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PREVENTION OF NONRHEUMATIC AORTIC VALVE DISEASE PROGRESSION - CURRENT EVIDENCE

PREVENÇÃO DA PROGRESSÃO DA DOENÇA VALVAR AÓRTICA NÃO REUMÁTICA – EVIDÊNCIAS ATUAIS

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ABSTRACT

Degenerative aortic stenosis is a pathology with high incidence in elderly patients. Its pathophysiology is related to valve calcification and has not been fully elucidated. However, it is known to be very similar to the atherosclerotic process in the initial stages. Once calcium deposition begins, this process is self-perpetuating, generating further calcification and progressive degeneration of the valve anatomy. The number of tests used to diagnose the early stages of calcification is still insufficient. However, in the late stages, the use of computed tomography aortic valve calcium scoring and echocardiogram scans is well established. Regarding medical treatment aimed at reducing or slowing heart valve disease progression, we must emphasize the need for treatment of atherosclerosis risk factors. However, statins have thus far proven ineffective, and new drug products, such as desonumab and bisphosphonates, are still being studied.

Keywords: Aortic Valve Stenosis; Vascular Calcification; Tomography; Echocardiography.

RESUMO

A estenose aórtica degenerativa é uma patologia com incidência elevada em pacientes idosos. Sua fisiopatologia está relacionada à calcificação valvar e não está totalmente elucidada. Sabe-se, entretanto, que inicialmente há grande semelhança com o processo de aterosclerose e, após o inicio da deposição do cálcio, tal processo se autoperpetua, gerando mais calcificação e piora da gravidade anatômica valvar progressivamente. Ainda há uma carência de testes para o diagnóstico das fases iniciais de calcificação. Porém, nas fases finais, a utilização da tomografia com escore de cálcio valvar e o ecocardiograma estão bem estabelecidos. Com relação ao tratamento medicamentoso para reduzir ou deter a progressão da doença valvar, devemos reforçar a necessidade de tratamento para os fatores de risco de aterosclerose. Entretanto, a estatina provou-se ineficaz até o momento e novas medicações, como o desonumabe e os bifosfonados, ainda estão em estudo.

Descritores: *Estenose da Valva Aórtica; Calcificação Vascular; Tomografia; Ecocardiografia.*

INTRODUCTION

With the increase in population aging, there has been a dramatic increase in the incidence of pathologies such as degenerative aortic stenosis (AoS).[1,2] Symptomatic patients with AoS, when not subjected to interventional treatment, have a mortality rate of approximately 93% in five years, that is, by the time this pathology is diagnosed, its evolution is fatal.[3] Many technological advances have occurred for the early and definitive diagnoses of AoS in addition to the advent of the transcatheter aortic valve implantation (TAVI), a less invasive therapeutic option for patients who were previously prone to high morbidity and mortality in clinical treatment. Nevertheless, to date, there is no drug treatment capable of altering or reducing the progression of aortic valve calcification, which is central to the pathophysiology of AoS.

PATHOPHYSIOLOGY OF CALCIFICATION

The process of aortic valve calcification is complex and not completely elucidated. AoS is degenerative, also described as calcific or atherosclerotic, and has pathophysiological characteristics and risk factors similar to atherosclerosis in its early stages, such as age, smoking, and systemic arterial hypertension.[4,5] The process begins with an endothelial lesion due to mechanical stress on the cusps, followed by valve lipid infiltration, mainly of lipoprotein A and low-density lipoprotein (LDL) cholesterol.[6] Endothelial lesions associated with lipid oxidation generate an inflammatory response mediated by macrophages, T cells, and mast cells, leading to lipid deposition and microcalcifications.[7] Microcalcifications probably occur by cellular apoptosis, a mechanism similar to the deposition of hydroxyapatite in bones.

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The pathophysiology of the process up to this point, in which there is a predominance of inflammation and lipid deposition, is called the calcification initiation stage and is followed by a propagation stage, in which there is a cycle of calcification and endothelial valve lesion that participates in a "feedback" loop.[8] This second phase begins with collagen deposition due to the reduction in nitric oxide expression after endothelial lesion formation, and it is believed that the renin–angiotensin system may also play a role in pro-fibrotic effects via AT1.[9,10] These changes cause fibrosis, leading to thickened, fibrotic, and calcified aortic leaflets, which in turn leads to immobility and valve obstruction. Calcification is caused by cells with characteristics similar to osteoblasts; however, their origin is still unknown, and it is suggested that valve interstitial cells (VICs) may play a central role in this process.[11,12] In the calcification initiation phase, VICs show osteoblastic characteristics due to the influence of pro-inflammatory cytokines. In the final phase, mutations in Notch-1 (cell surface receptor) and imbalance in the receptor activator of nuclear factor kappa-Β/receptor activator of nuclear factor kappa-Β ligand/osteoprotegerin (RANK/RANKL/OPG) pathway seem to have a significant interference in this process.[13] When RANK binds to RANKL, osteoclastic activation occurs in the bones, but this is counterbalanced by the binding of OPG to RANKL, thus preventing it from binding to RANK. However, the RANK/RANKL binding has an inverse effect on the vasculature, activating osteoblasts and calcification, leading to the hypothesis that patients with AoS lack OPG in their valve cells.[14] Valve calcification generates mechanical stress and turbulence in blood flow, causing new endothelial lesions and restarting the process in a self-perpetuating cycle. (Figure 1)

GENETICS

The initial studies relating genetics and AoS were criticized for the small number of participants and difficulty in replicating the results.[15-21] However, in 2013, a comprehensive study showed an association between the incidence of aortic valve calcification and single nucleotide polymorphism in the locus of lipoprotein A (rs10455872), a genetic determinant of plasma lipoprotein A levels.[22] This study proved that there is a association between this genetic variation and valve calcification and that there is the causal relationship between lipoprotein A and AoS by evaluating >6,000 European patients from three cohorts who had aortic valve calcification using tomography and validating the results in cohorts with patients from other ethnic groups.[22]

TESTS FOR DIAGNOSIS OF THE FINAL PHASE (PROPAGATION) OF CALCIFICATION

Aortic valve calcification is an important marker of the anatomical severity of AoS and its evaluation has recently proved to be of great value. In addition, it can be measured in a noninvasive way by both echocardiography and valve calcium score tomography.

Echocardiography, the most widespread examination used in daily clinical practice for valve evaluation, can define the anatomical severity of AoS by measuring the valve area, mean gradient, and velocity of the transvalvular jet.[23] It can also define the etiology of valve disease and visualize calcification; however, the quantification of the degree of calcification is not as reliable as that measured by tomography.[24] Valve calcium score tomography, in addition to quantifying the degree of calcification more accurately, is useful in cases where there is difficulty defining the anatomical severity, such as in patients with low-flow and low-gradient AoS.[25] In this subgroup of patients in which the echocardiogram demonstrates disagreement between the valve area and the gradients (valve area $\leq$1.0 cm^2 and mean gradient $<$40 mmHg), the Agatston score of >1650 for calcium defines AoS as significant and supports the interventionist treatment.[25] Other studies have shown that the valve calcium score for the definition of significant AoS may vary according to gender, making use of lower cut-off values for women compared to men (1275 AU *vs.* 2065 AU, respectively).[26] Similar to the coronary calcium score, this examination is performed synchronized with the cardiac cycle (gated), without the use of contrast or with a low-dose protocol. The latter allows defining the location of calcium deposits in the cusps and, when predominantly central, seems to be associated with the anatomical severity of AoS in detriment to the degree of calcification.[27] Another important aspect of the evaluation of the valve calcium score is its predictive capacity for disease progression and cardiovascular events in those with significant calcification.[26]

TESTS FOR DIAGNOSIS OF THE INITIAL PHASE (ONSET) OF CALCIFICATION

As the identification of valve calcification becomes increasingly simple, there is a need to recognize patients in the early stages of the valve degeneration process because, as previously described, after the deposit of calcium in the cusps, a process is initiated that is self-perpetuating and generates more and more calcification. So far, drug treatment has not been effective in this late phase at inhibiting or delaying such evolution. There is a desire to identify patients in the initial phase of calcification to try and prevent AoS. However, population screening is still lacking, and it is common to find patients with moderate or significant AoS in daily practice.

Echocardiography, as a noninvasive method, seems to be the most promising tool, thus far, for the screening of initial AoS (anatomically mild/discrete) since in this phase, the hemodynamic defect is minimal and does not cause symptoms. The most frequent finding is aortic valve sclerosis, defined as the presence of thickening and irregularity of the cusps with focal increase in echogenicity and normal flow velocity in the absence of commissural fusion without affecting the mobility of the cusps.[1,28] The clinical significance of valve sclerosis is its evolution to AoS, which indicates changes in lifestyle, treatment of risk factors for atherosclerosis, and annual echocardiographic follow up.[29] A recent study using PET with ^{18}F-FDG, a glucose analogue absorbed by metabolically active cells and an indicator of vascular inflammation, demonstrated that patients with AoS have greater ^{18}F-FDG activity than controls and there was a progressive increase depending on the anatomical severity.[30] However, PET with ^{18}F-FDG is only performed in large centers and is not cost-effective; hence, it is difficult to use this method routinely for initial screening.

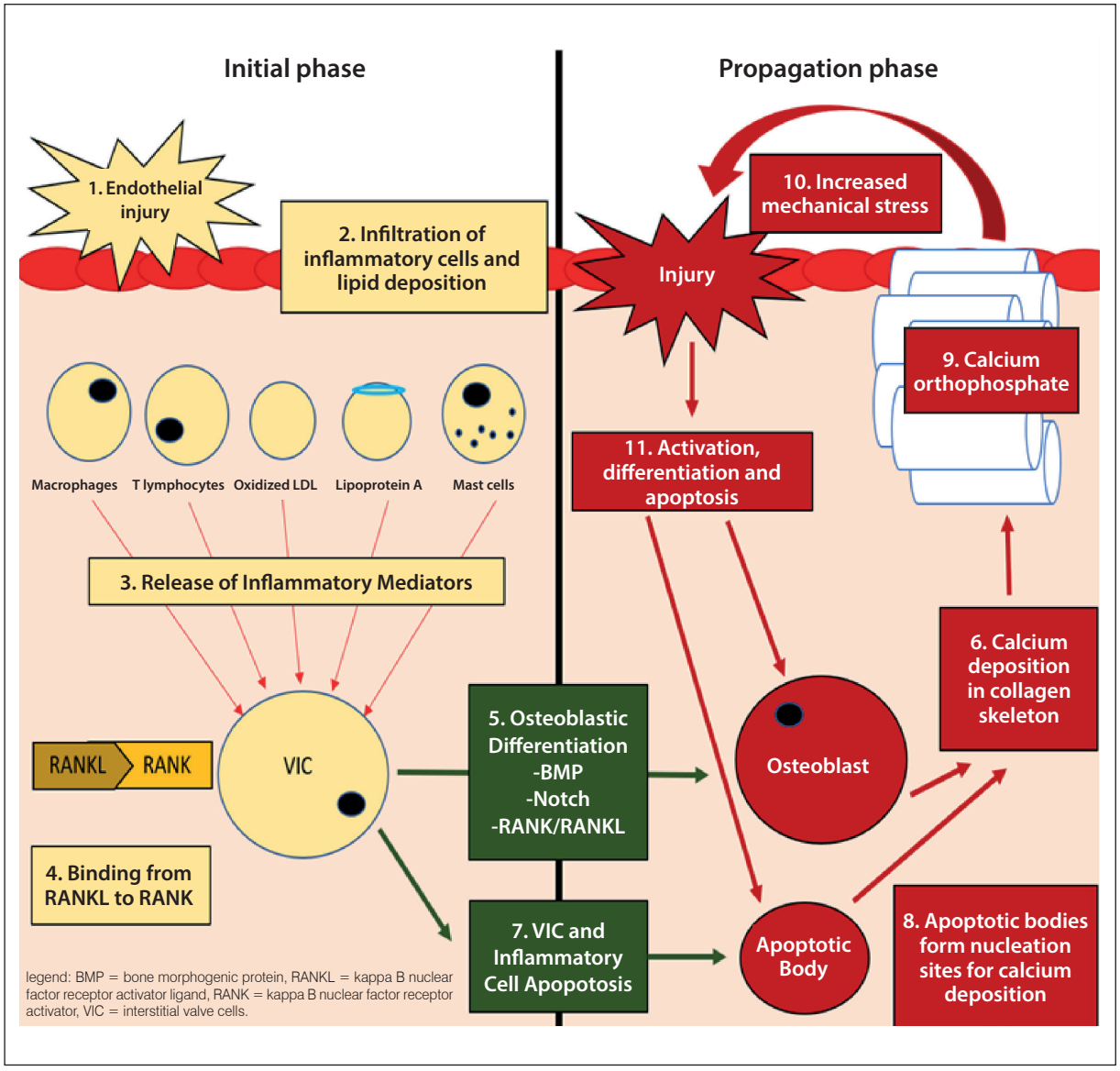

Figure 1. Schematic representation of the pathophysiology of aortic valve calcification (adapted from Pawade et al.8). Endothelial lesion (1) causes infiltration of inflammatory cells and lipid deposition (2) in addition to release of inflammatory mediators (3). Such processes, associated with binding of RANK to RANKL (4), lead to VIC differentiation into cells with osteoblastic characteristics (5), resulting in a matrix of collagen associated with proteins related to ossification (6). This causes thickening and hardening of the cusps before the calcification is formed. VIC and inflammatory cell apoptosis (7) then occurs, generating apoptotic bodies that form nucleation sites for calcium deposits (8). Valve calcification (9) leads to valve obstruction and turbulence, resulting in mechanical stress and endothelial lesions (10) that initiates new activation, differentiation, and cellular apoptosis (11) in a self-perpetuating cycle.

DRUGS WITH THE POTENTIAL TO ALTER THE EVOLUTION OF CALCIFICATION

Statins: Three large randomized studies (SEAS[31], SALTIRE[32], and ASTRONOMER[33]) tested the use of statins to reduce the inflammatory process and AoS progression. However, despite significant reductions in LDL values, there was no change in the evolution of valve disease. Although lipid deposition and infiltration of inflammatory cells are part of the calcification process, treatment with the strains was instituted in the propagation phase of the disease, in which the calcification itself is part of the inflammatory process feedback loop. It is assumed that treatment with statins could be useful if started in the early stages of the calcium deposition process (Figure 2).

Bisphosphonates: A recent retrospective observational study demonstrated that the use of bisphosphonates in women was associated with the reduction of valve and vascular calcification.[34] Such findings may be due to the effects of such medication on bones, reducing the release of calcium and phosphates and the possible action on VIC differentiation in osteoblasts by reducing the release of cytokines and reducing extracellular valve mineralization (Figure 2).

Denosumab: This medication is a monoclonal human antibody and is considered one of the most promising treatments today. Its mechanism of action is preventing RANKL from binding to RANK, thus reducing VIC differentiation in cells with osteoblastic characteristics (Figure 2).

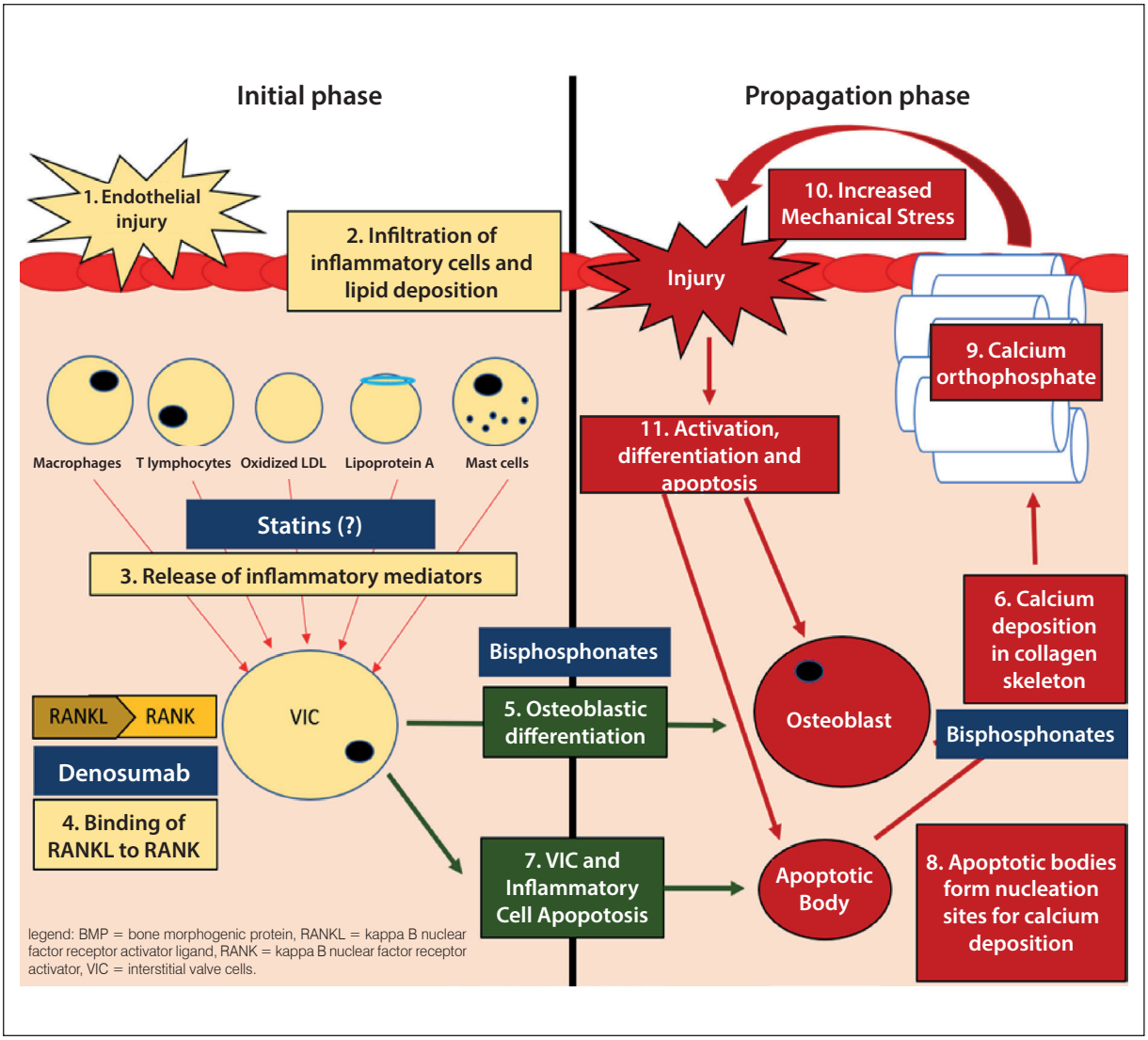

Figure 2. Possible mechanism of action of medications in the pathophysiology of aortic valve calcification (adapted from Pawade et al.8). The statins have a possible action on infiltration of inflammatory cells, lipid deposition, and release of inflammatory mediators; however, they has not been tested on patients in the initial phase of calcification. Denosumab acts by binding to RANKL, preventing it from binding to RANK. Bisphosphonates act by reducing the VIC differentiation in osteoblasts and reducing extracellular mineralization.

CONCLUSION

The incidence of AoS is high and it is associated with significant morbidity and mortality; however, no treatment has been developed to stop or reduce disease progression after the initiation of valve calcification. The current recommendation is to treat risk factors for atherosclerosis; however, the results of ongoing studies, especially SALTIRE II (*Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis* - NCT02132026), which investigates the use of bisphosphonates and denosumab on the evolution of AoS, may add further insights. This study is being conducted by the University of Edinburgh and will evaluate the evolution of calcification through tomography. Even with proof of efficacy of these drugs, there is still an absence of methods for the early diagnosis of valve calcification in the initial phase and further studies are expected for this purpose.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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REFERENCES

1. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. Circulation. 2005;111(24):3316-26.
2. Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol. 1993;21(5):1220-5.
3. **Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2485-91.**
4. Thanassoulis G, Massaro JM, Cury R, Manders E, Benjamin EJ, Vasan RS, et al. Associations of long-term and early adult atherosclerosis risk factors with aortic and mitral valve calcium. J Am Coll Cardiol. 2010;55(22):2491-98.
5. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol. 1997;29(3):630-4.
6. **Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, et al. Association of low-density lipoprotein cholesterol–related genetic variants with aortic valve calcium and incident aortic stenosis. Jama. 2014;312(17):1764-71.**
7. 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(2):844-53.
8. **Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. J Am Coll Cardiol. 2015;66(5):561-77.**
9. O'Brien KD, Shavelle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM , et al. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. Circulation. 2002;106(17):2224-30.
10. Helske S, Lindstedt KA, Laine M, Mäyränpää M, Werkkala K, Lommi J, et al. Induction of local angiotensin II-producing systems in stenotic aortic valves. J Am Coll Cardiol. 2004;44(9):1859-66.
11. Liu AC, Joag VR, Gotlieb AI. The emerging role of valve interstitial cell phenotypes in regulating heart valve pathobiology. Am J Pathol. 2007;171(5):1407-18.
12. Mathieu P, Voisine P, Pépin A, Shetty R, Savard N, Dagenais F. Calcification of human valve interstitial cells is dependent on alkaline phosphatase activity. J Heart Valve Dis. 2005;14(3):353-7.
13. Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, et al. Mutations in NOTCH1 cause aortic valve disease. Nature. 2005;437(7053):270-4.
14. Kaden JJ, Bickelhaupt S, Grobholz R, Haase KK, Sarıkoç A, Kılıç R, et al. Receptor activator of nuclear factor κB ligand and osteoprotegerin regulate aortic valve calcification. J Mol Cell Cardiol. 2004;36(1):57-66.
15. Gaudreault N, Ducharme V, Lamontagne M, Guauque-Olarte S, Mathieu P, Pibarot P, et al. Replication of genetic association studies in aortic stenosis in adults. *Am J Cardiol*. 2011;108(9):1305-10.
16. Morgan TM, Krumholz HM, Lifton RP, Spertus JA. Nonvalidation of reported genetic risk factors for acute coronary syndrome in a large-scale replication study. Jama. 2007;297(14):1551-61.
17. Ortlepp J, Hoffmann R, Ohme F, Lauscher J, Bleckmann F, Hanrath P. The vitamin D receptor genotype predisposes to the development of calcific aortic valve stenosis. Heart. 2001;85(6):635-8.
18. Novaro GM, Sachar R, Pearce GL, Sprecher DL, Griffin BP. Association between apolipoprotein E alleles and calcific valvular heart disease. Circulation. 2003;108(15):1804-8.
19. Nordstrom P, Glader CA, Dahlén G, Birgander LS, Lorentzon R, Waldenstrom A, et al. Oestrogen receptor α gene polymorphism is related to aortic valve sclerosis in postmenopausal women. J Intern Med. 2003;254(2):140-6.
20. Avakian S, Annicchino-Bizzacchi JM, Grinberg M, Ramires JA, Mansur A. Apolipoproteins AI, B, and E polymorphisms in severe aortic valve stenosis. Clini Genet. 2001;60(5):381-4.
21. Ortlepp JR, Schmitz F, Mevissen V, Weiss S, Huster J, Dronskowski R, et al. The amount of calcium-deficient hexagonal hydroxyapatite in aortic valves is influenced by gender and associated with genetic polymorphisms in patients with severe calcific aortic stenosis. Eur Heart J. 2004;25(6):514-22.
22. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013;368(6):503-12.
23. **Tarasoutchi F, Montera MW, Ramos AIO, Sampaio RO, Rosa VEE, Accorsi TAD, et al. Atualização das Diretrizes Brasileiras de Valvopatias: Abordagem das Lesões Anatomicamente Importantes. Arq Bras Cardiol. 2017;109 (6 suppl 2):1-34.**
24. Messika-Zeitoun D, Aubry MC, Detaint D, Bielak LF, Peyser PA, Sheedy PF, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation. 2004;110(3):356-62.
25. Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart. 2011;97(9):721-6.
26. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013;62(24):2329-38.
27. **de Santis A, Tarasoutchi F, Araujo Filho JAB, Vieira MC, Nomura CH, Katz M, et al. Topographic pattern of valve calcification: a new determinant of disease severity in aortic valve stenosis. JACC Cardiovasc Imaging. 2018;11(7):1032-1035.**
28. Gharacholou SM, Karon BL, Shub C, Pellikka PA. Aortic valve sclerosis and clinical outcomes: moving toward a definition. Am J Med. 2011;124(2):103-10.
29. 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(3):142-7.
30. Dweck MR, Jones C, Joshi N, Fletcher AM, Richardson H, White A, et al. Assessment of valvular calcification and inflammation by positron emission tomography in patients with aortic stenosis. Circulation. 2012;125(1)-76-86.
31. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Eng J Med. 2008;359(13):1343-56.
32. Cowell S, Newby DE, Prescott RJ, Blomfield P, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med. 2005;352(23):2389-97.
33. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. 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(2):306-14.
34. Elmariah S, Delaney JA, O'Brien KD, Budoff MJ, Vogel-Claussen J, Fuster V, et al. Bisphosphonate use and prevalence of valvular and vascular calcification in women: MESA (The Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2010;56(21):1752-9.