diabetes mellitus	[9,10,16,47,49]
Elevated creatinine	[25,26,30]
Elevated calcium	[25,27]
Elevated parathyroid hormone	[3,28]
Uremia	[26]
Homocysteine	[31]
PCR	[33]
Apo E4 allele	[32]
Matrix metalloproteinases	[34–36]
TGF β1	[37]

Other several risk factors such as hypertension [3,4,10,21], smoking [4,11,25], and diabetes mellitus [9,10,16], have been linked to the development of aortic stenosis, although their exact disease-promoting actions are not well defined. Other factors that may be associated with aortic valve disease include: age [3,4,12,13], male sex [4,11], obesity [12], uremia [26], elevated calcium [27], elevated parathyroid hormone [3,28], osteoporosis [3,4], Paget disease [29], significant renal failure [26,30], elevated homocysteine [31], presence of apolipoprotein E4 allele [32], increase in C reactive protein concentrations [33], presence of matrix metalloproteinases [34–36] and presence of cytokine transforming growth factor beta 1 [37].

These studies demonstrate that many of the same risk factors initiating vascular atherosclerosis are also implicated in aortic valve disease.

Studies that have found no or only a weak association between atherosclerotic risk factors and aortic stenosis have mostly been small in sample size or had less representative patient populations for comparison [11,38,39]. In 1997 Otto et al. [40] reported that aortic sclerosis, described as focal areas of increased echogenicity and thickening of aortic valve leaflets without restricted leaflets, was found in 29% of subjects in the cardiovascular health study. During 5 years of follow-up, the presence of aortic sclerosis was associated with an increase of 50% in the risk of death for all cardiovascular causes, even in the absence of haemodynamically significant obstruction to left ventricular outflow. Rosenheck et al. [41] evidenced that the extent of aortic valve calcification represents an important predictor of poor outcome in patients with aortic stenosis. When aortic stenosis tend to progress, the valve area decreases by an