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The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis

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Abstract
Objectives: We wished to comprehensively review the epidemiology of ASc and its association with cardiovascular events.
Background: Aortic sclerosis (ASc), thickening or calcification of the aortic valve without significant obstruction to 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 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 with mean age 54 years to 42% in a study with mean age 81 years. 1·8-1·9% of participants with ASc progressed 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) 1·31-2·15), a 27% increased risk of stroke (HR 1·27, 95% CI 1·01-1·60), a 69% increased risk of cardiovascular mortality (HR 1·69, 95% CI 1·32-2·15), and a 36% increased risk of all-cause mortality (HR 1·36, 95% CI 1·17-1·59).
Conclusions: Aortic sclerosis is a common finding that is more prevalent with older age. Despite low rates of progression to aortic stenosis, there is an independent increase in morbidity and mortality associated with the condition.

Key Words: Aortic valve stenosis, aortic valve sclerosis, heart valve diseases, epidemiology, systematic review, meta-analysis

Abbreviations
AS – aortic stenosis
ASc – aortic valve sclerosis
AVC – aortic valve calcium
CAC – coronary artery calcium
CAVD – calcific aortic valve disease
CT – computed tomography
MACE – major adverse cardiovascular events
TEE – transesophageal echocardiography
TTE – transthoracic echocardiography

Introduction

Aortic valve sclerosis (ASc) is thickening and/or calcification of the aortic valve, without significant obstruction to flow, and is a common finding in older men and women. A proportion of people with ASc progress to haemodynamically 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, 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 haemodynamic effect, which is usually indicated by a maximum transvalvular velocity (Vmax) of less than 2-2·5m/s (1).

The subjective and primarily qualitative nature of the echocardiographic diagnosis of ASc, subject as it is to errors due to operator experience, gain settings and harmonic imaging, led to the search for more quantitative and objective measures of early CAVD. A quantitative technique based on 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 non-linear correlation with aortic valve area and maximum 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 generalised vascular disease is currently under debate, as some studies have shown an increased risk of cardiovascular events in people with ASc (8), while 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 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 until April 2013. Given the overlap between aortic stenosis and sclerosis and the varying definitions of ASc used, we elected to use a broad search strategy including both aortic sclerosis and aortic stenosis 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 aortic stenosis 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, 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 was then extracted as described below from suitable full-text articles. Additional appropriate articles were added when discovered by citation-tracking.

Inclusion and exclusion criteria

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

Hospital or patient-group specific studies were excluded, with the exception of studies performed in hypertensive patients. Studies based 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 type of event, the crude event rate in the ASc 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 articles without full datasets were contacted in an effort to gather any required information not reported.

Statistical methods

The differences between ages in the studies precluded meaningful meta-analysis of prevalence, incidence and progression figures. To confirm the link between age and prevalence, we used linear regression to examine the association between average age reported in the study and prevalence of ASc (Stata version 12·1, Statacorp, College Station, Texas).

We wished to meta-analyse 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 only being identified after abstract review. 22 articles were retrieved for data extraction and these form the basis of the results.

Prevalence

19 articles were identified that examined the prevalence of ASc (Table 1) (9, 12–29). Transthoracic echocardiography based studies all diagnosed ASc on the basis of increased thickening and/or echogenicity, with a variable maximum transvalvular velocity (indicated on Table 1) being used to differentiate aortic sclerosis and aortic stenosis. In the Cardiovascular Health Study, two different criteria were used, 2.5 and 2.0 meters/second, 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, as the diagnosis of ASc was made by different methods (14, 23). The association with age seen within studies was also seen across studies (Fig. 2), with an

increase of 1·5% in prevalence per year of increase in average age of study participants (95% confidence interval 0·75 to 2·25%, p=0·0007, R^2 0·549). Those studies with average age less than 60 years had low levels of ASc, with all but two of these studies showing less than 10% prevalence (13, 21, 23–26). Figure 2 shows relatively similar prevalence obtained by any of the diagnostic modalities used.

Incidence

Five articles documented the incidence of ASc (Table 2) (12, 15, 17, 22, 30). Here a clear difference was found between CT and TTE based methods, with a yearly incidence of 1·7-4·1% seen with CT based diagnosis compared to 7·5-8·8% with TTE based diagnosis.

Progression

Five articles examined the progression of ASc (Table 3) (12, 15, 17, 22, 30), with three of these focusing on imaging outcomes and two on progression to clinical aortic stenosis. 1·8-1·9% of subjects with ASc progressed to clinical aortic stenosis per year (15, 22).

Risks

6 articles relate baseline ASc to risk of death and major adverse cardiovascular events (MACE) (8, 9, 19, 24, 25). 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 for three out of the four studies (8, 24, 27), while one study showed a non-statistically significant increase (9). It should be noted that this 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 of 1·72 (95% confidence interval [CI] 1·19 – 2·49). Whether the other studies would have retained statistical significance if CAC had been included as a co-variate is not clear – it is certain that there is a strong link between coronary and valvular calcification (9). Meta-analysis showed a combined hazard ratio of 1·68 (95% CI 1·31-2·15), with, as might be expected, substantial heterogeneity between results (I^2=62%) (Figure 3).

All of the studies reporting stroke as an outcome showed a small but non-statistically significant increase in risk of stroke in subjects with ASc (8, 9, 25). The meta-analysis of these results showed a statistically significant increase in stroke, with HR 1·27 (95% CI 1·01-1·60) 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 36% higher than those without (HR 1·36, 95% CI 1·17-1·59), while the risk of cardiovascular death was 69% higher (HR 1·69, 95% CI 1·32-2·15). Notably, in the study by Owens et al 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 have comprehensively described the current epidemiology of ASc. As expected, there was a clear increase in prevalence of ASc with increasing age of the population surveyed, which makes ASc, similar to more advanced CAVD, a modern problem related to an ageing 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 mean age of 61 years (30), while 9% with mean age 72 years developed 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 to 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 diagnosis of AVC and echocardiographic diagnosis of ASC do however appear to both represent the same disease process. Using any AVC detected by CT as the criteria for ASc diagnosis leads to a higher prevalence of ASc, but still with 67% agreement between the two modalities, while higher AVC cutoffs lead to progressively lower prevalence estimates (31, 32).

The overall rate of progression of aortic sclerosis to AS was low, being less than 2% per year. Medical therapies such as statins have shown no benefit with regards 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 aortic valve calcification, once calcium is detectable in the aortic valve, traditional cardiovascular risk factors play much less of a role. In two studies, age was not associated with rate of progression (15, 30), while 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 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 coronary artery calcium in MESA compared to 45% in participants without ASc (9). However the increase in cardiovascular mortality seen even after CAC is accounted for indicates that, while 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 being a separate disease process. In the study by Novaro et al, only 1% of those with normal valves developed AS over five years compared to 9% of those with aortic sclerosis (22). None of those with normal valves at baseline developed moderate or severe AS in the study by Messika-Zeitoun et al (15). While 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 Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) 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 aortic sclerosis. The Cardiovascular Health Study is an exception, which showed an all-cause mortality of 41.3% for participants with AS compared to 21.9% for those with aortic sclerosis (including those with baseline coronary disease) and 14.9% for those with normal valves over the five 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%), and stroke (11.6% vs 8.0% vs 6.3%) showed similar patterns. Aortic sclerosis therefore appears to confer an intermediate risk between normal valves and stenotic valves.

A recent meta-analysis has 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 cardiovascular mortality, while the additional risk of stroke was not statistically different (41). It is likely that the patient subgroups included were at 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 due to non-prospective enrolment or restriction to a particular disease sub-group, such as those with advanced renal disease. In addition, we included a study they identified but did not include (19) and we used the first report from the Cardiovascular Health Study, which used echocardiography from an earlier time point in the study, thereby reducing the risk of survivorship bias (8). Although no statistically significant increase in stroke risk was seen in the individual studies, our meta-analysis found a 27% increased risk of stroke in those with ASc compared to those with normal aortic valves (HR 1·27, 95% CI 1·01-1·60). It should be noted that the meta-analysis was performed on ratios obtained after adjusting for other risk factors, and 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 carried out in all people with ASc and at least 5-year life expectancy.

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 are based in ethnically homogenous populations – the Atherosclerosis Risk in Communities (ARIC) study examined African-Americans (24), the Age, Gene-Environment Susceptibility (AGES)-Reykjavik Study examined Icelanders (12), and the Strong Heart Study examined Native American Indians (25), while the Framingham Offspring study consisted predominantly of white Americans of European descent (14). Differences in definition of exposure comes down predominantly to the imaging modality used to diagnose ASc, as discussed above. 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, CVD and all cause mortality. Despite these caveats, the risk associated with ASc was remarkably consistent across studies.

In conclusion, ASc is common in the general population, increases in prevalence with the average 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.

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Figure legends

Figure 1. Results of search strategy.

Figure 2. Prevalence of aortic sclerosis according to average age of participants in the study. The average age was either the mean or median according to the study report, and two 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, R2 0•549. Abbreviations: CT, computed tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Figure 3. Forest plot of major adverse events, according to presence of aortic sclerosis. Abbreviations: ASc, aortic sclerosis; CI, confidence interval; IV, inverse variance; Random, random effects model.

Table 1. Prevalence of aortic valve sclerosis.

Reference	Number of participants	Diagnosis method	Population	Age	Female %	Prevalence
Messika-Zeitoun et al (15) (2007)	262	CT	Randomly selected Americans without previous cardiac surgery (ECAC study)	Mean 68 (sd 5)	57	27
Thanassoulis et al (14) (2010)	1323	CT	Healthy American subjects (Framingham Offspring study)	Mean 64 (sd 9)	52	39
Kaelsch et al (13) (2011)	4083	CT	Randomly selected German subjects (Heinz-Nixdorf Recall study)	Mean 59·4 (sd 7·7)	51	11·2
Kearney et al (12) (2012)	3149	CT	Randomly selected Icelandic subjects (AGES-Reykjavik study)	Mean 75 (sd 5)	58	43
Owens et al (9) (2012)	6685	CT	American participants free of cardiovascular disease at	Mean 62 (sd 10)	53	13·4

			baseline (MESA)			
Agmon et al (16) (2001)	381	TEE*	Randomly selected American subjects (SPARC study)	Mean 67 (min 51 – max 101)	48	35·4
Sverdlov et al (17) (2012)	204	TTE backscatter	Randomly selected Australian subjects	Mean 63 (sd 6)	57·6	17·6
Gotoh et al (28) (1995)	784	TTE§	Subjects aged 35 years old and over, resident in a single village in Japan	Mean 61·9 (sd 10·6)	55·7	18·2
Aronow et al (27) (1999)	2358	TTE†	American subjects, residents of a long term care facility without terminal illness	Mean 81 (sd 8)	68·4	41·6
Taylor et al (24) (2005)	2279	TTE*	African-American subjects free of cardiovascular disease (ARIC study)	Mean 59·1 (sd 5·6)	65	7·7
Kizer et al (25)	2723	TTE*	American Indian subjects	Mean 59·2 (sd 7·7)	64·9	7·5

(2005)			without cardiovascular disease (Strong Heart study)			
Agno et al (26) (2005)	1624	TTE§	Hypertensive American subjects (Hypertension Genetic Epidemiology Network study)	Mean 54 (sd 11)	64·9	9·4
Fox et al (23) (2006)	3047	TTE*	Healthy American subjects (Framingham Offspring study)	Mean 59 (sd 10)	52	6·2
Novaro et al (22) (2007)	5621	TTE§‡	Randomly selected Medicare-eligible Americans (Cardiovascular Health Study)	Mean 72·9 (sd 5·5)	57·5	29
Stritzke et al (21) (2009)	953	TTE*	Randomly selected German subjects (KORA/MONICA study)	Mean 57·7 (sd 11·7)	52	28
Völzke et al (19) (2010)	2081	TTE*	German subjects free of cardiovascular disease and cancer (SHIP study)	Women: median 60 (IQR 53-68) Men: median 61 (IQR 54-69)	51·1	25·4

Sashida et al (20) (2010)	2085	TTE*	American subjects free from stroke (Northern Manhattan study)	Mean 68·2 (sd 9·7)	60	51·7
Lowery et al (18) (2012)	3010	TTE¶	Healthy volunteers from the UK	Minimum 60	NR	2·33

* No maximum transvalvular velocity specified † Maximum transvalvular velocity less than 1.5 meters/second § Maximum transvalvular velocity less than 2.0 meters/second ‡ Maximum transvalvular velocity less than 2.5 meters/second ¶ Full description of diagnostic criteria not reported.

Abbreviations: AGES-Reykjavik: Age, Gene-Environment Susceptibility-Reykjavik; ARIC: Atherosclerosis Risk in Communities; CT: computed tomography; ECAC: Epidemiology of Coronary Artery Calcification; IQR: inter-quartile range; KORA/MONICA: Cooperative Research in the Region of Augsburg/Monitoring of Trends and Determinations in Cardiovascular Disease-Augsburg; max: maximum; MESA: Multi-Ethnic Study of Atherosclerosis; min: minimum; NR: not reported; sd: standard deviation; SHIP: Study of Health in Pomerania; SPARC: Stroke Prevention: Assessment of Risk in a Community; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography

Table 2. Incidence of aortic valve sclerosis.

Reference	Number of participants	Diagnosis method	Population	Mean age (sd)	Female %	Follow up years (sd or min-max)	Incidence per year
Messika-Zeitoun et al (15) (2007)	192	CT	Randomly selected Americans without previous cardiac surgery (ECAC study)	67 (5)	60	3·8 (0·9)	2·6
Novaro et al (22) (2007)	3917	TTE*	Randomly selected Medicare-eligible Americans (Cardiovascular Health Study)	72 (5)	60	5	8·8 (or 9% if AS is included)
Owens et al (30) (2010)	5142	CT	American	62 (10)	45·5	2·4 (0·9)	1·7

			participants free of cardiovascular disease at baseline (MESA)				
Kearney et al (12) (2012)	1934	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

* Maximum transvalvular velocity less than 2.0 or 2.5 meters/second. †Baseline information for participants in the study by Sverdlov and colleagues(17) taken from all 204 participants without aortic sclerosis at baseline in Ngo and colleagues(42).

Abbreviations: AGES-Reykjavik: Age, Gene-Environment Susceptibility-Reykjavik; CT: computed tomography; ECAC: Epidemiology of Coronary Artery Calcification; MESA: Multi-Ethnic Study of Atherosclerosis; NR, not reported; sd: standard deviation; TTE: transthoracic echocardiography.

Table 3. Progression of aortic valve sclerosis.

	Reference	n	Diagnosis method	Population	Mean age (sd)	Female %	Baseline prevalence in study	Follow up years (sd or max-min)	Progression definition	Progression rate per year
Progression of imaging outcomes	Messika-Zeitoun et al (15) (2007)	70	CT	Randomly selected Americans without previous cardiac surgery (ECAC study)	70 (5)	47	27	3·8 (0·9)	Increased AVC	Mean 39 Agatston units (sd 53)
	Owens et al (30) (2010)	738	CT	American participants free of cardiovascular disease at baseline (MESA)	70 (8)	39	13.4	2·4 (0·9)	Increased AVC	Median 2 Agatston units (IQR -21 to 37)
	Kearney et al (12) (2012)	1215	CT	Randomly selected Icelandic subjects (AGES-Reykjavik study)	NR	NR	43	5·3 (2·6-9·2)	Increased AVC	Median 10 Agatston units (IQR 3 to 31)
	Sverdlov	44	TTE	Randomly selected	63 (6)	57·6	17·6	4	Increase in	11·95% of

	et al (17) (2012) *		back-scatter	Australian subjects					backscatter	subjects
Progression to aortic stenosis	Messika-Zeitoun et al (15) (2007)	70	CT	Randomly selected Americans without previous cardiac surgery (ECAC study)	70 (5)	47	27	3·8 (0·9)	Moderate or severe aortic stenosis	1·9% of subjects
	Novaro et al (22) (2007)	1610	TTE†	Randomly selected Medicare-eligible Americans (Cardiovascular Health Study)	74 (6)	51	29	5	Aortic stenosis	1·8% of subjects

* Baseline information for participants in the study by Sverdlov and colleagues (17) is taken from the description of the entire group of 49 subjects with aortic sclerosis at baseline in Ngo and colleagues (42). † Maximum transvalvular velocity less than 2.5 or 2.0 meters/second. Abbreviations: AGES-Reykjavik: Age, Gene-Environment Susceptibility-Reykjavik; CT: computed tomography; ECAC: Epidemiology of Coronary Artery Calcification; IQR: inter-quartile range; MESA: Multi-Ethnic Study of Atherosclerosis; NR: not reported; sd: standard deviation; TTE: transthoracic echocardiography

Table 4. Studies examining major adverse events in participants with aortic sclerosis.

Reference	n	Diagnosis	Population	Age	Female %	Follow up years (min-max or sd)	Multivariate analysis adjusted for:
Otto et al (8) (1999)	4073 (4271 for coronary events and stroke)	TTE§	Randomly selected Medicare-eligible American participants (Cardiovascular Health Study). Only those without prevalent cardiovascular disease are shown here.	Mean 72·9 (5·5)	57·5	5	Age, sex, height, presence of hypertension, current smoking, elevated LDL cholesterol levels, presence of diabetes.
Aronow et al (27) (1999)	1980	TTE†	American subjects, reidents of a long term care facility without terminal illness	Mean 81 (8)	68·4	3·8 (2·3)	Age, prior coronary artery disease, sex.
Taylor et al (24)	2279	TTE*	African-American subjects	Mean	65	NR	Age, gender, diabetes mellitus status,

(2005)			free of cardiovascular disease (ARIC study)	59·1 (5·6)			systolic blood pressure, hypertension medication status, smoking status, high-density lipoprotein levels, carotid intimal-medial thickness, fibrinogen levels, and von Willebrand factor levels.
Kizer et al (25) (2005)	2273	TTE*	American Indian participants without cardiovascular disease at baseline (Strong Heart study)	Mean 59·2 (7·7)	65	7	Age and sex.
Völzke et al (19) (2010)	2081	TTE*	German subjects free of cardiovascular disease and cancer (SHIP study)	Women : median 60 (IQR 53-68)	51·1	8·6	Age, sex, education, smoking status, diabetes mellitus, serum LDL cholesterol, use of antihypertensive medication.

				Men: median 61 (IQR 54-69)			
Owens et al (9) (2012)	6685	CT	American participants free of cardiovascular disease at baseline (MESA study)	Mean 62 (sd 10)	53	5·8 (5·6-5·9)	Age, sex, race, BMI, systolic and diastolic BP, diabetes status, use of antihypertensive medication, smoking status, family history of heart attack, total cholesterol, high density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medications, renal function, log(CRP), log(coronary artery calcium score+1)

* No maximum transvalvular velocity specified † Maximum transvalvular velocity less than 1.5 meters/second § Maximum transvalvular velocity less than 2.0 or 2.5 meters/second Abbreviations: ARIC: Atherosclerosis Risk in Communities; CT: computed tomography; ECAC:

Epidemiology of Coronary Artery Calcification; IQR: inter-quartile range; MESA: Multi-Ethnic Study of Atherosclerosis; NR: not reported; sd: standard deviation; SHIP: Study of Health in Pomerania; TTE: transthoracic echocardiography

Table 5. Risk of major adverse events in participants with aortic sclerosis.

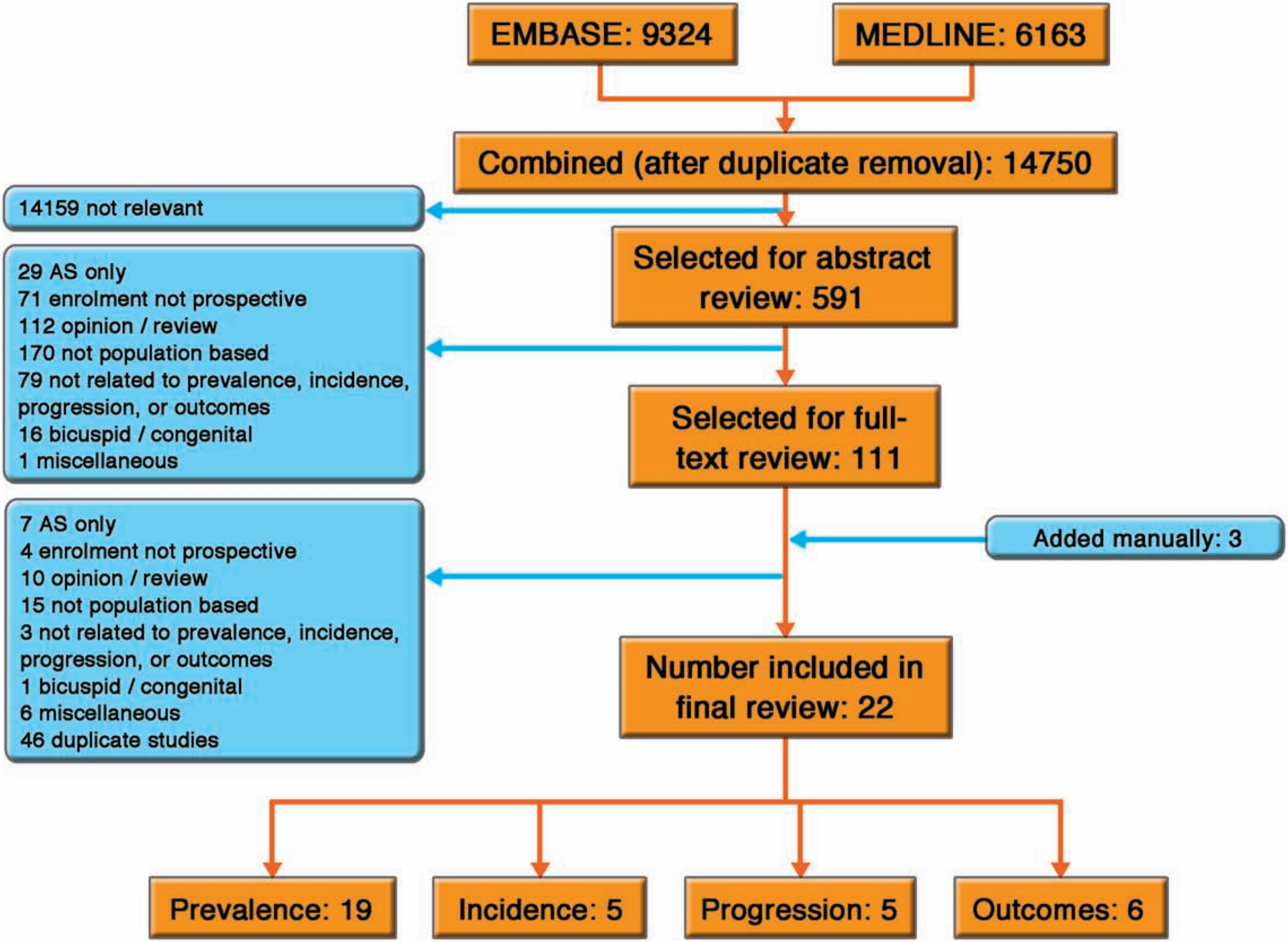
	Reference	Event definition	Absolute rate per year ASc	Absolute rate per year CG	Adjusted hazard ratio/risk ratio (95% confidence interval)
Coronary events					
	Otto et al (8) (1999)	Myocardial infarction	1·6%	0·9%	RR 1·40 (1·07-1·83)
	Aronow et al (27) (1999)	New coronary events - fatal or nonfatal 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	6·9%	1·9%	HR 1·41 (0·98-

		arrest, cardiovascular death			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%	0·21%	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 incidence rate ratio (IRR) and 95% confidence interval published by Kizer and colleagues (25) of 0·45 to 2·49 are not statistically consistent, and the true figure is likely to be IRR 1·15 (95% CI 0·45-2·94).

Abbreviations: ASc: aortic sclerosis; CABG: coronary artery bypass grafting; CG: comparison group; CI: confidence interval; HR: hazard ratio; IRR: incidence rate ratio; MI, myocardial infarction; PCI: percutaneous coronary intervention; RR: risk ratio; SCD: sudden cardiac death.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MEDLINE: 6163
Combined (after duplicate removal): 14750
14159 not relevant
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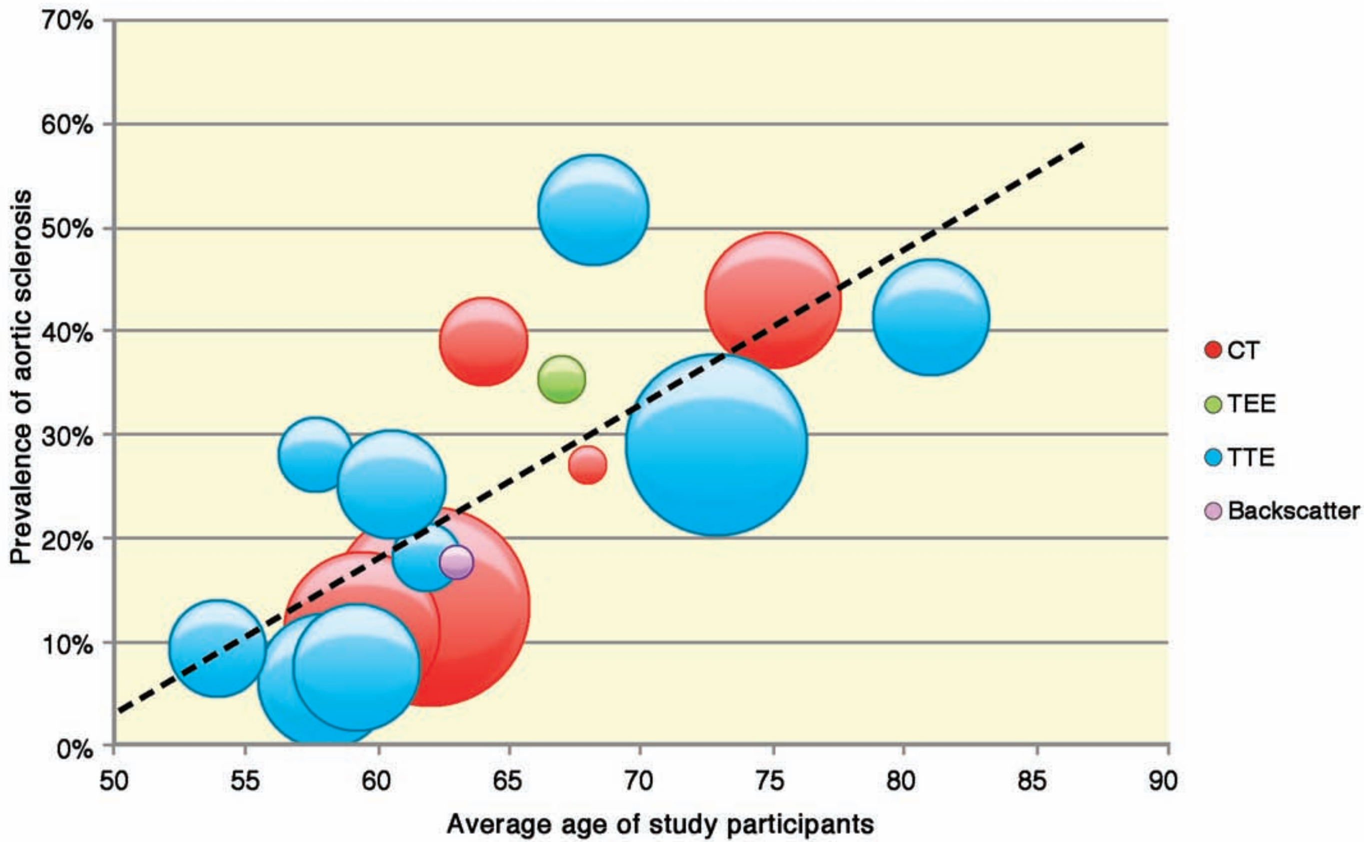
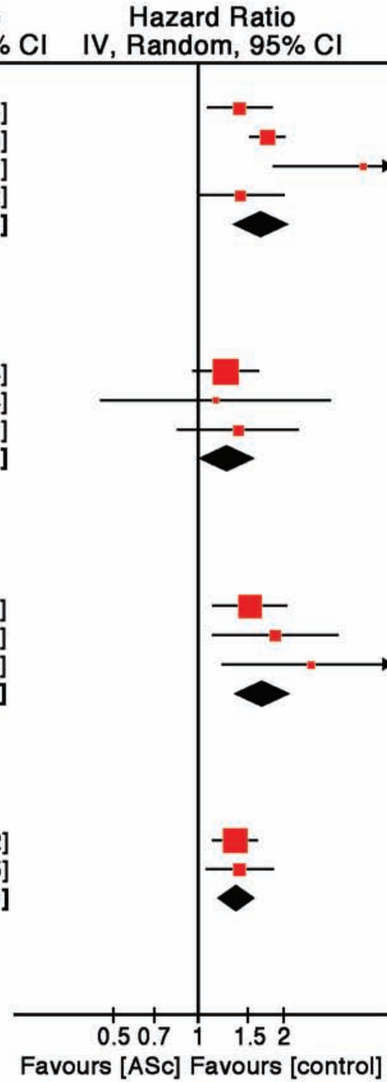
29 AS only
71 enrolment not prospective
112 opinion / review
170 not population based
79 not related to prevalence, incidence, progression, or outcomes
16 bicuspid / congenital
1 miscellaneous
Selected for full-text review: 111
Added manually: 3
7 AS only
4 enrolment not prospective
10 opinion / review
15 not population based
3 not related to prevalence, incidence, progression, or outcomes
1 bicuspid / congenital
6 miscellaneous
46 duplicate studies
Number included in final review: 22
Prevalence: 19
Incidence: 5
Progression: 5
Outcomes: 6



70%
60%
50%
40%
30%
20%
10%
0%
Prevalence of aortic sclerosis
50
55
60
65
70
75
80
85
90
Average age of study participants
CT
TEE
TTE
Backscatter

	ASc Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Coronary events				
Otto et al (1999)	1115	2958	29.2%	1.40 [1.07, 1.83]
Aronow et al (1999)	981	999	38.8%	1.76 [1.52, 2.03]
Taylor et al (2005)	175	2104	9.0%	3.82 [1.83, 7.97]
Owens et al (2012)	894	5791	23.0%	1.41 [0.98, 2.02]
Subtotal (95% CI)	**3165**	**11852**	**100.0%**	**1.68 [1.31, 2.15]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 7.84$, df= 3 (P= 0.05); $I^2 = 62\%$				
Test for overall effect: Z= 4.10 (P < 0.0001)				
Stroke				
Otto et al (1999)	1115	2958	72.7%	1.25 [0.96, 1.64]
Kizer et al (2005)	204	2519	6.0%	1.15 [0.45, 2.94]
Owens et al (2012)	894	5791	21.4%	1.38 [0.84, 2.27]
Subtotal (95% CI)	**2213**	**11268**	**100.0%**	**1.27 [1.01, 1.60]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df= 2 (P= 0.92); $I^2 = 0\%$				
Test for overall effect: Z= 2.04 (P < 0.04)				
Cardiovascular mortality				
Otto et al (1999)	1115	2958	65.7%	1.52 [1.12, 2.05]
Völzke et al (2010)	617	1464	23.1%	1.87 [1.12, 3.11]
Owens et al (2012)	894	5791	11.2%	2.51 [1.21, 5.21]
Subtotal (95% CI)	**2626**	**10213**	**100.0%**	**1.69 [1.32, 2.15]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.75$, df= 2 (P= 0.42); $I^2 = 0\%$				
Test for overall effect: Z= 4.19 (P < 0.0001)				
All-cause mortality				
Otto et al (1999)	1115	2958	69.7%	1.35 [1.12, 1.62]
Völzke et al (2010)	617	1464	30.3%	1.40 [1.06, 1.85]
Subtotal (95% CI)	**1732**	**4422**	**100.0%**	**1.36 [1.17, 1.59]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df= 1 (P= 0.83); $I^2 = 0\%$				
Test for overall effect: Z= 3.98 (P < 0.0001)				



Test for subgroup differences: $Chi^2 = 4.67$, df= 3 (P= 0.20), $1^2 = 35.8\%$

Online Appendix for the following *J Am Coll Cardiol* article

Title: The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis

Authors: Sean Coffey, MB BS, Brian Cox, MB ChB, Michael J. A. Williams, MD

Supplemental methods

EMBASE search as run:

1. aortic sclerosis.mp.
2. aortic valve disease.mp. or exp aorta valve disease/
3. aortic stenosis.mp. or exp aorta stenosis/
4. exp epidemiology/
5. cross sectional study.mp. or exp cross-sectional study/
6. cohort study.mp. or exp cohort analysis/
7. exp incidence/ or incidence.mp.
8. prevalence.mp. or exp prevalence/
9. 1 or ((2 or 3) and (4 or 5 or 6 or 7 or 8))

MEDLINE search as run:

1. aortic sclerosis.mp.
2. aortic valve disease.mp.
3. aortic stenosis.mp. or exp Aortic Valve Stenosis/
4. exp Epidemiology/
5. cross sectional study.mp. or exp Cross-Sectional Studies/
6. cohort study.mp or exp Cohort Studies/
7. incidence.mp. or exp Incidence/
8. exp Prevalence/
9. 1 or ((2 or 3) and (4 or 5 or 6 or 7 or 8))