Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2012.02520.x

Redefining the natural history of calcific aortic stenosis: lessons from Laennec

Aortic stenosis (AS) represents a major cause of cardiovascular morbidity and mortality amongst ageing populations. The only treatment shown to be effective for advanced symptomatic AS is aortic valve replacement (AVR), which improves symptomatic status, reverses the associated propensity towards gastrointestinal haemorrhage [1] and reduces mortality. Although severe AS may develop early in life, for example, as a complication of bicuspid aortic valve (BAV), rheumatic heart disease or congenital AS, in most cases, AS becomes severe and symptomatic only in the eighth decade or later [2]. By this time, frailty and comorbidities make treatment relatively difficult, and indeed, it can be argued that AVR may not always be cost-effective in such individuals.

There is considerable evidence to suggest that the clinical course of calcific AS developing on initially normal valves is very slow, progressing from barely perceptible valve thickening without any significant transvalvular pressure gradient (termed aortic sclerosis [ASc]) through to severe valve narrowing. However, very little information is available regarding the precise time course of this process, particularly in the early stages.

Most detailed studies in recent years have focused on 'accelerated' stages and forms of AS. It is clear that the presence of BAV is frequently, although not consistently, associated with rapid development of aortic valve narrowing and/or of dilatation of the ascending aorta [3, 4], but it is likely that the pathophysiology of BAV includes a unique combination of impaired nitric oxide generation [5] and marked inflammatory activation [4]. Similarly, in recent years, a number of randomized clinical trials, all evaluating the potential efficacy of lipid-lowering therapies as a means of limiting the rate of progression of AS, have focused on the period between the emergence of moderate AS and its worsening towards symptomatic severe disease [6–8]. These studies have served two purposes: they have demonstrated that AS progression under the conditions of the study is unaffected by lipid lowering, and they have also shown that in most patients included in these trials progression towards severe AS tends to occur rapidly (summary of progression data for ASc and AS is shown in Table 1). Similarly, a rabbit model of accelerated AS, developed by Drolet *et al.* [9], has provided much in the way of mechanistic information but no understanding of the normal course of the disease.

Most of our understanding of the natural history of AS developing in the initially normal valve (the overwhelmingly predominant form of the disease) has been provided by the results of two Scandinavian studies [10, 11], each evaluating a cohort of the normal population for over 15 years. Gulati and Bodegard [12] initially reported the prospective evaluation of a cohort of 2014 apparently healthy Norwegian men aged 40–59 years, who were then followed up for a mean period of 21.5 years. Cardiac evaluation was based on findings at auscultation. Subjects with soft systolic murmurs (comprising 22% of the total cohort) had a fivefold increase in risk of AVR, and those with moderate/loud murmurs had more than a 100-fold increase in AVR risk over the study period.

A more recent study by this group, reported in the current issue of the *Journal of Internal Medicine* [10], has extended the follow-up period to a mean of 35 years. This remarkably long follow-up reveals considerable information about long-term outcomes in this subject cohort. Over the period concerned, AVR was undertaken in just 3% of the individuals who initially had a low-grade systolic murmur, compared to 0.7% of those without a murmur and 44% of those with a more pronounced murmur. However, it is not certain that all subjects who developed severe AS underwent AVR. It is therefore clear that AVR will never be needed in the vast majority of middle-aged men in whom a murmur, clinically corresponding to ASc, is heard. The clear implication of this finding is that in most individuals the rate of progression of ASc towards severe AS is extremely slow.

Clinically based studies of this type have the obvious caveat that the presence of a soft systolic murmur does not equate to the presence of organic heart disease, much less to the presence of ASc. In the study by Bodegard *et al.* [10], half of the men in whom a soft murmur was heard at baseline had no murmur

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Table 1 *Progression of aortic valve disease: comparison between evaluations of ASc and AS*

Stage of disease	Study	Number of subjects	Diagnostic modality	Mean follow-up	Outcomes
ASc	Bodegard *et al.* [10]	2014	Auscultation	35 years	AVR: 0.7% (no murmur), 3% (soft murmur) and 44% (moderate murmur)
ASc	Dey *et al.* [11]	973	Auscultation	15 years	In the absence of baseline coronary disease, relative risk for 15-year mortality in the presence of baseline murmur: 1.16 (males) and 1.35 (females)
ASc	Novaro *et al.* [16]	5621	Echocardiography	5 years	Baseline normal valves: 44% developed ASc and 1% developed AS Baseline ASc: 9% developed AS
AS (moderate)	Cowell *et al.* [7]	155	Echocardiography	25 months	Annualized increase in AS pressure gradient: 6.48 ± 7.43 mmHg (placebo group) and 6.56 ± 7.10 mmHg (atorvastatin group)
AS (mild–moderate)	Rossebo *et al.* [8]	1873	Echocardiography	52 months	Annualized increase in AS pressure gradient: 2.7 ± 0.1 mmHg (simvastatin–ezetimibe group) and 2.8 ± 0.1 mmHg (placebo group)
AS (mild–moderate)	Chan *et al.* [6]	269	Echocardiography	42 months	Annualized increase in AS pressure gradient: 6.1 ± 8.2 mmHg (placebo group) and 6.3 ± 6.9 mmHg (rosuvastatin group)

detected at re-examination after 7 years. The routine availability of echocardiography would have improved the precision of the initial diagnosis of ASc, and indeed, quantitation of valve echogenicity by echocardiographic backscatter techniques [13] might have facilitated evaluation by removing any subjective interpretation of echocardiographic data. This, however, does not detract from the main findings of the study [10]. It should be noted that the selection of a healthy cohort of males in this study may have excluded population subsets at particular risk of rapid progression of ASc to AS, such as individuals with renal insufficiency [14].

The similar study by Dey *et al.* [11], in a cohort of 973 Swedish 70-year-old men and women who were followed up for 15 years, provides complementary information. In this group of older subjects, 31% had a

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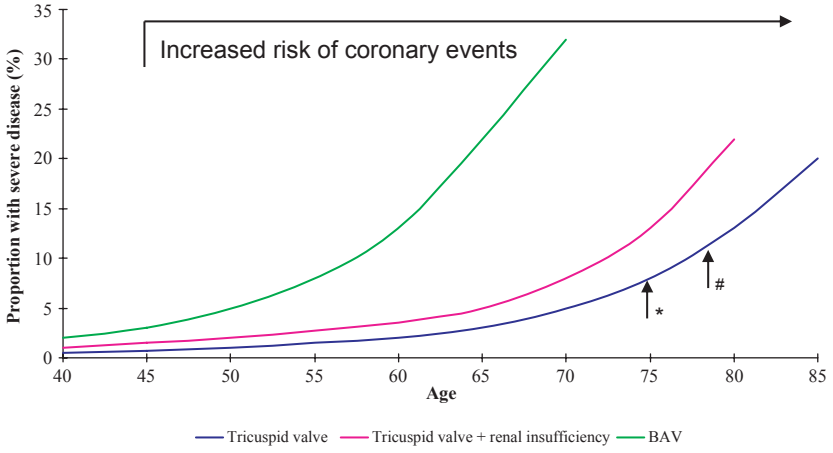

Fig. 1 *Schematic diagram of probable outcomes in patients with ASc at age 40 years: progression, coronary risk and emergence of symptoms. *Increased prevalence of Heyde's syndrome; #increased incidence of classical symptoms (dyspnoea, angina and syncope).*

systolic murmur at baseline, but this largely reflected a greater prevalence of female subjects. Data regarding AVR were not collected; the focus of this Swedish study was the impact of systolic murmurs on the development of congestive heart failure (CHF) and mortality rates during follow-up. This was complicated by the fact that systolic murmurs were more likely to be detected at baseline in individuals with associated hypertension, known coronary disease or CHF. This association is consistent with previous reports indicating that ASc is a marker of risk of coronary events [15].

However, in both these Scandinavian studies [10,11], the presence of systolic murmurs was associated with only a nonsignificant excess of subsequent coronary events. This weak trend may be 'dilutional': as it is not clear which patients in either study had ASc, it is impossible to define associated coronary risk precisely.

Therefore, the results of the study by Bodegard *et al.* [10] suggest that the time course of the pathogenesis of AS should be redefined. It is necessary to delineate special cases, such as BAV and ASc, occurring in the presence of renal insufficiency. However, the majority of ASc patients can be considered to represent a relatively low-risk cohort for many years (see Fig. 1) prior to acceleration of disease and emergence of symptoms. This study also serves to remind us that purely clinical studies may still be valuable almost 200 years after Laennec.

Conflict of interest statement

No conflict of interest was declared.

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