Aortic valve calcification in 499 consecutive patients referred for computed tomography

Anna Galas[1], Tomasz Hryniewiecki[1], Ilona Michałowska[2], Cezary Kępka[3], Elżbieta Abramczuk[1], Ewa Orłowska-Baranowska[1], Witold Rużyłło[4]

[1]Department of Valvular Heart Disease, Institute of Cardiology, Warsaw, Poland
[2]Department of Radiology, Institute of Cardiology, Warsaw, Poland
[3]Department of Coronary and Structural Heart Diseases, Institute of Cardiology, Warsaw, Poland
[4]Institute of Cardiology, Warsaw, Poland

Corresponding author:
Anna Galas
Department of Valvular
Heart Disease
Institute of Cardiology
42 Alpejska St
04-628 Warsaw, Poland
Phone: +48 601 800 541
E-mail: agalas@ikard.pl

Abstract

Introduction: Aortic valve calcification (AVC) is the most common cause of aortic stenosis. The aim of the study was to assess the prevalence of aortic valve, coronary artery and aortic calcifications and to evaluate the correlation between calcification of the aortic valve, coronary arteries and aorta.
Material and methods: The study included 499 patients aged 60 years and over who underwent coronary computed tomography because of chest pain. Beside coronary artery calcium score (CAC), we evaluated AVC and ascending aorta calcifications (AAC).
Results: Aortic valve calcification was found in 144 subjects (28.9% of the whole study population). Prevalence of CAC and AAC was higher than AVC and amounted to 73.8% and 54.0%. Prevalence of AVC, CAC and AAC was significantly lower in the group of patients ≤ 70 years than in the group of patients > 70 years of age ($p = 0.0002$, $p < 0.0001$, $p < 0.0001$). Aortic valve calcification was more often observed in men than women (34.7% vs. 25.4%, $p = 0.02$). Degree of aortic valve calcification was also significantly higher among men than women (median score 4 vs. 0, $p = 0.01$). Similar observations were true for CAC and AAC, where both prevalence and degree of calcification was higher among men than women. In the whole study population no correlation was noted between AVC and CAC or AAC ($p = 0.34$, $p = 0.85$). There was a significant correlation between AAC and CAC ($p < 0.0001$).
Conclusions: Despite some similarities in pathological mechanism and risk factors, a degenerative defect of the aortic valve could be independent of atheromatous lesions in the coronary arteries and aorta.

Key words: aortic valve, calcification, computed tomography.

Introduction

Aortic valve stenosis is the most common valvular disease. Most frequently the defect is of degenerative etiology (82%), involving gradual fibrotic thickening of the valve, followed by calcification that resembles osteogenesis [1, 2]. It was believed that calcification of the aortic valve is a passive process occurring as a natural result of ageing. However, results of more recent studies demonstrated that it is a complex mechanism, involving deposition of lipoproteins, chronic inflammation and the calcification cascade [3].

AMS

Some researchers claim that development of valve calcification resembles the atherosclerotic process [4, 5]. In their opinion, it is started by epithelial injury. Accumulation of inflammatory cells – macrophages and T cells – is observed in both processes. Valve cells differentiate into osteoblasts under the influence of various factors such as interleukin 1 (IL-1), transforming growth factor β (TGF-β), and tumor necrosis factor α (TNF-α) [6–8]. Development of aortic valve calcification involves multiple signaling pathways, e.g. extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein (MAP) kinase, nuclear factor-κB (NF-B), or the receptor activator of NF-κB (RANK) and its ligand RANKL [9].

Some studies have demonstrated that factors leading to calcification of the aortic valve are similar to the risk factors for coronary artery disease (CAD) and atherosclerosis, including age, male gender, body weight, nicotine addiction, arterial hypertension, diabetes and dyslipidemias [10–12]. Genetic factors seem equally important in the development of changes leading to the degenerative form of aortic stenosis. The most common of them include presence of the 4 apoE allele, mutation of the NOTCH1 gene and vitamin D receptor polymorphism, and genetic variation in the apolipoprotein(a) gene (LPA) locus [13–15]. The pathological mechanism of degenerative aortic sclerosis and precise association with the atheromatous process as well as a complete list of causative factors have not been clearly determined yet. The level of calcification of vessels and aortic valve can be determined using computed tomography (CT). The examination also allows the lumen and wall of a vessel to be evaluated, and provides information regarding the morphology of the aortic valve – the number of cusps, presence of raphe and area of the valve [16–21].

The purpose of the study was to assess: (1) prevalence of calcifications of the aortic valve, coronary arteries and aorta in consecutive patients referred for diagnostic evaluation of coronary atherosclerosis using CT; (2) correlation between calcifications involving the aortic valve, coronary arteries and aorta.

Material and methods

Between September 2011 and December 2012, consecutive patients aged 60 and over referred for CT diagnostic assessment of coronary atherosclerosis in order to exclude CAD were included in the study. These referrals were prompted by chest pain symptoms. A total of 499 patients were included: 315 females (63.1%) and 184 males (36.9%). Mean age was 69.5 ±6.5 years (70.1 ±6.6 years for females and 68.5 ±6.3 years for males). Patients were divided into two groups based on the mean age. The first group consisted of patients aged less than 70 years of age (276 individuals), and the second group included patients over 70 years of age (223 individuals). Blood creatinine level and estimated glomerular filtration rate (eGFR) were determined for each patient before CT examination. Creatinine clearance was calculated according to the Cockcroft-Gault formula. A detailed history taken from all patients included comorbidities, allergies and any previous procedures on coronary vessels or cardiac valves. Coronary CT angiography was performed using a dual-source Somatom Definition scanner (Siemens, Forchheim, Germany). Each study began with determining the coronary artery calcium score (CAC). Calcifications were defined as areas with a density of > 130 Hounsfield units and volume of at least 1 mm³. Calcifications were evaluated using the Agatston score. Coronary CT angiography was not performed if CAC was > 1000. The contrast volume ranging from 60 ml to 120 ml was injected at a rate of 5–6 ml/s. To induce maximal coronary vasodilatation, patients were given 0.8 mg of nitroglycerin, except for patients with severe aortic stenosis, in whom the dose was reduced to 0.4 mg or not administered at all. If the resting heart rate was above 65 bpm or extrasystoles were present, metoprolol was administered intravenously in sequential doses of 2.5 mg (up to 15 mg). Verapamil was given in patients with contraindications to β-blockers (e.g. severe asthma). Conventional invasive coronary angiography was subsequently performed in patients with at least one > 50% stenosis, artifacts due to calcifications, or motion artifacts. The acquisition protocol was retrospectively gated with an electrocardiogram. The CT tube voltage was 100 kV in patients with a body mass of < 80 kg and 120 kV in the remaining patients. Tube current ranged from 370 mAs to 450 mAs and was set automatically according to a protocol to reduce radiation dose (Care4Dose, Siemens). Pitch ranged from 0.2 to 0.5 depending on the heart rate during acquisition. Radiation dose was 4.6 mSv to 16.2 mSv, depending on the acquisition parameters and the scanning range. Besides coronary vessels, the CT examination also involved the aortic valve and a visible part of the ascending aorta. The aorta was evaluated to the tracheal bifurcation level. The evaluation also involved assessment of aortic valve calcification (AVC) and ascending aorta calcification (AAC). Scans were evaluated by radiologists and cardiologists experienced in both invasive and non-invasive coronary vessel diagnostics.

Exclusion criteria were the following: diagnosed aortic valve disease, regardless of its severity, CAC ≥ 1000 Agatston units (AU), history of

Anna Galas, Tomasz Hryniewiecki, Ilona Michałowska, Cezary Kępka, Elżbieta Abramczuk, Ewa Orłowska-Baranowska, Witold Rużyłło

Table I. Baseline characteristics of subjects

Characteristic	Female (n = 315)	Male (n = 184)
Age, mean ± SD [years]	70.1 ±6.6	68.5 ±6.3
Hypertension, n (%)	248 (78.7)	155 (82.2)
Dyslipidemia, n (%)	214 (67.9)	131 (72.2)
Diabetes, n (%)	33 (10.5)	46 (25.0)
Current smoking, n (%)	30 (9.6)	35 (19.0)

coronary angioplasty, history of coronary artery bypass grafting (CABG), condition after cardiosurgical therapy of the aortic and mitral valves, arrhythmia (atrial fibrillation, frequent ventricular and supraventricular premature beats), eGFR < 60 ml/min/1.73 m², allergy to iodine contrast agents, and lack of patient's consent. The study was approved by the local Bioethics Committee.

Statistical analysis

The data are presented as medians (if values were non-parametric) or percentages. A χ^2 test and a Wilcoxon rank sum test were used for comparisons between groups for non-normally distributed variables as appropriate. Correlations between AVC, CAC and AAC scores were calculated using Pearson's correlation. All analyses were performed using SAS statistical software. Value of $p < 0.05$ (two-sided) was considered as statistically significant.

Results

Aortic valve calcification was demonstrated in 144 subjects (29% of the whole study population).

The baseline characteristics of the study subjects are summarized in Table I. Prevalence of calcification of the aortic valve, coronary arteries and aorta was significantly lower in the group of patients ≤ 70 years of age than in the group of patients > 70 years of age (Table II). Also the degree of calcification (measured with cardiac calcium scoring) of the aortic valve, coronary arteries and the aorta increased with age (Table III). In the whole study population, the prevalence and degree of AVC, CAC and AAC were significantly higher in males than in females (Tables II, III). Significant changes in coronary vessels (> 50% stenosis) were diagnosed in 148 patients (58 females and 90 males). Coronary artery stenosis was more common in subjects with AVC ($p < 0.0001$).

No correlation was noted between AVC and CAC or AAC in the whole study population ($p = 0.34$, $p = 0.85$). After patients were divided into two age groups, a significant correlation between AVC and CAC was noted only in subjects > 70 years of age ($p = 0.0009$). In the total population and in both age groups (≤ 70 and > 70 years), there was a significant correlation between AAC and CAC ($p < 0.0001$, $p = 0.0014$, $p = 0.0002$, respectively). Bicuspid aortic valve was noted in 4 individuals (0.8%).

Discussion

Considering the fact that aortic stenosis has become the most common cardiac defect in adults, an increased interest is observed in various methods of aortic valve imaging. These methods are aimed at detecting not only the presence of aor-

Table II. Prevalence of calcification of aortic valve, coronary arteries, aorta in whole study population, in two age groups and in both genders

Calcification	All n (%)	≤ 70 years n (%)	> 70 years n (%)	Value of p	Female n (%)	Male n (%)	Value of p
AVC > 0	144 (28.9)	61 (22.1)	83 (37.2)	0.0002	80 (25.4)	64 (34.7)	0.02
CAC > 0	368 (73.8)	182 (66)	186 (83.9)	< 0.0001	213 (67.6)	155 (84.2)	0.0001
AAC > 0	269 (54)	118 (42.7)	151 (67.7)	< 0.0001	161 (51.1)	108 (58.7)	0.01

AAC – Ascending aorta calcification, AVC – aortic valve calcification, CAC – coronary artery calcification.

Table III. Calcium score of the aortic valve, coronary arteries and aorta in the entire examined population as well as in both groups divided according to age and gender

Calcium score	Female	Male	Value of p	Female			Male		
				≤ 70 years	> 70 years	Value of p	≤ 70 years	> 70 years	Value of p
AVC, median (range)	0 (0–843)	4 (0–10054)	0.01	0 (0–650)	0 (0–843)	NS	6 (0–10059)	48 (0–972)	< 0.001
CAC, median (range)	25 (0–999)	125 (0–996)	< 0.0001	7 (0–999)	55 (0–999)	< 0.0001	69 (0–998)	261 (0–999)	0.001
AAC, median (range)	2 (0–3406)	11 (0–3048)	0.04	0 (0–1325)	21 (0–3406)	< 0.0001	0 (0–1650)	61 (0–2048)	< 0.0001

AAC – Ascending aorta calcification, AVC – aortic valve calcification, CAC – coronary artery calcification, NS – not significant.

tic stenosis but also the processes that may lead to development of the defect, e.g. calcification of the valve. Computed tomography (performed also for non-cardiological reasons) has become a tool commonly used for evaluating the degree of calcification of the valve or vessels. Numerous studies on the prevalence of AVC have been performed using this method [22, 23].

Raju *et al.* evaluated incidence of AVC in 416 consecutive patients examined with CT; AVC was identified in 22.8% of the examined population [24]. In the study by Messika-Zeitoun *et al.* on 262 patients aged 60 and older, AVC rate evaluated with CT was 27% [25]. In the Multi-Ethnic Study of Atherosclerosis (MESA) study that included 6809 individuals aged 45–84 years, AVC was found in 13% of the study population [26]. Therefore it seems that prevalence of AVC is not precisely determined and depends on the number and/or characteristics of the study group. The majority of studies have demonstrated that prevalence of AVC and the degree of valve calcification depend on age [27, 28]. In the study by Walsh, incidence of AVC was 3% for subjects < 50 years of age, 6% for subjects 50–59 years of age, 17% for subjects 60–69 years of age, and 34% for subjects ≥ 70 years of age ($p < 0.0001$) [29]. Also, in the present study, prevalence and degree of AVC were higher in the older age group.

A correlation between gender and AVC is a different matter. Some studies indicate that more advanced AVC is observed in males than in females [30, 31]. Aggarwal *et al.* demonstrated that among patients diagnosed with aortic stenosis of similar severity, AVC is lower in females than in males (1703 ±1321 AU vs. 2694 ±1628 AU; $p < 0.0001$) [32]. On the other hand, Koos *et al.*, analyzing AVC in 402 individuals aged 32–91 years undergoing chest CT, found no correlation between gender and AVC [33].

Our study revealed a significant correlation between gender and the prevalence and degree of AVC in the whole study population.

Some authors claim that the valve calcification process may be an equivalent of the atheromatous process. Others, however, stress some important differences between these two processes. First, the basic role in valve calcification is played by fibroblasts [34]. In the case of vessels, there are smooth muscle cells that, under the influence of certain factors (e.g. IL-1, TGF-β, TNF-α), differentiate into osteoblasts [35, 36]. The manifestation of the disease is another dissimilarity. In CAD the atheromatous plaque may crack or become eroded, leading in consequence to an acute coronary syndrome. That is not observed in aortic stenosis.

Considering a possible link between AVC and atherosclerosis, some studies were carried out involving evaluation of AVC and CAC using CT examination. Blaha *et al.* used CT to assess the degree of calcification of the aortic valve and coronary vessels in 8401 subjects without a diagnosed ischemic heart disease [37]. Patients with AVC had greater mean CAC (421 ±748 AU vs. 121 ±344 AU, $p < 0.0001$). A significant correlation between CAC and AVC ($p < 0.0001$) was observed. Koos *et al.* evaluated calcifications of the aortic valve and coronary vessels in patients with aortic stenosis [38]. No correlation between the AVC and the total coronary calcium scores was observed. In the present study there was no correlation between AVC and CAC in the whole population. Figure 1 shows an example of heavy calcification of the aortic valve without coronary artery calcification. Figure 2 shows the opposite situation. After dividing the patients into two age groups, a correlation between AVC and CAC was noted in patients > 70 years old. Perhaps the pathological mechanism
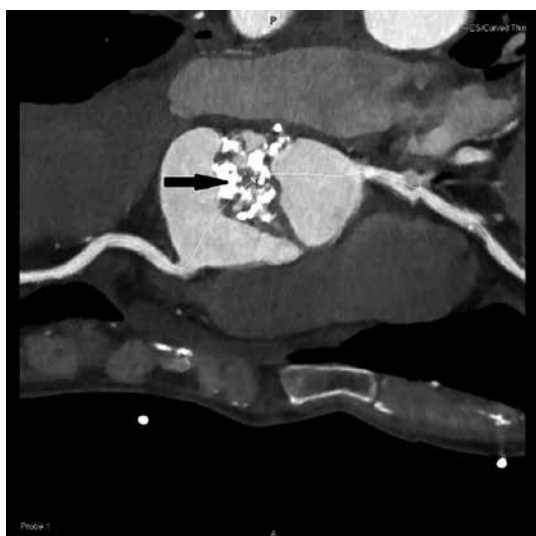

Figure 1. Severe aortic valve calcification (AVC = 10 050) in patients with non-calcified coronary arteries (CAC = 0)

Figure 2. Severe coronary artery calcification (CAC = 890) in patients without aortic valve calcification (AVC = 0)

Anna Galas, Tomasz Hryniewiecki, Ilona Michałowska, Cezary Kępka, Elżbieta Abramczuk, Ewa Orłowska-Baranowska, Witold Rużyłło

of AVC is different or more complex than in atherosclerosis among subjects aged 70 years old or younger. Besides evaluating AVC and CAC, CT was also used for analyzing calcifications within the descending aorta and the whole thoracic aorta. In the MESA study, Takasu *et al.* found a strong association between descending thoracic aortic calcification and CAC [39]. Wong *et al.* evaluated calcification of the aortic valve, coronary vessels and the thoracic aorta in 1754 males and 986 females aged 20–79 years, without a diagnosed CAD [40]. A significant correlation was found between calcification of the aortic valve, coronary vessels and thoracic aorta. Our study also demonstrated a correlation between AAC and CAC.

Some researchers underline the fact that the same risk factors are responsible for AVC and atherosclerosis [41–43]. There have been a number of retrospective evaluations of statins in aortic stenosis, suggesting an average 50% reduction in the rate of progression of aortic stenosis with statin use [44].

However, large prospective studies completed at a later time did not confirm that hypothesis [45–47]. The SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Therapy), SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) and ASTRONOMER (Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin) trials indicate that lipid-lowering treatment, being so favorable for patients with ischemic heart disease, has no effect on aortic stenosis. That fact may undermine the hypothesis of the common pathological mechanism of AVC and atherosclerosis.

The data collection was confined to one center. We studied exclusively patients referred for coronary artery diagnostics because of chest pain. We excluded young patients (below 60 years of age), with kidney failure or with previously diagnosed aortic valve disease. Results in this group could be different. Coronary CT angiography was not performed if CAC was > 1000 AU. Persons with hypertension, diabetes or hypercholesterolemia were diagnosed and treated adequately before inclusion in our study.

In conclusion, calcification of the aortic valve, coronary arteries and aorta was frequent in our patients (occurring respectively in one third, three quarters and half of the study population). Furthermore, their prevalence and degree increased with age. In the whole study population there was no significant correlation between the prevalence and degree of calcification of the aortic valve and coronary vessels. A significant correlation was noted only in subjects over 70 years old. A significant correlation exists between calcification of the ascending aorta and coronary arteries. Despite some similarities in pathological mechanism and risk factors, a degenerative defect of the aortic valve could be independent of atheromatous lesions in the coronary arteries and aorta.

Conflict of interest

The authors declare no conflict of interest.

References

1. Hjortnaes J, Butcher J, Figueiredo JL, et al. Arterial and aortic valve calcification inversely correlates with osteoporotic bone remodelling: a role for inflammation. Eur Heart J 2010; 31: 1975-84.
2. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003; 24: 1231-43.
3. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis disease of the valve and the myocardium. J Am Coll Cardiol 2012; 60: 1854-63.
4. Poggianti E, Venneri L, Chubuchny V, Jambrik Z, Baroncini LA, Picano E. Aortic valve sclerosis is associated with systemic endothelial dysfunction. J Am Coll Cardiol 2003; 41: 136-41.
5. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease. Pathogenesis, disease progression, and treatment strategies. Circulation 2005; 111: 3316-26.
6. Goldbarg SH, Elmariah S, Miller MA, Fuster V. Insights into degenerative aortic valve disease. J Am Coll Cardiol 2007; 50: 1205-13.
7. Donghyun L. Vascular calcification: Inducers and inhibitors. Materials Science and Engineering: B 2011; 15: 1133-41.
8. Yu PJ, Skolnick A, Ferrari G, et al. Correlation between plasma osteopontin levels and aortic valve calcification: potential insights into the pathogenesis of aortic valve calcification and stenosis. J Thorac Cardiovasc Surg 2009; 138: 196-9.
9. Ngo DT, Sverdlov AL, Horowitz JD. Prevention of aortic valve stenosis: a realistic therapeutic target? Pharmacology and Therapeutics 2012; 135: 78-93.
10. Novaro GM, Katz R, Aviles RJ, et al. Clinical factors, but not C-reactive protein, predict progression of calcific aortic-valve disease: the Cardiovascular Health Study. J Am Coll Cardiol 2007; 50: 1992-8.
11. 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: 619-25.
12. Olsen MH, Wachtell K, Bella JN, et al. Aortic valve sclerosis and albuminuria predict cardiovascular events independently in hypertension – a Losartan Intervention for Endpoint-reduction in Hypertension (LIFE) Substudy. Am J Hypertens 2005; 18: 1430-6.
13. Novaro GM, Sachar R, Pearce GL, Sprecher DL, Griffin BP. Association between apolipoprotein E alleles and calcific valvular heart disease. Circulation 2003; 108: 1804-14.
14. Timmerman LA, Grego-Bessa J, Raya A, et al. Notch promotes epithelial-mesenchymal transition during cardiac development and oncogenic transformation. Genes Dev 2004; 18: 99-115.
15. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med 2013; 368: 503-12.
16. de Graaf FR, van Velzen JE, de Boer SM, et al. Non-invasive computed tomography coronary angiography

as a gatekeeper for invasive coronary angiography. Int J Cardiovasc Imaging 2013; 29: 221-8.

17. Chen JJ, Manning MA, Frazier AA, Jeudy J, White CS. CT angiography of the cardiac valves: normal, diseased, and postoperative appearances. Radiographics 2009; 29: 1393-412.

18. Lee SC, Ko SM, Song MG, Shin JK, Chee HK, Hwang HK. Morphological assessment of the aortic valve using coronary computed tomography angiography, cardiovascular magnetic resonance, and transthoracic echocardiography: comparison with intraoperative findings. Int J Cardiovasc Imaging 2012; 28: 33-44.

19. Mark DB, Berman DS, Matthew J, et al. ACCF/ACR/AHA/NASCI//SAIP/SCAI/SCCT 2010 Expert Consensus Document on Coronary Computed Tomographic Angiography: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus. J Am Coll Cardiol 2010; 55: 2663-99.

20. Noll D, Kruk M, Pregowski J, et al. Lumen and calcium characteristics within calcified coronary lesions. Comparison of computed tomography coronary angiography intravascular ultrasound. Postep Kardiol Inter 2013; 1: 1-8.

21. Veselka J, Cadova P, Adla T, Zemanek D. Dual-source computed tomography angiography and intravascular ultrasound assessment of restenosis in patients after coronary stenting for bifurcation left main stenosis: a pilot study. Arch Med Sci 2012; 3: 455-61.

22. 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: 209-13.

23. Pohle K, Otte M, Mäffert R, et al. Association of cardiovascular risk factors to aortic valve calcification as quantified by electron beam computed tomography. Mayo Clinic Proceedings 2004; 79: 1242-6.

24. Raju P, Sallomi D, George B, Patel H, Patel N, Lloyd G. Aortic valve calcification – a commonly observed but frequently ignored finding during CT scanning of the chest. Int J Clin Pract 2012; 66: 552-5.

25. Messika-Zeitoun D, Bielak LF, Peyser PA, et al. Aortic valve calcification. Determinants and progression in the population. Arterioscler Thromb Vasc Biol 2007; 27: 642-8.

26. 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 Tomog 2010; 4: 41-6.

27. Boona A, Cheriexb E, Lodderc J, Kesselsd F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. Heart 1997; 78: 472-4.

28. O'Brien KD. Pathogenesis of calcific aortic valve disease: a disease process comes of age (and a good deal more). Arterioscler Thromb Vasc Biol 2006; 26: 1721-8.

29. Walsh CR, Larson MG, Kupka MJ, et al. Association of aortic valve calcium detected by electron beam computed tomography with echocardiographic aortic valve disease and with calcium deposits in the coronary arteries and thoracic aorta. Am J Cardiol 2004; 93: 421-5.

30. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. J Am Coll Cardiol 1997; 29: 630-4.

31. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikila J, Tilvis R. Factors associated with calcific aortic valve degeneration in the eldery. Eur Heart J 1994; 15: 865-70.

32. Aggarwal SR, Clavel MA, Messika-Zeitoun D, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circulation Cardiovasc Imag 2013; 6: 40-7.

33. Koos R, Kuhl HP, Muhlenbruch G, Wildberger JE, Gunther RW, Mahnken AH. Prevalence and clinical importance of aortic valve calcification detected incidentally on CT scans: comparison with echocardiography. Radiology 2006; 241: 76-82.

34. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994; 90: 844-53.

35. Mohler ER 3rd. Mechanisms of aortic valve calcification. Am J Cardiol 2004; 94: 1396-402.

36. Kaden JJ, Dempfle CE, Grobholz R, et al. Interleukin-1 beta promotes matrix metalloproteinase expression and cell proliferation in calcific aortic valve stenosis. Atherosclerosis 2003; 170: 205-11.

37. 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: 1787-91.

38. Koos R, Mahnken AH, Sinha AM, Wildberger JE, Hoffmann R, Kuhl HP. Aortic valve calcification as a marker for aortic stenosis severity: assessment on 16-MDCT. AJR Am J Roentgenol 2004; 183: 1813-8.

39. Takasu J, Budoff MJ, O'Brien KD, et al. Relationship between coronary artery and descending thoracic aortic calcification as detected by computed tomography: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2009; 204: 440-6.

40. Wong ND, Lopez VA, Allison M, et al. Abdominal aortic calcium and multi-site atherosclerosis: the Multiethnic Study of Atherosclerosis. Atherosclerosis 2011; 214: 436-41.

41. Aranow WS, Ahn C, Kronzon I, Goldman ME. Association of coronary risk factors and use of statins with progression of mild valvular aortic stenosis in older persons. Am J Cardiol 2001; 88: 693-5.

42. Sashida Y, Rodriguez CJ, Boden-Albala B, et al. Ethnic differences in aortic valve thickness and related clinical factors. Am Heart J 2010; 159: 698-704.

43. Kearney LG, Ord M, Buxton BF, et al. Progression of aortic stenosis in elderly patients over long-term follow up. Int J Cardiol 2013; 167: 1226-31.

44. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Established and emerging vascular risk factors and the development of aortic stenosis: an opportunity for prevention? Expert Opin Ther Targets 2008; 12: 809-20.

45. Cowell SJ, Newby DE, Prescott RJ, et al. Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005; 352: 2389-97.

46. Rossebo AB, Pedersen TR, Boman K, et al. SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008; 359: 1343-56.

47. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J; the ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis. Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) Trial. Circulation 2010; 121: 306-14.