Journal of Cardiovascular Computed Tomography 13 (2019) 190–195

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.elsevier.com/locate/jcct

Research paper

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

Matteo Nicola Dario Di Minno[a,1], Paolo Poggio[b,*,1], Edoardo Conte[b,2], Veronika Myasoedova[b,2], Paola Songia[b], Saima Mushtaq[b], Laura Cavallotti[b], Donato Moschetta[b], Alessandro Di Minno[b], Gaia Spadarella[c], Paolo Pizzicato[a], Gianluca Pontone[b], Mauro Pepi[b], Daniele Andreini[b,d]

[a] Federico II University, Naples, Italy
[b] Centro Cardiologico Monzino, IRCCS, Milan, Italy
[c] Department of Diagnostic and Interventional Radiology, University of Milan, San Paolo Hospital, Milan, Italy
[d] Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Italy

ARTICLE INFO

Keywords:
Aortic valve calcification
Coronary artery calcification
Overall morality

ABSTRACT

Background: Aortic valve calcification (AVC) is an active process that involves inflammation, disorganization of matrix disposition, lipid accumulation and lamellar bone formation. AVC without hemodynamic changes has been associated with cardiovascular (CV) risk factors and increased risk of coronary and CV events. Nowadays, echocardiography is the standard imaging technique to evaluate aortic valve pathologies. However, cardiac computed tomography (CT) allows high accuracy and reproducible measurement of AVC, without exposing the patients to excessive radiation or contrast administration.

Aims: To better understand if AVC assessment may improve CV risk-prediction, we performed a systematic search and meta-analysis of literature studies, evaluating the relationship among AVC, coronary artery disease (CAD), and overall mortality.

Methods and results: A detailed search, according to PRISMA guidelines, was performed to identify all available studies investigating AVC, measured by CT scan, and CV events. Thirteen studies on 3,782 AVC patients and 32,890 controls were included in the final analysis. Patients with AVC have a higher risk of CAD (OR 1.7, 95%CI: 1.04–2.87; $p = 0.04$) when compared to controls. We also found an association between AVC and coronary artery calcification (OR 3.8; 95%CI: 2.4–6.0; $p < 0.001$.) Finally, AVC had 93.2% specificity for overall mortality (95%CI: 92.8–93.6) with a negative predictive value of 98.8% (95%CI: 98.7–98.8).

Conclusion: AVC is associated with coronary artery calcification and overall mortality. The present data cannot support the use of cardiac CT over echocardiography for AVC assessment in all patients, but when cardiac CT is performed for suspected CAD, AVC evaluation may contribute to risk stratification and patient management. *Ad hoc* designed studies should address this issue in the next future.

1. Introduction

Calcification of the aortic valve is an active process that involves inflammation, disorganization of matrix disposition, lipid accumulation and lamellar bone formation.[1] Indeed, it has been shown that the initial degenerative process occurring in the aortic valve shares several features with atherogenesis.[2] Aortic valve calcification (AVC) without hemodynamic changes has been associated with cardiovascular (CV) risk factors, such as age, male gender, body mass index, current smoking, and the use of both antihypertensive and lipid-lowering medications.[3,4] In addition, increased risk of coronary and CV events has been seen in patients with AVC compared to healthy subjects.[5–8] Other conditions strongly correlated with AVC are represented by coronary artery calcification (CAC) and the presence, extent, and vulnerable characteristics of coronary plaque (CP).[9,10] However, the prognostic value of AVC is still controversial.

* Corresponding author. Head of the Unit for the Study of Aortic, Valvular and Coronary Pathologies, Centro Cardiologico Monzino, IRCCS, Via Parea 4, 20138, Milan, Italy.

E-mail address: paolo.poggio@ccfm.it (P. Poggio).

[1] These authors equally contributed.
[2] These authors equally contributed.

https://doi.org/10.1016/j.jcct.2019.06.006
Received 7 September 2018; Received in revised form 9 April 2019; Accepted 10 June 2019
Available online 11 June 2019

Nowadays, echocardiography is the standard imaging technique to evaluate aortic valve pathologies.[11] However, cardiac computed tomography (CT) allows high accuracy and reproducible measurement of AVC, without exposing the patients to excessive radiation or contrast administration.[10,12-14] Indeed, the AVC may be assessed with the same scan dedicated to CAC measurement, without the need for additional radiation.

To better understand if the AVC may improve cardiovascular risk prediction, we performed a systematic search and meta-analysis of literature studies, evaluating the relationship among AVC, coronary artery disease (CAD), CAC, CPs and overall mortality.

2. Methods

2.1. Search strategy

A detailed search, according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines,[15] was performed to identify all available studies investigating AVC and CV events. A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search string: (aortic valve calcification OR aortic valve calcium) AND (cardiovascular risk OR cardiovascular events OR cardiovascular mortality OR overall mortality OR acute coronary syndrome OR coronary artery disease OR coronary artery calcification OR coronary artery plaques) AND (cardiac computed tomography OR cardiac CT scan) NOT (transcatheter) NOT (stenosis). The last search was performed in December 2018.

Three independent authors (VM, LC, and DM) analyzed each article and performed the data extraction independently. In case of disagreement, a fourth investigator was consulted (PP). Discrepancies were resolved by consensus.

2.2. Data extraction and quality assessment

According to the pre-specified protocol, all studies evaluating fatal and non-fatal CV and cerebrovascular events in patients with AVC and in controls were included. Case-reports, case-series without a control group, reviews and animal studies were excluded. Only studies in which CT was used to identify AVC were considered. In almost all of the studies, the presence of aortic valve calcification (AVC) was defined as a structure with a density of more than 130 HU. Then, using the Agatston methodology, single-lesion calcium contents were summed to give a total AVC score. Only in the study by Alder et al.[16] AVC was defined as any visually detected calcified deposit in the region of the aortic valve and calcified elements were defined as a structure with a density of more than 90 HU. All studies included in the analysis excluded patients with overt and known aortic valve stenosis. To be included in the analysis, a study had to provide the number (raw data, percentages or adjusted Odds Ratio/Hazard Ratio) of at least one variable among the following: CAD, CAC, CP or overall mortality. In each study, data regarding sample size, major clinical and demographic variables, and the prevalence of the outcome of interest in patients with AVC and controls were extracted.

Formal quality score adjudication was not used since previous investigations failed to demonstrate its usefulness.[17]

2.3. Risk of bias assessment

Publication bias was assessed by the Egger's test and represented graphically by funnel plots of the log-odds ratio 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.[18] In case of significant publication bias, the Duval and Tweedie's trim and fill method was used to allow for the estimation of an adjusted effect size.[19] 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.

In the frame of a sensitivity analysis, we have repeated analyses dividing, where possible, AVC identified by CT or electron beam tomography (EBCT). In addition, we have repeated the analysis excluding one study at a time.

2.4. Meta-regression analyses

We hypothesized that differences among included studies may be affected by demographic variables (mean age, male gender) and coexistence of traditional CV risk factors (hypertension, diabetes, dyslipidemia, obesity and smoking habit). 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 CAD, CAC, CP and overall mortality as dependent variables (y) and the above-mentioned covariates as independent variables (x). This analysis was performed with Comprehensive Meta-analysis [Version 2, Biostat, Englewood NJ (2005)].

2.5. Statistical analysis

Statistical analysis was carried out using Comprehensive Meta-analysis [Version 2, Biostat, Englewood NJ (2005)]. Differences among cases and controls were expressed as Odds Ratio (OR) or relative risk (RR) with pertinent 95% Confidence Intervals (CI). 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 an 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. The absolute risk of CAD, CAC, CPs and overall mortality in AVC patients and controls were calculated as (number of subjects experiencing event)/(total number of subjects) in each group. The attributable risk was defined as (risk of an event in AVC patients - the risk of an event in controls)/(risk of an event in AVC patients).

3. Results

After excluding duplicate results, the search retrieved 134 articles. Of these, 71 were excluded because they were off the topic after scanning the title and/or the abstract or because they were reviews, comments, case reports. Forty-nine studies were excluded after full-length paper evaluation because they lacked data of interest or used imaging techniques different from CT scan to identify AVC. One study was removed since the sample population was already present in another study. Thus, 13 studies on 3,782 AVC patients and 32,890 controls were included in the final analysis (Supplemental Fig. S1).

The analysis was split into primary and secondary outcomes. Primary outcomes were the association of AVC with CAC and overall mortality. Secondary outcomes analyzed the association of AVC with CAD and calcific CPs.

3.1. Study characteristics

Major characteristics of the included studies are shown in Table 1. Six[4,7,20-23] had a prospective design, two[5,24] had a cross-sectional design, three[6,16,25] were case-control study, and two[26,27] retrospectively evaluated the outcomes.

3.2. Coronary artery calcification (CAC)

In seven studies,[4,7,16,21,24,25,27] the prevalence of CAC was higher in 1,804 AVC patients compared to 11,300 controls with an OR of 3.8

Table 1
Demographic and clinical data of included controls and patients with aortic valve calcification.

1st Author and year	Design	Technology	Subject	Patients (n)	Males (%)	Age (years)	HT (%)	Diabetes (%)	Dyslipidemia (%)	BMI (kg/m²)	Smoking (%)	Follow-up (years)
Acuña-Valerio 2017[24]	Cross-sectional	CT	**AVC**	252	59.9	59.5	-	22.5	-	-	15.4	-
			Controls	1015	43.5	52.2	-	10.9	-	-	20.5	
Adler 2002[16]	Case-control	CT	**AVC**	70	51.4	66	100	33	37	-	16	-
			Controls	306	52.6	67	100	29	40	-	15	
Ann 2013[26]	Retrospective	CT	**AVC**	80	61.3	70.3	71.3	31.3	47.5	24.8	16.9	-
			Controls	120	59.2	61.5	65.8	32.5	51.7	25	7.8	
Blaha 2010[20]	Prospective	EBCT	**AVC**	517	70	61	45	10	35	-	11	5
			Controls	7884	69	52	27	6	25	-	9	
Faustino 2015[6]	Case-control	CT	**AVC**	100	44	-	-	26.5	70.4	-	12.2	-
			Controls	54	40.7	-	-	18.9	84.9	-	20.8	
Kalsh 2014*[4]	Prospective	EBCT	**AVC**	423	63.4	65	-	20.1	-	-	19.1	-
			Controls	3521	45	58.6	-	11.3	-	-	23.5	
Kamperidis 2014[27]	Retrospective	CT	**AVC**	39	59	66	56	36	46	26	21	2.8
			Controls	330	60	54	38	29	34	26	16	
Mahabadi 2009[5]	Cross-sectional	CT	**AVC**	37	75.7	65.8	64.9	21.6	54.1	28.4	53.9	-
			Controls	320	59.1	51.5	35.9	8.8	34.7	28.9	48.8	
Nasir 2010[7]	Prospective	CT/EBCT	**AVC**	911	60	71	64	22	-	28	11	-
			Controls	5898	45	61	42	13	-	28	13	
Piers 2009[21]	Prospective	EBCT	**AVC**	23	70	66	78	26	52	-	57	-
			Controls	40	53	51	58	8	83	-	50	
Shalev 2012[22]	Prospective	CT	**AVC**	762	-	-	-	-	-	-	-	6.5
			Controls	7642	-	-	-	-	-	-	-	
Smith 2010[23]	Prospective	CT	**AVC**	482	-	-	-	-	-	-	-	5.4
			Controls	5570	-	-	-	-	-	-	-	
ten Kate 2015[25]	Case-control	CT	**AVC**	86	-	-	-	-	-	-	-	-
			Controls	190	-	-	-	-	-	-	-	

AVC: aortic valve calcification; HT: hypertension; BMI: body mass index; CT: computed tomography; EBCT: electron beam computed tomography. * Random population.

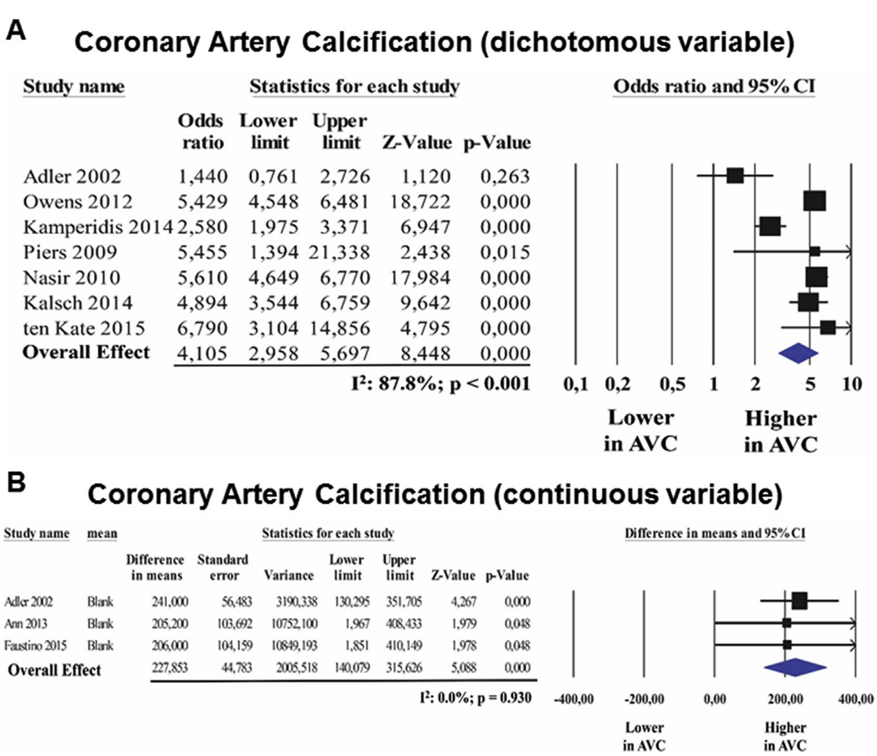

Fig. 1. Forest plot of coronary artery calcification (CAC) in aortic valve calcification (AVC) patients and controls. (**A**) Positive calcification was evaluated with an Agatston score higher than 130 HU (dichotomous variable). (**B**) Calcification was evaluated as a continuous variable (Agatston score). The diamond represents the estimated overall effect, while the squares represent each study with 95%CI.

(95%CI: 2.4–6.0; $p < 0.001$; Fig. 1A). The heterogeneity among studies was significant (I^2: 95.0%; $p < 0.001$) and it was not reduced by the exclusion of one study at a time. The absolute risk of CAC in AVC patients was 86.9% (95%CI: 79.1–94.6), whereas in controls was 63.0% (95%CI: 50.2–75.7) with an attributable risk of 27.1% (95%CI: 6.1–48.0).

The analysis was repeated after stratifying data according to study design. Results were confirmed in the three prospective studies[4,7,21] on 1,357 AVC patients and 9,459 controls (OR: 5.3, 95%CI: 4.6–6.0; $p < 0.001$; Supplemental Fig. S2A) without heterogeneity (I^2: 0%; $p = 0.61$). They were confirmed also in the four studies[16,24,25,27] with a cross-sectional, case-control or retrospective design on 447 AVC patients and 1,841 controls (OR: 2.9, 95%CI: 1.6–5.4; $p < 0.001$; I^2: 93.7%; $p < 0.001$; Supplemental Fig. S2B).

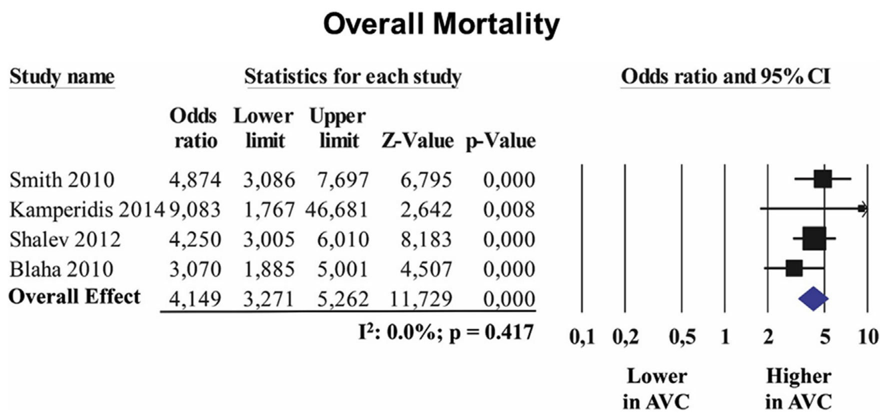

Fig. 2. Forest plot of overall mortality in aortic valve calcification (AVC) patients and controls. Patients with aortic valve calcium load higher than 130 HU were considered AVC positive. The diamond represents the estimated overall effect, while the squares represent each study with 95%CI.

Three studies[6,16,26] evaluated CAC score as a continuous variable (Agatston score). We found significantly higher CAC levels in 250 AVC patients compared to 480 controls (mean difference: +227.9 HU, 95%CI: 140.1–315.6; $p < 0.001$; Fig. 1B) without heterogeneity among studies (I^2: 0%; p = 0.94).

3.3. Overall mortality

Four studies[20,22,23,27] showed higher overall mortality in the 1,038 AVC patients than in the 13,784 controls with an absolute risk of 5.7% (95%CI: 1.0–10.5) *vs.* 1.1% (95%CI: 0.6–1.7), respectively. The AVC patients had overall mortality OR of 4.2 (95%CI: 3.3–5.3; $p < 0.001$; Fig. 2) with an attributable risk of 77.8% (95%CI: 50.9–104.6). Interestingly all the included studies revealed no heterogeneity (I^2: 0%; p = 0.42). Indeed, even after removing the only retrospective study,[27] results were entirely confirmed. In particular, the 3 prospective studies[20,22,23] showed that 1761 AVC patients had an OR of 4.1 (95%CI: 3.2–5.2; $p < 0.001$) as compared to 21096 controls.

3.4. Coronary artery disease (CAD)

The six studies included in the analysis[5,6,16,26-28] showed a higher prevalence of CAD in the 1,220 AVC patients than in the 6,921 controls with an odd ration (OR) of 1.7 (95%CI: 1.0–2.9; p = 0.035; Supplemental Fig. S3A). The heterogeneity among studies was significant (I^2: 74.2%; p = 0.002), however, it was reduced to 0% (p = 0.46) after the exclusion of Ann 2013 et al.[26] (OR: 2.1, 95%CI: 1.6–2.8; $p < 0.001$).

The analysis was repeated considering only prospective studies[5,16,27,28] and the results were confirmed on 1,040 AVC patients and 6,747 controls (OR: 2.1, 95%CI: 1.6–2.7; $p < 0.001$) with a heterogeneity of 0% (p = 0.56).

3.5. Coronary plaques (CP)

Three studies[5,6,26] took into consideration the presence of calcific plaques in AVC. A calcific CP was considered when the calcific portion was greater than 50% of the plaque area (density > 130HU in native scans). Calcific CP presence was significantly higher on 217 AVC patients than 494 controls with an OR of 4.2 (95%CI: 1.6–11.1; p = 0.004; Supplemental Fig. S3B) and a heterogeneity among studies of 80.7% (p = 0.006). The AVC patients had a relative risk (RR) of 1.9 (95%CI: 1.5–2.5; $p < 0.001$) to have CPs compared to controls.

3.6. Publication bias

Funnel plots of effect size versus standard error for all the performed analysis were rather symmetrical and the Egger's test showed the absence of publication bias (CAD analysis: p = 0.98, Supplemental Fig. S4; CAC analysis: p = 0.87, Supplemental Fig. S5; CAC continuous variable analysis: p = 0.56, Supplemental Fig. S6; CPs analysis: p = 0.10, Supplemental Fig. S7; overall mortality analysis: p = 0.58, Supplemental Fig. S8).

3.7. Meta-regression analyses

Regression models showed that male gender (Z-score: -2.0; p = 0.04) and diabetes (Z-score: -2.9; p = 0.004) inversely impacted on the difference in the prevalence of CAD between AVC patients and controls (Supplemental Fig. S9). In CAC analysis, only diabetes (Z-score: -3.3; p = 0.001) inversely impacted in AVC patients and controls (Supplemental Fig. S10). In contrast, when analyzing CAC as a continuous variable, no variable affected differences in CAC score between AVC patients and controls (Supplemental Fig. S11). Similarly, meta-regression models showed that neither CP presence nor overall mortality were significantly influenced by any considered variable (Supplemental Fig. S12 and Supplemental Fig. S13).

3.8. Aortic valve calcification predictivity

Sensitivity and specificity analyses (Supplemental Table S1) revealed that AVC had 95.2% specificity for CAC (95% CI: 94.6–95.8) and 93.2% specificity for overall mortality (95% CI: 92.8–93.6). In addition, AVC showed a positive predictive value of 84.5% (95% CI: 82.6–86.2) for CAC and a negative predictive value of 98.8% (95% CI: 98.7–98.8) for overall mortality. Finally, receiving operator characteristic (ROC) curve analyses showed an area under the curve of 0.70 ± 0.16 for AVC and CAC (Fig. 3A) and 0.90 ± 0.07 for AVC and overall mortality (Fig. 3B).

4. Discussion

In this meta-analysis, we evaluated the relationship between AVC, coronary atherosclerosis and overall mortality. One of the main findings of the study was the association between AVC and CAC (OR 3.8; 95%CI: 2.4–6.0; $p < 0.001$) that was significant even when only prospective studies were considered (OR: 5.3, 95%CI: 4.6–6.0; $p < 0.001$). The extent of CAC score, in AVC patients, ranged from 300 to 550, consistent with high coronary calcification, thus indicating high cardiovascular risk. While CAC score, in controls, ranges from 100 to 350, consistent with moderate coronary calcification and thus indicating moderate cardiovascular risk. Moreover, beyond CAC, patients with AVC have a higher risk of CAD (OR 1.7, 95%CI: 1.0–2.9; p = 0.035) and calcific CP presence (OR: 4.1, 95%CI: 1.6–11.1; p = 0.004). Our results

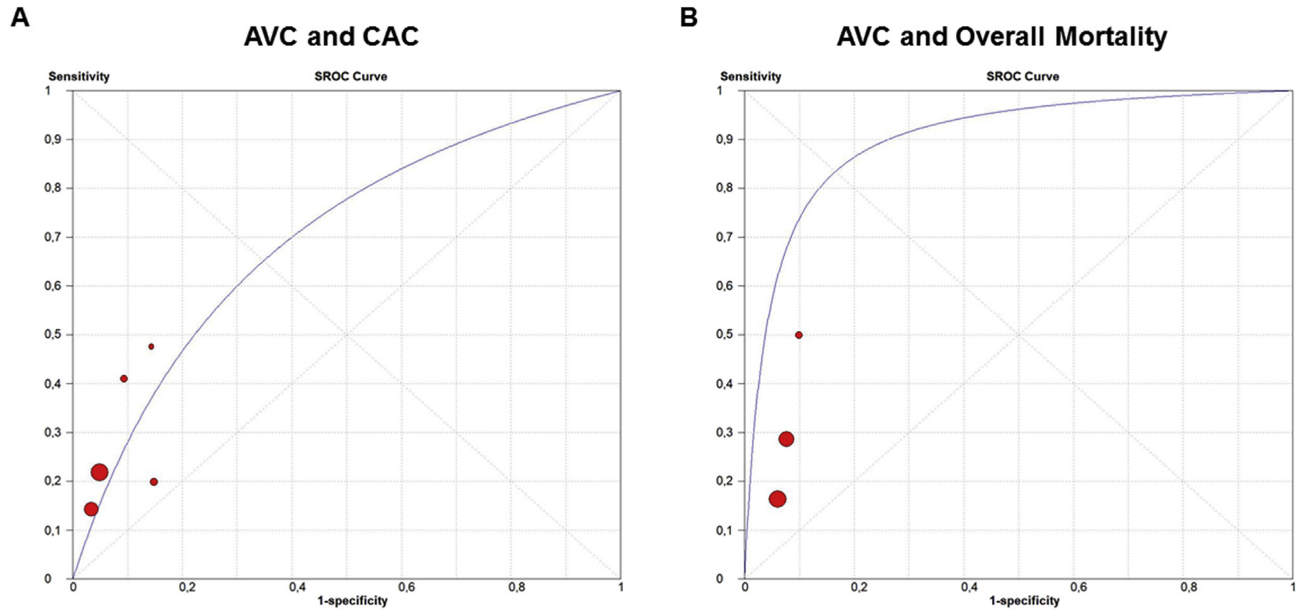

Fig. 3. Summary Receiver Operating Characteristic (sROC) curves. (**A**) Association between aortic valve calcification (AVC) and coronary artery calcification (CAC). (**B**) Association between aortic valve calcification (AVC) and overall mortality. Red circles represent the included studies, while the breadth represents the dimension of the studied population. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

suggest that, in both coronary arteries and aortic valve, the local endothelial damage occurs because of insults from mechanical, genetic, and inflammatory cell-mediated factors, in agreement with a common pathobiological mechanism. This common pathophysiological background leads the normal endothelium progression to aortic stenosis and CAD through lipid deposition, inflammatory cell infiltration, cytokine release, and calcification.[29]

Even more important, our meta-analysis shows the association between AVC and overall mortality, with an attributable risk to AVC of 77.8% (95%CI: 50.9–104.6). These data confirm previously echocardiographic findings, suggesting that aortic valve sclerosis alone is associated with a 50% increased risk of myocardial infarction or death from cardiovascular causes[30,31]. Interestingly, the four studies evaluated, taking into account the mortality, had a prospective design with no heterogeneity among them (I^2: 0%; p = 0.42).

The meta-regression analyses are useful to understand the heterogeneity among the studies. However, when we took into account only prospective studies for CAC in AVC patients and controls, the heterogeneity was 0.0%. Moreover, the meta-regression analyses evidenced that, in AVC patients and controls, neither CP presence, nor CAC (considered as a continuous variable), nor overall mortality were significantly influenced by any analyzed variable. These findings support the direct association of AVC with CPs and mortality independently from other well-known risk factors like diabetes, male gender, or age.

These data could be clinically relevant and need to be put in the contest of the well-known prognostic value of calcium score and coronary CT angiography,[32,33] on top of which aortic calcium evaluation could be added. Although, due to the intrinsic nature of the current meta-analysis (pooled-data assessment) it was not possible to demonstrate incremental prognostic value of AVC over CAC. However, the aortic calcium evaluation is free from additional costs since it is included in the non-contrast scan for calcium score and this analysis is not time demanding at post-processing level, as it takes less than 1 min to be completed.

4.1. Clinical impact of AVC evaluation

The clinical relevance of cardiac CT as an important prognostic tool, that is confirmed by data on aortic calcium prognostic value presented in this study, is concordant with the growing role of cardiac CT in the clinical field as both diagnostic and prognostic tool in the assessment of patients with stable chest pain.[34] Indeed, the last ESC guidelines on stable angina suggested that CT may be indicated as a first-line test in the setting low-to-intermediate probability of CAD.[35] More recently, NICE guidelines suggested cardiac CT as the first step in all patients with chest pain in whom stable angina could not be excluded by clinical evaluation alone.[36] Furthermore, the recent introduction in the clinical arena of new generation scanners, enabling a further reduction of radiation dose exposure, leaded some authors to suggest cardiac CT as non-invasive diagnostic and prognostic tool in the primary prevention setting, especially in selected subset of high-risk patients, such as diabetics[37–39] and subjects with family history of CAD.[40,41] The present data cannot support the use of cardiac CT over echocardiography for AVC assessment in all patients, but when cardiac CT is performed for suspected CAD, AVC evaluation may contribute to risk stratification and patient management. Indeed, AVC measurement could have a significant impact when aortic valve hemodynamic falls within the normal range (i.e. aortic valve sclerosis)".

4.2. Study limitations

As in any meta-analysis, our study reflects the limitations of the studies that have been included. Six studies, among the 13 included, had a prospective design and only four collected data on patient mortality. Moreover, clinical data on cardiovascular risk factors are available in the majority, but not in all included studies; this may limit the assessment of possible interaction among traditional cardiovascular risk factors and the independent prognostic values of aortic valve calcium. Finally, the impact of AVC on coronary atherosclerosis might vary depending on "pre-test probability" of the study population. Indeed, only one study included a general population, while the others enrolled the patients attending the clinics/hospital where the studies were performed. Thus, our results cannot be generalized. Based on available data, it is not possible to evaluate if adding AVC assessment may lead to an increase in the prediction of CV events as compared to CAC evaluation alone. In the present meta-analysis, we evaluated pooled data and individual-patient-level data were not available. *Ad hoc* designed studies should address this issue in the next future.

4.3. Conclusions

In conclusion, in this meta-analysis, including 13 studies, on 3,782 AVC patients and 32,890 controls, aortic valve calcium evaluated by CT is associated with coronary calcification prevalence and, importantly, with high-risk of all-cause mortality. In the future, this non-invasive assessment could be added to the more traditional prognostic tool, taking into consideration the growing diagnostic and prognostic role of low-dose cardiac CT as first step-test in the clinical setting of suspected CAD and primary prevention.

Sources of funding

Gigi e Pupa Ferrari ONLUS and the Italian Ministry of Health [RC2016-BIO34-2627243]

Disclosures

Daniele Andreini is on speaker bureau from GE Healthcare and received research grant (to the Institution) from GE Healthcare and Bracco.

All the other Authors have nothing to declare.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2019.06.006.

References

1. Leopold JA. Cellular mechanisms of aortic valve calcification. *Circulation. Cardiovascular interventions.* 2012;5:605–614.
2. Rajamannan NM, Evans FJ, Aikawa E, et al. Calcific aortic valve disease: not simply a degenerative process: a review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: calcific aortic valve disease-2011 update. *Circulation.* 2011;124:1783–1791.
3. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD. Incidence and progression of aortic valve calcium in the Multi-ethnic Study of Atherosclerosis (MESA). *Am J Cardiol.* 2010;105:701–708.
4. Kalsch H, Lehmann N, Mahabadi AA, et al. Beyond Framingham risk factors and coronary calcification: does aortic valve calcification improve risk prediction? The Heinz Nixdorf Recall Study. *Heart.* 2014;100:930–937.
5. Mahabadi AA, Bamberg F, Toepker M, et al. Association of aortic valve calcification to the presence, extent, and composition of coronary artery plaque burden: from the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) trial. *Am Heart J.* 2009;158:562–568.
6. Faustino A, Providencia R, Paiva L, et al. Additional value of associating aortic valve calcification to coronary calcium as a gatekeeper for coronary tomography angiography. *BMC Cardiovasc Disord.* 2015;15:61.
7. Nasir K, Katz R, Al-Mallah M, et al. Relationship of aortic valve calcification with coronary artery calcium severity: the Multi-Ethnic Study of Atherosclerosis (MESA). *J. Cardiovasc. Comput. Tomogr.* 2010;4:41–46.
8. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med.* 1999;341:142–147.
9. Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. *Circulation.* 2006;113:861–866.
10. Utsunomiya H, Yamamoto H, Kunita E, et al. Combined presence of aortic valve calcification and mitral annular calcification as a marker of the extent and vulnerable characteristics of coronary artery plaque assessed by 64-multidetector computed tomography. *Atherosclerosis.* 2010;213:166–172.
11. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation.* 2017:2017.
12. Koos R, Mahnken AH, Kuhl HP, et al. Quantification of aortic valve calcification using multislice spiral computed tomography: comparison with atomic absorption spectroscopy. *Investig Radiol.* 2006;41:485–489.
13. Hecht HS, Blaha MJ, Kazerooni EA, et al. CAC-DRS: coronary artery calcium data and reporting system. An expert consensus document of the society of cardiovascular computed tomography (SCCT). *J. Cardiovasc. Comput. Tomogr.* 2018;12:185–191.
14. Hecht HS, Cronin P, Blaha MJ, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: a report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J. Cardiovasc. Comput. Tomogr.* 2017;11:74–84.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
16. Adler Y, Shemesh J, Tenenbaum A, Hovav B, Fisman EZ, Motro M. Aortic valve calcium on spiral computed tomography (dual slice mode) is associated with advanced coronary calcium in hypertensive patients. *Coron Artery Dis.* 2002;13:209–213.
17. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *J Am Med Assoc.* 1999;282:1054–1060.
18. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ.* 2001;323:101–105.
19. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56:455–463.
20. Blaha MJ, Budoff MJ, Rivera JJ, et al. Relation of aortic valve calcium detected by cardiac computed tomography to all-cause mortality. *Am J Cardiol.* 2010;106:1787–1791.
21. Piers LH, Touw HR, Gansevoort R, et al. Relation of aortic valve and coronary artery calcium in patients with chronic kidney disease to the stage and etiology of the renal disease. *Am J Cardiol.* 2009;103:1473–1477.
22. Shalev A, Gransar H, Nakazato R, et al. Thoracic aorta, aortic valve and mitral annular calcifications present No incremental risk for all cause mortality in the presence of coronary artery calcium. *Circulation.* 2012;126.
23. Smith TW, Gurudevan S, Cheng V, et al. Aortic valve calcium score is independently associated with all-cause mortality. *Circulation.* 2010;122.
24. Acuna-Valerio J, Rodas-Diaz MA, Macias-Garrido E, et al. [Aortic valve calcification prevalence and association with coronary risk factors and atherosclerosis in Mexican population]. *Arch Cardiol Mex.* 2017;87:108–115.
25. ten Kate GJ, Bos S, Dedic A, et al. Increased aortic valve calcification in familial hypercholesterolemia: prevalence, extent, and associated risk factors. *J Am Coll Cardiol.* 2015;66:2687–2695.
26. Ann SH, Jung JI, Jung HO, Youn HJ. Aortic valve calcium score is associated with coronary calcified plaque burden. *Int Heart J.* 2013;54:355–361.
27. Kamperidis V, de Graaf MA, Broersen A, et al. Prognostic value of aortic and mitral valve calcium detected by contrast cardiac computed tomography angiography in patients with suspicion of coronary artery disease. *Am J Cardiol.* 2014;113:772–778.
28. Owens DS, Budoff MJ, Katz R, et al. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population. *JACC Cardiovasc. Imaging.* 2012;5:619–625.
29. Milin AC, Vorobiof G, Aksoy O, Ardehali R. Insights into aortic sclerosis and its relationship with coronary artery disease. *J. Am. Heart Assoc.* 2014;3:e001111.
30. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation.* 1997;95:2262–2270.
31. Di Minno MND, Di Minno A, Ambrosino P, et al. Cardiovascular morbidity and mortality in patients with aortic valve sclerosis: a systematic review and meta-analysis. *Int J Cardiol.* 2018;260:138–144.
32. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol.* 2011;58:849–860.
33. Andreini D, Pontone G, Mushtaq S, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. *JACC Cardiovasc. Imaging.* 2012;5:690–701.
34. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography guidelines committee: endorsed by the north American society for cardiovascular imaging (NASCI). *J. Cardiovasc. Comput. Tomogr.* 2016;10:435–449.
35. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* 2013;34:2949–3003.
36. Lee AJ, Michail M, Quaderi SA, Richardson JA, Aggarwal SK, Speechly-Dick ME. Implementation of NICE Clinical Guideline 95 for assessment of stable chest pain in a rapid access chest pain clinic reduces the mean number of investigations and cost per patient. *Open Heart.* 2015;2:e000151.
37. Kang SH, Park GM, Lee SW, et al. Long-Term prognostic value of coronary CT angiography in asymptomatic type 2 diabetes mellitus. *JACC Cardiovasc. Imaging.* 2016;9:1292–1300.
38. Min JK, Labounty TM, Gomez MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. *Atherosclerosis.* 2014;232:298–304.
39. Andreini D. Screening CT angiography in asymptomatic diabetes mellitus? *JACC Cardiovasc. Imaging.* 2016;9:1301–1303.
40. Otaki Y, Gransar H, Berman DS, et al. Impact of family history of coronary artery disease in young individuals (from the CONFIRM registry). *Am J Cardiol.* 2013;111:1081–1086.
41. Leipsic J, Taylor CM, Grunau G, et al. Cardiovascular risk among stable individuals suspected of having coronary artery disease with no modifiable risk factors: results from an international multicenter study of 5262 patients. *Radiology.* 2013;267:718–726.