Population-Wide Trends in Aortic Stenosis Incidence and Outcomes

Running title: Bonow et al.; Trends in aortic stenosis

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A number of registries and population-based cohort studies have shown a consistent and significant association between age and the prevalence of calcific aortic stenosis\(^1\)\(^-\)\(^3\). It is therefore generally assumed that the progressive aging of the population in developed countries will result in an increasing number of patients presenting with clinically significant aortic stenosis. Data from Medicare fee-for-service beneficiaries\(^4\) support this concept, in which the number of patients over the age of 65 hospitalized for aortic valve surgery increased from 24,568 in 1989 to 31,380 in 2011, a rate of increase greater than that of the general U.S. population over the age of 65 during the same period\(^5\). The rate of increase in surgical procedures was most striking in patients aged 85 or older in whom the adjusted rate rose from 48 to 91 per 100,000 person-years during that decade\(^6\). Data based on surgical procedures alone, of course, does not provide accurate insights into the true incidence of aortic stenosis, as surgical data pertain predominantly to symptomatic patients with severe aortic stenosis, excluding the larger number of patients with either asymptomatic disease or less severe stenosis, as well as those with extensive comorbidities considered too high risk for surgery. Increasing numbers of aortic valve replacements also reflect advances in surgical expertise and the greater comfort of referring physicians in referring elderly patients for surgery. In other words, the use of this type of data as a surrogate for true incidence is flawed because the referral patterns are not stable. This is a form of ascertainment bias.

The natural history of aortic stenosis, as proposed by Ross and Braunwald in 1968\(^6\), based on a handful of patients, has been confirmed in numerous studies over the last 45 years\(^7\)\(^-\)\(^9\), characterized by a relatively benign course in patients with asymptomatic disease but a rapid mortality rate once symptoms develop. Although Ross and Braunwald conceptualized this symptomatic demarcation occurring in middle age (Figure 1), the natural history curve now
often shifts to the right, with patients developing symptoms in the seventh through ninth decade, with the same predictably adverse outcome unless valve replacement is performed. This recognition has prompted the growing numbers of patients referred for surgical aortic valve replacement noted above, and transcatheter procedures have transformed the outlook of patients previously considered too high risk for valve replacement.

It is also now well established that degenerative calcific aortic valve disease is not a result of passive wear and tear, but represents an active, proliferative, and inflammatory process\textsuperscript{10-14} with risk factors similar to those associated with atherosclerotic vascular disease\textsuperscript{2,14,15}. It is thus conceivable that improved control of such risk factors in a broader segment of the population, through smoking cessation and other lifestyle interventions along with drug treatment of hypercholesterolemia and hypertension, might reduce the true incidence of aortic stenosis or the rate of progression of its severity. Thus, risk factor modification might alter the natural history of the disease, which combined with appropriate intervention could yield reductions in disease-related morbidity and mortality. The study by Martinsson, et al., in this issue of \textit{Circulation}\textsuperscript{16} provides unique insights at the level of the Swedish population into the trends in aortic stenosis incidence, intervention, and mortality rates over a period of two decades.

The data reported by Martinsson et al\textsuperscript{16} from 1989 through 2009 represent inpatient data and thus presumably identify those patients with hospitalizations related to symptomatic aortic stenosis who ultimately underwent surgery, those with symptomatic aortic stenosis deemed too high risk for surgery, or those in whom aortic stenosis was a secondary diagnosis made during a hospitalization for heart failure, acute myocardial infarction or other unrelated conditions. As aortic valve replacement was performed in 37% to 42.5% of patients during this period, it would appear that over 50% of patients fit into this latter group, in whom the ascertainment of disease
and severity of aortic stenosis are uncertain. Although the “majority” of aortic stenosis diagnoses were based on echocardiographic measurements and “mainly” comprise moderate to severe disease, the adjudication of this process appears to have been based on a relatively small number of patients.

In this inpatient sample, the number of cases of aortic stenosis increased from 4,694 in the 3-year period 1989-1991 to 5,963 in 2007-2009 (a 27% increase), during which the age at diagnosis increased by a mean of 4 years, but the crude incidence rate per 100,000 did not increase and the age-adjusted incidence rate decreased significantly, from 15.0 to 11.4 per 100,000 in men and 9.8 to 7.1 in women. Importantly, the crude mortality rates and age-adjusted mortality rates declined markedly. These reductions in mortality paralleled those related to heart failure and acute myocardial infarction during the same period. The declines in adjusted aortic stenosis incidence and mortality rates were similar in patients younger than 75 years and those over 75 years.

The number of aortic valve replacements increased from 1920 in 1989-1991 to 2424 in 2007-2009 (a 26% increase). Although the rate of aortic valve surgery remained relatively constant, there was an increase in the rate of surgery noted in those over the age of 75 during the two decades (supplementary table 6). The reductions in 30-day mortality were striking and in keeping with those reported in the U.S. Medicare database.

The combined inpatient and outpatient samples (from 2001 through 2009) provide a more complete picture of the true incidence of aortic stenosis as it presumably includes those with asymptomatic and/or less severe disease who have no indications for hospitalization or surgery. These data indicate no difference in overall numbers with the diagnosis of aortic stenosis (slightly more than 11,000 in 2001-2003 and 2007-2009) but, similar to the trends of the
inpatient sample there were significant reductions in age-adjusted incidence and mortality rates.

The data in patients who underwent surgery in this study represent the hard data. Ascertainment of diagnosis and disease severity in both the inpatient and outpatient databases creates some “softness” to the data that should be interpreted as such. For example, assuming that echocardiography was used more fully in Sweden over the course of time in the diagnosis and management of aortic stenosis, as it has been in the United States, it is possible that the apparent decline in aortic stenosis incidence represents the identification of those patients with true aortic stenosis and the exclusion of those with sclerotic valves and heart murmurs but insignificant gradients, who may have been coded as aortic stenosis in the earlier time periods. Thus, a more complete picture of the incidence (and outcomes) could be obtained by a sharper analysis of the echocardiographic data rather than relying on more crude administrative data.

These concerns do not detract from the important observations on Martinsson et al regarding the very favorable trends in mortality for aortic stenosis, heart failure, and myocardial infarction, related to lifestyle, preventive therapies, and interventions, in keeping with those witnessed in the United States over the past several decades.

These national data appear to fully capture all patients with aortic stenosis, which is a unique strength of this database. However, the accuracy of ascertainment of disease and of disease severity, in both the inpatient and outpatient cohorts, is an area of uncertainty and one that merits further investigation of the trends in aortic stenosis incidence and outcomes in this and other healthcare systems.

Conflict of Interest Disclosures: None.
References:


Figure Legend:

**Figure 1.** The natural history of aortic stenosis. After a latent period of gradually increasing valvular stenosis and left ventricular pressure overload, the onset of symptoms heralds an ominous outcome with over 50% of patients succumbing over the next 2-3 years. Although Ross and Braunwald in 1968 conceptualized this symptomatic demarcation occurring in middle age (light gray curve), in the current era the natural history curve often shifts to the right with patients presenting with symptomatic calcific aortic stenosis in the seventh through ninth decades. Numerous studies confirm the same predictably poor survival after symptom onset in this elderly population unless aortic valve replacement is performed. Modified from Ross J Jr, Braunwald E. Aortic stenosis. *Circulation.* 1968;38 (Suppl V):61-67.
Survival (percent) vs. Age (years)

- Latent Period
- Increasing obstruction, myocardial overload
- Symptoms
- Average Age Death
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