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Calcific aortic stenosis

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Abstract

Calcific aortic stenosis (AS), the most prevalent heart valve disorder in developed countries,, is characterized by progressive fibro-calcific remodelling and thickening of the aortic valve leaflets that evolve over years to cause severe obstruction to cardiac outflow. In developed countries, AS is the second-most frequent cardiovascular disease after coronary artery disease and systemic arterial hypertension with a prevalence of 0.4% in the general population and 1.7% in the population >65 years old. Congenital abnormality (bicuspid valve) and older age are powerful risk factors for calcific AS. Metabolic syndrome and an elevated plasma level of lipoprotein(a) have also been associated with increased risk of calcific AS. The pathobiology of calcific AS is complex and involves genetic factors, lipoprotein deposition and oxidation, chronic inflammation, osteoblastic transition of cardiac valve interstitial cells and active leaflet calcification Although no pharmacotherapy has proven to be effective in reducing the progression of AS, promising therapeutic targets include lipoprotein(a), the renin-angiotensin system, tumor necrosis factor ligand superfamily member 11 (also called receptor activator of NF-κB ligand (RANKL)) and ectonucleotidases. Currently, aortic valve replacement (AVR) remains the only effective treatment

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for severe AS. The diagnosis and staging of AS are based on the assessment of stenosis severity and left ventricular systolic function by Doppler echocardiography and the presence of symptoms. The introduction of transcatheter AVR in the past decade has been a transformative innovation for patients at high or extreme-high risk for surgical AVR and this new technology might extend to lower-risk patients in the near future.

Graphical abstract

Calcific aortic stenosis (AS) involves fibro-calcific remodeling of the aortic valve that causes restriction of blood flow. Pibarot and colleagues discuss the mechanisms, diagnosis and management of AS and highlight how the introduction of transcatheter-based valve replacement has transformed patient outcomes.

Introduction

Calcific aortic valve disease is, by far, the most prevalent form of aortic stenosis (AS) worldwide. In the developing world, AS may also be caused by rheumatic heart disease. Calcific aortic valve disease is characterized by slowly progressive fibro-calcific remodelling of the valve leaflets. In the first phase of the disease, termed aortic sclerosis, the valve becomes thickened and mildly calcified but these changes do not cause any obstruction to blood flow. Over the years, the disease evolves to severe valve calcification with impaired leaflet motion and vast blood flow obstruction, which are hallmarks of calcific AS (Table 1)[1]. In developed countries, AS is one of the third most common cardiovascular diseases after coronary artery disease and systemic arterial hypertension[2]. Over the past five decades, the management of calcific AS has changed dramatically. Doppler echocardiography has replaced cardiac catheterization as the method of choice for the diagnosis and follow-up of AS, and transcatheter valve therapy has emerged as an alternative to surgery for aortic valve replacement (AVR). However, no pharmacotherapy has proved to reduce either the progression of valve stenosis or the resulting adverse effects on left ventricular (LV) function and patient outcomes. Hence, surgical or transcatheter AVR are the only effective treatment options for severe AS[3;4]. Overall, this disease is directly responsible for approximately 85,000 AVRs and 15,000 deaths per year in North America[2]. In this Primer, we discuss the epidemiology, mechanisms, diagnosis and management of calcific AS and highlight how the introduction of transcatheter-based valve replacement has transformed patient outcomes.

Epidemiology

Calcific AS is the consequence of progressive fibro-calcific remodelling occurring on an initially normal (tricuspid) aortic valve or a congenitally abnormal (bicuspid) aortic valve. Although the prevalence of bicuspid aortic valve is only 0.5–1% in children, it accounts for nearly half of aortic valves that are surgically removed due to calcific AS[5]. During their lifetime, most individuals with a bicuspid aortic valve develop some kind of aortic valve pathology, the most common being AS[5–8]. Furthermore, patients with bicuspid valve develop calcific AS 1 or 2 decades earlier than those with a tricuspid valve.

Aortic sclerosis, the preclinical phase of calcific aortic valve disease, is defined as focal areas of valve calcification and leaflet thickening without significant cardiac blood flow obstruction (aortic jet velocity of <2.0 m per sec)[3]. The prevalence of aortic sclerosis increases sharply with age. In developed countries, it is estimated to be 25% in those over 65 years old and almost 50% in those aged over 85 years[9–11]. According to a recent meta-analysis, the rate of progression to AS in individuals with aortic sclerosis is 1.8–1.9% of patients per year[11]. Therefore, the prevalence of calcific AS is much lower than that of aortic sclerosis, and has been estimated to be 0.4% in the general population and 1.7% in the population aged over 65 years[12] in developed countries. There is a marked increase in the prevalence of calcific AS in those aged > 65, which has been reported by several population-based studies in the United States and Europe (Figure 1)[9;13–15]. For individuals aged ≥ 75 years, a pooled analysis of available epidemiologic data in developed countries produced an estimated severe AS prevalence of 3.4% (95% confidence interval of 1.1%–5.7%), with 75% of those with severe AS presenting with symptoms[16]. The incidence of calcific AS has been assessed in a longitudinal Norwegian study and was estimated to be 4.9 per 1000 people per year in a population that had a mean age of 60 years at inclusion[13]. The geographical distribution of calcific AS is heterogeneous and displays a clustering effect which is probably the consequence of genetic factors[17].

Although mitral valve regurgitation has a higher prevalence than AS in population-based studies, AS has a more important clinical impact[18]. In the Euro Heart Survey, AS was more prevalent than mitral valve regurgitation in patients who were referred for in-hospital care and cardiac surgery[18]. Furthermore, calcific AS accounted for 34% of all native (non-prosthetic) valve diseases, as compared with 25% for mitral regurgitation, and 47% of patients operated for valvular disease, as compared with 14% for mitral regurgitation among patients operated for valvular disease[18].

The burden of calcific AS in the community is expected to increase over the next decades owing to population aging and the lack of a prevention strategy aimed at reducing disease progression. Estimates based on current prevalence rates and demographic forecasts predict that the number of patients with calcific AS >70 or >75 years of age will increase twofold to threefold over the next 50 years in developed countries[15;16;19].

The epidemiology of AS in developing countries and resource poor settings differs in some respects to that seen in developed countries, in part due to higher rates of rheumatic fever and rheumatic heart disease in poorer communities. Rheumatic heart disease is a chronic condition resulting from acute rheumatic fever, which in turn is caused by an untreated throat infection with group A *Streptococcus*. Both rheumatic fever and rheumatic heart disease may cause damage to the heart valves and can result in stenosis and regurgitation, in particular of the mitral and aortic valves. Valvular remodelling markedly differs between rheumatic heart disease and calcific AS. Fusion of aortic leaflets at commissures is one hallmark and distinctive feature of rheumatic heart disease. Rheumatic heart disease rarely affects the aortic valve alone (less than 10% in countries where rheumatic fever remains endemic) and most often involves the mitral valve. When the aortic valve is affected, the dysfunction is often mixed: aortic stenosis combined with some degree of aortic regurgitation[20;21]. The proportion of AS caused by calcific AS is expected to increase in

industrially developing countries owing to the decreasing incidence of rheumatic fever. In addition, the overall burden of calcific AS is expected to increase owing to the increasing in life expectancy in these regions.

Mechanisms/pathophysiology

For a long time, calcific aortic valve disease was thought to be a ‘degenerative’ process caused by time-dependent wear-and-tear of the leaflets and passive calcium deposition. Now, there is compelling histopathologic and clinical data suggesting that calcific valve disease is, in fact, an active and multifaceted condition involving lipoprotein deposition, chronic inflammation, osteoblastic transition of valve interstitial cells and active leaflet calcification[2223].

Aortic valve anatomy and remodelling of the aortic valve

The aortic valve is typically composed of three leaflets that are named according to their location with respect to the coronary artery, specifically the left coronary, right coronary and non-coronary leaflets (Figure 2). Each leaflet has a trilaminar structure that determines the biomechanical properties of the aortic valve[24]. The outermost layers of the leaflet are formed by the fibrosa and ventricularis, which face the aorta and the LV outflow tract, respectively. The spongiosa, which has a high proteoglycan content, is located between the fibrosa and ventricularis (Figure 3). The fibrosa is rich in circumferentially oriented collagen type I and III fibers[25], whereas in the ventricularis, radially oriented elastic fibers predominate. The ventricularis composition provides more compliance (the ability to expand under pressure) and allows the apposition of free edge regions of leaflets, thus preventing the backward flow of blood into the LV during diastole. The cellular population of these aortic valve layers includes valve interstitial cells (VICs), smooth muscle cells (SMCs) (<5% of the population) and endothelial cells. The endothelial cells cover the aortic and ventricular surface and therefore provide an interface between the blood and the aortic valve[26]. VICs is the predominant population of cells in the aortic valve, whereas SMCs reside at the base of the ventricularis[27].

Inspection of surgically explanted valves with calcific AS reveals two features, fibrosis and calcification (Figure 3), which substantially alter the biomechanical properties of the aortic valve leaflets. A small proportion (10–15%) of calcific AS valves show advanced osteogenic metaplasia with the presence of osteoblast-like cells, chondrocytes and bone marrow[28]. Calcified valves often contain dense inflammatory infiltrates, which consist mostly of macrophages[29;30]. Mineralization starts in the fibrosa layer and it is often in the vicinity of lipid deposits. Together, these observations suggest that the fibro-calcific process in the aortic valve is a response to injury, which might be triggered by lipid-derived species and inflammation (Figure 4)[31].

In addition, excess production and disorganization of collagen fibers is an important feature of calcific AS. Fibrosis increases the stiffness of the aortic valve and might play a considerable part in promoting mineralization. To this effect, the collagen produced by VICs serves as a scaffold on which the nucleation of calcium and phosphorus can start[32]. *In vitro*, serum-induced mineralization of collagen is increased by a population of VICs harbouring a

pro-calcifying phenotype with elevated alkaline phosphatase (ALP) expression[33;34]. In addition, the increased production of several components of the extracellular matrix, including periostin, tenascin (also called tenascin-c) and proteoglycans contributes to the remodelling of the aortic valve during AS[35;36]. The exact role of non-collagenous proteins in the pathophysiology of AS is still largely unknown, but growing evidence indicates that complex interactions between extracellular matrix proteins and cells provide crucial signals during normal reparative and pathological processes in the aortic valve[37].

Lipids

Lipid infiltration and oxidation—Increasing evidence suggests that infiltration of the aortic valve by lipoproteins has a central role in promoting inflammation, which precedes the pathologic mineralization that is characteristic of calcific AS[38]. Therefore, the retention of lipids promotes a chronic low-grade inflammatory process, which, in turn, might induce an osteogenic program in aortic valves. In this regard, histological studies have demonstrated that several apolipoproteins (apos) such as apoB, apoE, apoA1 and apo(a) are present in surgically removed stenotic aortic valves[39].

Oxidative stress has also been implicated in calcific AS. For instance, immunostaining has demonstrated that apoB co-localizes with oxidized low-density lipoproteins (Ox-LDLs) in valves from patients with calcific AS,[40;41] and that there is an association between the level of Ox-LDL and the degree of inflammation and fibro-calcific remodelling in surgically removed AS valves[40;42]. Oxidative stress is increased in AS valves and is related, at least in part, to the uncoupling of the nitric oxide synthase (NOS) pathway[43]. Also, the expression NAD(P)H oxidase is increased in surgically explanted calcific AS valves and contributes to the production of reactive oxygen species (ROS)[44]. Therefore, the production of peroxide and superoxide anions, in the vicinity of calcified areas might participate in the production of oxidatively-modified lipid species with osteogenic properties[43]. Work conducted *in vitro* has shown that Ox-LDL and several oxidized phospholipid (Ox-PL) species promote the calcification of isolated vascular cells[45]. *In vivo*, circulating Ox-PLs are mostly carried by the lipoprotein(a) (Lp(a)) fraction,[46] a LDL-like particle in which the apoB protein is linked by a disulfide bridge to apo(a)[47]. Recent studies that used a Mendelian randomization design showed that the gene encoding apo(a) (*LPA*) is potentially causally related to calcific aortic valve disease[48–50]. In addition, Capoulade and colleagues showed that circulating Lp(a) and Ox-PL levels were independently associated with faster progression of calcific AS[51]. Together, these studies suggest that high circulating levels of Lp(a) might promote the accumulation of Ox-PLs in the aortic valve, which could, in turn, trigger an osteogenic response (Figure 4).

Lipid retention and enzymatically-modified lipid species—Proteoglycans such as biglycan and decorin are overexpressed in aortic valves during calcific AS and might actively participate in lipid retention and modification (Figure 4)[52–54]. Moreover, transforming growth factor β-1 (TGF-β1), which is activated in calcific AS, has been shown to promote the elongation of glycosaminoglycan (GAG) chains[55]. In turn, GAG chain elongation increases the interaction between proteoglycans and lipoproteins[55]. The accumulation and retention of lipoproteins in the aortic valve is a crucial event as lipids

might be used by different enzymes to produce bioactive lipid-derived compounds, such as lysophospholipids[56].

Lipoprotein-associated phospholipase A2 (Lp-PLA2) levels are increased in stenotic aortic valves and this increase is associated with fibro-calcific remodelling (Figure 4)[57;58]. Circulating levels of Lp-PLA2 are also positively and independently related to the progression of calcific AS[59]. Lp-PLA2 is transported by apoB-containing lipoproteins and is enriched in small, dense LDL and Lp(a)[60]. Lp-PLA2 transforms Ox-PLs into lysophosphatidylcholine (LysoPC), which promotes the loss of mitochondrial membrane potential and apoptosis of VICs[57;61]. In addition, Bouchareb and colleagues recently showed that ectonucleotide pyrophosphatase/phosphodiesterase family member 2 (also called autotaxin), a lysophospholipase D, is likely transported into the aortic valve by Lp(a) and is also secreted by VICs in response to diverse stimuli including tumor necrosis factor alpha (TNF-α)[62]. Autotaxin transforms LysoPC into lysophosphatidic acid (lysoPA). Of interest, *in vitro* knockdown of autotaxin prevented the mineralization of VICs induced by LysoPC, suggesting that LysoPA is probably the mediator that promotes osteogenic programing in VICs. To this effect, in a murine model, the administration of LysoPA increased the deposition of hydroxyapatite (a form of calcium apatite) in the aortic valve and accelerated the development of calcific AS. Therefore, it is possible that autotaxin and lysophosphatidic acid are key factors that explain the link between Lp(a) and AS[63].

In addition to lysophospholipids, the arachidonic acid pathway, which produces leukotrienes and prostaglandins, has been shown to also play a considerable part in the mineralization of the aortic valve (Figure 4)[64]. For instance, the expression of 5-lipoxygenase, which is required for leukotriene synthesis, is increased in aortic valves during calcific AS and leukotriene C4 promotes the expression of bone morphogenetic proteins 2 and 6 (BMP2 and BMP6) as well as the mineralization of VICs in culture[64]. A recent study has shown that prostaglandin G/H synthase 2 (also called cyclooxygenase 2 (COX2)) is expressed by VICs isolated from AS valves[65]. In support of a role for COX2 in calcific AS, a loss of function of *Cox-2* in *Klotho* deficient mice, which develop calcification of the aortic valve amongst other features, reduced the mineralization of the aortic valve[65]. Taken together, these findings suggest that several processes promote the retention of lipids in the aortic valve and produce bioactive lipid species, which promote inflammation and mineralization of aortic valve leaflets.

Inflammation

Tissue remodelling and neovascularization—Fibro-calcific remodelling and inflammation of the aortic valve are intricately linked processes that have several important cross-talks. Inflammatory infiltrate in mineralized aortic valves removed surgically is composed of macrophages, mast cells, CD4+ T cells and CD8+ T cells[66]. Several oxidized lipid species might activate the innate immune response through toll-like receptors (TLRs) and the nuclear factor-kappa B (NF-κB) pathway. TLRs are also expressed by VICs (TLR2 and TLR4) and may promote an osteogenic phenotype in isolated VICs[67;68]. On the other hand, the role of adaptive immunity in calcific AS is still largely unknown, but studies have shown that a subset of memory T cells is activated during AS and that clonal expansion of a

T cell receptor repertoire is present in surgically removed calcific AS valves[69]. These data suggest that both innate and adaptive immune responses are likely involved in the pathobiology of calcific AS.

A histopathologic study performed on 285 aortic valves from patients with calcific AS revealed that the presence of dense, chronic inflammatory infiltrates was related to the remodelling score of the leaflets and to the presence of neovascularization[29]. Although the exact role of neovascularization in driving AS is still largely unknown, it is possible that it is involved in the recruitment of inflammatory and osteoprogenitor cells (Figure 4). In support of this hypothesis, mice deficient of chondromodulin-1 (encoded by *Lect1*), which is an anti-angiogenic factor, have thickened and mineralized aortic valve leaflets[70]. Aged $Lect1^{-/-}$ mice develop capillary-like structures in their aortic valve leaflets, which is accompanied by the presence inflammatory cells and lipid deposits[70]. In human stenotic aortic valves, CD34+ endothelial progenitor cells, which participate in new vessel formation, are observed in clusters in close proximity to SPARC (also called osteonectin) and MMP9[71]. SPARC is a matricellular protein expressed by VICs during calcification that is cleaved by MMPs into peptides with angiogenic activity[71]. Several MMPs, including MMP2, MMP9 and MMP12, are overexpressed in human calcific AS valve tissue[72]. As such, angiogenic SPARC peptides might promote neovascularization by CD34+ endothelial progenitor cells and cause inflammation as well as remodelling of the aortic valve. In addition, cathepsins K, V and S, which are proteases that can degrade extracellular matrix proteins, are expressed and activated during AS[73], and in $ApoE^{-/-}$ mice, cathepsin S promoted elastolysis and mineralization of the aortic valve[74]. Therefore, inflammation and neovascularization are linked to remodelling and mineralization of the aortic valve.

Cytokines—TNFα is secreted by monocytes and macrophages and activates TNF receptor superfamily member 1A (TNF-R1). TNF-R1 activation results in activation of NF-κB and its downstream targets including interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) (Figure 4)[75–78]. These cytokines promote the mineralization of VICs and activate an osteogenic program, which may involve the expression of homeobox protein MSX-2 (MSX-2)[75–78]. To this effect, treatment of adventitial fibroblasts with TNFα increased the expression of MSX-2 through the production of ROS[79]. Mice deficient of IL-1 receptor antagonist protein (encoded by *IL-1rn*) have higher plasma levels of TNFα than wildtype mice and develop a thickening of the aortic valve[78]. However, double knockout $IL\text{-}1rn^{-/-}$ $Tnf^{-/-}$ mice are protected and do not develop a thickening of the aortic valve, suggesting that TNFα plays important part in promoting the remodelling of the aortic valve. In humans, the expression of TNF ligand superfamily member 10 (also called TNF-related apoptosis inducing ligand(TRAIL)), a member of the TNF-related cytokines, is increased in calcific AS valves and promotes the mineralization of VIC cultures through the death receptor 4[80].

IL-6, another cytokine with pleiotropic activities, has been implicated in calcific AS. IL-6 is increased in human calcified stenotic valves and is secreted in large amounts by cultured human VICs when they are treated with an osteogenic medium[81]. In addition, knockdown of *IL6* substantially reduces the expression of *BMP2* and the mineralization of VIC cultures[81]. Moreover, though not yet investigated in VICs, IL-6 induces the expression of tumor necrosis factor ligand superfamily member 11 (RANKL) in bone cells, which activates its

cognate receptor RANK[82]. Overexpression of RANKL during calcific AS might have an important role in the pathogenesis, as secreted RANKL activates VICs to produce extracellular matrix (Figure 4)[83]. In support of this role, the administration of osteoprotegerin (OPG), a decoy receptor for/RANKL, to low-density lipoprotein receptor knockout ($Ldlr^{-/-}$) mice decreased calcification and the expression of osteogenic genes in aortic valves[84]. Of interest, in bone, RANKL is expressed by osteoblasts and promotes the resorption of mineral by osteoclasts. Therefore, it is possible that a dysregulation of tumor necrosis factor ligand superfamily member 11 (RANKL)/RANK/OPG explains the link between osteoporosis and vascular and valvular calcification[66]. In this regard, several epidemiological studies have underlined an association between osteoporosis and vascular/valvular calcification[66;85–87].

Angiotensin II

Angiotensin converting enzyme (ACE) and chymase are overexpressed in calcific AS valves and are involved in the production of angiotensin II (Figure 4)[88;89]. Chymase is secreted by mast cells present in calcific AS valve tissues and converts angiotensin I into angiotensin II[88]. In addition, patients with calcific AS have elevated blood plasma levels of angiotensin II, which correlates with the valvular expression of TNFα and IL-6[90]. Angiotensin II is a potent activator of the NF-κB pathway and promotes a strong fibrotic response in isolated cells. In mice, the administration of angiotensin II promotes fibrosis of the aortic valve[91]. Moreover, in a rabbit model of hypercholesterolaemia, the administration of olmesartan, an angiotensin receptor blocker (ARB), prevents the thickening of the aortic valve that normally develops in these rabbits[92]. Retrospective non-randomized studies have reported that administration of ARBs, but not ACE inhibitors, are associated with less fibro-calcific remodelling of aortic valve leaflets and slower progression of valve stenosis[93;94]. Therefore, it is possible that a substantial amount of angiotensin II is produced by chymase in the aortic valve, the effect of which is blocked downstream by ARBs but not by ACE inhibitors.

Mineralization

Osteogenic differentiation—The endothelium that covers the healthy aortic valve expresses several anti-osteogenic genes in a spatially distributed manner[95]. The endothelium that covers the aortic side of leaflets shows less expression of anti-osteogenic genes compared with the endothelium on the ventricular side. For instance, aortic side endothelium expressed lower levels of chordin and OPG, respectively negative regulators of BMP2/BMP4 and RANKL. A potential explanation for this difference in expression could be shear stress. Oscillatory shear stress has been shown to modulate the expression of ~1,000 genes and ~30 microRNAs in human primary cultures of aortic valve endothelial cells[96]. For instance, the expression of miRNA-187, which promotes cell growth and proliferation, was increased when these cultures were exposed to oscillatory shear. Endothelial cells covering the fibrosa (facing the aorta) are exposed to low oscillatory shear stress compared to cells facing the LV. Though the functional relevance of these findings remains to be fully investigated shear stress might explain, at least in part, why the fibro-calcific process predominantly occurs in the fibrosa layer.

In human stenotic aortic valves, several osteogenic genes are overexpressed[72], whereas others display altered function that can affect their role in signalling pathways. For instance, Garg and colleagues showed that mutations in *NOTCH1* were associated with bicuspid aortic valves, which are prone to developing calcific AS[97]. The Notch family of receptors are involved in cell fate determination. The activation of NOTCH1 in VICs leads to the formation of the notch intracellular domain (NICD), which associates with the recombining binding protein suppressor of hairless (encoded by *RBPJ*) in the nucleus where it promotes the expression of the hairy repressors. The hairy repressors prevent the expression of the osteogenic factors in VICs — BMP2 and runt-related transcription factor 2 (RUNX2)[98] — suggesting that VICs are driven towards an osteogenic differentiation pathway in calcific AS. To this effect, heterozygous *Notch1*$^{+/-}$ and *Rbpj*$^{+/-}$ mice develop mineralization of the aortic valve[99]. Additionally, the NICD interferes in the nucleus with catenin β-1 (β-catenin), a downstream effector of the Wnt pathway, which is also a key driver of osteogenic differentiation[100]. A recent study showed in endothelial cells that NOTCH1 regulates the expression of more than a 1,000 genes involved in inflammation and osteogenesis by altering the epigenetic signature at enhancer regions[101]. Moreover, in human stenotic aortic valves, WNT3a, an agonist of the Wnt pathway, is overexpressed[102]. The activation of a coreceptor formed by low-density lipoprotein receptor-related protein 5 and G-protein coupled Frizzled receptors, which are expressed by VICs, leads to the stabilization of β-catenin and the osteogenic differentiation (Figure 4)[102]. In vascular cells, BMP2 promotes the expression of MSX2, a positive regulator of the Wnt pathway[103]. Several factors, including inflammatory cytokines and oxidized lipid derivatives have been shown to induce the expression of BMP2 in several cell types including VICs[104].

Recent studies have also highlighted that the expression of several microRNAs is dysregulated in AS and this might affect the osteogenic programming of VICs. In this regard, miRNA-30b, which is decreased in mineralized aortic valves, is a negative regulator of RUNX2.[105] Hence, a dysfunction of Notch and Wnt pathways as well as a dysregulation of microRNAs contribute to increased pro-osteogenic signals in VICs.

Mineral deposition—Osteogenic reprograming of VICs entrains a series of events that promote the deposition of a calcified matrix. The mechanism(s) whereby VICs mineralize the extracellular matrix is still poorly defined but recent observational and experimental work suggests that cells secrete small vesicles rich in ectonucleotidases that promote the nucleation of calcium and phosphorus[106;107]. A build-up of phosphate in calcifying vesicles, which also contain the annexinV-S100A9 complex that binds calcium, promote the nucleation of mineral[108]. Classically, secretion of calcifying vesicles has been attributed to cells that transdifferentiate into osteoblast-like cells, in which case calcification proceeds with the deposition of well-organized bone-like mineral matrix (hydroxyapatite).[109]. However, programmed cell death leads to the production of apoptotic bodies with similar properties to calcifying vesicles. Apoptosis in VICs is promoted by different stimuli including cytokines, ROS and altered purinergic signalling. Apoptotic bodies serve as nidi for dystrophic calcification, a form of mineralization that consists of amorphous deposits of calcium and phosphorus crystals. In human aortic valves, it is likely that both osteogenic and apoptotic processes contribute to the mineralization process and rely, at least in part, on

ectonucleotidases[110]. In support of this involvement, several ectonucleotidases such as ALP, ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (E-NPP 1) and 5′-nucleotidase (5′-NT, also called CD73) are overexpressed in human stenotic aortic valves (Figure 4)[110–112]. These membrane-bound enzymes use nucleotides and nucleosides secreted by cells as substrates and produce phosphate-derived products that promote mineralization[112]. For instance, E-NPP 1 hydrolyzes ATP into AMP and pyrophosphate (PPi), a strong inhibitor of mineralization. On the other hand, ALP has a broad spectrum of substrates including the mineralization inhibitor PPi from which it produces phosphate with strong pro-mineralizing activity. Moreover, the over activity of E-NPP 1 and 5′-NT in human stenotic aortic valves depletes extracellular ATP and produces adenosine[111]. A decrease in the level of extracellular ATP also diminishes purinergic signalling through the P2Y purinoreceptor 2 (P2Y2). In VICs, P2Y2 prevents the mineralization of cells by interfering with apoptosis and also by promoting the activation of carbonic anhydrase 12 (CA12).[110;113] CA12 in VICs is normally expressed at the cell membrane following activation of P2Y2 and promotes the acidification of the extracellular space leading to resorption of mineral deposits[113]. As such, purinergic signalling, which is under the control of ectonucleotidases, plays a central part in controlling the mineralization of the aortic valve.

In summary, studies conducted in the past several years have shown that oxidation and infiltration of the aortic valve by lipids generate several bioactive lipid-species that trigger inflammation of the aortic valve. The activation of several pathways with multiple points of crosstalk disrupts the normal biology of the aortic valve and promotes fibro-calcific remodelling.

Pathophysiology of LV dysfunction

The symptoms in AS are essentially due to an imbalance between the increase in LV haemodynamic load caused by valvular obstruction, on the one hand, and the capacity of the LV to overcome this increase in load both at rest and during exercise, on the other hand. AS results in increased LV systolic pressure that leads to hypertrophy of the cardiomyocytes and interstitial fibrosis (Figure 5). The mechanical signal generated by increased LV systolic pressure initiates a cascade of biological events, including re-expression of immature fetal genes, which lead to coordinated cardiac growth in patients with AS[114]. This increase in cardiac mass is due to the hypertrophy of existing myocytes rather than hyperplasia, because cardiomyocytes become terminally differentiated soon after birth. The concurrent addition of sarcomeres (force-generating units) causes an increase in myocyte width, which in turn increases wall thickness and therefore contributes to normalize LV wall stress and maintain LV ejection performance despite elevated systolic pressure. To support the increased biomechanical load, the myocyte growth must be accompanied by coordinated increases in the surrounding architecture of connective tissue as well as the capillary and nerve networks[114]. This ‘reactive’ interstitial fibrosis that results from the increase in collagen synthesis by myofibroblasts in response to pressure overload has a diffuse distribution within the interstitium and might be, at least in part, reversible following AVR[115].

The pattern of the LV adaptive response to pressure overload in AS is highly heterogeneous and includes concentric remodelling, concentric hypertrophy and eccentric hypertrophy

(Figure 6) The pattern and magnitude of LV hypertrophic remodelling is influenced not only by AS severity but also by several other factors including age, sex, genetic factors, metabolic factors and the coexistence of coronary artery disease or hypertension[116–119]. For the same degree of AS, women tend to predominantly develop concentric remodelling/hypertrophy, whereas men are more prone to developing eccentric hypertrophy[116]. In patients with calcific AS, LV concentric remodelling or hypertrophy has been linked to worse myocardial function and increased risk of cardiac events and mortality compared to patients with normal LV geometry or with LV eccentric hypertrophy[120–122]. Obesity, metabolic syndrome and diabetes also predispose to the development of more concentric hypertrophy in the presence of AS[117;118].

The LV hypertrophy, leading to a reduced density of coronary arteriolar vessels, and increased LV transmural pressures, leading to increased coronary vascular resistance, result in the reduction of coronary flow reserve in patients with AS[123;124] The reduction of coronary flow reserve limits the ability of coronary circulation to increase flow to match myocardial oxygen demand, especially during exercise, and it is therefore a key factor in the development of myocardial ischaemia and the occurrence of symptoms. Repetitive myocardial ischaemia related to the exhaustion of coronary flow reserve leads to apoptosis of myocytes and development of ‘replacement’ myocardial fibrosis. This type of fibrosis occurs predominantly in the subendocardial and mid-wall layers of the LV wall and is generally not reversible following relief of LV pressure overload by AVR. The impairment of coronary flow reserve might also explain why patients with severe AS can present with angina symptoms despite having angiographically normal coronary arteries and why these symptoms might regress immediately after AVR[125].

LV diastolic dysfunction occurs early in the disease course and worsens with progression of stenosis severity and myocardial fibrosis (Figure 5). In the more advanced stages of the disease, the increased LV filling pressures lead to secondary pulmonary hypertension and dyspnoea symptoms[126;127]. The global LV systolic function, which is measured using the LV ejection fraction (LVEF), and cardiac output are generally well preserved even in the presence of severe AS because the increase in LV wall thickness allows wall stress to remain relatively normal. Reduced LVEF or cardiac output occurs only in end-stage disease and is usually preceded by clinical symptoms. However, a large proportion of patients with preserved LVEF have subtle LV systolic dysfunction that is characterized by impaired LV longitudinal function with relatively well preserved radial and circumferential function (Box 1) The LV myocardial wall is composed of 3 layers from the inside to the outside of the left ventricle: the subendocardial layer that surrounds the LV cavity, the mid-wall layer, and the subepicardial layer. In pressure overload cardiomyopathies, there is an early and selective alteration of the shortening of myocardial fibers within the subendocardial layer where ischaemia and fibrosis are generally more pronounced (Figure 5)[128–130]. The fibers in this layer are oriented longitudinally (compared with circumferentially in the mid-wall layer), which explains the selective alteration of the LV longitudinal function in these patients. Hence, a considerable proportion of patients with AS may have subclinical LV systolic dysfunction despite preserved LVEF and the absence of symptoms.

Diagnosis, screening and prevention

Risk factors and prevention

Although some clinical and genetic risk factors have been associated with the onset and progression of calcific AS, no strategy has been yet proven to be efficient for primary or secondary prevention of this disease. Calcific AS shares several risk factors with coronary artery disease but it also presents some important distinctive features.

Clinical risk factors—Congenital leaflet abnormality and older age are both powerful risk factors for developing calcific AS. For instance, the lifetime risk of AVR is around 50% in individuals with a bicuspid valve. Bicuspid aortic valves have two functional leaflets often of unequal size. This abnormality results from incomplete separation of commissures during embryonic development[8]. Although leaflet orientation varies among patients, the most common form consists of a fusion of the right and left coronary leaflets (~60% of patients) followed by fusion between the right and non-coronary leaflets (~35% of patients) and then fusion between left and non-coronary cusp (~5% of patients) (Figure 2)[131]. Bicuspid aortic valve is associated with an increased risk of aortopathy, in which genetic, haemodynamic and mechanical factors might participate in the mineralization of aortic valve[132]. In both individuals with a bicuspid valve and those with a tricuspid valve, age is a powerful risk factor for AS[9;133]. The other clinical risk factors associated with AS are similar to those associated with atherosclerosis and include male sex, smoking, hypertension, hypercholesterolaemia, obesity, metabolic syndrome, diabetes and elevated Lp(a)[9;13448;135;136].

In patients with AS, the rate of stenosis progression over time varies substantially from one patient to another. The clinical factors associated with faster stenosis progression include older age, female sex, severity of the stenosis and degree of aortic valve calcification at diagnosis, smoking, hypertension, obesity, metabolic syndrome, secondary hyperparathyroidism, renal failure elevated circulating levels of Lp(a), and increased activity of Lp-PLA2 (also called lipoprotein–associated phospholipase A2)[51;59;94;137–142]. In particular, the presence of elevated plasma Lp(a) (>50 mg per dL; the upper normal limit is <30 mg per dL)) is associated with a twofold faster stenosis progression[51].

Additionally, hypertension, and particularly systolic hypertension, is highly prevalent in these patients, affecting 30–70% of those with AS[94;143;144]. Recent studies suggest that hypertension accelerates the progression of AS, potentially owing to increased mechanical stress on the valve leaflets and activation of renin-angiotensin system (as discussed above)[94]. Moreover, hypertension further increases the LV afterload (Box 1) that is already elevated in patients with AS and contributes to the risk of developing symptoms and adverse cardiac events[94;144].

Genetic risk factors—Several studies suggest that a genetic component is involved in promoting calcific AS associated with bicuspid or tricuspid aortic valves[6;17;48;145]. However, despite the evidence of a strong inheritance pattern for some cases of bicuspid aortic valve with an incomplete penetrance, the genetic architecture of calcific AS is still poorly understood[145]. So far, variants of *NOTCH1* and GATA binding protein 5 (*GATA5*) have

been associated with bicuspid aortic valves in humans[97;146;147]. *NOTCH1* mutations explain approximately 4% of sporadic cases of AS that occurs in the context of a bicuspid aortic valve[148;149]. As discussed above, some mutations in *NOTCH1* that affect its function might promote aortic valve mineralization. Therefore, it is possible that gene variants that predispose individuals to developing a bicuspid aortic valve also promote valve mineralization later in life, thus further exacerbating the risk of developing calcific AS. Recently, a study has identified in a genome wide association study that variants located in *RUNX2* and *CACNA1C*, which encodes for an osteogenic transcription factor and a voltage-dependent calcium channel subunit respectively, were associated with calcific AS and were found to upregulate their respective mRNA levels.[150] Also, studies using a candidate gene approach have linked several gene variants with calcific AS. Although variants of *VDR, APOE, APOB, IL10, NOTCH1* and *ENPP1* have been found to be significantly associated with AS, these studies suffer from small sample size and require replication in larger series[6].

A large study using a Mendelian randomization design identified the single nucleotide polymorphism (SNP) rs10455872 in the *LPA* gene as the only genome-wide significant SNP associated with the presence of aortic valve calcification and clinical calcific AS[48]. Subsequent studies have validated these findings and also reported an association between elevated Lp(a) plasma levels with the prevalence of calcific AS and the need for AVR in the general population[49;50]. The presence of the rs10455872 allele is associated with a 1.5–2.0-fold increase in the risk of incident calcific AS[48–50]. When considered in the light of the clinical and basic research findings on Lp(a) discussed above, Lp(a) lowering appears to be a promising novel target for the treatment of this disease, particularly to prevent disease progression. However, further studies are needed to evaluate the role of Lp(a) in AS in more detail.

A second study using a Mendelian randomization design reported a strong association between genetic predisposition to elevated LDL-cholesterol, as measured by weighted genetic risk scores, and the presence of aortic valve calcification and incident cases of calcificAS[151]. However, three randomized clinical trials (RCTs) failed to demonstrate any significant benefit of LDL lowering with statins on the progression of AS[152–154]. Therefore, it is possible that elevated LDL-cholesterol promotes the initiation of calcific aortic valve disease but has minimal or no effect on AS progression. Moreover, the protective effect of statin therapy in AS might be counterbalanced by its off-target effects including pro-osteogenic properties, worsening of insulin resistance and increased Lp(a) levels[51;141]. Whether other lipid-lowering strategies (for instance, PCSK9 inhibitors) would prevent or slow AS progression is unknown and this question needs to be addressed. In summary, no pharmacotherapy has proven to be effective in reducing the progression of AS.

Diagnosis

Diagnosis of AS is generally established using an echocardiographic exam, which provides a wealth of information regarding heart valve anatomy and blood flow parameters (Figure 7)[155]. The same techniques can be used for the diagnosis of calcific AS and rheumatic AS. In the vast majority of patients, the referral to echocardiography is motivated by the auscultation of a systolic murmur and/or the development of symptoms including dyspnoea,

angina, syncope and dizziness. In some cases, AS is first recognized on echocardiography requested for other indications. Although most patients are diagnosed long before the onset of symptoms and are followed prospectively on a regular basis until AVR is indicated, a small proportion (5–10%) of patients are not diagnosed with AS until late in the disease course when they present with symptoms of heart failure[156]. The identification of the presence and stage of AS includes the assessment of the aortic valve anatomy and morphology, the haemodynamic severity of AS, the response of the LV to the pressure overload caused by AS, and the patient's symptomatic status[3;4]. On the basis of these assessments, patients can be diagnosed with mild, moderate or severe AS, which can all occur in the presence or absence of symptoms (Table 1). Although Doppler echocardiography is the primary modality to assess the stage of AS, cardiac catheterization, which can measure cardiac blood pressure and flow, may be used to confirm the haemodynamic severity of the stenosis in patients with inconclusive or discordant echocardiography results[157]. However, this invasive technique is associated with increased risk of bleeding and cerebral embolism[158] and should therefore only be considered in patients in whom the reclassification of the stenosis severity by catheterization would change the therapeutic management of the patient (such as AVR versus conservative management). For instance, individuals who might benefit from catheterization assessment include symptomatic patients where there is uncertainty between whether they have moderate or severe AS using echocardiography.

Patients at risk for AS—Individuals with aortic sclerosis and those with a bicuspid valve (irrespective of the presence or absence of sclerosis) are considered to be at risk of developing AS. The identification of bicuspid valve is generally done by echocardiography but might require other imaging modalities such cardiac magnetic resonance (CMR) or CT if the valve is calcified.

Aortic valve sclerosis is defined echocardiographically by focal areas of valve calcification and thickening with normal leaflet mobility and normal valvular haemodynamics(Figure 7, Table 2). A systolic outflow murmur may be auscultated on physical examination. Although aortic sclerosis is clinically asymptomatic, its presence is independently associated with a 40% increase in the risk of a coronary event and a 50% increase in the risk of cardiovascular death[159]. The mechanism of adverse outcomes with aortic sclerosis is not entirely clear but the presence of aortic valve mineralization might be a marker for atherosclerosis and/or for altered phospho-calciummetabolism[22;160].

Mild or moderate AS—Patients with mild or moderate AS (Figure 7, Tables 1 and 2) are generally asymptomatic unless they have other comorbidities that contribute to the emergence of symptoms. Classic physical findings of AS are a harsh, crescendo-decrescendo systolic murmur, a single second heart sound and a delayed carotid upstroke (Box 1). Using Doppler-echocardiography, the haemodynamic severity of AS can be measured accurately and reliably on the basis of the peak aortic jet velocity, mean transvalvular pressure gradient (mean gradient) and aortic valve area (AVA). With the development of calcific AS, there is a progressive reduction in the AVA that causes an acceleration of the flow (i.e. increase in peak aortic jet velocity) and a loss of pressure (i.e. increase in mean gradient) across the

valve (Figure 6, Table 2). AS is confirmed upon the visualization of a thickened aortic valve with a restricted opening and increased peak aortic velocity/mean gradient confirms the diagnosis of AS. Echocardiography is also useful to assess the effects of AS on the geometry and function of cardiac chambers, in particular of the LV (Figures 5 and 6).

Severe AS—Patients with severe AS (typically, those who have a peak aortic jet velocity of ≥ 4m/s, a mean gradient of ≥ 40mmHg and an AVA of ≤1cm^2; Tables 1 and 2) may or may not have symptoms and require a closer clinical and Doppler-echocardiographic follow-up than those with mild or moderate forms of the disaese[3]. Classic symptoms of severe AS include dyspnoea and other symptoms of heart failure, angina and syncope. Patients with severe AS who are apparently asymptomatic according to medical history and physical examination should undergo exercise testing to confirm their asymptomatic status. Indeed, about one-third of patients with severe AS who are a priori asymptomatic in fact have exercise-limiting symptoms detected at an exercise stress test and these patients should be referred for AVR[161;162]. In addition, a potential marker for risk in AS is a marked increase in mean gradient (absolute increase in gradient >18–20 mmHg) during exercise stress echocardiography, which predicts higher risk of cardiac events in the short-term, independently of symptoms[161;162].

Low-gradient AS—The majority of patients with severe AS have a high peak aortic jet velocity and gradient (mean gradient ≥ 40 mmHg). However, a substantial proportion of patients may have a low peak aortic jet velocity and mean gradient despite the presence of a small AVA (<1.0 cm^2). The most frequent cause of 'low gradient' AS is the presence of low-flow state. There are two main subtypes of low-flow, low-gradient AS (Tables 1 and 2): 'classical' low-flow (stroke volume index <35 ml per m^2), low-gradient (mean gradient <40 mmHg) AS with reduced LVEF (<50%)[163]; and 'paradoxical' low-flow (stroke volume index <35 ml per m^2), low-gradient (mean gradient <40 mmHg) AS with preserved LVEF (≥50%)[164].

In classical low-flow, low-gradient AS, the decrease in stroke volume and thus in transvalvular flow rate (stroke volume divided by LV ejection time) are predominantly related to LV systolic dysfunction whereas in paradoxical low-flow, low-gradient AS, the low flow state is generally owing to pronounced LV concentric remodelling with impaired LV diastolic filling and reduced LV longitudinal systolic function[156]. Other conditions, such as mitral regurgitation, mitral stenosis or atrial fibrillation can also contribute to the reduced LV outflow in both classical and paradoxical low-flow, low-gradient AS.

In the presence of low flow, it is thus difficult, using resting Doppler-echocardiography or catheterization, to differentiate truly severe stenosis from pseudo-severe stenosis, that is, a situation wherein the stroke volume is not sufficient to completely open a valve that is only mildly or moderately stenotic. In such low flow conditions, the gradient might underestimate the stenosis severity, whereas the AVA might overestimate the severity. Low-dose dobutamine stress echocardiography should be used for patients with classical (low LVEF) low-flow, low-gradient AS to confirm stenosis severity. Dobutamine is used to mimic the effect of exercise on the heart, thereby increasing cardiac blood flow. Patients with mean gradient ≥40 mmHg (or a peak aortic jet velocity ≥ 4 m per s) and an AVA of <1.0 cm^2 on

dobutamine stress echocardiography are considered to have truly severe AS (Table 2). In patients who show a limited increase in flow (percent increase in transvalvular flow rate <15%) and persistent discordant grading (small AVA with low mean gradient) during dobutamine stress echocardiography, it is useful to calculate the projected AVA at normal flow rate; a projected AVA of <1.0 cm^2 suggests the patient has true severe stenosis[165;166]. Patients who have no or minimal increase in stroke volume (percent increase <20%) upon dobutamine administration have a high risk of operative mortality with surgical AVR[163;167]. Low-dose dobutamine stress echocardiography or dobutamine stress cardiac catheterization may also be used in patients with paradoxical low-flow, low-gradient AS[168]. However, these approaches are often not feasible owing to the presence of restrictive LV physiology or their results are inconclusive owing to limited increases in flow in response to stress.

In patients with classical or paradoxical low-flow, low-gradient AS in whom dobutamine stress echocardiography is not feasible or inconclusive, multidetector computed tomography (MDCT), a high-resolution form of CT, can be used to quantitate aortic valve calcium load and thereby corroborate stenosis severity and indication of AVR (Figure 7 and Table 2). The region of the aortic valve is assessed in contiguous axial slices and the calcium score is measured by the Agatston modified method, in which calcification is defined as 4 adjacent pixels with density >130 Hounsfield units on the MDCT images. Studies have shown that different cut-off values of aortic valve calcium score (AU) should be used in women (>1200 AU) compared with men (>2000 AU) to identify haemodynamically severe stenosis[169;170]. Furthermore, these studies suggest that aortic valve calcium density (the ratio of calcium load to cross-sectional area of the aortic annulus) might be superior to absolute calcium load to predict hemodynamic severity and clinical outcomes. These studies also demonstrated that different cut-off values should be used in women (>300 AU per cm^2) compared with men (500 AU/cm^2)[169;170]. The aortic valve calcium load or density is also a powerful predictor of the risk of fast stenosis progression and of mortality[170–172].

Finally, a substantial proportion of patients with AS have a small AVA and low mean gradient but a normal flow (stroke volume index > 35 ml per m^2). This category is often referred as to normal-flow, low-gradient AS and might be related to inherent discrepancies in the criteria used to define severe AS (in terms of AVA and mean gradient)[173] and/or to markedly reduced aortic compliance[169]. Patients with normal-flow, low-gradient AS generally have less advanced disease and better outcomes compared with patients who have high gradient or low-flow, low-gradient AS[174]. However, if the patient is symptomatic, aortic valve calcium scoring using MDCT can be considered to confirm stenosis severity[169].

Emerging Biomarkers

Other imaging or blood biomarkers of the severity of AS and its deleterious effects on the LV and other cardiac chambers may also be useful to predict risk of rapid disease progression and adverse events. In particular, these biomarkers may be helpful in identifying patients with asymptomatic severe AS who may benefit from early ‘prophylactic’ AVR.

Biomarkers of aortic valve biology and flow pattern—Positron emission tomography (PET) combined with MDCT (PET-MDCT) is a feasible and reproducible

method that combines anatomical imaging from MDCT with the molecular imaging from PET. The valvular uptake of ^{18}F-sodium fluoride (^{18}F-NaF) measured by PET-MDCT is a marker for active mineralization process within the valve (Figure 8)[175–177]. ^{18}F-NaF uptake correlates well with AS severity and it might provide incremental value beyond aortic valve calcium scoring to predict AS progression over time[172]. This method might also be useful in assessing the effect of new pharmacotherapies on AS progression. In addition, CMR might be useful to assess valve biology and flow. For instance, data from a previous study suggests that in the future CMR might be able to assess not only the amount of valvular calcification (as can be achieved with MDCT) but also the amount of fibrous-rich and lipid-rich valve tissue[178]. Moreover, CMR with 4D flow modality might also one day be used to visualize flow patterns in the aorta and therefore to identify patients with AS who are at risk of developing aortic aneurysm and aortic dissection (a breach in the lining of the aorta that causes blood to flow between the layers of the wall of the aorta, forcing layers apart) (Figure 9)[179;180].

Biomarkers of impact of AS on the left ventricle—Detection of sub-clinical LV dysfunction using biomarkers might prove useful in identifying patients who may need early therapeutic intervention. For example, reduced longitudinal strain is useful to identify subclinical LV dysfunction and predict risk of cardiac events in patients with asymptomatic AS and preserved LVEF[181–186]. However, further studies are needed to harmonize the different strain analysis platforms between vendors and to propose an optimal cut-off value of longitudinal strain that identifies patients at higher risk of developing LV dysfunction and symptoms in the short-term.

Blood levels of B-type natriuretic peptide (BNP) might also be a useful marker of LV function, as it is secreted from the LV in response to mechanical stress. Although BNP can be used for risk stratification, there is an important inter-study variability in the cut-off serum values of BNP that have been used to identify high-risk patients. A previous study proposed using the BNP ratio (the measured value of BNP divided by the expected value of BNP adjusted for the age and sex of the patient) to overcome this limitation. A BNP ratio of >1 was found to be a powerful independent predictor of mortality in AS, even in patients with asymptomatic AS[187]. Hence, the BNP ratio as well as its increase during follow-up might be helpful in enhancing risk stratification in AS.

Besides longitudinal strain and BNP, the extent of myocardial fibrosis represents a maladaptive response of the LV to pressure overload from AS. Previous studies[188–191] have reported that approximately 20 to 30% of patients undergoing AVR for severe AS have severe myocardial fibrosis documented by CMR or myocardial biopsies. Myocardial fibrosis is often not reversible (or only partially reversible) and is associated with increased risk of cardiovascular events and mortality during follow-up as well as persistence of LV dysfunction and symptoms following AVR[188–190;192;193]. Therefore, the quantification of myocardial fibrosis by CMR (Figure 10) could potentially be useful to recommend early AVR in patients with asymptomatic severe AS before extensive fibrosis and ensuing irreversible myocardial dysfunction have developed or to improve operative risk stratification and assess potential utility versus futility of AVR in patients with low-flow, low-gradient AS. However, further studies are needed to improve the standardization of the

different CMR methods for quantitation of myocardial fibrosis and to establish the thresholds that should be used clinically to identify patients who are at risk for irreversible myocardial dysfunction. The large scale utilization of CMR in the AS population is also limited by its high cost and low availability.

Emerging blood biomarkers, such high-sensitivity cardiac troponin[194;195], growth/differentiation factor 15, soluble interleukin-1 receptor-like 1 (also called protein ST2) and micro RNAs[196–198], might be helpful to detect subclinical and/or irreversible myocardial dysfunction but their incremental value beyond already established clinical, echocardiographic, tomographic and blood biomarkers is yet to be demonstrated.

The main limitation of all aforementioned imaging and blood biomarkers of LV function is that they are non-specific and may be altered by other concomitant diseases, such as hypertension, diabetes mellitus and coronary artery disease. Therefore, these biomarkers should always be interpreted in conjunction with the standard parameters of stenosis severity. Finally, further studies are needed to establish the incremental role of these emerging blood or imaging biomarkers to identify the patients who might benefit from earlier intervention.

Conclusions

In summary, the two main risk factors for calcific AS are older age and bicuspid aortic valve. Other risk factors include metabolic syndrome, diabetes, hypertension, smoking and increased plasma Lp(a). There is currently no preventive or pharmaco-therapeutic approach that has proven effective to prevent the onset or slow the progression of calcific AS The initial screening for this disease is generally based on the auscultation of a systolic murmur by the primary care physician or general cardiologist. Doppler-echocardiography is the method of choice to diagnose AS and assess its severity as well as to follow disease progression over time. Quantitation of aortic valve calcium load by MDCT may be useful to corroborate stenosis severity in patients in whom echocardiography is neither feasible nor conclusive, which is often the case in the setting of low-flow, low-gradient AS. Measurement of circulating BNP levels, assessment of global longitudinal strain by speckle tracking and detection of myocardial fibrosis by CMR are emerging biomarkers that might improve the detection of subclinical LV dysfunction and thus the determination of the optimal timing for AVR.

Management

The only treatment available to treat patients with symptomatic severe AS is to implant a prosthetic heart valve either surgically or percutaneously (through a catheter). The therapeutic management is similar for calcific versus rheumatic AS. As discussed above, there is no pharmacotherapy specifically targeting AS to prevent progressive leaflet calcification or to delay time to valve replacement[3;199]. Although there was hope that statins would fill that void, several randomized trials showed no effect of statins on haemodynamic progression or AS-related clinical events[152–154]. However, the combination of simvastatin (drug that lowers plasma LDL cholesterol levels) and ezetimibe (drug that decreases cholesterol absorption in the small intestine) did reduce ischaemic cardiovascular events in

patients with mild to moderate AS[153]. Therefore, as valve stenosis progresses into the moderate to severe range, greater vigilance is required regarding assessment for symptoms associated with significant AS to decide when to perform AVR.

Management decisions regarding AVR are often straightforward (Figure 11). However, in the current era of transcatheter AVR (TAVR), there are more options to consider when intervention is contemplated than in previous decades (Figure 12). In addition, older (> 80 years) and sicker patients who previously were not candidates for definitive therapy are being treated[200;201]. Increasingly, clinicians must integrate complex information about the severity of AS, ambiguous symptoms, LV remodelling and function, comorbidities, frailty and disabilities to make decisions about whether, when, and how to perform AVR[3;199;202]. This complex information ought to be discussed and debated in the context of a heart valve team — a multidisciplinary group comprised of cardiac surgeons, interventionalists, cardiac imaging experts, and often nurses, geriatricians and anesthesiologists[203–205]. In addition, it is important for management decisions to be patient-centered and not myopically focused on AS severity alone[3]. First, a decision should be made whether valve replacement is indicated. Subsequently, consideration can be given to how the valve should be replaced (surgical versus transcatheter) (Table 3 and Figure 12). Finally, at any stage of AS, associated medical conditions such as atrial fibrillation, coronary disease, hypertension and heart failure should be treated according to guideline recommendations[3;4;199].

Indications for aortic valve replacement

Symptomatic severe AS—Severe high-gradient AS accompanied by symptoms related to AS is the most common and straightforward indication for AVR, and those with severe AS who present with symptoms and/or LV systolic dysfunction (defined as a LVEF of <50%) have a firm (Class I, Box 1) indication for AVR (Figure 11, Table 1)[3;4]. Low-flow, low gradient AS presents somewhat of a challenge as the combination of a small AVA with a low gradient raises uncertainty about the severity of the stenosis and thus the indication of AVR. Symptomatic patients with classical low-flow, low-gradient and reduced LVEF (<50%) are reasonable candidates for AVR (Class IIa indication, Box 1) provided there is anatomic evidence (MDCT calcium score) or haemodynamic evidence (peak aortic jet velocity ≥4 m per sec or mean gradient ≥40 mmHg with dobutamine stress echocardiography) that the AS is truly severe[3;4;170]. AVR may be considered in patients with classical low-flow, low-gradient AS having no flow reserve at dobutamine stress echocardiography, but the operative risk is higher[4;163;167;206]. It is also reasonable to perform AVR in symptomatic patients with paradoxical low-flow, a low-gradient and preserved LVEF (≥50%) (Class IIa indication) provided there is clinical, haemodynamic and anatomic evidence that the obstruction is severe and the most likely cause of symptoms[3;4;168]. Although there has been some debate about the outcome and therapeutic management of patients with paradoxical low-flow, low-gradient AS, a recent meta-analysis confirms that these patients have worse outcomes compared to moderate or high-gradient severe AS and that their survival is markedly improved by AVR[174].

Asymptomatic severe AS—Patients with severe AS who are asymptomatic by history but who have a reduced LVEF (<50%) (Table 1) or are undergoing another cardiac surgical

procedure should have their valve replaced (Class I indication) (Figure 11)[3;4]. It also is reasonable to perform AVR (Class IIa indication) in asymptomatic patients with severe AS and decreased exercise tolerance or a drop in blood pressure with exercise, and in those at low surgical risk with very severe AS (peak aortic jet velocity >5 m/sec or 5.5 m/s, depending on the guidelines,), or findings suggestive of rapid progression (severe valve calcification or increase in peak aortic jet velocity of ≥0.3 m per sec per year)[3;4].

Surgical aortic valve replacement

The first successful surgical AVR was performed in 1960[207]. Over the past half century, tremendous advances in operative management, techniques and valve design have transformed the outlook for patients with AS. Despite increasing age and comorbidities, the mortality associated with AVR has decreased dramatically during the past two decades[208;209]. For an isolated AVR, the overall 30-day mortality rate is currently under 3% as reported in the Society of Thoracic Surgeons (STS) database and German Aortic Valve Registry (GARY)[209;210]. Table 3 presents the advantages and limitations of the different types of AVR. There has been a shift away from mechanical valves toward greater use of bioprosthetic valves, particularly in patients >65 years of age (Figure 12)[209]. Increasingly, younger patients or those with an active lifestyle opt for a bioprosthetic valve to avoid anticoagulation despite its shorter durability compared to a mechanical valve. The most frequently used bioprosthetic valves are the stented bioprostheses, which are composed of three biologic leaflets made from porcine aortic valve or bovine pericardium and mounted on a metal or polymeric stented ring. Bioprosthetic valves also include stentless bioprostheses that are manufactured from intact porcine aortic valves or from bovine pericardium. These valves have better hemodynamics compared to stented valves but their implantation is more complex and thus requires longer cardiopulmonary bypass time. Sutureless stent-mounted bioprosthetic valves have also been developed to allow easier and faster implantation of the valve without sutures.

Additional alternatives for AVR in younger patients include the implantation of an aortic homograft (aortic valve harvested from a donor) or the Ross procedure, which involves the replacement of the diseased aortic valve with the patient’s pulmonary valve followed by pulmonary valve replacement using a donor pulmonary valve[211–213]. These options are however more controversial and less frequently used. A recent propensity analysis showed no difference in mortality or stroke among patients 50–69 years of age treated with a bioprosthetic versus mechanical valve, although a bioprosthetic valve was associated with a higher incidence of reoperation and a mechanical valve was associated with a higher incidence of major bleeding during the 15-year follow-up[214]. A mini-sternotomy, which is a minimally invasive way of performing cardiac surgery, is a viable option for isolated AVR and is associated with similar mortality, but decreased morbidity and resource utilization, compared to a full sternotomy[215].

Operative mortality for AVR varies according to the skill and experience of the surgical team as well as hospital volume[216]. Increasing age and comorbidities substantially increase both operative and long-term mortality after AVR[217;218]. A number of risk scores, including the EuroSCORE (http://www.euroscore.org) and the STS risk calculator (http://riskcalc.sts.org),

incorporate these factors to estimate operative risk. These risk scores are imperfect and iteratively being refined. They often do not include important factors such as frailty, chest wall radiation, porcelain aorta, pulmonary hypertension and liver cirrhosis. Owing to age, LV dysfunction, multiple comorbidities and other factors, approximately one-third of patients with indications for AVR are not treated[200;219].

Transcatheter aortic valve replacement

TAVR is a minimally invasive procedure that involves insertion of a bioprosthetic aortic valve within the orifice of the native stenotic valve using a catheter. For patients at high or prohibitive risk of operative mortality, with surgical AVR, TAVR has been a transformative innovation, providing a life-saving treatment for patients who were previously not candidates for AVR (Table 3)[201;220–224]. In the PARTNER Trial, there was a 20% absolute reduction in 1-year mortality (HR 0.55; 95% CI 0.40 to 0.74) with TAVR compared to standard therapy (30.7% versus 50.7%)[201]. This survival benefit was accompanied by relief of symptoms and improvement in functional capacity in many patients[201;225]. Randomized trials of balloon-expandable and self-expanding valves have also demonstrated that TAVR is a viable alternative to surgery in patients at high risk for AVR (Table 4)[220;221].

TAVR may be performed by several different approaches; the most common access routes include transfemoral, transapical and transaortic (Figure 12, Table 5). Approximately two-thirds (56–75%) of TAVR procedures are performed via a transfemoral approach[226–229]. As catheter sheath sizes decrease, the balance is anticipated to shift even more toward a transfemoral approach. A transfemoral approach is associated with lower mortality and quicker recovery compared to alternative access approaches[227–229]. Other approaches include via the subclavian, axillary or carotid arteries. There have even been recent reports of transcaval approaches[230].

Balloon-expandable and self-expanding transcatheter valves have been the most rigorously studied to date, specifically the CoreValve (Medtronic, Dublin, Ireland) and SAPIEN (Edwards, Irvine CA, USA) valves (Figure 11, Table 5)[201;220;221;224;226;231;232]. This clinical arena is a very active area of development including iterative improvements on existing valves and novel designs[233]. Although TAVR has been a successful therapy in many ways, several complications and challenges have been encountered[233]. The most notable has been paravalvular aortic regurgitation[234–236]. The association between moderate or severe paravalvular aortic regurgitation and increased mortality has been clearly established, with some studies even suggesting that this adverse association extends to mild regurgitation[235;237;238]. Other complications of TAVR have included major vascular injury, heart block requiring a permanent pacemaker and acute kidney injury; more rare complications include stroke, aortic rupture and coronary obstruction[233].

The TAVR field is rapidly evolving. Clinical trials comparing TAVR to surgery in intermediate risk populations are ongoing with results expected soon (Table 4). Surgical AVR has excellent results with low mortality in low risk populations[209]. For TAVR to make inroads into lower risk populations, device improvements are needed (principally to reduce paravalvular regurgitation and heart block, which is an arrhythmia that occurs when electrical impulses in the heart are blocked or delayed), vascular and stroke complications

must be minimized and valve durability needs to be demonstrated. There is a growing movement away from general anesthesia to conscious sedation that might decrease the morbidity of the procedure[239]. Finally, valve-in-valve procedures for failed bioprostheses are becoming more common as an alternative to re-doing surgical AVR[240].

Choice of surgical versus transcatheter aortic valve replacement

The choice of how to perform AVR should occur only after a decision that AVR is indicated (Table 1)[3]. Currently, surgical AVR is indicated for patients with low to moderate surgical risk and TAVR is indicated for patients at prohibitive risk for surgery (Figure 11, Table 3)[3;4]. Patients may be at prohibitive risk for surgery owing to technical factors (such as porcelain aorta) or for clinical reasons (such as multiple comorbidities or frailty)[3;241]. Presently, intermediate risk patients may be treated with surgical AVR or enrolled in a clinical trial for TAVR. High-risk patients who are candidates for either surgical AVR or TAVR should have their therapy determined by careful consideration by the heart valve team[3;4]. Factors to weigh in this decision include anatomic considerations, concomitant coronary disease and associated mitral or tricuspid valve disease. In patients with considerable associated mitral or tricuspid regurgitation, it is unclear whether concomitant surgical repair of the mitral or tricuspid valve at the time of AVR would improve clinical outcomes[242;243].

Although, in general, TAVR is associated with a survival advantage compared to conservative (no AVR) management, there is a sizable sub-group that dies soon after TAVR or does not experience an improvement in quality of life, suggesting potential futility of TAVR in some patients[201;202;220;244;245]. For instance, among inoperable patients treated with TAVR in the PARTNER I Cohort B trial (Table 4), at 1 year after the procedure approximately 31% were dead and 18 % had less than a moderate improvement in their quality of life or New York Heart Association functional class[201;244] Among patients treated in the high-risk Cohort A of the PARTNER I trial with TAVR or surgical AVR (Table 4), death from non-cardiovascular causes was more common than death from cardiovascular causes[48]. Moreover, when cause of death was difficult to categorize, it often occurred in frail patients who were failing to thrive[246]. Therefore, when lifespan or quality of life is profoundly limited by frailty, noncardiac disease, mental or physical disability, the potential benefit of AVR may be low[11]. These cases highlight the importance of a heart valve team in the management decisions of these complex patients[3;4]. In some of these patients, the most appropriate approach is palliative care, taking the values and preferences of the patient and family into consideration in the decision making process[202].

Management of coronary artery disease in patients with AS

The prevalence of considerable coronary disease in the setting of severe AS increases with age and was as high as 75% in recent trials comprised mostly of very elderly patients[201;220]. Decisions regarding revascularization at the time of valve replacement used to be somewhat simpler when surgical valve replacement was the only option. If significant coronary artery stenosis was present at preoperative coronary angiogram, coronary artery bypass graft was performed at the time of valve replacement surgery. With the emergence of TAVR, decisions regarding the treatment of coronary disease have become more complex, including which coronary lesions to treat versus leave alone, how to treat them (percutaneous versus bypass)

and when to treat them (before, during, or after valve replacement)[247]. These decisions are influenced by numerous factors including lesion location and complexity, overall burden of coronary disease, the presence or absence of angina, LV function, bleeding risk on dual antiplatelet therapy and other factors. How these decisions affect clinical outcomes requires further investigation as many questions remain[247;248]. The way in which coronary disease should influence decisions between valve replacement with TAVR versus surgical valve replacement is also unclear in some scenarios. A detailed discussion of these complex decisions is beyond the scope of this Primer, but has been recently reviewed elsewhere[247;249].

Balloon aortic valvuloplasty

Balloon aortic valvuloplasty (BAV), which uses the pressure of an inflated balloon to widen the opening of the stenotic valve, is not a definitive therapy for AS[3]. The changes produced by BAV in valve area and transvalvular pressure gradient are usually modest and short-lived (weeks to months)[250;251]. In particularly ill patients, BAV may be used as a 'bridge' to stabilize the patient prior to definitive therapy with valve replacement[3]. When there is uncertainty whether a patient will benefit clinically from valve replacement owing to markedly depressed LV function or concomitant oxygen dependent lung disease or other factors, a BAV may have diagnostic utility to determine whether valve replacement is appropriate[202]. In patients with severe AS undergoing non-cardiac surgery, a BAV is generally not warranted unless the patient is symptomatic or hemodynamically unstable and needs to undergo non-cardiac surgery before aortic valve replacement can be performed[3]. In some circumstances, a BAV may be utilized for palliative care as there is some evidence that it might provide a short-term benefit in terms of improved survival, functional capacity and quality of life, but these benefits are not sustained[251].

Quality of life

Severe AS primarily impairs quality of life by causing heart failure symptoms including shortness of breath, fatigue and diminished functional capacity[199;252]. However, because patients who develop severe AS are usually older adults, these symptoms may also result, in part, from normal aging, numerous comorbidities or frailty[202]. In older patients at high or extreme surgical risk undergoing TAVR, disease-specific and generic health status are often extremely poor[221;224;244;245]. Given the high prevalence of frailty and disability in this patient population, the relationship between valvular stenosis and overall quality of life is also complex and variable.[202]

AVR is indicated in patients with severe symptomatic AS both to increase life expectancy and improve symptoms and quality of life[3;4;199;202;252;253]. For a patient with severe AS and heart failure symptoms, who is at low surgical risk, surgical AVR is associated with a fairly predictable improvement in shortness of breath and functional capacity. For patients who are at high-risk for surgical interventions were previously not treated with AVR, TAVR has been a transformative innovation that has improved survival and quality of life[200;201]. Compared with inoperable patients treated with conservative management, patients treated with TAVR

had less severe heart failure symptoms and better disease-specific and generic health status over the year after randomization[201;244].

To determine the anticipated benefit of valve replacement in terms of quality of life, it is important to consider how much of the patient's symptoms and impaired health status are due to the valvular obstruction and heart failure versus other comorbidities and geriatric conditions[253]. This can be challenging to determine. When a patient's diminished quality of life is clearly related to heart failure symptoms from severe AS, valve replacement conveys a predictable and noticeable improvement in quality of life and extends life expectancy. Notably, however, some patients have residual heart failure symptoms (albeit not as severe) after valve replacement owing to persistent diastolic dysfunction; this may manifest similar to the common syndrome of heart failure with preserved LVEF. When poor health status is principally due to comorbidities and geriatric conditions, valve replacement might lead to an unsatisfactory result both in terms decreased survival and a decline or lack of improvement in quality of life[253–256]. Elucidating which factors contribute to worse quality of life after TAVR and identifying how those factors might be targeted with adjunctive interventions to improve outcomes require further study. It is likely that systemic, non-cardiac factors play an important role.

Outlook

Valve biology

Although long considered to be a passive and degenerative process, it is now clear that calcific AS results from an active biology that promotes fibrosis and calcification of the valve leaflets[1]. The pathobiology of AS is complex and likely involves genetic factors, multiple signalling pathways, ageing, sex hormones, haemodynamic factors and shear stress, and the systemic milieu. Disease initiation and progression are influenced by different factors. Several laboratories worldwide are working to elucidate the pathobiology of aortic sclerosis and stenosis, which will likely yield novel insights into potential therapeutic targets to prevent or reverse calcific aortic valve disease.

Pilot trials to slow disease progression

Several intervention studies have been performed to test the hypothesis that lipid lowering with statin medications would slow the progression of AS, however the results were generally disappointing[152–154]. Equipped with new insights into valve biology, there will likely be a new wave of clinical trials testing interventions that target diverse pathways to slow the progression of (or even reverse) calcific AS. Specific interventions might target the initiation of disease or the progression of disease. Promising targets on the horizon include Lp(a), the renin-angiotensin system, RANKL and ectonucleotidases. Novel composite endpoints are likely to be developed for these trials based on the mechanism of action of the intervention and the phase of disease targeted.

AS as a disease of the ventricle

The LV response to chronic pressure overload from AS is characterized by hypertrophic remodelling (myocyte hypertrophy and fibrosis) and diastolic and systolic dysfunction. In

many ways, this LV response considerably influences the morbidity and mortality of the disease[199;257–260]. Future research will likely clarify the mechanisms driving the formation of fibrosis in the pressure overloaded heart and elucidate the abnormal diastolic properties (such as stiffness versus relaxation) involved in AS. In asymptomatic patients, targeting the adverse remodelling sequelae of the valvular stenosis with a therapeutic medical intervention might delay the onset of symptoms and allow us to put new valves into healthier hearts, thereby potentially improving long-term cardiac performance and functional capacity.

TAVR will move into lower risk populations

With iterative improvements in transcatheter valves and lower procedural complications (less paravalvular leak, permanent pacemakers, stroke and vascular injury), TAVR will likely move into lower risk populations (Table 4). However, questions about valve durability will need to be addressed. Although TAVR might become a viable option in low-risk patients with isolated AS, there will likely continue to be a group of patients for whom surgical AVR is preferable because it allows for more optimal treatment of concomitant pathology such as left main coronary disease or severe mitral or tricuspid valve disease. The currently available option of a transcatheter valve-in-valve procedure might lead cardiac surgeons to implant bioprosthetic valves (rather than mechanical valves) in younger patients, with the understanding that a new bioprosthetic valve can be subsequently implanted using TAVR.

Improved accuracy of risk prediction for TAVR

Although the STS score and EuroSCORE have reasonable accuracy in predicting morbidity and mortality after TAVR, they were developed in younger patient cohorts with fewer comorbidities undergoing cardiac surgery[261]. With multiple clinical trials and registries collecting detailed data on patients undergoing TAVR, there will be several risk prediction models developed specifically in and for TAVR patients that will improve upon existing ones. These scores will incorporate geriatric factors (for example, frailty, disability and cognitive impairment) and will be developed to predict quality of life outcomes, not just mortality.

Increased use of biomarkers

Biomarkers have not been widely utilized in the management of patients with AS. Natriuretic peptides, such as BNP, are somewhat of an exception, but their role in management decisions has not been clearly defined[3;4]. In the coming years, there will be more specific cut-offs of natriuretic peptide levels to guide management decisions[187]. High sensitivity cardiac troponin will be more routinely integrated into our evaluation of patients with AS[194]. Increasingly, as in non-AS heart failure populations, a multimarker approach will be taken to measure diverse biological pathways in a more integrated manner to gain insight into ventricular health and systemic factors that might affect clinical outcomes and influence management strategies regarding valve replacement and adjunctive therapies[198].

Tailored management strategies for AVR

Treatment decisions will become more personalized regarding when, whether and how to perform valve replacement. Previously, management decisions were largely conceptualized

in terms of the severity of AS and the presence or absence of symptoms. Phenotyping and risk stratification has and will become more sophisticated, allowing for more nuanced management decisions. The LV response to a given degree of pressure overload, systemic factors, biomarkers, patient symptoms and operative risk will be integrated alongside an assessment of AS severity to influence management strategies regarding valve replacement.

In the near future, the realization of randomized trials might pave the way for new indications for AVR. The trials that should be considered a priority by the cardiology community include: early ‘prophylactic’ AVR versus a watchful waiting strategy in asymptomatic patients with severe AS; and TAVR combined with heart failure therapy versus heart failure therapy alone in patients with moderate AS, low LVEF and heart failure symptoms (Table 4). Also, the data from the ongoing and future trials will help to better individualize the type of AVR according to the baseline risk profile of patients. Results from some recent studies suggest that TAVR might be preferable to surgical AVR in patients with diabetes, chronic obstructive pulmonary disease, pulmonary hypertension, small aortic annulus and low-flow, low-gradient AS[262–266].

Interventions after AVR to improve clinical outcomes

Given that AS is conceptualized as a mechanical problem (valve obstruction) in need of a mechanical solution (valve replacement), it is common to view the problem or disease of AS as ’fixed or solved’ after the valve is replaced, with little attention directed toward strategies and interventions that might improve clinical outcomes in the post-valve replacement period. We anticipate that there will be a growing recognition of factors that impair an optimal clinical outcome in patients with AS after valve replacement, with interventions identified that might improve these outcomes. These might include interventions such as adjunctive medical therapies (for example, anti-fibrotic and anti-hypertrophic agents) to improve LV reverse remodelling and function or lifestyle interventions targeting frail patients undergoing TAVR.

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Box 1

Key measurements and tools used for AS assessment

- Aortic valve area (AVA): surface of the aortic valve orifice. It can be measured by Doppler echocardiography, left heart catheterization, or cardiac magnetic resonance.
- Aortic valve calcium density: aortic valve calcium score measured by computed tomography divided by the cross-section area of the aortic annulus measured by echocardiography or computed tomography. It is expressed in Agatston unit per cm^2.
- Carotid upstroke: The pulse pressure of the carotid artery that can be assessed at the level of the neck is characterized by a smooth, relatively rapid upstroke and a smooth, more gradual downstroke. In patients with severe aortic stenosis, the carotid upstroke is delayed.
- Circumferential function: circumferential contraction of the LV wall that is in large part driven by the myocytes located in the mid portion of the LV wall.
- Class of recommendation for the procedure (aortic valve replacement in the case of AS): Class I: the benefit of the procedure largely outweigh the risk and the procedure should be performed; Class IIa: it is reasonable to perform the procedure; Class IIb: the procedure may be considered; Class III: the procedure is not recommended because it is not useful and may be harmful.
- Coronary flow reserve: the maximum increase in blood flow through the coronary arteries above the normal resting flow. The coronary flow reserve can be measured by cardiac catheterization, Doppler-echocardiography or positron emission tomography. The normal coronary flow reserve is 3 to 4. In patients with AS the coronary flow reserve is reduced. When the ratio is 1, the coronary flow reserve is exhausted.
- Dobutamine stress echocardiography: echocardiography performed during intravenous infusion of dobutamine, which increases cardiac contractility and flow across the aortic valve.
- Mean transvalvular gradient (mean gradient): average value of the pressure loss (or gradient) across the aortic valve. This corresponds to the difference between the pressure in the LV cavity versus that in the aorta. The mean gradient can be measured by Doppler echocardiography of by left heart catheterization.
- Left ventricular afterload: pressure in the wall of the left ventricle during ejection

- Left ventricular ejection fraction (LVEF): measurement of how much blood is being pumped out of the left ventricle of the heart. It is calculated as the percent decrease in the volume of the LV cavity. It can be measured by echocardiography, angiography, or cardiac magnetic resonance.
- Left ventricular longitudinal function: longitudinal (i.e. long-axis direction) contraction of the LV wall that is in large part driven by the myocytes located in the subendocardial layer of the LV wall.
- Longitudinal strain: percent shortening of the LV wall in the longitudinal axis during systole. The longitudinal strain is measured by speckle tracking echocardiography.
- Peak aortic jet velocity: peak value of the blood flow velocity across the aortic valve. The blood velocity is measured by continuous-wave Doppler.
- Radial function: longitudinal (i.e. short-axis direction) contraction of the LV wall that is in large part driven by the myocytes located in the mid-wall layer of the LV wall.
- Stress AVA: AVA measured by Doppler echocardiography during dobutamine or exercise stress.
- Stress mean gradient: mean gradient measured by Doppler echocardiography during dobutamine or exercise stress.
- Stroke volume index: stroke volume (i.e. volume of blood ejected by the heart during systole) indexed to (divided by) the patient’s body surface area.
- Transvalvular velocity: blood flow velocity across the aortic valve.

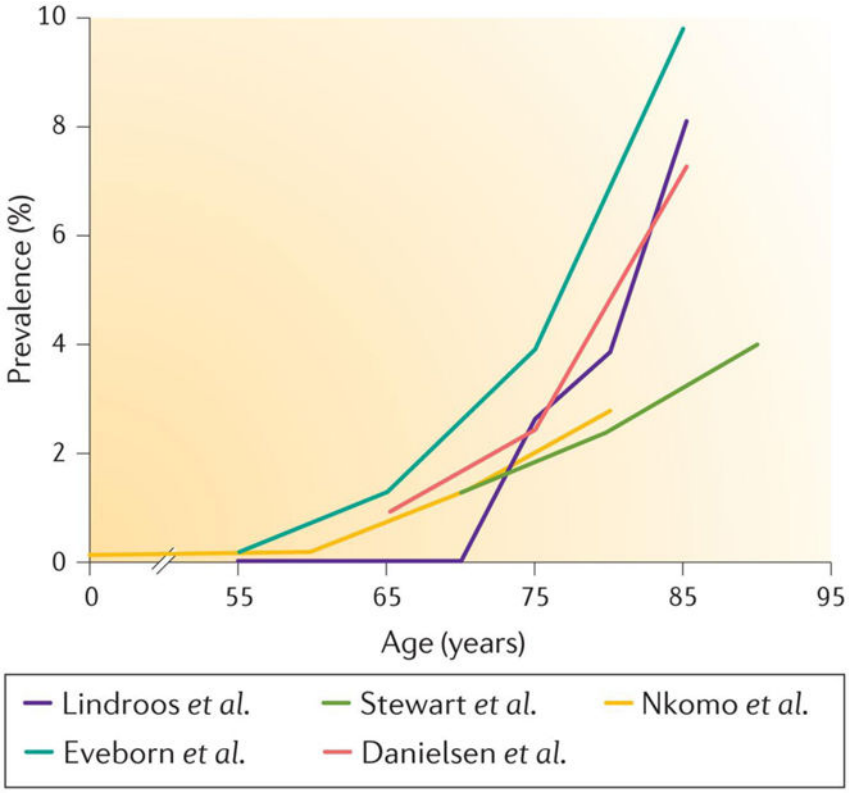

Figure 1. The prevalence of aortic stenosis as a function of age

The prevalence of aortic stenosis (AS) according to age in the following population-based series from the USA or Europe: Lindroos et al. (Finland)[14], in which AS was defined as an aortic valve area of < 1.2 cm^2; Stewart et al. (Cardiovascular Health Study, USA)[9], in which AS was defined as a peak aortic jet velocity of > 2.5 m per sec; Nkomo et al. (USA)[12], in which AS was defined as an aortic valve area of < 1.5 cm^2; Eveborn et al. (Tromsø Study, Norway)[13], in which AS defined was as a mean gradient of ≥ 15 mmHg; Danielsen et al. (AGES-Reykjavik Study, Iceland)[15], in which AS was defined as an indexed aortic valve area of ≤ 0.6 cm^2 per m^2.

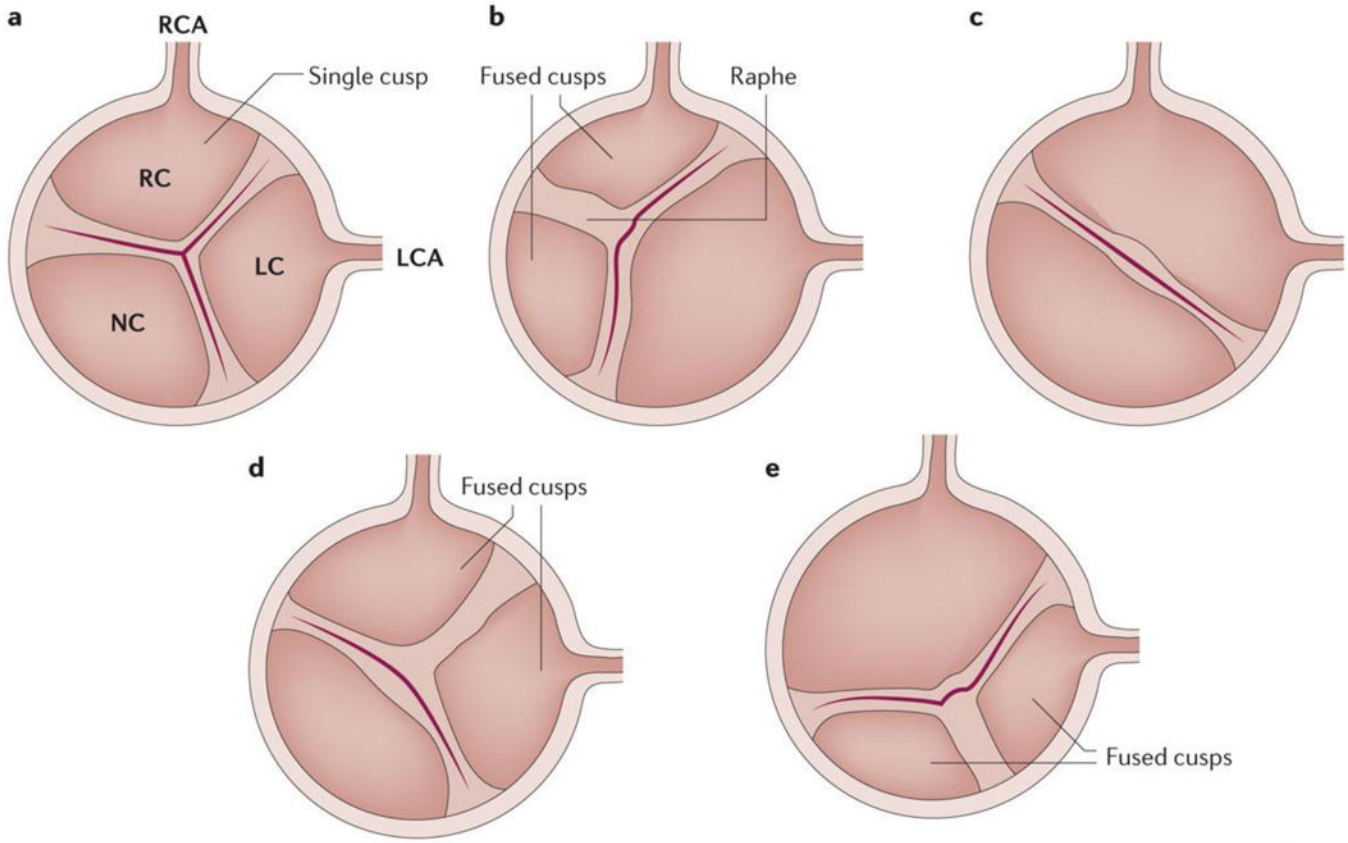

Figure 2. Comparison of tricuspid and bicuspid aortic valve structures

Schematic representation of A) a normal — tricuspid — aortic valve with the 3 cusps, B) a bicuspid valve with right-left coronary cusp fusion and one raphe (the line of union between the fused cups), C) a bicuspid valve with fusion of the right-left coronary cusps and no raphe, D) a bicuspid valve with right-non coronary cusp fusion and one raphe and E) a bicuspid valve with fusion of the left-non coronary cups and one raphe. LC, left coronary; LCA, left coronary artery; NC, non-coronary; RC, right coronary; RCA, right coronary artery.

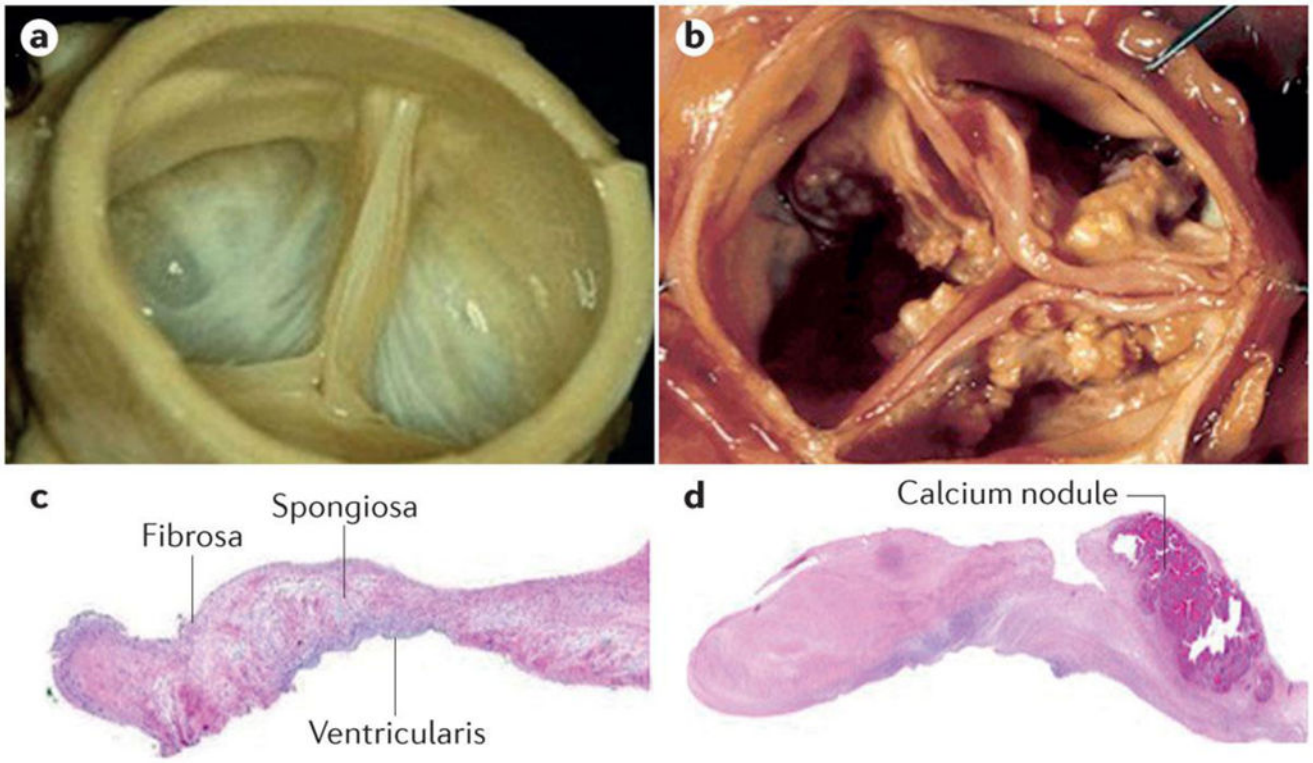

Figure 3. Macroscopic and histopathologic appearance of normal and abnormal aortic valves

Photographs of A) a normal aortic valve and B) an aortic valve with severe calcific aortic stenosis (AS). C) Histopathologic section of normal aortic valve with hematoxylin staining showing the trilaminar structure of the valve from top to bottom. D) Histopathologic section of a valve with severe calcific AS with hematoxylin staining showing the presence of fibrotic material (pink) and calcified nodule. The tissue is thickened by the excess of fibrotic material and the calcified nodule, located in the fibrosa, contributes to alter the normal architecture of the leaflet.

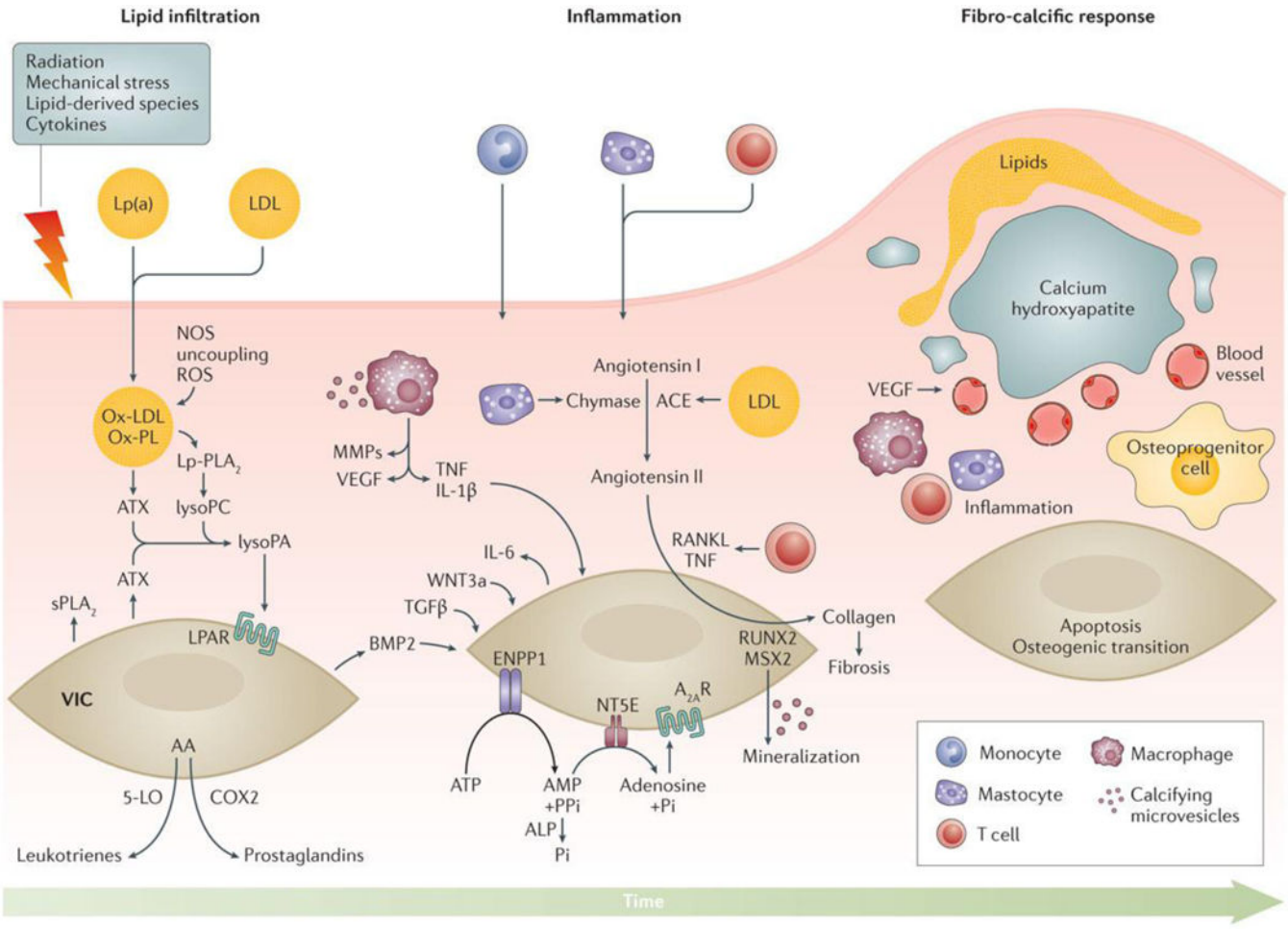

Figure 4. Pathogenesis of calcific aortic stenosis

Endothelial damage allows infiltration of lipids, specifically low density lipoprotein (LDL) and lipoprotein(a) (Lp(a)) into the fibrosa and triggers the recruitment of inflammatory cells into the aortic valve. Endothelial injury can be triggered by several factors including lipid-derived species, cytokines, mechanical stress and radiation injury. The production of reactive oxygen species (ROS) is promoted by the uncoupling of nitric oxide synthase (NOS), which increases the oxidation of lipids and further intensifies the secretion of cytokines. Enzymes transported in the aortic valve by lipoproteins (LDL and LP(a)) such as Lp-PLA2 and autotaxin (ATX) produce lysophospholipid derivatives. ATX, which is also secreted by valve interstitial cells (VICs), transforms lysophosphatidylcholine (LysoPC) into lysophosphatidic acid (LysoPA). Several factors including LysoPA, the receptor activator of nuclear factor kappa-B ligand (RANKL) and Wnt3a promote the osteogenic transition of VICs. Arachidonic acid (AA) generated by cytosolic PLA2 promotes the production of eicosanoids (prostaglandins and leukotrienes) through the cyclooxygenase 2 (COX2) and 5-lipoxygenase (5-LO) pathways respectively. In turn, eicosanoids promote inflammation and mineralization. Chymase and angiotensin converting enzyme (ACE) promote the production of angiotensin II, which increases the synthesis and secretion of collagen by VICs. Owing to increased production of matrix metalloproteinases (MMPs) and decreased synthesis of tissue

inhibitors of metalloproteinases (TIMPs), disorganized fibrous tissue accumulates within the aortic valve. Microcalcification begins early in the disease, driven by microvesicles secreted by VICs and macrophages. In addition, overexpression of ecto-nucleotidases (NPP1, 5′-NT, ALP) promotes both apoptosis and osteogenic-mediated mineralization. Bone morphogenetic protein 2 (BMP2) entrains osteogenic transdifferentiation, which is associated with the expression of bone-related transcription factors (RUNX2 and MSX2). Osteoblast-like cells subsequently coordinate calcification of the aortic valve as part of a highly regulated process analogous to skeletal bone formation. Deposition of mineralized matrix is accompanied by fibrosis and neovascularization, which is abetted by vascular endothelial growth factor (VEGF). In turn, neovascularization increases the recruitment of inflammatory cells and bone marrow-derived osteoprogenitor cells.

IL-1β, interleukin-1–β; Lp(a), lipoprotein (a); LDL, low-density lipoprotein; OxPL, oxidized phospholipid; TGF-β transforming growth factor beta; NPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; 5′-NT, 5′ nucleotidase; ALP, alkaline phosphatase.

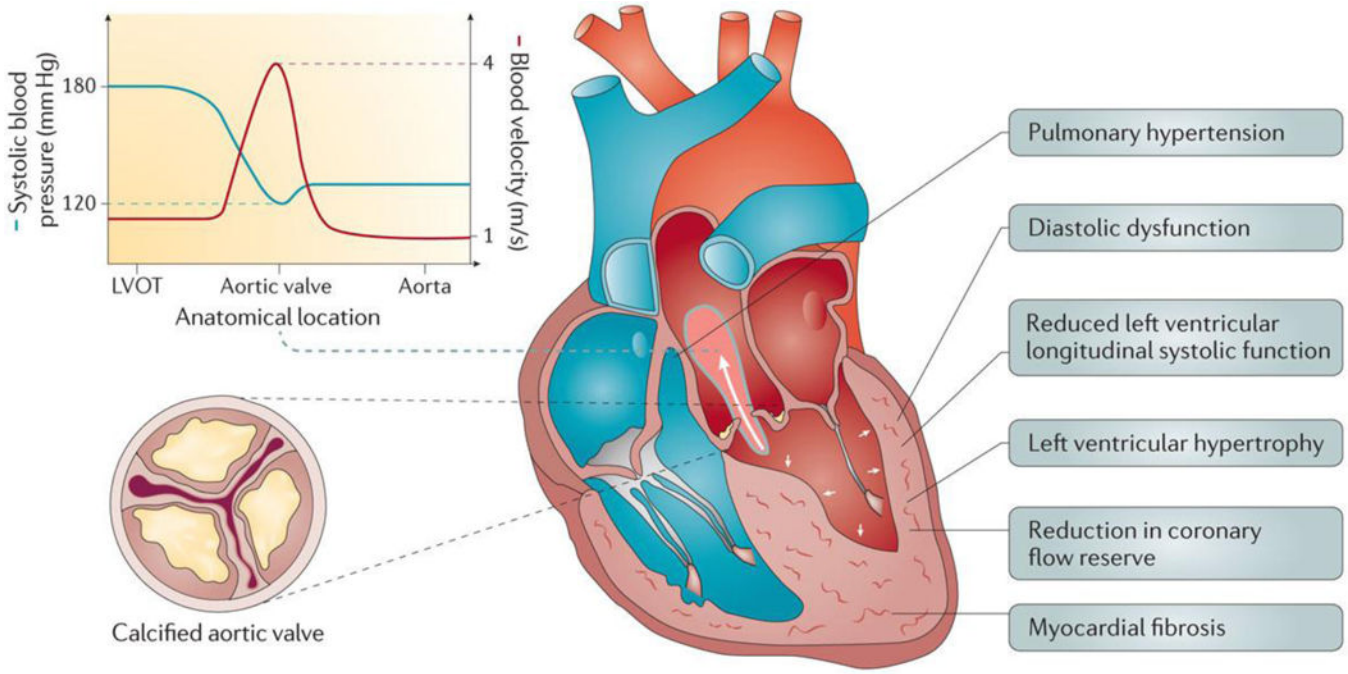

Figure 5. Maladaptive remodelling and impaired function of the left ventricle in response to pressure overload from AS

The narrowing of the aortic valve orifice causes an acceleration of the blood flow velocity with a concomitant decrease in systolic blood pressure between the left ventricular (LV) outflow tract (LVOT) and the aorta. The increased LV pressure imposed by AS results in LV hypertrophy (augmentation of the LV myocardial mass), reduced coronary flow reserve, myocardial fibrosis, diastolic dysfunction and decreased longitudinal systolic shortening, although the ejection fraction remains normal in most patients. Left atrial enlargement is common owing to elevated LV filling pressures. The latter often leads to secondary pulmonary hypertension and right ventricular dysfunction in the more advanced stages of the disease.

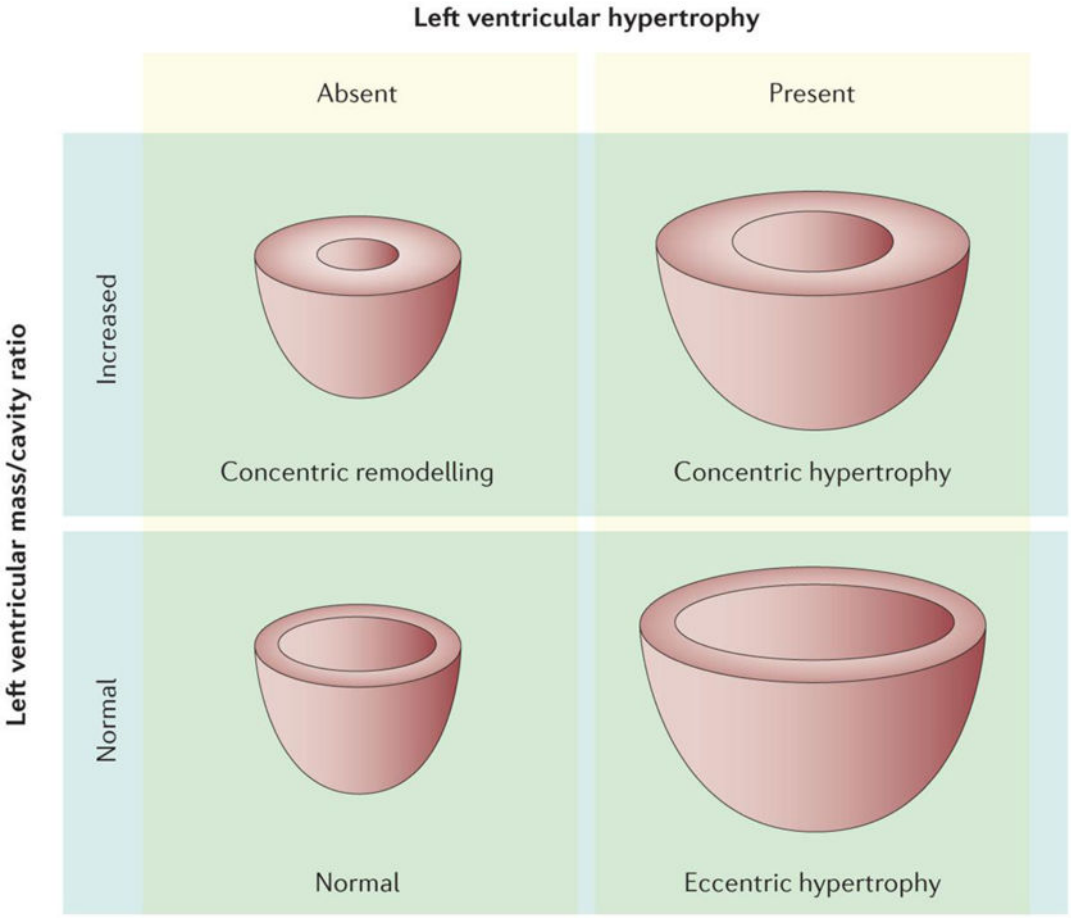

Figure 6. Patterns of left ventricular remodelling

Four left ventricular (LV) remodelling patterns can be defined according to the left ventricular mass and the ratio of the LV mass to the LV cavity size: Normal pattern: both LV mass and mass/cavity ratio are normal; Concentric remodelling: the LV mass is normal but the mass/cavity ratio is increased (thick LV walls with small cavity); Concentric hypertrophy: both LV mass and mass/cavity ratio are increased; Eccentric remodelling: LV mass is increased but the mass/cavity ratio is normal (thickness of LV walls is normal or slightly increased and the LV cavity is enlarged). Reproduced with permission from[267]

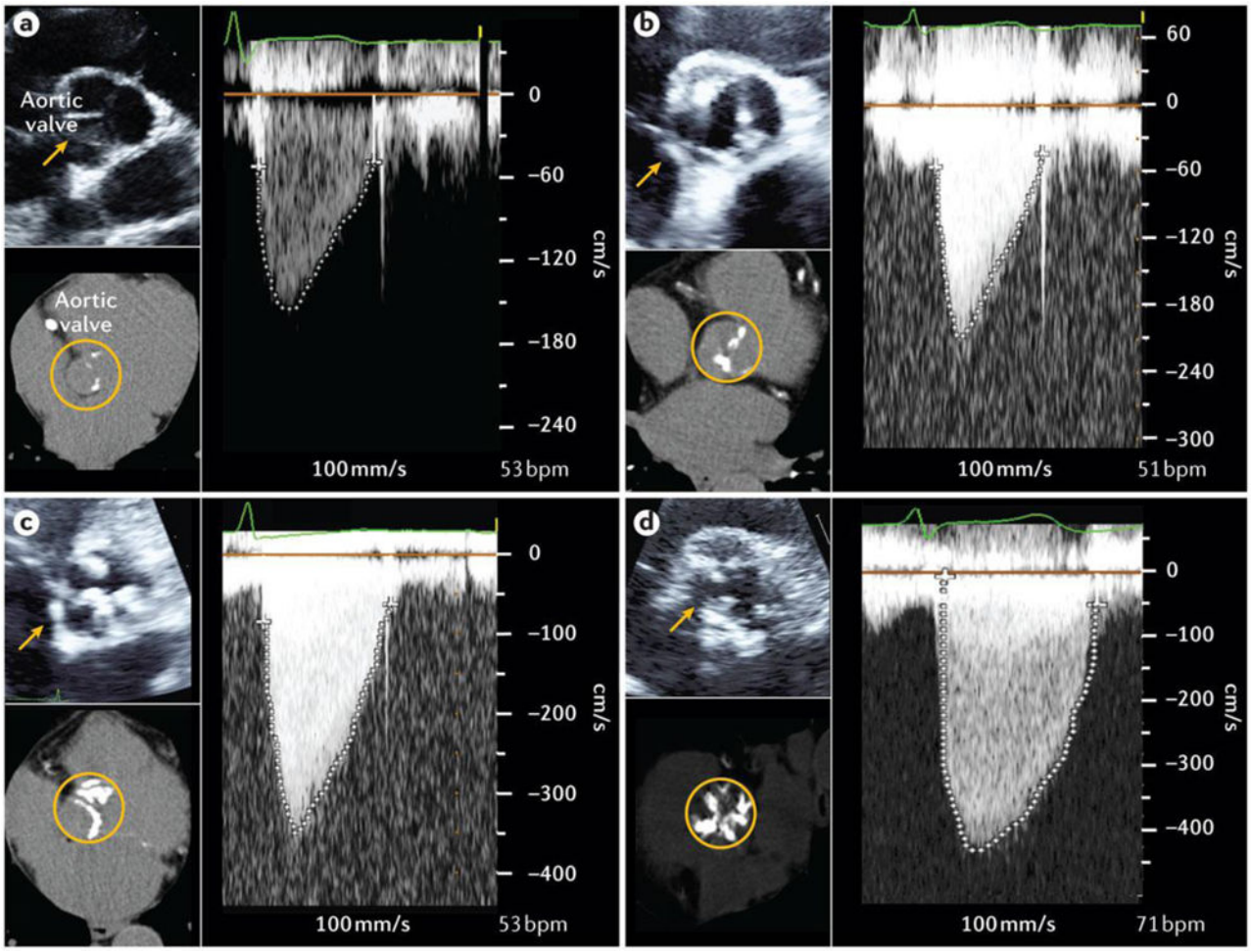

Figure 7. Assessment of aortic stenosis severity by Doppler-echocardiography

For each degree of disease severity including aortic valve sclerosis (A), mild aortic stenosis (AS) (B), moderate AS (C), and severe AS (D), this figure shows a 2D echocardiographic short-axis view of the aortic valve (top left), the transvalvular velocity by continuous-wave Doppler (right), and the multidetector computed tomography (MDCT) view of aortic valve calcification (bottom left). In the patient with aortic sclerosis (A), there are some small isolated spots of calcification (appears white on the MDCT images) in the aortic valve leaflets but there is no obstruction to blood flow (i.e. no stenosis). The peak aortic jet velocity (1.47 m/s), mean gradient (5 mmHg) and aortic valve area (AVA: 2.87 cm^2) are normal. In the patient with mild AS (B), there is mild aortic valve calcification with mild obstruction to blood flow. The peak aortic jet velocity is 2.08 m/s, mean gradient: 9 mmHg, and AVA: 1.62 cm^2. In the patient with moderate AS (C), there is more extensive aortic valve calcification with moderate obstruction of blood flow: peak aortic jet velocity: 3.51 m/s, mean gradient: 28 mmHg, and AVA: 1.21 cm^2. In the patient with severe AS (D), there is severe aortic valve calcification and severe obstruction to blood flow: peak aortic jet velocity: 4.35 m/s, mean gradient: 48 mmHg, and AVA: 0.75 cm^2.

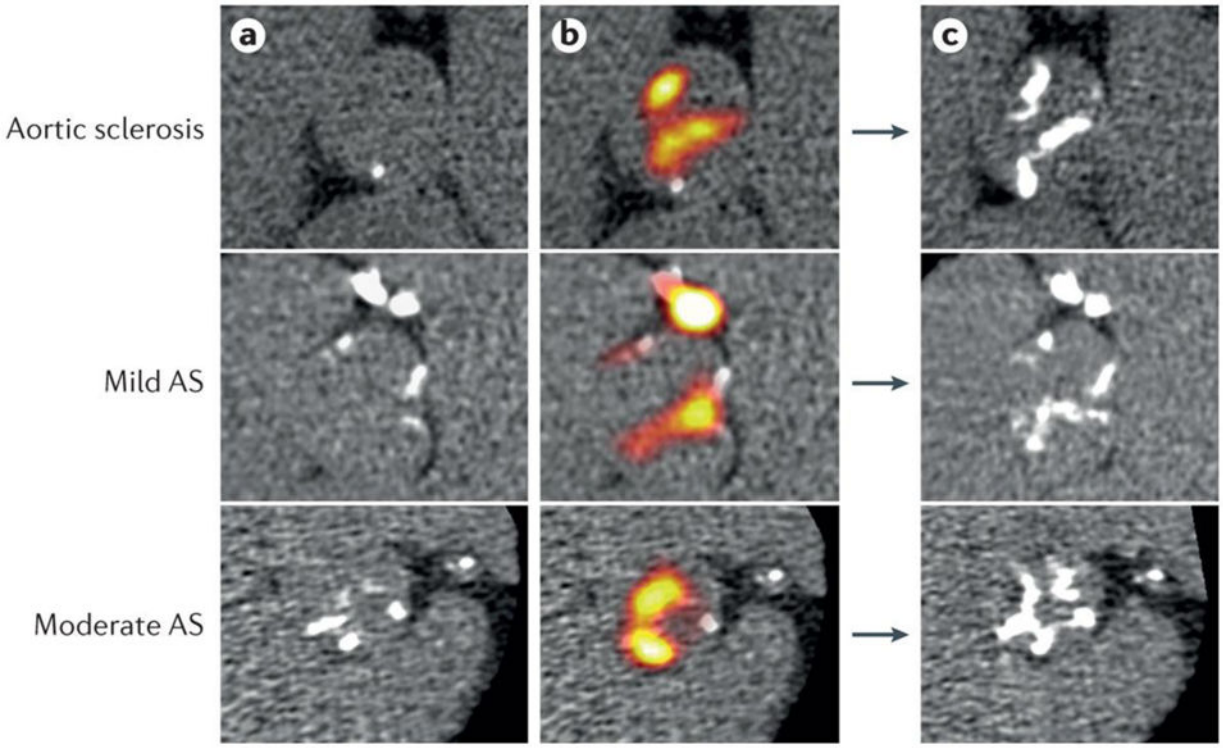

Figure 8. Assessment of aortic valve mineralization activity by positron emission tomography – computed tomography

Coaxial short axis views of the aortic valve from one patient with aortic sclerosis, one patient with mild aortic stenosis and one patient with moderate aortic stenosis. Left panels: baseline multi-detector computed tomography (MDCT) images of the aortic valve; regions of macrocalcification appear white. Middle panels: baseline fused MDCT and ^{18}F-sodium fluoride (NaF) positron emission tomography (PET) images showing intense 18F-NaF uptake (red yellow areas) both overlying and adjacent to existing calcium deposits on the MDCT. Right panels: One-year follow-up (without intervention) MDCT images demonstrate increased calcium accumulation in much the same distribution as the baseline PET activity. Reproduced with permission from[172].

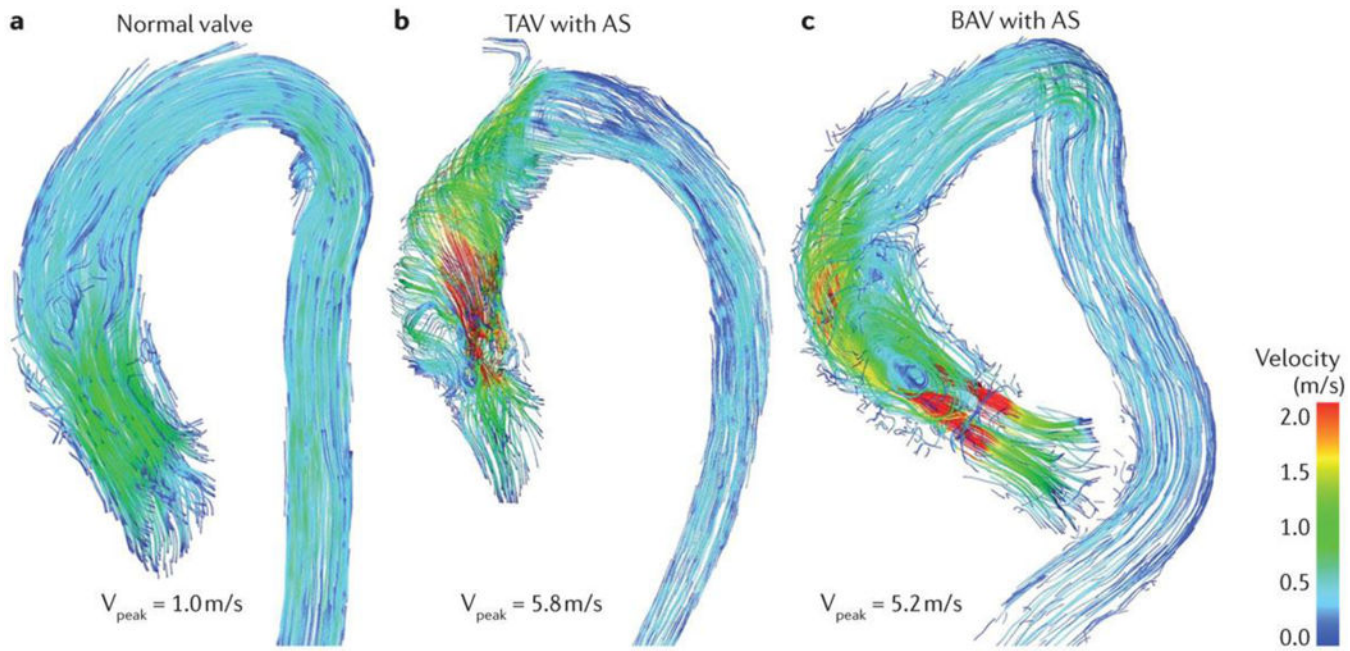

Figure 9. Assessment of flow patterns in the Aorta by 4D flow cardiac magnetic resonance according to aortic valve phenotype

(A) A normal valve systolic flow in a healthy control. (B) A tricuspid aortic valve (TAV) with severe aortic stenosis (AS) and altered systolic flow with helical patterns in the ascending aorta. (C) A bicuspid aortic valve (BAV) with right-left (RL) cusp fusion and severe AS. Altered blood flow with asymmetric helical flow patterns are observed in the proximity of the aortic valve. Courtesy of Julio Garcia, Alex Barker and Michael Markl, Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.

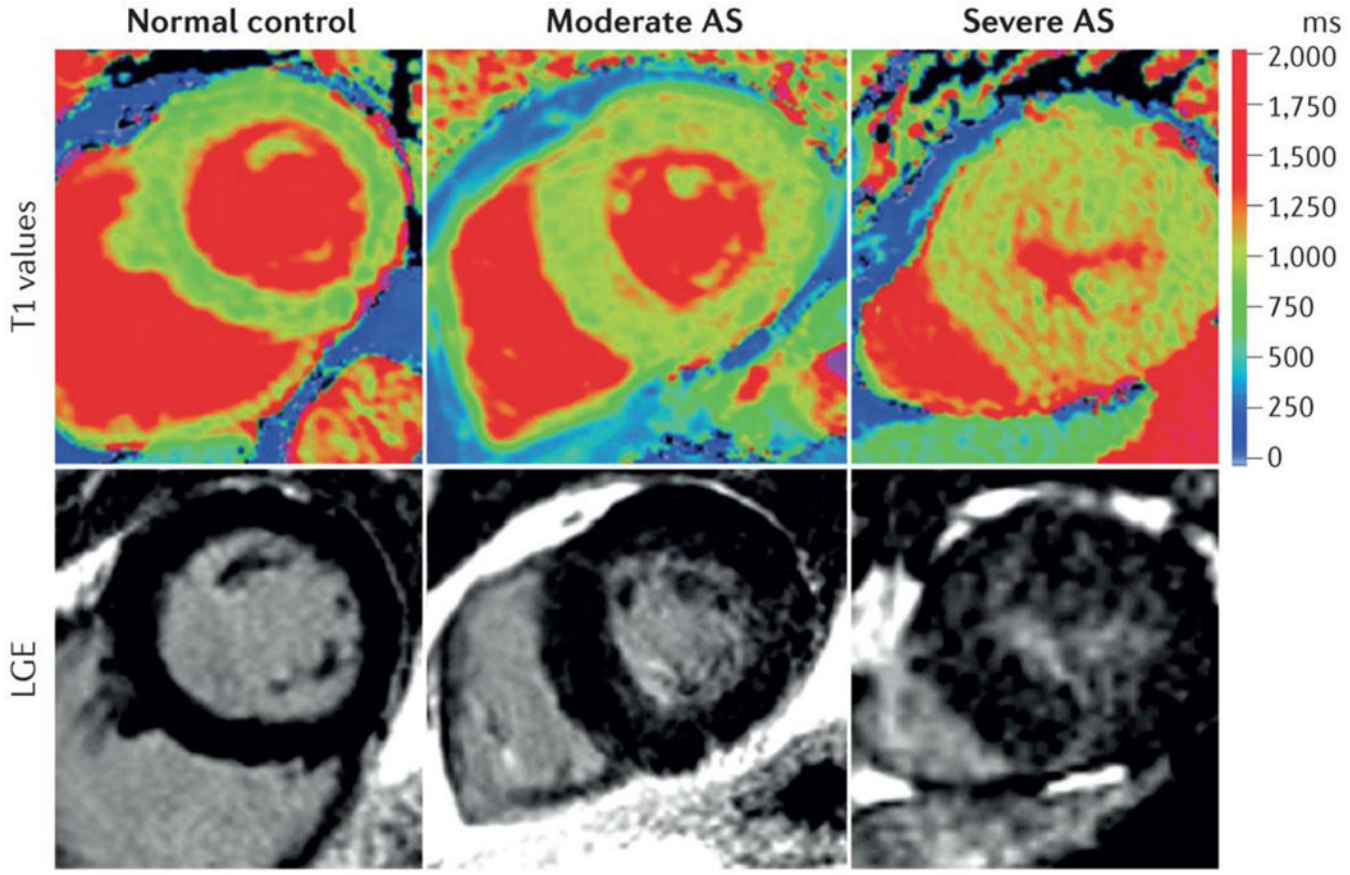

Figure 10. Assessment of myocardial fibrosis by cardiac magnetic resonance in patients with aortic stenosis

Top panel: colour maps of T1 values using shortened modified Look–Locker inversion in a mid-ventricular short-axis slice; bottom panel: the corresponding slice with late gadolinium enhancement (LGE) imaging. The left panel shows a normal volunteer. The middle panels show moderate aortic stenosis (AS) with moderate left ventricular hypertrophy. The right panel shows severe AS with severe LV hypertrophy. Regions with high T1 values (orange and red) within the LV wall correspond to myocardial fibrosis. Reproduced with permission from Bull et al.[268].

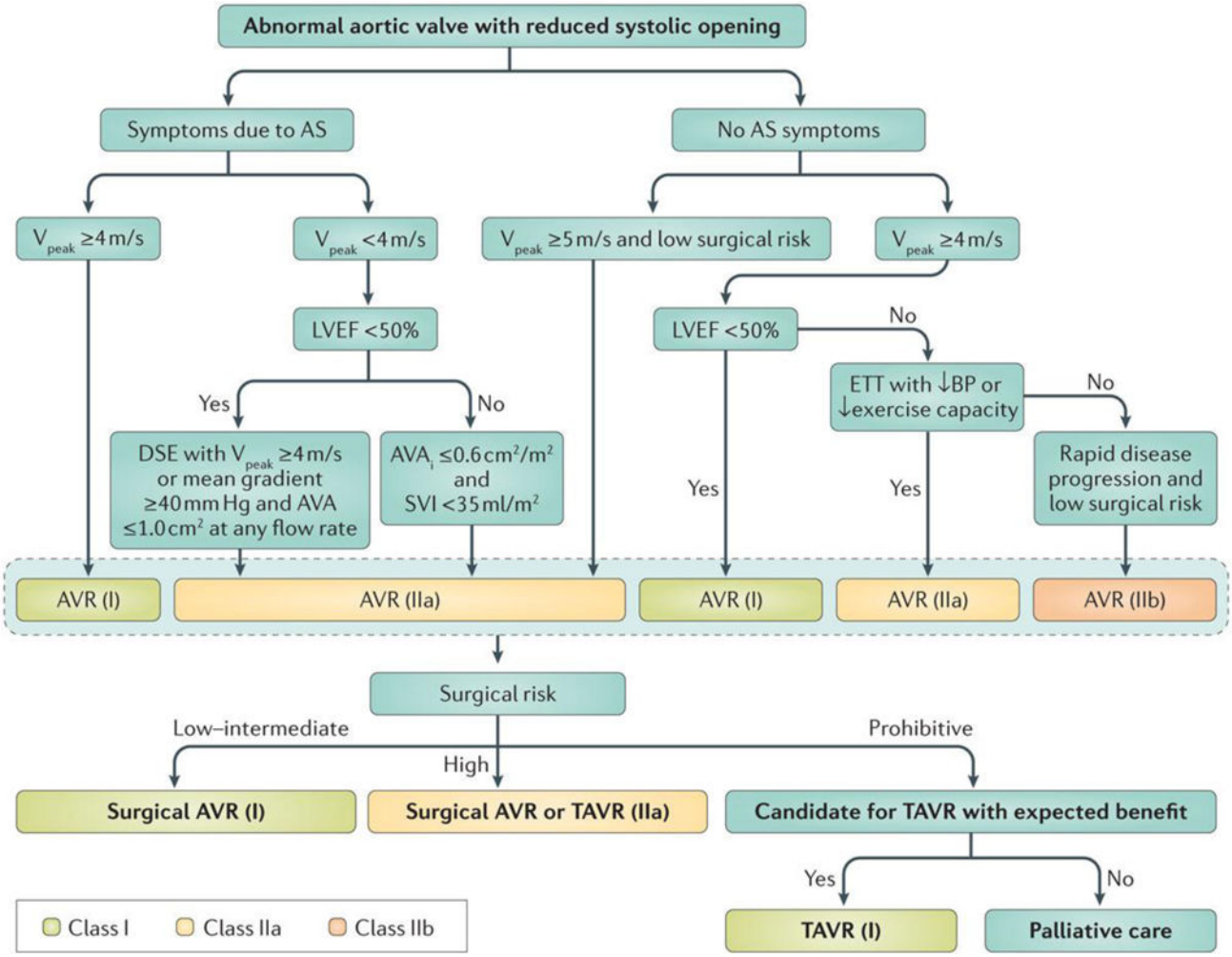

Figure 11. Algorithm for the management of aortic stenosis

This figure presents the algorithm recommended by the 2014 ACC/AHA guidelines for the management of aortic stenosis[3]. AS:, aortic stenosis; AVA, aortic valve area; AVAi, AVA indexed for body surface area; BP, blood pressure; AVR, aortic valve replacement; ETT, exercise treadmill test; LVEF, LV ejection fraction; SVi, stroke volume index; TAVR, tr anscatheter AVR; V_{Peak}, peak aortic jet velocity.

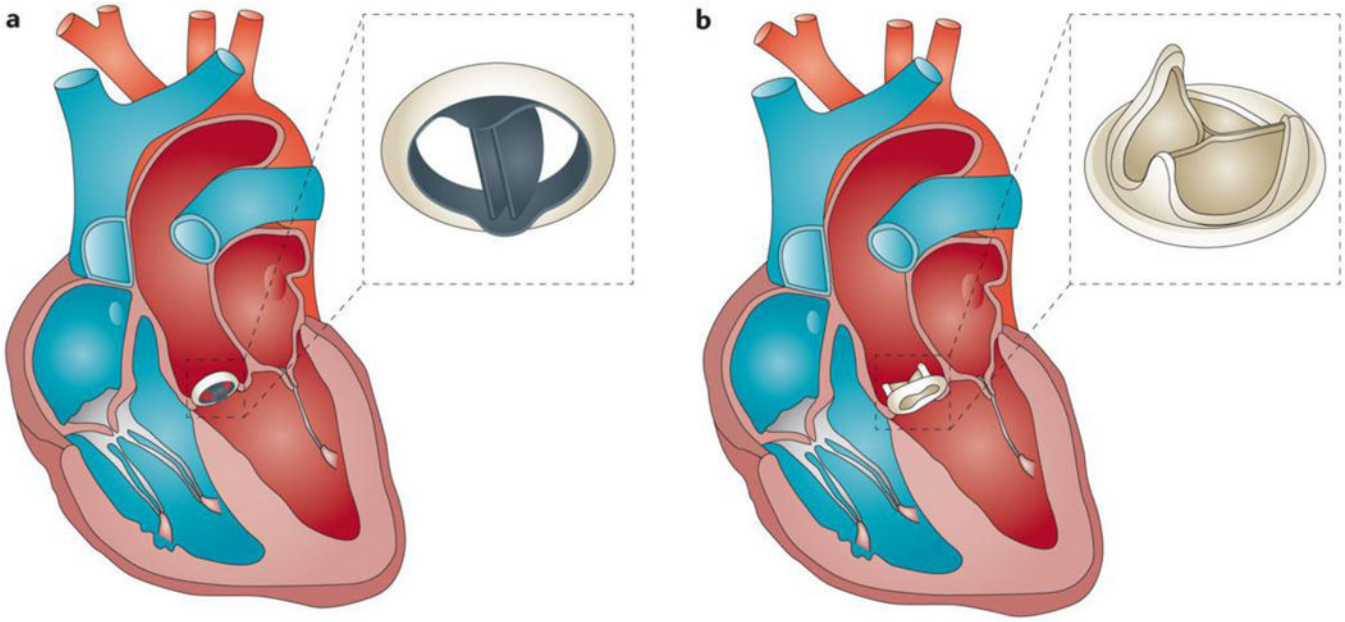

Figure 12. Different types of surgical aortic valve replacement

(A) Surgical aortic valve replacement with a bileaflet mechanical valve. (B) Surgical aortic valve replacement with a bioprosthetic valve.

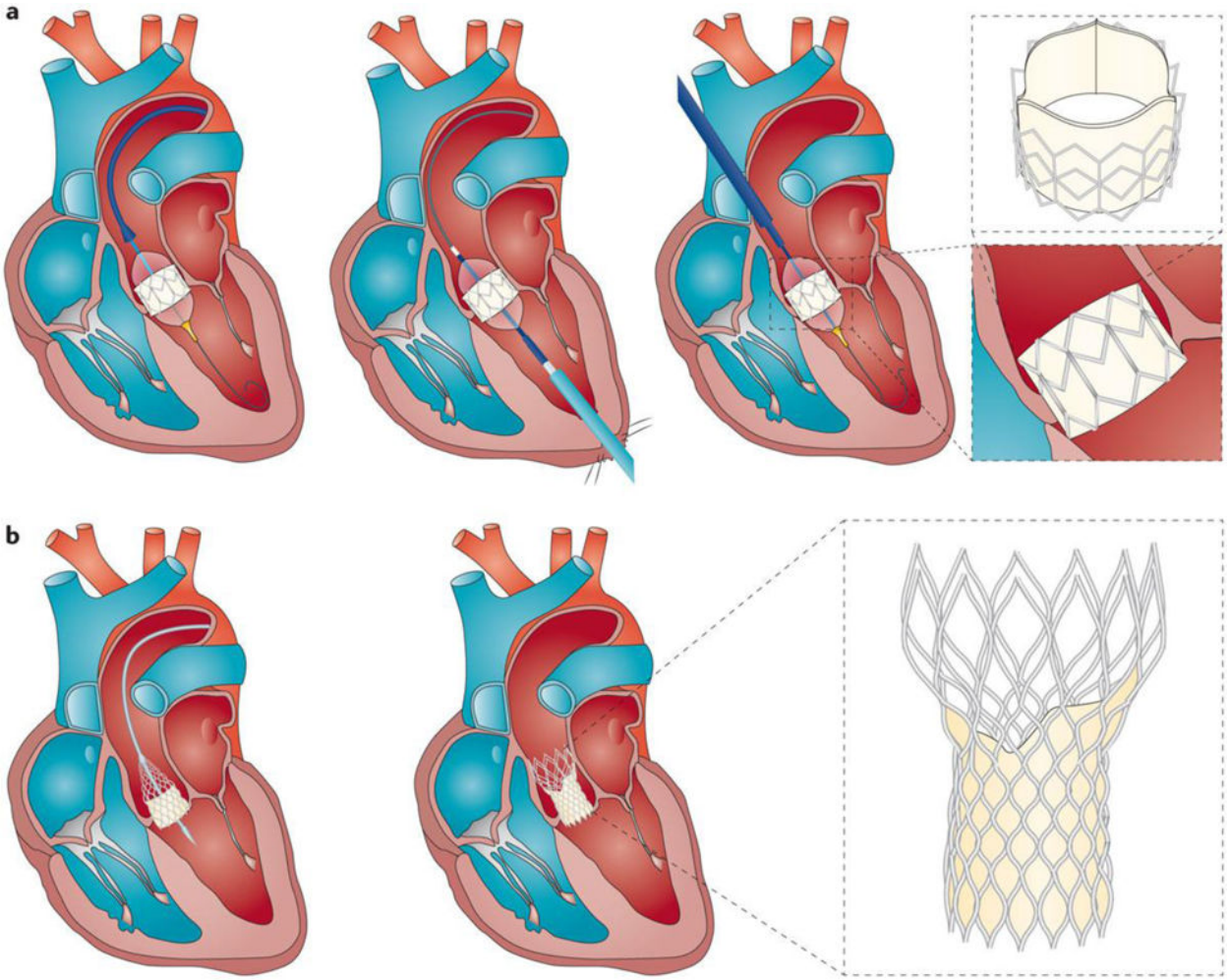

Figure 13. Different types of transcatheter aortic valve replacement

(A) Transcatheter aortic valve replacement with a balloon expandable valve via the transfemoral, transapical or transaortic approach. (B) Transcatheter aortic valve replacement with a self-expanding valve via the transfemoral approach.

Table 1

Disease progression stages in calcific aortic stenosis

Disease Stage	Sub-stage	Description	Management
At risk of AS	N/A	• Bicuspid aortic valve (or other congenital valve anomaly) aortic valve sclerosis • No obstruction to blood flow • No symptoms	• Clinical and echocardiographic follow-up every 3–5 years • No indication of AVR
Mild or moderate AS	N/A	• Mild-to-moderate leaflet calcification of a bicuspid valve or tricuspid valve with some reduction in systolic motion • Mild or moderate AS * • Early LV diastolic dysfunction might be present, normal LVEF • No symptoms	• Clinical and echocardiographic follow-up every 3–5 years for mild AS and every 1–2 years for moderate AS • No indication of AVR
Severe AS	Asymptomatic severe AS with normal LV systolic function	• Severe leaflet calcification or congenital stenosis with a severely reduced leaflet opening • Severe AS * • LV diastolic dysfunction, normal LVEF • No symptoms	• Clinical and echocardiographic follow-up every 6–12 months • Indication of AVR (Class IIa) if stenosis is very severe * and low surgical risk
	Asymptomatic severe AS with LV systolic dysfunction	• Severe leaflet calcification or congenital stenosis with a severely reduced leaflet opening • Severe AS * • LVEF of <50% • No symptoms	• Indication of AVR (Class I)
	Symptomatic severe high-gradient AS	• Severe leaflet calcification or congenital stenosis with a severely reduced leaflet opening • Severe AS with high gradient * • LV diastolic dysfunction, impaired LV longitudinal systolic function and pulmonary hypertension may be present • Symptoms: exertional dyspnoea, angina, syncope or pre-syncope and decreased exercise tolerance	• Indication of AVR (Class I)

Disease Stage	Sub-stage	Description	Management
	Symptomatic low-flow, low-gradient severe AS with preserved LVEF	• Severe leaflet calcification or congenital stenosis with a severely reduced leaflet opening • Severe AS with low gradient * • Small LV cavity with pronounced concentric remodelling and restrictive diastolic filling, normal LVEF • Symptoms: heart failure, angina, syncope or pre-syncope	• Indication of AVR (Class IIa)
	Symptomatic low-flow, low-gradient severe AS with deduced LVEF	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening • Severe AS with low gradient * • LV diastolic dysfunction, LVEF of <50% • Symptoms: heart failure, angina, syncope or pre-syncope	• Indication of AVR (Class IIa; Class IIb if no LV flow reserve)

Indication of AVR: Class I: AVR should be performed; Class IIa: AVR is reasonable; Class IIb: AVR may be considered.

* See Table 2 for definitions. AS, aortic stenosis; AVR, aortic valve replacement; LV, left ventricular; LVEF, LV ejection fraction.

Table 2

Parameters and criteria for the assessment of aortic stenosis severity

Technique	Parameter	Aortic Sclerosis	Mild AS	Moderate AS	Severe AS	Very Severe AS	Low Gradient Severe AS
Doppler-echocardiography	Peak aortic jet velocity (V_{Peak})	< 2 m/s	2 – 3 m/s	3 – 4 m/s	≥ 4 m/s	≥ 5 m/s	< 4 m/s
	Mean gradient ΔP_{Mean}	<10 mmHg	10 – 19 mmHg	20 – 39 mmHg	≥ 40 mmHg	≥ 50 mmHg	<40 mmHg
	Aortic Valve Area (AVA=SV_{LVOT}/VTI_{Ao})	> 2.0 cm^2	1.6 – 2.0 cm^2	1.1 – 1.5 cm^2	≤1.0 cm^2	≤0.6 cm^2	≤1.0 cm^2
	Indexed AVA (AVAi=AVA/BSA)	> 1.2 cm^2/m^2	1.0 – 1.2 cm^2/m^2	0.7 – 0.9 cm^2/m^2	≤0.6 cm^2/m^2	≤0.45 cm^2/m^2	≤0.6 cm^2/m^2
Dobutamine stress echocardiography	Stress mean gradient	NA	NA	NA	NA	NA	≥ 40 mmHg
	Stress AVA	NA	NA	NA	NA	NA	≤1.0 cm^2
MDCT	Aortic valve calcification score	NA	NA	Men ≥1200 AU Women ≥700 AU	Men ≥2000 AU Women ≥1200 AU	NA	Men ≥2000 AU Women ≥1200 AU

AVA, aortic valve area; AVAi, indexed AVA; BSA, body surface area; ΔP_{Mean}, mean transvalvular gradient; MDCT, multidetector computed tomography; SV, stroke volume; V_{Peak}, peak aortic jet velocity; VTI_{Ao}, velocity-time integral of the transvalvular flow; NA, not applicable or not available.

Table 3

Key management decisions when selecting a technique and prosthetic valve for aortic valve replacement.

AVR technique or valve type	Indication	Contra-indication	Advantages	Limitations
Surgical AVR	Indication of AVR Low to high surgical risk	Prohibitive surgical risk Life expectancy < 1 year	Standard therapy with well-established record of safety, efficacy and durability	Invasive
Surgical AVR with biological valve	Patient preference Achievement of good anticoagulation unlikely Age > 65 years	Life expectancy < 1 year	Does not require anticoagulation	Limited long-term durability
Surgical AVR with mechanical valve	Patient preference Patients already on anticoagulation	Life expectancy < 1 year	Long-term durability	Requires life-time anticoagulation (increased risk of bleeding)
Transcatheter AVR *	Indication of AVR High or prohibitive surgical risk	Life expectancy < 1 year	Less invasive than surgical AVR	Long-term durability unknown Higher risk of paravalvular AR

* With balloon-expandable or self-expanding valves.

AR, aortic regurgitation; AVR, aortic valve replacement

Table 4

Completed, ongoing and future clinical trials on different AS of therapeutic procedures and strategies

Trial name	Patient population and surgical risk	Number of patients	Design	Intervention(s)	Endpoints and results	Status
PARTNER-IB[201;222;269]	Symptomatic Severe AS Inoperable	358	Randomized	TAVR (SAPIEN) vs. conservative management	1-year mortality: 30.7% TAVR vs. 49.7% conservative * 1-year mortality of Major Stroke: 33% TAVR vs. 50.3% conservative * 5-year mortality: 71.8% TAVR vs. 93.6% conservative *	Completed
PARTNER-IA[220;223;270]	Symptomatic Severe AS High risk	699	Randomized	TAVR (SAPIEN) vs. SAVR	30-day mortality: 3.4% TAVR vs. 6.5% SAVR 1-year mortality: 24.2% TAVR vs. 26.8% SAVR 1-year mortality or major stroke: 26.5% TAVR vs. 28% SAVR 5-year mortality: 67.8% TAVR vs. 62.4% SAVR	Completed
PARTNER-IIB[271]	Symptomatic Severe AS Inoperable	560	Randomized	TAVR (SAPIEN) vs. TAVR (SAPIEN-XT)	30-day mortality: 5.1% SAPIEN vs. 3.5 % SAPIEN-XT 1-year mortality: 23.3% SAPIEN vs. 22.3% SAPIEN-XT 1-year major stroke: 5.5% SAPIEN vs. 4.8% SAPIEN-XT	Completed
SAPIEN 3-HR[272;273]	Symptomatic Severe AS High risk/inoperable	583	Non-Randomized	TAVR (SAPIEN 3)	30-day mortality: 2.2% 30-day major stroke: 0.86% 1-year mortality: 14.4% 1-year major stroke: 2.4%	Ongoing
SAPIEN 3-IR[272]	Symptomatic Severe AS Intermediate risk	1076	Non-Randomized	TAVR (SAPIEN 3)	30-day mortality: 1.1% 30-day major stroke: 1.02%	Ongoing
CoreValve ER[224]	Symptomatic Severe AS Inoperable	509	Non-Randomized	TAVR (SAPIEN 3)	1-year mortality: 26 % 1-year major stroke: 2.3 %	Completed
CoreValve IR[221;274]	Symptomatic Severe AS Intermediate risk	750	Randomized	TAVR (CoreValve) vs. SAVR	1-year mortality: 19.1 % TAVR vs. 14.2 % SAVR * 1-year major stroke: 22.2 % TAVR vs. 28.6 % SAVR * 2-year mortality: 22.2 % TAVR vs. 28.6 % SAVR * 2-year major stroke: 22.2 % TAVR vs. 28.6 % SAVR *	Completed
CHOICE[275]	Symptomatic Severe AS Low risk	241	Randomized	TAVR (SAPIEN-XT) vs. SAVR (CoreValve)	30-day mortality: 4.1% (SAPIEN-X) vs. 4.3% (CoreValve) 30-day stroke: 5.8% (SAPIEN-XT) vs. 2.6% (CoreValve)	Completed

Trial name	Patient population and surgical risk	Number of patients	Design	Intervention(s)	Endpoints and results	Status
NOTION[276]	Symptomatic Severe AS Low risk	280	Randomized	TAVR vs. SAVR	1-year mortality: 4.9% TAVR vs. 7.5% SAVR 1-year all stoke: 2.9% TAVR vs. 4.6% SAVR	Completed
PARTNER-IIA[277]	Symptomatic Severe AS Intermediate risk	2000	Randomized	TAVR (SAPIEN-XT) vs. SAVR	Primary end-point: 2-year mortality or major stroke	Ongoing
SURTAVI[277]	Symptomatic Severe AS Intermediate risk	2500	Randomized	TAVR (CoreValve) vs. SAVR	Primary end-point: 2-year mortality or major stroke	Ongoing
TAVR-UNLOAD[277]	Moderate AS Low LVEF HF symptoms	600	Randomized	HF therapy alone vs. HF therapy plus TAVR	Primary end-point: hierarchical composite of 1-year death, stroke, HF hospitalization and quality of life	Future
AVATAR RECOVERY EARLY-TAVR[277]	Asymptomatic Severe AS	144–800	Randomized	Early AVR (SAVR and/or TAVR) vs. watchful waiting	Primary end-point: composite of death, stroke, myocardial infarction, HF hospitalization, LV systolic dysfunction and quality of life	Future

* Difference between groups is statistically significant.

AS, aortic stenosis; AVR, aortic valve replacement; HF, heart failure; LVEF, Left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; HF, heart failure.

Table 5

Comparison of TAVR access routes

Approach	Indication	Contra-indication	Advantages	Limitations
Transfemoral	Default approach for TAVR	Small, tortuous or calcified femoro-iliac arteries	Least invasive approach	Requires a minimal femoral and iliac artery diameter of 6–6.5 mm
Transapical (via the chest between the ribs)	Femoral and other vascular access not possible	LV aneurysm or thrombus Severe pulmonary disease * Severe LV systolic dysfunction *	Better control of the positioning of the valve	More invasive More myocardial injury More respiratory complications
Transaortic (via mini-sternotomy)	Femoral and other vascular access not possible Viable alternative to transapical	Complete porcelain aorta (rare)	Avoids manipulation and suturing of LV apex with potential resulting apical dysfunction	Requires a non-calcified area on the aorta for access and purse suture
Other approaches#	Alternative access routes in the context of severe peripheral artery disease	Unsuitable anatomy or size of the alternative artery	Provides an option to transfemoral that is potentially less invasive that transapical or transaortic	Depends on route (carotid approach may increase stroke risk; transcaval approach may have bleeding or damage to the aorta that is difficult to control)

*Relative contra-indication

#Left subclavian or axillary artery, carotid artery or transcaval route. LV, left ventricle; TAVR, transcatheter aortic valve replacement