Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.04.018

The Prevalence, Incidence, Progression, and Risks of Aortic Valve Sclerosis

A Systematic Review and Meta-Analysis

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Objectives The aim of this study was to comprehensively review the epidemiology of aortic sclerosis (ASc) and its association with cardiovascular events.

Background ASc, which is defined as thickening or calcification of the aortic valve without significant obstruction of blood flow, is a common finding on cardiac imaging.

Methods We searched MEDLINE and EMBASE from inception to April 2013 for studies describing the epidemiology of ASc and performed a meta-analysis of the risk of adverse events using a random effects model.

Results Twenty-two studies were identified from the systematic review. The prevalence of ASc increased in proportion to the average age of study participants, ranging from 9% in a study in which the mean age was 54 years to 42% in a study in which the mean age was 81 years. In total, 1.8% to 1.9% of participants with ASc had progression to clinical aortic stenosis per year. There was a 68% increased risk of coronary events in subjects with ASc (hazard ratio [HR]: 1.68; 95% confidence interval [CI]: 1.31 to 2.15), a 27% increased risk of stroke (HR: 1.27; 95% CI: 1.01 to 1.60), a 69% increased risk of cardiovascular mortality (HR: 1.69; 95% CI: 1.32 to 2.15), and a 36% increased risk of all-cause mortality (HR: 1.36; 95% CI: 1.17 to 1.59).

Conclusions ASc is a common finding that is more prevalent with older age. Despite low rates of progression to ASc, there is an independent increase in morbidity and mortality associated with the condition. (J Am Coll Cardiol 2014;63:2852–61) © 2014 by the American College of Cardiology Foundation

Aortic valve sclerosis (ASc) is thickening and/or calcification of the aortic valve without significant obstruction of flow and is a common finding in older men and women. A proportion of people with ASc progress to hemodynamically significant calcific aortic valve disease (CAVD), which is then called aortic stenosis (AS).

ASc is, by its nature, asymptomatic and is diagnosed by cardiac imaging with either echocardiography or computed tomography (CT). In general, diagnosis of ASc on echocardiography relies on a subjective assessment of focal or diffuse aortic valve thickening with or without increased echogenicity (suggestive of calcification) but with relatively unrestricted leaflet opening and no significant hemodynamic effect, which is usually indicated by a maximal transvalvular velocity of <2 to 2.5 m/s (1).

The subjective and primarily qualitative nature of the echocardiographic diagnosis of ASc (which is subject to errors attributable to operator experience, gain settings, and harmonic imaging) led to the search for more quantitative and objective measures of early CAVD. A quantitative technique developed on the basis of transthoracic echocardiography (TTE) is direct measurement of the ultrasonic backscatter of the valve (2). However, the most widely used quantitative measure of CAVD is aortic valve calcification (AVC) as measured by CT. Using different CT techniques, AVC, measured in Agatston units, has been shown to have a strong linear correlation with calcium weight in explanted aortic valves as well as a definite and nonlinear correlation with aortic valve area and maximal transvalvular aortic gradient in patients with both normal and depressed ejection fraction (3–6).

Another area of contention is the significance of the valvular lesion. ASc is associated with traditional cardiovascular risk factors (7). Whether ASc is a marker of a purely valvular disease or generalized vascular disease is currently under debate; some studies have shown an increased risk of

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Manuscript received December 21, 2013; revised manuscript received March 6, 2014, accepted April 18, 2014.

cardiovascular events in people with ASc (8), whereas others have shown that many of these risks are reduced or eliminated once other risk factors for cardiovascular events are taken into account (9).

To help resolve these issues, we performed a systematic review to examine the epidemiology of ASc in the general population. In particular, we wished to determine the prevalence, incidence, and rate of progression of ASc and to combine estimates of the risk of adverse events.

Methods

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting the systematic review (10).

Search strategy. The search strategy was designed prospectively. MEDLINE and EMBASE were searched from inception to April 2013. Given the overlap between AS and aortic sclerosis and the varying definitions of ASc, we elected to use a broad search strategy including both aortic sclerosis and AS that focused on incidence, prevalence, progression, or outcomes (the exact search terms used are listed in the Online Appendix). We eliminated those that focused solely on AS in the subsequent search. No language restrictions were used. Conference proceedings were not excluded.

Citation details and abstracts were stored in a database (FileMaker Pro 11.0v4, FileMaker, Santa Clara, California). Initially, titles alone were reviewed for suitability. The abstracts of suitable titles were obtained, and these were then reviewed for suitability for full-text retrieval. Data were then extracted as described in the following text from suitable full-text reports. Additional appropriate reports were added when discovered by citation tracking.

Inclusion and exclusion criteria. We designed a relatively strict set of inclusion and exclusion criteria and considered studies meeting these criteria to be of acceptable quality. Any population-based study that examined ASc was included. ASc was considered to mean any thickening or calcification of the aortic valve without significant hemodynamic effect and could be diagnosed by any means, such as TTE, transesophageal echocardiography, or CT. Electron beam and multidetector CT were treated similarly for the purposes of this review. Only studies with prospective enrollment were included. Most of the studies performed off-line retrospective image analysis; these were included as long as the studies had prospective enrollment and image acquisition.

Hospital- or patient group–specific studies were excluded, with the exception of studies performed in hypertensive patients. Studies that focused solely on congenital valve disease, including bicuspid aortic valves, were excluded.

Data extracted. In addition to publication details, we extracted details about the number of participants, the age and sex distribution of the population examined, the means of diagnosing ASc, and, as appropriate, the prevalence, incidence, or progression of ASc, along with the definition of progression. For outcome studies, we extracted the definition of the type of event, the crude event rate in the ASc group and the control group, and the adjusted risk due to ASc. We also extracted the type of risk ratio and how the risk ratio was adjusted. The authors of reports without full datasets were contacted in an effort to gather any required information not reported.

Abbreviations and Acronyms

- **AS** = aortic stenosis
- **ASc** = aortic valve sclerosis
- **AVC** = aortic valve calcification
- **CAC** = coronary artery calcium
- **CAVD** = calcific aortic valve disease
- **CI** = confidence interval
- **CT** = computed tomography
- **HR** = hazard ratio
- **TTE** = transthoracic echocardiography

Statistical methods. The differences between the ages of the participants in the studies precluded meaningful meta-analysis of the data on prevalence, incidence, and progression. To confirm the link between age and prevalence, we used linear regression to examine the association between the average age reported in the study and the prevalence of ASc (Stata version 12.1, StataCorp, College Station, Texas).

We wished to meta-analyze the information on adverse outcomes, in particular coronary events, stroke, cardiovascular mortality, and all-cause mortality. Given the expected heterogeneity between studies with regard to diagnostic criteria and definition of outcomes, we used a random effects model. The DerSimonian and Laird model with inverse variance weights was used to combine hazard and risk ratios using RevMan version 5.2.5 (11).

Results

Systematic review. Figure 1 shows the results of the search strategy. Automated duplicate identification was inefficient, leading to a number of duplicates identified only after abstract review. Twenty-two reports were retrieved for data extraction and form the basis of the results.

Prevalence. Nineteen reports were identified that examined the prevalence of ASc (Table 1) (9,12–29). In all TTE-based studies, ASc was diagnosed on the basis of increased thickening and/or echogenicity, with a variable maximal transvalvular velocity (indicated in Table 1) used to differentiate aortic sclerosis from AS. In the Cardiovascular Health Study, 2 different criteria were used, 2.5 and 2.0 m/s, but the second of these was used only in a supplemental cohort of 687 participants (8,22). Two reports from the Framingham Offspring Study were included, because ASc was diagnosed by different methods (14,23). The association with age seen within studies was also seen across studies (Fig. 2), with an 1.5% increase in prevalence per year of increase in the mean age of study participants (95% confidence interval [CI]: 0.75% to 2.25%; $p = 0.0007$, $R^2 = 0.549$). Studies in which the mean age of the participants was younger than 60 years had low levels of ASc, with all but 2 of