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Review article

Aortic valve calcification and risk of stroke: A systematic review and meta-analysis

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ABSTRACT

Aortic valve calcification (AVC) is common among aged population and reported to be associated with the risk of stroke. However, the conclusions are inconsistent among studies. We performed a rigorous meta-analysis to unravel the AVC-stroke relationship. Embase, PubMed and Cochrane library were retrieved for related cohort studies investigating the correlations between AVC and risk of stroke. The language was limited to English. We selected risk ratio (RR) and 95% confidence intervals (CIs) as the effect size. Random-effects model was used in the data synthesis. A total of 7 cohort studies were identified in our meta-analysis with 21,395 participants and 1025 strokes. We detected statistically significant correlation between AVC and stroke (RR, 1.20; 95% CI, 1.02–1.40, P = 0.02) with low heterogeneity (I^2 = 6.9%, P = 0.375). Statistically significant results were detected only in the subgroup of "+" degree of adjustment (P = 0.04). Therefore, a definite relationship between AVC and risk of stroke couldn't be decided based on current available data, and more large scale prospective studies were needed to verify the AVC-stroke relationship.

1. Introduction

Aortic valve calcification (AVC) is common among aged population and the prevalence is estimated to be 25% for individuals over 65 years old [1]. Though previously being regarded as an incidental echocardiographic findings with little clinical value, AVC is now recognized to be a highly regulated process similar to atherosclerosis [2]. Usually, clinical precursor of atherosclerosis is the risk factor for cardiovascular disease [3,4] and AVC has been considered to be related to stroke. However, different clinical studies have different conclusions about the relationship between AVC and stroke. Two meta-analyses have also explored whether presence of AVC was associated with stroke and they reach opposite conclusions [5,6]. What's more, not all pertinent studies are included in these 2 reviewing studies. Therefore, we conduct this systematic review and meta-analysis according to published literatures, hoping to unravel the relationship between AVC and risk of stroke.

2. Methods

2.1. Search strategy

The present meta-analysis was conducted based on the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement [7]. Its protocol was not registered previously. Two authors (D.F. Z. and J.Y. W.) searched Cochrane library, Embase and PubMed independently for prospective cohort studies examining the associations between aortic valve calcification (AVC) and stroke on August 18th 2017. There was no date limit to our retrieval, while only articles written in English were included. We combined free word "stroke" with "aortic valve sclerosis" or "aortic valve calcification" or "aortic valve calcium" or "calcific aortic valve" in the search. The reference lists of included studies were also screened. The search algorithm for PubMed was described in online-only Data Supplement.

2.2. Definitionof AVC and stroke

AVC was defined as the visualization of bright echoes on the AV leaflets by echocardiography, irrespective of impairment of leaflet excursion [8] or lesions (Hounsfield unit >130) located on the

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aortic valve cusps on CT scan [9]. Stroke was considered as lesions on brain imaging consistent with a localized ischemic or hemorrhagic event [10].

2.3. Inclusion criteria

We included studies only if they (1) were prospective cohort studies; (2) investigated the relationship between AVC and risk of stroke; (3) reported hazard ratio (HR) or relative risk (RR) with 95% confidence intervals (CIs) for stroke. Studies recruiting subjects with congenital valve disease were excluded.

2.4. Data extraction and quality assessment

Study characteristics and relevant data were extracted by 3 authors (D.F. Z., X.L. D. and C.Q. W.), including the family name of first author, publication year, study design, population, sample size, age and sex of participants, method of diagnosis, definition of AVC and stroke, degree of adjustment, HR or RR with 95% CIs for stroke. We classified the degree of adjustment into three levels: "+" for no adjustment or age and sex only; "++" for age and sex plus ≤5 risk factors, such as body mass index, smoking, diabetes mellitus; "+++" for age and sex plus >5 factors, such as systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, prevalent coronary heart disease, prevalent atrial fibrillation. In order to avoid the disturbance from confounders, we included the effect sizes from the maximally adjusted model. Newcastle-Ottawa Scale was used in the quality assessment. We sought to joint review in case of discrepancies.

2.5. Statistical analysis

RRs and associated 95% CIs were selected as the effect size and pooled using random-effects model. In cohort studies, HR was considered equivalent to RR. If results were provided separately for different types of AVC or stroke in one study, we pooled them with a fixed-effects model firstly to produce an overall effect size. We conducted subgroup analysis according to the degree of adjustment and sample size. Sensitivity analysis was carried out by omitting studies one by one. Egger's test was used in the analysis of

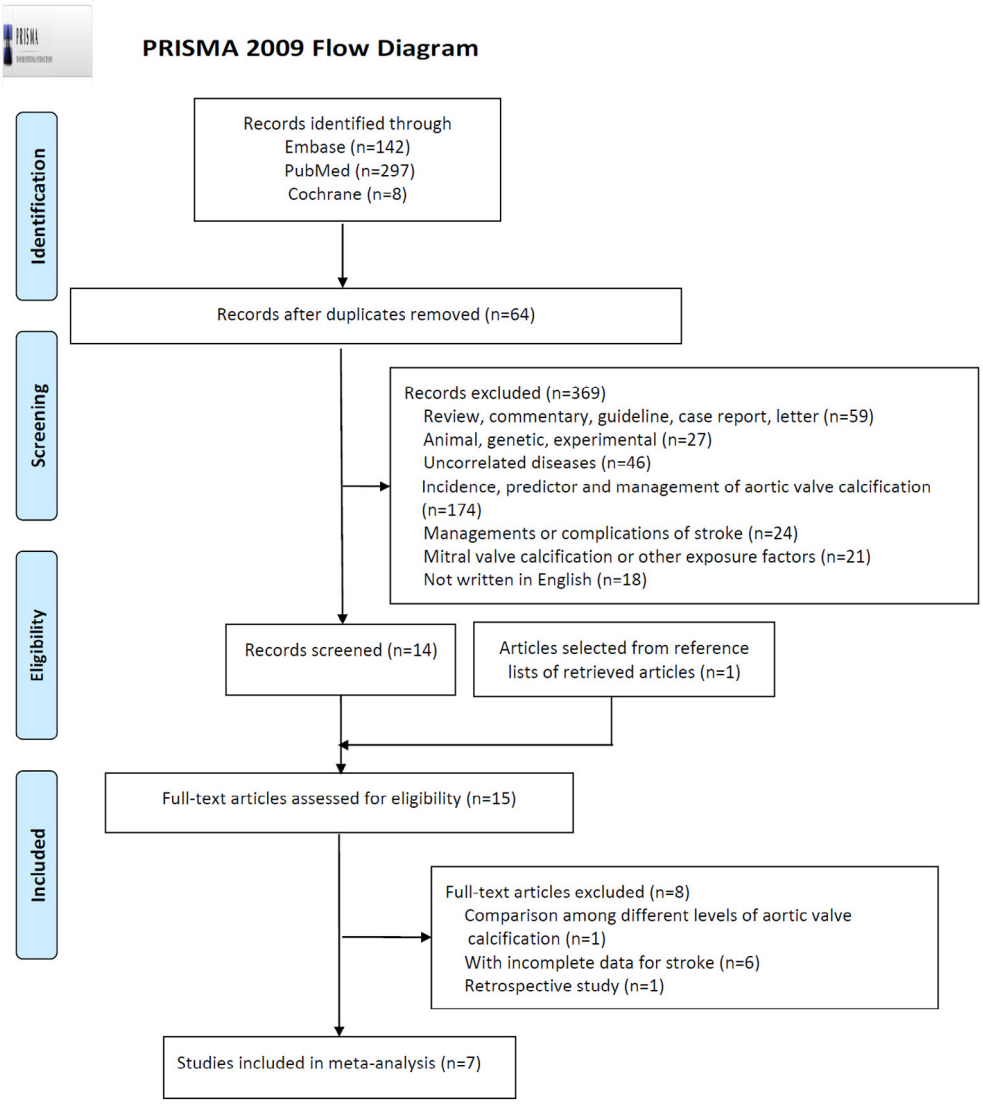

Fig. 1. The flow diagram of the search process.