The Impact of Antihypertensive Treatment on the Progression of Cardiac Dysfunction and Aortic Stenosis

Mémoire

Macarena Yamila López González

Maîtrise en sciences cliniques et biomédicales - avec mémoire
Maître ès sciences (M. Sc.)

Québec, Canada

© Macarena Yamila López González, 2021

The Impact of Antihypertensive Treatment on the Progression of Cardiac Dysfunction and Aortic Stenosis

Mémoire

Sous la direction de :

Marie-Annick Clavel, directrice de recherche

Philippe Pibarot, codirecteur de recherche

RÉSUMÉ

L'hypertension artérielle et la sténose aortique (SA) font partie des maladies cardiovasculaires qui sont le plus répandues dans les pays à revenus élevés. La SA affecte 2% des adultes de plus de 65 ans et son incidence augmente avec l'âge. L'hypertension est une comorbidité qui affecte de 30 à 80% des patients atteints de SA. Elle a un impact sur le développement et la progression de la SA. Chez les patients atteints des deux maladies, le ventricule gauche (VG) fait face à une double charge ce qui accélère son remodelage et sa perte de fonction. Ainsi, l'hypertension est associée à un mauvais pronostic chez les patients atteints de SA.

Jusqu'à aujourd'hui, il n'y a pas de traitement pharmacologique pour arrêter ou réduire la progression de la SA, la dysfonction systolique du VG et le remodelage ventriculaire conséquents à la maladie. Quelques études ont montré que les bloqueurs des récepteurs de l'angiotensine (BRA), qui sont un des traitements principaux de l'hypertension, peuvent avoir un impact bénéfique sur les mécanismes physiopathologiques de la SA et aussi un effet protecteur contre la dysfonction systolique du VG. Peu d'études ont évalué l'impact des BRA sur la progression de la SA et la dysfonction systolique du VG simultanément. De plus, aucun essai clinique n'a étudié les effets des traitements hypertenseurs par les BRA sur la progression de la SA ainsi que sur la dysfonction systolique du VG causée par ces deux maladies.

Par conséquent, l'**hypothèse principale** de ce projet de maîtrise est que les BRA réduisent la dysfonction systolique du VG chez les patients hypertendus atteints de SA.

L'**objectif principal** est de déterminer l'impact des traitements hypertenseurs (BRA) sur la progression de la dysfonction systolique du VG chez les patients hypertendus atteints de SA.

ABSTRACT

Hypertension and aortic stenosis (AS) are two cardiovascular diseases with elevated prevalence in high-income countries. AS affects 2% of adults over 65 years old and its incidence increases with age. Hypertension is a comorbidity that affects 30% to 80% of patients with AS. It has an impact on the development and the progression of AS. In patients with both diseases, the left ventricle (LV) faces a double load, accelerating its remodeling and function impairment. Thus, hypertension is linked to worse clinical outcomes and prognosis in those patients.

To date, there is no pharmacological treatment to stop or reduce the progression of AS, LV systolic dysfunction, or LV remodeling produced by this disease. Some previous studies have shown that angiotensin receptor blockers (ARBs), one of the first-line treatments of hypertension, may have a beneficial impact on the physiopathological mechanism of AS and a protective effect on LV systolic function as well. Few studies have evaluated the impact of ARBs on AS progression and LV systolic dysfunction at the same time. Moreover, no clinical trial has studied the effect of antihypertensive treatment by ARBs on the AS progression and the LV systolic dysfunction caused by both diseases.

Therefore, the **principal hypothesis** of this master project is that the ARBs reduce the LV systolic dysfunction in hypertensive patients with AS.

The **principal objective** of this pilot study is to determine the impact of antihypertensive treatment with ARBs on the progression of LV systolic dysfunction in hypertensive patients with AS.

TABLE OF CONTENTS

LIST OF TABLES

Chapter 1

Chapter 2

Chapter 3

LIST OF FIGURES

Introduction

Chapter 1

Chapter 2

Chapter 3

ABBREVIATIONS

ΔAVA: delta of thea ortic valve area
ΔAVAi: delta of the aortic valve area index
ΔA wave: delta of the A wave
ΔDVI: delta of the velocity ratio
ΔE/A ratio: delta of the E/A ratio
ΔE/e' ratio: delta of the E/e' ratio
ΔGLS: delta of the global longitudinal strain
ΔLVEF: delta of the left ventricular ejection fraction
ΔMG: delta of the mean transaortic pressure gradient
ΔP: delta of the pressure
ΔQmean: delta of the mean transaortic flow
ΔSAC: delta of the systemic arterial compliance
ΔSV: delta of the stroke volume
ΔSVi: delta of the stroke volume index
ΔV_{max}: delta of the peak aortic jet velocity
ΔZ_{va}: delta of the valvulo-arterial impedance
π: *pi* number
2D: two-dimensional
A_2: sound of the aortic valve closure
A_{Ao}: aortic cross-sectional area
ABPM: ambulatory blood pressure monitoring
ACEI(s): angiotensin-converting enzyme inhibitor(s)
AF: atrial fibrillation
A_{LVOT}: left ventricular outflow cross-sectional area
Ang I: angiotensin I
Ang II: angiotensin II
Ao: aortic
AOBP: automated office blood pressure monitoring
ARB(s): angiotensin receptor blocker(s)
AS: aortic stenosis
ASE: American Society of Echocardiography
AT: anaerobic threshold
AT1: angiotensin type 1 receptor
AT2: angiotensin type 2 receptor
AV: atrioventricular
AVA: aortic valve area
AVAi: aortic valve area index
AVC: aortic valve calcium
AVR: aortic valve replacement
BAV: bicuspid aortic valve
BMI: body mass index
BMP: bone morphogenetic protein
BP: blood pressure
BRA : *bloqueurs des récepteurs de l'angiotensine*
BSA: body surface area
Ca^{2+}: calcium
CAVD: calcific aortic valve disease
CCB(s): calcium channel blocker(s)
CI: confidence interval
CKD: chronic kidney disease
Cl^-: chloride
CMR: cardiac magnetic resonance
CNS: central nervous system
CT: computed tomography
CV: cardiovascular
CW: continuous wave
DASH: Dietary approach to stop hypertension
DBP: diastolic blood pressure
DBT: diabetes
D_{LVOT}: diameter of the left ventricular outflow tract
DVI: velocity ratio
EDV: end-diastolic volume
EF: ejection fraction
eGRF: estimated glomerular filtration rate
ESV: end-systolic volume
ET-1: endothelin-1
GFR: glomerular filtration rate
GLS: global longitudinal myocardial strain
h: wall thickness
HF: heart failure
HOMA-IR: homeostatic model of assessment-insulin resistance
HR: hazard ratio
HTN: hypertension
IL-6: interleukin 6
IUCPQ: *Institute Universitaire de Cardiologie et Pneumonologie de Québec*
JNC-7: the seventh report of the Joint National Committee on prevention, evaluation, and treatment of high blood pressure.
K^+: potassium
LCA: left coronary artery
LDL: low-density lipoprotein
LIFE: The *losartan* intervention for endpoint reduction in hypertension
LPC: lysophosphatidylcholine
Lp-PLA_2: lipoprotein-associated phospholipase A_2
Lp(a): lipoprotein (a)
LV: left ventricle/left ventricular
LVEF: left ventricular ejection fraction
LVET: left ventricular ejection time

LVOT: left ventricular outflow tract
MCP-1: monocyte chemoattractant protein-1
MESA: The multi-ethnic study of atherosclerosis
MG: mean transaortic pressure gradient
MMP: matrix metalloproteinase
Na^+: sodium
NaCl: sodium chloride
NF-κB: nuclear factor- κB
NO: nitric oxide
NYHA: New York Heart Association
OBPM: office blood pressure measurement
OR: odds ratio
ox-LDL: oxidized low-density lipoprotein
P_2: sound of the pulmonic valve closure
PAI-1: plasminogen activator type 1
PC: 25^{th} and 75^{th} percentiles
Q_{mean}: mean transaortic flow
r: radius
RAS: renin-angiotensin-aldosterone system
RCA: right coronary artery
RIAS: the *Ramipril* in Aortic Stenosis trial
ROS: reactive oxygen species
S_2: second heart sound
SA : *sténose aortique*
SAC: systemic arterial compliance
SBP: systolic blood pressure
SEAS: *Simvastatin* and *ezetimibe* in aortic stenosis study
SV: stroke volume
SVi: stroke volume index
SVR: systemic vascular resistance
T: tension
TAVI: transcatheter aortic valve implantation
TEE: transesophageal echocardiography
TNF-α: tumor necrosis factor-alpha
TGF-β: transforming growth factor-beta
TTE: transthoracic echocardiography
V: velocity
VCAM: vascular cell adhesion molecule
VECs: valvular endothelial cells
VG : *ventricule gauche*
VICs: valvular interstitial cells
V_{max}: peak aortic jet velocity
VR: velocity ratio

INTRODUCTION

THE HEART

The **heart**, slightly larger than a clenched fist, is situated in the middle mediastinum (from 2nd to 5th intercostal space). This muscle pump imparts the energy necessary to circulate the blood by generating the pressure head that drives the flow of blood through the vascular system. The **myocardium**, the principal component of the heart, is a hollow contractile muscle, which is coated, internally and externally by a serous membrane system. From superficial to deep, they are the epicardium, formed by the visceral layer of the serous pericardium, the myocardium, and the endocardium, a lining membrane of the heart that also covers its valves.[1]

From a macroscopic viewpoint, the heart has four chambers: two superiors, which are characterized by thin walls and called **atriums**, and two inferiors, with thicker and important muscular walls, called the **ventricles**. The atrioventricular septum separates the two atriums, and the interventricular septum splits the two ventricles. The inflow part of the ventricles receives blood from the atriums through the atrioventricular (AV) orifices. The AV valves guard these orifices, which are also surrounded by a fibrous ring, **the annulus**. The right AV valve is the **tricuspid valve** and it has three valve cusps, and the left AV valve is the **mitral valve** and has two flaps resembling a bishop's miter.[1]The chambers and the valves are detailed in Figure 0-1.

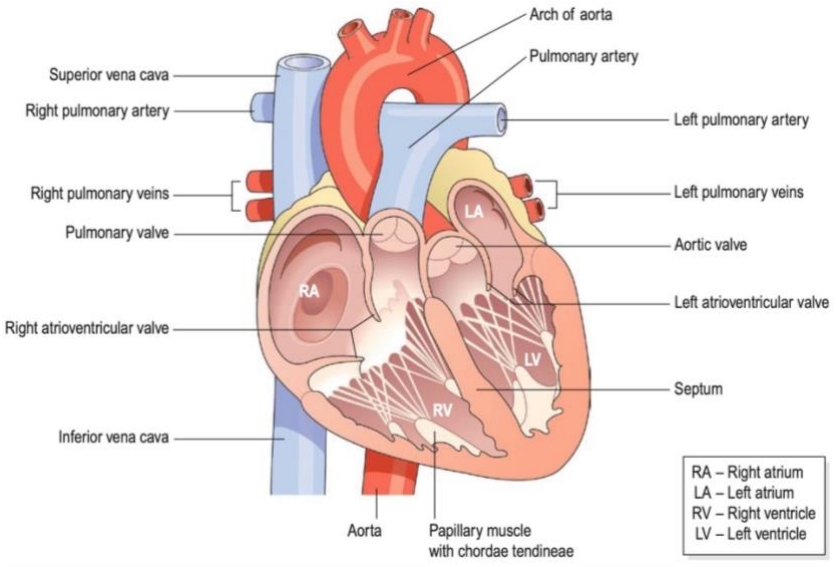

Figure 0-1. **Interior view of the heart**. View of its four chambers and the greats vessels. Adapted with permission from (2).

Moreover, the outlet valves of the ventricles are the semilunar valve, which both are composed of three leaflets. They led blood to flow from each ventricle into a large outflow tract vessel. The **pulmonary valve** is located between the right ventricle and pulmonary artery and the **aortic valve** is located between the left ventricle (LV) and the aorta (Figure 0-2)

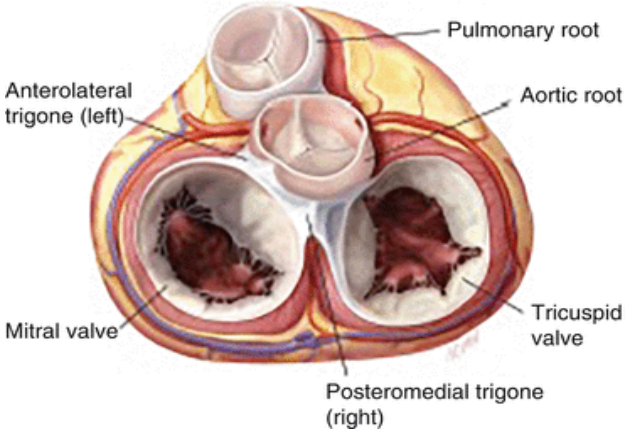

Figure 0-2. View of the base of the heart (atriums have been removed). It illustrates the anatomic location of the AV and the outlet valves of the ventricle and their relations in the heart. Reproduced with permission from (4).

THE AORTIC VALVE

The central role of the aortic valve is to prevent regurgitant blood flow to the left ventricle. It opens during systole as a result of a positive pressure gradient from the left ventricle to the aorta, and it closes during diastole, preventing the regurgitant flow from the aorta to the left ventricle. The aortic valve is obliquely placed and is posterior to the left side of the sternum at the level of the 3rd intercostal space.[1]

The aortic apparatus

The aortic valve is attached to the **aortic valve annulus** in the ventriculo-aortic junction (the junction of the left ventricle outflow tract -LVOT- and the aortic root) and, contrary to the mitral and tricuspid valve, there is no true fibrous ring. It is surgically located at the origins of the aortic valve leaflet attachments and represents the smallest diameter area in the ventriculo-aortic junction. The aortic valve annulus is drawn by a green line in Figure 0-3.[3]

The **aortic root** is made up of the aortic valve leaflets with their attachments, the three interleaflet triangles, the sinuses of Valsalva, and the left and right coronary ostia (from the coronary arteries), as illustrated in Figure 0-3. It is demarcated inferiorly by the aortic annulus and superiorly by the

sinotubular junction (blue-line in Figure 0-3), which is a thickened rim of the aortic tissue called the supra-aortic ridge (Figure 0-4).[3,4]

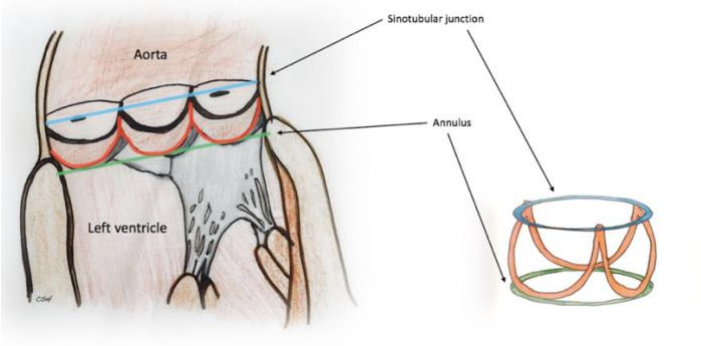

Figure 0-3. Anatomy of the aortic root. The contour of the aortic valve cusp resembles a "crown-like ring." The aortic root is enclosed superiorly by the sinotubular junction (blue-line) and inferiorly by the aortic annulus (green-line). Reproduced with permission from (3).

The **sinuses of Valsalva** (the aortic sinuses) are the spaces at the origin of the ascending aorta between the dilated wall of the vessel and each cusp of the aortic (semilunar) valve, as illustrated by figure 0-4. They are related to the coronary arteries: the opening of the right coronary artery is in the right aortic sinus; the opening of the left coronary artery is in the left aortic sinus; no artery arises from the posterior aortic (noncoronary) sinus.[1,3,4] These structures are illustrated in Figure 0-5.

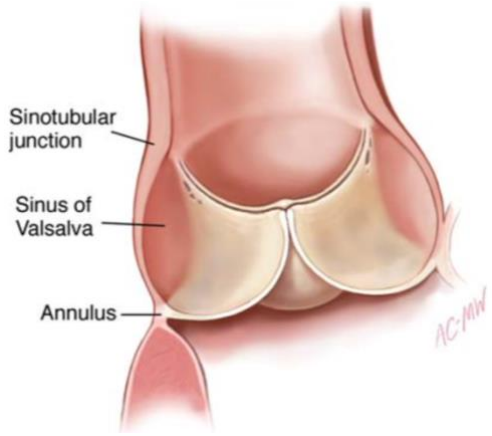

Figure 0-4. Image of the sinus of Valsalva and its anatomical relations with the aortic annulus and the sinotubular junction. Reproduced with permission from (4).

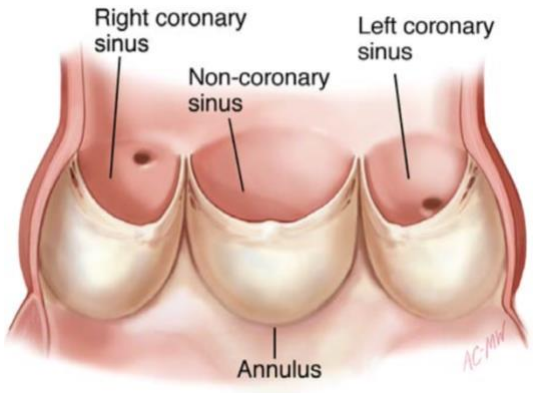

Figure 0-5. Illustration of the three aortic sinuses. Reproduced with permission from (4).

Each leaflet of the aortic valve represents one semilunar cusp of the valve. Each aortic valve cusp has a basilar attachment to the ventricular myocardium in the LVOT. Each leaflet is smooth, thin, and opalescent with a thickness of less than 1mm. They are made up of a fibrous core with an endothelial lining (Figure 0-6).[3,5]

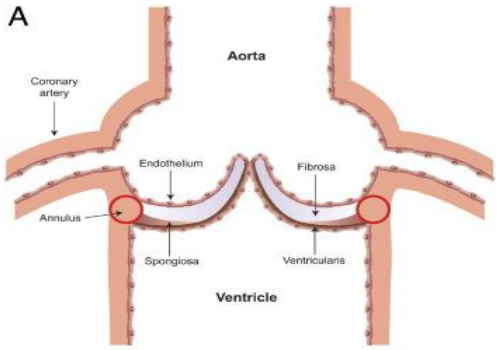

Figure 0-6. Schematic illustration of the aortic valve leaflets and their anatomical relations with the aortic annulus, the aorta, the left ventricle, and the coronary arteries. Reproduced with permission from (5).

Normal Histology of the Aortic Valve and its leaflets

The normal aortic valve consists of three layers (Figure 0-7). On the inflow side of the leaflet, the *ventricularis*, composed of elastin-rich fibers aligned in a radial direction, facilitates valve tissue movement by allowing extension and recoil of the valve during the cardiac cycle.[6-9] On the outflow side of the leaflet, the *fibrosa*, which consists primarily of fibroblasts and (type I and III) collagen fibers distributed circumferentially, parallel to the leaflet margin.[6,8,9] The *fibrosa* layer gives tensile stiffness to support the hemodynamic stresses that the valve apparatus encounters.[6,8,9] Between these two layers, the *spongiosa* is predominantly a lax connective tissue at the base of the leaflet and is composed of

fibroblasts mesenchymal cells, and a mucopolysaccharide-rich matrix. This matrix provides tissue compressibility and integrity to the valve.[6,8,9] Both the fibrosa and the *ventricularis* layers are covered by an endothelial monolayer, which is composed of valvular endothelial cells (VECs). Another type of resident cell are the valvular interstitial cells (VICs), which are the main component of the aortic valve and play a critical role in the maintenance, repair, and production of each layer. These cells are fibroblast-like cells and can transdifferentiate *in vitro* into osteogenic, adipogenic, chondrogenic, and myofibroblastic lineages.[7,8,10-12]

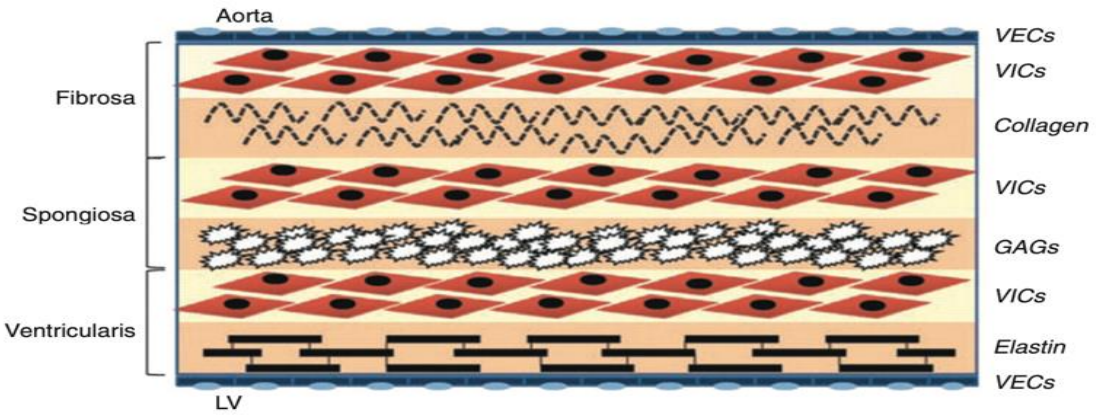

Figure 0-7. **Schematic illustration a of aortic valve histology**. Description of its layers and components. *GAGs,* glycosaminoglycans *LV*, left ventricle; *VECs*, valvular endothelial cells; *VICs*, valvular intersticial cells. Reproduced with permission from (8).

1. AORTIC STENOSIS

Aortic stenosis (AS), the third most prevalent cardiovascular disease[13], is defined by the narrowing of the aortic valve obstructing the LV blood flow during the ejection.

1.1. EPIDEMIOLOGY AND NATURAL HISTORY

AS may start with a thickening or calcification of the aortic valve leaflets, defined as aortic valve sclerosis, but with neither a significant obstruction to the flow nor a hemodynamic impact. The prevalence of aortic valve sclerosis is estimated to be 25% in patients over 65 years old and almost 50% in those aged over 85 years in high-income countries.[14-16] Furthermore, the incidence rate for aortic valve calcium (AVC), which can be measured by computed tomography (CI), is higher in older patients (Figure 1-1). This was demonstrated by the Multi-ethnic study of atherosclerosis (MESA) study, a long prospective study focusing on a relatively healthy and young population. The incidence rate was measured by comparing the absence or not of AVC at baseline and follow-up visits. Subjects aged 70–79 years had a 6-fold higher rate of incident AVC than subjects aged 50–54 years.[17]

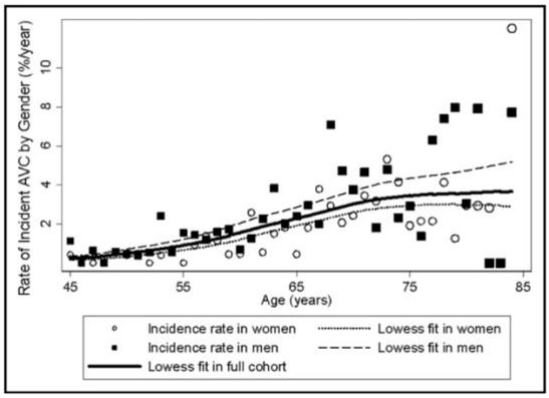

Figure 1-1. Average incidence rate of AVC (%per year) by yearly age increments among those free of AVC at baseline (n=5142), for both men (squares) and women (circles). The size of the scatter points is weighted for the number at risk at each age category; nonlinear Lowess smooth curves are displayed for the full cohort (solid), women (dotted), and men (dashed). A marked increase in AVC incidence rate was seen with advancing age. Reproduced with permission from (17).

Aortic valve sclerosis is asymptomatic, but its finding is independently associated with a 40% increased risk of coronary events and a 50% augment in the risk of cardiovascular death.[14,18] Furthermore, hemodynamic progression to AS occurs in almost all patients having aortic valve sclerosis between 5 and 10 years.[14,15,19-21] Its rate is between 1.8 and 1.9% of patients per year, according to a meta-analysis.[14,15]

AS affects 2% to 4% of adults older than 65 years of age.[9,16,22,23] Its incidence increases with age rising to 12.4% of people who are 75 or older.[8,16,17,19,21,24-26] In a sub-analysis from the Cardiovascular Health Study, a population-based prospective study done in the elderly, the prevalence of AS was 2% in the entire study cohort (older than 65 years of age) and, in subjects older than 75 years of age, it was 2.6%.[3,8,16,19] The prevalence of AS is also increasing in high-income countries with the increasing advanced age of this population and their life expectancy,

The **natural history of AS** typically shows a long latent period of progressive valvular obstruction during which the patient remains asymptomatic and its survival is close to that of an otherwise healthy person. Once the patient becomes symptomatic, presenting exertional dyspnea, angina, dizziness, syncope or signs of heart failure, the outcome without aortic valve replacement (AVR) is ominous with survival rates as low as 50% at 2 years and 20% at 5 years, as plotted in figure 1-2[19,26-29]

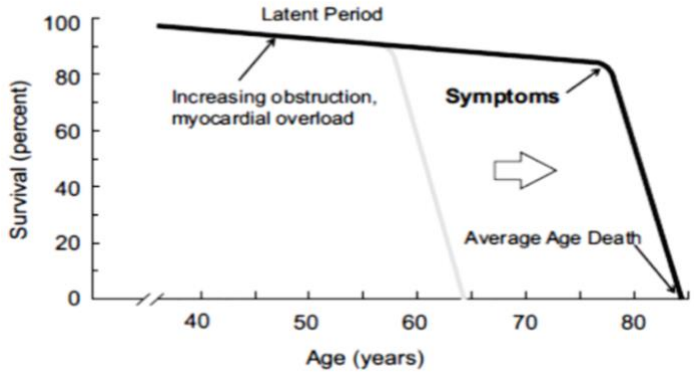

Figure 1-2. Natural history of CAVD. Reproduced with permission from (29).

The rate of progression is highly variable from one patient to the other, however, it is faster in moderate or severe AS.[9,19,28-31] When the obstruction to the flow becomes severe and the symptoms overcome, the only available treatment to these patients is AVR, which implied to replace the sick valve with a mechanic or a bioprosthetic valve by surgery or to implant a bioprosthetic valve using a catheter percutaneously.[14,19,27,32] Before 2013, it was estimated 85 000 AVR procedures in North America.[14,33] From the moment that the transcatheter aortic valve implantation (TAVI) was approved, it increases steeply, achieving 58 782 procedures from 2012 to 2015 only in the United States.[23] Despite all the advancements about this disease, there is no pharmacological treatment to prevent its progression or to delay the time of valve replacement or symptoms onset.[14,19,30,32]

1.2. ETIOLOGY

AS has three principal causes: 1) secondary to a bicuspid valve or congenitally malformed valve which both were non-obstructive at birth; 2) calcification and degeneration of a normal tricuspid valve that occurred with age and, 3) rheumatic or infective AS. Except for this last one, the natural history and the pathophysiology appear to be similar although patients with bicuspid AS develop symptoms earlier or may have associated other cardiac defects or aortic aneurysm. The morphologies of these different causes are illustrated in Figure 1-3.

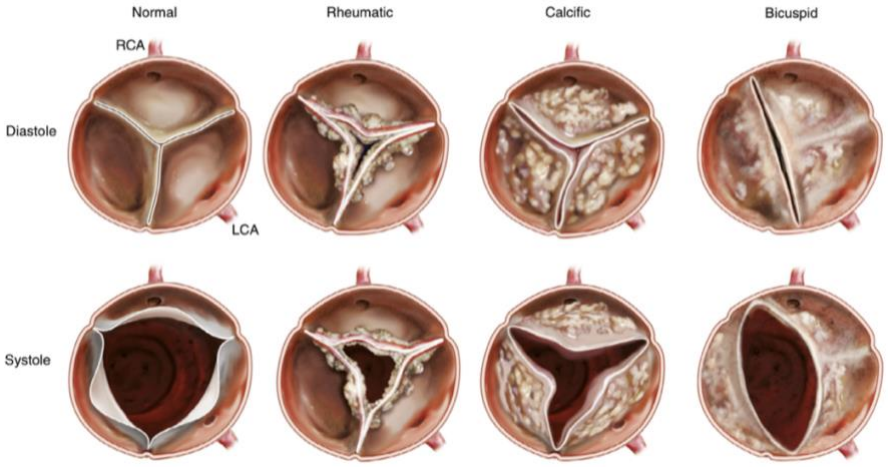

Figure 1-3. Aortic valve morphology in a normal tricuspid valve, rheumatic, calcific (tricuspid,) and congenital (bicuspid) aortic stenosis. The upper row shows the valves during diastole when they are closed, and the low row shows they during systole when they are opened. *LCA,* Left coronary artery*; RCA,* right coronary artery. Reproduced with permission from (8).

Although being rare cases, congenital AS from severe malformed valve is another cause of this disease. It may occur in infancy or childhood or it could manifest due to other congenital valves diseases, rare causes as homozygous type II hypercholesterolemia or ochronosis with alkaptonuria.[19]

1.2.1. CALCIFIC AORTIC VALVE DISEASE

Calcific aortic valve disease (CAVD) is nowadays the most common cause of aortic stenosis in adults, and it is strongly related to aging. Its hallmark characteristic is a progressive accumulation of calcium deposits on the valve that makes it thicker and stiffer, resulting in a gradual narrowing of the valve opening (Figure 1-4). For years, it was thought to be the result of mechanical stress and degenerative process on a normal valve during years: a "wear and tear" process. However, it is also an active biological and inflammatory process that promotes lipids deposition, neoangiogenesis, fibrosis deposition and

calcification remodeling of the normal tricuspid, bicuspid, or malformed valves. Thus, calcific aortic valve disease should be treated as a systemic disease with increased risk for myocardial infarction, cardiovascular and all-cause mortality.[8,19]

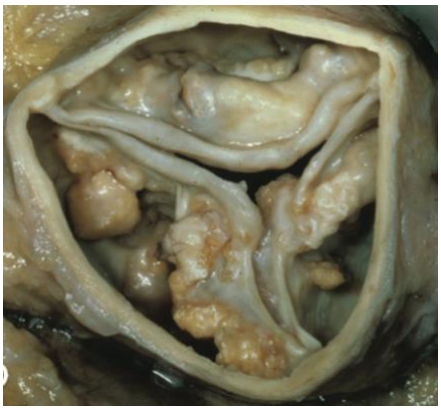

Figure 1-4. Image of a calcific AS on a tricuspid valve. Reproduced with permission from (19).

1.2.2. BICUSPID AORTIC VALVE DISEASE

Bicuspid aortic valve disease (BAV) is a valve dysgenesis due to two rather than three valve leaflets, as shown in Figure 1-5. BAV affects between 1 and 2% of the population, depending on the study. It is the most common congenital heart disorder and, it is more prevalent in males than females, responding to a ratio of 3:1.[8,19,34-39]

It could be associated with complex congenital heart defects, aortic aneurysm syndromes, connective tissue disease, or Turner disease.[19] Moreover, as a consequence of its pathogenesis, it may be associated with aortopathy, namely ascending aortic enlargement or aneurysm formation, which may lead to aortic dissection.[8,19]

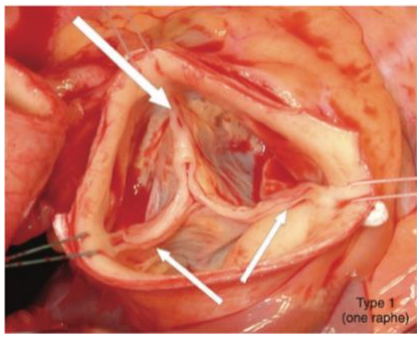

Figure 1-5. **Image of a BAV** type 1: one raphe in the developing left and right coronary cups, showing by the big arrow. The small arrows show the other completely developed commissures. Reproduced with permission from (8).

However, most patients develop an earlier calcifying AS and their symptoms may start to manifest earlier in comparison to patients with calcific AS and normal trileaflet valves It should be noted that patients with BAV are at higher risk for early valve calcification, clinically significant AS, earlier onset of symptoms and early replacement of the valve. .[8,19,28,36] One study from 2005 examining excised stenotic aortic valves of 932 patients (age: 72 ± 12 years) had demonstrated that 54% of patients having aortic valve replacement had congenitally malformed valves and, the rest of patients (45%) had tricuspid valves. However, in older patients, tricuspid valves having aortic valve replacement were more frequent (age 51-60: 18.4%, age 61-70: 30%, age 71-80: 54.3% and age 81-90: 66.2%).[36]

1.3. PHYSIOPATHOLOGY OF AORTIC STENOSIS

1.3.1. RISK FACTORS

Clinical and genetic risk factors were associated with CAVD. **Genetic risk factors** cannot be excluded from the pathogenesis of calcific AS. Indeed, BAV may be sporadic or inherited as an autosomal dominant condition with incomplete penetrance, as was suggested by familial clustering.[8,19,40] Furthermore, one study has shown familial aggregation in tricuspid calcific AS.[40,41] In families with congenital aortic abnormalities and valve calcification, mutations in NOTCH1 and GATA binding protein 5 have been documented.[14,40,42] A genome-wide association study has identified variants in RUNNX2 and CACNA1C, which encode for an osteogenic transcription factor and a voltage-dependent calcium channel subunit, respectively, associated with calcific AS.[14,43] Studies from small sample size have indicated that some variants from genes, such as VDR, APOE, APOB, IL-10, and ENPP, are significantly associated with calcific AS.[14] A large genome-wide linkage meta-analysis from the Cohorts for Heart and Aging Research in Genetic Epidemiology consortium identified a specific polymorphism from LPA gene and it was strongly associated with elevated serum levels of lipoprotein(a) (LP(a)), aortic valve calcification and incident AS.[14,44,45] This polymorphism could double the risk for calcium valve build-up and incident AS.[45] Subsequent population-based studies and cohorts have validated these findings revealing a strong association between high LP(a) plasma levels and calcific AS and AVR risk.[14,44-49]

Clinical risk factors were mostly studied from observational studies, using population- or hospital-based sampling. Those studies had demonstrated that "traditional" cardiovascular risk factors have a strong association with the presence of CAVD; however, their association with CAVD progression is less clear.

As it was mentioned, the prevalence and incidence of AS are associated with **age** and **male sex**.[8,16,17,19]According to several studies using multivariate analyses, CAVD is more frequent in men.[8,16]In

the MESA study, male gender was associated with higher risk for aortic valve calcium, measured by CT, after adjustment for traditional cardiovascular risk factors.[17] Another study has shown a trend for higher prevalence of aortic valve stenosis in men than in women; also, after adjustment for age.[25] However, those studies did not consider the valve phenotype. BAV represents nearly 50% of AVR.[8] Since the prevalence of BAV is higher in men, the valve phenotype could be an explanation for the increased prevalence of AS among men.

Multiple observational studies have shown the association between CAVD and **dyslipidemia** measured by total cholesterol and low-density lipoprotein (LDL).[16,17,48,50-57] It was noted in some observational studies that dyslipidemia has more impact on early-stage aortic disease.[17,58] Older patients with CAVD and/or AS have better lipid serum profiles.

BMI and waist circumference have been associated with CAVD and, also, atherosclerotic diseases. It is not known if BMI is directly associated with CAVD, or whether it is part of dysglycemia, insulin-resistant, or metabolic syndrome.[16,17,55] One large population-based study analyzed the relationship between genetic, obesity, and AS or AVR. Obesity measured by BMI, waist circumference or waist-hip ratio was linked with high risk for AS and also for AVR.[59]

Diabetes (DBT), **insulin resistance**, and **metabolic syndrome** were also associated with CAVD and strongly associated with coronary atherosclerosis. In the MESA study, the homeostatic model of assessment-Insulin Resistance (HOMA-IR) index,[60] diabetes, and metabolic syndrome have been linked with incident CAVD and increased prevalence for AVC.[17,57,61] From these metabolic conditions, case-control analyses had shown mixed results regarding the relationship between DBT and incident CAVD.[16,53-55,61] One cross-sectional report indicated a higher prevalence of AVC in patients with DBT.[62] On the other hand, metabolic syndrome, a disorder with several metabolic conditions as dysglycemia, insulin resistance, dyslipidemia, obesity, hypertension, and microalbuminuria[28] has a higher prevalence of CAVD, and patients with this disorder are at higher risk for incident CAVD.[17,61,63,64] Besides, it was shown that they present a faster hemodynamic progression, measured by echocardiography; and in patients who have bioprosthetic valves, their prothesis deteriorates faster.[64-68]

Chronic kidney disease (CKD) is a systemic condition that occurs when renal function declines and is less than 90 mL/min per 1.73 m^2 (or, equal to and greater of 90 mL/min per 1.73 m2 with signs of kidney damage as micro-, more than 15 mg/g of urinary albumin concentration, or macroalbuminuria - more than 30 mg/g). Some studies demonstrated that patients with ESRD and under hemodialysis have premature vascular and valvular calcification.[8] Regarding different stages of CKD, the association with incident CAVD or AS is mixed. However, one population-based report has established a higher risk for

AS with every stage of CKD, increasing inversely proportional to the decline of estimated GRF (eGRF).[69] In the MESA population, analysis of the estimated GRF and cystatin C concentrations (a sensitive marker for renal damage) indicated trends for association.[8,17] High serum creatinine concentration (> 2.1 mg/dl) is also associated with degeneration of bioprothesis.[70]

Furthermore, some biomarkers of **phosphocalcic metabolism** were tested and also associated with greater risk for CAVD.[16] Higher calcium-phosphorus was associated with bioprosthetic valve leaflet calcification.[71,72] However, results are mixed and complex to show well-defined associations between serum calcium, parathyroid hormone, or 25-OH vitamin D concentrations and risk for CAVD.[8,16,73]

Smoking is a well-known risk factor for atherosclerosis, like coronary, carotid, and peripheral vascular disease. Several studies have demonstrated that smoking is also linked with cross-sectional and incident CAVD.[16,17,54,74] Inflammatory biomarkers, as C reactive protein, were also associated with CAVD.

Hypertension is another clinical risk factor for AS. It will be explained in chapter two of this thesis.

1.3.2. FIBROCALCIFIC REMODELING

1.3.2.1. The initiation phase: epithelium disruption and lipid infiltration

The disruption of the epithelium of the valve is the earliest histopathologic change contributing to the beginning of fibrocalcific remodeling of the valve. Injury to the endothelium of the valve may be provoked by increased mechanical stress, altered shear stress due to BAV or hypertension, or increased oxidative stress.[7,8,10] The mentioned risk factors in the previous section may promote damage to the endothelium of the valve (Figure 1-6).

The remodeling process starts at the fibrosa layer and then extends through the valve modifying its normal architecture. The early aortic valve lesion consists of infiltrations of lipids and inflammatory cells or lipid-laden VICs stimulated by the injury of the endothelium. They contribute to lesion progression by the interaction of modified lipoproteins, monocyte-derived macrophages, lymphocytes T cells, and cellular components of the valve; provoking an inflammatory response (Figure 1-6).[10,75,76] The expression of adhesion molecules allows infiltration of these inflammatory cells, such as monocytes that differentiate into macrophages and T-cells that release pro-inflammatory cytokines.[5,10,76] This initial inflammatory response may stimulate and establish the subsequent fibrotic and calcific processes of the AS valve.[5]

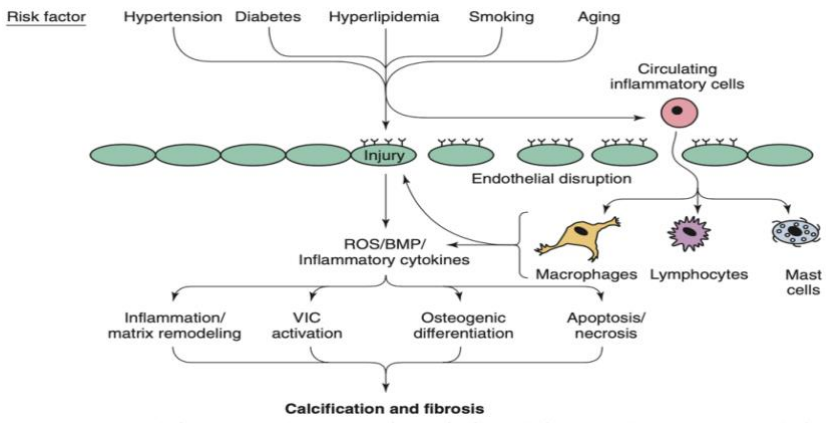

Figure 1-6. Schematic networking explained the risk factor and the pathophysiologic mechanism implicated in the fibrocalcific remodeling of the aortic valve in CAVD. *BMP*, bone-morphogenetic protein; *ROS*, reactive oxygen species; *VIC*, valve interstitial cell. Reproduced with permission from (8).

1.3.2.2. Propagation phase: inflammation and osteogenic transdifferentiation.

Some studies demonstrated that oxidized lipid species are present in the vicinity of the mineralized nodules and they could stimulate an intense inflammatory activity,[77] and later, mineralization.[47,62] It is likely that oxidation of lipids (preferably, small, dense LDL) is stimulated by abnormalities in the oxidative stress mechanism.[12,50,78,79] Oxidative stress may be related to the uncoupling of the nitric oxide synthase (NOS) pathway[14,50,78] and reductions in antioxidant enzyme expression, which both contribute to a higher production of reactive oxygen species (ROS).[14,80] ROS enhance the secretion of cytokines and inflammation[14] and might contribute to the production of oxidatively-modified lipid species with osteogenic properties as well as an osteogenic molecular pathway,[8,14,78,80]

Other proteins that may be implicated in this process are lipoprotein-associated phospholipase A2 (Lp-PLA2), which converts oxidized LDL into lysophosphatidylcholine (LPC) [10,14] and LP(a).[10] LPC, a strong promoter of mineralization, promotes the loss of mitochondrial membrane potential and apoptosis of VICs.[14] LP(a)transports oxidized-phospholipids[10] and a lysophospholipase D, called autotaxin (an ectonucleotide pyrophosphatase/phosphodiesterase family member 2) into the aortic valve.[14,81]Autotaxin is also secreted by the VICs in response to different stimuli or cytokines, such as tumor necrosis factor-alpha (TNF-α).[14,81] This enzyme transforms LPC into lysophosphatidic acid, which was suggested to contribute to the osteogenic transition of VICs and increase mineralization of aortic valve accelerating the development of calcific AS.[14,81] Other factors that enhance the osteogenic differentiation of VICs are the activation of Wnt/ß-catenin signaling pathway, the receptor activator of nuclear factor kappa-B ligand

(RANKL) and the toll-like receptors.[8,14]These two last one also activate the innate immune response, enhancing inflammation.[14]

Cytosolic Lp-PLA2 promotes the arachidonic acid pathway by 5-lipoxygenase and cyclooxygenase, which both may play a role in the mineralization of the aortic valve.[8,14] 5-lipoxygenase is a key enzyme for the biosynthesis of leukotrienes, which are a family of eicosanoid inflammatory mediators.[82] This enzyme is increased in calcified aortic valves.[83] Further leukotriene C4 enhances the expression of bone morphogenetic proteins 2 and 6 implicated in the mineralization of VICs.[14,84] Cyclooxygenase 2 has a key role in prostaglandin synthesis and is implicated in inflammation and bone formation and repair.[84] It is also expressed by VICs in isolated AS valves.[8,14,84]

Furthermore, the inflammatory processes may be sustained and propagated by the neoangiogenesis in the valve. of the AS valves, thin neovessels are commonly observed in regions of intense inflammation proximate to calcific deposits.[5,85] Adhesion molecule expression, such as intercellular adhesion molecule-1 and vascular adhesion molecule-1, is augmented in these neovessels, which may play a role in the migration of inflammatory cells.[5,85]

1.3.2.3. Fibrotic response and renin-angiotensin-aldosterone system activation

The inflammatory response incited by the disruption of the aortic valve endothelium and the subsequent lipid infiltration produces the secretion of inflammatory and profibrotic cytokines; which increases extracellular matrix production and turnover; resulting in fibrosis deposition and stiffening (figure 1-6).[75] In addition, a subpopulation of VICs can transdifferentiate into myofibroblasts, which may play a role in extracellular matrix remodeling and cell turnover.[5,86] Besides, myofibroblasts and inflammatory cells secrete matrix metalloproteinase that has an important and complex role in the restructuring of the valve leaflet matrix.[5,10,75]

Furthermore, regarding the association between hypertension and the development of CAVD, it was considered that the renin-angiotensin system (RAS) could be activated and contribute to the molecular burden of this disease. Locally activated RAS contributes to inflammation, oxidative stress, fibrosis, and plaque expansion. Regarding calcified aortic valves, enzymes of RAS, as angiotensin-converting enzyme (ACE) and chymase, two angiotensin II-forming enzymes, have been found in human AS lesions.[8,87,88] One study revealed from histological analyses of explanted aortic valves that ACE was presented in all valves with aortic sclerosis or stenosis lesions, but it was not found in normal aortic valves.[87,88] ACE was detected primarily in an extracellular matrix, but also within macrophages. The enzymatic product of ACE, angiotensin II (Ang II) was colocalized with ACE in the lesions.[87] In addition to these findings,

both messenger ribonucleic acid and protein expression of angiotensin type 1 receptor (AT1) was significantly increased in stenotic aortic valves.[88] All these results suggest an upregulation of RAS in the aortic valve. Besides, ACE was observed in plasma LDL, detected by Western blotting, and colocalized with LDL through the extracellular matrix in a large proportion of valve lesions.[87] Thus, it suggested that ACE could be delivered by LDL to aortic valve lesions.[87] In explanted AS valves, ox-LDL was documented near calcified areas and colocalized with Ang II, IL-6, and TNF-α. Ang II is a well-known profibrogenic protein that participates in tissue fibrosis and remodeling of the aortic valve. In an observational study with prehypertensive patients with CAVD, the serum levels of Ang II were associated with increased valvular inflammation (TNF-α and IL-6) and tissue remodeling.[89] Also, in an animal model of hyperlipidemic mice, the administration of Ang II provoked a significant thickening of the aortic leaflets.[90]

1.3.2.4. Calcification of the aortic valve

The hallmark of CAVD is the calcification of the aortic valve cups causing a progressive loss of the leaflet mobility and, when the disease progresses, the obstruction of the aortic valve to the LV ejection. It was shown by histologic evidence that calcium deposits are the principal characteristic of stenotic aortic valve[91] and it was seen prominent calcium deposition in early lesion.[76,90] In histologic samples, calcium can appear either amorphous or osteogenic, which means that a process of ossification is implicated, resulting in a bone matrix formation (Figure 1-6).[10,76,79] As it was mentioned in the previous sections, several pro-osteogenic factors are involved in the calcification of the valve and its progression: induction of osteogenic signaling pathway,[8,14,81]proinflammatory cytokines and inflammatory cell infiltration,[8,14,78,80,84]which both may promote VICs to transdifferentiate in osteoblast-like cells. Nevertheless, non-osteogenic mechanisms are implicated in aortic calcification: a reduction of certain proteins that can prevent accumulation of calcium at ectopic sites, such as Fetuin-A and Matrix Gla Protein,[8,92-95] and cell death by necrosis or apoptosis, which both contribute to the formation of calcified nodules.[8,74,92] Besides, calcified nodules, following induction of cell death, have a crystalline ultrastructure and lack live cells within the core of calcified mass itself.[8,74]

In brief, it seems that once the calcification mechanism is initiated, it would be a self-sustaining process, involving increased mechanical stress imposed on the aortic valve continuously damaging the valve endothelium, mechanisms of apoptosis, and activation of osteogenic pathways and differentiation. All would contribute to the progression of CAVD and AS.[96] This self-sustaining process is illustrated in Figure 1-7.

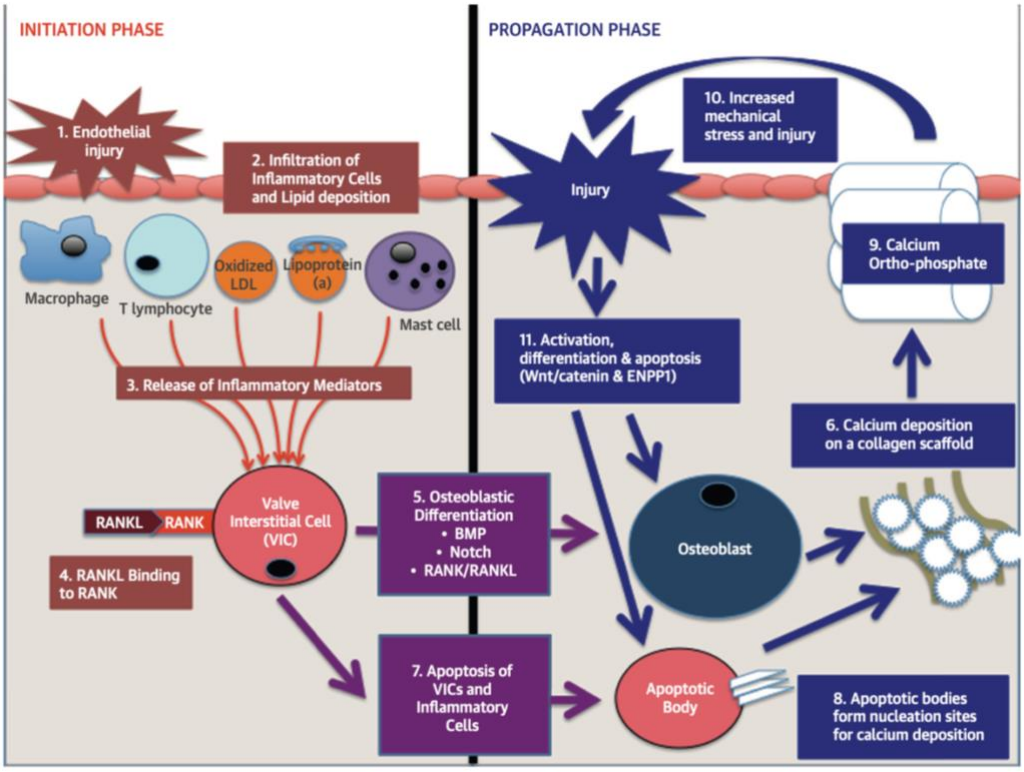

Figure 1-7. Pathogenesis of CAVD and AS. *BMP*, bone morphogenetic protein; *ENPP1*, ectonucleotide pyrophosphate 1; *LDL*, low-density lipoprotein; RANK, receptor activator of nuclear kappa B; *RANKL*, receptor activator of nuclear kappa B ligand; *RAS*, renin-angiotensin system; *VIC*, valvular interstitial cell. Reproduced with permission from (93)

1.4. CALCIFIC AORTIC VALVE DISEASE: ALSO, A DISEASE OF THE MYOCARDIUM.

1.4.1. EARLY CHANGES

As the disease progresses, the valve becomes stiffer, and the orifice area diminishes. Even mild obstruction caused by the morphological changes of CAVD may cause subclinical consequences to the LV, becoming pathological and deleterious with the progression of AS.

Normally, the afterload of the LV, which is the opposing forces (load) that the LV must overcome after the onset of the contraction, can be nearly represented by the diastolic aortic pressure. But, in AS, this assumption is not possible. As the valve obstruction increases, the resistance to LV outflow increases, then the LV afterload. Thus, the pressure, that the LV must achieve to overcome those forces and eject the blood to the aorta, is greater. Therefore, the LV work ($W = \Delta V \; x \; P$, where ΔV is represented by the volume of blood ejected and P by the intraventricular blood pressure), determinant of myocardial oxygen

consumption, also increases. If the contractility of the heart does not change, the stroke volume (the blood volume ejected by cycle) will be reduced as well as the left ventricular ejection fraction (LVEF). However, in a normal heart, contractility increases and other mechanisms to overcome this flow obstruction are setting in. With time, those mechanisms may start to fail.[97]

Moreover, the increased afterload implies a raise in wall stress. The walls stress can be approximately estimated from the parietal tension described by Laplace's law ($T = \frac{\Delta P \, x \, r}{2h}$), where tension ($T$) is the product of the transmural pressure gradient (ΔP) and the radius (r) of the sphere divided by the wall thickness ($2h$). Although the LV is not exactly a sphere, it is assumed as one. Hence, the augmentation in the resistance caused by the flow obstruction requires an increase in the wall tension and so, an increase in the intraventricular pressure, rising the mechanical stress of myocardial fibers. Chronically, the radius and the wall thickness may be modified due to morphological adaptations to wall stress, which may change the ventricular geometry, thereby its produced tension.[97,98]

Besides, the isovolumic contraction time of the LV enlarges because of the increased afterload. Thus, the wall stress is kept for longer times during systole, increasing the tension heat and the energy consumption. So, again, myocardial oxygen consumption is raised.[97,99]

1.4.2. MYOCARDIAL REMODELING AND HYPERTROPHY

It should be noted that LV hypertrophy and remodeling in response to pressure-overload involve both adaptive and maladaptive process[19,100,101] and the degree to which LV hypertrophic remodeling is maladaptive versus adaptative have not been clearly established yet. Hypertrophy remodeling starts as an adaptative response of the myocardium to manage the increased afterload due to the obstructed valve, tending to normalize myocardial wall stress and to maintain cardiac output (the volume of blood ejected per minute). It is characterized by myocyte hypertrophy and increased wall thickness. It may be one of the most important compensatory mechanisms to normalize LV ejection performance, by normalizing afterload and LV work.[8,19,99] This compensatory response is based on LaPlace's law, which explains why the increased wall thickness may decrease the wall stress (and then, the afterload).

Furthermore, this compensatory response may manifest differently according to several factors other than AS severity; for example, sex, genetic expression, vascular load, metabolic abnormalities, or concomitant diseases.[8,19,102,103]In some patients, or in different stages of the disease, this response may present as concentric remodeling (meaning an increase in wall thickness with a reduction in LV volume without increasing LV mass), others may develop concentric hypertrophy (reduced LV volume with increasing LV mass and wall thickness), and some others, or in advanced stages of the disease, may show

eccentric hypertrophy (LV mass increase with LV enlargement and wall thinning).[5,8,19,98,99,104] These types of adaptation to pressure-volume overload are illustrated in Figure 1-8.

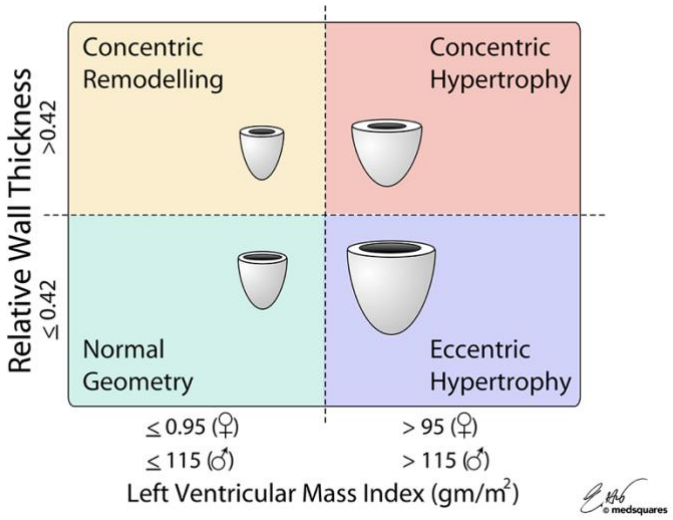

Figure 1-8. Patterns of LV compensatory response to pressure-volume overload. With permission from https://www.medsquares.com

To simply define those patterns of hypertrophy by echocardiography, it can be by calculating LV mass with one of the different methods and relative wall thickness (RWT). LV mass is commonly indexed by height or BSA, the guidelines suggest indexing it by BSA.[105] The reference upper value of normal LV mass are 95 g/m^2 in women and 115 g/m^2 in men.[105] RWT allows to categorize the hypertrophy as either concentric (RWT higher than 0.42) or eccentric (RWT equal or lower than 0.42,) and also, permits to identify the presence of concentric remodeling (normal LV mass with increased RWT).[105]

Moreover, concentric LV hypertrophy results in abnormal coronary blood flow and blood flow reserve.[8,19,106,107] Normally the subendocardium receives about 20% more blood flow than the epicardium, but this ratio is reversed in LV hypertrophy.[8,107] Thus, the myocardial layer with the highest oxygen demand receives the least oxygen supply. Additionally, the increased LV end-diastolic pressure and the shorter diastole time in hypertrophied LV support this situation decreasing the coronary blood flow. Further, myocardial oxygen consumption is higher in LV hypertrophy due to prolongation of the ejection time and the increased systolic pressure. Besides, coronary reserve, meaning the capacity to increase coronary blood flow during stress, is limited in concentric LV hypertrophy.[8,106,108] Therefore, abnormal flow reserve and flow distribution lead to subendocardial ischemia and contractile dysfunction during periods of stress, provoking symptoms like angina, especially during exercises or stress states when the imbalance between myocardial oxygen supply and consumption rises.[8,19,109]

Myocardial ischemia and increased mechanical stress may trigger myocyte apoptosis and fibrotic response in the myocardium[110,111], activating profibrotic mediators such as angiotensin II,[110,112-114] transforming growth factor (TGF)-beta,[110,115] and matrix metalloproteinases.[110,116] As a consequence, myocardial fibrosis enhances, increasing collagen type I deposition as well as activation and differentiation of cardiac fibroblast into myofibroblast.[117] Two different patterns of myocardial fibrosis have been described in AS.[111] Reactive interstitial fibrosis, which begins even in early stages of AS, is a diffuse and reversible pattern, in which there is no cardiac cell damage.[111,117] It shows increased myofibroblast activity and collagen deposition.[111] Contrary, replacement fibrosis is irreversible and occurs later in the progression of AS.[111] In this pattern, cardiac cells are damaged and replaced by, predominantly, collagen type I forming a scar.[117]

In studies of hypertrophy, LV hypertrophy leads to increased cardiac mortality, especially in the presence of coronary artery disease.[8,101,118] In a study of Duncan et al, they propensity matched 964 pairs of patients with AS undergoing aortic valve replacement with and without concentric LV hypertrophy and/ or remodeling.[5,119] Patients with concentric LV hypertrophy had double the operative risk and double the postoperative morbidity in comparison with patients without this pattern.[119] Another study found similar results.[120]

Although in the beginning, LV hypertrophic remodeling reduces wall tension, it may have long-term deleterious effects that translate into damaged LV function, impairing relaxation (diastolic function) and contraction (systolic function), and poor clinical outcomes.[101,118,121-123]

1.4.3. LEFT VENTRICULAR DYSFUNCTION

LV diastolic function may be impaired with the progression of AS and, mainly, with the progression of hypertrophic myocardial remodeling.[8,19,124] The ability of LV to relax is reduced and the stiffness of the myocardium increases. In those patients, cardiovascular diseases as hypertension, coronary artery disease, or others, and also, metabolic comorbidities increase the risk of diastolic dysfunction and higher stiffness.[125] Some pathological changes have been demonstrated to be implicated and contributed to the progression of diastolic dysfunction: higher myocyte stiffness, myocardial fibrosis, advanced glycation end-products, and metabolic abnormalities.[120,124,125]

Diastolic dysfunction and higher myocardial stiffness can be diagnosed by Doppler echocardiography, in which higher end-diastolic pressures and left atrial are measured, and altered LV filling pattern.[8,19,28] To fill this stiff and hypertrophic remodeled ventricle, the atrial contraction plays a key role allowing to maintain the LV filling with higher end-diastolic pressure, but without increasing mean left atrial pressure,

which could have a deleterious effect on the pulmonary circulation.[19] Also, responding to the Frank-Starling law, which is based on the relationship between the initial length of myocardial fibers and the force generated by contraction[97], the increase in end-diastolic pressure (preload), and subsequently, the augmented stretch of the myocardial fibers during diastole, leads to keep the cardiac performance (cardiac output) of a hypertrophied LV.

Nevertheless, this increased and vigorous atrial contraction has consequences on cardiac performance. With time and progression of the disease, loss of synchronized atrial contraction as seen in atrial fibrillation or atrioventricular dissociation may become resulting in rapid clinical deterioration in patients with severe AS.[8,19,28] Though, in those patients with several comorbidities, atrial fibrillation may coexist with AS from the beginning of the disease.

In most patients with AS and without severe comorbidities, **LV systolic function**, measured by the LVEF, remains normal until late in the disease progression.[19,126] The development of systolic dysfunction from a hypertrophy LV is when the LV starts to fail in face of an increased pressure afterload and cannot maintain forward flow through the obstructed valve.[5] This transition depends on a complex interplay of several factors: the severity of valve obstruction, metabolic abnormalities, vascular load and/or systolic blood pressure (SBP), inadequate or maladaptive hypertrophy, myocardial ischemia and increased myocardial apoptosis and fibrosis.[8,19,120,126,127]

In addition to systolic dysfunction, LV hypertrophy, the progression of myocardial fibrosis, and other pathological mechanisms that may alter ion conduction and cell membranes can contribute to LV arrhythmias.[19]

In patients with systolic dysfunction or a reduced LVEF, systolic function usually improves after AVR. Its recovers might depend on several factors, including the degree to which systolic dysfunction was affected by the afterload mismatch.[19,128,129]

1.4.4. PULMONARY VASCULATURE AND HEART FAILURE

With the progression of the disease, all the compensatory mechanisms start to fail and the pressure overload from a hypertrophied and rigid LV starts to transmit increased pressure to the pulmonary vasculature, which may lead to pulmonary hypertension. First, this increased pressure is transmitted to the pulmonary venous system; with time or depending on patients' comorbidities, some patients may develop augmented pulmonary vascular resistance, which leads to pulmonary arterial hypertension.[19,130,131]

As expected, the presence and severity of pulmonary hypertension are associated with worse outcomes and mortality.[19,32,130,131] Besides, among asymptomatic patients, exercise-induced pulmonary hypertension is also associated with reduced event-free survival.[19,131]

If treatment is not done, with the decrease of LVEF and pulmonary hypertension, the next scenario is heart failure and pulmonary congestion, in which patients may have the worst outcome and several rehospitalizations.[8,19,26-28]

All these pathophysiology changes seen in AS are summarized in Figure 1-9. Also, in Figure 1-10, one suggested sequence of these changes are illustrated and exemplified with cardiac resonance images.

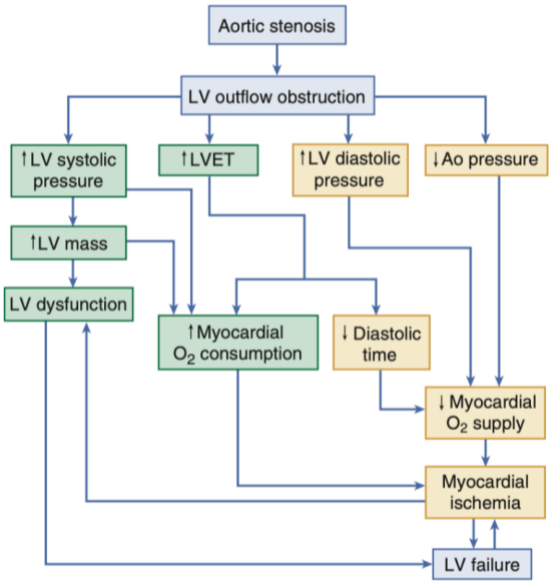

Figure 1-9. **Scheme of the pathophysiology of AS and its consequences on heart performance.** *Ao*, aortic; *LVET*, left ventricular ejection time; O_2, oxygen. Reproduced with permission from (19).

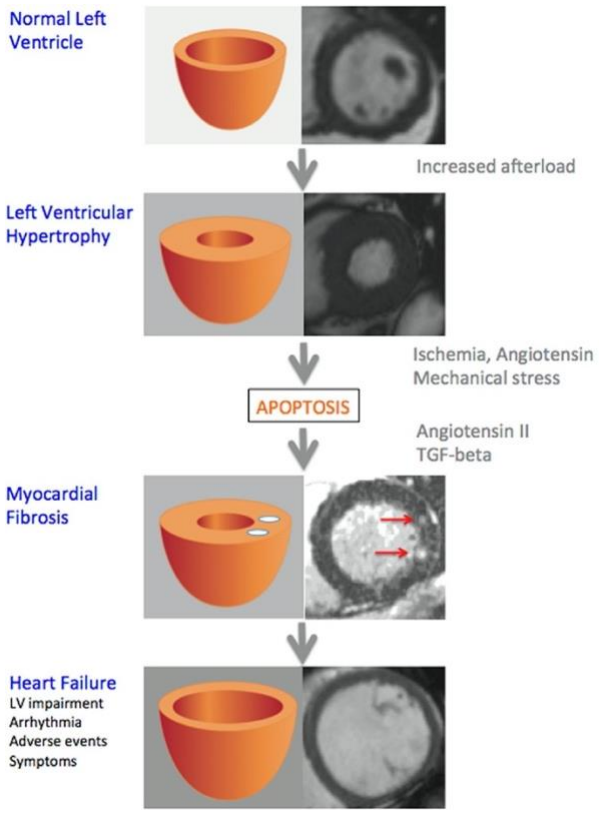

Figure 1-10. Schematic illustration and cardiac magnetic resonance (CMR) of LV modifications during the progression of cardiac dysfunction in AS. Suggested sequences of LVH, myocardial fibrosis and heart failure in patients with AS. Reproduced with permission from (5).

1.5. DIAGNOSIS AND ASSESSMENT OF AORTIC STENOSIS

1.5.1. SIGNS AND SYMPTOMS

During the anamnesis, it is essential to evaluate the presence and the severity of symptoms.[19,28] The cardinal manifestations of AS symptoms are exertional dyspnea, angina, dizziness or syncope, and ultimately heart failure.[8,19,28,29,31,32] However, most patients are diagnosed before symptoms onset on the incidental finding of a systolic murmur on physical examination, which is confirmed by echocardiography.[8,19,28]

The mechanism of exertional dyspnea may be LV diastolic dysfunction, with an excessive rise in end-diastolic pressure leading to pulmonary congestion. Also, these exertional symptoms may be a response to the limited capacity to increase cardiac output with exercise.[19] Furthermore, more severe symptoms may be related to pulmonary congestion, including severe exertional dyspnea, orthopnea, paroxysmal

nocturnal dyspnea, and pulmonary edema.[19] These symptoms may be the result of higher pulmonary venous pressure. However, generally, intervention may be decided before these symptoms begin.

Another frequent symptom in patients with severe AS is angina caused by myocardial ischemia which is exacerbated by exertion and relieved by rest.[19,28] The mechanism of this symptom was explained before. It is worth mentioning that patients with coronary artery disease may have the same symptoms. Thus, it is essential to differentiate both.

During the anamnesis, it is essential to estimate the severity of those symptoms and the capacity for physical and ordinary activity. For that, scores are used; the most widely used score is the New Heart Association (NYHA) Functional Classification[132], which places patients in one of four categories based on how much they are limited during physical activity. It is described in Table 1-1. There are several other scores to assess the quality of life in patients with those symptoms or cardiovascular diseases.

NYHA Functional Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Table 1-1. NYHA Functional Class. This classification is used to evaluate heart failure symptoms as angina and dyspnea and how they limit patients' physical activity. *NYHA*, New York Heart Association

Syncope is another sign that may appear in severe AS and is often caused by inadequate cerebral perfusion that can occur during exertion. The insufficient cerebral perfusion during effort may be caused by an inadequate increase in cardiac output due to outflow obstruction by the valvular stenosis and by a decrease in afterload (arterial pressure) due to systemic vasodilation.[19,28] Other mechanisms that can contribute are the malfunction of baroreceptors in severe AS as well as a vasodepressor response to a greatly elevated LV systolic pressure during exercise.[19,28]

Additionally, evaluation of other comorbidities and cardiovascular diseases is required to assess the associated risk factors and other diseases that may increase the progression of AS or the damage to the heart, reducing its performance.

1.5.2. DIAGNOSIS

1.5.2.1. Physical Examination

The hallmarks of the cardiovascular evaluation in patients with AS are palpation of the carotid upstroke, evaluation of the systolic murmur, assessment of splitting of the second heart sound (S_2), and examination for signs of heart failure, including pulmonary auscultation, edema assessment, and neck veins.[19,28]

Regarding the cardiac examination, the rhythm is generally regular until late in the course; otherwise, atrial fibrillation can be associated with an irregular rhythm.[19] Though, AS and atrial fibrillation commonly coexist in older patients. The systemic arterial pressure is usually normal; however, in late stages, the arterial blood pressure may fall, and the pulse pressure narrows when cardiac output declines.[19] The arterial pulse in AS, assessed normally at the carotid artery, is called *pulsus parvus et tardus* because it rises slowly and has a delayed peak. A thrill or anacrotic "shudder" may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the *a* wave in the jugular venous pulse is accentuated, which results from the diminished distensibility of the right ventricular cavity caused by the bulging, hypertrophied interventricular septum.[19,28]

About the cardiac auscultation, the classic murmur of AS is found during the ejection phase (mid-systolic), and typically is late-peaking and heard best at the base of the heart, with radiation to the carotids. Cessation of the murmur before A_2 (closing of the aortic valve sound) is helpful in differentiation from a pansystolic murmur of mitral regurgitation. In patients with severe calcified aortic valves, the systolic murmur is loudest at the base of the heart, but high-frequency components may radiate to the apex. This phenomenon is known as the *Gallavardin* phenomenon, and it can be mistaken with mitral regurgitation murmur. Normally, a louder or/and later-peaking murmur indicates more severe stenosis.[19,28] Moreover, with severe AS, the splitting of S_2 tends to disappear and S_2 may be single. This may be due to calcification and immobility of the aortic valve that make A_2 inaudible, to the closure of the pulmonic valve (P_2) is buried in the prolonged aortic ejection murmur and/or to the prolongation of LV systole makes A_2 coincide with P_2.[19]

Also, it should be noted that the murmur of valvular AS is augmented by squatting, which increases stroke volume, and it is reduced in intensity during the strain of the Valsalva maneuver and on standing, both of which reduce transvalvular flow.[19,28]

1.5.2.2. Echocardiography

Transthoracic echocardiography is the gold-standard for AS diagnosis, severity classification, and progression assessment.[19,30,98] It allows evaluating valve morphology, the etiology of AS, and severity of valve calcification. It also lets to assess hemodynamic severity and progression of AS, which is the hallmark for AS classification.[19,30,98,133] Moreover, echocardiographic imaging is indispensable to evaluate LV adaptations in AS e.g. LV hypertrophy, systolic and diastolic dysfunction, and also associated findings, including mitral or aortic regurgitation, mitral annular calcification, pulmonary hypertension, coronary artery disease, and concomitant subvalvular obstruction.

Analyzing **aortic valve morphology** on 2-dimensional echocardiography leads to classifying the etiology of AS. It should be analyzed from the parasternal long- and short-axis (Figure 1-11). The short-axis allows to the assessment of the cuspidity and the degree of valve calcification, and the long-axis permits visualizing the LV outflow tract and the opening of the valve. The cuspidity and the opening of the valve both help to define AS etiology and BAV diagnosis.[98]

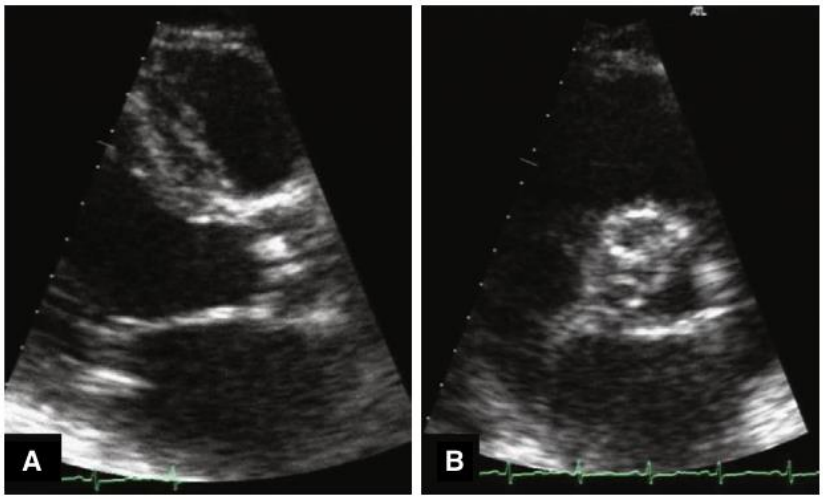

Figure 1-11. (A)**Parasternal long- and** (B) **short-axis view of the aortic valve**, in which the mobility and the calcification of the cusp can be assessed. Adapted with permission from (98).

The morphology and the valve opening of the different etiologies of AS are demonstrated in Figure 1-11. It should be noted that the assessment of AS etiology could be difficult according to the severity of the calcification, patients' echogenicity, et cetera.[98]

Also, from a short-axis view, the degree of calcification can be classified into mild (isolated, small spots), moderate (multiple bigger spots), and severe calcification (extensive thickening/ calcification of all cusps).[30,98,133,134]

Besides, it is possible to get a direct planimetry and size of the anatomic valve area using transesophageal echocardiography. Transesophageal echocardiography also allows for detailed visualization of valve morphology, differentiation of various forms of congenital AS or differential diagnosis of BAV when it is not possible with transthoracic echocardiography, and better observation of the degree and distribution of valve calcifications.[98] Nonetheless, transesophageal echocardiography is not performed routinely and has specific indications because it is a semi-invasive procedure that requires sedation.[135] Then, it has some contraindications and a few risks of complications.[135]

During routine transthoracic echocardiography, it is also important to observe the aortic root and the ascending aorta, which could be dilated, a common finding in patients with AS, especially with bicuspid valves.

1.5.2.2.1. Hemodynamic Assessment of Aortic Stenosis

For hemodynamic assessment of AS severity, Doppler echocardiography is crucial. It applies the Doppler effect to generate imaging of the movement of tissues and blood and their relative velocity to the transducer. This last feature allows the measurement of peak transaortic jet velocity (V_{max}), pressure gradients, and aortic valve area (AVA), which are crucial for the assignment of AS severity, progression, and prognosis. [8,30,98,133,134,136]

Continuous-wave Doppler is used to measuring the $\mathbf{V_{max}}$ (Figure 1-12). Continuous-wave Doppler leads to record high-frequency velocity, but spatial localization of the velocities is lacking. It is extremely important to obtain the maximum velocity signal to avoid underestimation of AS severity. Therefore, it is required to evaluate it from different echocardiography views (apical five-chamber, right parasternal, subcostal view, et cetera) and multiple acoustic windows during the echocardiography study. Also, a good parallel alignment of the Doppler beam to the stenotic jet is essential. Furthermore, in the same frame with the highest velocity, it can be measured the velocity-time integral of the transaortic flow (VTI_{Ao}), which is get from the integral calculation of each velocity recorded by the Doppler beam during the ejection time.[30,98,136]

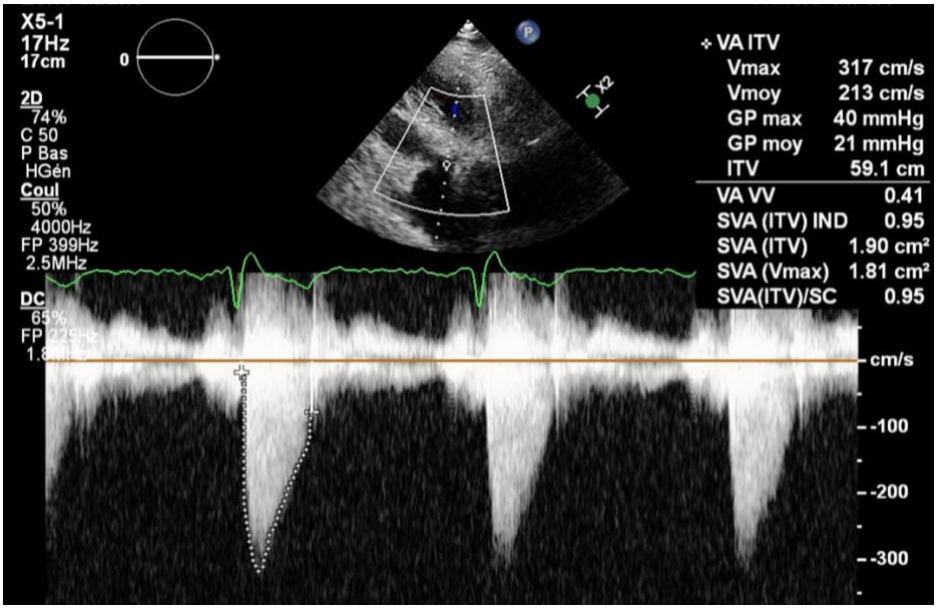

Figure 1-12. Assessment of AS severity. CW Doppler to measure peak velocity, mean and maximal pressure gradient, and aortic velocity-time integral. Image from the laboratory of Dr. Clavel and Dr. Pibarot.

The **mean** and **maximal transaortic pressure gradients** are calculated by the Bernouilli equation $\Delta P = 4(V_{Ao}^2 - V_{LVOT}^2)$, where ΔP is the pressure gradient and V_2 is the velocity recorded in the aorta by the Doppler beam). when LVOT velocity is equal or less than 1.2 m/s^2, the pressure gradients can be calculated by the modified version: $\Delta P = 4(V_{Ao}^2)$.[98] (Figure 1-12)

It is also mandatory to measure **LVOT diameter** and **LVOT velocities**. The LVOT diameter (D_{LVOT}) is measured from a zoomed parasternal-long axis and allows to estimate the LVOT area. For velocities, pulse-wave Doppler (Figure 1-13) is employed in an apical five-chamber view, positioning the Doppler beam parallel to the LVOT and near the aortic valve where the flow is laminar. Also, the velocity-time integral of the LVOT flow (VTI_{LVOT}) can be gotten.[98] Therefore, stroke volume can be calculated as the product of velocity-time integral of flow (VTI_{LVOT}) and cross-sectional area ($A_{LVOT} = \pi\, x\, (\frac{D_{LVOT}}{2})^2$)

$$SV = VTI_{LVOT}\, x\, A_{LVOT}$$

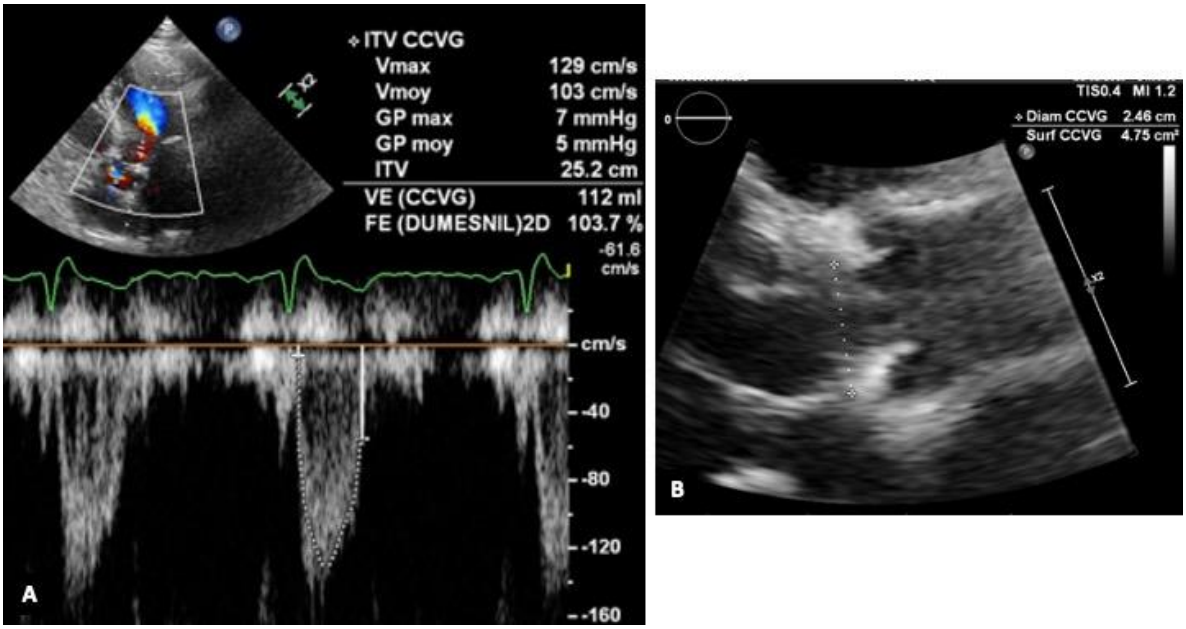

Figure 1-13. Assessment of LVOT velocity, LVOT diameter and AVA. (A) Pulsed-wave Doppler to measure prestenotic velocity and velocity-time integral in the LV outflow tract. (B) LV outflow tract diameter *(d)* in zoom modus to calculate LV outflow tract area. Image from the laboratory of Dr. Clavel and Dr.Pibarot.

SV is another important parameter to evaluate, because it may estimate the systolic performance of the LV and, in case of discordant AS severity, may be a parameter to reclassify it. [98] Nevertheless, this measure is always indexed (SVi) by the BSA. A SVi of less than 35 ml/m² is considered a low-flow state and may have clinical implications.[30,98,136] Besides, small hearts with concentric hypertrophy can present low-flow states, which is frequently in women, in patients with long-lasting hypertension and AS, or both. Other situations that reduced SVi can be present are mitral or tricuspid regurgitation or atrial fibrillation.[19,98]

Assuming the conservative law, i.e. the stenotic area has the same stroke volume as the prestenotic area, the continuity equation can be used to calculate the **effective AVA** from, the VTI_{Ao}, VTI_{LVOT}, and the A_{LVOT}.[30,98,136] (Figure 1-14)

$$A_{LVOT} x\, VTI_{LVOT} = A_{Ao}\, x\, VTI_{Ao}$$

$$AVA = A_{Ao} = A_{Lvot}\, x\, \frac{VTI_{LVOT}}{VTI_{Ao}}$$

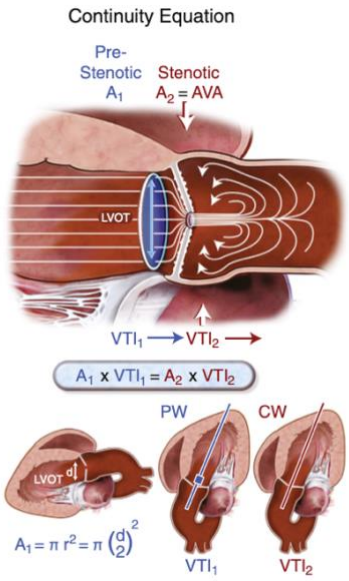

Figure 1-14. Continuity equation. VTI_1, LVOT velocity-time integral of flow; VTI_2, aortic velocity-time integral of flow, A_1, LVOT cross-sectional area and A_2, aortic cross-sectional area. Adapted with permission from (98).

If a laminar flow is not possible to acquire due to an acceleration of flow, AVA estimation from Doppler echocardiography will not be possible as the LVOT velocity will be overestimated.

The **AVA index** (AVAi), in which the effective AVA is divided by BSA is also calculated and considered for AS grading. [30,98,136] This parameter allows associating the size of the valve with the body surface of the patient.

Another measure for the assessment of AS severity is the **velocity ratio** (DVI). DVI, lower than 0.25 defines severe AS, between 0.25 and 0.50 defines moderate AS, and higher than 0.50 defines mild AS. It is calculated as follow:[30,98]

$$DVI = VTI_{LVOT} / VTI_{Ao} \ or \ VR = V_{LVOT} / V_{Ao}$$

1.5.2.2.2. Left ventricle systolic function

Nevertheless, the AS assessment is not completed without analyzing the LV systolic and diastolic function. The LV systolic function is normally used as a parameter to assess LV contractility. However, only if a synchronous contraction is present, heart rate is stable, and loading conditions (preload and afterload) are constant does a change in performance indicate a change in contractility. LV systolic function can be assessed from the left ventricular ejection fraction (LVEF). It is calculated from the

difference in LV volumes, measured by 2D echocardiography. These measures should be taken at the end of the diastole (EDV) and systole (ESV).

$$LVEF = \frac{EDV - ESV}{EDV}$$

Another way to get the LVEF is by eyeballing or by other validated methods. One of them is the modified Simpson biplane method, which is recommended by the *American Society of Echocardiography* (ASE).[30] This method requires the measurement of LVEF by tracing the endocardial border in both the apical four-chamber and two-chamber views in end-systole and end-diastole. These tracings eventually divide the LV cavity into a predetermined number of disks (usually 20), which their volumes are based on the tracings obtained from the study.[98]

It is worthy to mention that the evaluation of SBP before doing echocardiography is essential in the hemodynamic assessment of AS severity.[19,30,137] The presence of systemic hypertension can affect it due to the closed interaction between valvular and arterial hemodynamics. During the hemodynamic assessment of AS, the evaluated parameters are flow-dependent and might be modified in cases of hypertension because of the increased arterial afterload. One study suggested that hypertension can lead to underestimation of AS hemodynamic severity.[138] Therefore, reevaluation after normalization of blood pressure is suggested by the guidelines, especially in discordant AS.[19,137]

1.5.2.2.3. Global longitudinal strain

Global longitudinal strain (GLS) has been validated as a quantitative index for global LV function[139,140] and represents the percentage of myocardial deformation (*strain*) in the longitudinal direction (Figure 1-15).[139] During systole, ventricular myocardial fibers shorten with a translational movement from the base to the apex, and the deformation caused by this shortening is analyzed.[98,139] GLS can be analyzed from a 4-chamber, 2-chamber, and 3-chamber apical long-axis views (Figure 1-15), in which segmental or regional and global (average value of all segments) strain values can be acquired. It can be analyzed using speckle-tracking echocardiography, an echocardiographic method that is based on the analysis of acoustic speckles during the cardiac cycle[98,139] and measures local displacement in echocardiographic images allowing an angle-independent strain measure.[98] The speckles are created by interference of ultrasound beams in the myocardium and are seen in gray-scale B-mode images as a characteristic speckle pattern (Figure 1-16). These patterns can be tracked from frame-to-frame by software during the cardiac cycle[98,139] and thereby, it can be calculated displacement, the rate of displacement (myocardial velocity vectors), deformation (strain), and the rate of deformation (strain rate) of the selected segments.[139]

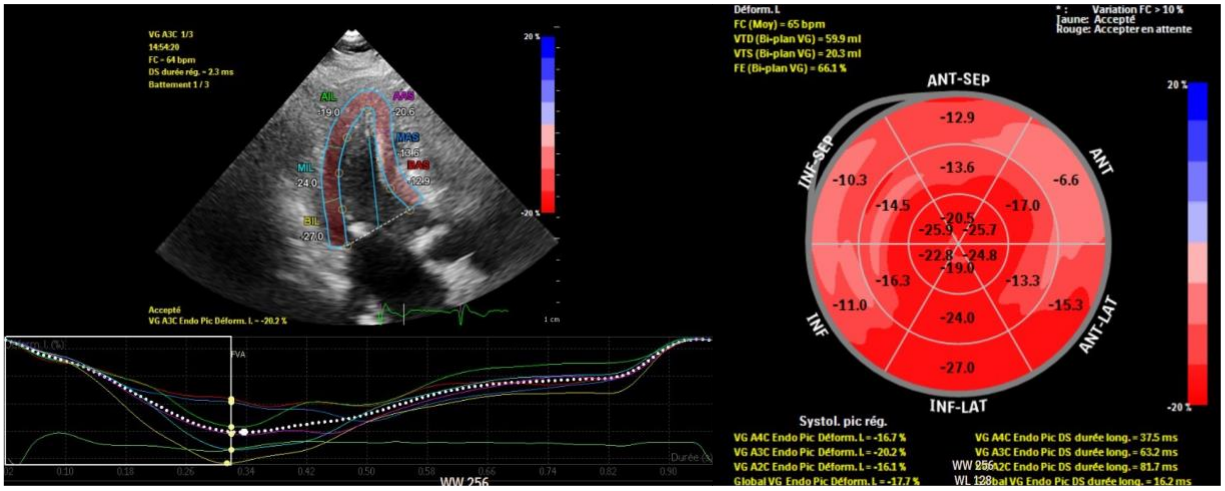

Figure 1-15. GLS with 2-dimensional speckle tracking echocardiography. The figure demonstrates analysis of LV GLS from a 3-chamber view. Image from the laboratory of Dr. Clavel and Dr.Pibarot

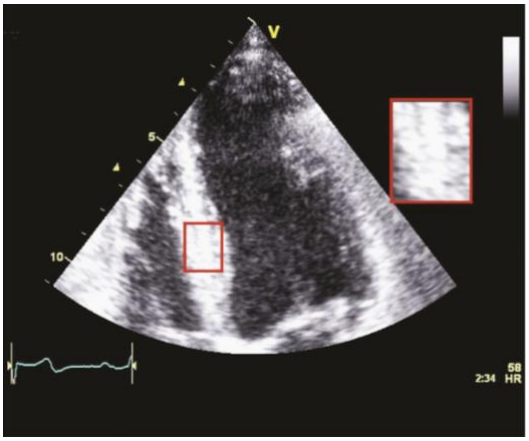

Figure 1-16. Speckle tracking echocardiography. A part of the septum *(red box)* from a four-chamber view is enlarged, wherein speckels can be observed. Adapted with permission from (98).

Strain from the LV can be analyzed radially, circumferentially, and longitudinally (Figure 1-15). However, the derivation of GLS from averaging multiple regions has become the selected method to quantify LV strain and provides a robust LV systolic function marker, which consequently can be used in routine clinical assessment.[141,142] The accuracy of this method has been validated against sonomicrometry and tagged magnetic resonance imaging, demonstrating feasibility and reproducibility.[139,143,144] However, this technique requires high-quality 2-dimensional images and has a high dependence on the frame rate.[98,139]Also, it is almost not possible to even conduct strain measurements in patients with non-sinus rhythms.[139]

During the early phases of the development of strain, one of the disadvantages that GLS presented was significant intervendor variability, and vendor-independent software was used to circumvent it.[141,145] Since the publication of the consensus from the European Association of Cardiovascular Imaging/ASE Industry Task Force,[146] intervendor difference has been reduced to levels similar to those of standard parameters, including LVEF.[142,147] Thereby, it allowed to use GLS widely in research as well as in clinical settings, becoming a feasible alternative to LVEF for the assessment of myocardial function.[141]

Normal values of GLS have not been established by the guidelines yet. Though, they suggest that -20% (±2%) may be considered normal. [141148] In a meta-analysis analyzed more than 2500 healthy and young (mean age 47 11 years) individuals, in which 51% were males, the normal values of GLS were from -15.9% to -22.1%, depending on the vendor-specific software used for longitudinal strain analysis. Besides, it was a heterogenous population (with different clinical characteristics, e.g., age, gender, BMI, blood pressure) even though they were healthy subjects.[149,150] Population-based studies suggested that GLS might be more impaired in male patients as well as in the elderly. [150-152]

GLS has been suggested as an early marker of subclinical LV systolic dysfunction, identifying myocardial dysfunction before a decline in LVEF, even in a community-based cohort or general population studies.[139,151-156] Furthermore, one analysis from "The Copenhagen City Heart Study," a general population-based study, indicated that GLS is an independent and strong predictor of all-cause mortality and a composite outcome of incident heart failure, cardiovascular death, and myocardial infarction.[151] Consisting with previous results, the authors found that GLS provides incremental prognostic information about long-term risk of cardiovascular events beyond the Framingham Risk Score, the Systemic Coronary Evaluation risk chart, and the modified American College of Cardiology/American Heart Association Pooled Cohort Equation.[151] One study analyzing the incremental value of GLS found that this technique was a superior predictor of outcome (in this case, all-cause mortality) to either LVEF or wall motion score index (which is assessed by tissue-Doppler echocardiography) in unselected patients with known or suspected LV dysfunction.[155]

In patients with heart failure and reduced LVEF, GLS presents an incremental prognostic value although LVEF has a well-known prognostic value, especially in patients with ischemic cardiomyopathy.[141,157] Peri-infarct GLS was a good independent predictor of ventricular tachycardia and fibrillation in those patients. [141,157] Specific scar site indicated by regional strain might be more proarrhythmogenic than other sites. [141,158] Regional analysis of longitudinal strain can be useful in coronary artery disease.[141]

Furthermore, in patients with preserved LVEF (between 50 and 60%), decreased GLS was highly prevalent even among patients with LVEF higher than 55%.[154] Another study found similar results: an

incremental prognostic value of longitudinal strain for predict cardiovascular death, heart failure hospitalization, and the composite outcome of both; also after adjustment of clinical and conventional echocardiographic variables.[159]

Moreover, GLS has been proposed as the test of choice in guidelines from cardiovascular imaging society for monitoring of asymptomatic cardiotoxicity related to chemotherapy,[141,160] which is associated with LV dysfunction and cardiovascular morbidity and mortality.[148] As impairments in GLS precede decreases in LVEF, a relative reduction of GLS early in treatment can be associated with a subsequent LVEF decline.[141,161] Besides, reduced GLS has been found in several populations at risk of heart failure, such as hypertensive patients,[141,162] diabetic cardiomyopathy,[141,163,164] or patients with metabolic syndrome.[141] However, its indication in these diseases has not been established.[141]

About the valvulopathies, GLS has also a role in them. In severe mitral regurgitation, GLS impairment before mitral valve replacement is an independent and strong predictor of LV dysfunction after surgery regardless of pre-operative LVEF.[141,165-167] In aortic regurgitation, symptomatic patients with severe aortic regurgitation demonstrated a significantly lower longitudinal strain compared with those without symptoms.[168] In asymptomatic aortic regurgitation, a reduced longitudinal strain was independently associated with a need for aortic valve surgery after adjustment for clinical variables and LV volumes.[168] Further, an impaired longitudinal strain was associated with disease progression in patients with moderate-to-severe aortic regurgitation during conservative management (frequent clinical visits and sequential echocardiography).[169]

Lastly, in patients with AS, some studies have demonstrated that patients with asymptomatic severe AS have impairment of the GLS despite normal (LVEF ≥ 60%) or preserved LVEF.[156,170,171] Vollema et al. found that GLS was significantly lower in this kind of patients compared with age- and sex-matched controls without AS (mean ± SD LV GLS, -17.9±2.5% vs. -19.6±2.1%).[156] During follow-up (12, interquartile range: 7-23 months), patients with AS significantly deteriorated GLS while LVEF remained unchanged.[156] The authors divided into two groups the study sample (n=220) according to the median value of baseline GLS (preserved group, ≤-18.2% vs. impaired group, > -18.2%) and patients with more impaired GLS had a higher prevalence of coronary artery disease and atrial fibrillation, larger LV mass index and lower LVEF.[156] Besides, this group showed a higher risk for developing symptoms and needing aortic valve intervention.[156] Other studies found a similar association between GLS decline and AS progression and worse clinical outcomes.[14,30,98,148,156,171,172] Another study analyzing the correlation between GLS and the severity of AS demonstrated that GLS gradually declines as the severity of AS increases. One hundred thirteen patients were stratified into three groups according to AS severity and these groups were compared.[171] While LVEF was not significantly different among these groups, GLS

revealed a significant difference among them.[171] By post-hoc analysis, significant differences were also found comparing mild with severe AS and moderate with severe AS.[171] Furthermore, GLS was significantly correlated with AVA, mean pressure gradient, LVEF, LV mass index, and early diastolic mitral annular velocity (one parameter of diastolic LV function).[171]

Furthermore, lowered GLS was also correlated with LV fibrosis and associated with poor symptomatic recovery after AVR.[148] In patients with LV hypertrophy and normal LVEF, reduced GLS was independently associated with myocardial fibrosis assessed by CMR.[173] Besides, it was also linked to an increased risk for ventricular arrhythmia, heart failure, transplantation, and all-cause mortality.[174]

Therefore, in this setting, GLS can improve risk prediction in patients with moderate-to-severe AS and thus, may facilitate the selection of patients who would gain benefit from an earlier intervention than guidelines currently recommend.[141]

1.5.2.3. Cardiac Computed Tomography

The use of cardiac computed tomography (CT) in AS is enlarging, especially in those patients with CAVD. Anatomic AVA can be evaluated in CT and shows a good correlation to the one measured by TEE.[98,175] It is also useful for studying aortic dilatation in suspected patients of aortic root disease or bicuspid valve.[19,98]. Additionally, the use of CT is crucial before transcatheter AVR because it allows taking precise measures of aortic dimensions in several levels, including the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta.[19,98] Thus, CT is required for intervention planning.[19,98]

Nowadays, CT is gaining relevance in the measurement of aortic valve calcification and AS severity stratification, which provides independent information of echocardiographic indices (flow-dependent parameters) of AS severity and may grow relevance in discordant or doubtful cases, especially in low-flow, low-gradient AS. [19,98,176-178] Furthermore, CT allows the assessment of coronary artery disease, which is presented in 50% of patients with AS.[98]

1.5.2.4. Cardiac Magnetic Resonance Imaging

CMR allows assessing LV volume, function, and mass, especially in situations where this information cannot be precisely obtained from echocardiography due to poor quality image.[8,19] It is also useful for measuring aortic dimensions and it was correlated as an alternative method for the measurement of anatomic AVA and LV outflow area having similar results to TTE.[8,19,98] Additionally, it can be acquired CMR measurement of four-dimensional flow within the LV outflow tract and the stenotic valve.[98,179,180] Moreover, the added value of CMR is the quantification and pattern analysis of myocardial fibrosis which

is related to longitudinal LV function.[148,181,182] Myocardial fibrosis is associated with bad prognosis and adverse outcomes in patients with AS,[5,19,98,148,180,181] and it can be measured by late-gadolinium enhancement or by percentage of extracellular volume from T1 mapping. These parameters can be used to risk-stratify patients.[19,123]

In addition, CMR can distinguish between bicuspid or trileaflet valve anatomy and assess aortic root and ascending aortic anatomy in patients with a bicuspid valve.[19]

1.6. AORTIC STENOSIS PROGRESSION AND STAGES

According to the ASE, patients with aortic valve sclerosis or BAV (and with V_{max} lower than 2.0 m/s) are at risk for developing AS. Mild AS is considered when (a) V_{max} is between 2.0 and 2.9 m/s, (b) MP is less than 20 mm Hg, and moderate AS, when (a) V_{max} is between 3.0 and 3.9 m/s, (b) MP is between 20- and 39-mm Hg. In those patients, AVA is greater than 1.0 cm^2. [19,30,98] AS is defined as severe when (a) an aortic jet of 4 m/sec or greater, (b) a mean transvalvular pressure gradient at least 40 mmHg in the presence of a normal flow, (c)an effective AVA smaller than 1.00 cm^2 or an AVAi smaller than 0.6 cm^2/m^2 and/or (d) a VR lower than 0.25. [19,30,98] However, some patients with AS have a low transaortic volume flow rate who are diagnostic and management challenges for physicians. These "low-flow" type of AS is classified: low-flow/low-gradient AS with reduced LVEF (patients with LV systolic dysfunction and less than 50% LVEF), and low-flow/low-gradient AS with preserved LVEF (50% or more LVEF), for example in patients with small, hypertrophied ventricles. [19,30,98]

The American guidelines define each stage of AS by valve anatomy, valve hemodynamics, the consequences of valve obstruction on the LV, and vasculature, as well as by patient symptoms (Table 1-2).[30]

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodinamic consequences	Symptoms
A	**At risk of AS**	- BAV or another congenital valve anatomy - Aortic valve sclerosis (CAVD)	Aortic V_{max} < 2 m/s with normal leaflet motion	None	None
B	**Progressive AS**	- Mild to moderate leaflet calcification/fibrosis of bicuspid or trileaflet valve with some reduction in systolic motion, or -Rheumatic valve changes with commisural fussion	**Mild AS**: aortic Vmax 2.0–2.9 m/s or mean ΔP <20 mm Hg **Moderate AS**: aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mm Hg	- Early LV diastolic dysfunction may be present. - Normal LVEF	None
C: Asymptomatic severe AS					
C1	**Asymptomatic severe AS**	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening.	Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg. AVA typically is ≤1.0 cm^2 (or AVAi 0.6 cm^2/m^2) but not required to define severe AS. **Very severe AS** is an aortic V_{max} ≥5 m/s or mean P ≥60 mm Hg	- LV diastolic dysfunction. - Mild LV hypertrophy. - Normal LVEF.	Exercise testing is suggested to confirm symptom status
C2	**Asymptomatic severe AS with LV systolic dysfunction**	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening .	Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically ≤1.0 cm^2 (or AVAi 0.6 cm^2/m^2) but not required to define severe AS	LVEF < 50%	None
D: Symptomatic severe AS					
D1	**Symptomatic severe high-gradient AS**	Severe leaflet calcification/ fibrosis or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA typically ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2) but may be larger with mixed AS/AR.	- LV diastolic dysfunction. - LV hypertrophy. - Pulmonary hypertension may be present	- Exertional dyspnea, decreased exercise tolerance, or HF - Exertional angina - Exertional syncope or presyncope
D2	**Symptomatic severe low-flow, low-gradient AS with reduced LVEF**	Severe leaflet calcification/ fibrosis with severely reduced leaflet motion	AVA ≤1.0 cm^2 with resting aortic V_{max} <4 m/s or mean ΔP <40 mm Hg Dobutamine stress echocardiography shows AVA <1.0 cm^2 with V_{max} ≥4 m/s at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	- HF -Angina - Syncope or presyncope
D3	**Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS**	Severe leaflet calcification/ fibrosis with severely reduced leaflet motion	AVA ≤1.0 cm^2 (indexed AVA ≤0.6 cm^2/m^2) with an aortic V_{max} <4 m/s or mean ΔP <40 mm Hg AND Stroke volume index <35 mL/m^2 Measured when patient is normotensive (systolic blood pressure <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	- HF - Angina - Syncope or presyncope

Table 1-2.[30] **Stage of AS** as defined by the 2020 AHA/ACC guideline for the management of patients with valvular heart disease.[30] **Δ*P***, pressure gradient; *AS*, aortic stenosis; *AVA*, aortic valve area; *AVAi*, aortic valve area index; *LVEF*, left ventricular ejection fraction; *Vmax*, peak jet aortic velocity

Once the diagnosis is made and confirmed with echocardiography, repeat imaging is recommended every 3-5 years in patients with mild AS and every 1-2 years in patients with moderate AS and normal LV function. In patients with severe AS and normal LV function, it is recommended to repeat echocardiography every 6-12 months.[19,30,98] Certainly, if there are symptoms onset or a change in the course of the disease, echocardiography or other diagnostic tests may be repeated sooner. Several studies have aimed to establish the hemodynamic progression rate of AS before symptom onset and they showed an average rate of increase in aortic jet peak velocity between 0.2 and 0.4 m/sec/year, and in mean pressure gradient of about 8 mmHg per year, with a decrease in valve area of 0.15 cm^2.[8,20,21,98,133] In general, the rate of hemodynamic progression is likely linear but highly variable in each patient.

1.7. TREATMENT

1.7.1. MEDICAL TREATMENT

Nowadays, no pharmacological therapy has been demonstrated to, at least, slow the progression of AS. Several clinical studies have failed to find a strong impact, especially those including statins and antihypertensive medication.[183-187]Thus, the only possible treatment for AS is the replacement of the aortic valve or the transcatheter implantation of a bioprosthesis.

Nevertheless, comorbidities conditions or associated diseases should be treated with the best standard of care. One of those conditions is hypertension; 70% of the AS population has also hypertension. Some time ago, it was certain hesitance to treat hypertension because of the concerns that vasodilation could provoke a fall in cardiac output. Different studies (clinical and animal) have demonstrated that anti-hypertensive drugs could reduce the progression of AS and LV dysfunction, symptoms, and improve clinical outcomes.[19,184,185,187-190]

Additionally, these studies have indicated that the afterload reduction elicited by the antihypertensive treatment leads to an increase in stroke volume, except in patients with critical AS. The medical treatment for hypertension in AS patients has not been established. Conversely, RAS blockade therapy seems like an interesting avenue. Clinical and in vitro studies have shown positive results.[185,187,190-193] RAS is upregulated in the valve and ventricles of patients with AS.[8,87,88,110,112-114] Besides, small studies have exhibited clinical benefits.[185] More large-scale studies should be done.[19,31]

1.7.2. AORTIC VALVE REPLACEMENT

AVR is recommended for adults with symptomatic severe AS, even if the symptoms are mild. It is also recommended for severe AS with LVEF less than 50% and for patients with asymptomatic severe AS who are undergoing coronary bypass grafting or other forms of heart surgery.[8,69,95,104] Besides, it is also suggested for apparently asymptomatic patients with severe AS that exercise testing provokes symptoms or a fall in blood pressure.[19,30,136] AVR could be considered in patients with asymptomatic severe disease, but with markers of rapid disease progression or very severe AS. In those cases, careful evaluation of the benefices and risks of an earlier intervention should be made.

1.7.2.1. Surgical Aortic Valve Replacement

Since the first surgical AVR, medical technology advances in operative management, techniques, and valve design have transformed the outlook for patients with AS, decreasing surgical morbidity and mortality.[14,19] In patients younger than 70 with minimal comorbidities, the operative risk is less than 1% in many centers,[19,194] and the overall 30-day mortality rate is currently under 3%.[14,195,196] The operative mortality associated with AVR is dependent on both patient risk factors and the skill and experience of the surgical team.[32] Assessment of surgical risk can be done using available surgical risk scores, such as EuroSCORE, the Society of Thoracic Surgeons risk calculator, and the valve-specific risk calculator of Ambler et al, which can help to predict the 30-day mortality risk.[32] Factors associated with a higher 30-day mortality risk are low NYHA functional class, impaired LV function, advanced age, the presence of coronary artery disease, previous coronary artery bypass grafting, renal insufficiency, and chronic pulmonary disease.[19,30,32,136] The contraindications for surgical AVR are prohibitive surgical risk and life expectancy of less than 1 year.[19,32]

In recent years, there has been a shift in surgical AVR: from open-heart surgery toward minimally invasive techniques, from mechanical valves to greater use of bioprosthetic valves.[14,32] Options for surgical AVR are shown in Figure 1-17 and Figure 1-18. Mechanical valves are prosthetic valves manufactured from nonbiological tissues and the three major designs are the tilting disc or monoleaflet, the bileaflet, and the caged ball, which are no longer implanted (Figure 1-18).[14,98,197] The monoleaflet valves consist of a single disk that rotates around a pivot axis and is secured by lateral or central metal struts.[98,197] These valves divide the flow into two regions due to the opening angle.[98,197] The bileaflet valves are made of 2 semilunar disks hinged to a rigid valve ring and the opening of the leaflet divide the flow into three regions: two lateral major orifices and a central minor one.[98,197] The last ones are made of a silastic ball with a circular sewing ring and a cage formed by 3 metal arches.[98,197] Mechanics valves require lifetime anticoagulation due to their high thrombogenicity and have longer durability.[14,19,32,98,197] Contrary, bioprosthetic or

biological valves are prosthetic valves manufactured from animal tissues and can be classified into three categories: stented xenograft, unstented xenograft, and homograft valves (from a cadaveric donor) or autograft (Ross procedure). [19,98,197] The first ones can be from porcine aortic valve leaflets or bovine pericardium, and both are mounted on a supporting stent (Figure 1-18).[98,197] The unstented valves are manufactured from a whole porcine aortic valve or bovine pericardium (Figure 1-18).[98,197] All these valves have a single orifice and no leakage after valve closure.[98,197] Although tissue valves are less thrombogenic compared with mechanical valves (do not require anticoagulant treatment, the hemodynamic profile and their durability are points of concern.[98] These valves suffer from calcification of the leaflets or material fatigue eliciting valve failure because of leaflet rupture or tearing.[98] They degenerate more rapidly in young patients (< 65 years of age) or during pregnancy.[14,19,32,98,197]

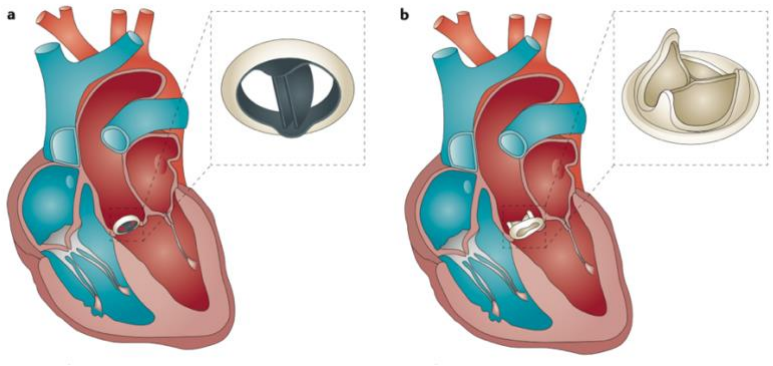

Figure 1-17. **Different types of surgical AVR.** (A) Surgical aortic valve replacement with a bileaflet mechanical valve. (B) Surgical aortic valve replacement with a bioprosthetic valve. Reproduced with permission from (14).

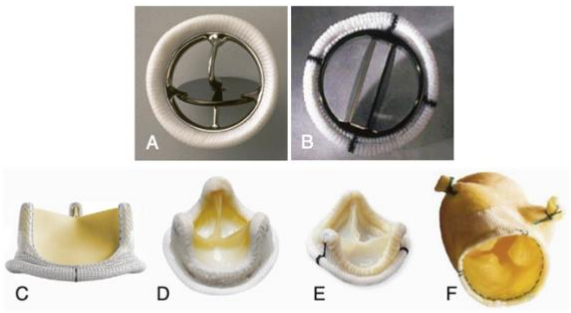

Figure 1-18. Types of prosthetic heart valves. (A) Monoleaflet valve, (B)bileaflet valve, (C) stented pericardial bioprothesis from Edward, (D)stented porcine bioprothesis from Medtronic, (E) stented porcine bioprothesis from St. Jude Medical and (F) stentless bioprothesis. Reproduced with permission from (98).

Selection of the valve type and design depends on many factors, such as the patient's age, life expectancy, preference, indication or contraindication for warfarin therapy, and comorbidities.[197] Choosing the right valve for the right patient is essential to optimize the outcome of patients undergoing an AVR.[197]

1.7.2.2. Transcatheter Aortic Valve Implantation

The transcatheter implantation of a bioprothesis (TAVI) transformed the treatment of patients with calcific symptomatic severe AS and who were not candidates for conventional AVR.[14,32,198] The TAVI is a minimally invasive procedure that implies the insertion of a bioprosthetic aortic valve within the orifice of the native stenotic valve using a catheter (Figure 1-18).[14] These valves are mounted onto a collapsible stent, so the valve can be collapsed onto a catheter and delivered through it.[98] This minimal invasive procedure avoids cross-clamping and cardiopulmonary bypass and, in this manner, it reduces procedure duration and risks.[98]

Transcatheter bioprosthesis can be delivered in the transfemoral, or transapical approach.[199] Other approaches less frequently performed are: transaortic, subclavian and transcarotid approaches.[98,199] The first mentioned approach is the most common, in which the catheter gains access to the stenotic valve by entering through the femoral artery and backtracking through the aorta to the heart.[98,199] In patients with severe peripheral vascular disease, the transapical or the other approaches can be selected.[199] A balloon aortic valvuloplasty is commonly performed before valve implantation.[98] Most of the currently available prostheses employ either balloon- or self-expandable technologies.[200] Although these technologies are considered comparable, differences exist and device characteristics play a role in prosthesis selection.[200] The first prototype implanted in humans was a balloon-expandable aortic stent valve consisting of a trileaflet bovine pericardial valve tissue mounted in a stainless steel frame.[200,201] During the following years, improvements of the valve and delivery systems resulted in a newer generation of this type of prothesis: Edwards SAPIEN, SAPIEN XT and SAPIEN 3 valves (Edwards Lifesciences, Irvine, CA). [200,202] The prototype of self-expandable valves is the CoreValve (Medtronic Inc; Minneapolis, MN) and is comprised of a trileaflet porcine pericardial tissue sutured into a wireframe of nitinol, a nickel-titanium alloy that has temperature-associated shape-memory features.[200,203]

TAVI has been firstly a life-saving treatment for patients at high or prohibitive operative risk with surgical AVR.[14] It was shown to be non-inferior and may be superior to surgical AVR in patients who were not candidates for surgery.[14,34,35,204-208] The progress in both technical and technology of transcatheter valve systems, as well as in the patient selection, has yielded TAVI as an optional treatment for more patients with AS or structural heart disease.[199] More recently, TAVI has demonstrated its equivalence with surgical AVR in intermediate-risk patients.[37,209,210] Nowadays randomized clinical trials demonstrate its safe use

in low-risk patients and noninferiority in comparison to the surgical approach.[211] However, concerns about long-term valve durability, paravalvular regurgitation and adverse events, such as stroke, vascular injury, heart block are still present.

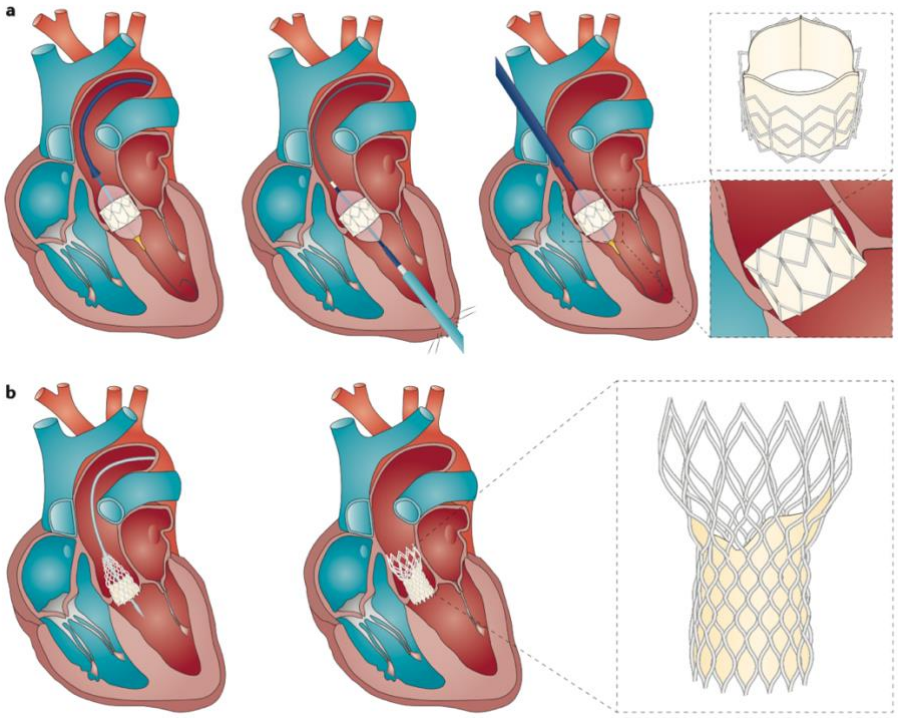

Figure 1-19. **Different surgical approach of TAVI.** (A)Transcatheter aortic valve replacement with a balloon-expandable valve via the transfemoral, transapical or transaortic approach. (B) Transcatheter aortic valve replacement with a self-expanding valve via a transfemoral approach. Reproduced with permission from (14).

2. HYPERTENSION IN AORTIC STENOSIS

2.1. HYPERTENSION

Hypertension is classically defined by office blood pressure (BP) of 140/90 or higher.[212,213] But, recent guidelines from the American Heart Association and the American College of Cardiology suggested that stage 1 hypertension should be considered in patients with SBP between 130-139 mm Hg or diastolic blood pressure (DBP) between 80-89 mm Hg, [214,215] which was before considered as a prehypertensive state or high normotensive state.[213]

2.2. EPIDEMIOLOGY

Hypertension affects over 1 billion people worldwide and is the most important risk factor for cardiovascular disease, including myocardial infarction, stroke, coronary artery disease, heart failure, atrial fibrillation, aortic dissection, peripheral arterial disease, renal failure, and cognitive damage; which are the leading cause of mortality.[19,216] Approximately 54% of strokes and 47% of coronary heart diseases, worldwide, are attributable to high BP.[216,217] In 2015, 7.8 million deaths (13-15% of total deaths) and 143 million disability-adjusted life years worldwide were attributable to hypertension.[23,218] In the United States, hypertension affects approximately 47% of people[19,23] and, 22,6% of the Canadian population.[212] Besides, the prevalence of high BP is increasing worldwide, especially in developing countries.

HTN is the second more prevalent cardiovascular disease worldwide and its prevalence, as CAVD and AS, increases with age.[23,219] Approximately, 65.4% of people over 60 years of age and almost 90% of subjects over 78 years of age may have hypertension[19,28], and 3% of people over 75 may be affected by AS.[19,28]

Additionally, hypertension is highly prevalent in patients with AS. Several lines of evidence have shown a variable prevalence ranging from 30% to 80%, depending on the mean age of the study. The prevalence rates from different studies are shown in table 3-1. Systolic hypertension (SBP over 140 mmHg) is the most common type seen in patients with AS.[220,221] Another article found elevated DBP as associated with a risk for AS requiring surgery in subjects below 60 years of age.[222]

Study (authors - year)	n	Mean age (years)	Population	HTN Prevalence (%)	HTN Definition
Rossebø AB et al. 2008[183]	1873	67±9	Mild-to-moderate, asymptomatic AS	51.5	Not mentioned
Cowell SJ et al. 2005[223]	155	68±11	Mild, moderate, and severe AS	65.8	Not mentioned
Briand M et al. 2005[224]	105	69±12	At least moderate AS	81	HTN diagnosis or use of antihypertensive treatment or SBP>140 mmHg or DBP>90 mmHg at the baseline clinical visit.
Rosenhek R et al. 2004[133]	176	58±19	Mild-to-moderate, asymptomatic AS	41	BP≥140/90mmHg based on the average of repeated readings
Antonini-Canterin F et al. 2003[225]	193	68±9	Symptomatic AS	32.1	History of HTN and/or antihypertensive treatment
Otto CM et al. 1997[226]	123	63±16	Asymptomatic AS	34.1	History of HTN or use of antihypertensive drugs.
Rieck AE et al. 2012[227]	1616	67±10	Asymptomatic AS	83	History of HTN or use of antihypertensive treatment or SBP>140 mmHg or DBP>90 mmHg at the baseline clinical visit.
Tastet et al. 2017[228]	101	69±10	Mild-to-moderate AS	84	Not mentioned.
Saeed S et al. 2020[229]	314	65±12	Moderate and severe AS	73.6	History of elevated BP values, past or current treatment with antihypertensive agents or a BP at the baseline clinic visit of ≥140/ 90 mmHg
Capoulade et al. 2015[46]	338	66±13	Asymptomatic AS	74	History of HTN
Capoulade et al[191]	243	57±13	Asymptomatic AS	30	HTN diagnosis or use of antihypertensive treatment or SBP>140 mmHg or DBP>90 mmHg at the baseline clinical visit.

Table 3-1. Prevalence of hypertension in AS population. *AS*, aortic stenosis; *DBP*, diastolic blood pressure; *HTN*, hypertension and *SBP*, systolic blood pressure

2.3. PHYSIOPATHOLOGY: A RELATIONSHIP OF TWO DISEASES

2.3.1. ENDOTHELIAL DYSFUNCTION AND LIPID INFILTRATION

As it could be concluded from Table 2-1, the vascular damage induced by hypertension, and the degenerative aortic valve stenosis are age-related conditions that frequently coexist due to sharing many pathophysiologic mechanisms. One of them is the increasing stiffness of the arterial system seen with aging, which implies an augmentation of systemic vascular resistance and a reduction of artery compliance.[28] This means that small increments in vascular volume induce relatively large increments of pressure, which manifests by widening pulse pressure, increasing pulse wave velocity of the pulsatile aortic flow, increasing and modifying central aortic pressure waveform, which is the sum of the pressure

wave generated by the LV and the reflected waves from the peripheral circulation. These parameters are associated with high shear stress and tension on the aortic valve leaflets, which promotes endothelial dysfunction or injury, inflammation, and afterward, calcification.[8,10,76,230,231] Furthermore, wide pulse pressure, high SBP, reduced systemic arterial compliance (SAC) are parameters associated with AS development.[224,230,232]

Both diseases are characterized by a substantial activation of proinflammatory and profibrotic markers leading to endothelial dysfunction and the development of atherosclerotic-like lesions. As was mentioned in chapter 1, histologic studies have shown that an early step in the AS development is the disruption of the aortic valve endothelium and the infiltration of oxidized lipid and lipoprotein depositions, macrophage, and T-lymphocyte infiltration, and microscopic calcification.[10,47,75,76,233] Those findings fit with the fact that arterial segments with turbulent blood flow, such as those at branch points or arterial surfaces of the aortic valve cups, show a predisposition to atherosclerotic-like lesion development that is strengthened by high blood pressure.[233-236] Thus, a possible mechanism that could explain, at least in part, the effects of hypertension on the development of AS is the synergy between elevated blood pressure and other atherogenic stimuli to induce oxidative stress (Figure 2-1).[233,237] This also could be suggested by the shreds of clinical evidence related to metabolic diseases and cardiovascular comorbidities as clinical risk factors of AS.

2.3.2. INFLAMMATION AND FIBROSIS

Activation of several profibrotic and inflammatory cytokines stimulated by endothelial injury may modulate aortic valve remodeling, subsequent calcification, and fibrosis (Figure 2-1). Further, primary hypertension promotes vascular calcium deposits which may contribute to aortic calcification (Figure 2-1).

One study found that an extracellular matrix glycoprotein, Tenascin C, which is increased in aortic stenotic valves, is associated with calcification and progression of AS.[238] Tenascin C has been implicated in cell proliferation, migration, differentiation, and apoptosis. Moreover, another study confirmed that augmented focal tenascin expression by vascular smooth muscle cells is linked with hypertension and may mediate ANG II-induced changes in vascular structure.[239] Both diseases have pathophysiological changes that lead to many pro-oxidants molecules and an increase in oxidative stress and ROS production.[80,240]

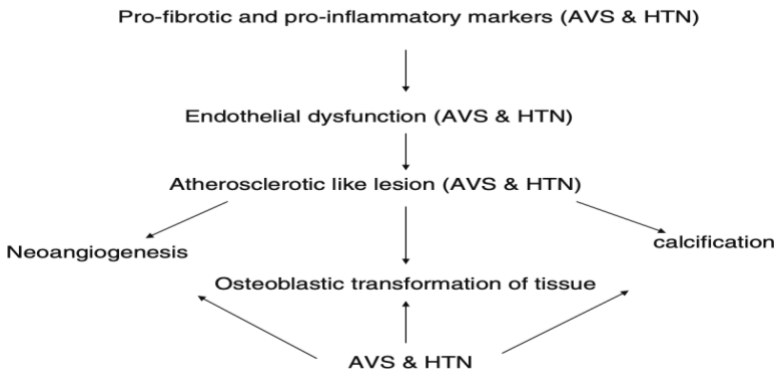

Figure 2-1. **Proposed common pathophysiologic pathway of hypertension and AS.** *AVS*, aortic valve stenosis; *HTN*, hypertension. Reproduced with permission from (146).

2.3.3. RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ACTIVATION AND ROLE

As it was explained in chapter 1, tissue renin, ACE, and Ang II are important intermediaries in AS pathophysiology contributing to inflammation, oxidative stress, fibrosis, and plaque expansion. They are found in higher concentrations in stenotic aortic valves compared to normal valves.[87,88] Additionally, cathepsin G, a protease capable of cleaving Ang I, and chymase present increased levels in stenotic valves;[88,230,241] and the serum levels of Ang II were linked with inflammation and tissue remodeling.[89] As it is well-known, increased activity in RAS is seen in hypertensive patients and it has an essential role in the hypertensive pathophysiology and endothelial cell dysfunction, particularly by the vasoconstrictor properties of Ang II and the sodium-retaining properties of aldosterone and vasopressin. In Figure 2-2, the RAS axis, its targets and elicited mechanisms are summarized.

Ang II can interact with angiotensin type 1 (AT1) or angiotensin type 2 (AT2) receptors and activates different cellular processes, which are illustrated in Figure 2-3.[19,28] AT1 receptors are the principal responsible for the contribution of Ang II to hypertension and hypertensive end-organ damage, including vasoconstriction, ROS generation, vascular inflammation and dysfunction, vascular/cardiac remodeling, and production of aldosterone, which is another cause of hypertension and end-organ damage (Figure 2-2). For example, it was observed that Wnt/ ß-catenin pathway enhanced by Ang II was implicated in renal injury and cardiac remodeling in animal-model studies.[242,243] Moreover, this pathway is also implicated in the calcification process of aortic valve.[8,10,244,245] AT1 receptors are widely expressed in the vasculature, kidneys, adrenals, heart, liver, and brain (Figure 2-2). The enhanced AT1-mediated signaling is also associated with insulin resistance and atherosclerosis, upregulating transcriptional and nuclear factors. These are also implicated in vascular calcification, tissue regeneration, proliferation, and remodeling.[246,247]

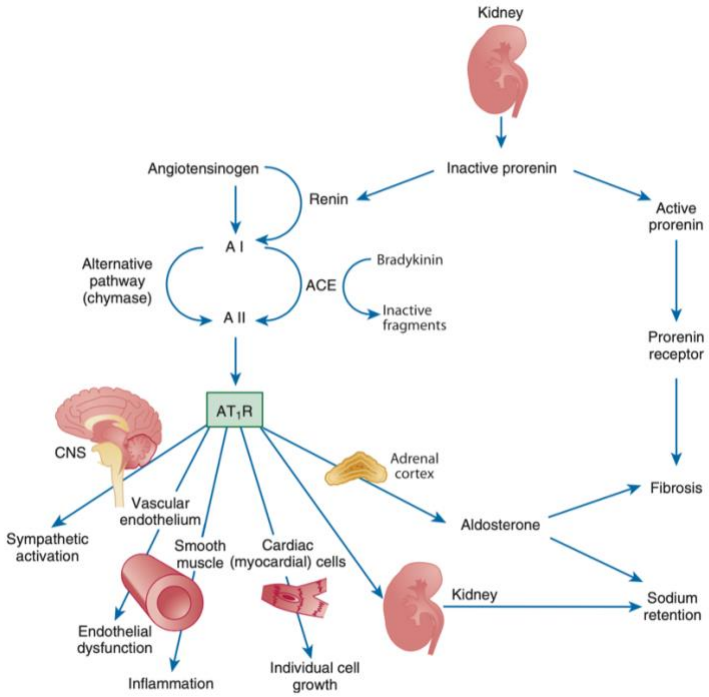

Figure 2-2. Diagram of the RAS and its targets. *A I*, Angiotensin I; *A II*, angiotensin II; *ACE*, angiotensin-converting enzyme; *AT1R*, angiotensin type 1 receptor; *CNS*, central nervous system. Reproduced with permission from (9).

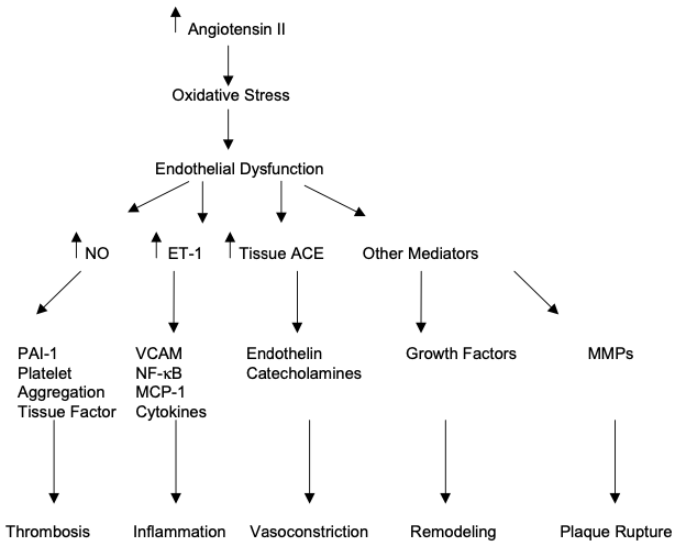

Figure 2-3. **Schematic representation of the multiple effects of increased tissue Ang II**. *ET-1*, endothelin-1; MCP-1:monocyte chemoattractant protein–1; *MMP*, matrix metalloproteinase; *NF-κB*, nuclear factor-κB; *NO*, nitric oxide; *PAI-1*, plasminogen activator type 1; *VCAM*, vascular cell adhesion molecule. Reproduced with permission from (266).

Aldosterone, another key product of RAS, is a mineralocorticoid and its release is stimulated by Ang II. It has effects on Na^+ reabsorption and this leads to expanding the plasma volume, contributing to hypertension. Besides, mineralocorticoid receptors are also expressed in the heart and kidneys, where they can be implicated in myocardial and kidney fibrosis (nephrosclerosis), and vascular inflammation. It was also shown that aldosterone contributes to LV hypertrophy and dysfunction.[19,28]

Lastly, NO generation is impaired in both diseases. One study found that plasma concentrations of asymmetric dimethylarginine, an endogenous inhibitor of NO synthase and a mediator of endothelial injury, are augmented in patients with AS in comparison to controls.[230,248]

As it was deeply mentioned, aortic valve sclerosis, stenosis, and hypertension are not inevitable consequences of aging and may be associated with specific comorbidities or clinical factors. Some of them are shared with both diseases as, diabetes, metabolic syndrome, or renal diseases.

2.4. IMPACT OF HYPERTENSION ON AORTIC STENOSIS: HYPERTENSION, ONLY A RISK FACTOR?

2.4.1. HYPERTENSION AND THE DEVELOPMENT OF CAVD

As it was mentioned, hypertension is an independent risk factor for the development of CAVD, aortic valve sclerosis, and AS.[16,52,53,73,249,250] Several observational studies have suggested an association between hypertension and aortic valve sclerosis.[16,251,252] In a sub-study of the Helsinki aging study, high arterial blood pressure, measured by 24hs-ambulatory blood pressure monitoring (ABPM), has been linked with an increased risk of aortic valve calcification (OR 1.74 [1.19-2.55]), assessed by echocardiography.[22,73] This study leads to avoiding bias from white coat hypertension due to the use of 24hs ABPM. Another epidemiological study from a public hospital in Ireland found more drastic results, concluding a 4-fold greater risk for CAVD.[253] From more than three million discharges, the authors found a prevalence of hypertension in 21% of discharges with aortic stenosis and aortic stenosis in 1.1% of those with hypertension. In the MESA study, 4274 participants were enrolled and stratified by age (younger than 65 years of age or 65 years or over). It was demonstrated a link between stage I or II hypertension, defined by JNC-7,[254] and high risk for AVC, measured by CT, in younger patients.[249] Similarly, SBP and pulse pressure were strongly associated with prevalent AVC in those under 65 years of age than those over 65 years of age.[249] All these results were adjusted for common cardiovascular risk factors and patients taking antihypertensive medications were excluded. Another study from 2017 indicated hypertension as the strongest predictor of the development of severe AS.[255]

There are not many animal studies evaluating this association. One study in a hypertensive model developed in rabbits has shown inflammatory nodules and leaflets thickening in the aortic valve, accompanied by a decrease in AVA and an increase in mean transvalvular gradient pressure.[233] However, this model was created by clamping the renal arteries and this provoked renal dysfunction, which can be another cause for AS. Another model for AS was developed in hypercholesterolemic/hypertensive mice.[256] Neither of these models has demonstrated calcification changes in the aortic valves. Besides, experimental (*ex-vivo* and *in vitro*) studies have induced the calcification of the aortic valve in response to an elevated cyclic stretch of 15%, which represents the hypertensive conditions seen in the arterial vascular system in hypertensive patients.[231,257] These results suggest that hypertension may increase the mechanical stress imposed to the valve leaflets leading to the activation of pathophysiological mechanisms that incite the development of CAVD.

2.4.2. HYPERTENSION AND THE PROGRESSION OF AS

Therefore, there is no doubt that systemic hypertension is an important and strong risk factor for the development, or the prevalence of CAVD, evidencing as aortic valve sclerosis and/or AS. However, the impact of hypertension on AS progression is more discussable. Several studies have failed to indicate an association between hypertension or high blood pressure and a faster progression of AS.[56,64,67,258-261] One of the first studies which have analyzed the impact of several clinical risk factors on the progression of aortic stenosis has not found an association between hypertension and faster progression of this disease.[259] One limitation of this study could be the difficulties to establish the etiology of AS implying that its sample might have not been representative of CAVD.[259] Another limitation was its little sample size (n=49), from which only 20% of the patients had hypertension and did not allow to show a significant difference between subgroups.[259] Another retrospective study has revealed similar results although its sample size was larger (n=170).[260] There was no significant difference between slow and fast progression groups regarding the diagnosis of hypertension.[260] From one sub-study of the "Epidemiology of Coronary Artery Calcification" (ECAC) study, neither the history of hypertension nor high blood pressure had been associated with the progression of the aortic valve calcification (measured by CT) [56] However, only 70 patients from 262 could be assessed their advancement of the aortic valve calcification. Moreover, the prevalence of AS in this study was difficult to estimate due to the lack of an initial evaluation of AS by echocardiography from a large proportion of patients.[56] An analysis post-hoc of the "*Simvastatin Ezetimibe* in Aortic Stenosis" (SEAS) study could not show an impact of hypertension on the progression of the AS assessed by echocardiography.[261] Hypertension was considered by a history of it, antihypertensive prescription, or high blood pressure at the baseline visit. However, this study revealed a

strong association between hypertension and higher cardiovascular events, increasing more than two-folds the risk.[261]

Furthermore, some recent studies could demonstrate hypertension as a risk factor for the progression of aortic valve narrowing.[191,228] Also, they have revealed hypertension as a risk factor for increasing all-cause and cardiovascular mortality or events (as hospitalizations). Indirect parameters linked with high blood pressure and arterial stiffness as low compliance or high arterial impedance have been also linked with risk for faster AS progression, LV systolic dysfunction, cardiovascular and all-cause mortality.[224,225,232,261] One retrospective study including 338 patients has separated them into four groups: no hypertensive patients and not treated by RAS inhibitors (control [ctrl] group), hypertensive patients but not treated with RAS inhibitors (HTN group), patients with hypertension and treated with ACEis (ACEIs group) and hypertensive patients treated with ARBs treatment (ARBs group).[191] The hemodynamic progression rate of AS was calculated from peak aortic jet velocity measured by echocardiography.[191] The HTN group was significantly associated with faster hemodynamic progression of AS, as seen in figure 2-4, panel A.[191] This result was kept after adjustment for the weighted variables[191] Besides, as it was mentioned, during a mean follow-up of 6.2 ± 2.4 years, the HTN group and the ACEIs group were associated with a significant increase risk in all-cause mortality or AVR compared with control group (figure 2-4, panel B).[191] Similar results were obtained from Cox proportional hazard model after further adjustment for the weighted variable (figure 2-4, panel C).[191]

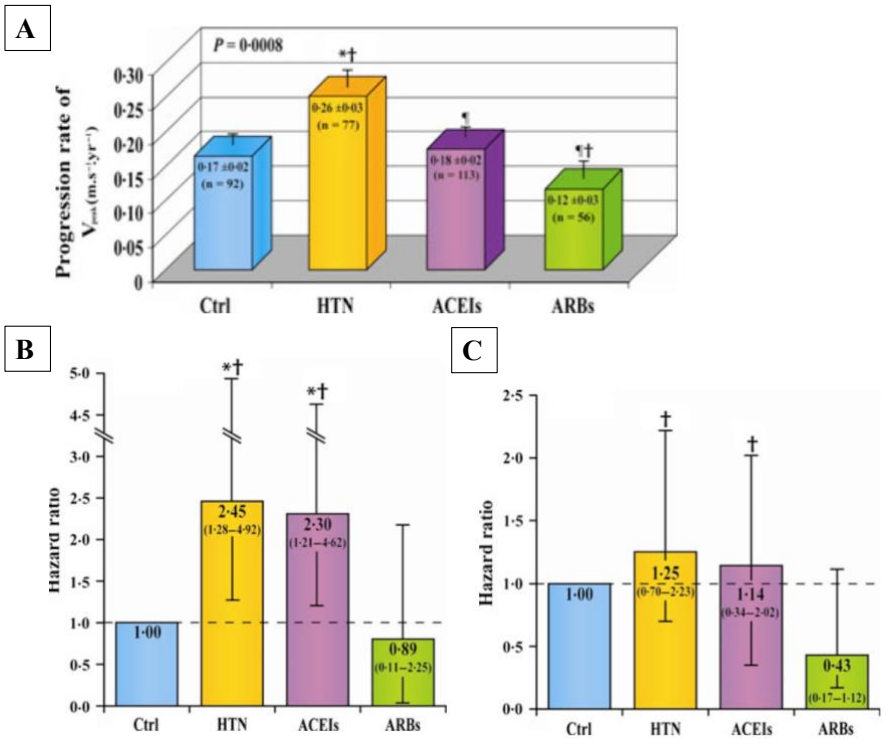

Figure 2-4. Hypertension and AS progression. (A) Comparison between groups of the AS progression rate. **(B)** Comparison between groups of the individual hazard ratio for all-cause mortality. **(C)** Comparison between groups of the adjusted hazard ratio for all-cause mortality. *ACEIs,* angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin receptor blockers; *Ctrl*, control and *HTN*, hypertension. Reproduced with permission from (191).

Another research paper analyzing the association between systemic hypertension and AS progression suggested that hypertension was associated with faster AS progression, assessed by CT. AS severity was evaluated by Doppler-echocardiography and CT at baseline and two-year visits.[228] Tastet et al demonstrated that AVC progression in patients with hypertension was steeper as compared to those without it (+370AU, 25th and 75th percentiles [PC]: 126;824 AU vs. +157AU, 25th and 75th PC: 14;82AU).[228] Consistent results were seen evaluating $AVC_{density}$ progression.[228] After adjustment for age, sex, metabolic comorbidities, antihypertensive medication, creatine level, baseline V_{max} (or baseline mean pressure gradient or baseline AVAi and baseline AVC or $AVC_{density}$, SBP (expressed in a continuous variable), systemic hypertension, or isolated systemic hypertension were significantly associated with AVC or $AVC_{density}$ progression.[228] However, evaluating the AS progression by Doppler-echocardiography, they could not reveal a significant difference in the progression of V_{max} comparing patients with hypertension and those without hypertension at baseline.[228] Similar results were gotten analyzing mean pressure gradient progression or AVAi difference from baseline to 2-year follow-up.[228] Interestingly, the author did not find an association between AVC progression and V_{peak} progression,

whereas in patients without hypertension, AVC progression was significantly correlated with V_{peak} progression.[228] These last results were consistent with other studies that have revealed that hypertension might interfere with hemodynamic assessment of AS severity by Doppler-echocardiography or cardiac catheterization.[113,224,228,262,263] Hypertension may lead to underestimation of stenosis severity and its hemodynamic progression rate.[137,228] Because of that, guidelines recommend the assessment of hemodynamic AS severity to be performed once blood pressure is normalized.[30,264]

The principal fact to remark of these last studies is that hypertension may be one strong risk factor for AS progression and worse clinical outcomes. Therefore, it may be essential to accurately treat hypertension and to establish optimal blood pressure levels in patients with AS. Only one article has suggested that blood pressure should be below 130 mmHg in patients with AS and recent AVR.[265] More recently, a study of mild-to-moderate asymptomatic aortic stenosis suggested an optimal SBP of 130– 139 mmHg and DBP of 70 – 90 mmHg.[266] In the recent AS guidelines, there are no recommendations about the expected threshold for optimal blood pressure control, and neither, suggestions for antihypertensive drug selection in those patients.[30,264] Further studies are needed.

2.5. AS AND HYPERTENSION: BOTH DISEASES OF THE MYOCARDIUM

Hypertension and AS are two diseases with chronic pressure overload that, when they coexist, the LV faces a double load leading to adaptative changes in LV geometry. In patients with AS, hypertension is associated with higher LV mass, wall thickness, a greater presence of asymmetric septal hypertrophy, and a higher prevalence of LV hypertrophy.[230,261,267] Asymmetric septal hypertrophy is recognized in both diseases, with and without LV hypertrophy (LV mass index $\geq$ 104 g/m^2 in women and $\geq$ 116 g/m^2 in men). It can be found in earlier stages of LV adaptation in hypertensive patients. The presence of asymmetric septal hypertrophy (interventricular septal/posterior wall thickness ratio > 1.5) in AS was studied with 1719 asymptomatic patients from the SEAS study.[267] It was found in 22% of patients and was associated with higher LV mass index, peak transaortic velocity, total peripheral resistance, and concomitant hypertension.[267] 34% of them had asymmetric septal hypertrophy and LV hypertrophy; interestingly, they had higher SBP, lower LVEF, and larger left atrial diameter than patients with asymmetric septal hypertrophy only.[267] Moreover, hypertension was the most important predictor both for asymmetric septal hypertrophy and for asymmetric LV hypertrophy.[267] In previous studies, the presence of asymmetric septal hypertrophy in AS may affect the extent of surgery and influence the surgical approach. It has also been associated with higher perioperative morbidity.[268,269]

LV hypertrophy is the pathognomonic characteristic of hypertensive heart disease and constitutes a powerful independent risk factor for heart failure, ventricular arrhythmias, and sudden cardiac death,

ischemic stroke, atrial fibrillation, and embolic stroke in those patients.[19,28] As in AS, it implies several morphological changes that culminate in a maladaptive response because of the overload produced by high blood pressure and increased systemic arterial resistance. In the case of the cardiac adaptation to hypertension, it may exist as concentric remodeling, concentric or eccentric hypertrophy (which were illustrated in the first chapter). This response can be modified by the stage of hypertension and its duration, the type and efficacy of hypertensive medical treatment and its duration, and, also, different clinical or hemodynamic factors.[270] Genetic factors may also play a role.[270] From 30 to 50% of hypertensive patients present one type of hypertrophy; mostly eccentric hypertrophy, which is a different type of the most frequently found in AS (concentric hypertrophy).[99,225,270-272] Ganau et al have reported that 48% of patients with untreated hypertension (n=165) have abnormal LV geometry and 27% of them present eccentric hypertrophy when the partition value of RWT was 0.44.[272] Being this last one lower (RWT= 0.41), the prevalence of eccentric hypertrophy was 19%; concentric remodeling, 21% and concentric hypertrophy, 15%.[272] Another study found a 35% of prevalence of abnormal LV geometry in hypertensive patients, being concentric remodeling more prevalent. A further publication found a prevalence of 23% of eccentric hypertrophy in 280 hypertensive patients without preexisting heart disease.[273] In the LIFE study, from 960 patients, 46% of them had eccentric hypertrophy and 24% of them had concentric.[122]

In the case of AS, LV hypertrophy has been considered as a parameter of severity. However, epidemiologic findings, clinical experience, and newer publications have revealed the presence of LV hypertrophy in mild-to-moderate asymptomatic AS, and hypertension was one of the risk factors associated with this finding. From the SEAS study, which has randomized patients aged 45 to 85 years with asymptomatic AS to a fixed combination of *simvastatin* 40 mg and *ezetimibe* 10 mg once daily[274] and without known coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, or any condition requiring lipid-lowering therapy, several sub-studies have evaluated the impact of hypertension on LV geometry, systolic function, and cardiovascular mortality in those patients. Follow-up was defined as the last echocardiogram evaluation before the occurrence of any cardiovascular study endpoint.[227] After 4.3 years of follow-up, among patients with normal LV geometry (n = 903), hypertension predicted a 51% higher risk of having abnormal LV geometry at the last follow-up visit, even after adjustment for severity of AS, age, LVEF, sex and SBP at this visit.[227] In another sub-study, the hypertensive group had higher wall thickness, relative wall thickness, LV mass/height ratio, and circumferential end-systolic wall stress.[227,261] It was associated with higher LV mass independent of significant associations with aortic valve regurgitation, male sex, higher body mass index, lower LVEF, and circumferential end-systolic stress, whereas no independent association was found with patients' age or AVA.[261] Besides, systolic, mean, and DBPs were weakly associated with LV mass/height ratio.[261]

However, it is more complex to define the type of LV adaptation to chronic pressure overload in the case of AS and concomitant hypertension. In the SEAS study, at baseline, most of the patients (n = 1616 patients) have normal LV geometry despite being hypertensive or normotensive. From the 41% of the hypertensive patients with AS and abnormal geometry, eccentric hypertrophy was the most prevalent type, and concentric hypertrophy was more frequent than concentric remodeling in those patients (Figure 2-5).[261] At follow-up, the prevalence of concentric LV hypertrophy increased three times and became the most common abnormal LV geometry in both groups, remaining more prevalent in hypertensive patients (figure 2-7).[227] Further, 49% of hypertension patients with eccentric LV hypertrophy at baseline had concentric LV hypertrophy at the final study visit.[227,261] When the severity of AS was contemplated dividing all the study-population into tertiles of Vmax, LV geometry differed significantly between both groups (figure 2-8).[261] Consisting with some results of this study, Antonini-Canterin et al found that concentric LV hypertrophy was the most prevalent in patients (n=193) with severe, symptomatic AS whether they were hypertensive or not.[225] Similar findings were reported by another study, in which concentric hypertrophy was significantly prevalent in patients with severe AS and hypertension compared with those without it.[275]

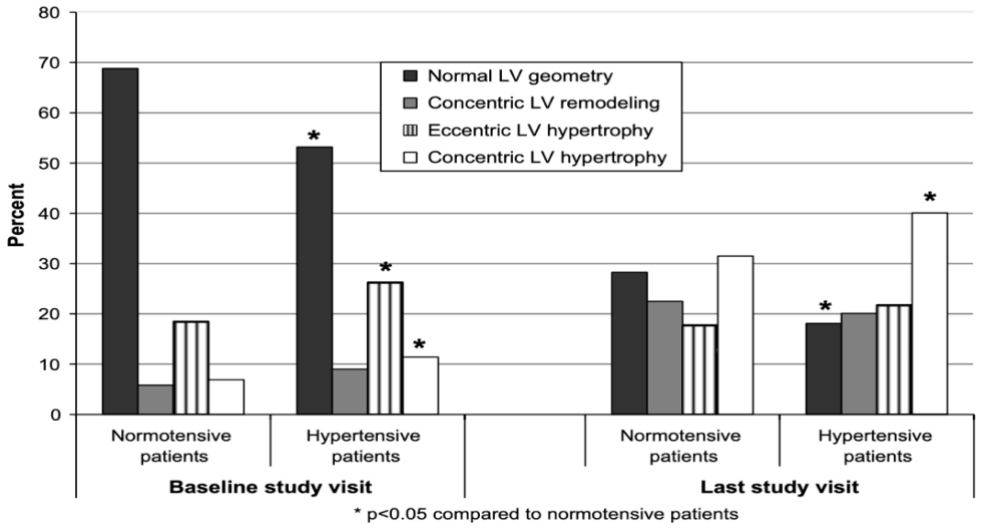

Figure 2-5. LV geometry in normotensive and hypertension patient groups at baseline and the last study visit. *LV*, left ventricular. Reproduced with permission from (142).

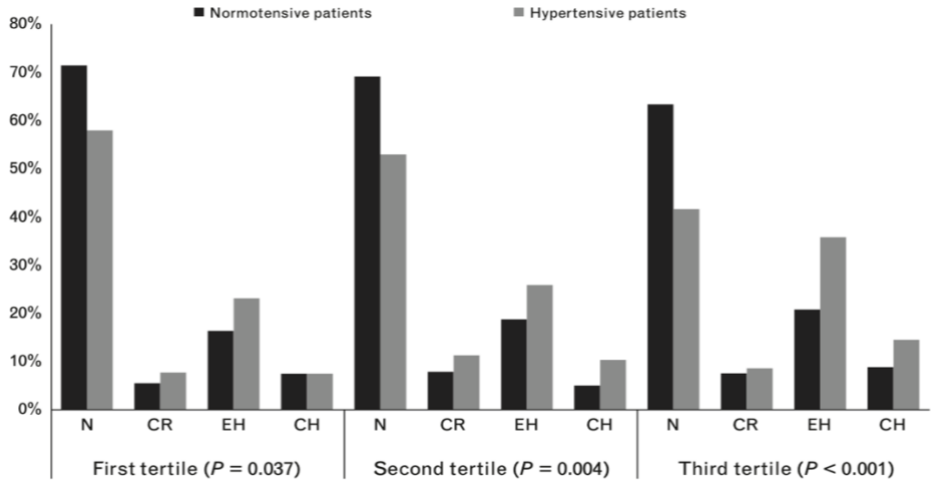

Figure 2-6. LV geometry in patients grouped by tertiles of peak transaortic velocity. Given p-values compare LV geometry between hypertensive and normotensive groups of patients within individual tertile. *N*, normal LV geometry; *CR*, concentric remodeling; *EH*, eccentric hypertrophy; *CH*, concentric hypertrophy. Reproduced with permission from (179).

In brief, it seems that the progression of AS is associated with a change from predominantly normal geometry, with eccentric hypertrophy being the most frequent abnormal LV geometric pattern, to predominantly concentric LV geometry both in normotensive and hypertensive patients. Conversely, hypertension may lead to different types of LV geometric adaptation, depending on the dominant clinical and hemodynamic factors. Therefore, when these two diseases coexist, it may be difficult to establish the impact of each one on LV hypertrophy. One study using numerical simulations has shown that concomitant mild-to-moderate hypertension may have a major impact on LV wall volume and LV hypertrophy in contrast to mild-to-moderate aortic stenosis because concomitant systemic hypertension may cause a noticeable augmentation in LV afterload and systolic wall stress (figure 2-9).[276] However, when the stenosis becomes severe, its impact on the LV geometry might rise exponentially and may even become preponderant comparatively to that of hypertension (as it is graphed in figure 2-10). These findings are consistent with the hypothesis from the study of Rïeck et al., in which they demonstrate that eccentric hypertrophy was the most common abnormal LV geometric pattern (as it is in essential hypertension)[99,272,277] in patients with mild-to-moderate asymptomatic AS and concomitant hypertension.[261] Moreover, they are also consistent with previous publications in which LV mass and the prevalence of LV hypertrophy were similar in normotensive and hypertensive patients with severe and symptomatic AS.[225,278] Some limitations of this study are inherent to numerical studies, in which a mathematical model is created to simulate physiological changes. This model is simpler, and several parameters are not taking account. The authors only considered the mechanical aspects of LV hypertrophy whereas hormonal and neurogenic factors that might be involved were not taken into

account.[276] Diastolic function was considered normal as well as LVEF, heart rate, and SV.[276] Wall stress was constant, and all the cardiovascular parameters were fixed in the simulations.[276]

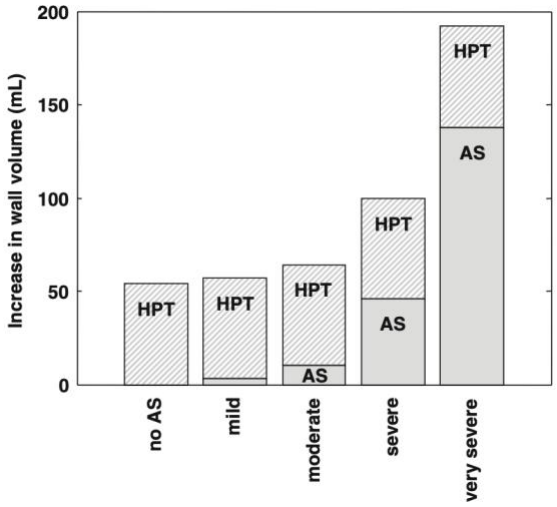

Figure 2-7. Theoretical increase in LV wall volume for different severities of AS with concomitant mild hypertension (150/95 mmHg). *AS*, aortic stenosis, *HPT*, hypertension. Reproduced with permission from (196).

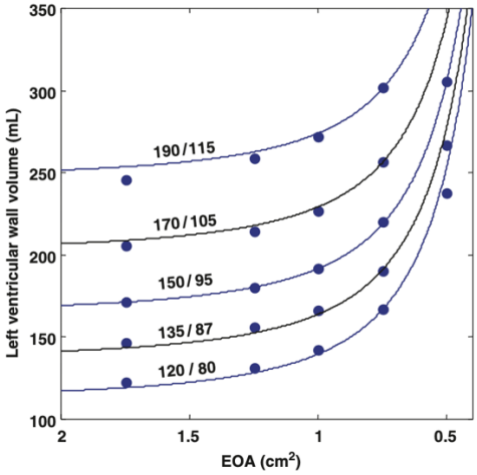

Figure 2-8. Theoretical LV wall volume as a function of effective orifice area for different grades of systemic hypertension. Numbers above curves refer to systolic and diastolic aortic pressures and each dot represents one simulation. The fitting curves are issued from equation of the proposed model. *EOA*, effective orifice area. Reproduced with permission from (196).

The higher prevalence of abnormal LV geometry and LV hypertrophy is associated with greater increased wall stress and decreased myocardial function, which both are associated with worse cardiovascular outcomes,[121,279-281] still after the AVR.[121,170,282] Likewise, the presence of hypertension is still associated with lower LV mass reduction after AVR and is considered one of the major independent risk factors

for death, postoperative heart failure (in the case of SAVR), and worse clinical outcome.[283-285] Furthermore, LV hypertrophy may coexist with myocardial fibrosis, increased LV chamber stiffness, delayed LV relaxation, increased filling pressure and diastolic and systolic dysfunction.[286] Some evidence suggests that the presence of myocardial fibrosis may impair the electrical coupling of myocardial cells by separating these cells with collagen, which creates tissue heterogeneity from which reentrant tachyarrhythmias may appear.[287-289] Moreover, LV hypertrophy may lead to myocardial ischemia, symptoms, and ominous outcomes as heart failure or sudden cardiac death. Conclusively, it is an independent risk factor for cardiovascular morbidity and mortality.[227,276,290] For example, in the SEAS study, it was found from a Cox regression analysis that 1 SD higher baseline LV mass index can predict increases in HR of 12% for major cardiovascular events (composite endpoint consisting of death from cardiovascular causes, aortic valve replacement, heart failure hospitalization due to progression of AS, non-fatal myocardial infarction, hospitalization for unstable angina pectoris, coronary artery bypass grafting, percutaneous coronary intervention, and non-hemorrhagic stroke), 28% for ischemic events, 34% for cardiovascular mortality, and 23% for all-cause mortality and hospitalization for heart failure after adjustment for age, sex, BMI, AS severity, LVEF, concentric LV geometry, and concomitant hypertension.[227] Using time-varying models, which consider the progressive increase in LV mass index during follow-up, similar results were found: 1 SD higher in LV mass index was associated with 13% to 61% higher HR for cardiovascular events, independent of age, sex, Zva, LVEF, concentric geometry, and hypertension.[227]As it can be noted, hypertension was not a predictor for cardiovascular mortality, but it was associated with a higher rate of ischemic cardiovascular mortality and 2-fold augmented all-cause mortality.[227]

As it was said, myocardial fibrosis can be directly diagnosed by CMR imaging with gadolinium late enhancement technique, and indirectly diagnosed by reduced GLS by speckle tracking echocardiography, [282,286,291] which is also a subclinical parameter of LV systolic dysfunction. Recent studies in AS using CMR with late gadolinium enhancement have shown an association between myocardial fibrosis, lower myocardial shortening or deformation, and worse prognosis.[123,181,292] One publication has confirmed that myocardial fibrosis is particularly presented in the LV midwall in patients with moderate-to-severe AS and higher LV mass and this midwall fibrosis was an independent predictor of mortality in patients with AS.[181]

Patients with compensatory LV hypertrophy may have reduced myocardial systolic function despite normal LVEF. One surrogate of LVEF, which can be more sensible, is midwall fractional shortening, which can be easily assessed by a standard echocardiogram using a validated equation.[293] One recent publication from the SEAS study analyzing the prognostic importance of the development of LV mid-

wall dysfunction during the progression of AS in patients with normal LVEF found a higher prevalence and incidence of low midwall fractional shortening (gender-specific cutoffs: <16% in women and < 14% in men)[294] in patients with milder stages of AS and comorbidities like hypertension and obesity, reflecting an impact of these diseases in LV mechanics and systolic function.[279]

One cross-sectional has assessed the changes in subendocardial and subepicardial LV deformation in patients with moderate-to-severe AS, which might be useful in detecting subclinical LV systolic dysfunction in those patients.[295] This publication included 115 patients with moderate (n=47) and severe (n=68) AS with preserved LVEF and 89 age-matched normotensive (n=37) and hypertensive controls (n=52) matched by age and sex.[295] LV hypertrophy parameters gradually rose from controls across moderate-to-severe AS and LVEF was similar between groups.[295] However, as it was expected, GLS and circumferential strains were significantly lower in AS than in control groups even after adjustment for LV mass index and total cholesterol; both strains in all three layers (endocardial, mid-myocardial, and epicardial) were also significantly reduced among AS patients.[295] Also, global and all layer-specific longitudinal strains were significantly lower in hypertensive patients with severe AS in contrast to their normotensive counterparts; and global circumferential strain was only reduced among hypertensive patients with moderate AS.[295] Interestingly, longitudinal strain gradient was the lowest in hypertensive participants with moderate aortic AS, whereas circumferential strain gradient was similar between all AS groups, but still significantly lower than in the control group.[295] Those results could not be neglected and denoted the relevance of hypertension, in addition to LV hypertrophy, on LV systolic function and mechanics. Moreover, SBP, LV mass index and aortic valve mean gradient were independently correlated with LV longitudinal and circumferential strain after adjustment of BMI and age.[295] The meaning of the difference in layer-specific strain and gradients should be further studied. It may reflect the increasing mismatch between subendocardial blood flow and oxygen demand as a result of an increased wall thickness. The subendocardial layer may receive the highest tension during the increase in systolic pressure, with lower wall stress in the other two layers, affecting its deformation. It should be noted that reduced GLS is associated with worse outcomes also after AVR.[156,291,296-298]

It is worthy to mention that not only the concomitance of hypertension in AS is associated with higher LV mass index, higher prevalence of abnormal LV geometry and LV hypertrophy, and sooner subclinical systolic dysfunction, it is also associated with earlier onset of symptoms during the disease in patients with severe AS.[225] Antonini-Canterin et al. has performed a study with 193 patients (mean age 68 ±9) with symptomatic AS, in which only 32% of patients had a history of systemic hypertension and/or the administration of antihypertensive drugs.[225] Hypertensive patients had larger AVA and lower stroke work loss with a similar degree of symptoms.[225] Despite being the distribution of the symptoms similar between

groups, these mentioned results may indicate that the clinical symptoms may have developed at an earlier stage of the disease.[225] In another study conducted by Saeed et al., lower peak SBP and rapid early rise in heart rate were associated with a higher risk of revealed symptoms during the exercise treadmill test.[299] Rapid early rise in heart rate was strongly associated with hypertension whereas lower peak SBP was not.[299] As it was previously mentioned, the onset of symptoms are one strong predictor for adverse prognosis.[9,14,20,32,120,137,225]

2.6. DIAGNOSIS OF HYPERTENSION AND SYSTEMIC ARTERIAL HEMODYNAMICS EVALUATION

2.6.1. DIAGNOSIS OF HYPERTENSION

Hypertension is known as the "silent killer" because it is an asymptomatic chronic disorder that, uncontrolled, can silently and severely damage blood vessels, brain, heart, and kidneys. However, if symptoms are developed, target organs are normally injured. Examples of injuries to these organs (end-organ damage) are exemplified in Table 2-2. Symptoms related to hypertension and end-organ damage are, for example, exertional dyspnea from diastolic dysfunction, nocturia from the increased sustained pressure to rise natriuresis, and erectile dysfunction from endothelial damage. Antihypertensive treatment can improve those symptoms.[19,28]

The initial evaluation of a hypertensive patient should include a complete clinical history, physical examination, and laboratory tests. The objectives of this assessment should be the accurate measurement of blood pressure, the evaluation of the patient's global cardiovascular risk, the screening of end-organ damage (Table 2-2), the screening of secondary form of hypertension, and the assessment of lifestyle behaviors related to high blood pressure.[28]

Examples of End-organ Damage	
Brain and Eyes	Cerebrovascular disease Stroke Ischemic stroke and transient ischemic attack Intracerebral hemorrhage Aneurysmal subarachnoid hemorrhage Dementia Vascular dementia Mixed vascular dementia and dementia of the Alzheimer's type Hypertensive retinopathy
Heart	LV dysfunction LV hypertrophy Heart failure Coronary artery disease Myocardial infarction Angina pectoris Acute coronary syndromes
Kidneys	Renal disease Chronic kidney disease (GFR < 60 mL/min/1.73 m2) Albuminuria
Peripheral Artery System	Peripheral artery disease Intermittent claudication Erectile dysfunction Abdominal aortic aneurysm Aortic Dissection

Table 2-2. Examples of end-organ diseases caused by uncontrolled hypertension.

Ambulatory blood pressure monitoring (ABPM) is considered the "gold-standard" for hypertension diagnosis because of its accuracy. It consists of automated measurements of blood pressure during 24-hours or 48-hours while patients are doing their usual activities. It also allows measuring nighttime blood pressure that best predicts cardiovascular outcomes.[300] It is established that patients with mean awake SBP of 135 mm Hg or higher, or DBP of 85 mm Hg or mean 24-hour SBP of 130 mm Hg or higher, or DBP of 80 mm Hg or higher have (out-of-office) hypertension.[301] Also, some consensuses consider hypertension in patients with nighttime SBP of 120 mm Hg or higher or DBP of 70 mm Hg or higher.[19]

2.6.2. EVALUATION OF THE SYSTEMIC ARTERIAL HEMODYNAMICS

Chronic endothelial cell dysfunction, neurohormonal activation, and elevated blood pressure cause remodeling of blood vessels with further hypertension perpetuating.[19,28,302,303] Vascular remodeling manifests as geometrical alterations of the vessel wall and then, decreases vessel lumen affecting systemic vascular resistance (SVR). SVR is principally determined by vascular radius, in which small decreases in lumen size significantly increase vascular resistance.[19] Another factor implicated in SVR augmentation and vascular mechanism of hypertension is the reduction in artery compliance, which was already mentioned in the pathophysiology section of this chapter.[28] Those modifications may be part of the phenomenon denominated medial elastocalcinosis, which could be also implicated in the pathogenesis of AS.[7,304]

The reduced SAC, which contributes to increase LV afterload and myocardial oxygen demand and to decrease coronary flow during systole,[224,305] is a strong and independent predictor of LV dysfunction and adverse outcomes in hypertension.[224,306,307] Briand et al. have shown that SAC, defined as the ratio of SV or SVi and pulse pressure (PP), was associated with higher blood pressure, AS severity, and higher SVR.[224] From a multivariable analysis, diastolic dysfunction was also associated with lower SAC (SVi/PP ≤ 0.6 ml/m2/mm) and severe AS, and systolic dysfunction (LVEF<50%) was also independently associated with much lower SAC (SVi/PP ≤ 0.5 ml/m2/mm), severe AS and coronary artery disease.[224] Thus, reduced SAC has an ominous consequence to LV mechanics, and therefore, it is associated with earlier onset of symptoms.[224] In another study, SAC was also associated with myocardial systolic dysfunction and increased LV global load.[308] Hence, SAC is another important parameter to evaluate in patients with AS, especially when hypertension coexists.

Being already mentioned, the LV faces a double load from the systemic arterial system and the obstructed valve. This double load can be evaluated by an index called the valvulo-arterial impedance (Zva). It can be calculated by dividing the estimated LV systolic pressure, which is the sum of the systolic arterial blood pressure and the mean transvalvular pressure gradient, by the SVi. Schematic representation of this double load is illustrated in Figure 2-12. This allows to assess the global LV hemodynamic load, and indeed, it has been proved to be superior to the standard indexes of AS severity in predicting LV (diastolic and systolic) dysfunction.[190,224,232] It is also a good predictor of mortality in asymptomatic severe AS.[309] Further, increased Zva was independently associated with all-cause mortality (regardless of whether or not there was an AVR).[232] In Figure 2-12, the proposed classification of Zva levels and the overall survival associated with each Zva level are illustrated.

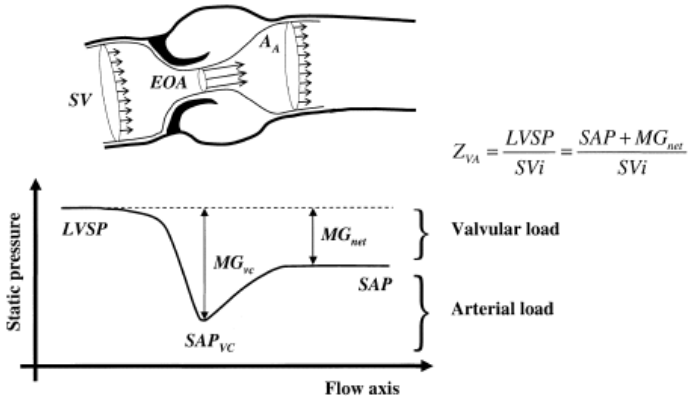

Figure 2-9. Schematic representation of the flow and static pressure across the LVOT, aortic valve, and ascending aorta during systole. A_A, aortic cross-sectional area; *EOA*, effective orifice area (i.e., the cross-sectional area of the vena contracta); *LVSP*, left ventricular systolic pressure; MG_{net}, transvalvular pressure gradient after pressure recovery (i.e., net MG); MG_{vc}, transvalvular pressure gradient at the vena contracta; *SAP*,

systolic aortic pressure; SAP_{vc}, systolic aortic pressure at the vena contracta; SV, stroke volume; SVi, stroke volume index; Z_{VA}, valvulo-arterial impedance." Reproduced with permission from (139).

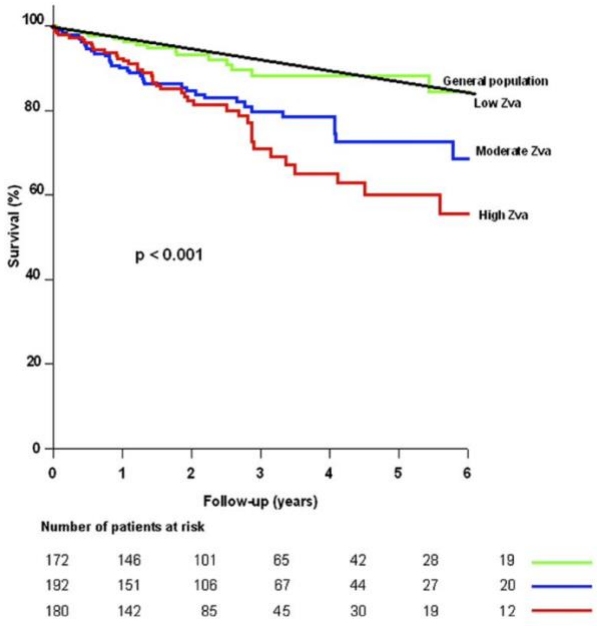

Figure 2-10. Overall survival as a function of the level of the Zva. Low Zva ≤3.5 (green line), moderate Zva >3.5 and < 4.5 (blue line), high Zva ≥ 4.5 (red line). The control group was the general population of Quebec matched for age and sex (black line). Reproduced with permission (148).

2.7. TREATMENT

Hypertension treatment is not only important for lowering arterial blood pressure, but also yields large reductions in the risk for cardiovascular comorbidities and mortality, renal failure, and all-cause mortality. Patients with the highest global cardiovascular risk may have the most benefit.[19,301] The medical treatment for lowering blood pressure is wide and several alternatives can be taken to adjust it, and so, to achieve the blood pressure goals.

First of all, it is important to apply with patients lifestyle interventions that favorably decrease blood pressure has positive effects on the prevention and treatment of hypertension.[19,28,301] Health-lifestyle interventions are recommended for subjects with prehypertension or high-normal blood pressure and as an adjunct to drug therapy in hypertensive patients.[19,214,215,301] These interventions should also address cardiovascular disease risk. Some of them are mentioned in Table 2-3.

Suggested lifestyle modifications to manage hypertension	
Weight Reduction	Attain and maintain BMI < 25 kg/m^2.[310-313]
Dietary salt reduction	2-4 g NaCl/day. [113,242,314-316]
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat. [19,317-321]
Moderation of alcohol consumption	For those who drink alcohol, consume ≤2 drinks/day in men and ≤1 drink/day in women.[322]
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/day.[19,28,323,324]
Cigarette Smoking Cessation	To decline the deleterious effect of smoking on cardiovascular risk.[19,325]

Table 2-3. Suggested lifestyle modifications. *NaCl*, sodium chloride. Adapted from (14).

Drug therapy is strongly recommended to start with individuals presenting SBP equal to or higher of 140 or DBP of 90 mmHg.[19,28,212-215,301] However, in patients with diabetes, chronic renal failure or high-risk for cardiovascular disease, other blood pressure thresholds can be suggested, for example, in diabetic patients with coronary artery disease or with orthostatic hypotension, excessive BP lowering should be avoided.[326] The degree of benefit derived from the antihypertensive therapy is related to the magnitude of the reduction in arterial blood pressure, with minor differences related to major drug classes.[327] Monotherapy or combined therapy by several agents with complementary antihypertensive mechanisms can be needed to achieve blood pressure control. The most common drugs are described in Table 2-4.

Drug Class	Mechanisms of action and indication
FIRST-LINE THERAPY	
Diuretics	**Thiazide-type diuretics:** inhibit the Na^+/Cl^- cotransporter in the convoluted tubule of the nephron. They produce first a contraction of blood volume and after, a vasodilatory effect. [28]
	Loop diuretics: block the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending loop of Henle and lead to a more potent diuretic effect, but they are less effective to reduce BP.[28] For patients with reduced GFR, HF, or sodium retention and edema for some other reason.[19,28]
Calcium channel blockers	They inhibit the opening of voltage-gated (L-type) Ca^{2+} channels in cardiac myocytes and vascular smooth cells, reducing intracellular Ca^{2+} concentrations and blunting vasoconstriction. Then, they also have antianginal and antiarrhythmic effects. However, they provided less protection against HF.[328]
RAS inhibitors	**ACEIs:** decrease the production of Ang II by blocking ACE, increase the bradykinin levels and reduce the sympathetic nervous system activity.[28] ACEI monotherapy are more effective in reducing the risk of HF.[329,330]
	ARBs: selectively block the action of Ang II on AT1 receptors, allowing Ang II to bind AT2 receptors which may increase the vasodilator and hypotensive effect of ARBs. They may confer the same antihypertensive benefits as ACEIs without cough, which is a frequent ACEI-related side effect.
ADD-ON DRUGS	
Aldosterone Antagonists	They are also diuretics drugs and antagonize the action of aldosterone at the mineralocorticoid receptors. For patients with resistant hypertension, low-renin HTN, and HF.[28,331,332]
Beta-adrenergic blockers	They lower BP by decreasing cardiac output from reducing heart rate and contractibility, and by inhibiting renin release.[28]

Table 2-4. Most common antihypertensive drugs. *ACEIs*, angiotensin-converting enzyme inhibitors; *Ang II*, angiotensin-II; *ARBs*, angiotensin receptor blockers; *BP*, blood pressure; *Ca^{2+},* calcium; *Cl*, chloride; *GFR*,

glomerular filtration rate; *HF*, heart failure; *HTN*, hypertension; *K^+,* potassium; *Na+,* sodium; *RAS*, Renin-angiotensin-aldosterone system.

Antihypertensive treatment in patients with AS and concomitant hypertension has not been established. Traditionally, there were some concerns about it in patients with severe AS, especially with negative inotropic agents and vasodilators due to the adverse effects (as LV dysfunction or hypotension) that they can produce in the presence of a fixed resistance (the aortic valve).[137,270,333] However, growing evidence has demonstrated that these drugs may not only be safe, but they can also be beneficial in the context of AS and concomitant hypertension.[137,333-336] These findings may suggest that there is no reason not to treat hypertension in patients with AS. New guidelines for heart valve diseases suggest that medical therapy for hypertension should follow standard recommendations, starting at a low dose and gradually titrating upward to achieve blood pressure control.[30]

2.7.1. RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS

RAS inhibitors are a well-known antihypertensive therapy with a positive impact on cardiovascular mortality, risk of heart failure, coronary events, and stroke.[301,337-340] However, in the context of AS, there were also some concerns about its safety and tolerance. O'Brien et al. have shown that ACEI therapy was safe and was well-tolerated by patients with mild-to-moderate AS and preserved LVEF.[184] There were no statistically significant differences in all the renal and hemodynamic parameters analyzed between baseline and the last visit at the maximal dose of *ramipril*.[184] Another publication analyzing 56 patients with severe and symptomatic AS, the "Symptomatic Cardiac Obstruction-Pilot Study of *Enalapril* in Aortic Stenosis" (SCOPE-AS), showed that *enalapril* was well-tolerated without hypotension or syncope when LVEF was preserved, and normal or high blood pressure was presented.[341] Moreover, this study indicated an improvement in NYHA functional class, Borg dyspnea index, and 6-minute walk test.[341] Consisting with those results, from a post hoc analysis of the SEAS study, it was shown that RAS inhibitors were not associated with sudden cardiac death, cardiovascular or all-cause mortality in patients with asymptomatic AS and preserved LVEF, even after adjustment to confounders (age, gender, Vmax, LVEF, eGFR, LDL, high-density lipoprotein, LV mass index, SBP, DBP, BMI, concomitant beta-blocker, calcium antagonist, diuretic and aspirin or other platelet inhibitor treatment).[342] These results were confirmed by a propensity-matched analysis. From a prospective cohort study using information from a health registry describing drug prescriptions, echocardiographic information, morbidity and mortality database from a population of Scotland; it was revealed that patients treated with ACEIs or ARBs (n= 699, 33% of the study population) had significantly lower all-cause mortality rates and fewer CV events; including hospitalizations, death, and AVR.[185]

Following biological plausibility, it seems that RAS inhibition would present benefits to slow the progression of LV remodeling. From the recently mentioned sub-analysis of the SEAS study, the authors also indicated an association between the use of RAS inhibitors, a larger reduction in SBP, and less progression of LV mass.[342] Bull et al. developed the first prospective, randomized, double-blind, controlled trial with the use of ramipril, "the *Ramipril* In Aortic Stenosis" (RIAS) trial.[187] The published study included only 100 patients with moderate and severe AS and they underwent cardiac magnetic resonance to evaluate a possible reduction in LV mass. After one year, the *ramipril* group showed a reduction in mean LV mass of -3.9 grams compared with an increase of 4.5 grams in the placebo group, which could not be explained by a reduction in SBP or DBP.[187] The change in LV mass was progressive.[187] This study also analyzed myocardial hemodynamics by echocardiography and cardiac magnetic resonance and, contrary, those analyses did not show significant improvements. Only tissue Doppler systolic velocity was slightly significant.[187] Similarly, in another randomized clinical trial using *candesartan (*an ARBs*)* after AVR was associated with significant LVH regression compared with standard treatment, but no significant difference in change in systolic blood pressure during 12-month follow-up.[343]

Moreover, several trials demonstrated LV mass regression in hypertensive patients.[337,338,344] In the echocardiographic prospective cohort sub-study of "*Losartan* Intervention for Endpoint reduction in hypertension" (LIFE) trial, a total of 960 subjects with hypertension and LV hypertrophy screening by electrocardiogram were enrolled and randomized to receive *losartan*-based therapy or *atenolol*-based therapy during a follow-up of 5 years. Other antihypertensive drugs could be added to achieve blood pressure control. *Losartan*-based therapy induced a greater reduction in LV mass index from baseline to the last available study than *atenolol* with adjustment for baseline LV mass index and blood pressure and in-treatment pressure.[338] These changes were more relevant during the first year of the study.[338] Further, from the 660 patients that presented either eccentric or concentric LV hypertrophy at baseline, 52% had normal LV geometry in the final echocardiogram; and 82% of patients with concentric remodeling at baseline had normal LV geometry at the end of the study.[122] LV mass reduction during antihypertensive treatment was significantly associated with lower rates of cardiovascular mortality and all-cause mortality, but it was not associated with stroke.[344] One limitation of this study is that it was not possible to compare *losartan* therapy with placebo due to ethical reasons. So, the study could overestimate or underestimate the cardiac effects of the study treatments. Also, it was difficult to determine if the cardiac effects are due to the molecule per se or due to the reached blood pressure and the subsequent decrease in LV global systolic load. However, all those results underline the importance of treating hypertension and achieving blood pressure control in patients with increased LV afterload.

About ARBs, there is more paucity of data concerning their efficacy in the progression of AS compared to ACEIs. Theoretically, as non-ACE pathways for converting Ang I to Ang II such as chymase or cathepsin G, and AT1 are increased in stenotic aortic valves, ARBs may have increased impact compared with ACEIs in CAVD. From a retrospective study, hypertensive patients on ARBs had slower AS progression (assessed by Doppler echocardiography) compared with normotensive patients with AS and hypertensive patients without RAS inhibitors.[191] From a multivariable model ARBs were also independently associated with slower AS progression.[191] Additionally, ARBs presented a 2-fold decrease in the risk of AVR or death and were associated with reduced all-cause mortality compared with the control group.[191] These results are depicted in Figure 2-4 and Figure 2-5. Consisting with some of these results, a histological study has revealed that the explanted stenotic aortic valve of patients under ARBs treatment showed lower aortic valve weights and remodeling scores.[345] Similar findings were achieved after multivariable analysis.[192]

Although there are favorable outcomes with RAS inhibitors therapy, more large-scale clinical studies are needed, especially randomized clinical trials, to assess the best therapy for hypertensive patients with AS and the therapy goals to control BP.

3. MASTER RESEARCH PROJECT

3.1. INTRODUCTION AND RATIONALE OF THE RESEARCH PROJECT

Hypertension and CAVD are two prevalent cardiovascular diseases in high-income countries.[9,24,25] As it has already been mentioned, between 30% to 70% of patients with AS have hypertension.[5,9,74] Hypertension has been associated with CAVD as an independent risk factor for the development and faster progression of it.[228,249,250] Moreover, increases in all-cause mortality and worse prognosis have been revealed in those patients.[228,249,250]

In those patients, the increased systemic vascular load caused by hypertension (due to reduced compliance and higher SVR) adds overload to the LV afterload, which is already elevated by the aortic valvular obstruction. This double load can be measured by the Z_{va}.[224,225,232] High levels of Z_{va} have a strong implication on geometrical and morphological changes in the LV, causing early hypertrophic remodeling and function impairment.[190,224,225,227,232] Those consequences are associated with rapid onset of symptoms and worse clinical outcomes compared with normotensive patients with AS.[190,224,225,227,232] Besides, the reduced SAC caused by aging and hypertension was also independently associated with a higher prevalence of LV systolic and diastolic dysfunction in patients with AS.[224]

Uncontrolled hypertension can be fatal due to its complications and should be treated in every patient. However, there is no recommendation about hypertensive treatment in AS patients. Further, no pharmacological treatment has been shown to improve the prognosis in AS. Several publications have indicated positive outcomes when hypertension has been treated in patients with AS,[185,188-190] and some recent investigations have pointed out ARBs can slow the progression of AS due to complete blockage of RAS in the aortic valves. Moreover, ARBs may slow the development of myocardial fibrosis, LV remodeling, and LV dysfunction or heart failure.[190,346-349] Thus, these medications might protect the LV from this double load, avoiding a bad prognosis and a faster onset of symptoms.

Hence, the **principal objective** of this study is to show the impact of one-year antihypertensive treatment with an ARB (*losartan*) on LV systolic function measured by GLS using speckle-tracking echocardiography in patients with mild to moderate AS and concomitant hypertension. If this study demonstrates a positive effect of ARBs on the LV function, this could translate into a significant improvement in the medical management of patients with AS and concomitant hypertension.

Principal hypothesis: One year of antihypertensive treatment with an ARB (*losartan*) increases the GLS measured by speckle-tracking echocardiography at least by 10% in hypertensive patients with mild to moderate AS and LVEF ≥ 50%.

Secondary objectives: Other objectives of this project were to: (1) to evaluate the impact of ARBs in the LV afterload (by Z_{va}), and to determine its consequence on LV damage, evaluated by a cardiac biomarker (N-terminal fraction of the brain natriuretic peptide [NT-ProBNP]), and (2) to determine the safety of ARBs on renal function as measured by creatinine clearance and serum creatinine levels.

Secondary hypotheses: (1) the Z_{va} is reduced by ~15% after one year of treatment compared to the control group. The NT-proBNP decreases in patients with antihypertensive treatment, whereas the LV diastolic dysfunction progress, and therefore, the NT-proBNP augments in the control group. (2) There are no significant changes in creatinine clearance and creatinine serums levels in both groups.

All these objectives will be assessed within the *Losartan* group and compared within a historical control group of hypertensive patients with mild to moderate AS and LVEF ≥ 50% but without ACEi or ARB medication.

3.2. METHODS

3.2.1. Study Patients

We recruited 22 patients with mild to moderate AS (defined by peak aortic jet velocity from 2 to 4 m/s and AVA less than 1.5 cm^2), preserved ejection fraction (LVEF ≥50%), and SBP at least 140 mm Hg. Subjects were excluded based on the following criteria: a) moderate to severe aortic or mitral regurgitation, b) moderate to severe mitral stenosis, c) those who have current prescriptions or contraindications of ACEIs or ARBs, d) renal failure (serum creatinine more than 150 mmol/L or creatinine clearance less than 60 $mL/min/1.73\ m^2$), e) hepatic failure, f) those with NYHA class III or IV angina or dyspnea; or recent myocardial infarction (less than 3 months), g) those with other severe comorbidities or h) pregnant or breastfeeding women. Inclusion and exclusion criteria are illustrated in Figure 3-1. Subjects were identified from their medical history and their last echocardiography at the *Institut Universitaire de Cardiologie et Pneumologie de Québec* (IUCPQ).

The study was approved by the Ethics Committee of the IUCPQ. Eligible patients who accepted to participate were asked to sign an informed consent form.

At baseline, patients underwent a noninvasive 24-hour ABPM to exclude white coat hypertension, a blood draw to screen for renal dysfunction, hepatic dysfunction, and/or pregnancy (as required), and a Doppler-echocardiographic assessment. Then, each patient has received *losartan* 50 mg once a day, and the doses were adjusted to achieve a SBP lower than 140 mmHg. At one-year follow-up, Doppler-echocardiography and blood draw were repeated.

3.2.2. Clinical Data

Clinical data, including age, sex, anthropometric measures, medical and pharmacological history as smoking, diagnosis of hypercholesterolemia, diabetes, obesity, and coronary artery disease (CAD) were collected at baseline visit. Symptoms as dyspnea or angina were assessed by standardized and validated questionnaires at baseline and follow-up.

3.2.3. Laboratory blood test

Blood samples were performed at baseline and 1-month to ensure there were no contraindications or side effects to treatment (hepatic, renal, and electrolytes evaluation) and to measure the NT-proBNP. BNP assay was performed with commercially available electrochemiluminescence immunoassay. Differences from baseline to one-year visit was considered. Creatinine clearance was calculated by the Cockcroft-Gault equation.

3.2.4. Doppler echocardiographic data

Doppler echocardiographic examinations were performed with the use of an EpiQ 33 ultrasound machine (Philips, Canada). M-mode, 2-dimensional, color Doppler, pulsed-wave, and continuous-wave Doppler echocardiogram data were stored on a dedicated workstation for offline analysis. For each measurement, at least three cardiac cycles were averaged. **AS severity** was assessed by Doppler echocardiography. LV outflow tract diameter was measured at the hinge point of the aortic valve leaflets. Using continuous-wave Doppler, it was evaluated the mean transvalvular gradient with the use of the modified Bernoulli equation, peak aortic jet velocity, and the AVA which was got by the continuity equation and indexed to BSA (AVAi). DVI was also calculated. SV was measured and indexed to BSA (SVi). The mean transvalvular flow (Q mean) was calculated by the stroke volume divided by the LV ejection time. AVC score was also calculated by using a dual-source multidetector computed tomographic scanner (Somatom Definition, Siemens Medical Systems) and following the protocol described by Clavel et al.[177] **LV systolic function** was assessed by the modified Simpson biplane method. **GLS** was performed offline by speckle-tracking echocardiography using commercially available software (TomTec

Imaging System, Munich, Germany). In brief, the endocardial borders were traced manually at the end-systolic frame of 2-chamber, 3-chamber, and 4-chamber apical views. Then, an automated speckle tracking analysis on the LV myocardium was performed on successive frames throughout the cardiac cycle. The LV wall was divided into 6 segments in each view. Finally, the software automatically generated time-domain strain curves in 6 segments, with which end-systolic strain was subsequently calculated. GLS was defined as the average longitudinal strain at the end-systole in those segments. The adequacy of the tracking was verified visually, and if tracking was deemed suboptimal, a manual adjustment of both the endocardial border was performed. If tracking was still judged unsatisfactory in all the examined views, the subjects were excluded from the analysis. The final stated GLS was the average of the longitudinal strain at the end-systole in all the segments from the best tracked apical view. The interobserver variability of GLS in our laboratory was 7.5%, which was reported before.[350] GLS data were expressed in absolute value (%). **LV diastolic function** was assessed from mitral inflow using pulsed-wave Doppler echocardiography and tissue doppler. Mitral E/A ratio and E/e' ratio were calculated. Diastolic dysfunction was classified according to the latest guideline of the American Society of Echocardiography[233] only in the *Losartan* group. **LV geometry and mass** were evaluated in the left parasternal long-axis view. LV diameter was measured at the end-diastole and was indexed to BSA. LV mass was calculated by the recommended formula of the ASE[105] and was indexed to BSA. According to the ASE guideline, LV hypertrophy was considered in men who present a higher LV mass index of 115 g/m^2 and in women whose LV mass index was higher than 95 g/m^2.[105]

3.2.5. Systemic arterial hemodynamics and global left ventricle hemodynamic load

Systemic arterial blood pressure was measured by an arm-cuff sphygmomanometer at the end of the Doppler-echocardiographic exam at baseline and follow-up. A 24-hour ABPM was also performed to confirm hypertension before giving treatment and to measure adherence to it. SAC and global LV hemodynamic load represented by the Z_{va} were calculated. The interventional (*Losartan*) group was classified as low ($\leq$ 3.5 $mmHg.mL^{1}.m^{2}$, medium ($>$ 3.5 $mmHg.mL^{1}.m^{2}$, $<$ 4.5 $mmHg.mL^{1}.m^{2}$) and severe ($\geq$4.5 $mmHg.mL^{1}.m^{2}$) Z_{va}.[232]

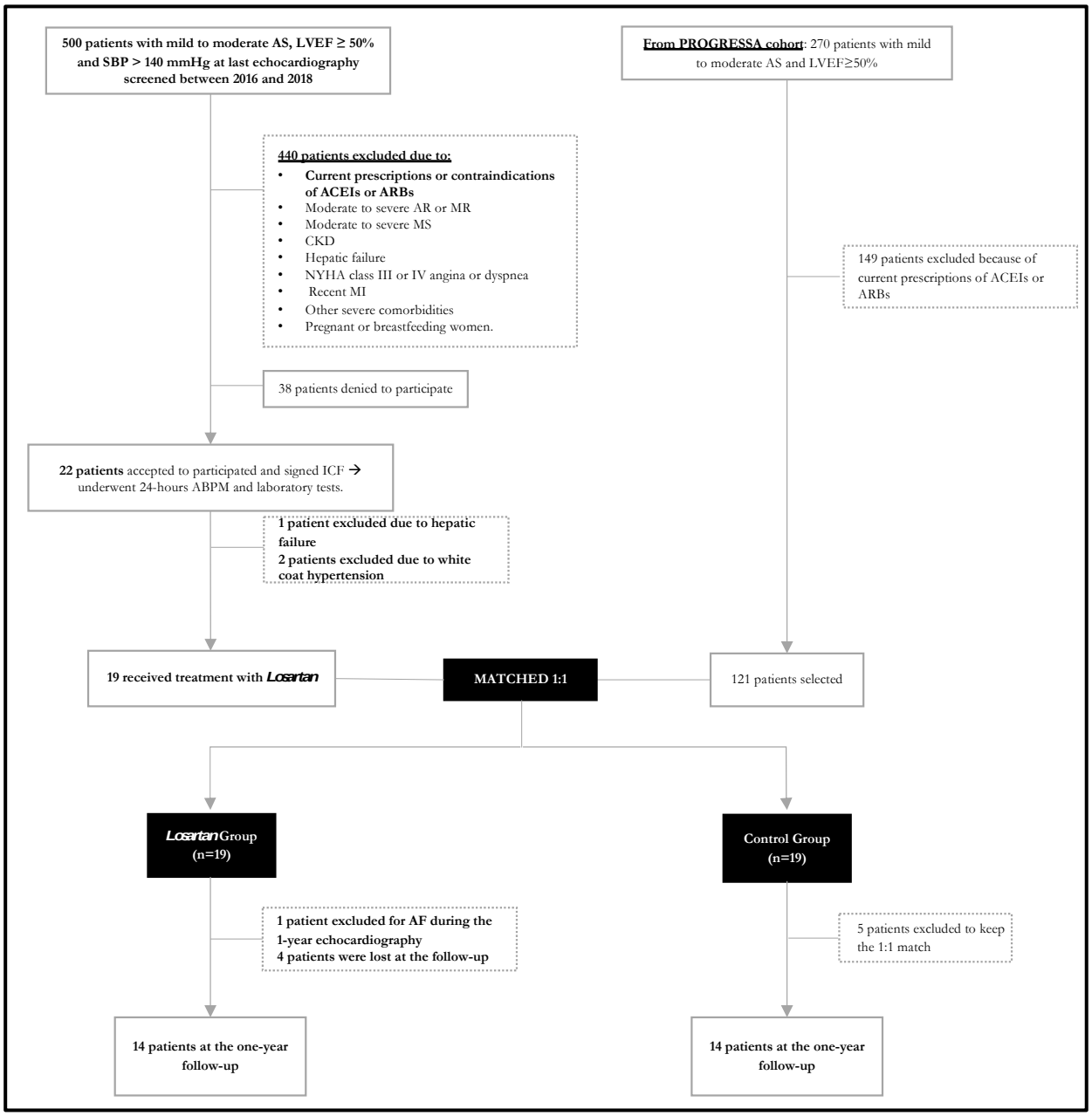

Figure 3-1. Flowchart of the patient recruitment and the study design. *ACEIs*, angiotensin-converting enzyme inhibitors; *AF*, atrial fibrillation; *AR*, aortic regurgitation; *ARBs*, angiotensin receptor blockers; *CKD*, chronic kidney disease; *MI*, myocardial infarction; *MR*, mitral regurgitation; *MS*, mitral stenosis; *NYHA*, New York Heart Association.

3.2.6. Control Patients

Case patients were matched 1:1 for age (within ± 10 years), sex (exact match), V_{max} (within ± 50 cm/s), SVi (± 20 mL/m²), mean transvalvular pressure gradient (within ± 10 mm Hg) and LVEF (within ±5%) with patients from a historical cohort (2011-2015) from the study PROGRESSA[46] and who have not

received antihypertensive therapy with RAS inhibitors (Control group). In this study, patients underwent clinical history assessment, measurements of systemic arterial blood pressure by only an arm-cuff sphygmomanometer, echocardiography study, and laboratory tests at baseline and follow-up.

3.2.7. Clinical Outcomes

The primary endpoint was the annualized difference of GLS values in the *Losartan* group after one-year treatment with ARBs and comparing it with the control group. Secondary endpoints were: (1) the annualized difference of Z_{va}, (2) the annualized difference of NT-proBNP, (3) the annualized difference of diastolic function parameters, and lastly, (4) as safety endpoint, the annualized difference in creatinine clearance and serum creatinine levels. All these endpoints will be measured and compared in both groups.

3.2.8. Statistical Analysis

Continuous data were expressed as median and its 25^{th} and 75^{th} percentiles (PC) and comparisons between the two study groups were done using Wilcoxon rank-sum (Mann Whitney U) tests. Categorical data were expressed as percentages and compared with Fisher exact test due to the small sample size.

Annualized differences were used to express the variables implicated in the study endpoint. *Wilcoxon* signed-rank test was used to compare the difference between both visits (baseline and follow-up) for continuous data and McNemar test was used for nominal data.

A two-tailed *P* values <0.05 were considered statistically significant in our analysis.

Data was collected by the RedCap system. Statistical analysis was performed by IBM SPSS Statistics version 25.0 (SPSS Inc, Chicago, IL) and Stata 16.1 (StataCorp LLC).

3.3. RESULTS

Even though 22 patients were recruited from 2016 to 2019, only 15 patients achieved the one-year visit. At baseline, three patients were excluded: one for hepatic failure and two for white coat hypertension. Then, patients were matched as mentioned in the Methods section. Due to the COVID-19 situation, the one-year visit of 4 patients was not done. Another patient was excluded because of atrial fibrillation during the echocardiographic assessment at follow-up. Finally, only 14 matched pairs of patients were analyzed (Figure 3-1).

3.3.1. Baseline characteristics of the study patients

Baseline characteristics of both groups are shown in Table 3-1. Regarding demographic data and medical history, there were no statistically significant differences between both groups. SBP and DBP were similar. However, the *Losartan* group has a slightly but no significant higher prevalence of paroxysmal atrial fibrillation (7 patients [50%] in the *Losartan* group and 2 [14.3%] in the control group, *p*-value = 0.103). About antihypertensive drugs, there were no significant differences between groups in the use of alternative antihypertensive classes from RAS inhibitors.

Table 3-1 also shows laboratory test results at baseline. There were no statistically significant differences between them.

The baseline echocardiography characteristics and hemodynamic AS assessment are shown in table 3-2. There were no statistically significant differences between both groups. The hemodynamic severity of AS was similar in both groups and is confirmed by the AVC score. but Q-mean was slightly higher in *Losartan* group (*Losartan* group: 252 mL, PC: [195.7; 287.9] and control group: 199 mL, PC: [186; 221], *p*-value: 0.095). Both groups showed similar and normal LV systolic functions (all parameters *p*-value >0.095). Values of GLS were similar in both groups. Regarding LV geometry, control group exhibited a trend of higher prevalence of LV hypertrophy (3 patients [21%] in *Losartan* group and 6 [43%] in control group, *p*-value = 0.420), and higher LV mass index (*Losartan* group: 85.10 mg/m^2, PC: [75.33;99.58] and control group: 97.49mg/m^2 PC: [89.93;105.61], *p*-value = 0.056), but without significant statistical difference. The *Losartan* group had a significantly larger LV end-diastolic diameter, but there was no statistically significant difference when it was indexed to BSA. About diastolic function, A wave was greater in the *Losartan* group (*p*-value = 0.001). E/A ratio was statistically significant different (*Losartan* group: 0.74, PC: [0.56;0.94] and control group: 1.09, PC: [0.95; 1.21], *p*-value = 0.020). Diastolic dysfunction grade could be estimated only in 11 patients from the *Losartan* group. Most patients had grade I diastolic dysfunction, one presented grade II and another one had a normal diastolic function. Global hemodynamic load and SAC were similar between both groups (Zva *p*-value = 0.685, SAC *p*-value = 0.519).

	All n = 28	***Losartan* group** n = 14	**Control group** n = 14	***p*-value**
	Median (25^{th};75^{th}PC)	Median (25^{th};75^{th}PC)	Median (25^{th};75^{th}PC)	
Age	70 (62; 77)	72 (67; 83)	70 (61; 77)	0.394
Women – nº (%)	24 (57.1)	8 (57.1)	8 (57.1)	1.000
BSA – m^2	1.77 (1.69; 1.94)	1.79 (1.72; 2.03)	1.73 (1.59; 1.91)	0.101
BMI – kg/m^2	27.5 (25.6; 29.6)	27.6 (26.4; 30.1)	26.5 (24.1; 28.6)	0.114
NYHA Functional Class - nº (%)				0.420
I	17 (63.0)	9 (69.2)	8 (57.1)	
II	9 (33.3)	3 (23.0)	6 (42.9)	
III	1 (3.7)	1 (7.69)	0	
IV	0	0	0	
SBP – mmHg	139 (131; 152)	141 (135; 151)	145 (131; 153)	0.865
DBP –mmHg	74 (72; 82)	79 (73; 83)	74 (69; 83)	0.420
Heart Rate (bpm)	66 (57; 69)	66 (57; 69)	63 (56; 69)	0.829
Hypertension – nº (%)	23 (88.5)	14 (100.0)	11 (78.6)	0.225
Diabetes – nº (%)	3 (10.7)	2 (14.3)	1 (7.1)	1.000
Obesity (IMC > 30) – nº (%)	5 (17.9)	4 (28.6)	1 (7.1)	0.326
Metabolic Syndrome – nº (%)	5 (17.9)	2 (14.9)	3 (21.4)	1.000
Smoking (Current or history) – nº (%)	16 (57.1)	7 (50.0)	9 (64.3)	0.704
AF or history of AF – nº (%)	9 (32.1)	7 (50.0)	2 (14.3)	0.103
MI history – nº (%)	8 (28.6)	4 (28.6)	4 (28.6)	1.000
Coronary Artery Diseases – nº (%)	10 (35.7)	6 (42.9)	4 (28.6)	0.695
Medication				
Anti-hypertensive Medication				
ß-Blockers – nº (%)	9 (32.1)	4 (28.6)	5 (35.7)	1.000
Ca^{2+} - Blockers – nº (%)	9 (32.1)	5 (35.7)	4 (28.6)	1.000
Diuretics – nº (%)	3 (10.7)	2 (14.3)	1 (7.1)	1.000
Statins or other lipid-lowering medication – nº (%)	21 (75.0)	12 (85.7)	9 (64.3)	0.385
Anti-diabetic medications– nº (%)	3 (10.7)	2 (14.3)	1 (7.1)	1.000
Serum Measures				
NT-ProBNP – pg/mL	157.0 (63.0; 323.5)	130.5 (104.0; 220.0)	219.0 (41.0; 445.0)	0.992
Creatinine –µmol/L	73.0 (62.0; 88.0)	68.5 (62.0; 94.0)	75.0 (63.0; 95.0)	0.643
Creatinine Clearance - mL/min	72.0 (62.0; 94.5)	73.7 (57.8; 104.0)	71.3 (48.2; 92.9)	0.472

Table 3.1 Baseline clinical characteristics and laboratory results. Values are median (25^{th} percentile; 75^{th} percentile) or number of patients (percentage difference within the whole cohort)**.** *p*-value represents the comparison between both groups (Losartan vs. control group). *AF*, atrial fibrillation; *ß-Blockers*; beta-adrenergic blocking agents; *BMI*, body-mass index; *BSA*, body surface area; *Ca^{2+} - blockers*, calcium channel blockers; *MI*, myocardial ischemia; *NT-ProBNP*, N-terminal fraction of the brain natriuretic peptide; and *NYHA*, New York Heart Association.

	All n = 28	*Losartan* group n = 14	Control group n = 14	*p*-value
	Median (25th;75thPC)	Median (25th;75thPC)	Median (25th;75thPC)	
Hemodynamic Parameters				
Peak aortic Velocity- cm/seg	257.5 (237.0; 285.0)	263.0 (240.0; 284.0)	254.0 (234.0; 285.0)	0.795
Mean Pressure Gradient - mmHg	15.4 (12.2; 18.5)	15.50 (12.0; 18.7)	15.1 (12.4; 18.2)	0.847
AVA – cm^2	1.15 (1.00; 1.42)	1.21 (1.06; 1.37)	1.02 (1.00; 1.42)	0.198
AVA index – cm^2/m^2	0.65 (0.57; 0.76)	0.67 (0.61; 0.70)	0.60 (0.57; 0.78)	0.641
DVI	0.32 (0.28; 0.38)	0.32 (0.28; 0.36)	0.33 (0.29; 0.38)	0.943
SV – mL	71.3 (65.8; 85.9)	77.33 (65.2; 90.6)	68.9 (66.8; 74.8)	0.326
SV index – mL/m^2	41.5 (39.0; 45.7)	41.86 (37.9; 48.4)	40.6 (39.3; 44.2)	0.650
Q mean – mL	221 (186; 284)	252 (195.70; 287.90)	199 (186; 221)	0.095
LV Parameters				
LVEF	61 (58; 68)	61 (58; 65)	64 (58; 70)	0.454
GLS average - %	-17.8 (-18.8; -15.6)	-17.6 (-19.1; -15.4) n=12	-17.8 (-18.8; -15.8) n=7	0.967
LVEDD – mm	47.2 (42.3; 49.5)	49.0 (46.2; 51.0)	44.4 (41.5; 47.4)	0.019
Indexed LVEDD – mm/m^2	26.2 (24.2; 28.0)	26.2 (24.4; 28.5)	26.5 (24.0; 27.8)	0.571
LV mass index – mg/m^2	93.16 (82.92; 105.00)	85.10 (75.33; 99.58)	97.49 (89.93; 105.61)	0.056
LV hypertrophy – nº (%)	16 (39.0)	3 (21.4)	6 (42.9)	0.420
LV diastolic function				
E wave – cm/seg	73.85 (67.30; 91.30)	73.95 (65.20; 94.90)	76.50 (61.00; 87.80)	1.000
A wave – cm/seg	87.30 (71.8; 91.9)	91.80 (88.75; 118.00)	79.95 (66.30; 89.50)	0.001
E/A ratio	0.98 (0.70; 1.13)	0.74 (0.56; 0.94)	1.09 (0.95; 1.21)	0.020
E/e' ratio	10.98 (8.66; 12.93)	10.98 (9.32; 16.10)	10.93 (8.33; 12.31)	0.374
Arterial Parameters and Global hemodynamic LV load				
SAC– $mL.m^{-1}.mmHg^{-2}$	0.69 (0.54; 0.77)	0.62 (0.51; 0.72)	0.68 (0.56; 0.81)	0.519
Zva - $mmHg.mL^{1}.m^2$	3.87 (3.45; 4.29)	3.93 (3.45; 4.61)	3.82 (3.54; 4.12)	0.685
AS Assessment by CT				
AVC Score	544.2 (397.1; 775.8)	693.7 (505.7; 776.5)	470.9 (374.1; 627.3)	0.310

Table 3-2. Baseline echocardiographic characteristics. Values are median (25th percentile; 75th percentile) or number of patients (percentage difference). *p*-value represents the comparison between both groups (Losartan vs. control group). *AVA*, aortic valvular area; *AVC*, aortic valve calcium; *GLS*, global longitudinal strain; *LVEDD*, left ventricular end-diastolic diameter; *SAC*, systemic arterial compliance; *SV*, stroke volume and *Zva*, valvulo-arterial impedance.

3.3.2. Evaluation of annualized ratios of echocardiographic parameters at follow-up

Annualized ratios of echocardiographic parameters are described in Table 3-3.

	***Losartan* group n = 14**		**Control group n = 14**		***p*-value**
	Median (25^{th};75^{th}PC)	Paired *p*-value	Median (25^{th};75^{th}PC)	Paired *p*-value	
Hemodynamic Parameters					
Peak aortic Velocity- cm/seg	17.1 (-1.0; 33.1)	0.010	10.3 (-3.9; 20.0)	0.296	0.227
Mean Pressure Gradient - mmHg	2.4 (1.1; 3.2)	0.006	0.7 (-0.2; 1.8)	0.210	0.186
AVA – cm^2	-0.03 (-0.13; 0.05)	0.463	-0.10 (-0.18; -0.04)	0.054	0.252
AVA index – cm^2/m^2	-0.02 (-0.06; 0.03)	0.542	-0.06 (-0.09; 0.01)	0.097	0.402
DVI	-0.01 (-0.05; 0.005)	0.091	-0.03 (-0.03; -0.01)	0.080	0.375
SV – mL	-1.0 (-9.4; 8.8)	1.000	-0.3 (-8.0; 1.3)	0.455	0.650
SV index – mL/m^2	-0.5 (-5.3; 4.2)	0.952	0.2 (-5.0; 1.3)	0.588	0.756
Q mean – mL/seg	7 (-23; 35)	0.588	-8 (-15; -1)	0.033	0.153
LV systolic function and geometry					
LVEF	2.0 (-4.7; 5.0)	0.622	2.0 (-2.1; 2.8)	0.791	0.799
GLS average - %	-0.6 (-1.6; -0.4)	0.092			
LVEDD- mm	-0.5 (-3.7; 1.5)	0.349	0.5 (0.1; 1.6)	0.115	0.311
LV mass index – mg/m^2	-5.31 (-13.57; 1.49)	0.217	-5.00 (-8.72; 2.63)	0.376	0.390
Left Ventricle Diastolic Function					
E wave – cm/seg	8.64 (-1.00; 13.34)	0.131	-0.25 (-8.42; 5.72)	0.915	0.259
A wave – cm/seg	-11.25 (-13.04; -8.12)	0.010	9.20 (-7.78; 15.70)	0.268	0.031
E/A ratio	0.16 (0.05; 0.27)	0.002	-0.10 (-0.26; 0.10)	0.194	0.013
E/e' ratio	-0.07 (-1.11; 1.12)	0.846	0.56 (-0.22; 1.75)	0.194	0.341
Systemic arterial hemodynamics and global hemodynamic load					
SBP - mmHg	-11 (-18; -1)	0.012	-8 (-20; 8)	0.452	0.163
SAC $mL.m^{-1}.mmHg^{-2}$	0.14 (0.04; 0.27)	0.011	0.01 (-0.11; 0.18)	0.542	0.202
Zva - $mmHg.mL^{1}.m^2$	-0.29 (-0.79; 0.23)	0.085	0.29 (-0.51; 0.48)	0.747	0.141

Table 3-3. Changes in systemic arterial hemodynamics and echocardiographic parameters from baseline to 1-year follow-up. Values are median (25^{th} percentile; 75^{th} percentile) or number of patients (percentage difference)**.** Paired *p*-values represent the comparison between follow-up and baseline within each group and *p*-value refer to the comparison of the annualized difference of each parameter between both groups. *AVA*, aortic valvular area; *GLS*, global longitudinal strain; *LV,* left ventricular*; LVEDD*, left ventricular end-diastolic diameter; *LVEF*, left ventricular ejection fraction*; SAC*, systemic arterial compliance, *SBP*, systolic blood pressure; *SV*, stroke volume; and *Zva*, valvulo-arterial impedance.

3.3.2.1. Global longitudinal strain, left ventricle systolic and diastolic function, and left ventricle geometry

The primary endpoint was not met due to the loss of follow-up and thus suboptimal statistical power of this endpoint. **GLS** could only be measured in only twelve patients from the *Losartan* group and showed a slight improvement with a borderline significant trend (**Δ**GLS: -0.6%, PC: [-1.6;0.4], paired *p*-value = 0.092). The absolute value of GLS at baseline and the follow-up are depicted in Figure 3-2. There were missing data from the control group at follow-up, and GLS could be got in only two patients. Thus, it

was impossible to compare. The major cause of missing GLS was the poor quality of images (poor echogenicity and inadequate frame rate; ie, <50 fp[139,350,351]). **LV systolic function**, estimated by LVEF, did not present a statistically significant difference between groups (*p*-value = 0.799) and the median ΔLVEF was the same in both. Further, there were not any significant differences within each group (*Losartan* group: paired *p*-value = 0.622 vs. control group: paired *p*-value = 0.791).

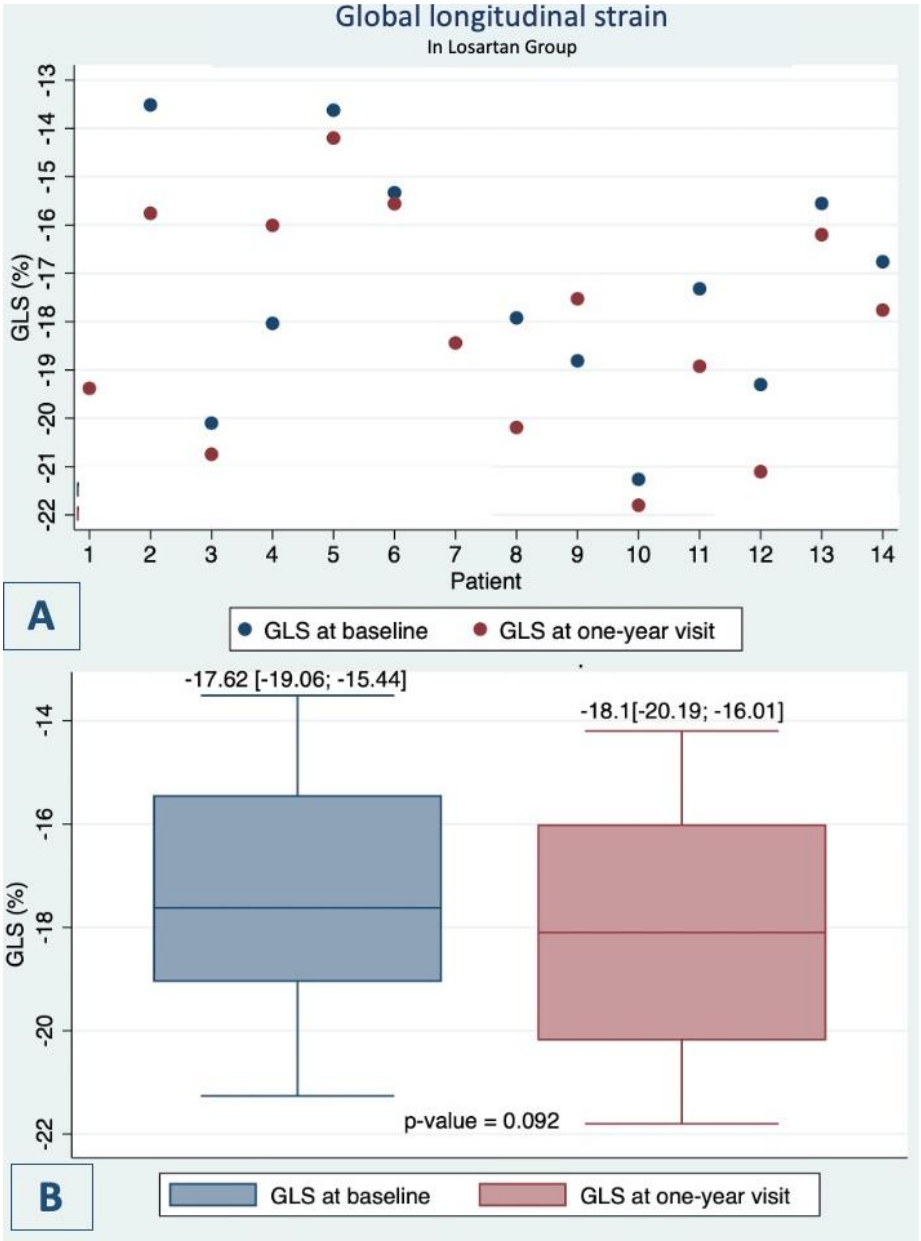

Figure 3-2. GLS at baseline and follow-up in the *Losartan* group. A) Scatterplot of individuals values of GLS at baseline (blue points) and at follow-up (red points). **(B)** The box (blue box, at baseline; red box, at follow-up) shows the 25th to 75th percentiles, the median line on the box shows the median value, and the error bars the 10th and 90th percentiles; circles are outliers; the numbers of the top of the graph are median [25th - 75th percentiles]. *p*-value obtained from this comparison is shown. *GLS*, global longitudinal strain.

About **LV diastolic function**, the annualized difference in A wave was statistically significant, decreasing in *Losartan* group and augmenting in the control group (*Losartan* group ΔA wave: - 11.25 cm/s, PC: [-13.0; - 8.12], paired *p*-value = 0.012 vs. control group, ΔA wave: 9.20 cm/s, PC [- 7.78; 15.70 cm/s], paired *p*-value = 0.313; *p*-value = 0.022). In *Losartan* group, the E/A ratio was significantly increased after one year (ΔE/A ratio: 0.16, PC [0.05; 0.27], paired *p*-value: 0.001 vs. ΔE/A ratio: -0.10, PC [-0.26; 0.10], paired *p*-value: 0.194), and the difference between groups was also significant (*p*-value: 0.013). Contrary, there was no statistically significance difference concerning the E/e' ratio. In the *Losartan* group, at follow-up, only one patient improved its grade I diastolic dysfunction becoming normal, and another worsened it from grade I to grade II. Apropos **LV geometry**, LV mass index ratios were not significant in each group (*Losartan* group, paired *p*-value = 0.217, control group paired *p*-value: 0.376) and certainly, no significant difference between groups (*p*-value = 0.390). Same results were got concerning LV diastolic diameter (*Losartan* group, paired *p*-value =0.349, control group paired *p*-value = 0.115, *p*-value = 0.311). One patient of each group was no longer considered to have LV hypertrophy according to the definition from the guideline.[105]

3.3.2.2. Aortic stenosis progression

There were no statistically significant changes in AS severity according to the hemodynamic parameters evaluated by Doppler-echocardiography in both groups. The annualized difference of AVAi were not significant in *Losartan* group but presented a statistically tendence in control group (in *Losartan* group, ΔAVAi: -0.02 cm^2/m^2, PC: [-0.06; 0.03], paired *p*-value = 0.542 vs. ΔAVAi: -0.06 cm^2/m^2, PC: [-0.09; 0.01], paired *p*-value = 0.097). The difference between groups were not statistically significant (p-value = 0.402). However, DVI showed a borderline significant difference in both groups (in *Losartan* group, ΔDVI: -0.01, PC: [-0.05; 0.005], paired *p*-value = 0.091 and control group, ΔDVI: -0.03, PC: [-0.03; 0.01], paired *p*-value = 0.08; *p*-value between groups = 0.375). On the other hand, only *Losartan* group presented a statistically significant increase in peak transaortic jet velocity (ΔVmax: 17.1 cm/s, PC: [-1.0; 33.1], paired *p*-value = 0.007 vs. control group ΔVmax: 10.3 cm/s, PC: [-3.9; 20.0], paired *p*-value = 0.424) and MP (ΔMP: 2.4 mm Hg, PC: [1.1; 3.2], paired *p*-value = 0.006 vs. control group ΔMP: 0.7 mm Hg, PC: [-0.2; 1.8], paired *p*-value = 0.333). Between both groups, there were no significant differences (ΔVmax *p*-value = 0.227, ΔMP *p*-value = 0.186).

The annualized changes in SV, SVi and Q mean were not statistically significant. While in the *Losartan* group, the SVi was maintained (ΔSVi: -0.5 mL/m^2, PC: [-5.3; 4.2], *p*-value = 0.952) after treatment, Q mean slightly increased (ΔQ mean: 7 mL/s, PC: [-23 ; 35], *p*-value = 0.588); the opposite changes were observed in the control group (ΔSVi: 0.2 mL/m^2, [PC: -5.0; 1.3], paired *p*-value = 0.588 and ΔQ mean: -

8 mL/s, PC: [-15; -1], paired p-value = 0.033), being the decrease in Q mean statistically significant. No significant differences were observed between groups.

3.3.2.3. Systemic arterial hemodynamics and global left ventricle hemodynamic load

Control of blood pressure was achieved in the intervention group. Treatment was intensified as needed; however, only three patients needed more than 50 mg of Losartan for blood pressure control. They also had prescriptions for calcium blockers or diuretics and presented more comorbidities as atrial fibrillation or coronary artery disease. In the control group, antihypertensive treatment was the same throughout the study, although only one patient changed his therapy of beta- and calcium channel blocker to ACEI. SBP was significant decreased in *Losartan* group (*Losartan* group, SBP: -11 mm Hg, PC: [-18; -1], paired *p*-value: 0.007 vs. control group, SBP: -8 mm Hg, PC: [-20; 8], paired *p*-value: 0.453). Nevertheless, there was no significant difference between groups (*p*-value: 0.163). Although the *Losartan* group has significantly improved the SAC (paired *p*-value: 0.011) and decreased the Z_{va} with a borderline significant trend (ΔZ_{va}: - 0.29 mmHg.mL^{1}.m^{2}, PC: [- 0.79; 0.23], paired *p*-value: 0.085 vs. control group, ΔZ_{va}: 0.29 mmHg.mL^{1}.m^{2}, PC: [- 0.51; 0.48], paired *p*-value:0.747), there were no statistically significant differences (ΔSAC p-value: 0.202, ΔZ_{va} p-value: 0.141) between groups. Those results are illustrated in Figures 3-3, 3-4, 3-5 and 3-6, respectively. Sub-analysis of Z_{va} classification in the *Losartan* group indicated that 6 patients had an improvement in their Z_{va} category (Figure 3-8). Contrary, in the control group, 4 subjects worsened their Z_{va} class, only two improved it.

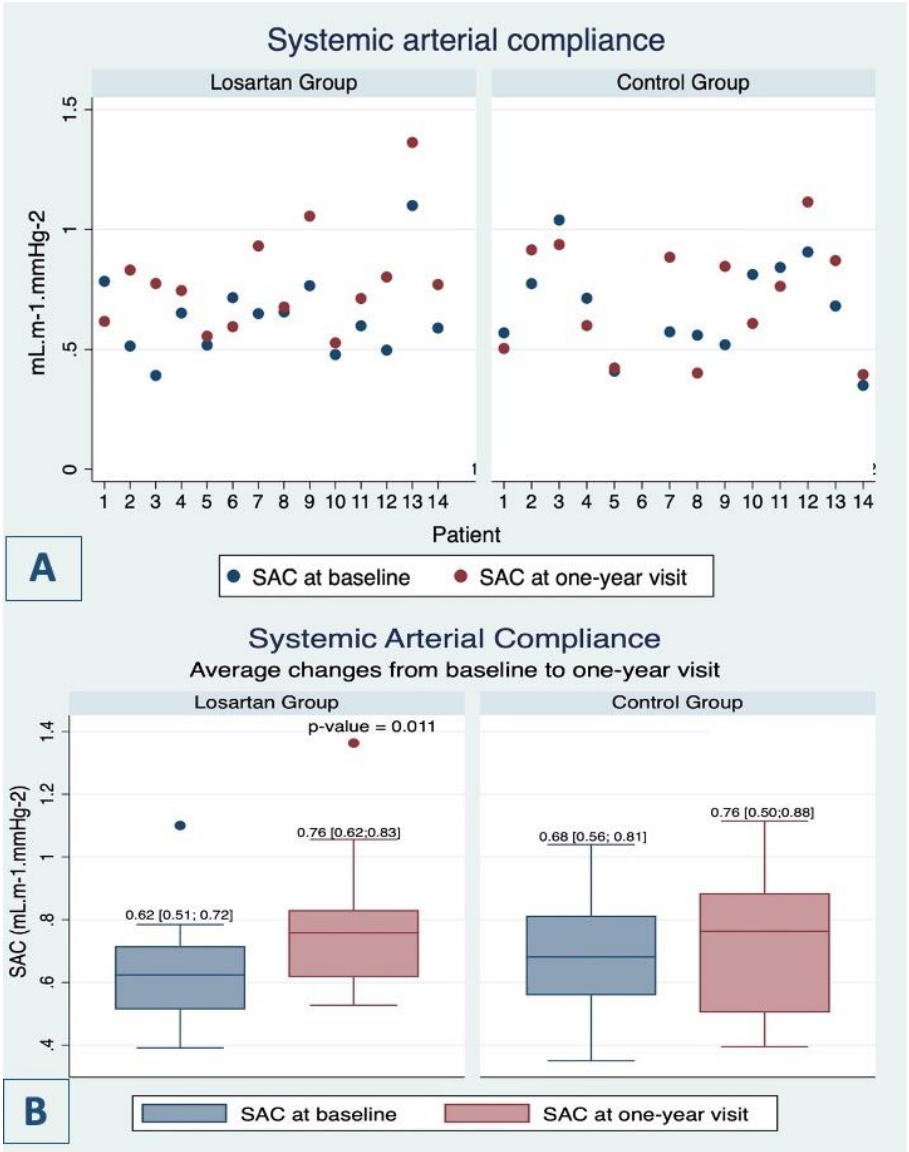

Figure 3-3. SAC at baseline and follow-up within both groups. (A) Scatterplot of individuals values of SAC at baseline (blue points) and at follow-up (red points). **(B)** The box (blue box, at baseline; red box, at follow-up) shows the 25th to 75th percentiles, the median line on the box shows the median value, and the error bars the 10th and 90th percentiles; circles are outliers; the numbers of the top of the graph are median [25th - 75th percentiles]. *p*-values obtained from this comparison within each group are shown. *SAC*, systemic arterial compliance.

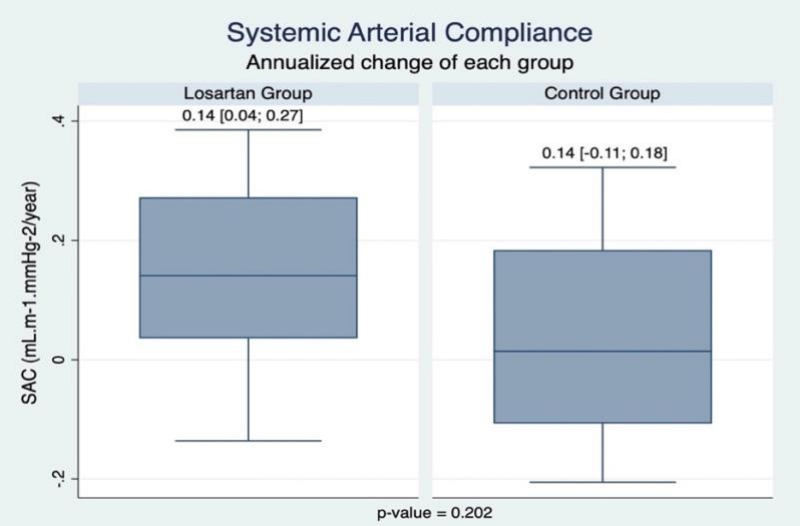

Figure 3-4. Comparison of the annualized ratio of SAC between both groups. The box shows the 25th to 75th percentiles, the median line on the box shows the median value, and the error bars the 10th and 90th percentiles; circles are outliers; the numbers of the top of the graph are median [25th - 75th percentiles]. *p*-value obtained from this comparison is shown. *SAC*, systemic arterial compliance.

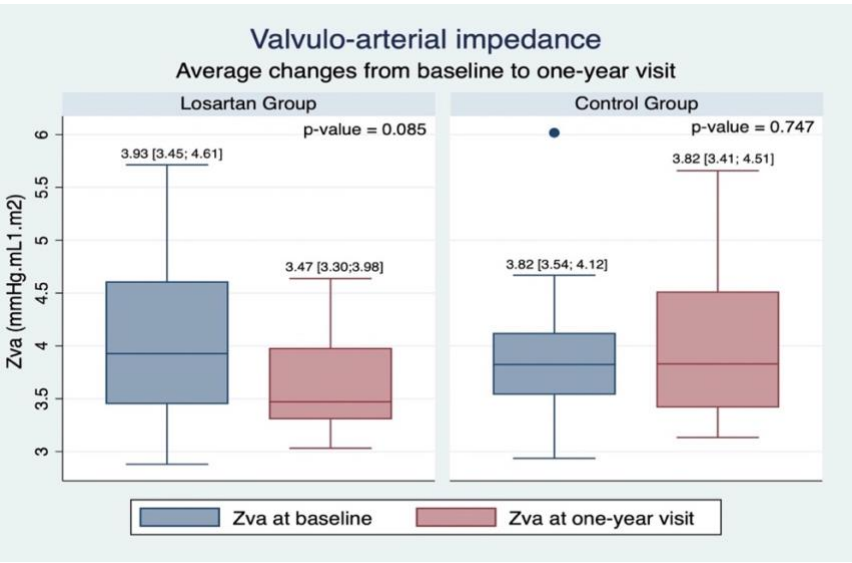

Figure 3-5. Comparison of Zva at baseline (blue box) **and follow-up** (red box) **within both groups.** The box shows the 25th to 75th percentiles, the median line on the box shows the median value, and the error bars the 10th and 90th percentiles; circles are outliers; the numbers of the top of the graph are median [25th - 75th percentiles]. *p*-values obtained from this comparison within each group are shown. *Zva*, valvulo-arterial impedance.

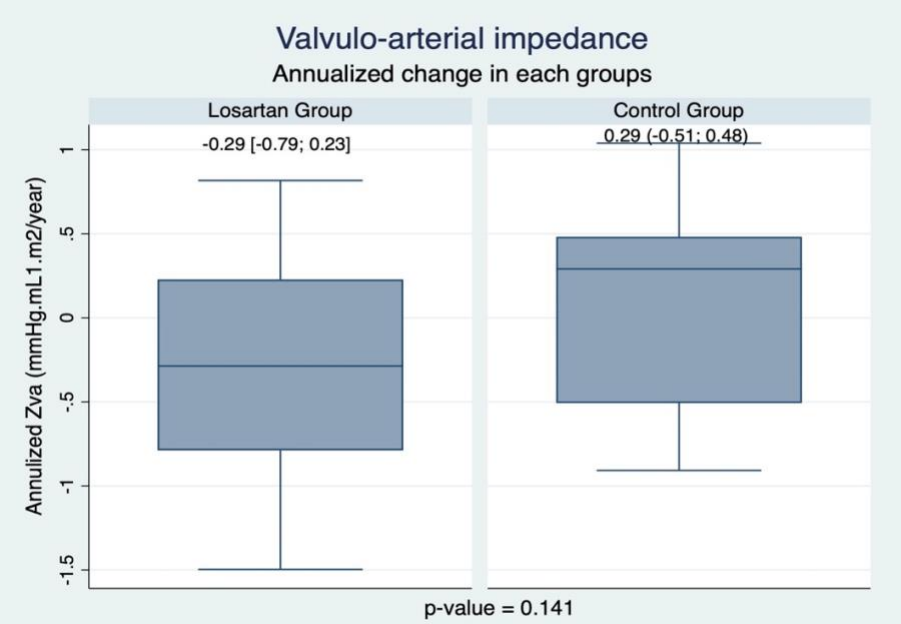

Figure 3-6. Comparison of the annualized ratio of Zva between both groups. The box shows the 25th to 75th percentiles, the median line on the box shows the median value, and the error bars the 10th and 90th percentiles; circles are outliers; the numbers of the top of the graph are median [25th - 75th percentiles]. *p*-value obtained from this comparison is shown. *Zva*, valvulo-arterial impedance.

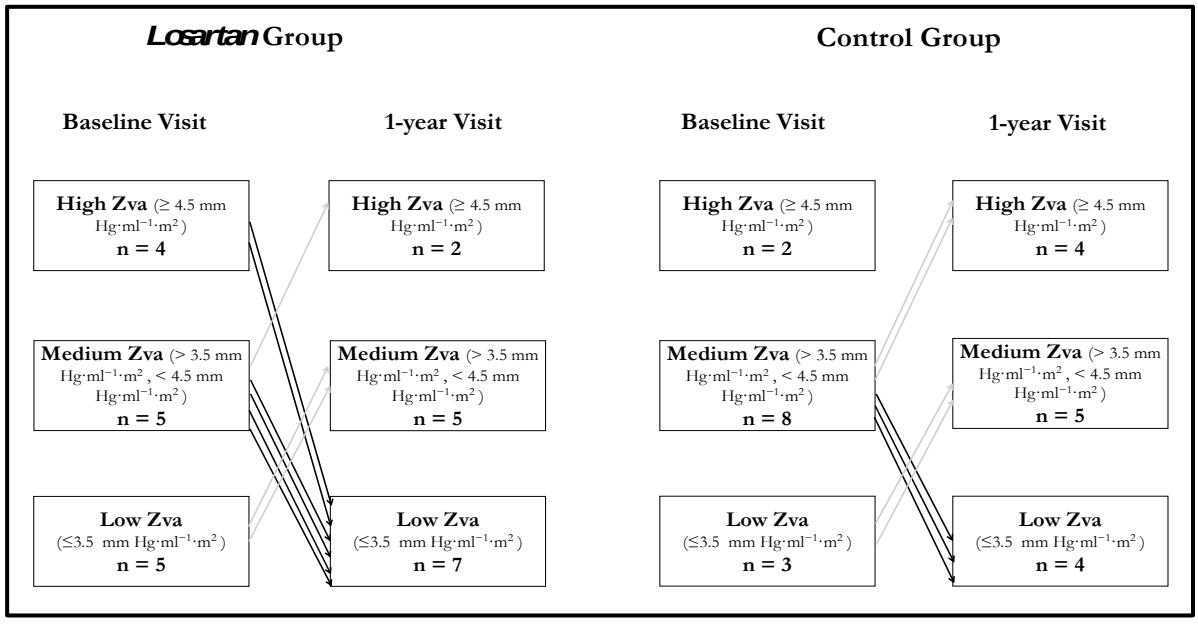

Figure 3-7. Comparison in Z_{va} group changes from baseline to follow-up between *Losartan* group and control group. Categories was considered as follow: low Z_{va} (≤ 3.5 mmHg.mL^{1}.m^{2}, medium Z_{va} (> 3.5 mmHg.mL^{1}.m^{2}, < 4.5 mmHg.mL^{1}.m^{2}) and severe Z_{va} (≥4.5 mmHg.mL^{1}.m^{2}). Lines represent the Z_{va} group change.

3.3.2. Evaluation of annualized ratios of cardiac biomarker (NT-ProBNP)

At the follow-up, there were no statistically differences in NT-ProBNP serum concentrations in both groups (*Losartan* group paired *p*-value = 0.622, control group paired *p*-value = 0.391) Indeed, no significant difference was seen between groups (*p*-value = 0.742). Those results are shown in Table 3-4.

3.3.3. Evaluation of angiotensin-receptors blockers safety

In the *Losartan* group, there were no reports of side effects. Moreover, the minor decrease observed in creatinine clearance was not statistically significant in this group (paired *p*-value = 0.597). In contrast, it was a statistically significant decline in the control group (paired *p*-value = 0.006). There was no difference between groups (*p*-value: 0.820). Those results are shown in Table 3-4.

		***Losartan* group n = 14**		**Control group n = 14**		***p*-value**
		Median (25^{th};75^{th}PC)	Paired *p*-value	Median (25^{th};75^{th}PC)	Paired *p*-value	
NT-ProBNP – pg/mL		-2.5 (-43.7; 137.6)	0.622	24.1 (-42.3; 51.5)	0.391	0.742
NYHA Functional Class - nº (%)			1.000		0.625	0.252
	I	8 (61.5)		6 (42.9)		
	II	4 (30.8)		8 (57.1)		
	III	1 (7.69)		0		
	IV	0		0		
Creatinine –μmol/L		-0.1 (-6.2: 13.2)	0.865	3.1 (1.0; 7.9)	0.008	0.403
Creatinine Clearance - mL/min		-4.6 (-10.0; 5.6)	0.569	-2.5 (-6.3; -2.1)	0.001	0.820

Table 3-4. Cardiac serum biomarker, NHYA Functional Class and Renal Safety. Values are median (25^{th} percentile; 75^{th} percentile) or number of patients (percentage difference)**.** Paired *p*-values represent the comparison between follow-up and baseline within each group and *p*-value refer to the comparison the annualized difference of each parameter between both groups. *NT-ProBNP*, N-terminal fraction of the brain natriuretic peptide; and *NYHA*, New York Heart Association.

3.4. DISCUSSION

This is one of the first studies to evaluate the impact of antihypertensive treatment on LV systolic function using GLS in patients with AS. GLS has been well-validated as a quantitative index for global LV function,[139,140] and is an early marker of subclinical LV systolic dysfunction that deteriorates before a decline in LVEF.[139,153-156] In patients with preserved LVEF, decreased GLS was highly prevalent even among patients with LVEF higher than 55%.[154] Vollema et al. revealed that patients with AS significantly deteriorated GLS while LVEF remained unchanged.[156] Patients with more impaired GLS had a greater

LV mass index, lower LVEF, a higher prevalence of atrial fibrillation and coronary artery disease, and a higher risk for the development of symptoms.[156] Further, its impairment is associated with worse clinical outcomes and prognosis.[14,30,98,156,171,308,349,350] Moreover, GLS has been correlated with myocardial fibrosis, measured by cardiac magnetic resonance in patients with severe AS.[352]

Our study found that GLS was slightly lower than normal at baseline in both groups (Losartan group, -17.6, PC:[-19.1;-15.4] and control group, -17.81, PC:[-18.8;-15.8]) in comparison to the reported normal GLS.[142,149] Most of our selected views for GLS analysis was 4-chamber apical view, which was reported to be -21.4% using TomTec.[142] One meta-analysis reported a normal GLS of 19.7% (95%CI, 20.4% to 18.9%).[149] These results demonstrated that those patients with hypertension and mild or moderate AS, being mild AS more prevalent, could already have some type of LV systolic dysfunction despite their normal LVEF. Besides, it is foreseeable that the decrease in GLS would be greater while AS severity progress. Miyasaki et al. found a significant correlation between GLS, AVA and mean pressure gradient. Further, he showed statistically significant differences among three groups according to AS severity.[171]

Therefore, our study aimed to identify an improvement in GLS values when an ARBs therapy is given to hypertensive patients with mild or moderate AS. Unfortunately, it was not accomplished, and the hypothesis of our study cannot be accepted due to the lack of power for the estimated outcome. However, a statistical tendency was established, and GLS values exhibited a slight improvement with ARBs therapy. Unluckily, it was not possible to compare this outcome with the control group because of the poor quality of the images, and only three subjects presented measurable images. We cannot know if this non-significant improvement is due to the intervention or by chance. Nevertheless, this treatment seems not to worse LV systolic function.

Previously published studies could neither evidence an increase in LV systolic function following antihypertensive therapy in patients with AS even though there was a regression of LV mass index or an improvement in other parameters.[137,184,187,341] One meta-analysis, including 24 studies done in moderate-to-severe AS, investigated the effect of several different antihypertensive treatments on LVEF, other echocardiographic parameters, AS progression and mortality.[353] The authors did not find an advantage of antihypertensive treatment on LVEF or other parameters of LV systolic function, as S-wave; probably, because of the presence of substantial heterogeneity.[353] Only one publication has shown an impact on S-wave with the use of *ramipril* in moderate and severe AS. Are these results meaning that antihypertensive treatment, particularly RAS inhibitors, is not effective in improving LV systolic function? It may be possible that LVEF or S-wave measured by tissue Doppler echocardiography are not enough sensitive to show a difference in LV systolic function, especially in those patients with mild or moderate AS and preserved LVEF. Moreover, this meta-analysis found a statistically significant reduction in all-cause

mortality using RAS inhibitors.[353] Several studies have also reported improvements in symptoms or exercise tolerance.[87,185,187,190,341,346-349] Moreover, ARBs were found to abolish the increased risk of mortality associated with hypertension.[191] Hence, although it has not been proved that RAS inhibitors could improve or regress LV systolic dysfunction, it was vastly shown that antihypertensive treatment has beneficial effects in patients with AS and concomitant hypertension.

Control of blood pressure was achieved in the intervention group. As it was expected, SBP was rather reduced with a statistically significant difference in this group. Thus, SAC presented a statistically significant increase in the *Losartan* group owing to a decrease in pulse pressure and, in a lesser way, a possible increase in SV. Arterial stiffening has been linked to reduced SAC and is a major factor in the development of hypertension. Arterial stiffening is commonly seen in elderly patients and is associated with other comorbidities, such as dyslipidemia, diabetes, and atherosclerosis.[305,307,354-356] Patients from the intervention group were slightly older, but comorbidities were similar between both groups. It is not possible to know whether or not they have comparable arterial stiffness. RAS inhibitors were associated with decreasing arterial stiffness, which is measured by carotid-femoral pulse wave velocity, independently of blood pressure lowering.[357,358] *Losartan* treatment may impact positively by decreasing it. Furthermore, reduced SAC impacts on LV mechanics increasing LV afterload and myocardial oxygen demand, and it was also associated with a fall in coronary flow during diastole.[305] Thus, it is an independent predictor of LV dysfunction and adverse outcomes.[224,306,307,355,356]

Briand et al. found that SAC was an independent predictor of LV dysfunction. Conversely, when Zva was considered into the multivariable model became the only hemodynamic factor to be independently associated with LV diastolic and systolic dysfunction, representing the respective contribution of AVAi and SAC.[224] Thus, it allows to better evaluate the global LV afterload in the context of AS and hypertension. In our study, there was a diminution of it with a borderline significant trend in the *Losartan* group. However, there was no statistically significant difference between groups. Interestingly, considering the Zva groups established by Hachicha et al.[232], the low Zva group was more prevalent after one year of treatment in the *Losartan* group in comparison with the control group, in which patients were dispersed between the Zva groups. Although there was not a statistically significant difference, these outcomes could have a clinical implication because of the association between Zva and myocardial systolic dysfunction[190], and Zva and mortality.[232] Besides, higher global LV hemodynamic load is linked to earlier onset of symptoms in patients with AS. Only one study has evaluated the impact of antihypertensive treatment on Zva in patients with moderate-to-severe AS.[335] Despite its positive results, the study was done using *metoprolol*, a beta-adrenergic blocker, which is not the first choice to treat

hypertension due to its side effects. Besides, RAS inhibitors or diuretics have demonstrated better outcomes in randomized clinical trials of hypertension.

NT-proBNP is a biomarker of cardiac damage because its synthesis and secretion are stimulated by mechanical stretch of the myocyte. It is released in response to ventricular volume expansion and increased wall stress.[359] It is highly increased during acute heart failure, myocardial infarction and other diseases. Chronic heart failure or LV dysfunction leads to upregulation of its secretion. Normal ranges depend on age, gender, and assay method. Moreover, NT-proBNP and serum B-type natriuretic peptide are well-known predictors of prognosis in heart failure.[359,360] Values correlate well with the severity of AS and are associated with symptoms and adverse clinical outcomes in moderate-to-severe and severe AS.[359,361-363] One recently published study including only patients with moderate AS has revealed that the all-cause mortality rate was superior in patients with higher-median NT-ProBNP levels (> 888 pg/dl) in comparison with lower-median NT-ProBNP.[359] Further, higher NT-ProBNP level was linked to lower LVEF levels as well as larger LV mass indexes, larger LV dimensions and more elevated medial E/e' levels; suggesting an association with systolic and diastolic dysfunction in patients with moderate AS.[359] Dalsgaard et al. carried out a study using RAS inhibitors in severe AS (follow-up: 49 days) and indicated a significant improvement in NT-proBNP values. This result was accompanied by an amelioration of SBP and SAC. Thus, it showed that the reduction of NT-proBNP might have been a consequence of unloading the LV. We could not demonstrate a difference in the annualized ratios of NT-proBNP levels, although there were significant changes in SBP and SAC in the *Losartan* group. At baseline, the NT-proBNP values were low and similar between groups. The effects of ARBs may be denoted with further higher levels of NT-proBNP.

In this study, hemodynamic parameters of SV and Q mean were preserved in the *Losartan* group, contrary to the control group and the expected outcome in those patients. In the control group, a statistically significant decrease of Q-mean was observed. Both diseases are associated with a decline in SV and Q mean through time.[364,365] Hence, these results may be in response to the decrease in SBP and the amelioration in SAC due to antihypertensive treatment and the vasodilatory effects of ARBs.[346-348.] It also suggests a protective effect of the treatment on the LV systolic function, probably due to a decrease in the global LV afterload.

Hypertension and AS have strong implications in the development of LV remodeling and hypertrophy. These occur as a compensatory mechanism to increased afterload accompanied by an increased LV chamber stiffness and higher LV filling pressures. In the RIAS trial, a modest and progressive reduction of LV mass, measured by cardiac magnetic resonance, was observed in the intervention group.[187] Similar results were observed with the use of *candesartan* (an ARBs).[343] In the recently published meta-analysis, it

did not find a statistically significant difference.[353] However, the inclusion criteria, the measurements methods and the follow-up were very different between each study. Thus, it is not possible to conclude. Studies in hypertension using ARBs or ACEIs have also demonstrated favorable outcomes regarding LV geometry.[337,338,344] Our study was not planned to find a difference in LV mass index despite being an important parameter to assess in the setting of AS and concomitant hypertension. As it was largely described, hypertension may have a preponderant role in LV remodeling and hypertrophy while AS is moderate, whereas when AS become severe, the fixed obstruction of the valve would become the principal cause of the LV afterload.[276] In our study, there were no statistically significant differences at baseline, whereas there was a higher prevalence of LV hypertrophy in the control group. Even though LV diastolic diameter was larger in the intervention group, this difference was not seen after indexing to BSA. The annualized ratios were not significant in each group and between them. After treatment, only one patient in each group had hypertrophy. It is difficult to make conclusions, as these results could be because of the inter-observer variability or lack of time. It would be desirable to measure these outcomes by cardiac magnetic resonance, which is the gold-standard for the assessment of LV mass and myocardial fibrosis.

In our study, LV diastolic function assessment was inconclusive. A wave significantly decreased, and the E/A ratio increased in the *Losartan* group after treatment. The clinical significance of those findings is questionable. Does it mean that treatment leads to a less rigid LV, decreasing LV filling pressure and reducing the importance of atrial contraction? Or does it mean that LV became stiffer, decreasing LV filling flow and increasing filling pressure with an early rapid filling, and so, diastolic dysfunction has advanced becoming a pseudonormal pattern?[366] Nevertheless, E/e' ratio was non-significantly reduced in this group indicating that LV filling pressure may have decreased, improving LV relaxation and decreasing its stiffness. No previous study could find a statistically significant improvement in LV diastolic function parameters measured by echocardiography with antihypertensive treatment. Nonetheless, Eleid et al. found an important decrease in LV filling and pulmonary artery pressures with the administration of nitroprusside, a potent vasodilator, in patients with low-gradient severe AS, systemic hypertension and preserved LVEF.[137] Even though this study was done in a very different population (low-gradient severe AS vs. mild, moderate AS), it would be interesting to observe similar results in our population, who normally are aged and presented at least a restrictive pattern at the echocardiographic assessment. Intriguingly, one study has found that the administration of an ACEI into left coronary arteries in patients with LV hypertrophy and AS declines the curves of LV pressure-volume and LV pressure-dimension measured by ventriculography and echocardiography, respectively, implicating an amelioration in diastolic distensibility.[114] It also showed an acceleration in isovolumic relaxation time.[114]

Those results suggest that RAS is activated in those patients contributing to impaired diastolic function and RAS inhibitors may be an effective therapy to slow the progression of diastolic dysfunction.[114]

ARBs therapy was associated with slower progression of AS, assessed by Doppler-echocardiography.[191] In our study, there were no differences in the severity of AS between groups; which was confirmed by measuring the AVC score with computed tomography. We have included the AVC score, due to the hemodynamic dependence of the AS assessment by Doppler echocardiography, and the possible discordance that could exist in patients with hypertension and AS. There are some reports that concomitant hypertension can influence the echocardiographic evaluation of AS severity.[367-370]Thus, AVC score, an independent measurement of transaortic flow, allows to correctly evaluate the severity of AS and its use is recommended in case of discordances in the severity of AS.[177,371,372] Regarding the progression of AS, peak jet aortic velocity and mean pressure gradient increased significantly in the *Losartan* group. Those parameters are strongly dependant on the flow state, and the increase in SAC and the concomitant decrease in LV afterload may impact positively on the LV systolic function improving its contractibility and increasing the transaortic flow. Therefore, it may not mean that AS has progressed.

Lastly, about our safety point, there were no reported side-effects during the follow-up, neither dyspnea nor hypotension. As it could be an idiosyncratic side effect on the kidneys, especially in patients with chronic renal failure, diabetes, or older patients; creatinine clearance and serum concentration were measured. There were no changes in creatinine clearance or creatinine serum levels, suggesting that this medication may be safe for renal function. Moreover, there was no report of hyperkalemia.

3.5. LIMITATIONS

Due to the COVID-19 pandemic, it was not possible to finish the follow-up in several patients. This has compromised the statistical power and the sample size of this study. Consequently, our null hypotheses could not be rejected. However, we have performed a large list of analyses to extensively evaluate the effects of ARBs treatment on LV systolic function and global LV hemodynamic load. We also included analyses about LV diastolic function and AS progression. Another important limitation was that we could not compare the results of GLS in our interventional group with the control group due to the poor echogenicity of several patients. It would be interesting and desirable to match our interventional patients to two controls or to use GLS as one parameter to match our patients. However, in this way, it would be a risk that our two (interventional and control) groups were not homogenous.

Moreover, there were limitations inherent to our study design. The best way to investigate a new drug or a new indication for a drug is through a randomized controlled trial, in which the intervention group can

be compared with a control group receiving a placebo or no intervention. Every subject is allocated randomly, and this leads to reducing the sources of confounder factors and bias. In our study design (historical controlled), it would not be possible to set causality, although we would have enough statistical power. To reduce bias, we had matched the patients with our historical cohort. However, there were some limitations; for example, when we could not match the patients by their SBP. We have taken it into account, but the differences between each patient were large (± 20 mmHg). This could be part of a selection bias; even though there was no statistically significant difference at baseline. Furthermore, there was also no possibility to supervise the hypertensive treatment of the control group if there were one. Hence, it is not possible to know if the outcomes that we got are because of the ARBs therapy or because of the treatment intensity to control blood pressure.

Randomized controlled trials are extremely expensive and non-randomized controlled trials allow screening the possible outcomes of the future random controlled trial before starting one, evaluating possible harms, the feasibility of a new therapy or a new indication, and possible benefices. Our study was a pilot one and, although our results were not conclusive, we could observe that ARBs therapy in patients with mild to moderate AS and concomitant hypertension may be safe and well-tolerated.

Myocardial fibrosis, which is strongly associated with rapid AS progression, poor outcomes and cardiovascular mortality, could not be assessed, despite indirectly analyzing LV mass and GLS. Even if this last one is an early marker of myocardial fibrosis, GLS narrowly depends on cardiac load conditions (preload and afterload), which are easily modifiable. Besides, GLS presented high interobserver variability (7.5% in our laboratory).[350] Cardiac magnetic resonance could be done to adequately evaluate myocardial fibrosis, LV remodeling and LV mass. Moreover, the results in GLS could be correlated with the one of cardiac magnetic resonance.

AS progression could not be evaluated due to the study time and methods. AVC score by computational tomography is a more accurate parameter to define AS progression and the impact of the therapy on it. Although it was assessed at the baseline, for the timing of AS progression and radiation purpose, computational tomography was not repeated at the one-year visit but will be done at the 2-year follow-up.

CONCLUSION

AS and hypertension are two of the three more prevalent cardiovascular diseases in the high-income countries,[4] and their coexistence is highly prevalent. Their prevalence augments each year, due to the increasing life expectancy. Both diseases trigger myocardial damage, principally, by increasing the LV afterload and eliciting myocardial fibrosis. There is no pharmacological treatment to slow the progression of AS. Contrary, there are wide options to treat hypertension. There is a paucity of data regarding the efficacy of ARBs in AS, especially compared to ACEI. Theoretically, as non-ACE pathways such as chymase activation are increased in the aortic valves and AT1 receptors are increased in the aortic valves, ARBs may have comparable benefits to ACE inhibitors in patients with AS. ARBs may be more effective than ACEI to slow the calcification of the aortic valve and regress LV remodeling. However, both classes of RAS inhibitors have been shown to improve SAC, decrease global LV hemodynamics, improve symptoms related to LV dysfunction and decrease cardiovascular and all-cause mortality. However, the impact of RAS inhibitors on LV systolic function is not clear.

Therefore, our study aimed to demonstrate the impact of ABRs treatment on LV systolic dysfunction by principally measuring it with GLS. Our endpoints were not met due to the loss of follow-up during the COVID-19 pandemic. However, the revised literature and our study highlighted the importance of treating systemic hypertension in patients with AS, independently of the severity of AS. Nowadays, the new guidelines recommend:

> *"Medical therapy for hypertension follows standard guidelines, starting at a low dose and gradually titrating upward as needed to achieve blood pressure control. (…) Consideration should be given to a higher target blood pressure for patients with AS than is recommended for the general population"*[30] …

However, there is no clinical study that has indicated the targets of blood pressure for patients with AS; and it is less clear which is the best therapy for them and if this therapy might slow the progression of AS.

Our study could show that ARBs may be safe and well-tolerable in this population. Nevertheless, it will need evidence from larger, randomized controlled studies to conclude that ARBs would be a good therapy to slow the progression of AS and LV myocardial fibrosis and dysfunction.

One strength of our study was the use of GLS to measure subclinical LV systolic dysfunction. It would be desirable to repeat this study with a 1:2 matched historical controlled design. Further, our study also showed that blood pressure is optimized and control with ARBs therapy and, the antihypertensive

treatment leads to increase SAC; decreasing the stiffness of the systemic arterial system and the LV afterload.

BIBLIOGRAPHY

1. Moore KL, Agur AMR, Dalley AF. Essential clinical anatomy Fifth. ed: Lippincott Williams & Wilkins, 2015.
2. Waugh A, Grant A. Ross & Wilson anatomy and physiology in health and illness. 12th ed. London: Elsevier Health Sciences UK, 2014.
3. Hoffman J, Fullerton D. Surgical anatomy of the aortic and mitral valves. . American College of Cardiology; March 2018.
4. Carpentier A, Adams DH, Filsoufi F. Carpentier's Reconstructive Valve Surgery: From Valve Analysis to Valve Reconstruction. First. Saunders Elsevier. ed2010.
5. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol 2012;60(19):1854-63. DOI: 10.1016/j.jacc.2012.02.093.
6. Hinton RB, Yutzey KE. Heart valve structure and function in development and disease. Annu Rev Physiol 2011;73:29-46. (In eng). DOI: 10.1146/annurev-physiol-012110-142145.
7. Rajamannan NM, Evans FJ, Aikawa E, et al. Calcific aortic valve disease: not simply a degenerative process: A review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: Calcific aortic valve disease-2011 update. Circulation 2011;124(16):1783-91. DOI: 10.1161/CIRCULATIONAHA.110.006767.
8. Otto CM, Bonow RO. Valvular heart disease: a companion to Braunwald. Fourth ed: Elsevier Health Sciences, 2014.
9. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. Circulation 2005;111(24):3316-26. DOI: 10.1161/CIRCULATIONAHA.104.486738.
10. Mathieu P, Boulanger MC. Basic mechanisms of calcific aortic valve disease. Can J Cardiol 2014;30(9):982-93. DOI: 10.1016/j.cjca.2014.03.029.
11. Bogdanova M, Zabirnyk A, Malashicheva A, et al. Interstitial cells in calcified aortic valves have reduced differentiation potential and stem cell-like properties. Scientific Reports 2019;9(1):12934. DOI: 10.1038/s41598-019-49016-0.
12. Chen JH, Yip CY, Sone ED, Simmons CA. Identification and characterization of aortic valve mesenchymal progenitor cells with robust osteogenic calcification potential. Am J Pathol 2009;174(3):1109-19. DOI: 10.2353/ajpath.2009.080750.
13. Rajamannan NM, Bonow RO, Rahimtoola SH. Calcific aortic stenosis: an update. Nat Clin Pract Cardiovasc Med 2007;4(5):254-62. DOI: 10.1038/ncpcardio0827.
14. Lindman BR, Clavel M-A, Mathieu P, et al. Calcific aortic stenosis. Nature Reviews Disease Primers 2016;2(1):16006. DOI: 10.1038/nrdp.2016.6.
15. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. J Am Coll Cardiol 2014;63(25 Pt A):2852-61. DOI: 10.1016/j.jacc.2014.04.018.
16. Stewart BF, Siscovick D, Lind BK, et al. Clinical Factors Associated With Calcific Aortic Valve Disease fn1fn1This study was supported in part by Contracts NO1-HC85079 through HC-850086 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Journal of the American College of Cardiology 1997;29(3):630-634. DOI: 10.1016/s0735-1097(96)00563-3.
17. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD. Incidence and progression of aortic valve calcium in the Multi-ethnic Study of Atherosclerosis (MESA). Am J Cardiol 2010;105(5):701-8. DOI: 10.1016/j.amjcard.2009.10.071.
18. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341(3):142-7. DOI: 10.1056/NEJM199907153410302.
19. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Eleventh ed2018.
20. Otto CM. Calcific aortic valve disease: outflow obstruction is the end stage of a systemic disease process. Eur Heart J 2009;30(16):1940-2. DOI: 10.1093/eurheartj/ehp175.
21. Nistri S, Faggiano P, Olivotto I, et al. Hemodynamic progression and outcome of asymptomatic aortic stenosis in primary care. Am J Cardiol 2012;109(5):718-23. DOI: 10.1016/j.amjcard.2011.10.035.
22. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol 1993;21(5):1220-5. DOI: 10.1016/0735-1097(93)90249-z.
23. Virani S, Alonso A, Aparicio H, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation 2021. DOI: 10.1161/CIR.0000000000000950.
24. Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;62(11):1002-12. DOI: 10.1016/j.jacc.2013.05.015.
25. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. The Lancet 2006;368(9540):1005-1011. DOI: 10.1016/s0140-6736(06)69208-8.
26. Ross J, Jr., Braunwald E. Aortic stenosis. Circulation 1968;38(1 Suppl):61-7. DOI: 10.1161/01.cir.38.1s5.v-61.
27. Braunwald E. Aortic Stenosis: Then and Now. Circulation 2018;137(20):2099-2100. DOI: 10.1161/CIRCULATIONAHA.118.033408.

28. Kasper DL, Hauser SL, Jamseon JL, Fauci AS, Longo DL, Loscalzo J. Harrison's Principles of Internal Medicine. Nineteenth ed: Mc Graw-Hill Education, 2015.
29. Carabello BA. Introduction to aortic stenosis. Circ Res 2013;113(2):179-85. DOI: 10.1161/CIRCRESAHA.113.300156.
30. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143(5):e72-e227. DOI: 10.1161/CIR.0000000000000923.
31. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009;373(9667):956-66. DOI: 10.1016/S0140-6736(09)60211-7.
32. Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. Circ Res 2013;113(2):223-37. DOI: 10.1161/CIRCRESAHA.111.300084.
33. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;127(1):143-52. (In eng). DOI: 10.1161/CIR.0b013e318282ab8f.
34. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363(17):1597-607. DOI: 10.1056/NEJMoa1008232.
35. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364(23):2187-98. DOI: 10.1056/NEJMoa1103510.
36. Roberts WC, Ko JM, Hamilton C. Comparison of valve structure, valve weight, and severity of the valve obstruction in 1849 patients having isolated aortic valve replacement for aortic valve stenosis (with or without associated aortic regurgitation) studied at 3 different medical centers in 2 different time periods. Circulation 2005;112(25):3919-29. DOI: 10.1161/CIRCULATIONAHA.105.543280.
37. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374(17):1609-20. DOI: 10.1056/NEJMoa1514616.
38. El Oakley R, Kleine P, Bach DS. Choice of prosthetic heart valve in today's practice. Circulation 2008;117(2):253-6. DOI: 10.1161/CIRCULATIONAHA.107.736819.
39. Eggebrecht H, Schafer U, Treede H, et al. Valve-in-valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. JACC Cardiovasc Interv 2011;4(11):1218-27. DOI: 10.1016/j.jcin.2011.07.015.
40. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. N Engl J Med 2014;371(8):744-56. DOI: 10.1056/NEJMra1313875.
41. Probst V, Scouarnec SL, Legendre A, et al. Familial Aggregation of Calcific Aortic Valve Stenosis in the Western Part of France. Circulation 2006;113(6):856-860. DOI: doi:10.1161/CIRCULATIONAHA.105.569467.
42. Ducharme V, Guauque-Olarte S, Gaudreault N, Pibarot P, Mathieu P, Bosse Y. NOTCH1 genetic variants in patients with tricuspid calcific aortic valve stenosis. J Heart Valve Dis 2013;22(2):142-9. (https://www.ncbi.nlm.nih.gov/pubmed/23798201).
43. Guauque-Olarte S, Messika-Zeitoun D, Droit A, et al. Calcium Signaling Pathway Genes RUNX2 and CACNA1C Are Associated With Calcific Aortic Valve Disease. Circ Cardiovasc Genet 2015;8(6):812-22. DOI: 10.1161/CIRCGENETICS.115.001145.
44. Perrot N, Theriault S, Dina C, et al. Genetic Variation in LPA, Calcific Aortic Valve Stenosis in Patients Undergoing Cardiac Surgery, and Familial Risk of Aortic Valve Microcalcification. JAMA Cardiol 2019;4(7):620-627. DOI: 10.1001/jamacardio.2019.1581.
45. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med 2013;368(6):503-12. DOI: 10.1056/NEJMoa1109034.
46. Capoulade R, Mahmut A, Tastet L, et al. Impact of plasma Lp-PLA2 activity on the progression of aortic stenosis: the PROGRESSA study. JACC Cardiovasc Imaging 2015;8(1):26-33. DOI: 10.1016/j.jcmg.2014.09.016.
47. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. Arterioscler Thromb Vasc Biol 1996;16(4):523-32. DOI: 10.1161/01.atv.16.4.523.
48. Zheng KH, Tsimikas S, Pawade T, et al. Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis. J Am Coll Cardiol 2019;73(17):2150-2162. DOI: 10.1016/j.jacc.2019.01.070.
49. Arsenault BJ, Boekholdt SM, Dube MP, et al. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. Circ Cardiovasc Genet 2014;7(3):304-10. DOI: 10.1161/CIRCGENETICS.113.000400.
50. Rajamannan NM, Subramaniam M, Stock SR, et al. Atorvastatin inhibits calcification and enhances nitric oxide synthase production in the hypercholesterolaemic aortic valve. Heart 2005;91(6):806-10. DOI: 10.1136/hrt.2003.029785.
51. Rajamannan NM, Subramaniam M, Caira F, Stock SR, Spelsberg TC. Atorvastatin inhibits hypercholesterolemia-induced calcification in the aortic valves via the Lrp5 receptor pathway. Circulation 2005;112(9 Suppl):I229-34. DOI: 10.1161/01.CIRCULATIONAHA.104.524306.
52. Boon AC, Emile; Lodder, Jan and Kessels, Fons. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. Heart 1997;78:472-474. DOI: 10.1136/hrt.78.5.472.
53. Aronow W, Schwartz K, Koenigsberg M. Correlation of serum lipids, calcium and phosphorus, diabetes mellitus with presence or absence of calcified or thickened aortic cusps or root in elderly patients. . The American Journal of Cardiology 1987;59(9):998-999.

54. Thanassoulis G, Massaro JM, Cury R, et al. Associations of long-term and early adult atherosclerosis risk factors with aortic and mitral valve calcium. J Am Coll Cardiol 2010;55(22):2491-8. DOI: 10.1016/j.jacc.2010.03.019.
55. Novaro GM, Katz R, Aviles RJ, et al. Clinical factors, but not C-reactive protein, predict progression of calcific aortic-valve disease: the Cardiovascular Health Study. J Am Coll Cardiol 2007;50(20):1992-8. DOI: 10.1016/j.jacc.2007.07.064.
56. Messika-Zeitoun D, Bielak LF, Peyser PA, et al. Aortic valve calcification: determinants and progression in the population. Arterioscler Thromb Vasc Biol 2007;27(3):642-8. DOI: 10.1161/01.ATV.0000255952.47980.c2.
57. Deutscher S, Rockette HE, Krishnaswami V. Diabetes and hypercolesterolemia among patients with calcific aortic stenosis. Journal of Chronic Disease 1984;37(5):407-415.
58. Mohty D, Pibarot P, Despres JP, et al. Age-related differences in the pathogenesis of calcific aortic stenosis: the potential role of resistin. Int J Cardiol 2010;142(2):126-32. DOI: 10.1016/j.ijcard.2008.12.068.
59. Kaltoft ML, Anne; and Grønne Nordestgaard, Børge. Obesity as a causal risk factor for aortic valve stenosis. Journal of the American college of Cardiology 2020;75(2):163-176. DOI: https://doi.org/10.1016/j.jacc.2019.10.050.
60. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting glucose and insulin concentrations in man. Diabetologia 1985;28(7):412-419.
61. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. Circulation 2006;113(17):2113-9. DOI: 10.1161/CIRCULATIONAHA.105.598086.
62. Mohty D, Pibarot P, Despres JP, et al. Association between plasma LDL particle size, valvular accumulation of oxidized LDL, and inflammation in patients with aortic stenosis. Arterioscler Thromb Vasc Biol 2008;28(1):187-93. DOI: 10.1161/ATVBAHA.107.154989.
63. Katz R, Budoff MJ, Takasu J, et al. Relationship of metabolic syndrome with incident aortic valve calcium and aortic valve calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes 2009;58(4):813-9. DOI: 10.2337/db08-1515.
64. Capoulade R, Clavel MA, Dumesnil JG, et al. Impact of metabolic syndrome on progression of aortic stenosis: influence of age and statin therapy. J Am Coll Cardiol 2012;60(3):216-23. DOI: 10.1016/j.jacc.2012.03.052.
65. Tomiyama H, Koji Y, Yambe M, et al. Elevated C-reactive protein augments increased arterial stiffness in subjects with the metabolic syndrome. Hypertension 2005;45(5):997-1003. DOI: 10.1161/01.HYP.0000165018.63523.8a.
66. Briand M, Pibarot P, Despres JP, et al. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. Circulation 2006;114(1 Suppl):I512-7. DOI: 10.1161/CIRCULATIONAHA.105.000422.
67. Briand M, Lemieux I, Dumesnil JG, et al. Metabolic syndrome negatively influences disease progression and prognosis in aortic stenosis. J Am Coll Cardiol 2006;47(11):2229-36. DOI: 10.1016/j.jacc.2005.12.073.
68. O'Brien KD. Do bioprosthetic aortic valves deteriorate more rapidly in patients with the metabolic syndrome? Nat Clin Pract Cardiovasc Med 2007;4(4):192-3. DOI: 10.1038/ncpcardio0826.
69. Vavilis G, Back M, Occhino G, et al. Kidney Dysfunction and the Risk of Developing Aortic Stenosis. J Am Coll Cardiol 2019;73(3):305-314. DOI: 10.1016/j.jacc.2018.10.068.
70. Nitsche C, Kammerlander AA, Knechtelsdorfer K, et al. Determinants of Bioprosthetic Aortic Valve Degeneration. JACC Cardiovasc Imaging 2020;13(2 Pt 1):345-353. DOI: 10.1016/j.jcmg.2019.01.027.
71. Salaun E, Cote N, Clavel MA, Pibarot P. Biomarkers of aortic bioprosthetic valve structural degeneration. Curr Opin Cardiol 2019;34(2):132-139. DOI: 10.1097/HCO.0000000000000590.
72. Mahjoub H, Mathieu P, Larose E, et al. Determinants of aortic bioprosthetic valve calcification assessed by multidetector CT. Heart 2015;101(6):472-7. DOI: 10.1136/heartjnl-2014-306445.
73. Lindroos M, Kupari M, Valvannet J, Strandberg T, Heikkila J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. European Heart Journal 1994;15(7):865-870.
74. Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: artherosclerosis risk factors - a causal relationship? A clinical morphologic study. . Clinical Cardiology 1991;14(12):995-999.
75. Kumar V, Abbas AK, Aster JC. Robins Basic Pathology. Tenth. Elsevier Health Science ed2018.
76. Otto CM, Kuusisto J, Reichenbach D, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90(2):844-853.
77. Cote C, Pibarot P, Despres JP, et al. Association between circulating oxidised low-density lipoprotein and fibrocalcific remodelling of the aortic valve in aortic stenosis. Heart 2008;94(9):1175-80. DOI: 10.1136/hrt.2007.125740.
78. Miller JD, Chu Y, Brooks RM, Richenbacher WE, Pena-Silva R, Heistad DD. Dysregulation of antioxidant mechanisms contributes to increased oxidative stress in calcific aortic valvular stenosis in humans. J Am Coll Cardiol 2008;52(10):843-50. DOI: 10.1016/j.jacc.2008.05.043.
79. Steiner I, Kasparova P, Kohout A, Dominik J. Bone formation in cardiac valves: a histopathological study of 128 cases. Virchows Arch 2007;450(6):653-7. DOI: 10.1007/s00428-007-0430-7.
80. Liberman M, Bassi E, Martinatti MK, et al. Oxidant Generation Predominates Around Calcifying Foci and Enhances Progression of Aortic Valve Calcification. Arteriosclerosis, Thrombosis, and Vascular Biology 2008;28(3):463-470. DOI: doi:10.1161/ATVBAHA.107.156745.

81. Bouchareb R, Mahmut A, Nsaibia MJ, et al. Autotaxin Derived From Lipoprotein(a) and Valve Interstitial Cells Promotes Inflammation and Mineralization of the Aortic Valve. Circulation 2015;132(8):677-90. (In eng). DOI: 10.1161/circulationaha.115.016757.
82. Hammarström S. Leukotrienes. Annu Rev Biochem 1983;52:355-77. (In eng). DOI: 10.1146/annurev.bi.52.070183.002035.
83. Nagy E, Andersson DC, Caidahl K, et al. Upregulation of the 5-lipoxygenase pathway in human aortic valves correlates with severity of stenosis and leads to leukotriene-induced effects on valvular myofibroblasts. Circulation 2011;123(12):1316-25. (In eng). DOI: 10.1161/circulationaha.110.966846.
84. Wirrig EE, Gomez MV, Hinton RB, Yutzey KE. COX2 inhibition reduces aortic valve calcification in vivo. Arterioscler Thromb Vasc Biol 2015;35(4):938-47. (In eng). DOI: 10.1161/atvbaha.114.305159.
85. Mazzone A, Epistolato MC, De Caterina R, et al. Neoangiogenesis, T-lymphocyte infiltration, and heat shock protein-60 are biological hallmarks of an immunomediated inflammatory process in end-stage calcified aortic valve stenosis. J Am Coll Cardiol 2004;43(9):1670-6. DOI: 10.1016/j.jacc.2003.12.041.
86. Liu AC, Joag VR, Gotlieb AI. The Emerging Role of Valve Interstitial Cell Phenotypes in Regulating Heart Valve Pathobiology. The American Journal of Pathology 2007;171(5):1407-1418. DOI: https://doi.org/10.2353/ajpath.2007.070251.
87. O'Brien KD, Shavelle DM, Caulfield MT, et al. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. Circulation 2002;106(17):2224-30. DOI: 10.1161/01.cir.0000035655.45453.d2.
88. Helske S, Lindstedt KA, Laine M, et al. Induction of local angiotensin II-producing systems in stenotic aortic valves. J Am Coll Cardiol 2004;44(9):1859-66. DOI: 10.1016/j.jacc.2004.07.054.
89. Cote N, Pibarot P, Pepin A, et al. Oxidized low-density lipoprotein, angiotensin II and increased waist cirumference are associated with valve inflammation in prehypertensive patients with aortic stenosis. Int J Cardiol 2010;145(3):444-9. DOI: 10.1016/j.ijcard.2009.05.054.
90. Fujisaka T, Hoshiga M, Hotchi J, et al. Angiotensin II promotes aortic valve thickening independent of elevated blood pressure in apolipoprotein-E deficient mice. Atherosclerosis 2013;226(1):82-7. DOI: 10.1016/j.atherosclerosis.2012.10.055.
91. Mönckeberg JG. XIX. Der normale histologische Bau und die Sklerose der Aortenklappen. (Aus dem Dr. Senckenbergischen pathologisch-anatomischen Institute zu Frankfurt a. M.) (Hierzu Taf. XI und 4 Figuren im Text.). In: Johannes O, Oscar I, eds. Band 176: De Gruyter; 2021:472-514.
92. Miller JD, Weiss RM, Heistad DD. Calcific aortic valve stenosis: methods, models, and mechanisms. Circ Res 2011;108(11):1392-412. DOI: 10.1161/CIRCRESAHA.110.234138.
93. Mohty D, Pibarot P, Despres J-P, Cartier A, Arsenault B, Mathieu P. Reduced Fetuin-A Plasma Level is Associated with Faster Stenosis Progression and Increased Valvular Calcification in the Elderly Patients with Aortic Stenosis. Am Heart Assoc; 2007.
94. Capoulade R, Cote N, Mathieu P, et al. Circulating levels of matrix gla protein and progression of aortic stenosis: a substudy of the Aortic Stenosis Progression Observation: Measuring Effects of rosuvastatin (ASTRONOMER) trial. Can J Cardiol 2014;30(9):1088-95. DOI: 10.1016/j.cjca.2014.03.025.
95. Koos R, Brandenburg V, Mahnken AH, et al. Association of fetuin-A levels with the progression of aortic valve calcification in non-dialyzed patients. Eur Heart J 2009;30(16):2054-61. DOI: 10.1093/eurheartj/ehp158.
96. Pawade TA, Newby DE, Dweck MR. Calcification in Aortic Stenosis: The Skeleton Key. J Am Coll Cardiol 2015;66(5):561-77. DOI: 10.1016/j.jacc.2015.05.066.
97. Boron WF, Boulpaep EL. Medical Physiology. Second ed: Elsevier Health Science, 2012.
98. Otto CM. The Practice of clinical echocardiography. Fifth ed: Elsevier Health Sciences, 2017.
99. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56(1):56-64. DOI: 10.1172/JCI108079.
100. Kupari M, Turto H, Lommi J. Left ventricular hypertrophy in aortic valve stenosis: preventive or promotive of systolic dysfunction and heart failure? Eur Heart J 2005;26(17):1790-6. DOI: 10.1093/eurheartj/ehi290.
101. Carabello BA. Is cardiac hypertrophy good or bad? The answer, of course, is yes. JACC Cardiovasc Imaging 2014;7(11):1081-3. DOI: 10.1016/j.jcmg.2014.07.013.
102. Petrov G, Dworatzek E, Schulze TM, et al. Maladaptive remodeling is associated with impaired survival in women but not in men after aortic valve replacement. JACC Cardiovasc Imaging 2014;7(11):1073-80. DOI: 10.1016/j.jcmg.2014.06.017.
103. Lindman BR, Arnold SV, Madrazo JA, et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in patients with severe aortic stenosis. Circ Heart Fail 2011;4(3):286-92. DOI: 10.1161/CIRCHEARTFAILURE.110.960039.
104. Gjesdal O, Bluemke DA, Lima JA. Cardiac remodeling at the population level--risk factors, screening, and outcomes. Nat Rev Cardiol 2011;8(12):673-85. DOI: 10.1038/nrcardio.2011.154.
105. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(1):1-39.e14. (In eng). DOI: 10.1016/j.echo.2014.10.003.
106. Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. N Engl J Med 1982;307(22):1362-6. DOI: 10.1056/NEJM198211253072202.

107. Julius BK, Spillmann M, Vassalli G, Villari B, Eberli FR, Hess OM. Angina pectoris in patients with aortic stenosis and normal coronary arteries. Mechanisms and pathophysiological concepts. Circulation 1997;95(4):892-8. DOI: 10.1161/01.cir.95.4.892.
108. Nakano K, Corin WJ, Spann JF, Jr., Biederman RW, Denslow S, Carabello BA. Abnormal subendocardial blood flow in pressure overload hypertrophy is associated with pacing-induced subendocardial dysfunction. Circ Res 1989;65(6):1555-64. DOI: 10.1161/01.res.65.6.1555.
109. Garcia D, Camici PG, Durand LG, et al. Impairment of coronary flow reserve in aortic stenosis. J Appl Physiol (1985) 2009;106(1):113-21. DOI: 10.1152/japplphysiol.00049.2008.
110. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. Cell Mol Life Sci 2014;71(4):549-74. (In eng). DOI: 10.1007/s00018-013-1349-6.
111. Bing R, Cavalcante JL, Everett RJ, Clavel MA, Newby DE, Dweck MR. Imaging and Impact of Myocardial Fibrosis in Aortic Stenosis. JACC Cardiovasc Imaging 2019;12(2):283-296. (In eng). DOI: 10.1016/j.jcmg.2018.11.026.
112. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991;83(6):1849-65. (In eng). DOI: 10.1161/01.cir.83.6.1849.
113. Zou Y, Akazawa H, Qin Y, et al. Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. Nat Cell Biol 2004;6(6):499-506. DOI: 10.1038/ncb1137.
114. Friedrich SP, Lorell BH, Rousseau MF, et al. Intracardiac angiotensin-converting enzyme inhibition improves diastolic function in patients with left ventricular hypertrophy due to aortic stenosis. Circulation 1994;90(6):2761-71. (In eng). DOI: 10.1161/01.cir.90.6.2761.
115. Yang W, Wang BH, Wang I, et al. Inhibition of Apoptosis Signal-Regulating Kinase 1 Attenuates Myocyte Hypertrophy and Fibroblast Collagen Synthesis. Heart Lung Circ 2019;28(3):495-504. (In eng). DOI: 10.1016/j.hlc.2017.12.001.
116. Kandalam V, Basu R, Moore L, et al. Lack of tissue inhibitor of metalloproteinases 2 leads to exacerbated left ventricular dysfunction and adverse extracellular matrix remodeling in response to biomechanical stress. Circulation 2011;124(19):2094-105. (In eng). DOI: 10.1161/circulationaha.111.030338.
117. Hinderer S, Schenke-Layland K. Cardiac fibrosis – A short review of causes and therapeutic strategies. Advanced Drug Delivery Reviews 2019;146:77-82. DOI: https://doi.org/10.1016/j.addr.2019.05.011.
118. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322(22):1561-6. DOI: 10.1056/NEJM199005313222203.
119. Duncan AI, Lowe BS, Garcia MJ, et al. Influence of concentric left ventricular remodeling on early mortality after aortic valve replacement. Ann Thorac Surg 2008;85(6):2030-9. DOI: 10.1016/j.athoracsur.2008.02.075.
120. Mihaljevic T, Nowicki ER, Rajeswaran J, et al. Survival after valve replacement for aortic stenosis: implications for decision making. J Thorac Cardiovasc Surg 2008;135(6):1270-8; discussion 1278-9. DOI: 10.1016/j.jtcvs.2007.12.042.
121. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart 2011;97(4):301-7. DOI: 10.1136/hrt.2010.192997.
122. Gerdts E, Cramariuc D, de Simone G, Wachtell K, Dahlof B, Devereux RB. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). Eur J Echocardiogr 2008;9(6):809-15. DOI: 10.1093/ejechocard/jen155.
123. Everett RJ, Tastet L, Clavel MA, et al. Progression of Hypertrophy and Myocardial Fibrosis in Aortic Stenosis: A Multicenter Cardiac Magnetic Resonance Study. Circ Cardiovasc Imaging 2018;11(6):e007451. DOI: 10.1161/CIRCIMAGING.117.007451.
124. Falcao-Pires I, Hamdani N, Borbely A, et al. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation 2011;124(10):1151-9. DOI: 10.1161/CIRCULATIONAHA.111.025270.
125. Page A, Dumesnil JG, Clavel MA, et al. Metabolic syndrome is associated with more pronounced impairment of left ventricle geometry and function in patients with calcific aortic stenosis: a substudy of the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin). J Am Coll Cardiol 2010;55(17):1867-74. DOI: 10.1016/j.jacc.2009.11.083.
126. Monin JL, Lancellotti P, Monchi M, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation 2009;120(1):69-75. DOI: 10.1161/CIRCULATIONAHA.108.808857.
127. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. Circulation 2003;107(7):984-91. DOI: 10.1161/01.cir.0000051865.66123.b7.
128. Elmariah S, Palacios IF, McAndrew T, et al. Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort A). Circ Cardiovasc Interv 2013;6(6):604-14. DOI: 10.1161/CIRCINTERVENTIONS.113.000650.
129. Dauerman HL, Reardon MJ, Popma JJ, et al. Early Recovery of Left Ventricular Systolic Function After CoreValve Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv 2016;9(6). DOI: 10.1161/CIRCINTERVENTIONS.115.003425.
130. Lindman BR, Zajarias A, Maniar HS, et al. Risk stratification in patients with pulmonary hypertension undergoing transcatheter aortic valve replacement. Heart 2015;101(20):1656-64. DOI: 10.1136/heartjnl-2015-308001.

131. O'Sullivan CJ, Wenaweser P, Ceylan O, et al. Effect of Pulmonary Hypertension Hemodynamic Presentation on Clinical Outcomes in Patients With Severe Symptomatic Aortic Valve Stenosis Undergoing Transcatheter Aortic Valve Implantation: Insights From the New Proposed Pulmonary Hypertension Classification. Circ Cardiovasc Interv 2015;8(7):e002358. DOI: 10.1161/CIRCINTERVENTIONS.114.002358.
132. Athanasopoulos LV, Dritsas A, Doll HA, Cokkinos DV. Comparative value of NYHA functional class and quality-of-life questionnaire scores in assessing heart failure. J Cardiopulm Rehabil Prev 2010;30(2):101-5. DOI: 10.1097/HCR.0b013e3181be7e47.
133. Rosenhek R, Klaar U, Schemper M, et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. Eur Heart J 2004;25(3):199-205. DOI: 10.1016/j.ehj.2003.12.002.
134. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343(9):611-7. DOI: 10.1056/NEJM200008313430903.
135. Hahn RT, Saric M, Faletra FF, et al. Recommended Standards for the Performance of Transesophageal Echocardiographic Screening for Structural Heart Intervention: From the American Society of Echocardiography. J Am Soc Echocardiogr 2021. DOI: 10.1016/j.echo.2021.07.006.
136. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Rev Esp Cardiol (Engl Ed) 2018;71(2):110. DOI: 10.1016/j.rec.2017.12.013.
137. Eleid MF, Nishimura RA, Sorajja P, Borlaug BA. Systemic hypertension in low-gradient severe aortic stenosis with preserved ejection fraction. Circulation 2013;128(12):1349-53. DOI: 10.1161/CIRCULATIONAHA.113.003071.
138. Côté N, Simard L, Zenses AS, et al. Impact of Vascular Hemodynamics on Aortic Stenosis Evaluation: New Insights Into the Pathophysiology of Normal Flow-Small Aortic Valve Area-Low Gradient Pattern. J Am Heart Assoc 2017;6(7) (In eng). DOI: 10.1161/jaha.117.006276.
139. Mondillo S, Galderisi M, Mele D, et al. Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med 2011;30(1):71-83. DOI: 10.7863/jum.2011.30.1.71.
140. Brown J, Jenkins C, Marwick TH. Use of myocardial strain to assess global left ventricular function: A comparison with cardiac magnetic resonance and 3-dimensional echocardiography. American Heart Journal 2009;157(1):102.e1-102.e5. DOI: https://doi.org/10.1016/j.ahj.2008.08.032.
141. Potter E, Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. JACC: Cardiovascular Imaging 2018;11(2, Part 1):260-274. DOI: https://doi.org/10.1016/j.jcmg.2017.11.017.
142. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr 2015;28(10):1171-1181, e2. DOI: 10.1016/j.echo.2015.06.011.
143. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation 2000;102(10):1158-64. DOI: 10.1161/01.cir.102.10.1158.
144. Amundsen BH, Helle-Valle T, Edvardsen T, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47(4):789-93. DOI: 10.1016/j.jacc.2005.10.040.
145. Negishi K, Lucas S, Negishi T, Hamilton J, Marwick TH. What is the Primary Source of Discordance in Strain Measurement Between Vendors: Imaging or Analysis? Ultrasound in Medicine & Biology 2013;39(4):714-720. DOI: https://doi.org/10.1016/j.ultrasmedbio.2012.11.021.
146. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16(1):1-11. (In eng). DOI: 10.1093/ehjci/jeu184.
147. Yang H, Marwick TH, Fukuda N, et al. Improvement in Strain Concordance between Two Major Vendors after the Strain Standardization Initiative. Journal of the American Society of Echocardiography 2015;28(6):642-648.e7. DOI: https://doi.org/10.1016/j.echo.2014.12.009.
148. Weidemann F, Herrmann S, Stork S, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation 2009;120(7):577-84. DOI: 10.1161/CIRCULATIONAHA.108.847772.
149. Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013;26(2):185-91. DOI: 10.1016/j.echo.2012.10.008.
150. Abou R, van der Bijl P, Bax JJ, Delgado V. Global longitudinal strain: clinical use and prognostic implications in contemporary practice. Heart 2020;106(18):1438-1444. DOI: 10.1136/heartjnl-2019-316215.
151. Biering-Sørensen T, Biering-Sørensen SR, Olsen FJ, et al. Global Longitudinal Strain by Echocardiography Predicts Long-Term Risk of Cardiovascular Morbidity and Mortality in a Low-Risk General Population: The Copenhagen City Heart Study. Circ Cardiovasc Imaging 2017;10(3) (In eng). DOI: 10.1161/circimaging.116.005521.
152. Russo C, Jin Z, Elkind MS, et al. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. Eur J Heart Fail 2014;16(12):1301-9. DOI: 10.1002/ejhf.154.
153. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004;17(6):630-3. DOI: 10.1016/j.echo.2004.02.011.
154. Kraigher-Krainer E, Shah AM, Gupta DK, et al. Impaired Systolic Function by Strain Imaging in Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology 2014;63(5):447-456. DOI: https://doi.org/10.1016/j.jacc.2013.09.052.

155. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging 2009;2(5):356-64. (In eng). DOI: 10.1161/circimaging.109.862334.
156. Vollema EM, Sugimoto T, Shen M, et al. Association of Left Ventricular Global Longitudinal Strain With Asymptomatic Severe Aortic Stenosis: Natural Course and Prognostic Value. JAMA Cardiol 2018;3(9):839-847. DOI: 10.1001/jamacardio.2018.2288.
157. Ng AC, Bertini M, Borleffs CJ, et al. Predictors of death and occurrence of appropriate implantable defibrillator therapies in patients with ischemic cardiomyopathy. Am J Cardiol 2010;106(11):1566-73. DOI: 10.1016/j.amjcard.2010.07.029.
158. Biering-Sorensen T, Knappe D, Pouleur AC, et al. Regional Longitudinal Deformation Improves Prediction of Ventricular Tachyarrhythmias in Patients With Heart Failure With Reduced Ejection Fraction: A MADIT-CRT Substudy (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). Circ Cardiovasc Imaging 2017;10(1). DOI: 10.1161/CIRCIMAGING.116.005096.
159. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation 2015;132(5):402-414. DOI: doi:10.1161/CIRCULATIONAHA.115.015884.
160. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis. JAMA Cardiology 2019;4(10):1007-1018. DOI: 10.1001/jamacardio.2019.2952.
161. Thavendiranathan P, Poulin F, Lim K-D, Plana JC, Woo A, Marwick TH. Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy: A Systematic Review. Journal of the American College of Cardiology 2014;63(25, Part A):2751-2768. DOI: https://doi.org/10.1016/j.jacc.2014.01.073.
162. Szelenyi Z, Fazakas A, Szenasi G, et al. The mechanism of reduced longitudinal left ventricular systolic function in hypertensive patients with normal ejection fraction. J Hypertens 2015;33(9):1962-9; discussion 1969. DOI: 10.1097/HJH.0000000000000624.
163. Ernande L, Bergerot C, Rietzschel ER, et al. Diastolic dysfunction in patients with type 2 diabetes mellitus: is it really the first marker of diabetic cardiomyopathy? J Am Soc Echocardiogr 2011;24(11):1268-1275 e1. DOI: 10.1016/j.echo.2011.07.017.
164. Holland DJ, Marwick TH, Haluska BA, et al. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. Heart 2015;101(13):1061-6. DOI: 10.1136/heartjnl-2014-307391.
165. Witkowski TG, Thomas JD, Debonnaire PJ, et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. Eur Heart J Cardiovasc Imaging 2013;14(1):69-76. DOI: 10.1093/ehjci/jes155.
166. Mascle S, Schnell F, Thebault C, et al. Predictive value of global longitudinal strain in a surgical population of organic mitral regurgitation. J Am Soc Echocardiogr 2012;25(7):766-72. DOI: 10.1016/j.echo.2012.04.009.
167. Citro R, Baldi C, Lancellotti P, et al. Global longitudinal strain predicts outcome after MitraClip implantation for secondary mitral regurgitation. J Cardiovasc Med (Hagerstown) 2017;18(9):669-678. DOI: 10.2459/JCM.0000000000000526.
168. Ewe SH, Haeck ML, Ng AC, et al. Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis. Eur Heart J Cardiovasc Imaging 2015;16(9):992-9. (In eng). DOI: 10.1093/ehjci/jev019.
169. Olsen NT, Sogaard P, Larsson HB, et al. Speckle-tracking echocardiography for predicting outcome in chronic aortic regurgitation during conservative management and after surgery. JACC Cardiovasc Imaging 2011;4(3):223-30. (In eng). DOI: 10.1016/j.jcmg.2010.11.016.
170. Delgado V, Tops LF, van Bommel RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J 2009;30(24):3037-47. (In eng). DOI: 10.1093/eurheartj/ehp351.
171. Miyazaki S, Daimon M, Miyazaki T, et al. Global longitudinal strain in relation to the severity of aortic stenosis: a two-dimensional speckle-tracking study. Echocardiography 2011;28(7):703-8. DOI: 10.1111/j.1540-8175.2011.01419.x.
172. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging 2012;5(6):719-25. (In eng). DOI: 10.1161/circimaging.112.977348.
173. Saito M, Okayama H, Yoshii T, et al. Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy. European Heart Journal - Cardiovascular Imaging 2012;13(7):617-623. DOI: 10.1093/ejechocard/jer318.
174. Liu H, Pozios I, Haileselassie B, et al. Role of Global Longitudinal Strain in Predicting Outcomes in Hypertrophic Cardiomyopathy. The American Journal of Cardiology 2017;120(4):670-675. DOI: https://doi.org/10.1016/j.amjcard.2017.05.039.
175. Abdulla J, Sivertsen J, Kofoed KF, et al. Evaluation of aortic valve stenosis by cardiac multislice computed tomography compared with echocardiography: a systematic review and meta-analysis. J Heart Valve Dis 2009;18(6):634-43. (https://www.ncbi.nlm.nih.gov/pubmed/20099712).

176. Clavel MA, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. J Am Coll Cardiol 2014;64(12):1202-13. DOI: 10.1016/j.jacc.2014.05.066.
177. Clavel MA, Messika-Zeitoun D, Pibarot P, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol 2013;62(24):2329-38. DOI: 10.1016/j.jacc.2013.08.1621.
178. Owens DS, Budoff MJ, Katz R, et al. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population. JACC Cardiovasc Imaging 2012;5(6):619-25. DOI: 10.1016/j.jcmg.2011.12.023.
179. Garcia J, Kadem L, Larose E, Clavel MA, Pibarot P. Comparison between cardiovascular magnetic resonance and transthoracic Doppler echocardiography for the estimation of effective orifice area in aortic stenosis. J Cardiovasc Magn Reson 2011;13:25. DOI: 10.1186/1532-429X-13-25.
180. Barone-Rochette G, Pierard S, Seldrum S, et al. Aortic valve area, stroke volume, left ventricular hypertrophy, remodeling, and fibrosis in aortic stenosis assessed by cardiac magnetic resonance imaging: comparison between high and low gradient and normal and low flow aortic stenosis. Circ Cardiovasc Imaging 2013;6(6):1009-17. DOI: 10.1161/CIRCIMAGING.113.000515.
181. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58(12):1271-9. DOI: 10.1016/j.jacc.2011.03.064.
182. Bohbot Y, Renard C, Manrique A, et al. Usefulness of Cardiac Magnetic Resonance Imaging in Aortic Stenosis. Circulation: Cardiovascular Imaging 2020;13(5):e010356. DOI: doi:10.1161/CIRCIMAGING.119.010356.
183. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359(13):1343-56. DOI: 10.1056/NEJMoa0804602.
184. O'Brien KD, Zhao XQ, Shavelle DM, et al. Hemodynamic effects of the angiotensin-converting enzyme inhibitor, ramipril, in patients with mild to moderate aortic stenosis and preserved left ventricular function. J Investig Med 2004;52(3):185-91. DOI: 10.1136/jim-52-03-33.
185. Nadir MA, Wei L, Elder DH, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. J Am Coll Cardiol 2011;58(6):570-6. DOI: 10.1016/j.jacc.2011.01.063.
186. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J, Investigators A. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010;121(2):306-14. DOI: 10.1161/CIRCULATIONAHA.109.900027.
187. Bull S, Loudon M, Francis JM, et al. A prospective, double-blind, randomized controlled trial of the angiotensin-converting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). Eur Heart J Cardiovasc Imaging 2015;16(8):834-41. DOI: 10.1093/ehjci/jev043.
188. Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. N Engl J Med 2003;348(18):1756-63. DOI: 10.1056/NEJMoa022021.
189. Dalsgaard M, Iversen K, Kjaergaard J, et al. Short-term hemodynamic effect of angiotensin-converting enzyme inhibition in patients with severe aortic stenosis: a placebo-controlled, randomized study. Am Heart J 2014;167(2):226-34. DOI: 10.1016/j.ahj.2013.11.002.
190. Cramariuc D, Cioffi G, Rieck AE, et al. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS Substudy. JACC Cardiovasc Imaging 2009;2(4):390-9. DOI: 10.1016/j.jcmg.2008.12.021.
191. Capoulade R, Clavel MA, Mathieu P, et al. Impact of hypertension and renin-angiotensin system inhibitors in aortic stenosis. Eur J Clin Invest 2013;43(12):1262-72. DOI: 10.1111/eci.12169.
192. Cote N, Couture C, Pibarot P, Despres JP, Mathieu P. Angiotensin receptor blockers are associated with a lower remodelling score of stenotic aortic valves. Eur J Clin Invest 2011;41(11):1172-9. DOI: 10.1111/j.1365-2362.2011.02522.x.
193. Cote N, Mahmut A, Fournier D, et al. Angiotensin receptor blockers are associated with reduced fibrosis and interleukin-6 expression in calcific aortic valve disease. Pathobiology 2014;81(1):15-24. DOI: 10.1159/000350896.
194. Barreto-Filho JA, Wang Y, Dodson JA, et al. Trends in aortic valve replacement for elderly patients in the United States, 1999-2011. Jama 2013;310(19):2078-85. (In eng). DOI: 10.1001/jama.2013.282437.
195. Hamm CW, Möllmann H, Holzhey D, et al. The German Aortic Valve Registry (GARY): in-hospital outcome. Eur Heart J 2014;35(24):1588-98. (In eng). DOI: 10.1093/eurheartj/eht381.
196. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg 2009;137(1):82-90. (In eng). DOI: 10.1016/j.jtcvs.2008.08.015.
197. Pibarot P, Dumesnil JG. Prosthetic Heart Valves. Circulation 2009;119(7):1034-1048. DOI: doi:10.1161/CIRCULATIONAHA.108.778886.
198. Carabello BA. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. Curr Cardiol Rep 2011;13(3):173-4. DOI: 10.1007/s11886-011-0173-6.
199. Oliemy A, Al-Attar N. Transcatheter aortic valve implantation. F1000Prime Rep 2014;6:92. (In eng). DOI: 10.12703/p6-92.

200. Jose J, Richardt G, Abdel-Wahab M. Balloon- or Self-Expandable TAVI: Clinical Equipoise? Interv Cardiol 2015;10(2):103-108. (In eng). DOI: 10.15420/icr.2015.10.2.103.
201. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106(24):3006-8. (In eng). DOI: 10.1161/01.cir.0000047200.36165.b8.
202. Ribeiro HB, Urena M, Allende R, Amat-Santos IJ, Rodés-Cabau J. Balloon-expandable prostheses for transcatheter aortic valve replacement. Prog Cardiovasc Dis 2014;56(6):583-95. (In eng). DOI: 10.1016/j.pcad.2014.02.001.
203. Kumar R, Latib A, Colombo A, Ruiz CE. Self-expanding prostheses for transcatheter aortic valve replacement. Prog Cardiovasc Dis 2014;56(6):596-609. (In eng). DOI: 10.1016/j.pcad.2014.03.002.
204. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385(9986):2477-84. DOI: 10.1016/S0140-6736(15)60308-7.
205. Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. Circulation 2014;130(17):1483-92. DOI: 10.1161/CIRCULATIONAHA.114.009834.
206. Kapadia S, Stewart WJ, Anderson WN, et al. Outcomes of inoperable symptomatic aortic stenosis patients not undergoing aortic valve replacement: insight into the impact of balloon aortic valvuloplasty from the PARTNER trial (Placement of AoRtic TraNscathetER Valve trial). JACC Cardiovasc Interv 2015;8(2):324-333. DOI: 10.1016/j.jcin.2014.08.015.
207. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63(19):1972-81. DOI: 10.1016/j.jacc.2014.02.556.
208. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370(19):1790-8. DOI: 10.1056/NEJMoa1400590.
209. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387(10034):2218-25. DOI: 10.1016/S0140-6736(16)30073-3.
210. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376(14):1321-1331. DOI: 10.1056/NEJMoa1700456.
211. Waksman R, Corso PJ, Torguson R, et al. TAVR in Low-Risk Patients: 1-Year Results From the LRT Trial. JACC Cardiovasc Interv 2019;12(10):901-907. DOI: 10.1016/j.jcin.2019.03.002.
212. Leung AA, Nerenberg K, Daskalopoulou SS, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol 2016;32(5):569-88. DOI: 10.1016/j.cjca.2016.02.066.
213. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-20. DOI: 10.1001/jama.2013.284427.
214. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018;138(17):e426-e483. DOI: 10.1161/CIR.0000000000000597.
215. Casey DE, Jr., Thomas RJ, Bhalla V, et al. 2019 AHA/ACC Clinical Performance and Quality Measures for Adults With High Blood Pressure: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol 2019;74(21):2661-2706. DOI: 10.1016/j.jacc.2019.10.001.
216. Wu C-Y, Hu H-Y, Chou Y-J, Huang N, Chou Y-C, Li C-P. High Blood Pressure and All-Cause and Cardiovascular Disease Mortalities in Community-Dwelling Older Adults. Medicine (Baltimore) 2015;94(47):e2160-e2160. (In eng). DOI: 10.1097/MD.0000000000002160.
217. Stamler J, Stamler R, Neaton JD. Blood Pressure, Systolic and Diastolic, and Cardiovascular Risks: US Population Data. Archives of Internal Medicine 1993;153(5):598-615. DOI: 10.1001/archinte.1993.00410050036006.
218. Forouzanfar MH, Liu P, Roth GA, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA 2017;317(2):165-182. DOI: 10.1001/jama.2016.19043.
219. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology 2020;76(25):2982-3021. DOI: https://doi.org/10.1016/j.jacc.2020.11.010.
220. Pibarot P, Dumesnil JG. Improving assessment of aortic stenosis. J Am Coll Cardiol 2012;60(3):169-80. DOI: 10.1016/j.jacc.2011.11.078.
221. Jolobe OM. Systolic hypertension is also the neglected stepsister of aortic stenosis. Am J Med 2008;121(9):e21, author reply e23. DOI: 10.1016/j.amjmed.2008.03.047.
222. Ljungberg J, Johansson B, Engstrom KG, Norberg M, Bergdahl IA, Soderberg S. Arterial hypertension and diastolic blood pressure associate with aortic stenosis. Scand Cardiovasc J 2019;53(2):91-97. DOI: 10.1080/14017431.2019.1605094.
223. Cowell SJ, Newby DE, Prescott RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005;352(23):2389-97. DOI: 10.1056/NEJMoa043876.

224. Briand M, Dumesnil JG, Kadem L, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. J Am Coll Cardiol 2005;46(2):291-8. DOI: 10.1016/j.jacc.2004.10.081.
225. Antonini-Canterin F, Huang G, Cervesato E, et al. Symptomatic aortic stenosis: does systemic hypertension play an additional role? Hypertension 2003;41(6):1268-72. DOI: 10.1161/01.HYP.0000070029.30058.59.
226. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation 1997;95(9):2262-70. DOI: 10.1161/01.cir.95.9.2262.
227. Rieck AE, Cramariuc D, Boman K, et al. Hypertension in aortic stenosis: implications for left ventricular structure and cardiovascular events. Hypertension 2012;60(1):90-7. DOI: 10.1161/HYPERTENSIONAHA.112.194878.
228. Tastet L, Capoulade R, Clavel MA, et al. Systolic hypertension and progression of aortic valve calcification in patients with aortic stenosis: results from the PROGRESSA study. Eur Heart J Cardiovasc Imaging 2017;18(1):70-78. DOI: 10.1093/ehjci/jew013.
229. Saeed S, Mancia G, Rajani R, Parkin D, Chambers JB. Antihypertensive treatment with calcium channel blockers in patients with moderate or severe aortic stenosis: Relationship with all-cause mortality. Int J Cardiol 2020;298:122-125. DOI: 10.1016/j.ijcard.2019.09.007.
230. Katsi V, Marketou M, Kallistratos MS, et al. Aortic valve stenosis and arterial hypertension: a synopsis in 2013. Curr Hypertens Rep 2013;15(4):298-303. DOI: 10.1007/s11906-013-0357-0.
231. Bouchareb R, Boulanger MC, Fournier D, Pibarot P, Messaddeq Y, Mathieu P. Mechanical strain induces the production of spheroid mineralized microparticles in the aortic valve through a RhoA/ROCK-dependent mechanism. J Mol Cell Cardiol 2014;67:49-59. DOI: 10.1016/j.yjmcc.2013.12.009.
232. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. J Am Coll Cardiol 2009;54(11):1003-11. DOI: 10.1016/j.jacc.2009.04.079.
233. Cuniberti LA, Stutzbach PG, Guevara E, Yannarelli GG, Laguens RP, Favaloro RR. Development of Mild Aortic Valve Stenosis in a Rabbit Model of Hypertension. Journal of the American College of Cardiology 2006;47(11):2303-2309. DOI: https://doi.org/10.1016/j.jacc.2005.12.070.
234. Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. Arterioscler Thromb Vasc Biol 1995;15(5):551-61. (In eng). DOI: 10.1161/01.atv.15.5.551.
235. Sarphie TG. A cytochemical study of the surface properties of aortic and mitral valve endothelium from hypercholesterolemic rabbits. Exp Mol Pathol 1986;44(3):281-96. (In eng). DOI: 10.1016/0014-4800(86)90042-0.
236. Rajamannan NM. Mechanisms of aortic valve calcification: the LDL-density-radius theory: a translation from cell signaling to physiology. Am J Physiol Heart Circ Physiol 2010;298(1):H5-15. (In eng). DOI: 10.1152/ajpheart.00824.2009.
237. Alexander RW. Hypertension and the Pathogenesis of Atherosclerosis. Hypertension 1995;25(2):155-161. DOI: doi:10.1161/01.HYP.25.2.155.
238. Satta J, Melkko J, Pöllänen R, et al. Progression of human aortic valve stenosis is associated with tenascin-C expression. J Am Coll Cardiol 2002;39(1):96-101. (In eng). DOI: 10.1016/s0735-1097(01)01705-3.
239. Mackie EJ, Scott-Burden T, Hahn AW, et al. Expression of tenascin by vascular smooth muscle cells. Alterations in hypertensive rats and stimulation by angiotensin II. Am J Pathol 1992;141(2):377-88. (In eng).
240. Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? Hypertension 2004;44(3):248-52. (In eng). DOI: 10.1161/01.HYP.0000138070.47616.9d.
241. Helske S, Syvaranta S, Kupari M, et al. Possible role for mast cell-derived cathepsin G in the adverse remodelling of stenotic aortic valves. Eur Heart J 2006;27(12):1495-504. DOI: 10.1093/eurheartj/ehi706.
242. Cuevas CA, Tapia-Rojas C, Cespedes C, Inestrosa NC, Vio CP. beta-Catenin-Dependent Signaling Pathway Contributes to Renal Fibrosis in Hypertensive Rats. Biomed Res Int 2015;2015:726012. DOI: 10.1155/2015/726012.
243. Cuevas CA, Gonzalez AA, Inestrosa NC, Vio CP, Prieto MC. Angiotensin II increases fibronectin and collagen I through the beta-catenin-dependent signaling in mouse collecting duct cells. Am J Physiol Renal Physiol 2015;308(4):F358-65. DOI: 10.1152/ajprenal.00429.2014.
244. Khan K, Yu B, Kiwan C, et al. The Role of Wnt/β-Catenin Pathway Mediators in Aortic Valve Stenosis. Front Cell Dev Biol 2020;8:862-862. (In eng). DOI: 10.3389/fcell.2020.00862.
245. Gu GJ, Chen T, Zhou HM, Sun KX, Li J. Role of Wnt/β-catenin signaling pathway in the mechanism of calcification of aortic valve. J Huazhong Univ Sci Technolog Med Sci 2014;34(1):33-36. (In eng). DOI: 10.1007/s11596-014-1228-x.
246. Osako MK, Nakagami H, Shimamura M, et al. Cross-talk of receptor activator of nuclear factor-kappaB ligand signaling with renin-angiotensin system in vascular calcification. Arterioscler Thromb Vasc Biol 2013;33(6):1287-96. DOI: 10.1161/ATVBAHA.112.301099.
247. Kawai T, Forrester SJ, O'Brien S, Baggett A, Rizzo V, Eguchi S. AT1 receptor signaling pathways in the cardiovascular system. Pharmacol Res 2017;125(Pt A):4-13. DOI: 10.1016/j.phrs.2017.05.008.
248. Ngo DTM, Heresztyn T, Mishra K, Marwick TH, Horowitz JD. Aortic stenosis is associated with elevated plasma levels of asymmetric dimethylarginine (ADMA). Nitric Oxide 2007;16(2):197-201. DOI: https://doi.org/10.1016/j.niox.2006.10.003.

249. Linefsky J, Katz R, Budoff M, et al. Stages of systemic hypertension and blood pressure as correlates of computed tomography-assessed aortic valve calcium (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 2011;107(1):47-51. DOI: 10.1016/j.amjcard.2010.08.042.
250. Iwata S, Russo C, Jin Z, et al. Higher ambulatory blood pressure is associated with aortic valve calcification in the elderly: a population-based study. Hypertension 2013;61(1):55-60. DOI: 10.1161/HYPERTENSIONAHA.112.202697.
251. Rabkin SW. The association of hypertension and aortic valve sclerosis. Blood Press 2005;14(5):264-72. DOI: 10.1080/08037050500233320.
252. Agno FS, Chinali M, Bella JN, et al. Aortic valve sclerosis is associated with preclinical cardiovascular disease in hypertensive adults: the Hypertension Genetic Epidemiology Network study. J Hypertens 2005;23(4):867-73. DOI: 10.1097/01.hjh.0000163157.14493.c7.
253. Pate GE. Association between aortic stenosis and hypertension. J Heart Valve Dis 2002;11(5):612-4. (https://www.ncbi.nlm.nih.gov/pubmed/12358395).
254. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289(19):2560-72. DOI: 10.1001/jama.289.19.2560.
255. Yan AT, Koh M, Chan KK, et al. Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. Journal of the American College of Cardiology 2017;69(12):1523-1532. DOI: https://doi.org/10.1016/j.jacc.2017.01.025.
256. Chu Y, Lund DD, Doshi H, et al. Fibrotic Aortic Valve Stenosis in Hypercholesterolemic/Hypertensive Mice. Arterioscler Thromb Vasc Biol 2016;36(3):466-74. (In eng). DOI: 10.1161/atvbaha.115.306912.
257. Balachandran K, Sucosky P, Jo H, Yoganathan AP. Elevated cyclic stretch induces aortic valve calcification in a bone morphogenic protein-dependent manner. Am J Pathol 2010;177(1):49-57. DOI: 10.2353/ajpath.2010.090631.
258. Rosenhek R, Rader F, Loho N, et al. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. Circulation 2004;110(10):1291-5. DOI: 10.1161/01.CIR.0000140723.15274.53.
259. Peter M, Hoffmann A, Parker C, Luscher T, Burckhardt D. Progression of aortic stenosis. Role of age and concomitant coronary artery disease. Chest 1993;103(6):1715-9. DOI: 10.1378/chest.103.6.1715.
260. Palta S, Pai AM, Gill KS, Pai RG. New insights into the progression of aortic stenosis: implications for secondary prevention. Circulation 2000;101(21):2497-502. (In eng). DOI: 10.1161/01.cir.101.21.2497.
261. Rieck AE, Cramariuc D, Staal EM, Rossebo AB, Wachtell K, Gerdts E. Impact of hypertension on left ventricular structure in patients with asymptomatic aortic valve stenosis (a SEAS substudy). J Hypertens 2010;28(2):377-83. DOI: 10.1097/HJH.0b013e328332fa44.
262. Kadem L, Garcia D, Durand LG, Rieu R, Dumesnil JG, Pibarot P. Value and limitations of peak-to-peak gradient for evaluation of aortic stenosis. J Heart Valve Dis 2006;15(5):609-16. (https://www.ncbi.nlm.nih.gov/pubmed/17044364).
263. Kadem L, Dumesnil JG, Rieu R, Durand LG, Garcia D, Pibarot P. Impact of systemic hypertension on the assessment of aortic stenosis. Heart 2005;91(3):354-61. DOI: 10.1136/hrt.2003.030601.
264. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-2791. DOI: 10.1093/eurheartj/ehx391.
265. Imanaka K, Kohmoto O, Nishimura S, Yokote Y, Kyo S. Impact of postoperative blood pressure control on regression of left ventricular mass following valve replacement for aortic stenosis. Eur J Cardiothorac Surg 2005;27(6):994-9. DOI: 10.1016/j.ejcts.2005.02.034.
266. Nielsen OW, Sajadieh A, Sabbah M, et al. Assessing Optimal Blood Pressure in Patients With Asymptomatic Aortic Valve Stenosis: The Simvastatin Ezetimibe in Aortic Stenosis Study (SEAS). Circulation 2016;134(6):455-68. DOI: 10.1161/CIRCULATIONAHA.115.021213.
267. Tuseth N, Cramariuc D, Rieck AE, Wachtell K, Gerdts E. Asymmetric septal hypertrophy - a marker of hypertension in aortic stenosis (a SEAS substudy). Blood Press 2010;19(3):140-4. (In eng). DOI: 10.3109/08037051.2010.481816.
268. Mehta RH, Bruckman D, Das S, et al. Implications of increased left ventricular mass index on in-hospital outcomes in patients undergoing aortic valve surgery. J Thorac Cardiovasc Surg 2001;122(5):919-28. (In eng). DOI: 10.1067/mtc.2001.116558.
269. Haering JM, Comunale ME, Parker RA, et al. Cardiac risk of noncardiac surgery in patients with asymmetric septal hypertrophy. Anesthesiology 1996;85(2):254-9. (In eng). DOI: 10.1097/00000542-199608000-00005.
270. Orlowska-Baranowska E. Hypertension in aortic stenosis: more questions than answers. Cardiol J 2013;20(1):4-10. DOI: 10.5603/CJ.2013.0002.
271. Gerdts E. Left ventricular structure in different types of chronic pressure overload. European Heart Journal Supplements 2008;10(suppl_E):E23-E30. DOI: 10.1093/eurheartj/sun015.
272. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 1992;19(7):1550-8. DOI: 10.1016/0735-1097(92)90617-v.
273. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114(5):345-52. DOI: 10.7326/0003-4819-114-5-345.
274. Rossebo AB, Pedersen TR, Allen C, et al. Design and baseline characteristics of the simvastatin and ezetimibe in aortic stenosis (SEAS) study. Am J Cardiol 2007;99(7):970-3. DOI: 10.1016/j.amjcard.2006.10.064.

275. Hueb JC, Vicentini JT, Roscani MG, et al. Impact of hypertension on ventricular remodeling in patients with aortic stenosis. Arq Bras Cardiol 2011;97(3):254-9. DOI: 10.1590/s0066-782x2011005000081.
276. Garcia D, Pibarot P, Kadem L, Durand LG. Respective impacts of aortic stenosis and systemic hypertension on left ventricular hypertrophy. J Biomech 2007;40(5):972-80. (In eng). DOI: 10.1016/j.jbiomech.2006.03.020.
277. Devereux RB, de Simone G, Ganau A, Roman MJ. Left ventricular hypertrophy and geometric remodeling in hypertension: stimuli, functional consequences and prognostic implications. J Hypertens Suppl 1994;12(10):S117-27. (In eng).
278. Linhartova K, Filipovsky J, Cerbak R, Sterbakova G, Hanisova I, Beranek V. Severe aortic stenosis and its association with hypertension: analysis of clinical and echocardiographic parameters. Blood Press 2007;16(2):122-8. DOI: 10.1080/08037050701343241.
279. Cramariuc D, Bahlmann E, Egstrup K, et al. Prognostic impact of impaired left ventricular midwall function during progression of aortic stenosis. Echocardiography 2021;38(1):31-38. DOI: https://doi.org/10.1111/echo.14916.
280. Gerdts E, Rossebo AB, Pedersen TR, et al. Relation of Left Ventricular Mass to Prognosis in Initially Asymptomatic Mild to Moderate Aortic Valve Stenosis. Circ Cardiovasc Imaging 2015;8(11):e003644; discussion e003644. DOI: 10.1161/CIRCIMAGING.115.003644.
281. Gerdts E, Saeed S, Midtbo H, et al. Higher left ventricular mass-wall stress-heart rate product and outcome in aortic valve stenosis. Heart 2019;105(21):1629-1633. DOI: 10.1136/heartjnl-2018-314462.
282. Treibel TA, Kozor R, Schofield R, et al. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. J Am Coll Cardiol 2018;71(8):860-871. (In eng). DOI: 10.1016/j.jacc.2017.12.035.
283. Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011;124(4):425-33. DOI: 10.1161/CIRCULATIONAHA.110.001545.
284. Vanky FB, Hakanson E, Tamas E, Svedjeholm R. Risk factors for postoperative heart failure in patients operated on for aortic stenosis. Ann Thorac Surg 2006;81(4):1297-304. DOI: 10.1016/j.athoracsur.2005.11.036.
285. Ashikhmina EA, Schaff HV, Dearani JA, et al. Aortic valve replacement in the elderly: determinants of late outcome. Circulation 2011;124(9):1070-8. DOI: 10.1161/CIRCULATIONAHA.110.987560.
286. Saeed S, Gerdts E. Managing complications of hypertension in aortic valve stenosis patients. Expert Rev Cardiovasc Ther 2018;16(12):897-907. DOI: 10.1080/14779072.2018.1535899.
287. Saeed M, Liu H, Liang C-H, Wilson MW. Magnetic resonance imaging for characterizing myocardial diseases. The International Journal of Cardiovascular Imaging 2017;33(9):1395-1414. DOI: 10.1007/s10554-017-1127-x.
288. González A, López B, Díez J. New directions in the assessment and treatment of hypertensive heart disease. Current Opinion in Nephrology and Hypertension 2005;14(5):428-434. DOI: 10.1097/01.mnh.0000174143.30045.bd.
289. Assayag P, Carré F, Chevalier B, Delcayre C, Mansier P, Swynghedauw B. Compensated cardiac hypertrophy: arrhythmogenicity and the new myocardial phenotype. I. Fibrosis. Cardiovascular Research 1997;34(3):439-444. DOI: 10.1016/s0008-6363(97)00073-4.
290. Debry N, Maréchaux S, Rusinaru D, et al. Prognostic significance of left ventricular concentric remodelling in patients with aortic stenosis. Archives of Cardiovascular Diseases 2017;110(1):26-34. DOI: https://doi.org/10.1016/j.acvd.2016.05.010.
291. Kusunose K, Goodman A, Parikh R, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circ Cardiovasc Imaging 2014;7(6):938-45. (In eng). DOI: 10.1161/circimaging.114.002041.
292. Shah AS, Chin CW, Vassiliou V, et al. Left ventricular hypertrophy with strain and aortic stenosis. Circulation 2014;130(18):1607-16. DOI: 10.1161/CIRCULATIONAHA.114.011085.
293. de Simone G, Devereux RB, Roman MJ, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol 1994;23(6):1444-51. DOI: 10.1016/0735-1097(94)90390-5.
294. Bella JN, Palmieri V, Roman MJ, et al. Gender differences in left ventricular systolic function in American Indians (from the Strong Heart Study). Am J Cardiol 2006;98(6):834-7. DOI: 10.1016/j.amjcard.2006.03.069.
295. Tadic M, Cuspidi C, Pencic B, et al. The impact of arterial hypertension on left ventricular strain in patients with aortic stenosis and preserved ejection fraction. J Hypertens 2019;37(4):747-753. (In eng). DOI: 10.1097/hjh.0000000000001963.
296. Ng ACT, Prihadi EA, Antoni ML, et al. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. Eur Heart J Cardiovasc Imaging 2018;19(8):859-867. DOI: 10.1093/ehjci/jex189.
297. Huded CP, Kusunose K, Shahid F, et al. Novel Echocardiographic Parameters in Patients With Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Surgical Aortic Valve Replacement. Am J Cardiol 2018;122(2):284-293. DOI: 10.1016/j.amjcard.2018.03.359.
298. Fries B, Liu D, Gaudron P, et al. Role of Global Longitudinal Strain in the Prediction of Outcome in Patients With Severe Aortic Valve Stenosis. Am J Cardiol 2017;120(4):640-647. DOI: 10.1016/j.amjcard.2017.05.032.
299. Saeed S, Mancia G, Rajani R, Parkin D, Chambers JB. Hypertension in aortic stenosis: relationship with revealed symptoms and functional measures on treadmill exercise. J Hypertens 2019;37(11):2209-2215. DOI: 10.1097/HJH.0000000000002149.

300. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005;46(1):156-61. DOI: 10.1161/01.HYP.0000170138.56903.7a.
301. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. Can J Cardiol 2020;36(5):596-624. DOI: 10.1016/j.cjca.2020.02.086.
302. Garcia-Redondo AB, Aguado A, Briones AM, Salaices M. NADPH oxidases and vascular remodeling in cardiovascular diseases. Pharmacol Res 2016;114:110-120. DOI: 10.1016/j.phrs.2016.10.015.
303. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. J Hypertens 2006;24(6):983-91. DOI: 10.1097/01.hjh.0000226182.60321.69.
304. Dao HH, Essalihi R, Bouvet C, Moreau P. Evolution and modulation of age-related medial elastocalcinosis: impact on large artery stiffness and isolated systolic hypertension. Cardiovasc Res 2005;66(2):307-17. DOI: 10.1016/j.cardiores.2005.01.012.
305. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 2002;15(5):426-44. DOI: 10.1016/s0895-7061(01)02319-6.
306. Palmieri V, Bella JN, Roman MJ, et al. Pulse pressure/stroke index and left ventricular geometry and function: the LIFE Study. J Hypertens 2003;21(4):781-7. DOI: 10.1097/00004872-200304000-00022.
307. de Simone G, Roman MJ, Koren MJ, Mensah GA, Ganau A, Devereux RB. Stroke volume/pulse pressure ratio and cardiovascular risk in arterial hypertension. Hypertension 1999;33(3):800-5. DOI: 10.1161/01.hyp.33.3.800.
308. Lancellotti P, Donal E, Magne J, et al. Impact of global left ventricular afterload on left ventricular function in asymptomatic severe aortic stenosis: a two-dimensional speckle-tracking study. Eur J Echocardiogr 2010;11(6):537-43. DOI: 10.1093/ejechocard/jeq014.
309. Banovic M, Brkovic V, Vujisic-Tesic B, et al. Valvulo-arterial impedance is the best mortality predictor in asymptomatic aortic stenosis patients. J Heart Valve Dis 2015;24(2):156-63. (https://www.ncbi.nlm.nih.gov/pubmed/26204677).
310. Ostchega Y, Hughes JP, Terry A, Fakhouri TH, Miller I. Abdominal obesity, body mass index, and hypertension in US adults: NHANES 2007-2010. Am J Hypertens 2012;25(12):1271-8. DOI: 10.1038/ajh.2012.120.
311. Appel LJ, Clark JM, Yeh HC, et al. Comparative effectiveness of weight-loss interventions in clinical practice. N Engl J Med 2011;365(21):1959-68. DOI: 10.1056/NEJMoa1108660.
312. McGuire S. Institute of Medicine. 2013. "Sodium intake in populations: assessment of evidence." Washington, DC: The National Academies Press, 2013. Adv Nutr 2014;5(1):19-20. DOI: 10.3945/an.113.005033.
313. Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. J Am Coll Cardiol 2016;68(15):1609-1617. DOI: 10.1016/j.jacc.2016.07.745.
314. Hunt JC. Sodium intake and hypertension: a cause for concern. Ann Intern Med 1983;98(5 Pt 2):724-8. DOI: 10.7326/0003-4819-98-5-724.
315. Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). Arch Intern Med 2001;161(5):685-93. DOI: 10.1001/archinte.161.5.685.
316. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 2016;388(10043):465-75. DOI: 10.1016/S0140-6736(16)30467-6.
317. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. Br J Nutr 2015;113(1):1-15. DOI: 10.1017/S0007114514003341.
318. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. The New England Journal of Medecine 1997;236(16):1117-1124.
319. Steinberg D, Bennett GG, Svetkey L. The DASH Diet, 20 Years Later. JAMA 2017;317(15):1529-1530. DOI: 10.1001/jama.2017.1628.
320. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368(14):1279-90. DOI: 10.1056/NEJMoa1200303.
321. Nissensohn M, Roman-Vinas B, Sanchez-Villegas A, Piscopo S, Serra-Majem L. The Effect of the Mediterranean Diet on Hypertension: A Systematic Review and Meta-Analysis. J Nutr Educ Behav 2016;48(1):42-53 e1. DOI: 10.1016/j.jneb.2015.08.023.
322. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2012;14(11):792-8. DOI: 10.1111/jch.12008.
323. Rankinen T, Church TS, Rice T, Bouchard C, Blair SN. Cardiorespiratory fitness, BMI, and risk of hypertension: the HYPGENE study. Med Sci Sports Exerc 2007;39(10):1687-92. DOI: 10.1249/mss.0b013e31812e527f.
324. Veiras LC, Han J, Ralph DL, McDonough AA. Potassium Supplementation Prevents Sodium Chloride Cotransporter Stimulation During Angiotensin II Hypertension. Hypertension 2016;68(4):904-12. DOI: 10.1161/HYPERTENSIONAHA.116.07389.
325. Onat A, Ugur M, Hergenc G, Can G, Ordu S, Dursunoglu D. Lifestyle and metabolic determinants of incident hypertension, with special reference to cigarette smoking: a longitudinal population-based study. Am J Hypertens 2009;22(2):156-62. DOI: 10.1038/ajh.2008.332.

326. Solini A, Grossman E. What Should Be the Target Blood Pressure in Elderly Patients With Diabetes? Diabetes Care 2016;39(Supplement 2):S234-S243. DOI: 10.2337/dcS15-3027.
327. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387(10022):957-967. DOI: 10.1016/S0140-6736(15)01225-8.
328. Furberg CD, Psaty BM, Pahor M, Alderman MH. Clinical Implications of Recent Findings from the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT) and Other Studies of Hypertension. Ann Intern Med 2001;135(12):1074-8. DOI: 10.7326/0003-4819-135-12-200112180-00011.
329. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008;372(9638):547-53. DOI: 10.1016/S0140-6736(08)61236-2.
330. Blood Pressure Lowering Treatment Trialists C, Turnbull F, Neal B, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ 2008;336(7653):1121-3. DOI: 10.1136/bmj.39548.738368.BE.
331. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386(10008):2059-2068. DOI: 10.1016/S0140-6736(15)00257-3.
332. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341(10):709-17. DOI: 10.1056/NEJM199909023411001.
333. Kang TS, Park S. Antihypertensive Treatment in Severe Aortic Stenosis. J Cardiovasc Imaging 2018;26(2):45-53. (In eng). DOI: 10.4250/jcvi.2018.26.e9.
334. Bang CN, Greve AM, Rossebø AB, et al. Antihypertensive Treatment With β-Blockade in Patients With Asymptomatic Aortic Stenosis and Association With Cardiovascular Events. J Am Heart Assoc 2017;6(12) (In eng). DOI: 10.1161/jaha.117.006709.
335. Hansson NH, Sörensen J, Harms HJ, et al. Metoprolol Reduces Hemodynamic and Metabolic Overload in Asymptomatic Aortic Valve Stenosis Patients: A Randomized Trial. Circ Cardiovasc Imaging 2017;10(10) (In eng). DOI: 10.1161/circimaging.117.006557.
336. Rossi A, Temporelli PL, Cicoira M, et al. Beta-blockers can improve survival in medically-treated patients with severe symptomatic aortic stenosis. Int J Cardiol 2015;190:15-7. (In eng). DOI: 10.1016/j.ijcard.2015.04.083.
337. Devereux RB, Palmieri V, Sharpe N, et al. Effects of Once-Daily Angiotensin-Converting Enzyme Inhibition and Calcium Channel Blockade-Based Antihypertensive Treatment Regimens on Left Ventricular Hypertrophy and Diastolic Filling in Hypertension. Circulation 2001;104(11):1248-1254. DOI: doi:10.1161/hc3601.095927.
338. Devereux RB, Dahlof B, Gerdts E, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Circulation 2004;110(11):1456-62. DOI: 10.1161/01.CIR.0000141573.44737.5A.
339. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs--overview and meta-analyses. J Hypertens 2015;33(2):195-211. (In eng). DOI: 10.1097/hjh.0000000000000447.
340. Chen YJ, Li LJ, Tang WL, et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane Database Syst Rev 2018;11(11):Cd008170. (In eng). DOI: 10.1002/14651858.CD008170.pub3.
341. Chockalingam A, Venkatesan S, Subramaniam T, et al. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS). Am Heart J 2004;147(4):E19. DOI: 10.1016/j.ahj.2003.10.017.
342. Bang CN, Greve AM, Kober L, et al. Renin-angiotensin system inhibition is not associated with increased sudden cardiac death, cardiovascular mortality or all-cause mortality in patients with aortic stenosis. Int J Cardiol 2014;175(3):492-8. DOI: 10.1016/j.ijcard.2014.06.013.
343. Dahl JS, Videbaek L, Poulsen MK, et al. Effect of candesartan treatment on left ventricular remodeling after aortic valve replacement for aortic stenosis. Am J Cardiol 2010;106(5):713-9. DOI: 10.1016/j.amjcard.2010.04.028.
344. Devereux RB, Wachtell K, Gerdts E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 2004;292(19):2350-6. DOI: 10.1001/jama.292.19.2350.
345. Warren BA, Yong JL. Calcification of the aortic valve: its progression and grading. Pathology 1997;29(4):360-8. DOI: 10.1080/00313029700169315.
346. Schmieder RE. Mechanisms for the clinical benefits of angiotensin II receptor blockers. Am J Hypertens 2005;18(5 Pt 1):720-30. DOI: 10.1016/j.amjhyper.2004.11.032.
347. Opie LH. Fundamental role of angiotensin-converting enzyme inhibitors in the management of congestive heart failure. Am J Cardiol 1995;75(18):3F-6F. DOI: 10.1016/s0002-9149(99)80507-4.
348. O'Brien KD, Probstfield JL, Caulfield MT, et al. Angiotensin-converting enzyme inhibitors and change in aortic valve calcium. Arch Intern Med 2005;165(8):858-62. DOI: 10.1001/archinte.165.8.858.
349. Cameli M, Mondillo S, Righini FM, et al. Left Ventricular Deformation and Myocardial Fibrosis in Patients With Advanced Heart Failure Requiring Transplantation. J Card Fail 2016;22(11):901-907. DOI: 10.1016/j.cardfail.2016.02.012.
350. Dahou A, Bartko PE, Capoulade R, et al. Usefulness of global left ventricular longitudinal strain for risk stratification in low ejection fraction, low-gradient aortic stenosis: results from the multicenter True or Pseudo-

Severe Aortic Stenosis study. Circ Cardiovasc Imaging 2015;8(3):e002117. DOI: 10.1161/CIRCIMAGING.114.002117.
351. Teske AJ, De Boeck BW, Melman PG, Sieswerda GT, Doevendans PA, Cramer MJ. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. Cardiovasc Ultrasound 2007;5:27. DOI: 10.1186/1476-7120-5-27.
352. Hoffmann R, Altiok E, Friedman Z, Becker M, Frick M. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography in comparison to late gadolinium enhancement cardiac magnetic resonance for analysis of myocardial fibrosis in severe aortic stenosis. Am J Cardiol 2014;114(7):1083-8. DOI: 10.1016/j.amjcard.2014.07.018.
353. Sen J, Chung E, Neil C, Marwick T. Antihypertensive therapies in moderate or severe aortic stenosis: a systematic review and meta-analysis. BMJ Open 2020;10(10):e036960. DOI: 10.1136/bmjopen-2020-036960.
354. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. Hypertension 2001;38(3):429-33. DOI: 10.1161/01.hyp.38.3.429.
355. Schram MT, Kostense PJ, Van Dijk RA, et al. Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. J Hypertens 2002;20(9):1743-51. DOI: 10.1097/00004872-200209000-00017.
356. Mitchell GF. Pulse pressure, arterial compliance and cardiovascular morbidity and mortality. Curr Opin Nephrol Hypertens 1999;8(3):335-42. DOI: 10.1097/00041552-199905000-00010.
357. Ong KT, Delerme S, Pannier B, et al. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. J Hypertens 2011;29(6):1034-42. (In eng). DOI: 10.1097/HJH.0b013e328346a583.
358. Shahin Y, Khan JA, Chetter I. Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: a meta-analysis and meta-regression of randomised controlled trials. Atherosclerosis 2012;221(1):18-33. (In eng). DOI: 10.1016/j.atherosclerosis.2011.12.005.
359. Ito S, Miranda WR, Jaffe AS, Oh JK. Prognostic Value of N-Terminal Pro-form B-Type Natriuretic Peptide in Patients With Moderate Aortic Stenosis. Am J Cardiol 2020;125(10):1566-1570. (In eng). DOI: 10.1016/j.amjcard.2020.02.004.
360. Bergler-Klein J, Gyongyosi M, Maurer G. The role of biomarkers in valvular heart disease: focus on natriuretic peptides. Can J Cardiol 2014;30(9):1027-34. DOI: 10.1016/j.cjca.2014.07.014.
361. Weber M, Arnold R, Rau M, et al. Relation of N-terminal pro B-type natriuretic peptide to progression of aortic valve disease. Eur Heart J 2005;26(10):1023-30. DOI: 10.1093/eurheartj/ehi236.
362. Clavel MA, Malouf J, Michelena HI, et al. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. J Am Coll Cardiol 2014;63(19):2016-25. DOI: 10.1016/j.jacc.2014.02.581.
363. Bergler-Klein J, Klaar U, Heger M, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation 2004;109(19):2302-8. DOI: 10.1161/01.CIR.0000126825.50903.18.
364. Namasivayam M, He W, Churchill TW, et al. Transvalvular Flow Rate Determines Prognostic Value of Aortic Valve Area in Aortic Stenosis. J Am Coll Cardiol 2020;75(15):1758-1769. (In eng). DOI: 10.1016/j.jacc.2020.02.046.
365. Masugata H, Senda S, Goda F, et al. Influences of hypertension and diabetes on normal age-related changes in left ventricular function as assessed by tissue Doppler echocardiography. Clin Exp Hypertens 2009;31(5):400-14. (In eng). DOI: 10.1080/10641960802668722.
366. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29(4):277-314. DOI: 10.1016/j.echo.2016.01.011.
367. Inohara T, Manandhar P, Kosinski AS, et al. Association of Renin-Angiotensin Inhibitor Treatment With Mortality and Heart Failure Readmission in Patients With Transcatheter Aortic Valve Replacement. JAMA 2018;320(21):2231-2241. DOI: 10.1001/jama.2018.18077.
368. Goel SS, Aksoy O, Gupta S, et al. Renin-angiotensin system blockade therapy after surgical aortic valve replacement for severe aortic stenosis: a cohort study. Ann Intern Med 2014;161(10):699-710. DOI: 10.7326/M13-1505.
369. Razzolini R, Gerosa G, Leoni L, Casarotto D, Chioin R, Dalla-Volta S. Transaortic gradient is pressure-dependent in a pulsatile model of the circulation. J Heart Valve Dis 1999;8(3):279-83. (https://www.ncbi.nlm.nih.gov/pubmed/10399661).
370. Mascherbauer J, Fuchs C, Stoiber M, et al. Systemic pressure does not directly affect pressure gradient and valve area estimates in aortic stenosis in vitro. Eur Heart J 2008;29(16):2049-57. DOI: 10.1093/eurheartj/ehn209.
371. Aggarwal SR, Clavel MA, Messika-Zeitoun D, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging 2013;6(1):40-7. DOI: 10.1161/CIRCIMAGING.112.980052.
372. Cueff C, Serfaty JM, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart 2011;97(9):721-6. DOI: 10.1136/hrt.2010.198853.