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Aortic Stenosis - New Insights in Stenosis Progression and in Prevention

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1. Introduction

1.1 Prevalence

Aortic valve disease, in particular stenosis (AS), is the most common valvular abnormality detected in the aging population whit an AS prevalence of 3 to 5% in the population over 75 years of age (1, 2). Valvular aortic stenosis without accompanying mitral valve disease is more common in men than in women. A clear increase in prevalence of aortic sclerosis has been seen with age: 20% in patients aged 65–75 years, 35% in those aged 75–85 years, and 48% in patients older than 85 years. For the same age-groups, 1.3%, 2.4%, and 4% have frank aortic stenosis (3).

1.2 Etiology

AS is the obstruction of blood flow across the aortic valve. AS has several etiologies including rheumatic fever, congenital unicuspid or bicuspid valve, and degenerative calcific changes of the valve. Rheumatic heart disease is the main cause of valvular heart disease worldwide, but fewer than 10% of AS cases in the United States and Western Europe are rheumatic. In contrast, senile, calcific disease of the aortic valve and bicuspid valve disease are responsible for the vast majority of AS cases in those countries. Since the incidence of AS increases with age and the Western population as a whole is aging, increased numbers of patients presenting with AS are expected in the near future. Currently, the incidence of AS is estimated to be 1−2% among those over 65 years of age and 4% among octagenarians.

Rheumatic AS is rarely an isolated disease and usually occurs in conjunction with mitral valve stenosis. Rheumatic AS is characterized by diffuse fibrous leaflet thickening of the tricuspid valve with fusion of the commissures with scarring and eventual calcification of the cusps. A congenital malformation of the valve may also result in stenosis and is the most common cause in young adults. Bicuspid aortic valve is the most common cause of aortic stenosis in patients under age 65. About 2% of people are born with aortic valves that have only two cusps (bicuspid valves). Although bicuspid valves usually do not impede blood flow when the patients are young, they do not open as widely as normal valves with three cusps. Therefore, blood flow across the bicuspid valves is more turbulent, causing increased wear and tear on the valve leaflets. Over time, excessive wear and tear leads to calcification,

scarring, and reduced mobility of the valve leaflets. About 10% of bicuspid valves become significantly narrowed, resulting in the symptoms and heart problems of aortic stenosis.
The most common cause for AS in adults is senile degenerative AS, with the calcification of a normal trileaflet or a congenital bicuspid valve (4). Even if it was considered to be the result of years of mechanical stress on an otherwise normal valve, the evolving concept is that the degenerative process leads to proliferative and inflammatory changes. Calcific aortic-valve disease refers to progressive aortic leaflet thickening and calcification, beginning with the early lesion of aortic-valve sclerosis leading to advanced leaflet disease of aortic-valve stenosis, characterized by restricted leaflet motion and outflow obstruction. The pathobiology of the aortic-valve lesion involves an atheromatous, osteogenic, inflammatory process sharing some histologic similarities with coronary atherosclerosis (5)

1.3 Pathophysiology

Valvular aortic stenosis results in chronic left ventricular pressure overloading. At any stage of life, however, the natural history of aortic stenosis largely reflects the functional integrity of the mitral valve. As long as adequate mitral valve function is maintained, the pulmonary bed is protected from the systolic pressure overloading imposed by aortic stenosis. Compensatory concentric left ventricular hypertrophy allows the pressure-overloaded ventricle to maintain stroke volume with modest increases in diastolic pressure, and patients remain asymptomatic for many years. In early stages the development of concentric hypertrophy appears to be an appropriate and beneficial adaptation to compensate for high intracavitary pressures. Unfortunately, this adaptation often carries adverse consequences. The hypertrophied heart may have reduced coronary blood flow and also exhibit a limited coronary vasodilator reserve, even in the absence of epicardial coronary artery disease, that`s why one of the symptoms is angina. In later stages of severe AS, cardiac output declines, and the pulmonary artery pressure rises, leading to pulmonary hypertension. The first symptom of this condition is increasing shortness of breath and the last consequence is heart failure. The onset of any of the classic symptoms of left ventricular outflow obstruction—angina, syncope, or heart failure—in a patient with valvular aortic stenosis indicates advanced valve disease and should be carefully and promptly evaluated. Syncope most commonly is due to the reduced cerebral perfusion that occurs during exertion secondary to the decrease in arterial pressure consequent to peripheral vasodilation in the presence of a fixed cardiac output. For years the cause of the calcification of the aortic valve was thought to be the passive accumulation of calcium in the valve leaflets, causing nodular deposits and an eventual stenosis. Clinical studies have demonstrated that the risk factors for this process include hypercholesterolemia, diabetes, smoking, hypertension, male sex, and elevated high sensitivity C-reactive protein (6), suggesting that calcification of the aortic valve results from an inflammatory process triggered by these factors of atherosclerotic risk and that drug therapies to retard this process may be a useful strategy in the future. Hyperuricemia has been identified as another risk factor for development of aortic valvular disease. Calcific AS is also observed in a number of other conditions, including Paget disease of bone and end-stage renal disease. Ochronosis with alkaptonuria is another rare cause of AS, which also can cause a rare greenish discoloration of the aortic valve. Recent experimental models have shown that there is a relationship between hypercholesterolemia and the development of aortic valvular disease (7). Studies of human tissue also suggest

that the development of aortic valvular calcification represents an active cellular biology. O'Brien et al. have described the early valvular lesion (aortic sclerosis) as an entity very similar to the early lesion of the atherosclerotic plaque (8). These lesions show similarities to the atherosclerotic process, with a predominance of 'atherogenic' lipoproteins, especially LDL and lipoprotein(a), evidence of LDL oxidation, inflammatory cellular infiltrates and the development of calcification. The presence of lipids stimulates the production of many factors such as modified TGF-b1, tumor necrosis factor and cytokines in the aortic valve leaflets (9). In particular early valvular sclerotic lesions demonstrate a chronic inflammatory cell infiltrate (macrophages and T lymphocytes), lipid accumulation (apolipoprotein [apo] B, apo(A) and apo(E) and α-actin–expressing cells in the lesion and adjacent fibrosa; end-stage calcified valves contain mature lamellar bone with expression of specific bon markers important in the development of osteoblast bone formation (10). In addition, angiotensin-converting enzyme (ACE) and angiotensin II type 1 (AT1) and type 2 (AT2) receptors are present in stenotic aortic valves, implicating this signaling pathway in the disease process (11). These observations are analogous to the cellular findings in vascular atherosclerosis and corroborate epidemiological studies that showed similar associations of clinical risk factors with both atherosclerosis and aortic valve disease (12). The mechanism for valvular calcification is similar to skeletal bone formation and that calcification occurs in areas of neoangiogenesis, which is stimulated by an active inflammatory process and the release of vascular endothelial growth factor (VEGF). VEGF is well known to play a key role in angiogenesis in pathological inflammatory diseases.(13) Deckers et al (14) have suggested that VEGF regulates bone remodeling by attracting endothelial cells and by stimulating osteoblast differentiation. Our findings indicate that VEGF is localized to cells in inflammatory regions of the valve fibrosa, specifically the macrophages and myofibroblasts. Rajamannan recently demonstrated that an osteoblast phenotype is associated with nonrheumatic, degenerative calcific aortic stenosis. The current data, including the production of osteopontin and osteocalcin proteins (both osteoblast cell products) and proliferating myofibroblast cells synthesizing bone matrix proteins, indicate that a similar osteoblast-like process that occurs in degenerative calcific aortic stenosis develops in the calcification process in rheumatic valves (10). Although calcification in rheumatic valves has been described in the literature for years, the cellular mechanisms responsible for the calcification have not been previously described. These new observations support the hypothesis that mineralization of rheumatic cardiac valve tissue is similar to skeletal bone formation that is associated with neoangiogenesis and show that studying this disease process will provide important information on the treatment of valvular heart disease (15). In contrast to mitral valve degeneration, Caira et al. found that the Lrp5/Wnt3 signaling markers are present in the calcified aortic valve greater than the degenerative mitral valve. These data provide the evidence of a mechanistic pathway for the initiation of bone differentiation in degenerative valve lesions, which is expressed in the mitral valve as a cartilage phenotype and in the calcified aortic valve as a bone phenotype. These results indicate that there is a continuum of an earlier stage of osteoblast bone differentiation in the mitral valves as compared with the calcified aortic valves. In normal adult skeleton formation, the initiation of bone formation occurs with the development of a cartilaginous template, which eventually mineralizes and forms calcified bone. Therefore, the mitral valve expresses an early cartilage formation, and the aortic valve demonstrates the mineralized osteoblast phenotype,which follows the spectrum of normal skeletal bone formation. The

calcified aortic valves express an osteoblast phenotype: "bone" in the aortic valve that is responsible for the stenosis present in symptomatic aortic stenosis requiring surgical valve replacement. This study demonstrates that hypercholesterolemia may play a role in the initiating event of calcification. This is the first study to demonstrate the presence of chondrocytes in mitral valves, and osteoblasts in aortic valves implicating this pathologic mechanism in the development of mitral regurgitation in myxomatous mitral valves and stenosis in calcific aortic valves (16). In bicuspid aortic valve, the calcification and progressive stenosis typically occur faster than in tricuspid aortic valves, Rajamannan demonstred that the eNOS protein expression was decreased in the BAV vs. the tricuspid aortic valves. This data provides further evidence of the potential functional importance of eNOS enzymatic activity in the developmental level for the formation of the congenital heart abnormality in addition to the actual role in the calcification process. More, bone sialoprotein, osteocalcin, and osteopontin are increased and are markers of extracellular matrix synthesis in the valve whereas Notch1 is decreased in the valve. The protein and RNA expression also demonstrated a decrease in overall Notch1 in these disease tissues, indicating that the loss of normal Notch1 is necessary for valve calcification similar to the implications of the loss of function mutation in the genetic study. Overall, the loss of Notch1 function and the increase in Lrp5 signaling demonstrate the role of these important regulators of bone metabolism in these diseased tissues. Than, the mechanism of BAVD results in a decrease in Notch1 function and an increase in Lrp5 expression which activates bone formation within the valve myofibroblast (17).

2. Clinical presentation

The diagnosis of the aortic stenosis is usually made on physical examination with detection of the classical systolic outflow murmur. The severity of aortic stenosis can be determined reliably by echocardiography, based on the extent of the valvular calcification, the peak flow velocity across the valve, the mean gradient and the valvular area computed by the continuity equation. Evaluation of serial echocardiograms in patients with aortic stenosis make it possible to obtain valuable information over a period of time to determine the progression of the disease and the timing of surgery (9).

2.1 Signs and symptoms

The classical symptoms of AS are angina, dispnea, syncope, and heart failure, which represent also the dramatic inflection in the natural history of this disease.

In adults with AS, the obstruction develops gradually. Many patients with aortic stenosis will remain asymptomatic for decades. The diagnosis of aortic stenosis is usually made in the asymptomatic patient on the basis of a systolic murmur on auscultation and confirmed by echocardiography. The development of symptoms therefore is a critical point in the natural history of patients with AS, infact the risk of sudden death in asymptomatic patient with initial manifestation of severe aortic stenosis is very low (<1% per year), but it is high once any symptom is present, so that valve surgery is appropriate with even mild symptoms.

Most prospectively followed patients present with more subtle symptoms, typically decreased exercise tolerance, or dyspnea on exertion. It is not uncommon for patients to decrease their activity level below their symptom threshold—a careful history comparing

current and last year's activity levels is needed to recognize that these patients, in fact, are symptomatic.
In asymptomatic patients, the risks of valve surgery are weighed against the risk of an adverse outcome without surgical intervention. Aortic valve repair is not an option, so that the long-term durability and risks of a prosthetic valve also must be considered. (18)

2.2 Diagnosis

The physical examination, electrocardiogram, chest radiograph, echocardiography, and cardiac catheterization are important for the diagnosis.
The physical examination demonstrates a weak and slowly rising pulse ("parvus and tardus"). Systolic ejection murmur is best heard at the base of the heart and is harsh in quality, but does not correlate with the severity of stenosis.
The electrocardiogram demonstrated findings consistent with the presence of left ventricular hypertrophy and show an overload pattern.
The chest radiograph has a normal appearance in the vast majority of patients. Left ventricular hypertrophy may be present and is demonstrated in the rounding of the left ventricular free wall. Severe calcification of the aortic valve can frequently be seen in adult patients with severe or critical aortic stenosis.
Echocardiography is the most commonly used noninvasive diagnostic method for assessing the significance of aortic stenosis. Two-dimensional echocardiography can determine valvular motion and the presence or absence of valve thickening and calcification. However, Doppler echocardiography is necessary to assess the hemodynamic severity of the stenosis. Echocardiography is the clinical standard for evaluation of adults with suspected or known valvular AS. Anatomic images show the etiology of AS, level of obstruction, valve calcification, leaflet motion, and aortic root anatomy (19).
It is important to determine the severity of aortic stenosis based upon hemodynamic measurements. The echocardiographic criteria were established to define the grading of stenosis by ACC/AHA 2006 (20) and includes the following:
Valve area

1. mild aortic stenosis: area > 1.5 cm2
2. moderate aortic stenosis: area 1 to 1.5 cm2
3. severe aortic stenosis: area < 1.0 cm2.

Aortic velocity allows classification of stenosis as

1. mild (less than 3.0 m/s)
2. moderate (3 to 4 m/s)
3. severe (>4 m/s).

but in the revision and the update of ACC/AHA guidelines (2006) the grading of aortic stenosis in evaluated also by the transvalvular gradiente as following.

1. mild (mean gradient less than 25 mm Hg)
2. moderate (mean gradient 25 to 40 mm Hg)
3. severe (mean gradient greater than 40 mm Hg)

When stenosis is severe and ejection fraction (EF) is normal, the mean transvalvular pressure gradient is normally greater than 40 mm Hg. However, when cardiac output is low, severe stenosis can be present with a lower transvalvular gradient and velocity. So to grade the severity of the stenosis also the Ef must to be evaluated. Doppler echocardiography is also used to determine diastolic dysfunction by the presence of

abnormal left ventricular relaxation. Moderate to severe diastolic dysfunction does not increase early mortality but may increase late mortality after AVR. Stress echocardiography is used in patients with normal left ventricular function (LVF) to demonstrate the presence of diastolic dysfunction (i.e., signs of elevated left ventricular filling pressure) as the cause of symptom development during exercise.

Doppler echocardiography has replaced cardiac catheterization in most centers for evaluation of the hemodynamic severity of aortic stenosis (21). Cardiac catheterization is reserved for hemodynamic evaluation in patients in whom reliable echocardiographic data cannot be obtained or when the clinical and echocardiographic data are divergent. Catheterization is also necessary in most patients undergoing aortic valve replacement (usually men with age > 40, post menopausal women, history of coronary artery disease and suspected myocardial ischemia or LV systolic dysfunction) to determine if there is associated coronary artery disease that can be treated at the time of operation (9).

3. Predictors of Aortic Stenosis

3.1 C reactive protein

The dynamic and inflammatory nature of calcific aortic stenosis has been well appreciated in recent years, and many pathobiologic features of calcific aortic valve disease exhibit striking similarity to coronary atherosclerosis. C-reactive protein (CRP), which has been an useful predictive biomarker of the inflammatory process and prognosis of atherosclerosis, is increased in subsets of patients with calcific aortic stenosis, and this has led to the hope that CRP could be used as well to identify those patients likely to progress or develop severe calcific aortic stenosis (22).

Recent data suggest that oxidative stress and high-sensitivity CRP plasma levels as a marker of systemic inflammation could be involved in the pathogenesis of rheumatic valve disease. Therefore, the role of inflammation in rheumatic valve disease progression should be considered. Indeed, the persistence of high levels of high-sensitivity CRP has been shown in patients with chronic rheumatic valve disease, particularly in patients with multivalvular disease, who showed significantly higher plasma levels of CRP (23).

If inflammation is the fundamental process of early aortic valve disease, with calcification predominating in the later stages, one might anticipate that markers of inflammation, such as CRP, would reflect early aortic valve disease activity and perhaps be less useful as a marker in later stages. The available data do not support such a concept. CRP has been localized in the valve tissue of aortic stenosis in both native valves and bioprosthetic aortic valves, with a positive correlation between serum CRP values and valve CRP expression (24). C-reactive protein values are increased in patients with severe symptomatic aortic stenosis awaiting valve surgery compared with matched controls and decline after aortic valve replacement. On the other hand, Navaro et al show that there is no relationship between elevated CRP levels and the presence of calcific aortic-valve disease or of incident aortic stenosis. C-reactive protein appears to be a poor predictor of subclinical calcific aortic-valve disease. They observed that older age, male gender, hypertension, coronary artery disease, and renal insufficiency, but not CRP values, are associated with the presence of increasing calcific aortic valve abnormality and that CRP values are not related to the progression from a normal aortic valve to aortic sclerosis or stenosis, nor progression from aortic sclerosis to aortic stenosis. African-American ethnicity was significantly protective

from developing calcific aortic valve disease. How do we make sense of these apparent discrepancies that CRP appears not to reflect the early inflammation phase of calcific aortic valve disease but does reflect the later calcific stages of the disease? The first methodologic consideration is that the single CRP value at study entry may have been too distant from the time that calcific aortic stenosis was developing during the follow-up period to reflect the inflammatory change that would later occur. It is also possible that the inflammatory process in early calcific aortic valve disease was not substantial enough to lead to an elevated serum value. It is also clear from the previously noted associations between CRP and severe aortic stenosis that CRP may be a more active, direct participant in the later stages of the disease progression and not simply a biomarker passively reflecting the early inflammatory stages of disease. CRP provides valuable prognostic information concerning adverse cardiovascular events in coronary disease as well, but it does not reflect the presence or severity of subclinical anatomic coronary artery disease (25). The study by Novaro et al. does add important new understanding concerning the genetic determinants of calcific aortic valve disease. Genetic characteristics of calcium metabolism may be central to the development of valvular calcification, and the observation that African Americans are protected from development of calcific aortic valve disease, may be related to a genetic predisposition toward less calcification of vascular and valve tissue and lower incidence of osteoporosis. It would be of enormous value to identify a biomarker to predict patients likely to develop aortic sclerosis and those likely to progress to aortic stenosis. Only a few studies have examined the relationship between CRP and aortic stenosis. Galante et al. (6) published the initial study demonstrating elevated CRP levels in association with calcific aortic stenosis. In a surgical series, CRP levels were higher in severe aortic stenosis patients compared to patients with pure aortic regurgitation (26). In those who underwent aortic valve replacement for aortic stenosis, CRP levels decreased from before to 6 months after valve replacement. Recently, CRP has been localized in valve tissue of both calcific aortic-valve stenosis and degenerative aortic-valve bioprostheses , with a positive correlation between serum CRP levels and valvular CRP expression. Thus, from the available human studies, it is apparent that CRP levels are elevated in aortic stenosis patients with severe disease awaiting surgery, do not correlate with stenosis severity, and decrease after valve replacement, supporting the histologic evidence that the aortic valve is a site of active inflammation. (5)

3.2 Others predictors

Whereas cardiovascular risk factors and CRP levels failed to predict incident aortic stenosis, only 4 demographic variables (increasing age, male gender, white ethnicity, and shorter height) were associated with an increased risk of incident aortic stenosis. Increasing age is a well-recognized risk factor related to aortic stenosis. Gender appears to have an impact on the risk of both aortic stenosis and the degree of aortic valve calcification , with men showing a greater predilection of both (5).

Genetic factors can also be important in the development of valvular calcification. In a recent case–control study, 100 patients with similar demographic characteristics were compared, with and without aortic stenosis, and significant differences between the two groups were observed in the genotype of the vitamin D receptors (27). Another study identified polymorphisms of the apolipoproteins AI, B and E as predisposing factors for development of calcification and valvular stenosis (28). Finally, a unique study by Garg et al.

demonstrated the unique signaling pathway Notch as important in the development of calcific aortic stenosis and also congenital heart abnormalities. These important studies indicate that genetic predisposition and risk factors may play a role in the development of disease (9). In a recent study Kamalesh et al. revealed that diabetes accelerate progression of calcification in subjects who have moderately severe aortic stenosis. Therefore, for this patients may need intensive follow-up for their aortic stenosis rather than non diabetic subjects (29). The finding that the multifunctional glycophosphoprotein osteopontin (OPN) is involved in both cell-mediated inflammation and biomineralization has generated considerable interest in the role of OPN in ectopic calcification and calcific aortic valve disease as shown by Yu et al. (30). Although other serum markers, such as C-reactive protein and B-type natriuretic peptide have previously been shown to be associated with aortic calcification and stenosis, OPN is the only molecule that is implicated in both inflammation and biomineralization processes, which lead to aortic valve calcification and subsequent stenosis. Also Ferrari and Grau demonstrates a direct correlation of NT-pro-BNP, BNP, and osteopontin and the presence of calcific AS, while fetuin A showed an inverse correlation. Plasma ADMA and homocysteine levels were comparable in the calcific AS patients and healthy individuals. A new study analyzed osteopontin level and its phosphorilation status in CAVD and demostred that phospho-threonina levels of purified OPN are higher in healthy controls when compared to CAVD patients. This study showed that phospho-OPN prevent calcium deposition, whereas the dephosphorylated protein mimicking the patient's plasma OPN, lose its protective role allowing calcium deposition on the cellular surface. This data suggest the role of circulating OPN and its phosphorilation status as biomarker and inhibitory factor for the pathogenesis of calcific CAVD. (31)

4. Treatment

There are different choises of treatment, based on clinical symptoms, echocardiographical criterias and evaluation of risk factors.

The development of symptoms in patients with severe aortic stenosis is associated with a 50% mortality within a period of 5 years. Thus, symptomatic severe aortic stenosis is a clear class I recommendation for surgical intervention (21). At present, there is no medical treatment recommended for asymptomatic patients with aortic stenosis, and only clinical monitoring is recommended (5).

However, recent epidemiologic studies evaluating the independent risk factors for calcific aortic stenosis have demonstrated that the risk factors for aortic stenosis are similar to those of coronary artery disease, which include hypertension, elevated low-density lipoprotein, smoking, diabetes, and male gender (32). These atherosclerotic risk factors provide the evidence for the potential of medical therapy for this disease process. (19)

4.1 Initial treatment

The management of patients with aortic stenosis depends upon the severity of aortic stenosis and the presence or absence of symptoms. In patients with only mild stenosis and no symptoms, management is continued observation. Serial echocardiography should be performed every 3 years in patients with mild aortic stenosis and every 1–2 years in those with moderate stenosis. Prompt echocardiography should be performed anytime there is new symptom onset. Infective endocarditis prophylaxis should be followed. Patients with moderate-to-severe aortic stenosis should avoid athletics, which require high dynamic and

static muscular demands. There are no proven medical treatments to slow or prevent disease progression. However, aggressive lipid lowering therapy may be of benefit, especially in patients with less-severe valve calcification, and will ameliorate progression of vascular atherosclerosis that frequently coexists and increases their comorbidity. Patients with symptoms and severe aortic stenosis should be considered for operation with aortic valve replacement. Delays to surgery have been associated with poorer outcome following operation Over the past two decades, the risk of operation has decreased substantially. Isolated aortic valve replacement in a patient less than 70 years old should be able to be performed with a risk of less than 1%. The risk should be less than 2–3% among septuagenarians and even less than 5% in octogenarians in the absence of significant comorbidities. Therefore, age is not a contraindication to surgery. Concomitant coronary artery bypass grafting should be performed for coronary atherosclerosis when epicardial lesions are >50%.

Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, different studies hypothesized that people with elevated high-sensitivity C-reactive protein levels might benefit from statin treatment. (33) The treatment of the asymptomatic patient with severe aortic stenosis is more controversial. When there is left ventricular dysfunction, valve replacement is indicated even in asymptomatic patients. In these patients, the critical increase in afterload has started to overwhelm the compensatory mechanisms of left ventricular hypertrophy and the outcome is poor without surgical intervention. Importantly, aortic valve replacement can also now be done with a low operative mortality and there is enhanced durability of the new prostheses. Thus, surgery is reasonable to consider in asymptomatic patients when there is critical aortic stenosis and the expected operative mortality is <1.0%. Aortic valve replacement may also be considered for adults with severe asymptomatic aortic stenosis if there is evidence or high likelihood of rapid progression or when there may be delayed rapid access to medical care if symptoms arose. Progression of aortic stenosis may be considered rapid when the Doppler peak velocity increases by >0.3 m/s per year or when the valve area decreases by >0.1 cm2 per year .

4.2 Future directions in medical treatment

As greater understanding of the cellular mechanisms, pathogenesis and progression of aortic valvular disease evolves, new pharmacological strategies are being proposed that are targeted more directly to mechanisms of the disease, both for preventing its progression and ultimately for achieving its regression. The two pharmacological agents that have been studied experimentally and that demonstrate the most potential benefit are the HMG-CoA reductase inhibitors (statins) and the ACE inhibitors (19,20,22,33). The clinical implementation of these pharmacological treatments will require a strict validation of the experimental and retrospective studies to date (34–38), in order to establish a clear cause–effect benefit in any pharmacological treatment system.

Conventionally ACE-Is are contraindicated in patients with severe AS. However, we may safely administer ACE-Is to patients with mild AS because hemodynamic effects of stenotic aortic valve are well compensated in such patients. The renin-angiotensin system contributes to the inflammatory nature of the aortic valve lesion. Angiotensin converting enzyme (ACE), as well as angiotensin II and the angiotensin II type-1 receptor, have been identified in aortic sclerotic lesions , which stimulate monocyte infiltration and macrophage uptake of modified LDL (34). Calcification, the hallmark characteristic of aortic valve stenosis, is also clearly a feature of the active inflammatory process, occurring in valve

regions of lipid disposition, especially oxidized lipids, with additional stimulus provided by macrophage- and T lymphocyte-produced cytokines. Early in the disease process, active microscopic areas of calcification are seen co-localizing in areas of lipoprotein accumulation and inflammatory cell infiltration; as the disease progresses, active bone formation is seen.
ACE inhibitors are thought to interfere with the renin-angiotensin system and exert beneficial actions on vascular tissues beyond their blood pressure–lowering effects.
Regarding statins, there are a number of experimental models testing the effects of a cholesterol diet on the aortic valve in mice model. Sarphie (39) demonstrated the first histochemical effects of cholesterol on the development of valvular heart disease. Studies by Rajamannan and Charest et al have also shown that endothelial nitric oxide enzyme activity plays a role in the early valve lesions. Elevated cholesterol decreases the enzyme expression and induces early mineralization in the aortic valve. Therefore, these early studies provide the evidence that aortic valve disease has similar initiating mechanism of oxidative stress that is found in vascular atherosclerosis. The next critical step toward understanding of aortic valve calcification is to determine the signaling mechanisms involved in the development of this disease (40). The studies from Mohler (41) and Rajamannan (40) have shown that the aortic valve calcifies secondary to a bone phenotype. Recent studies from Rajamannan and Shao et al. have demonstrated that the mechanism by which calcification develops is activation of the LDL receptor 5 (Lrp5)/Wnt pathway in the vascular and valvular interstitial cells (40). These studies confirm that the presence of bone formation is the phenotypic expression of calcification in the aortic valve (10). Over time, the valve leaflet synthesizes bone matrix, which eventually calcifies and forms bone. If the aortic valve has an actual biology that is initiated by elevated cholesterol, then in the future, medical therapy such as statins or angiotensin-converting enzyme inhibitors may slow the progression of this disease.
Also Nagy et al. studied the role of proinflammatory signaling through the leukotriene (LT) pathway in aortic stenosis and demonstred that the messenger RNA levels of the LT-forming enzyme 5-lipoxygenase increased in thickened and calcified tissue compared with normal areas of the same valves. Moreover they showed that leukotriene C4 (LTC4) increased intracellular calcium, enhanced reactive oxygen species production, reduced the mitochondrial membrane potential, and led to morphological cell cytoplasm changes and calcification. This data suggest the up-regulation of the pathway LT and the potentially detrimental LT-induced effects on valvular myofibroblasts as possible role in the development of aortic stenosi and induce to considerate innovative therapeutic interventions(42).
The first landmark randomized, prospective trial published in this field, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE), (43) demonstrated, however, that high-dose atorvastatin does not slow the progression of this disease. SALTIRE initiated atorvastatin in patients who had more advanced aortic stenosis as defined by the mean aortic valve area of 1.03 cm2, with heavy burden of calcification as measured by aortic valve calcium scores. Newby et al recently acknowledged that the timing of therapy for aortic valve stenosis may play the key role in the future treatment of this disease. The important issue may be treating this disease earlier in its process to slow the progression of bone formation in the aortic valve (44). The potential benefit of statin therapy, however, is controversial and widely debated, as recent randomized studies done in patients with moderate to severe degrees of aortic stenosis failed to consistently show substantial benefits of this class of drugs. Antonini et al. provides evidence for a positive effect of statins in

reducing the progression of rheumatic AS and in a large series of patients with long-term follow-up, statins were effective in slowing the progression of aortic valve disease in aortic sclerosis and mild AS, but not in moderate AS. These results suggest that statin therapy should be taken into consideration in the early stages of this common disease (23). The RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium) study suggests that earlier treatment with statins is more efficacious in the prevention of progression of aortic valve stenosis than late treatment, similar to the effects of statins in the regression of vascular atherosclerosis (45). Importantly, results of the randomized trials will provide further evidence to define the treatment of this complex disease process, in which timing of therapy and characteristics of the valve lesion will need to be taken into account in the future treatment approaches. In the RAAVE trial, the rate of progression of aortic stenosis in those with hypercholesterolemia treated with rosuvastatin is slower than in those with lower lipid levels who are not treated. This is the first study to provide positive clinical evidence for the potential of targeted therapy in patients with asymptomatic aortic stenosis (45). Finally Parolari et al. (46) performed a meta-analysis of studies was performed comparing statin therapy with placebo or no treatment on outcomes and on aortic stenosis progression echocardiographic parameters. This meta-analysis identified 10 studies with a total of 3822 participants (2214 non-statin-treated and 1608 statin-treated). No significant differences were found in all-cause mortality, cardiovascular mortality or in the need for aortic valve surgery. Lower-quality (retrospective or non-randomised) studies showed that, in statin-treated patients, the annual increase in peak aortic jet velocity and the annual decrease in aortic valve area were lower, but this was not confirmed by the analysis in high-quality (prospective or randomised) studies. Statins did not significantly affect the progression over time of peak and mean aortic gradient. Taken together, this evidences suggest that the progression of calcific aortic stenosis is a complex process; the multitude of the mechanisms involved in AS indicates that drug therapy should address the earliest stages of the disease, as it is now evident that pharmacological treatment administered in more advanced stages of the disease may be ineffective (47). At the end, all studies of statins have had the "wrong target" trying to treat patients with severely calcified valves. In our opinion we should treat patients at earlier stages of the disease, since statins side-effects are considered marginal and moreover statins have been proven beneficial to delay atherosclerosis progression and CAD, than quite often accompany AS.

4.3 Surgical treatment

Aortic valve replacement is indicated in patients who have severe aortic stenosis in the absence of other major comorbidities. Patients who undergo aortic valve replacement have an improvement in symptoms and increased survival after valve replacement surgery. Currently, there is no indication for surgical valve replacement in patients who have asymptomatic critical aortic stenosis unless they have left ventricular dysfunction or abnormal hemodynamic response to exercise. Patients who have moderately depressed ventricular function do as well as those with normal ventricular function. Depressed ventricular function may be due to afterload mismatch or an intrinsic depression of contractility. Both the safety and prognosis of aortic valve replacement relate to distinguishing between these two causes of reduced ventricular function. Patients with true afterload mismatch do well after aortic valve replacement despite very low ejection fractions. Depressed contractility from myocardial disease does not respond as well to aortic valve replacement (19)

Aortic valve replacement in patients without symptoms is controversial, infact asymptomatic patients with AS have outcomes similar to age-matched normal adults. While the short-term prognosis in such patients is excellent without surgery, there is still a small but definite risk of sudden death. Obviously there is also a small but definite risk of morbidity and mortality related to aortic valve replacement and to complications resulting from the presence of a prosthetic valve.

4.4 Aortic valve replacement

When planning AVR, the chief issues related to surgical decision making involve the type of valve prosthesis to be inserted, the timing of surgery, and issues related to concomitant procedures. The ideal prosthesis for AVR is characterized by excellent hemodynamics, minimal residual transvalvular pressure gradient, and laminar flow through the prosthesis. In addition, the valvular prosthesis should be durable, easy to implant, quiet, biocompatible, and resistant to thromboembolism. The two major categories of valvular prostheses, which account for the vast majority of implanted aortic valves, include mechanical and bioprosthetic valves. Regarding the decision between bioprosthetic and mechanical valves, the primary advantage of mechanical valves is their durability and
reliable performance. Conversely, the primary disadvantage of mechanical valves relates to the need for lifelong warfarin anticoagulation and attendant lifestyle limitations and thromboembolic (TE) and bleeding risks. When anticoagulation is managed appropriately, the risk of TE with mechanical valves is similar to that for bioprosthetic valves. Bileaflet mechanical valves are the standard in current practice. Conversely, the primary advantage of bioprosthetic valves is that systemic anticoagulation with warfarin is not required. As a result, patients receiving tissue valves have a lower rate of anticoagulation-related bleeding complications. However, their limited durability (freedom from structural valve deterioration and need for reoperation) and suboptimal hemodynamics, due to a generally smaller effective orifice area size-for-size as compared to mechanical valves, have historically been the drawbacks of bioprosthetic valves. As a result, use of bioprosthetic valves has generally been recommended for patients older than 65 years of age or with reduced life expectancy. These tendencies are nowadays changing in light of improved tissue engineering, the increased lifespan of new generation tissue valves and the relative low risk of reoperation for isolate valve re-replacement. Moreover, the increasing trend to use transcatheter aortic valve implantation (TAVI) and the possibility to replace a previously implanted biological prosthesis with the method of valve in valve, the implantatation of a trancatheter valve into the old and degenerated prothesis, without a new open heart operation, moves the needle of the balance toward greater use of biological prosthesis, even if the duration of TAVi in young patient is not still known.
The most important problem in the use of mechanical prosthesis is anticoagulation for all the life. Anticoagulation for the long-term treatment has been accomplished by vitamin K antagonists for the last half century. Although effective under optimal conditions, the imminent risk of a recurrent adverse event of INR the risk of bleeding due to the narrow therapeutic window, numerous food- and drug interactions, and the need for regular monitoring complicate the long-term use of these drugs and render treatment with these agents complicated. But new anticoagulants which selectively block key factors in the coagulation cascade are being developed (48). Dabigatran is the first available oral direct thrombin inhibitor anticoagulant, it specifically and reversibly inhibits thrombin, the key enzyme in the coagulation cascade. Its oral bioavailability is low, but shows reduced

interindividual variability. Studies show a predictable pk/pd profile that allows for fixed-dose regimens. The anticoagulant effect correlates adequately with the plasma concentrations of the drug, demonstrating effective anticoagulation combined with a low risk of bleeding. Rivaroxaban will probably be the first available oral factor Xa (FXa) direct inhibitor anticoagulant drug. It produces a reversible and predictable inhibition of FXa activity with potential to inhibit clot-bound FXa. Its pharmacokinetic characteristics include rapid absorption, high oral availability, high plasma protein binding and a half-life of aprox 8 hours. (49)
The development of new anticoagulant, safer , with less risk of bleeding, and which allow to the patient the possibility of a fixe assumption, without monitoring INR every week, could change the choice criteria between biological and mechanical prosthesis.

4.5 Aortic balloon valvotomy

Percutaneous balloon aortic valvotomy (BAV) is a procedure in which 1 or more balloons are placed across a stenotic valve and inflated to decrease the severity of AS. Although BAV is useful in children with congenital AS, the calcified lesion of acquired AS in the adult does not respond well to BAV. After a modest acute reduction in stenosis severity, restenosis recurs usually within 6 months. Immediate hemodynamic results include a moderate reduction in the transvalvular pressure gradient, but the postvalvotomy valve area rarely exceeds 1.0 cm2. Despite the modest change in valve area, an early symptomatic improvement is usually seen. However, serious acute complications occur with a frequency greater than 10% (50, 51).

5. The future

Prolonged life expectancy has resulted in an aging population and, consequently, in an increased number of patients with degenerative calcific aortic stenosis (52). AS has increased markedly in developed countries and AS, caused by valve calcification in the elderly, will continue to increase as the aging of society accelerates. For symptomatic patients with severe aortic valve stenosis, open heart surgery for aortic valve replacement (AVR) with use of cardioplegia under cardiopulmonary bypass remains the gold standard. Although surgery is still the gold standard treatment, it is considered high risk in elderly patients because of high complication rates, which leads to substantial hesitation in submitting such patients to surgery. The surgical approach is associated with substantial operative mortality rates in high-risk patients. Consequently, almost one-third of patients with severe aortic stenosis are not offered surgery owing to a combination of reasons such as advanced age, impaired left ventricular function, re-do procedure, or multiple comorbidities (50). Moreover, as longevity within the general population is increasing, the proportion of aortic stenosis patients with contraindications for surgery is also expected to increase. Decision-making is particularly complex in the elderly who represent a heterogeneous population, resulting in a wide range of operative risk, as well as life expectancy, according to individual cardiac and non-cardiac patient characteristics. The two most striking characteristics of patients who were denied surgery were older age and LV dysfunction. Age and LV dysfunction are associated with an increased operative risk and a poor late outcome after surgery, which may explain the reluctancy to operate on such patients. Age is a strong predictor of operative risk and poor late survival in cardiovascular surgery, in particular, in the case of AS. Four percent of the elderly population has significant aortic

stenosis and the size of the population older than 65 years will grow 50% between 2000 and 2030. In very old patients with many comorbidities, the outcome of AVR is less favourable than in average poulation, and many of those patients may be inoperable or carry an unacceptably high perioperative risk. Some patients with aortic valve disease defer surgery in light of mild symptoms, whereas others are deemed too ill to undergo cardiac surgery. The latter currently have been treated expectantly or by balloon aortic valvuloplasty (BAV), but this technique offers poor magnitude and durability of the physiologic improvement in aortic valve orifice area. In most patients, balloon valvotomy reduces severe AS to moderately severe AS. The gradient typically is reduced by 50% and averages approximately 35 mm Hg after the procedure. Unfortunately, in 50% of patients, restenosis occurs within 6 months. Overall, balloon valvotomy has not reduced the high mortality seen in patients who do not undergo surgery for symptomatic AS. Recent technological advances, however, now indicate that catheter techniques similar to those used for BAV can be used for percutaneous aortic valve replacement, avoiding open cardiac access or the use of cardiopulmonary bypass. As with any medical procedure, the risk/benefit ratio of TAVI must be carefully considered. The benefits provided by this novel procedure must be weighed eventually against what is considered today the "gold standard" that is surgical AVR. Bearing in mind, however, the excellent track record of surgical AVR, it seems prudent to initially target those patients who are at high surgical risk due to severe comorbidities. Thus, the patients currently enrolled in these studies are chosen based on a risk score, such as the EuroSCORE or STS score. The other set of patients who may be considered at present are those with a deteriorated aortic bioprosthesis and deemed at high risk for surgical reoperation, and this "valve-in-valve" concept has already been reported. With technological advancements, it is expected that the ease of implantation will improve and complications will decrease. In order to consider lower risk and younger patients as candidates for this new technology, additional long-term durability data will be required before advocating this procedure as a possible substitute to surgical AVR. Risk algorithms have been used to assess operative risk, anticipate outcomes, and provide for comparability of patients among diverse centers and countries. Unfortunately, these tools are inherently imprecise and frequently exclude comorbidities encountered in this population. Therefore, the comparison of transcatheter procedural outcomes to anticipated results based upon predictive risk scoring remains somewhat subjective. The presence of CAD has been clearly demonstrated to increase procedural risk with conventional aortic valve replacement. However, its overall influence on outcomes of transcatheter therapy for aortic stenosis has not been clearly delineated. This is especially true given the fact that TAVI is generally considered a stand-alone procedure, with variable degrees of concomitant coronary artery disease tolerated without intervention. It has been shown that patients with CAD as indicated by previous CABG or PCI had significantly higher 30-day and overall mortality with transcatheter valve implantation.

6. Risk stratification

The Euro Heart Survey has shown that, in current practice, there is general agreement between the decision to operate and the existing guidelines in asymptomatic patients. However, in patients with severe symptoms, intervention is underused for reasons that are often unjustified. This stresses the importance of the widespread use of careful risk stratification. In the absence of evidence from randomized clinical trials, the decision to

intervene in a patient with VHD relies on an individual risk–benefit analysis, suggesting that improvement of prognosis compared with natural history outweighs the risk of intervention and its potential late consequences, in particular, prosthesis-related complications. Factors predicting operative mortality have been identified from large series of patients undergoing cardiac surgery or, more specifically, heart valve surgery. They are related to heart disease, the patient's age, comorbidity, and the type of surgery. The easiest way to integrate the weight of the different predictable factors is to combine them in multivariate scores, enabling operative mortality to be estimated.

6.1 Euroscore

It is a risk model which allows the calculation of the risk of death after a heart operation. The model asks for 17 items of information about the patient, the state of the heart and the proposed operation, and uses logistic regression to calculate the risk of death. First published in 1999, the model has been adopted worldwide, becoming the most widely used risk index for cardiac surgery, and its use is believed to have contributed substantially to the improvement in the results of heart surgery seen at the beginning of the millennium. It is now aging and a new model (EuroSCORE 2010) is being prepared. Briefly, comprehensive data were obtained for over 19,000 consecutive patients undergoing open heart surgery in 128 centers in eight European countries. The database thus generated was subjected to multiple logistic regression analysis to determine which risk factors were associated with operative mortality. Weights were allocated to each risk factor on the basis of the odds ratios and a risk model was constructed in which the percentage predicted mortality for a patient could be calculated by adding the weighted values of risk factors which are present. The additive EuroSCORE model, by virtue of its nature, tends to underestimate risk in very high-risk patients. Some very high-risk patients may be better assessed, for individual risk prediction, by using the full logistic EuroSCORE model. EuroSCORE was initially designed to be a user-friendly system, in the hope of encouraging as many units as possible to embark on programs of risk-adjusted quality monitoring. In this setting, although derived from a logistic regression methodology, only the simple additive version of the score was originally published. This score could be easily calculated at the bedside and could therefore be used widely in Europe even in hospitals with little information technology. Using the same risk factors, the logistic regression version of the score (the 'logistic EuroSCORE') can be calculated. Many risk factors have been associated with cardiac surgical mortality and morbidity. The EuroSCORE was derived from data obtained from patients operated on in 1995, and the details were first published in 1999. The system is now 10 years old, and is based on data that are even older. Yet, since the introduction of EuroSCORE, there has been a quantum improvement in cardiac surgical survival which mainly occurred during the first two to three years of the new millennium. Evidence from countries with national databases has suggested that mortality in some of these countries has approximately halved, despite a gradual worsening of the risk profile of patients. In the United Kingdom, for example, mortality has fallen to approximately 55% of logistic EuroSCORE prediction, giving a UK RAMR (risk adjusted mortality ratio obtained dividing the actual mortality by the predicted mortality) of around 0.55. In a consecutive series of patients with severe AS undergoing AVR, Kalavrouziotis and coworkers found that the logistic EuroSCORE was not an accurate risk assessment tool in all categories of risk but especially in high-risk patients. Therefore, this predictive model should not be used to determine procedural risk in patients with

severe AS. Furthermore, the utilization of the logistic EuroSCORE in the assessment of operability in patients with severe AS may not be appropriate.

6.2 STS (Society of Thoracic Surgeons) risk score

More than 20 years ago, the STS was one of the first specialty organizations to recognize the importance of developing a prospectively maintained clinical data registry. The resulting STS National Adult Cardiac Surgery Database (STS NCD) has achieved widespread acceptance by the provider community as well as interested third parties, including health policy researchers, government regulators, accrediting agencies, and payers. The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables. The models are primarily used to adjust for case mix when comparing outcomes across institutions with different patient populations. The STS currently has three risk models: CABG, Valve, and Valve + CABG. The models apply to seven specific surgical procedure classifications:

CABG model

1. Isolated Coronary Artery Bypass (CABG Only)

Valve model

2. Isolated Aortic Valve Replacement (AV Replace)
3. Isolated Mitral Valve Replacement (MV Replace)
4. Isolated Mitral Valve Repair (MV Repair)

Valve + CABG model

5. Aortic Valve Replacement + CABG (AV Replace + CABG)
6. Mitral Valve Replacement + CABG (MV Replace + CABG)
7. Mitral Valve Repair + CABG (MV Repair + CABG)

New STS models, developed using STS data from 2002 to 2006, account for endpoints as for operative mortality, permanent stroke, renal failure, prolonged ventilation (> 24 hours), deep sternal wound infection, reoperation for any reason, a major morbidity or mortality composite endpoint, prolonged postoperative length of stay, and short postoperative length of stay. Recently, the STS risk algorithm was reported to be the most sensitive score in defining the risk of patients undergoing isolated AVR. Predictive value of many of the currently available scoring systems is insufficient to allow a reliable risk assessment in patients undergoing isolated aortic valve replacement. The overestimation is most prominent in high-risk patients. Risk stratification using the STS score was accurate in predicting the risk of mortality in high-risk patients. Nevertheless, even this most recently built score systematically overestimates procedural risk. From the clinician's standpoint there is a need for an objective risk assessment tool.

6.3 Do we need new or better tailored risk models?

Risk stratification models for operative mortality have gained widespread acceptance in cardiac surgery. These models, however, are not 100% accurate. A number of factors can influence their performance. Generally speaking, available risk models for cardiac surgery can be divided into three categories: (1) **general cardiac surgery models -** that is, coronary artery bypass surgery, valve surgery or other related cardiac surgery; (2) **general valve surgery models**; and (3) **specific aortic valve surgery risk models**. Risk models can serve

multiple purposes if used correctly. Firstly, risk models can be used for benchmarking; they may allow for control of procedural complexity when analyzing hospital and surgeon performance. Secondly, risk models can help educate patients and improve informed patient consent. Risk models can also be incorporated into guidelines to help identify high risk patients who may benefit from additional work-up or alternative treatment strategies. If risk models can accurately identify high risk patients with expected longer lengths of stay in hospital, they may be useful for administrative logistic and budget planning. Differences in epidemiology of disease, risk profiles, surgical strategies, decision making, selection bias, and referral bias can all influence the applicability and performance of a model. Regarding EuroScore performance in valve surgery Parolari suggested that EuroSCORE might not be the appropriate tool for risk prediction in isolated valve operations or those combined with other cardiac procedures. The area under the curve (AUC) derived from the meta-analysis he performed provided estimates of 0.72 to 0.74, which are in a range of a performance considered less than satisfactory for a risk stratification algorithm. EuroSCORE discrimination is also substantially lower with respect to the performance of the Society of Thoracic Surgery (STS) algorithm, which is about 0.8 for isolated valve operations and about 0.75 for valves plus CABG. The explanation for this is that the STS score is updated almost annually, and, for this reason, it may better follow the changes occurring in valve patient population with relative ease, whereas the EuroSCORE is now undergoing its first revision since its introduction. The discriminatory power and precision in risk prediction of the EuroSCORE in valve surgery has recently become increasingly important for two reasons. The first is that in the most centers, valve procedures—either isolated or combined - actually represent more than 50% of the total caseload; therefore, accurate risk estimation in this patient population—mainly elderly and very elderly people—has become much more important. The second reason is strictly related to the recent evolution in technical options in aortic valve operations that has led to a steady increase in the adoption of transcathether aortic valve procedures in patients at the highest risk or in very elderly people.

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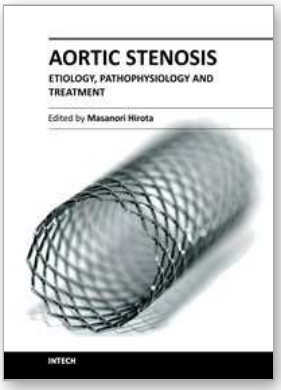

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Currently, aortic stenosis (AS) is the most prevalent valvular disease in developed countries. Pathological and molecular mechanisms of AS have been investigated in many aspects. And new therapeutic devices such as transcatheter aortic valve implantation have been developed as a less invasive treatment for high-risk patients. Due to advanced prevalent age of AS, further discovery and technology are required to treat elderly patients for longer life expectancy. This book is an effort to present an up-to-date account of existing knowledge, involving recent development in this field. Various opinion leaders described details of established knowledge or newly recognized advances associated with diagnosis, treatment and mechanism. Thus, this book will enable close intercommunication to another field and collaboration technology for new devices. We hope that it will be an important source, not only for clinicians, but also for general practitioners, contributing to development of better therapeutic adjuncts in the future.

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