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Cardiovascular morbidity and mortality in patients with aortic valve sclerosis: A systematic review and meta-analysis

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ABSTRACT

Aims: The association between aortic valve sclerosis (AVSc) and cardiovascular (CV) events is not consistent among different studies. We have performed a meta-analysis evaluating the association between AVSc and fatal and/or non-fatal CV and cerebrovascular events.

Methods and results: A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE). Studies evaluating coronary artery disease (CAD), stroke and CV mortality in AVSc patients and controls were included. Differences among cases and controls were expressed as Odds Ratio (OR) with pertinent 95% Confidence Intervals (CI). Thirty-one studies on 10,537 AVSc patients and 25,005 controls were included in the final analysis. The absolute risk of CAD was 45.8% (95% CI: 32.9–59.3) in AVSc patients and 29.4% (95% CI: 21.8–38.5) in controls with an OR of 2.02 (95% CI: 1.67–2.44) and an attributable risk of 35.8%. Moreover, stroke was reported in 11.8% (95% CI: 4.4–27.7) of AVSc patients and 7.9% (95% CI: 2.5–22.7) of controls (OR: 1.41, 95% CI: 1.16–1.71) with an attributable risk of 33.0%. CV mortality was 6.2% (95% CI: 2.7–13.5) in AVSc patients and 2.0% (95% CI: 0.5–7.9) in controls (OR: 2.70, 95% CI: 1.45–5.01), with an attributable risk of 67.7%. Results were confirmed when pooling together ORs for CAD, stroke and CV mortality obtained by means of multivariate analysis.

Conclusions: AVSc is associated with CAD, stroke and CV mortality. Taken together, these data suggest that patients with AVSc may benefit from a stricter CV risk monitoring and that AVSc screening may be included in the frame of CV risk stratification protocols.

1. Introduction

Aortic valve sclerosis (AVSc) is characterized by focal or diffuse aortic valve thickening with or without increased echogenicity and without any significant hemodynamic effects [1]. Based on AHA/ACC [2,3] guidelines, absence of hemodynamic significance in AVSc is defined as transvalvular velocity <2.0 m/s. The prevalence of this condition is estimated around 30% in patients older than 65 years and up to 40% in those older than 75 years [1]. In addition, a strong correlation between AVSc and conventional vascular risk factors (VRFs) has been reported in several studies [4]. In particular, the association with age, male gender, hypertension, hyperlipidemia, diabetes and smoking suggests that AVSc might be considered an atherosclerosis-like process [1]. Moreover, growing evidence suggested an association between AVSc and coronary artery events, stroke, cardiovascular (CV) mortality and all-cause mortality [5]. However, the association between AVSc and CV events is not consistent among different studies. Some studies showed an increased risk of CV events in people with AVSc [6], whereas others showed that once other risk factors for CV events are taken into account, AVSc risks are reduced or even eliminated [5,7].

To address this issue, we performed a meta-analysis of literature studies to evaluate the association of AVSc and CV morbidity and mortality.

2. Methods

See the on-line supplemental material.

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3. Results

3.1. Study characteristics

After excluding duplicate results, the search retrieved 216 articles. Of these, 152 were excluded because they were off the topic after scanning the title and/or the abstract or because they were reviews, comments, case reports. Thirty-three studies were excluded after full-length paper evaluation because they lacked data of interest or used imaging techniques different from echocardiography to identify AVSc.

Thus, 31 studies [4,6,8–36] on 10,537 AVSc patients and 25,005 controls were included in the final analysis (Supplemental Fig. 1). Representative images of two-dimensional echocardiography of normal and sclerotic aortic valves are depicted in Fig. 1.

Major characteristics of included studies are shown in Table 1. Twenty studies [8,9,12,14–18,20,22,23,26–29,31,32,34–36] had a retrospective design, whereas 11 [4,6,10,11,13,19,21,24,25,30,33] prospectively evaluated the outcome. The criteria used to determine AVSc and CAD are reported in Supplemental Table 1.

3.2. Coronary artery disease (CAD)

The 31 studies included in the analysis [4,6,8–36] showed that the absolute risk of CAD was 45.8% (95% CI: 32.9–59.3) in the 10,537 AVSc patients and 29.4% (95% CI: 21.8–38.5) in the 25,005 controls with a corresponding OR of 2.02 (95% CI: 1.67–2.44, Fig. 2) and an attributable risk of 35.8%. The heterogeneity among studies was significant (I^2: 79.9%, $p < 0.001$) and it was not reduced by exclusion of one study at a time.

When the 4 studies reporting on a composite outcome including cardio- and cerebro-vascular events [9,15,24,25] were excluded, similar results were confirmed (OR: 2.12, 95% CI: 1.71–2.62, I^2: 80.0%, $p < 0.001$).

The analysis was repeated after stratifying data according to study design and results were confirmed both in the 20 retrospective studies [8,9,12,14–18,20,22,23,26–29,31,32,34–36] on 5583 AVSc and 11,764 controls (OR: 2.11, 95% CI: 1.64–2.73; I^2: 69.8%, $p < 0.001$) and in the 11 prospective studies [4,6,10,11,13,19,21,24,25,30,33] on 4954 AVSc and 13,241 controls (OR: 1.89, 95% CI: 1.40–2.57; I^2: 88.1%, $p < 0.001$).

Moreover, after excluding studies potentially including the same population as other included studies [10,17,20,28], similar results were obtained (OR: 1.90, 95% CI: 1.56–2.31; I^2: 78.7%, $p < 0.001$).

Interestingly, a significant difference between AVSc patients and controls was confirmed both in the 11 studies [4,6,10–12,23–26,30,33] specifically evaluating myocardial infarction as outcome (OR: 2.13, 95% CI: 1.57–2.88, I^2: 89.3%, $p < 0.001$) and in the 14 studies [8,14,16–20,28,29,31,32,34–36] defining CAD as the presence of angiographically obstructive coronary artery stenosis (OR: 2.41, 95% CI: 1.85–3.14, I^2: 36.3, $p = 0.086$).

Similar results were also confirmed after excluding the 11 studies [4,13,15,17–19,28,30,31,33,36] including controls who were not age-matched with AVSc patients (OR: 1.94, 95% CI: 1.50–2.50).

When selecting only the 14 studies [14–17,19–21,24,25,28,33–36] providing data on the risk of CAD evaluated by means of multivariate analysis in 4541 AVSc and 12,798 controls, the association between AVSc and CAD was consistently confirmed (OR: 2.60, 95% CI: 1.87–3.62; I^2: 68.9, $p < 0.001$).

3.3. Stroke

In seven studies [6,12,13,21,23,24,33] the absolute risk of stroke was 11.8% (95% CI: 4.4–27.7) in 3870 AVSc patients and 7.9% (95% CI: 2.5–22.7) in 11,320 controls with a corresponding OR of 1.41 (95% CI: 1.16–1.71, Fig. 3A), without heterogeneity among studies (I^2: 33.7, $p = 0.171$). The risk of stroke attributable to the presence of AVSc was 33.0%. Interestingly, results were consistently confirmed both in the 2 studies [12,23] with a retrospective design (OR: 1.39, 95% CI: 0.79–2.45, I^2: 52.5, $p = 0.147$) and in the 5 studies [6,13,21,24,33] with a prospective design (OR: 1.50, 95% CI: 1.19–1.89, I^2: 18.0%, $p = 0.300$).

Similar results were also confirmed after excluding the 2 studies [13,33] including controls not age-matched with AVSc patients (OR: 1.32, 95% CI: 1.10–1.60).

The 4 studies [13,21,24,33] providing data on the risk of stroke evaluated by means of multivariate analysis, showed an OR for stroke of 1.57 (95% CI: 1.11–2.23), without heterogeneity among studies (I^2: 13.7%, $p = 0.324$).

3.4. CV mortality

Five studies [4,6,15,24,30] showed a higher CV mortality in the 4642 AVSc patients than in 11,523 controls [6.2% (95% CI: 2.7–13.5) *vs.* 2.0% (95% CI: 0.5–7.9); OR: 2.70, 95% CI: 1.45–5.01, I^2: 85.2%, $p < 0.001$, Fig. 3B], with an attributable risk of 67.7%. Interestingly, after excluding the only retrospective study [15], a similar difference was confirmed (OR: 2.17, 95% CI: 1.21–3.86, I^2: 68.3%, $p = 0.024$). Similar results were also confirmed after excluding the 3 studies [4,15,30] including controls not age-matched with AVSc patients (OR: 1.74, 95% CI: 1.43–2.13). In addition, evaluating the 3 studies [15,24,30] providing data

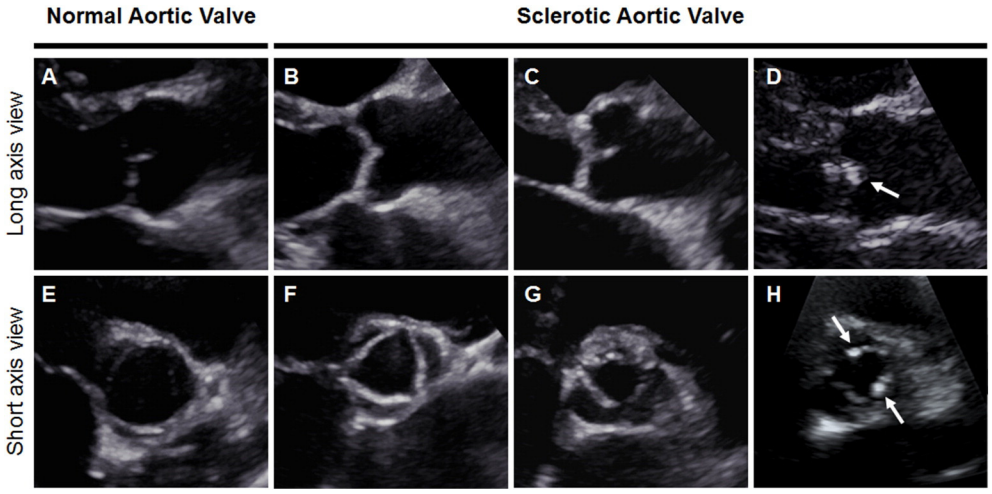

Fig. 1. Representative transthoracic two-dimensional echocardiography. Normal aortic valve (A and E); slight thickness of the aortic valve leaflets (B and F); marked thickness of the aortic valve leaflets (C and G); fibrocalcific leaflets of the aortic valve (D and H). White arrows indicate possible calcium nodules. Upper panels represent images acquired in long axis view (diastole) and lower panels represent images acquired in short axis view (systole).