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

A Systematic Review and Meta-Analysis

Sean Coffey, MBBS,*† Brian Cox, PhD,‡ Michael J. A. Williams, MD†

Oxford, United Kingdom; and Dunedin, New Zealand

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

From the *Department of Cardiology, Oxford University Hospitals, Oxford, United Kingdom; †Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; and the ‡Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand. Dr. Coffey was supported by the Tony Hocken Scholarship (Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand). Dr. Cox was supported by the Director's Cancer Research Trust. Dr. Williams has reported that he has no relationships relevant to the contents of this paper to disclose.

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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

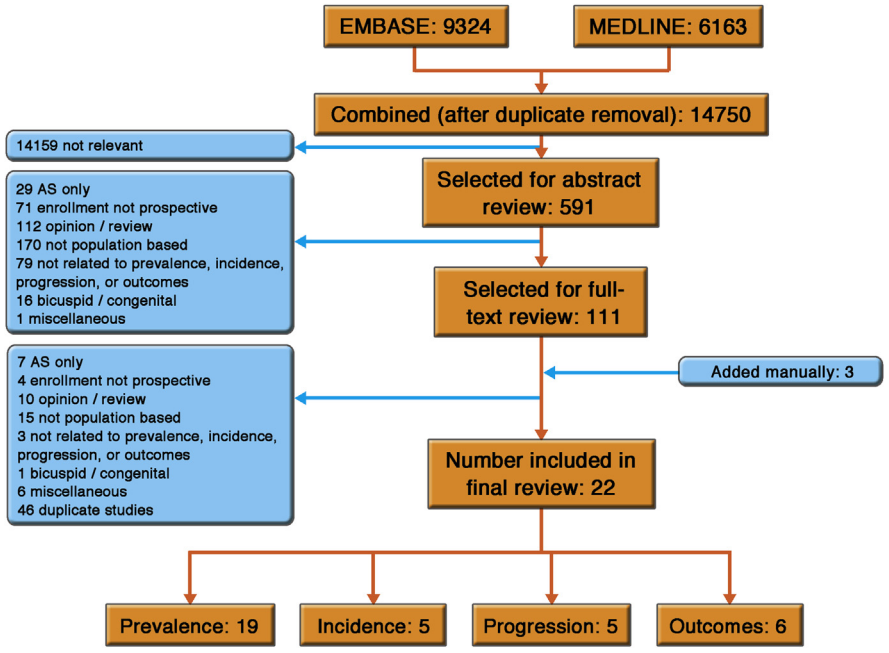

Figure 1 Results of Search Strategy

AS = aortic stenosis.

these studies showing <10% prevalence (13,21,23–26). Figure 2 shows relatively similar prevalence for all of the diagnostic modalities used.

Incidence. Five reports documented the incidence of ASc (Table 2) (12,15,17,22,30). A clear difference was found between CT- and TTE-based methods, with a yearly incidence of 1.7% to 4.1% with CT-based diagnosis compared with 7.5% to 8.8% with TTE-based diagnosis.

Progression. Five reports examined the progression of ASc (Table 3) (12,15,17,22,30), with 3 of these focusing on imaging outcomes and 2 on progression to clinical AS. In total, 1.8% to 1.9% of subjects with ASc progressed to clinical AS per year (15,22).

Risks. Six reports related baseline ASc to risk of death and major adverse cardiovascular events (8,9,19,24,25,27). Details of the studies are shown in Table 4, with the individual adverse event type and associated risk ratios shown in Table 5. A higher absolute event rate in subjects with ASc was evident across all event categories, with reduction of the risk once traditional cardiovascular risk factors were taken into account.

There was a statistically significant association with increased coronary risk in subjects with ASc in 3 of the 4 studies (8,24,27), although one study showed a non–statistically significant increase (9). The latter study included a coronary artery calcium (CAC) score in the fully adjusted model (9), and the model with all other cardiovascular risk factors but without CAC showed a statistically significant increase in coronary events, with a hazard ratio (HR) of 1.72 (95% CI: 1.19 to 2.49). Whether the other studies would have retained statistical significance if CAC had been included as a covariate is not clear; it is certain that there is a strong link between coronary and valvular calcification (9). Our meta-analysis showed a combined HR of 1.68 (95% CI: 1.31 to 2.15), with, as might be expected, substantial heterogeneity between results ($I^2 = 62\%$) (Fig. 3).

All of the studies that reported stroke as an outcome showed a small but not statistically significant increase in the risk of stroke in subjects with ASc (8,9,25). The meta-analysis of these results showed a statistically significant increase in stroke, with an HR of 1.27 (95% CI: 1.01 to 1.60) and no detectable heterogeneity ($I^2 = 0\%$).

There was a statistically significant increased risk of both cardiovascular and all-cause mortality in subjects with ASc (8,9,19). After full adjustment, subjects with ASc had a risk of dying from any cause that was 36% higher than that of those without ASc (HR: 1.36; 95% CI: 1.17 to 1.59), although the risk of cardiovascular death was 69% higher (HR: 1.69; 95% CI: 1.32 to 2.15). Notably, in the study by Owens et al. (9), the increased cardiovascular mortality remained even after adjusting for CAC. No detectable heterogeneity was seen for either cardiovascular or all-cause mortality ($I^2 = 0\%$ for both).

Discussion

In this systematic review and meta-analysis, we comprehensively described the current epidemiology of ASc. As

Table 1 Prevalence of Aortic Valve Sclerosis

First Author (Ref.#) (Year)	Number of Participants	Method of Diagnosis	Population	Age, yrs*	Female, %	Prevalence, %
Messika-Zeitoun et al. (15) (2007)	262	CT	Randomly selected American subjects without previous cardiac procedure (ECAC Study)	68 ± 5	57	27
Thanassoulis et al. (14) (2010)	1,323	CT	Healthy American subjects (Framingham Offspring Study)	64 ± 9	52	39
Kaelsch et al. (13) (2011)	4,083	CT	Randomly selected German subjects (Heinz Nixdorf Recall Study)	59.4 ± 7.7	51	11.2
Kearney et al. (12) (2012)	3,149	CT	Randomly selected Icelandic subjects (AGES-Reykjavik Study)	75 ± 5	58	43
Owens et al. (9) (2012)	6,685	CT	American subjects free of cardiovascular disease at baseline (MESA)	62 ± 10	53	13.4
Agmon et al. (16) (2001)	381	TEE†	Randomly selected American subjects (SPARC Study)	67 (51; 101)	48	35.4
Sverdlov et al. (17) (2012)	204	TTE backscatter	Randomly selected Australian subjects	63 ± 6	57.6	17.6
Lindroos et al. (29) (1993)	552	TTE†	Randomly selected Finnish subjects (Helsinki Ageing Study)	Number of participants in each age group: 55–71 yrs, 76; 75–76 yrs, 197; 80–81 yrs, 155; 85–86 yrs, 124.	71.4	39.7
Gotoh et al. (28) (1995)	784	TTE‡	Subjects 35 years of age and older who were residents of a single village in Japan	61.9 ± 10.6	55.7	18.2
Aronow et al. (27) (1999)	2,358	TTE§	American subjects who were residents of a long-term care facility without terminal illness	81 ± 8	68.4	41.6
Taylor et al. (24) (2005)	2,279	TTE†	African-American subjects free of cardiovascular disease (ARIC Study)	59.1 ± 5.6	65	7.7
Kizer et al. (25) (2005)	2,723	TTE†	Native American subjects without cardiovascular disease (Strong Heart Study)	59.2 ± 7.7	64.9	7.5
Agno et al. (26) (2005)	1,624	TTE‡	Hypertensive American subjects (Hypertension Genetic Epidemiology Network Study)	54 ± 11	64.9	9.4
Fox et al. (23) (2006)	3,047	TTE†	Healthy American subjects (Framingham Offspring Study)	59 ± 10	52	6.2
Novaro et al. (22) (2007)	5,621	TTE‡‖	Randomly selected Medicare-eligible American subjects (Cardiovascular Health Study)	72.9 ± 5.5	57.5	29
Stritzke et al. (21) (2009)	953	TTE†	Randomly selected German subjects (KORA/MONICA study)	57.7 ± 11.7	52	28
Völzke et al. (19) (2010)	2,081	TTE†	German subjects free of cardiovascular disease and cancer (SHIP Study)	Women: 60 (53–68) Men: 61 (54–69)	51.1	25.4
Sashida et al. (20) (2010)	2,085	TTE†	American subjects free of stroke (Northern Manhattan Study)	68.2 ± 9.7	60	51.7
Lowery et al. (18) (2012)	3,010	TTE¶	Healthy volunteers from the United Kingdom	60	NR	2.33

*Values are mean ± SD, mean (minimal; maximal), median (interquartile range), or minimal. †No maximal transvalvular velocity specified. ‡Maximal transvalvular velocity <2.0 m/s. §Maximal transvalvular velocity <1.5 m/s. ‖Maximal transvalvular velocity <2.5 m/s. ¶Full description of diagnostic criteria not reported.

AGES = Age, Gene-Environment Susceptibility; ARIC = Atherosclerosis Risk in Communities; CT = computed tomography; ECAC = Epidemiology of Coronary Artery Calcification; KORA/MONICA = Cooperative Research in the Region of Augsburg/Monitoring of Trends and Determinations in Cardiovascular Disease-Augsburg; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; SHIP = Study of Health in Pomerania; SPARC = Stroke Prevention: Assessment of Risk in a Community; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

expected, there was a clear increase in the prevalence of ASc with increasing age of the population surveyed, which makes ASc, similar to more advanced CAVD, a modern problem related to an aging population.

The rate of incident ASc was relatively high even in younger age groups, with 1.7% of those with normal aortic valves at baseline developing ASc per year in a population with a mean age of 61 years (30) and 9% with a mean age of 72 years developing some degree of CAVD per year (22). There was a difference in incidence measured by different diagnostic modalities, and it is likely that the lower sensitivity of TTE compared with CT led to a larger number of subjects with undetected CAVD at baseline in the TTE-based studies. Although lack of a diagnostic gold standard makes direct comparison difficult, CT-based diagnosis of AVC and echocardiographic diagnosis of ASC both appear to represent the same disease process. Using any AVC detected by CT as the criteria for diagnosis of ASc leads to a higher prevalence of ASc, but still with 67% agreement between the 2 modalities, whereas higher cutoffs for AVC lead to progressively lower estimates of prevalence (31,32).

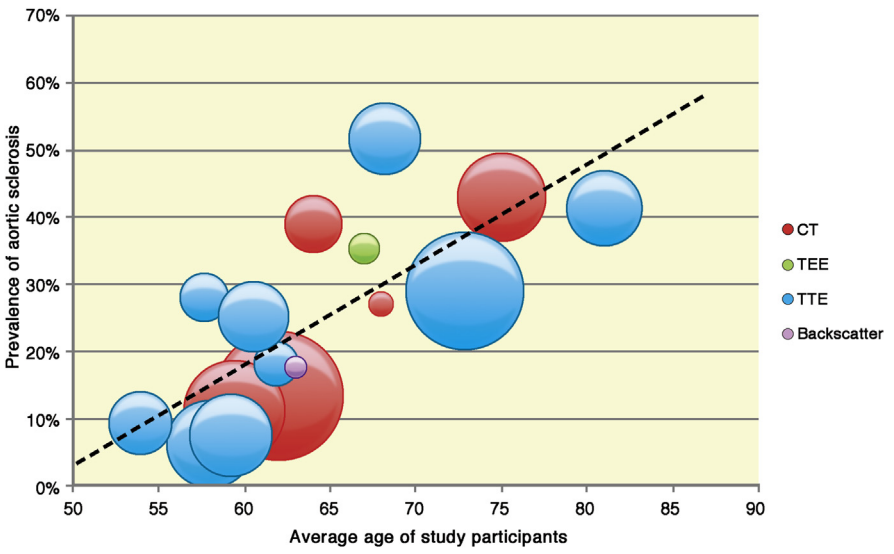

Figure 2 Prevalence of Aortic Sclerosis According to the Average Age of the Participants in the Study

The average age was either the mean or median according to the study report, and 2 studies without these data are not shown in the figure. The area of each data point is proportional to the number of study participants. The straight line indicates the linear regression line fitted, which showed a 1.5% (95% confidence interval: 0.75% to 2.25%) increase in prevalence for every year increase in average age ($p = 0.0007$, $R^2 = 0.549$). CT = computed tomography; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

The overall rate of progression of aortic sclerosis to AS was low: <2% per year. Medical therapies such as statins have shown no benefit with regard to slowing or halting the progression of AS (33–35), raising the possibility that the intervention came at a stage too late in the disease process (36). However the low rate of progression of ASc means more refined predictors of progression will be required to adequately target those who might benefit from disease-modifying therapies. Interestingly, in contrast to de novo development of AVC, once calcium is detectable in the aortic valve, traditional cardiovascular risk factors play much less of a role. In 2 studies, age was not associated with rate of progression (15,30), whereas higher diastolic blood pressure was associated with a decreased rate of progression (30). Baseline calcification score and male sex were associated with a higher rate of progression in both studies. Biomarkers such as calcium concentration and impaired platelet nitric oxide responsiveness have been shown to be predictive of

Table 2 Incidence of Aortic Valve Sclerosis

First Author (Ref. #) (Year)	Number of Participants	Method of Diagnosis	Population	Age, yrs*	Female, %	Follow-Up, yrs*	Incidence per Year, %
Messika-Zeitoun et al. (15) (2007)	192	CT	Randomly selected American subjects without previous cardiac procedure (ECAC Study)	67 (5)	60	3.8 ± 0.9	2.6
Novaro et al. (22) (2007)	3,917	TTE†	Randomly selected Medicare-eligible American subjects (Cardiovascular Health Study)	72 (5)	60	5	8.8 (or 9 if aortic stenosis is included)
Owens et al. (30) (2010)	5,142	CT	American subjects free of cardiovascular disease at baseline (MESA)	62 (10)	45.5	2.4 ± 0.9	1.7
Kearney et al. (12) (2012)	1,934	CT	Randomly selected Icelandic subjects (AGES-Reykjavik Study)	NR	NR	5.3 (2.6–9.2)	4.1
Sverdlov et al. (17) (2012)‡	160	TTE backscatter	Randomly selected Australian subjects	63 (6)	58	4	7.5

*Values are mean ± SD, mean, or median (minimal to maximal). †Maximal transvalvular velocity <2.0 or 2.5 m/s. ‡Baseline information for participants in the study by Sverdlov et al. (17) was taken from all 204 participants without aortic sclerosis at baseline in the study by Ngo et al. (42).

Abbreviations as in Table 1.

Table 3 Progression of Aortic Valve Sclerosis

First Author (Ref. #) (Year)	n	Method of Diagnosis	Population	Age, yrs*	Female, %	Baseline Prevalence in Study, %	Follow-Up, yrs*	Definition of Progression	Progression Rate per Year
Progression of imaging outcomes									
Messika-Zeitoun et al. (15) (2007)	70	CT	Randomly selected American subjects without previous cardiac procedure (ECAC Study)	70 (5)	47	27	3.8 ± 0.9	Increased AVC	Mean ± SD, 39 ± 53 Agatston units
Owens et al. (30) (2010)	738	CT	American subjects free of cardiovascular disease at baseline (MESA)	70 (8)	39	13.4	2.4 ± 0.9	Increased AVC	Median (IQR), 2 (−21 to 37) Agatston units
Kearney et al. (12) (2012)	1,215	CT	Randomly selected Icelandic subjects (AGES-Reykjavik study)	NR	NR	43	5.3 (2.6–9.2)	Increased AVC	Median (IQR), 10 (3–31) Agatston units
Sverdlov et al. (17) (2012)†	44	TTE backscatter	Randomly selected Australian subjects	63 (6)	57.6	17.6	4	Increase in backscatter	11.95% of subjects
Progression to aortic stenosis									
Messika-Zeitoun et al. (15) (2007)	70	CT	Randomly selected American subjects without previous cardiac procedure (ECAC Study)	70 (5)	47	27	3.8 ± 0.9	Moderate or severe aortic stenosis	1.9% of subjects
Novaro et al. (22) (2007)	1,610	TTE‡	Randomly selected Medicare-eligible American subjects (Cardiovascular Health Study)	74 (6)	51	29	5	Aortic stenosis	1.8% of subjects

*Values are mean ± SD, median (minimal to maximal), or mean. †Baseline information for participants in the study by Sverdlov et al. (17) was taken from the description of the entire group of 49 subjects with aortic sclerosis at baseline in the study by Ngo et al. (42). ‡Maximal transvalvular velocity <2.5 or 2.0 m/s.

Abbreviations as in Table 1. AVC = aortic valve calcification; IQR = interquartile range.

progression of TTE backscatter, but these biomarkers require further investigation before they can be considered ready for clinical use (17).

One hypothesis to explain the low rate of progression is that ASc is not in itself an early stage of CAVD but is simply a marker of general vascular disease, with an attendant increase in cardiovascular risk. Coronary disease is common in patients with CAVD; in those with severe AS requiring intervention, between 40% and 75% have concomitant coronary artery disease (37). The studies examining coronary events and cardiovascular death either excluded participants with prior coronary disease or included it as a covariate. A high rate of preclinical disease, as measured by CAC, is still seen in participants with ASc; 82% had some CAC in MESA (Multi-Ethnic Study of Atherosclerosis) compared with 45% in participants without ASc (9). However the increase in cardiovascular mortality seen even after accounting for CAC indicates that, although there is substantial overlap with coronary disease, ASc is accompanied by an additional risk. Similarly, the very low rate of progression to AS in subjects with normal valves supports the idea of aortic sclerosis as a separate disease process. In the study by Novaro et al. (22), only 1% of those with normal valves developed AS over 5 years compared with 9% of those with aortic sclerosis. None of those with normal valves at baseline developed moderate or severe AS in the study by Messika-Zeitoun et al. (15). Although a shorter interval between imaging would be required to definitively prove that all patients developing AS progress through aortic sclerosis initially, it seems likely on the basis of these studies that aortic sclerosis is indeed a necessary but not sufficient step to AS.

The link between adverse outcomes and ASc is seen clearly in this review, with an increased risk in all reported event types. How do event rates compare between those with aortic sclerosis and those with AS? The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial and other studies have consistently shown increasing event rates with increasing severity of AS (38–40). Most population-based studies have too few participants with AS to allow meaningful comparison between those with AS and those with aortic sclerosis. The Cardiovascular Health Study is an exception, which showed an all-cause mortality rate of 41.3% for participants with AS compared with 21.9% for those with aortic sclerosis (including those with baseline coronary disease) and 14.9% for those with normal valves over 5 years of follow-up (8). Cardiovascular mortality (19.6% vs. 10.1% vs. 6.1% for participants with AS, aortic sclerosis, and normal valves, respectively), myocardial infarction (11.3% vs. 8.6% vs. 6.0%, respectively), and stroke (11.6% vs. 8.0% vs. 6.3%, respectively) showed similar patterns. Therefore, aortic sclerosis appears to confer an intermediate risk between normal valves and stenotic valves.

A recent meta-analysis also reported on the risk of cardiovascular events and mortality in patients with ASc and found lower (but still present) risk of all-cause and

Table 4 Studies Examining Major Adverse Events in Participants With Aortic Sclerosis

First Author (Ref. #) (Year)	n	Method of Diagnosis	Population	Age, yrs*	Female, %	Follow-Up, yrs*	Adjustment in Multivariate Analysis
Otto et al. (8) (1999)	4,073 (4,271 for coronary events and stroke)	TTE†	Randomly selected Medicare-eligible American subjects (Cardiovascular Health Study); only those without prevalent cardiovascular disease are shown here	72.9 ± 5.5	57.5	5	Age, sex, height, presence of hypertension, current smoking, elevated LDL cholesterol level, presence of diabetes
Aronow et al. (27) (1999)	1,980	TTE‡	American residents of a long-term care facility without terminal illness	81 ± 8	68.4	3.8 (2.3)	Age, prior coronary artery disease, sex
Taylor et al. (24) (2005)	2,279	TTE§	African-American subjects free of cardiovascular disease (ARIC Study)	59.1 ± 5.6	65	NR	Age, sex, diabetes mellitus status, systolic blood pressure, hypertension medication status, smoking status, high-density lipoprotein level, carotid intimal-medial thickness, fibrinogen level, and von Willebrand factor level
Kizer et al. (25) (2005)	2,273	TTE§	Native American subjects without cardiovascular disease at baseline (Strong Heart Study)	59.2 ± 7.7	65	7	Age and sex
Völzke et al. (19) (2010)	2,081	TTE§	German subjects free of cardiovascular disease and cancer (SHIP Study)	Women: 60 (53–68) Men: 61 (54– 69)	51.1	8.6	Age, sex, education, smoking status, diabetes mellitus, serum LDL cholesterol level, use of antihypertensive medication
Owens et al. (9) (2012)	6,685	CT	American subjects free of cardiovascular disease at baseline (MESA)	62 ± 10	53	5.8 (5.6–5.9)	Age, sex, race, body mass index, systolic and diastolic blood pressure, diabetes status, use of antihypertensive medication, smoking status, family history of heart attack, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, use of cholesterol-lowering medication, renal function, log (C-reactive protein), log (coronary artery calcium score + 1)

*Values are mean ± SD, mean, or median (IQR). †Maximal transvalvular velocity <2.0 or 2.5 m/s. ‡Maximal transvalvular velocity <1.5 m/s. §No maximal transvalvular velocity specified.
Abbreviations as in Table 1. LDL = low-density lipoprotein.

Table 5 Risk of Major Adverse Events in Participants With Aortic Sclerosis

First Author (Ref. #) (Year)	Event Definition	Absolute Rate per Year for Aortic Sclerosis, %	Absolute Rate per Year for Comparison Group, %	Adjusted HR/RR (95% CI)
Coronary events				
Otto et al. (8) (1999)	MI	1.6	0.9	RR: 1.40 (1.07–1.83)
Aronow et al. (27) (1999)	New coronary events: fatal or nonfatal MI, SCD	13.9	8.16	RR: 1.76 (1.52–2.03)
Taylor et al. (24) (2005)	Definite or probable hospitalized MI, ECG evidence of silent MI, definite CAD death, CABG/PCI	NR	NR	HR: 3.82 (1.83–7.97)
Owens et al. (9) (2012)	MI, resuscitated cardiac arrest, cardiovascular death	6.9	1.9	HR: 1.41 (0.98–2.02)
Stroke				
Otto et al. (8) (1999)	Fatal and nonfatal stroke	1.6	1.0	RR: 1.25 (0.96–1.64)
Kizer et al. (25) (2005)	Fatal and nonfatal stroke	0.49	0.45	IRR: 1.15 (0.45–2.94)*
Owens et al. (9) (2012)	Fatal and nonfatal stroke	3.6	1.2	HR: 1.38 (0.84–2.27)
Cardiovascular mortality				
Otto et al. (8) (1999)	Death from cardiac causes	1.4	0.6	RR: 1.52 (1.12–2.05)
Völzke et al. (19) (2010)	Cardiovascular death	1.0	0.21	HR: 1.87 (1.12–3.11)
Owens et al. (9) (2012)	Cardiovascular death excluding fatal stroke	0.38	0.05	HR: 2.51 (1.22–5.21)
All-cause mortality				
Otto et al. (8) (1999)		3.7	1.9	RR: 1.35 (1.12–1.61)
Völzke et al. (19) (2010)		2.51	0.76	HR: 1.40 (1.06–1.85)

*The IRR and 95% CI reported by Kizer et al. (25) are not statistically consistent, and the true figure is likely to be an IRR of 1.15 (95% CI: 0.45 to 2.94).

Abbreviations as in Table 1. CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; ECG = electrocardiographic; HR = hazard ratio; IRR = incidence rate ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; RR = risk ratio; SCD = sudden cardiac death.

cardiovascular mortality, although the additional risk of stroke was not statistically different (41). It is likely that the patient subgroups included had a higher baseline risk, where the additional risk due to ASc is not as evident. We excluded many of the studies used in that meta-analysis because of nonprospective enrollment or restriction to a particular disease subgroup, such as those with advanced renal disease. In addition, we included a study that the authors of that meta-analysis identified but did not use (19) and included the first report from the Cardiovascular Health Study, which used

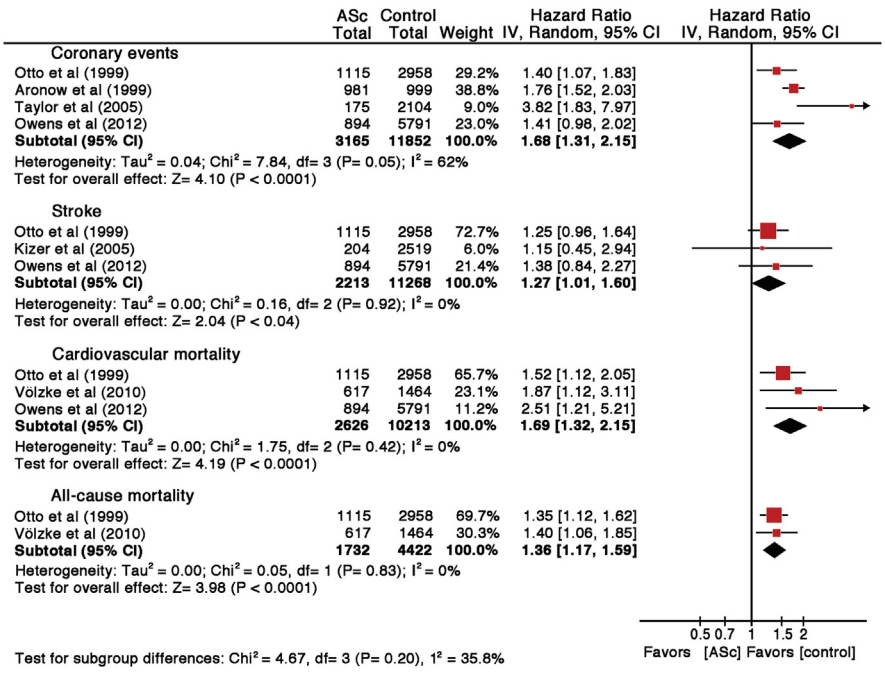

Figure 3 Forest Plot of Major Adverse Events According to the Presence of ASc

ASc = aortic sclerosis; CI = confidence interval; IV = inverse variance; Random = random effects model.

echocardiography from an earlier time point in the study, thereby reducing the risk of survivorship bias (8). Although no statistically significant increase in the risk of stroke was seen in the individual studies, our meta-analysis showed a 27% increased risk of stroke in those with ASc compared with those with normal aortic valves (HR: 1.27; 95% CI: 1.01 to 1.60). The meta-analysis was performed on ratios obtained after adjusting for other risk factors, so the presence of ASc appears to be an independent risk factor for major adverse events. Whether any current or future treatments will directly alter this risk remains to be tested, but in the meantime, these results imply that aggressive investigation and evidence-based treatment of other cardiovascular risk factors should be performed in all people with ASc and at least 5-year life expectancy.

Study limitations. Some of the limitations to this study are common to other meta-analyses, such as heterogeneity between study populations, definitions of exposure, and definitions of outcomes. For example, a number of these studies were conducted with ethnically homogeneous populations; the ARIC (Atherosclerosis Risk in Communities) study examined African-American subjects (24), the AGES (Age, Gene-Environment Susceptibility)-Reykjavik Study examined Icelandic subjects (12), and the Strong Heart Study examined Native American subjects (25), whereas the Framingham Offspring Study consisted predominantly of white American subjects of European descent (14). Differences in the definition of exposure are predominantly attributable to the imaging modality used to diagnose ASc, as discussed in the preceding text. Prevalence and progression rates were relatively consistent despite these differences in the included studies. Differences in definitions of outcomes, as shown in Table 5, are also a potential source of heterogeneity between studies. Finally, another limitation was the small number of studies reporting outcomes, in particular cardiovascular and all-cause mortality, limiting the ability to detect heterogeneity for coronary heart disease, stroke, cardiovascular disease, and all-cause mortality. Despite these caveats, the risk associated with ASc was remarkably consistent across studies.

Conclusions

ASc is common in the general population, increases in prevalence with the mean age of the population, and has a low rate of progression to AS. Despite this, it is independently associated with an increased risk of coronary events, stroke, cardiovascular mortality, and all-cause mortality. Investigation into whether these risks for ASc are modifiable is warranted.

Reprint requests and correspondence: Dr. Sean Coffey, OxValve Study, Room B15, Level 0, Cardiac Investigations Annexe, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom. E-mail: sean.coffey@ouh.nhs.uk.

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Key Words: aortic valve sclerosis ■ aortic valve stenosis ■ epidemiology ■ heart valve diseases ■ meta-analysis ■ systematic review.

APPENDIX

For the list of search terms used for the review, please see the online version of this article.