Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com

The Global Burden of Aortic Stenosis

Jeremy J. Thaden, Vuyisile T. Nkomo, Maurice Enriquez-Sarano*

Division of Cardiovascular Disease and Internal Medicine, Mayo Clinic, Rochester, MN

ARTICLE INFO

Keywords:
Aortic stenosis
Aortic valve replacement
Prevalence

ABSTRACT

Degenerative, calcific valvular aortic stenosis (AS), caused by an active process of atherosclerosis, calcification and ossification, is the most common cause of AS in industrialized nations. The prevalence of calcific AS is age-dependent, and thus is expected to increase due to demographic aging of the global population. It is well recognized that severe AS carries a poor prognosis if left untreated. Despite this recognition, many patients are inappropriately denied surgery because of perceived risk. This article will examine the etiology, prevalence, and current trends in the treatment of degenerative AS focusing on indications for surgical aortic valve replacement.

Etiology and pathophysiology

The normal aortic valve is comprised of three thin leaflets attached to the aortic annulus and the wall with a normal aortic valve opening of 3 to 5 cm^2 with unimpeded leaflet separation along the commissures during systole. Causes of aortic stenosis (AS) frequently are grouped into hereditary or acquired etiologies. The prevalence of bicuspid aortic valve is 1.4%, and it is the most common cause of AS in those under age 70 years at time of aortic valve replacement (AVR) surgery.[1,2] A unicuspid valve is the most common cause of fatal AS in the pediatric population and rarely is a cause of AS in older patients.

In adults, AS is commonly caused by progressive calcification of either a bicuspid or trileaflet aortic valve leading to progressive rigidity of the leaflets and restricted mobility and opening (Fig 1). AS is not a consequence of aging alone, but is a dynamic process of inflammation, lipid accumulation, and calcification. Clinical risk factors for the development of AS are similar to those of atherosclerosis, and include advanced age, hypertension (HTN), hyperlipidemia, smoking, and diabetes.[3,4] Additionally, associations between aortic valve calcification and chromosome 16q22.1-q22.3 and genetic polymorphisms in the lipoprotein(a) gene have recently been identified, suggesting that some patients may have a genetic predisposition to degenerative aortic valve disease.[5,6]

On histologic examination, the early lesion of degenerative AS is characterized by subendothelial thickening, lipid and calcium accumulation, and an inflammatory cell infiltrate consisting of foam cell macrophages, non-foam cell macrophages, and T lymphocytes.[7] Additionally, 25-hydroxycholesterol, a byproduct of cholesterol oxidation found in atherosclerotic plaque, has been shown to stimulate osteogenesis and calcification in valvular tissue.[8] With end-stage AS, ossification occurs in a manner similar to mature bone and histologic examination reveals expression of bone morphogenic proteins 2 and 4 (potent osteogenic morphogens), angiogenesis and frequently osteoblastic/osteoclastic activity consistent with active bone remodelling.[9] Oxidative stress also is increased in calcific AS, possibly due to dysregulation of antioxidant mechanisms.[10] Higher mechanical stress present in bicuspid valves is also associated with a propensity for structural degeneration and calcification.[2,11]

Of note, an early animal model suggested that treatment with HMG Co-A reductase inhibitors (statins) could decrease markers of osteoblastic bone formation in a rabbit model of

Statement of Conflict of Interest: see page 569.

* Address reprint requests to Vuyisile T. Nkomo, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
E-mail address: nkomo.vuyisile@mayo.edu (V.T. Nkomo).

0033-0620/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pcad.2014.02.006

Abbreviations and Acronyms

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CV = cardiovascular

HF = heart failure

HTN = hypertension

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

SEAS = Simvastatin and Ezetimibe Aortic Stenosis

STS = Society of Thoracic Surgery

TAVR = transcatheter aortic valve replacement

US = United States

hypercholesterolemia-related AS.[12] Subsequent retrospective observational studies also suggested that statin therapy was associated with decreased rates of hemodynamic progression and rate of valvular calcification.[13,14] However, two randomized controlled trials that followed found no effect of statin therapy on hemodynamic progression or valvular calcium accumulation in patients with mild to moderate AS.[15,16]

Prevalence of AS

In a population-based study from the National Health, Lung, and Blood Institute of 11,911 adults across the United States (US) where systematic echocardiography was performed, the prevalence of moderate or severe AS was age-dependent from a low of 0.02% in subjects aged 18–44 years to a high of 2.8% in patients aged ≥75 years (Fig 2). A similar distribution was seen in a community cohort of 16,543 adults referred for echocardiography in Olmsted County, Minnesota (Fig 2).[17] Similar trends are present in other economically developed nations. The EuroHeart Survey examined patients across Europe and the Mediterranean who presented with incident valve disease among 92 centers across 25 countries.[18] In this study, the mean age of those presenting with valve disease was 65 ± 14 years and AS was the most common form of left-sided native valve disease in this series, occurring in 43.1%.

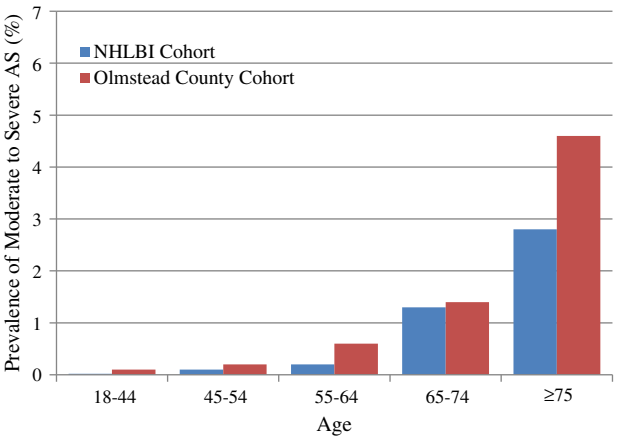

Fig 2 – Prevalent moderate-to-severe aortic stenosis in a randomly selected NHLBI study cohort who received screening echocardiography and a large cohort from Olmsted County, Minnesota referred for echocardiography. A slightly lower incidence of aortic stenosis was observed in the randomly selected NHLBI study cohort. AS, Aortic Stenosis; NHLBI, National Heart, Lung, and Blood Institute.

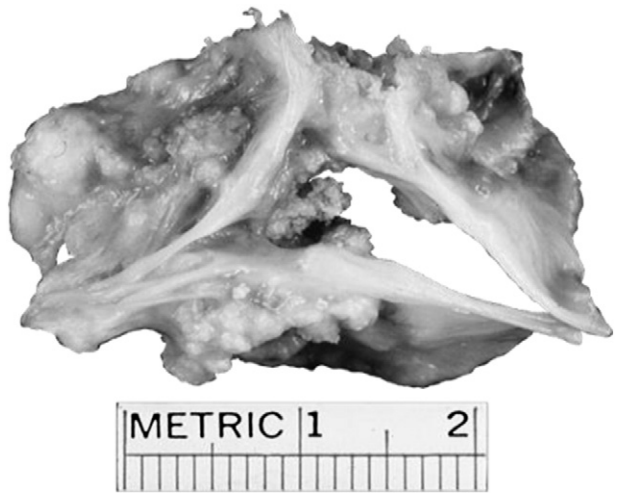

Fig 1 – Excised tricuspid aortic valve showing severe nodular calcification and stenosis.

Population-based studies estimating the prevalence of degenerative AS in Africa, Asia, or South America are not available. However, rheumatic valve disease remains a common cause of valvulopathy in developing countries.[19] In The Heart of Soweto prospective clinical registry from Chris Hani Baragwanath Hospital, which serves 1.1 million Africans, there were 481 adult presentations of primary valve disease; the mitral valve (stenosis or regurgitation) was most commonly affected and among all cases of primary valve disease 344 cases (72%) were rheumatic and 101 (21%) were degenerative.

In a meta-analysis and modeling study to estimate the number of candidates for transcatheter aortic valve replacement (TAVR), Osnabrugge and colleagues examined 9723 subjects from 7 studies.[20] The prevalence of severe AS was 3.4% in those aged 75 years or more and 75.6% were symptomatic. Among symptomatic patients approximately 40% were unoperated and another 5.2% of operated patients were high-risk, making them potential TAVR candidates. Based on their model the projected number of TAVR candidates is 189,836 in European countries and 102,558 in North America. In this study, the incidence of new TAVR candidates also was estimated at 17,712 for European countries and 9189 in North America. Of note, in a separate study of adoption of TAVR, a low rate of penetrance of this therapy was demonstrated, with only 17.9% of candidates receiving treatment. Adoption varied significantly by country, with penetrance heavily affected by national economic indices and reimbursement.[21]

The global prevalence of AS is expected to increase given the projected increase in the world's population, which is expected to surpass 10 billion by 2100 with Asia and Africa being the most populous regions.[22] In the US, there were