Aortic stenosis: insights on pathogenesis and clinical implications

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Abstract

Aortic stenosis (AS) is a common valvular heart disease in the Western populations, with an estimated overall prevalence of 3% in adults over 75 years. To understand its patho-biological processes represents a priority. In elderly patients, AS usually involves trileaflet valves and is referred to as degenerative calcific processes. Scientific evidence suggests the involvement of an active “atherosclerosis-like” pathogenesis in the initiation phase of degenerative AS. To the contrary, the progression could be driven by different forces (such as mechanical stress, genetic factors and interaction between inflammation and calcification). The improved understanding presents potentially new therapeutic targets for preventing and inhibiting the development and progression of the disease. Furthermore, in clinical practice the management of AS patients implies the evaluation of generalized atherosclerotic manifestations (i.e., in the coronary and carotid arteries) even for prognostic reasons. In counselling elderly patients, the risk stratification should address individual frailty beyond the generic risk scores. In these regard, the co-morbidities, and in particular those linked to the global atherosclerotic burden, should be carefully investigated in order to define the risk/benefit ratio for invasive treatment strategies. We present a detailed overview of insights in pathogenesis of AS with possible practical implications.

Keywords: Atherosclerosis; Clinical implications; Degenerative aortic stenosis; Pathogenesis; The elderly

1 Introduction

Although valvular heart disease (VHD) is less frequent than coronary artery disease (CAD), heart failure or hypertension, it is of interest for several reasons. It is still common and often requires interventions resulting in escalating costs of healthcare.

Aortic stenosis (AS) is a common type of VHD in the Western populations. In fact, according to the data coming from the Euro Heart Survey that analysed the distribution of VHD in a sample of about five thousand patients from 25 European countries, AS is the most frequent, single, native left-sided valve disease (43%).[1] The demographic changes in these developed countries has had inevitable implications as currently the degenerative origin of the most frequent etiology of the valvulopathy (82%), followed by rheumatic (11%) and congenital disease (aortic bicuspid valve, 5%). The reported prevalence is only about the 0.2% among adults aged 50–59 years, but increases to almost 10% in adults over age 80 years or older, with an estimated overall prevalence of 3% in adults over 75 years of age.[2] The population at risk rises in proportion to the improvement in life expectancy and a rapidly aging society, and it is also likely that this prevalence will progressively increase even further. Consequently, AS is now a major societal and economic burden that is likely to be substantiated in a near future and thus an urgent priority to understand the pathobiological processes leading to AS at the most fundamental level to improve preventive and therapeutic strategies. Aortic valve disease is a progressive chronic disease and spans a spectrum that begins with mild fibrocalkific leaflet changes, termed aortic sclerosis, and progresses to more severe calcification with the end stage causing significant obstruction to ejection of the left ventricle. An interesting overview has
recently been published about the time-course of calcific aortic stenosis, however, few data are available on the prevalence of disease initiation in at-risk patients, and that disease progression develops in only a subgroup of these patients (10%–15%), but results in severe stenosis in nearly all patients.[3] From a clinically point of view, AS is characterized by a long remarkable period (decades) and once symptoms develop, there is a poor prognosis and currently no medical therapies to prevent and/or promote the regression of the disease, whose natural history requires surgical valve replacement even in old, high-risk patients. Hence, it is of foremost importance to delineate and understand the key basic underlying mechanisms. Conventional teaching suggests that degenerative AS is a “mechanical” and passive condition of aging whereby “wear and tear” leads to the calcium deposition within the valve. In the past decade our comprehension has changed dramatically, emphasizing the concept of an active disease process with multiple phenomena at the tissue level with anatomical, clinical and genetic factors seemingly involved. On the basis of improved knowledge about these multiple patho-biological pathways, it is possible to hypothesize novel treatment strategies. The current understanding presents potentially new targets for preventing and inhibiting AS development.[4]

2 Degenerative AS and atherosclerosis

By 1970, rheumatic fever as a cause of AS already had begun to wane in developed countries and was replaced pathogenetically by degenerative calcific disease. The ambiguous term “degenerative” suggested that AS stemmed from wear and tear on the valve over time, perhaps explaining its greater incidence in older patients. Although calcification of the aortic valve is a disease of the elderly population, there is evidence that it is not simply a consequence of aging.[5] Other factors must be important for the pathogenesis of this disease. Many predisposing factors, such as age, hypertension and the turbulence of perivalvular blood flow, contribute to increase this process and favor the deposition of aggregates of calcium in the aortic cusps, especially on the arterial side of the valve leaflets and, indeed, the surface of non-coronary cusp that might play a role.[12] A reasonable hypothesis is that hemodynamic stress on the valve, suggesting that hemodynamic stress on the valve might play a role.[12] A reasonable hypothesis is that hemodynamic stress leads to lipid infiltration that in turn allows for inflammation and calcification.[13] There is a robust interplay between lipids, inflammation and calcific AS. Similar to atherosclerotic lesions, the lipoproteins [including LDL-cholesterol and lipoprotein (a), hereafter, Lp(a)] infiltrate and undergo oxidative modifications. These oxidized

analogy, it seems to be legitimate to speak of the pathogenesis as “atherosclerosis-like”.[9,10] However, there are significant differences between vascular atherosclerosis (an unstable process) and aortic valve degeneration (a stable process). In the progression of CAD, plaque rupture is the major complication leading to clinically relevant events, whereas in AS the progressive calcification, even with lamellar bone formation, causes the immobility of the valve. In other words, atherosclerotic progression often leads to destabilization, while in aortic stenosis the permanent massive calcification of the aortic valve represents the advanced stage of the disease.

It is possible to suppose that CAD and AS have a similar pathophysiologic background as far as “initiation” is concerned, but a different mechanism of “evolution” at tissue levels. While an inflammatory process and lipid infiltration may be involved in the initiation of aortic stenosis, it does not appear to be the principal driving force in disease progression. The identified factors associated with disease progression are, for example, mechanical stress, genetic factors and interaction between inflammatory cells and calcification mediators.

3 Pathogenesis of degenerative aortic stenosis

AS initiated in the vascular side of the leaflets with focal sub-endothelial lesions that are similar to atherosclerosis plaques of CAD. In microscopic observations, Otto, et al.[3] noted that in stenotic valves, the initial aortic lesions contain disorganized collagen fibers, chronic inflammatory cells, lipids and proteins of extracellular bone matrix and bone minerals. The above mentioned histological features are strongly suggestive of a chronic inflammatory process and resemble those ones sees in atherosclerotic disease.[11] The first process, which begins aortic damage, may be due to the endothelial damage consequent to mechanical stress. It is known that valve cusps are usually heterogeneous in size and shape potentially sharing stress differences among leaflets and, indeed, the surface of non-crownary cusp that corresponds to increased elastic stress area is precociously involved. It is known that DAS develops earlier in patients born with a bicuspid rather than a normal tricuspid aortic valve, suggesting that hemodynamic stress on the valve might play a role.[12] A reasonable hypothesis is that hemodynamic damage leads to lipid infiltration that in turn allows for inflammation and calcification.[13] There is a robust interplay between lipids, inflammation and calcific AS. Similar to atherosclerotic lesions, the lipoproteins [including LDL-cholesterol and lipoprotein (a), hereafter, Lp(a)] infiltrate and undergo oxidative modifications. These oxidized
lipoproteins are highly cytotoxic and are able to stimulate both the inflammatory response and the mineralization activity. In other words, the retention and processing of lipids have been recognized as an important mechanism that triggers inflammation. Once inflammatory cells, like macrophages and T lymphocytes, are recruited in the sub-endothelium, they release enzymes, such as matrix metalloproteinase, that degrade collagen, elastin and proteoglycans of aortic cusps. Inflammation promotes/enhances the mineralization of valve interstitial cells. On the other hand, transformation of valve interstitial cells into myofibroblasts and osteoblast-like cells is determined by several signalling pathways having reciprocal cross-talk. In addition, the mineralization of the aortic valve has been shown to rely on ectonucleotidase and purinergic signalling. The mineralization is a characteristic of both atherosclerotic lesions and aortic valvular lesions, although in the latter, mineralization is more precocious and extensive and histological studies have also showed the presence of significant differences between cellular and mineral elements of the two different types of lesions.

3.1 The lipid theory

It seems that the risk factors for atherosclerosis are also common to aortic stenosis. In this regard, one of the most representative studies is the Cardiovascular Health Study which showed that AS is associated with older age, male gender, smoking, arterial hypertension, high levels of Lp(a) and LDL cholesterol, and with particular attention given to cholesterol. Hypercholesterolemia affects not only the coronary artery, but also the aortic root, particularly the aortic valve. In patients with homozygous familial hypercholesterolemia (FH), plasma Lp(a) serum concentrations have been shown to be an independent risk indicator for aortic valve calcification and AS is often critical in their unfavourable prognosis. Models of atherosclerotic disease in rabbits and rats have also been used to determine the effects of hypercholesterolemia on the aortic valve morphology and function. In humans, a strong influence has been observed of the LDL cholesterol levels on the progression of AVC and coronary calcium, as quantified by electron beam tomography using a volumetric score. Patients (n = 104) were divided according to their LDL cholesterol level, using a predefined value of 130 mg/dL as an arbitrarily chosen cut point. In patients with lower LDL cholesterol level (Group 1) the mean annual progression of aortic valve calcification was 9 ± 22%, whereas in patients with higher LDL cholesterol levels (Group 2, n = 47), the mean annual progression was 43 ± 44%, (P < 0.001). Correspondingly, the mean annual coronary calcium progression was 16 ± 22% (Group 1) and 39 ± 46% (Group 2), respectively (P < 0.001). The authors found no influence of smoking, hypertension, diabetes or patient age on the rate of progression, probably because of the small size of the respective subgroups.

3.1.1 Implications of lipid theory in clinical practice

From the above mentioned evidence and pathophysiological substrate has come the rationale for the use of statins in DAS, which reduce the progression of atherosclerotic disease and significantly improves the clinical outcome in patients with CAD. Since DAS, like atherosclerosis, is an active disease process, it seems plausible that statins might slow its hemodynamic progression. Disappointingly, despite the early enthusiasm coming from retrospective studies, recent large prospective trials have not provided evidence for a role of statin therapy in reducing AS severity. Intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis, or induce its regression.

The first two randomized, placebo-controlled studies were the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) study and the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Both of these studies had neutral outcomes. In the SALTIRE, published in 2005 by Cowell, et al. 155 patients with calcified AS in advanced degree (mean area 1 cm²) were randomly treated with atorvastatin 80 mg, or placebo and were followed for an average period of 25 months. Patients with high cholesterol levels, who needed statin therapy according to the International Guidelines, were not enrolled. The annual evaluation estimated the valvulopathy in terms of transvalvular gradient, as assessed with Doppler echocardiography, and the degree of valve calcification measured through spiral computed tomography (CT). At the end of the study, no statistically significant differences were reported in the degree of disease progression among the two groups of patients (increases in aortic-jet velocity were 0.199 ± 0.210 m per second per year in the atorvastatin group and 0.203 ± 0.208 m per second per year in the placebo group), in spite of a significant reduction (> 50%) in serum levels of LDL cholesterol. Secondary endpoints, such as death, the need for valve replacement and hospitalization, were more common in the control group, but this trend did not reach statistical significance. The SEAS was instead a randomized, double-blind study that enrolled from 173 centers in seven European countries with about two thousand elderly, non-diabetic patients with mild to moderate AS (mean aortic-valve area 1.28 ± 0.47 cm²) who had no other indications for lipid-lowering therapy. Patients were ran-
domised to treatment with either simvastatin/ezetimibe 40/10 mg daily, or matching placebo after a four-week diet/placebo run-in period. The primary composite endpoint (aortic-valve and ischemic events) included aortic valve replacement (AVR), cardiovascular death, non-fatal myocardial infarction, congestive heart failure from AS progression, coronary revascularisation, hospitalized unstable angina and non-hemorrhagic stroke. The active treatment did not halt AS progression; moreover, it did not reduce the primary composite endpoint. Events occurred in 333 patients (35.3%) in the treated group and in 355 patients (38.2%) in the placebo group [hazard ratio = 0.96; 95% confidence interval (CI): 0.83–1.12; \( P = 0.59 \)]. Similarly, the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTROMER) recently confirmed this result.\[22,23\]

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is not currently recommended in patients with valvular aortic stenosis without conventional indication to lipid lowering treatment. Whether statin therapy could “prevent the onset” (vs. halt progression) of AS is still unknown. Indeed, although the first evidence in the literature seems to be unfavourable,,\[24,25\] currently some researchers believe that statins may have a benefit only if given early in the disease process, when inflammation (and not calcification) is the predominant process, in contrast to severe or advanced AS, where calcification (and not inflammation) predominates.

### 3.2 The skeleton key

Recently, an expanding body of research on pathophysiology of AS has focalized on the role of calcification; how calcium may be visualized and monitored through new technology of AS has focalized on the role of calcification; how positive feedback that amplifies subsequent calcification. The mechanisms underlying this “snowball effect” are not yet completely understood. It is possible to suppose a “passive” explanation, since the initial mechanical injury due to calcium deposition finally causes a positive feedback that amplifies subsequent calcification. However, something else has to be involved,\[29\] and certain features suggest the presence of an “active” process similar to lamellar bone formation.\[30\] In vitro studies of explanted stenotic aortic valves have, in fact, detected the presence of cells with osteoblastic characteristics able to spontaneous calcification. The source of these cells remains controversial. The most likely candidate appears to be a pool of resident pluripotent mesenchymal cells (or valvular interstitial cells that largely resemble fibroblasts). Their differentiation into an osteoblastic phenotype seems to be a central step in the development of AS and leads to production of a variety of bone matrix proteins including osteopontin and bone morphogenetic proteins.\[29,31\] The beginning of mineralization (nucleation) may be stimulated by lipid retention (in particular, oxidized lipids) or by products of cellular degradation following apoptosis. Specifically, lipids play an important role in activating cell signalling. Results from the study of animal models have recently demonstrated that lipids lead to the activation of molecular cell signalling which induce the transitions of valvular fibroblasts towards an osteoblastic phenotype. Among the most likely culprit pathways having reciprocal cross-talk, the axis receptor activator of nuclear kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) plays an important role.\[32\] RANKL is a soluble mediator and a member of the tumor necrosis factor cytokine family. This cytokine “in the bone” links to RANK - a transmembrane protein expressed on pre-osteoclasts and induces osteoclast differentiation and activity. OPG is a soluble secreted protein that, by binding to RANKL, inhibits osteoclast formation.\[29,33\] Some evidence suggest that the imbalance of the RANKL-OPG axis may regulate valvular calcification in AS. In cultured human aortic valve fibroblasts, an increased expression of RANKL and decreased OPG, inducing the expression of osteoblast-associated genes, has been found to be involved in the transition towards an osteogenic phenotype. So on cells in the “vasculature”, RANKL seems to have an opposite effect and induces an osteoblastic phenotype that results in the formation of calcific nodules. A possible explanation for the different effects of RANKL on these two tissues (bone and valve) may lie in the influence of different microenvironments.\[26,29,34\] Interestingly, OPG-deficient mice develop osteoporosis (characterized by severe trabecular and cortical bone porosity, marked thinning of the parietal bones of the skull and a high incidence of fractures) associated with widespread and accelerated calcification in the cardiovascular system (medial calcification of the aorta and renal arteries).\[35\] With regard to the detection of osteogenesis in the early stage of AS, Sainger, et al.\[36\] have identified a correlation between the levels of various plasma biomarkers and the disease severity. In particular, osteopontin is increased in AS patients in comparison with controls, with variations of its plasma levels occurring before the first
marker of macroscopic damage (calcium nodules) were visualized on transesophageal echocardiography. Important question also arises as to the possibility to investigate the effects of pharmacological protection against atherosclerotic valve degeneration (as possible with statins) by monitoring bone metabolism biomarkers. Apart from lipids, other mechanisms may be involved in mineralization. The mechanisms appear to be more closely related to calcium metabolism. There is, indeed, an inverse correlation between bone mineral density and aortic valve calcification (calcification paradox). Moreover, conditions characterized by increased bone turnover, such as osteoporosis, chronic kidney disease and Paget’s disease, are associated with increased calcification in vascular and valvular structures.

In this regard, particular attention has also been given to the interaction between genotype and development of AS. For example, an association has been found between a vitamin D receptor polymorphism (B allele) — which seems to predispose carriers to blunted calcium absorption, more rapid bone loss, reduced bone mineral density and raised parathormone secretion — and the prevalence of calcific aortic valves. There might be several hypotheses to explain this relationship. Individuals with a slightly unfavorable bone mineral density might develop mechanisms to overcome this alteration of calcium homeostasis. Like parathormone, other hormones, proteins, or second messengers might trigger calcification of extra osseous structures like the aortic valve. Another possible explanation is the hypothesis that vitamin D receptor polymorphism is merely a marker of linkage disequilibrium with another gene involved in calcium metabolism; this as yet unknown gene might be important for osseous and extra osseous calcification. The aortic valve is likely to be one of the first extra osseous structures involved because of the high level of mechanical stress to which it is subjected.

3.2.1 Implications of skeleton key theory in clinical practice

Retarding, inhibiting or reversing the calcification of the valve might provide an avenue for treatment of patients with mild to moderate AS. Future therapies of AS should aim at interrupting the snowball effect of calcification, mechanical injury and further calcification, without altering the bone integrity. Manipulation of the processes related to calcium homeostasis and bone metabolism may offer a means by which AS “progression” can be slowed. Anti-osteoporosis drugs are attractive candidates and have been the focus of research. Attention has been given in particular to denosumab and bisphosphonates. Denosumab is a fully human monoclonal antibody. Its action resembles the OPG, since it links and inhibits RANKL. In the FREEDOM trial (ClinicalTrials.gov number, NCT00089791), it was given for the treatment of osteoporosis in near four thousand post-menopausal women, and was well tolerated. Similarly, bisphosphonates, that are pyrophosphate analogs, are currently widely used with a good risk profile. They are both approved to inhibit the osteoclast activity and, consequently, the demineralization of bone in post-menopausal women. Furthermore, several small, observational, retrospective studies have shown a possible link between the use of bisphosphonates and slowing of AS progression. However, these case series have included a total of 234 patients with only 54 patients taking bisphosphonates, precluding the generalizability of these results to a broader population. More recently, data coming from the cross-sectional Multi-Ethnic Study of Atherosclerosis (MESA) have shown that nitrogen-containing bisphosphonate (NCBP) may limit valvular calcification, as detected by CT, in women ≥ 65 years old. Bisphosphonates are active in two different pathways affecting the pathophysiology of AS. Nitrogen-containing bisphosphonates have been shown to inhibit farnesyl-pyrophosphate synthase, an enzyme in the cascade in which ultimately statins exert their effects. As a result, bisphosphonates have an effect similar to that of the statins, by affecting lipid metabolism and inflammation. Furthermore, bisphosphonates also prevent bone resorption and slow the release of calcium phosphate particles from the bone, which might play a role in retarding calcium deposition in extraosseous (vascular and valvular) tissues. In conclusion, future studies, including animal models, are necessary and should provide an opportunity to better evaluate the mechanisms of calcification in AS in order to discover appropriate therapeutic targets and drugs to modify the natural course of the disease and reduce the need for AVR.

4 Degenerative AS and coronary atherosclerosis

Previous reports suggested a relationship between CAD and AS. It is interesting that less than half of patients receiving AVR have significant (obstructing) coronary disease requiring bypass surgery. Then, there is continuing debate as to whether coronary angiography is necessary before aortic valve replacement. Angina pectoris has been recognized as one of the principal symptoms of AS even in the presence of normal coronary arteries. However, the incidence of angina pectoris and related CAD in such patients is controversial. In a prospective evaluation of about 100 patients, Conte et al. have recently hypothesized that AS may be an independent predictive marker for obstructive
CAD in patients hospitalized for chest pain and, thus, it should be considered in the risk stratification of these patients.\textsuperscript{[50]} However, the results are conflicting since it has been previously reported that this symptom has a low positive predictive value (22%), whereas the negative predictive value of angina alone is 89%.\textsuperscript{[51]} So the absence of angina is not enough to exclude CAD in patients with aortic stenosis considered for AVR.\textsuperscript{[52]} In a recent study on about 600 consecutive patients undergoing AVR, significant CAD was found just in 10% of cases. In the logistic regression, the only variable identified as an independent predictor of CAD was age with coronary stenosis increasing significantly over 69 years. Having at least two cardiovascular risk factors was the most useful cut off to predict the utility of preventive angiography. According to the authors, angiography should be considered in patients with multiple risk factors for cardiovascular disease, or at least in patients older than age 69 without any other risk factor.\textsuperscript{[53]} Interestingly, it has been supposed that global cardiac calcification (AVC and mitral annular calcifications), as assessed by CT, is highly associated with the presence (Odds Ratio = 9.36, 95% CI: 6.6 to 13.9) and extent (P < 0.001) and vulnerable characteristics (Odds Ratio = 4.87, 95% CI: 1.85–12.83, P = 0.001) of coronary plaque.\textsuperscript{[54,55]} In a recently published paper, the incidence and severity of atherosclerotic cardiovascular (coronary and systemic) artery disease in patients undergoing transcatheter aortic valve implantation (TAVI) has been systematically evaluated and has been reported an increased long-term mortality in patients with a more compromised vascular situation.\textsuperscript{[56]} Subsequently, additional markers for a better stratification of cardiovascular and coronary risks in aortic stenosis should be investigated.

5 Degenerative AS and preclinical carotid atherosclerosis

Atherosclerosis is a generalized process involving several arterial vessels at the same time. There is a growing belief that carotid intima-media thickness (IMT) can be regarded as an indicator of generalized atherosclerosis. Hence, there is a probability of assessing its incidence in coronary arteries through the evaluation of carotid arteries prompted by their large diameter, superficial localization and good visualization. The carotid district can be easily explored by Doppler ultrasound and it can be used as a valid surrogate marker of coronary atherosclerosis and multi-districth atherosclerotic disease. Many clinical studies have confirmed that, even in asymptomatic subjects, the detection of asymptomatic carotid atherosclerosis is an early marker of ischemic heart disease and increased cardiovascular risk.\textsuperscript{[57,58]} Furthermore, preclinical atherosclerotic alterations in carotid arteries may reflect an atherosclerotic process in coronary arteries of patients with AS.\textsuperscript{[59]} In a recent study, we have investigated the association between DAS (defined for a trans-aortic peak velocity > 2 m/sec) and atherosclerosis of carotid arteries as assessed by echocolor Doppler of the supra-aortic vessels in a case-control study of 270 consecutive patients.\textsuperscript{[60]} Some 95.5% of the 135 patients with DAS (vs. 66.6% of controls, P < 0.0001) had an atherosclerotic disease of carotid arteries. In particular, 51.8% had intima-media thickening (IMT) and 69.6% had an atherosclerotic plaque (that was hemodynamically significant in 9.57% of patients). The mean values of carotid overall thickness were found higher in the group of cases. Interestingly, in the cases we found a positive linear correlation between the trans-aortic peak velocity and the carotid thickness. The increasing severity of aortic stenosis corresponds to an increase of the thickness of plaque and IMT (Pearson’s coefficient of correlation, r = 0.15 for plaque and r = 0.53 for IMT). Similar results were previously reported by Sgorbini, et al.\textsuperscript{[61]} who detected a positive correlation between aortic valve calcification (AVC), scoring from 0 to 5 on the basis of acoustic densitometry and IMT. Mean carotid IMT increased linearly with increasing valvular calcification score, ranging from 3.9 ± 0.48 mm in controls to 12.9 ± 1.8 mm in those subjects scoring 5 (P < 0.0001).\textsuperscript{[61]} Moreover, it has been postulated that in patients with DAS, the carotid IMT may have a prognostic value in assessing concomitant CAD. It has been shown that the presence of carotid atherosclerotic disease is a valid marker of coronary atherosclerosis in subjects with symptomatic aortic stenosis.\textsuperscript{[62]} The IMT of the common carotid artery, bulb, and internal carotid artery has been shown to be, indeed, significantly higher in patients with AS and CAD compared with both the control group (normal coronary arteries and no AS) and patients with AS only. A mean IMT value of greater than 1.2 mm was predictive (sensitivity, 73.5%; specificity, 72.7%) of concomitant CAD in patients with AS.\textsuperscript{[63]} Belhassen, et al.\textsuperscript{[64]} indicated that IMT values of less than 0.55 mm in patients with calcific AS were associated with a low probability of concomitant CAD, with sensitivity of 100% and a negative predictive value of either of 100%.\textsuperscript{[64]} What's the possible clinical implication of the above mentioned evidence? The incidental echocardiographic findings of AVC (regardless of the functional involvement) may represent a useful important prognostic parameter in patients without previous history of cardiovascular events, since it could be considered a manifestation of generalized atherosclerosis and may identify subgroups with different IMT and then, with different global cardio-

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vascular risk profiles. On the other hand, ultrasound scans of carotid arteries may be also considered a non-invasive method for cardiovascular risk stratification in patient with aortic stenosis of various degrees (with therapeutic implications especially for higher risk subgroups) and should be regarded as a valuable diagnostic instrument in the ultimate referral of patients for coronary angiography.

6 Practical implications in elderly patients with aortic stenosis

AS is the most common valvular lesion in patients above the age of 65. Etiology, clinical presentation and management differ in elderly compared to younger patients in many ways. The treatment of elderly patients with severe aortic stenosis is difficult and conventional medical treatment has a dismal prognosis, with an overall survival of three years from the onset of symptoms.\[65,66\] Despite the initial proofs for potential alternative strategies (i.e., with statins) specifically targeting the underlying pathobiological pathways, no medical therapy seems currently able to significantly slow progression, or reverse severity of the disease, especially in elderly patients. The only effective approach is AVR in restoring an almost normal life expectancy. However, in elderly patients there is often a reluctance to recommend valve replacement due to the presence of co-morbidities and the attendant surgical risk. Approximately 30%–40% are still denied surgery.\[67-69\] Most series published in the last 10 years have reported an approximately operative mortality rate of 10% among the octogenarians population. Operative morbidity is also higher and in particular, an incidence of stroke has been reported ranging between the 5%–10%. Post operative stroke and mortality is more frequent in patients who undergo associated concomitant coronary artery by-pass grafting. In fact, as previously mentioned, DAS has been currently considered related to cardiovascular risk factors and then a part of a multi districtual atherosclerotic process. It has been shown that a strong relation between operative mortality and some predictive factors: decreased left ventricle ejection fraction (LVEF), advanced New York Heart Association (NYHA) class, co-morbidities (i.e., renal insufficiency, diabetes), associated atherosclerosis and previous myocardial infarction. Moreover, the need for urgent surgery is the most important independent predictor for in-hospital and long term mortality.\[70-72\] TAVI has been shown to be a viable alternative for patients previously deemed in-operable. The TAVI approach in older people may solve the disease allowing personal independence and a good postoperative quality of life. Recently reported data, suggested good outcomes even in selected population of very older patients (> 85 years).\[73\] It should, however, be noted that in the PARTNER trial (Placement of Aortic Transcatheter Aortic Valve trial), the only currently published multi-center, randomized trial on TAVI in high risk patients for the surgical approach, have excluded patients with previous myocardial infarction, significant CAD requiring revascularization, severe reduction (< 20%) of LVEF, transient ischemic attack and stroke within the previous six months and also renal insufficiency.\[74,75\]

In conclusion, it seems reasonable to affirm that invasive approaches should not be denied to the “older” patient on the basis of age alone. In a cohort study, the patient’s choice of refusing valve replacement was associated with a > 12-fold increase in mortality risk.\[76\] The key may lie in patient selection and geriatricians should necessarily be part of the heart team. Discrepancies in therapeutic strategies might result from difficulties of risk stratification of elderly patients with AS. The multivariate scores, like the European System for Cardiac Operative Risk Evaluation (EuroSCORE), developed and validated for the general population seems to have limitations in the older cohort since this high-risk group only accounted for a small proportion of the population studies.\[77\] Moreover, the worldwide low referral of older, operable subjects to the high-volume tertiary centers may subject the literature data to potential bias, with consequent practical implications in the real world. When we say “old” we have to take in mind that the ageing process is highly individual. So in counselling these patients, clinicians should accurately evaluate patient overall frailty (combination of ageing, disease and risk factors that make people vulnerable).\[78\] Life expectancy is influenced by co-morbidities, which should be carefully determined and uncovered. In this setting with the associated common risk factors and pathophysiological mechanisms, the global atherosclerotic burden surely represents a negative impact factor on the risk/benefit ratio of AVR.\[79\] Conservative management remains a suitable option for patients who are too ill, or too frail.\[80\]

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