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Markers of subclinical atherosclerosis in patients with aortic valve sclerosis: A meta-analysis of literature studies

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ABSTRACT

Objective: Growing evidence suggested an association between aortic valve sclerosis (AVSc) and cardiovascular (CV) events. However, little is known about the association of AVSc with major markers of subclinical atherosclerosis. We performed a meta-analysis of literature studies to address this issue.
Methods: Studies on the relationship between AVSc and common carotid artery intima-media thickness (IMT), prevalence of carotid plaques (CPs), flow-mediated dilation (FMD), aortic pulse wave velocity (PWV) and augmentation index (AIx) were systematically searched in electronic databases. Thirteen studies enrolling 1086 AVSc patients and 2124 controls were included.
Results: Compared to controls, AVSc patients showed higher IMT (MD: 0.32 mm; 95%CI: 0.07, 0.58; $p = 0.014$), and higher prevalence of CPs (OR: 4.06; 95%CI: 2.38, 6.93; $p < 0.001$). Moreover, lower FMD (MD: −4.48%; 95%CI: −7.23, −1.74; $p = 0.001$) and higher PWV (MD: 0.96%; 95%CI: 0.11, 1.81; $p = 0.027$) were found in AVSc subjects than in controls, with no differences in AIx (MD: 0.76%; 95%CI: −0.97, 2.49; $p = 0.389$). In meta-regression analyses, body mass index and triglyceride levels have an impact on the difference in IMT between cases and controls, while male gender and smoking habit were associated with the difference in the prevalence of CPs between the two groups.
Conclusions: AVSc is significantly associated with altered markers of subclinical atherosclerosis, thus supporting the concept that AVSc and atherosclerosis share common etiopathological mechanism and/or risk factors.

1. Introduction

Aortic valve sclerosis (AVSc) has become, in the last decade, very popular among clinicians and scientists. This interest is due to the strong correlation that this condition has with aortic valve stenosis, coronary artery events, stroke, cardiovascular mortality and all-cause mortality [1].

AVSc is generally characterized by focal or diffuse aortic valve thickening with or without increased echogenicity and without any significant hemodynamic effects [2]. AVSc is identified by EAE/ASE and AHA/ACC guidelines as unrestricted leaflet opening with a maximal transvalvular velocity of <2.0 m/s [3] and <2.5 m/s [4] on Doppler echocardiographic measurement, respectively. 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 [2]. In addition, a strong correlation between AVSc and conventional vascular risk factors (VRFs) has been reported in several studies [5–7]. In particular, the association with age, male gender, hypertension, hyperlipidemia, diabetes and smoking suggests that AVSc might be considered an atherosclerosis-like process [2,7,8]. A recent study by Coffey et al. [1] has reported that AVSc patients have a low rate of progression (≈2% every year) to symptomatic aortic valve stenosis. In spite of the dramatic increase in the literature of the field, whether AVSc is just a marker of valve degeneration rather than a generalized vascular disease is still a matter of debate [1].

The recent advancement of imaging modalities has made possible the non-invasive assessment of a number of morphological and functional aspects of atherosclerosis disease, in all phases of its development. Carotid intima-media thickness (cIMT), carotid plaques (CPs), flow-mediated dilation (FMD), aortic pulse wave velocity (PWV) and aortic augmentation index (AIx) are all examples of these non-invasive arterial morphology or functional modalities. Convincing evidence are now available showing that each one of these variables is able to add prognostic information over and above conventional VRFs and all are independent predictors of CV events [9–15]. For these reason all

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these variables are now widely accepted as surrogate markers of subclinical and even clinical atherosclerosis. During recent years, a series of single studies have investigated the association between AVSc and these markers of atherosclerosis proving accelerated atherosclerosis [16], impaired endothelial function [17,18], and increased arterial stiffness [19] in patients with aortic valve sclerosis. However, no one has addressed this issue by using a meta-analytic approach.

To provide a comprehensive overview of these relationships, we performed a systematic review with meta-analysis of literature studies to evaluate the association of aortic valve sclerosis and major markers of subclinical atherosclerosis.

2. Methods

A protocol for this review was prospectively developed, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods.

2.1. Search strategy

To identify all available studies, a detailed search pertaining to aortic valve sclerosis and markers of CV risk (i.e. IMT, FMD, NMD, PWV, AIx) was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [20]. A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: *aortic valve sclerosis*, *intima-media thickness*, *carotid plaques*, *atherosclerosis*, *flow-mediated dilation*, *nitrate-mediated dilation*, *endothelium-dependent dilation*, *endothelium-independent dilation*, *endothelial dysfunction*, *pulse wave velocity*, *augmentation index*, *arterial stiffness*. The last search was performed on December 2015. The search strategy was developed without any language or publication year restriction.

The reference lists of all retrieved articles were manually reviewed. In case of missing data, study authors were contacted by e-mail to try to retrieve original data. Two independent Authors (MNDDM and ADM) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (PP). Discrepancies were resolved by consensus. Selection results showed a high inter-reader agreement (k = 0.97) and have been reported according to PRISMA flowchart (Supplemental Fig. 1).

2.2. Data extraction and quality assessment

According to the pre-specified protocol, all studies evaluating the impact of aortic valve sclerosis on the markers of CV risk were included. Case-reports, case-series without a control group, reviews and animal studies were excluded. To be included in the analysis, a study had to provide values (means with standard deviation) of at least one variable among the following: common carotid artery IMT (IMT), brachial artery FMD, carotid-femoral PWV, aortic AIx. Studies reporting the prevalence of CPs were also included. We included only studies defining aortic valve sclerosis as focal or diffuse leaflet thickening with or without calcification, with normal valve excursion, and peak Doppler flow velocity of <2.0 m/s [3,4,21]. In each study, data regarding sample size, major clinical and demographic variables, values of IMT, FMD, PWV and AIx and prevalence of CPs in patients with AVSc and healthy controls were extracted.

Formal quality score adjudication was not used, since previous investigations failed to demonstrate its usefulness [22].

2.3. Statistical analysis and risk of bias assessment

Statistical analysis was carried out using Comprehensive Meta-analysis [version 2, Biostat, Englewood NJ (2005)].

Differences among cases and controls were expressed as mean difference (MD) with pertinent 95% confidence intervals (95%CI) for continuous variables, and as Odds Ratio (OR) with pertinent 95%CI for dichotomous variables.

IMT has been expressed in millimeters (mm), FMD and AIx as percentage (%), and PWV as mm per second (mm/s).

The overall effect was tested using Z scores and significance was set at $p < 0.05$. Statistical heterogeneity between studies was assessed with chi square Cochran's Q test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [23].

Publication bias was assessed by the Egger's test and represented graphically by funnel plots of the standard difference in means versus the standard error. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, and Egger's test was used to assess publication bias, over and above any subjective evaluation. A $p < 0.10$ was considered statistically significant [24]. In case of a significant publication bias, the Duval and Tweedie's trim and fill method was used to allow for the estimation of an adjusted effect size [25]. In order to be as conservative as possible, the random-effect method was used for all analyses to take into account the variability among included studies.

2.4. Meta-regression analyses

Differences among included studies may be affected by demographic variables (age, male gender) and traditional CV risk factors (hypertension, smoking habit, diabetes mellitus, obesity). To assess the possible effect of such variables in explaining different results observed across studies, we performed meta-regression analyses after implementing a regression model with difference in IMT, FMD, PWV, AIx values, or presence of CPs as dependent variables and the above mentioned covariates as independent variables. This analysis was performed with Comprehensive Meta-analysis [Version 2, Biostat, Englewood NJ (2005)].

3. Results

3.1. Study characteristics

After excluding duplicate results, the search retrieved 176 articles. Of these, 160 were excluded because they were off the topic after scanning the title and/or the abstract or because they were reviews, comments, case reports or because they lacked of data of interest. Three studies were excluded after full-length paper evaluation.

Thus, 13 studies on 1086 AVSc patients and 2124 controls were included in the final analysis (Supplemental Fig. 1).

Major characteristics of included studies are shown in Table 1. All studies had a cross-sectional design. The number of patients varied from 41 to 1065, the mean age from 44.3 to 72 years, and the prevalence of male gender from 29.3 to 74.5%. The presence of hypertension was reported in 34.5–85.0% of patients, smoking habit in 6.3–50% and diabetes mellitus in 10.7–36.6%. Mean body mass index (BMI) varied from 22.1 to 32.0 kg/m^2.

3.2. Common carotid artery intima media thickness (IMT) and carotid plaques (CPs)

In 4 studies [17,26–28], we found a significantly higher IMT in 151 AVSc patients as compared to 404 controls (mean difference — MD: 0.325 mm; 95%CI: 0.067, 0.582; $p = 0.014$, Fig. 1 panel A). The heterogeneity among studies was significant ($I^2 = 95.9\%$; $p < 0.0001$) but, after excluding one study at a time, we found that all the results were confirmed (data not shown). Also, after excluding the study of Yamaura et al. [28], that reported the highest MD between AVSc patients and controls, the difference in IMT remained significant without heterogeneity (MD: 0.17 mm; 95%CI: 0.13, 0.21; $p < 0.0001$, $I^2 = 0\%$; $p = 0.48$). Five studies [16,17,29–31], showed an increased prevalence of CPs in 941 AVSc patients as compared to 1103 controls, with an OR of 4.06 (95%CI: 2.38, 6.93; $p < 0.001$, Fig. 1 panel B). The heterogeneity among studies was significant ($I^2 = 65.3\%$; $p = 0.021$). Also, in this case, after excluding one study at a time, we found that all the results were confirmed (data not shown). In addition, after excluding the study of Schönenberger et al. [30], that reported the highest OR between AVSc patients and controls, the same difference in the prevalence of carotid plaque was confirmed (OR: 3.62; 95%CI: 2.18, 6.01; $p < 0.001$, $I^2 = 64.8\%$; $p = 0.036$). Also, excluding studies [17,28] in which cases and controls were not age-matched, both the difference in IMT and in CPs prevalence were confirmed (MD: 0.18 mm; 95%CI: 0.11, 0.26; $p < 0.001$, $I^2 = 27.5\%$; $p = 0.24$ and OR: 3.98; 95%CI: 2.10, 7.55; $p < 0.001$, $I^2 = 73.2\%$; $p = 0.011$).

3.3. Flow-mediated dilation (FMD)

Two studies [17,18], evaluating a total of 63 cases and 146 controls, showed a significantly lower FMD in AVSc patients as compared to controls (MD: −4.48; 95%CI: −7.23, −1.74; $p = 0.001$, Fig. 2) with a significant heterogeneity among studies ($I^2 = 73.7\%$; $p = 0.0051$).