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Cardiac Amyloidosis in Aortic Stenosis: A Higher Risk Population?

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ABSTRACT

In recent decades, with an aging population, an increase in the prevalence of numerous cardiovascular pathologies have become evident, including aortic stenosis and infiltrative cardiomyopathies such as cardiac amyloidosis. The coexistence of both conditions is not uncommon, and since they share overlapping symptoms, echocardiographic findings, and biomarkers of myocardial damage, the diagnosis of infiltrative cardiomyopathy often remains masked. This underdiagnosis of cardiac amyloidosis in patients with symptomatic aortic stenosis can result in untimely and insufficient treatment. The objectives of this monograph are to analyze the predictors of cardiac amyloidosis caused by senile or wild type transthyretin in patients with symptomatic aortic stenosis, determine whether they constitute a higher-risk population, and explore the available therapeutic alternatives.

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Introduction

In recent decades, with the aging of the population, there has been an increase in the prevalence of a large number of cardiovascular (CV) diseases such as aortic stenosis (AS) and some infiltrative cardiomyopathies such as cardiac amyloidosis (CA) [1-6]. Amyloid deposition can occur in any tissue, and infiltration of this material into the aortic valve can contribute to both the onset and progression of AS. Therefore, the coexistence of both pathologies (AS + CA) is not an uncommon phenomenon [2,7-13].

Advances in imaging methods have enabled early diagnosis of CA without the need for endomyocardial biopsy in all affected patients. However, because both pathologies have overlapping symptoms, echocardiographic abnormalities, and biomarkers of myocardial damage, in most cases, the diagnosis of infiltrative cardiomyopathy remains obscure. The importance of delineating the clinical differences and increasing suspicion and diagnosis of CA lies in the fact that the presence of both pathologies likely implies a worse prognosis than either of them alone [2,3,11,13-17].

Underdiagnosis of CA in patients with symptomatic AS leads only to treatment for said valvular disease, the most established treatment currently being invasive. However, by not addressing the infiltrative pathology, this treatment is insufficient and inappropriate in many cases. Therefore, the need for CA screening in patients with AS is currently being evaluated, and new therapeutic modalities are being discussed. [7,8,11-13,16,18-22].

The Objectives of this Study are

- To analyze the predictors of CA in patients with symptomatic AS.
- To determine whether they constitute a higher-risk population and what therapeutic alternatives are available for these patients.

Methodology

This monograph is based on a bibliographic search Initial search in the MEDLINE medical database, through PubMed, using an advanced search scheme of the following MESH terms: aortic stenosis and cardiac amyloidosis, cardiac amyloidosis prevalence, cardiac amyloidosis clinical, cardiac amyloidosis diagnostic, cardiac amyloidosis treatment y aortic stenosis treatment.

Additional guided searches were then conducted based on the selected material. References from selected studies were used and review articles to identify all relevant works. New citations were obtained from expert references.

Table 1: Prevalence of Cardiac Amyloidosis in Patients with Aortic Stenosis

Study author, year	N	Cohort	Diagnostic Method	Prevalence of AC in AD (%)	ATTRwt (%)
Nietlispach, 2012	20	Autopsy or CRV after TAVI	Histology	33 (Autopsy Patients)	SE
Treibel, 2016	146	Severe AE undergoing CRV	Scintigraphy	4.1	81 confirmed
Longhi, 2016	43	AE referred for CRV or TAVI	Scintigraphy	9.4	(19 undetermined)
Castaño, 2017	151	AE referred for TAVI	Scintigraphy	16	100
Cavalcante, 2017	113	AE in CRV planning	MRI	8	Indeterminate
Scully, 2020	200	AE referred for TAVI	Scintigraphy with Perugini uptake of 1 to 3	13	SE
Nitsche, 2020	191	AE in TAVI planning	MRI scintigraphy	8.4	100
Nitsche, 2021	407	Severe AE undergoing CRV, TAVI, and medical treatment	Histology	8	93.75
Singal, 2021	46	Severe AE undergoing CRV	MRI	9.4	97
Rosenblum, 2021	204	Severe AE TAVI planning	Scintigraphy	13	100
Dobner, 2023	315	Severe AE referred for TAVI	Scintigraphy performed on 32 patients	9.5	92

AC: cardiac amyloidosis. AS: aortic stenosis. ATTR wt: wild-type transthyretin cardiac amyloidosis. VRS: valve replacement surgery. TAVI: transcatheter aortic valve implantation. SE: not otherwise specified. MRI: magnetic resonance imaging.

Development

Epidemiology

AS is the most common valvular heart disease in the elderly, with a prevalence of 3-4%, and can reach 10% in octogenarians [2,4,8,12-15,18,20,23]. CA is the most common infiltrative cardiomyopathy, with a prevalence close to 25% in patients over 80 years of age. In our setting, the diagnosis of CA is probably underestimated due to the lack of systematic screening [3,8,24-28]. Amyloid infiltration in patients with symptomatic AS has a highly variable prevalence, ranging from 4% to 33%. Most studies show that the type of amyloid associated with aortic stenosis is wild-type transthyretin. The highest prevalence reported to date is 33%, in a post-mortem study of patients undergoing transcatheter aortic valve implantation (Table 1) [2,3,7,8,12-18,29-34].

In 2022, Arshad et al. presented a meta-analysis in which they collected nine studies with a total of 1321 patients with AD, of which 139 (11%) had concomitant AC [11]. Other meta-analyses published that same year revealed similar prevalences. Sin-Ying Ho et al. included 21 studies with 4243 patients and associated 14.4% of AC in patients with AD, 12% by transthyretin (TTR). Myasoedova et al. included 17 studies with 1934 patients with AD, of which 330 (17%) had AC [21,22]. The variability in prevalence is probably due to the different population selection criteria and diagnostic methods used in the trials for the detection of AC [2,21].

Pathophysiology

AC is an infiltrative cardiomyopathy that occurs as a result of the deposition of amyloid, an insoluble material derived from the of misfolded products of protein precursors. The mechanism of this dysregulation is unknown. The type of amyloidosis is defined based on the precursor protein; the most common are: immunoglobulin light chain amyloidosis (AC-AL) produced by plasma cell dyscrasia and transthyretin amyloidosis (ATTR). AD is rarely associated with AC-AL; in contrast, ATTR usually infiltrates any cardiovascular structure [25,35-37].

TTR is synthesized in the liver and is composed of four beta-sheet-rich monomers that circulate as a tetramer, functioning as a thyroxine transporter protein and a retinol-binding protein. These molecules, when combined, stabilize TTR, so low concentrations could be a risk factor [20,36,38].

ATTR can be subclassified as hereditary (ATTRh), which is the result of a mutation, and senile or wild-type (ATTRwt), due to aging. The latter is the most common form of cardiac amyloidosis and is associated with AD. It affects the heart in 100% of cases, and the most common sites of deposition are the myocardium and heart valves, particularly the aortic valve [2,7,37,39].

Amyloid in the myocardium is usually deposited from base to apex, causing increased thickness and stiffness of the walls of both ventricles, leading to diastolic dysfunction initially and later systolic dysfunction in up to one-third of patients. The most common presentation is heart failure (HF), and a large percentage are associated with conduction disturbances [2,35].

Interestingly, these changes occur similarly in AS. In this condition, the restriction of left ventricular (LV) outflow due to thickening, stiffness, and narrowing of the valve orifice generates pressure overload. This mechanism induces concentric remodeling, which, although a compensatory change, generates diastolic dysfunction and increased end-diastolic pressures, leading to HF and predisposing to supraventricular arrhythmias. Therefore,

both pathologies present with LV parietal enlargement and HF, primarily due to diastolic dysfunction, leading to an increased risk of arrhythmias. [2,5,6,14,15,35,39].

Regarding the pathophysiology linking both entities, there are different hypotheses. The most established is that an inflammatory mechanism could precipitate amyloid deposition, which could infiltrate the valve and predispose to calcification, worsening AS. However, it is not ruled out that, due to the shared risk factors such as aging, both pathologies coexist without being related to each other [7-12].

Clinical Aspects

The typical symptoms of severe AS are angina, syncope, and dyspnea secondary to HF. The most frequently found signs are a peripheral pulse with a decreased amplitude and slow ascent (parvus tardus pulse), a rhomboidal systolic murmur in the aortic focus radiating to the neck, and a decreased second heart sound [5].

Regarding CAD, most patients present with symptoms of HF, so it often goes unnoticed in the presence of AS due to the shared symptoms [2,26,39,40].

There are Aspects that are Useful for Suspecting CAD in Patients with Severe AS:

Demographic Data

The prevalence of AS+CA increases with age. Patients with both pathologies tend to be older compared to those with isolated AS (86.6 years vs. 83.6 years; $p < 0.001$) and are predominantly older in men, according to most literature [2,8,11,14,16,17,19,21,22,31-33,36,37,40]. Other authors agree that the prevalence increases with age, but establish that the difference by sex is related to severity, which is greater in men [18,24,27,30].

Clinical Presentation

Orthopedic manifestations are a relevant finding in these patients to differentiate them from those with solitary AS. The most common is carpal tunnel syndrome (20.0% vs. 1.1%; $p<0.001$). Other positive findings are mentioned in the literature, such as biceps tendon rupture and lumbar spinal stenosis. Autonomic and peripheral neuropathy are another suggestive manifestation. The importance of these conditions lies in that they often precede CV manifestations [4,7,8,11,13,25,26,28,32,33,37,39].

No statistically significant association was found with high blood pressure (HBP), diabetes, or smoking. The "natural cure" for HBP refers to the need to reduce or discontinue antihypertensive medications, a condition frequently observed in patients with CA, as is intolerance to beta-blockers due to autonomic dysfunction [24,28,36,39,41].

The most common presentation of CAD is HF (67%), which in most cases presents with preserved LV ejection fraction (LVEF) and disproportionate symptoms. Most patients at diagnosis were in New York Heart Association (NYHA) functional class III/IV. Additionally, the presence of right-sided heart failure should lead us to consider the coexistence of CAD [2,8,12,20,26,39-41].

The 6-minute walk test showed a reduction in the dual-pathology groups ($p=0.038$). A single study found no differences in this test between patients with amyloid and those without this infiltration [11,13,18]. A decreased body mass index (BMI) was a statistically valid finding ($p=0.002$) [22,31].

One-third of patients with CAD had been misdiagnosed with other cardiac diseases. The most common are hypertensive heart disease, hypertrophic cardiomyopathy, and ischemic heart disease [25,26,33,41,42].

Conduction disturbances are frequently diagnosed during the course of CAD, and in some patients, they may even be the only clinical manifestation. Atrial fibrillation (AF) is the most common arrhythmia, present in approximately 56% of cases at some point during the course of the disease [4,7,8,11,16,26,32]. Seventeen percent of patients with amyloidosis require a pacemaker (PCM). In fact, infiltrative cardiomyopathy due to this protein appears to be related to premature pacemaker implantation [26,30]. Although these findings were found in two studies, the meta-analysis by Arshad et al. found no significant differences in patients with AC regarding the requirement for a PCM, as opposed to the population without amyloid infiltration [11].

Complementary Methods

AS is a well-defined pathology whose diagnosis and assessment of severity are based primarily on echocardiographic studies. Complementary studies should be performed to assess prognosis and treatment. If amyloidosis is suspected, a bone scan and/or magnetic resonance imaging (MRI) should be requested [1,5,6,35]. The overlap of symptoms between AS and AC leads to underdiagnosis of the latter. Routine studies ordered for the evaluation of valvular heart disease, while not diagnostic of CAD, may be useful in suspecting it [4,7,36].

The most relevant complementary studies for determining the presence of amyloid pathology in patients with AS are detailed below.

Biomarkers

They are not specific diagnostic markers for any form of CAD; however, their persistent elevation contributes to the suspicion, staging, and prognosis of CAD [8,11,18,27,33,36,38,39]. Chronic troponin elevation without significant coronary artery disease occurs more frequently in these patients [2,8,11,13,18,22,25,31,4]. Additionally, the disproportionate elevation of natriuretic peptides, especially N-terminal pro-brain natriuretic peptide (NT-proBNP), in the absence of kidney disease, is associated with the presence of CA in all its variants [2,7,8,11,13,14,18,21,22,25].

Electrocardiogram

It provides findings highly suggestive of CA. Conduction abnormalities are common. Although AS usually presents with electrical disturbances, the prevalence is higher when both pathologies coexist. AF is the most common arrhythmia, present in up to two-thirds of patients with dual pathology. Bundle branch blocks, especially on the right, are also seen more frequently in these patients compared to isolated valvular disease [2,7,8,13,14,16,18,22,26,29,31].

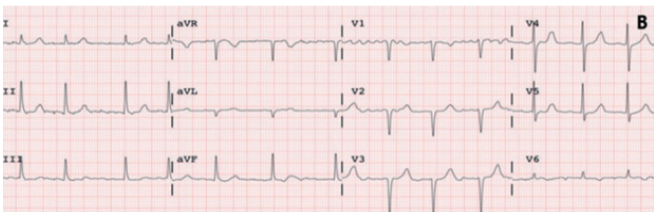

Figure 1: Electrocardiogram Showing Atrial Fibrillation and a Pseudo infarct Pattern in the Precordial leads [26].

Low voltage in relation to increased myocardial mass observed on echocardiogram, i.e. QRS less than 1 mV in the precordial leads or less than 0.5 mV in the frontal leads; or the Sokolow-Lyon index <1.9 mV is suggestive AC voltage, although it is only present in 20% of ATTR cases. This pattern is usually late-onset, so the absence of low voltages does not exclude the diagnosis. In fact, about 10% may present with LV hypertrophy (LVH), evidenced by the Sokolow-Lyon criteria [7,13,14,18,19,22,25,26,30,32,36,37,41].

Q waves or pseudo infarct pattern, particularly in leads previous cases, in patients without a history of heart attack, are found It is present in up to 70% of cases. It is the most frequently observed electrocardiographic pattern in patients diagnosed with AC (Figure 1) [2,7,26,37,39].
The finding of a prolonged QRS is more frequent in the dual pathology group [13,14,22].

Transthoracic Echocardiography (TTE)
This is the complementary study of choice due to its accessibility, ability to diagnose AS, and increased suspicion of CA. Regarding valvular disease, it allows, along with clinical data, to identify the etiology, degree of severity, and cavitary impact of the disease [1,5,6,38]. The population included in this monograph was considered moderate and/or severe AS according to the American Society of Echocardiography (ASE) criteria (Table 2). Regarding CA, echocardiography reveals a diffuse increase in wall thickness, posing a challenging scenario in trying to differentiate hypertrophy from myocardial infiltration.

The following relevant findings are proposed to identify a possible AC (Figure 2).

LV Remodelling
AS and CAD often present with an increased LV mass index [2,4,13,16,18,19]. Unlike other pathologies that present with concentric LVH, in CAD the first thing usually seen is myocardial widening, symmetrical in most cases, described as abnormal myocardial texture or sparkling with a bright, mottled appearance. In addition, an increase in the thickness of the interatrial septum is usually observed with preservation of the oval fossa and both ventricles, unlike what occurs in isolated AS that affects the LV [3,11,14,16,25,26,30,41].

Table 2: Recommendations for the Classification of Aortic Stenosis

	Aortic sclerosis	Living	Moderate	Severe
Aortic jet velocity (m/s)	<2.5 m/s	2.6 - 2.9	3 - 4	>4
Mean gradient (mmHg)	-	< 20	20 - 40	>40
AVA (cm^2)	-	> 1.5	1 - 1.5	<1
Indexed AVA (cm^2/m^2)	-	> 0.85	0.60 - 0.85	<0.6
Velocity ratio	-	> 0.50	0.25 - 0.50	<0.25

AVA: Aortic Valve Area [43].

Diastolic Function
Both conditions can present varying degrees of diastolic dysfunction depending on the stage of the disease. It tends to be greater in cases of concomitant disease, with severe dysfunction or a restrictive relaxation pattern occurring in approximately 35% of cases [2,3,7,13-15,26,27,32].

Systolic Function
LVEF is usually affected late in both isolated conditions and occurs more frequently when both are present. Therefore, this finding in patients with severe AS in the absence of coronary artery disease should be taken into account, although it is not statistically significant for all authors. [7,11,13,14,15,22,25,32]. The stroke volume ratio in patients with AS+CAD compared to those with isolated valvular disease is decreased [11,13,14,20,16,21,30-32,44]. Mitral annular tissue Doppler provides very important information. S-wave velocity is usually reduced in both conditions from the early stages of the disease [3,7,10,11,14,16,18,25,27,31,36,41]. It is important to note that an S' value ≤6 cm/s of the mitral annulus in patients with AS has a sensitivity of 100%, with a specificity of 57% in predicting a positive scan for AC, making it one of the most robust echocardiographic predictors (AUC 0.95, $p < 0.0001$). Right ventricular (RV) S' was also significantly lower in patients with ATTR compared to patients without amyloid infiltration.

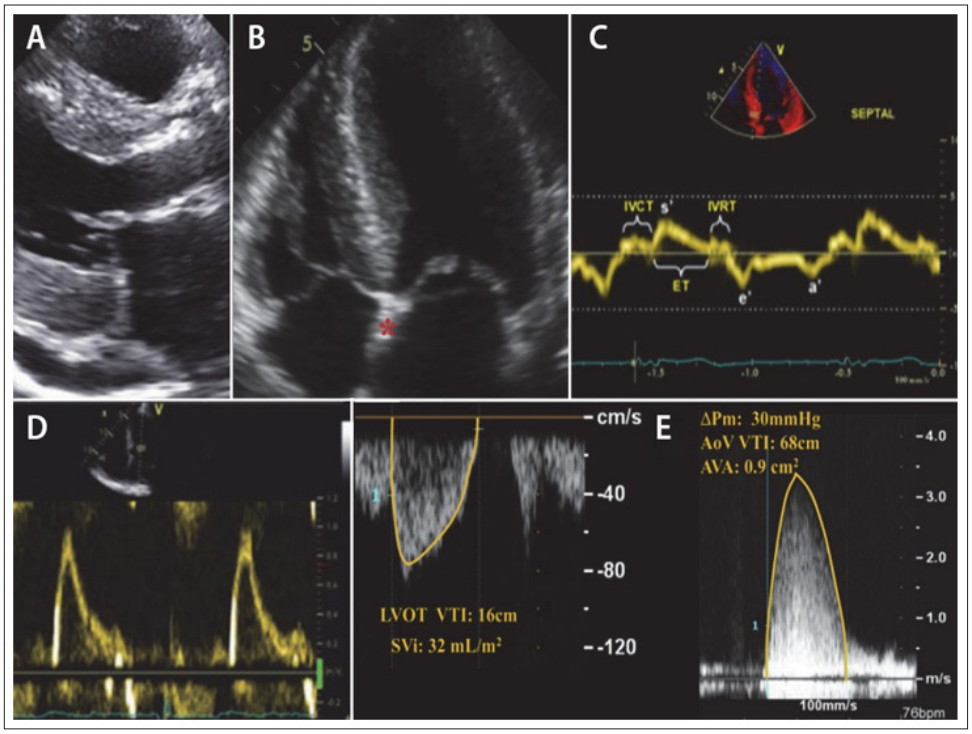

Figure 2: Echocardiographic Findings Suggestive of Cardiac Amyloidosis [2]

a) Parasternal long-axis view with bright and heterogeneous left ventricular wall enlargement associated with pericardial effusion.
b) Apical four-chamber view showing biventricular wall enlargement and interatrial septum (red asterisk) with preservation of the fossa ovalis.
c) Tissue Doppler of the mitral annulus with a velocity <5 cm/s observed in a patient with advanced AC.
d) Restrictive relaxation pattern.
e) AS assessment showing low flow and low gradient

Amyloid deposition, occurring mainly at the subendocardial level, affects LV longitudinal deformation, independently of LVEF. Traditionally, longitudinal strain (LS) is reduced, especially in the mid and basal segments, preserving the apex, generating the "bull's-eye" or "Japanese flag" appearance. This appearance is generally altered to a greater degree than in other causes and has a sensitivity of 93% and a specificity of 82% [7,8,14,15,18,25,27,29,30,36-39,41,45,46]. Although this pattern leads us to suspect the presence of AC, the coexistence with AS and the pressure overload that the latter entails could cause involvement of the apical segments and not be observed in the presence of this valvulopathy. Decreased RV strain could be more relevant for the suspicion of infiltrative cardiomyopathy [3,10,13,14,27,30,46].

Regarding rotational mechanics, LV detorsion is usually reduced in both pathologies due to diastolic dysfunction. In contrast, torsion is abnormally increased in pathologies that present with concentric ventricular hypertrophy, such as AS and in a large percentage of patients with early-stage CA. However, in the latter pathology, deterioration is observed as LVEF falls ($p < 0.0001$). The stiffness induced by transmural amyloid infiltration present in advanced stages of CA occurs Marked torsion impairment is observed in approximately two-thirds of patients, especially in the basal segments. [45,46].

A prospective cohort study evaluated biventricular myocardial deformation and LV rotational mechanics in patients with AC compared to other forms of LVH, finding that reduced LV and RV SL, along with impaired LV torsion, suggest AC with a specificity and sensitivity of 86% and 92%, respectively. Notably, in this trial, 100% of AC diagnosed by biopsy was due to light chains [46].

Other Findings

Patients with dual pathology are more likely to present with a low-flow, low-gradient AS phenotype. This is probably due to concentric remodeling and impaired diastolic function in both ventricles and the atria [3,10,13,16,19,22,30-32,36,40]. In patients with severe AS and CA, increased E/e', mild pericardial effusion, pulmonary hypertension, biatrial dilation, moderate or severe tricuspid regurgitation, and valvular thickening have been observed more frequently [3,11-14,16,30,32,38,39,41].

Combarro Eiriz et al. proposed, in a 2022 update of CA, an echocardiographic score to suggest the presence of CA [37]. The variables used are LVH (3 points), E/e' ratio >11 (1 point), and TAPSE. ≤19 mm (2 points) and apical and basal SL >2.9 (3 points). In their study, they established that a score <2 excludes the diagnosis of ATTR with a sensitivity of 98%, and a score ≥8 suggests the diagnosis with a specificity of 98% [37].

Among echocardiographic measurements, in a prospective study of 1240 patients with ATTR, the stroke volume index, right atrial area index, reduced SL, and increased E/e' were associated with a statistically significant increase in mortality ($p <0.05$) for patients

with either CAD alone or associated AS, likely indicating an advanced stage of the disease [40].

Computed Tomography (CT)

It evaluates characteristics of AS and is the imaging method of choice for assessing the possibility of transcatheter aortic valve implantation (TAVI). When used with contrast, it could provide an estimate of myocardial extracellular volume. However, it is not used as a diagnostic study for AC [5,6,10,47]. Oda et al. propose that this imaging method could be useful for detecting AC, as it is a necessary study for pre-TAVI evaluation in patients with AS [47]. CT findings significantly associated with the presence of amyloid infiltration are increased LV posterior wall thickness (odds ratio [OR] = 1.81; 95% confidence interval [95%CI]: 0.98–3.32; p = 0.05) and increased extracellular volume (OR = 7.80; 95%CI: 2.26–25.3; p < 0.01) [47].

Magnetic Resonance Imaging (MRI)

Although it is not an imaging study that provides diagnostic certainty, it is useful for generating suspicion of AC, evaluating its progression, assessing the degree of fibrosis, and establishing a prognosis [1,25,30,33,36,38,42]. Late gadolinium enhancement (LGE), native T1-weighted images, and extracellular volume (ECV) are the techniques that provide the most information about amyloidosis [16,25,30,33,37,41,42]. After contrast administration, a circumferential subendocardial late enhancement pattern is observed with variable extension to the myocardium, which may become transmural depending on the degree of infiltration. It also shows LV thickening, from base to apex in most cases. A sensitivity of approximately 85% and specificity of 95% have been established for estimating amyloidosis with this technique. Another distinctive feature is that the RV is almost always affected [2,3,16,25,27,28,37,38,39,42,61].

Patients with AS+CA have higher native T1 values, although they are usually higher in CA-AL than in ATTR [3,12,16,37,38,42]. ECV is typically increased in CA compared to isolated AS (p=0.003). This finding, in addition to being a marker of amyloid burden, is useful for assessing prognosis. Although this parameter is more frequently observed in ATTR, it is not possible to classify CA based on these findings. Cavalcante et al. established an ECV <25% as a protective factor for cardiovascular events, whether hospitalizations or death, up to 3 years, regardless of LVEF [3,16,30,37,38,42].

Other relevant features include the presence of small ventricular cavities with thickened biventricular walls, dilation of both atria, and associated pericardial effusion [61].

Cardiac Positron Emission Tomography (PET)

This is a high-cost, high-irradiation, and low-availability study with the potential to detect amyloid infiltration in various organs and quantify the burden. It is not currently established as a diagnostic method [33,39].

Cardiac Scintigraphy

This is the most widely used study to definitively establish the presence of AC due to its specificity and sensitivity close to 100%. Myocardial uptake radiotracers with technetium-99 are suitable for patients with AC; They represent the only noninvasive diagnostic method supported by a level of evidence IB [14,25,26,28,36,38,39,49,50].

There are various radiotracers, such as 99m-technetium pyrophosphate (99mTc-PYP), 3,3-diphosphono-1,2-propanedicarboxylic acid (DPD), or hydroxymethylene diphosphonate (HMDP). It is suggested to use any of these depending on the availability of the center, since all are highly specific in binding to amyloid material, with greater avidity for TTR than for AC-AL. The cause of this selectivity is unknown, although it is believed to be due to the higher calcium content in ATTR. However, amyloid typing cannot be performed using this method [37-39,51].

The Perugini classification establishes the degree of myocardial uptake, defining grade 0 as the absence of uptake, up to grade 3 with cardiac uptake exceeding that observed in the rib. Grade 1 indicates amyloid infiltration, not disease, with grade 2 or 3 uptake being positive for AC (Figure 3) [36,38,51]. Other benefits of this technique include the ability to evaluate amyloid infiltration in other organs and establish an early diagnosis, since the observed changes generally precede clinical manifestations [26,38].

Serum and Urine Immunofixation Free Light Chains in Blood

These are basic tests for differentiating the AC subtype by revealing a plasma cell proliferative disorder. AC-AL reveals a monoclonal gammopathy, and serum and/or urine light chain measurements are elevated in more than 90% of patients with this amyloid type. In contrast, ATTRwt patients, who do not present with monoclonal gammopathy, show a normal serum light chain index. It should be noted that approximately 5% of patients with ATTRwt present with an unrelated monoclonal gammopathy of uncertain significance, so this isolated finding should not constitute a diagnosis of AC. Typing the type of amyloidosis is essential for directing treatment, since chemotherapy in AC-AL improves life expectancy in this group, but not in the ATTR-associated amyloidosis, for which treatment is different [12].

Endomyocardial Biopsy and Pathological Evaluation

Endomyocardial biopsy remains the gold standard for diagnosing AC due to its specificity and sensitivity close to 100% with at least 4 samples [25,28,36,38]. Positive Congo red staining provides apple green birefringence observed by polarizing microscopy, facilitating the diagnosis of AC. For the purpose of this study, mass spectrometry analysis is considered the gold standard, although it does not differentiate between hereditary and wild-type ATTR [25,26,28,30,38].

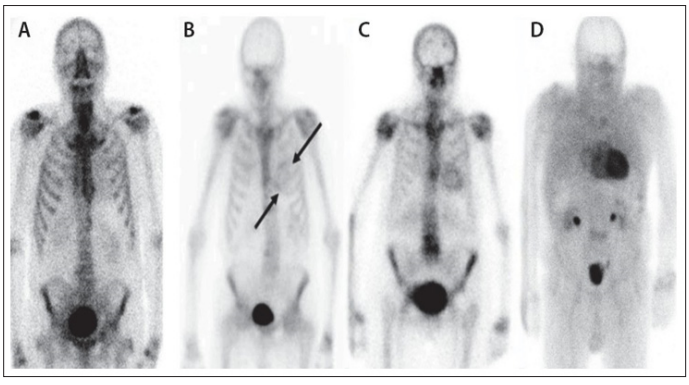

Figure 3: Perugini Classification on Cardiac Scintigraphy, with Grade 2 and 3 Uptake being Positive for Cardiac Amyloidosis [2]
a) Grade 0.
b) Grade 1.
c) Grade 2.
d) Grade 3.

However, today we have noninvasive diagnostic alternatives with high sensitivity and specificity, which even offer the possibility of monitoring the pathology. Therefore, currently, endomyocardial biopsy is not considered the study of choice due to its complexity and associated risks. It could be considered in the case of acquired hypertrophic cardiomyopathy without an identified genetic cause. [28,39].

Screening for Cardiac Amyloidosis in Patients with Aortic Stenosis CA shares many clinical characteristics with severe AS and is often underdiagnosed in the presence of this entity. Currently, there are no recommendations derived from diagnostic and treatment guidelines for screening for CA in patients with severe symptomatic AS. However, several authors recommend initiating a CA screening strategy in these patients. Thus, there are so-called "red flags," which represent a series of parameters that can be identified in patients with this condition [2,3,11-17,37].

Those mentioned in the literature are summarized below. It should be noted that the indicators included in this screening system vary depending on the author (Table 3).

General Clinical Manifestations

According to several authors, the prevalence increases with age and male gender. Autonomic neuropathy and associated musculoskeletal pathology suggest the presence of AC, with carpal tunnel syndrome being the most common feature [2,4,7,8,11,13-16,17,19,21,22,25,26,28,31-33,36,37,40]. The "natural cure" "ral" of hypertension is a frequently associated finding [24,28,36,39,41]. Disproportionate HF and right heart failure have also been mentioned as differentiating elements and the 6-minute walk test was reduced in these patients [2,8,11-13,20,26,39-41]. A history of erroneous diagnosis of another pathology is frequent [25,26,33,41,42].

Table 3: Main "red flags" for Suspected Cardiac Amyloidosis in Patients with Aortic Stenosis

Category	Demonstrations
General Clinical Manifestations	•Advanced age •Male sex •Muscle-skeletal pathology •Medication intolerance • Disproportionate HF • Decreased 6-minute walk test • Misdiagnosis of other cardiovascular pathology
Biomarkers	• Disproportionate elevation of NT-proBNP • Chronic elevation of troponins
ECG	• Pseudoinfarct pattern • AF • Hypovoltage • QRS prolongation
TTE	• Increased biventricular mass index with a mottled appearance and SIA • Restrictive diastolic pattern • Reduced minute volume index • S < 6 cm/s • Decreased SL in basal and midsegments • Normal or decreased LV torsion • Low-flow, low-gradient AS phenotype
MRI	• LGE of the LV and/or RV • Elevated native T1 • Elevated CVD

HF: heart failure. NT–proBNP: N-terminal pro-brain natriuretic peptide. ECG: electrocardiogram. AF: atrial fibrillation. TTE: transthoracic echocardiogram. IAS: interatrial septum. SL: longitudinal strain. LV: left ventricle. MRI: magnetic resonance imaging. LGE: late gadolinium enhancement. RV: right ventricle. ECV: extracellular volume.

Table 4: RAISE Score

Parameters	Points
Carpal tunnel syndrome	3
Right bundle branch block	2
Age ≥ 85 years	1
Troponins > 20 ng/L	1
Stroke volume ratio ≥ 18 mm	1
E/A ratio > 4	1
Sokolow index < 1.9 mV	1

Score	Specificity (%)	Sensitivity (%)
≥ 6 points	100	14.9
≥ 5 points	98.9	23.4
≥ 4 points	95	42.6
≥ 3 points	83.6	72.3
≥ 2 points	52.1	93.6
≥ 1 point	16.7	97.9

Extraído De: Nitsche C, Scully PR, Patel KP, Kammerlander A, Koschutnik M, Dona C, et al. Pre- valence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. J Am Coll Cardiol. 2021 [13].

Complementary Studies

Disproportionate elevation of NT-proBNP and chronic troponin levels raise suspicion. [8,11,18,27,33,36,38,39]. The ECG with a pseudoinfarct pattern is the most characteristic finding of this study. AF, hypovoltage, and QRS prolongation are also more frequently observed [2,7,26,37,39].

The TTE may show an increased biventricular mass index and a mottled interatrial septum. [2,4,13,16,18,19,36]. A restrictive diastolic pattern is more common in this group [2,3,7,13-15,26,27,32]. Reduced minute volume index, S' <6 cm/s in both ventricles, decreased SL in the basal and mid-biventricular segments, and normal or decreased LV torsion are the parameters of systolic dysfunction that should most alert us [11,14,31,45,46]. The low-flow, low-gradient AS phenotype should be considered a red flag [3,8,10,11,13,15,16,19,22,30-32,36,40]. Mild pericardial effusion, biatrial dilation, tricuspid regurgitation, and valvular thickening are relevant echocardiographic findings in these patients that increase suspicion [3,8,10,11,13,15,16,19,22,30-32,36,40]. Subendocardial LGE, especially with RV and atrial involvement, and elevated native T1 and ECV values are more frequently found on MRI in patients with amyloid infiltration [3,16,25,30,33,37,41,42].

Raise Score

In 2021, Nitsche et al., based on a prospective multicenter trial of 407 patients with AS, developed a clinical score called RAISE to predict the presence of CA in these patients [13].

Five variables were established based on the collected information: age >85 years (1 point), presence of carpal tunnel syndrome (3 points), troponin >20 ng/L (1 point), LVH and/or diastolic dysfunction (1 point), and electrical abnormalities such as right bundle branch block (2 points) or hypovoltage (1 point). The score allowed the detection with statistical validity of the presence of amyloid pathology in the population of this study (AUC: 0.86; 95% CI: 0.78-0.94; p<0.001). Scores ≥2 and ≥3 have high sensitivity with adequate expectation. cificiency for the presence of AC. Therefore, it is suggested that scores of 2 or higher would be the starting point for confirmatory studies of AC (Table 4) [13,49].

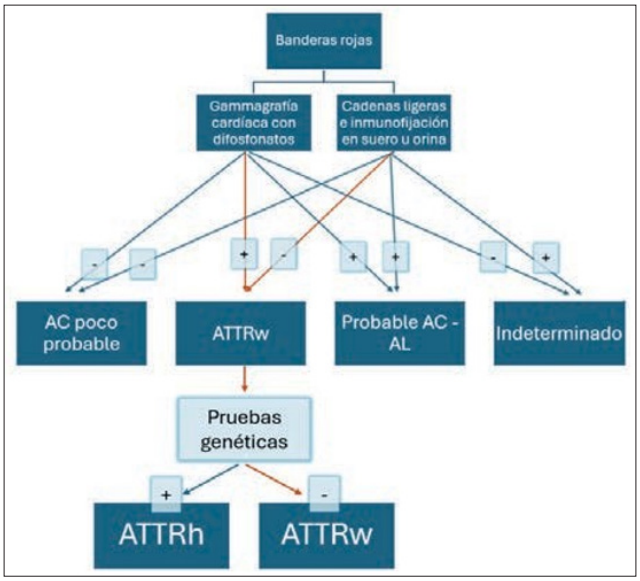

Figure 4: Diagnostic Algorithm for Cardiac Amyloidosis by Wild-Type Transthyretin. Ac: cardiac amyloidosis. Attrw: wild-type transthyretin cardiac amyloidosis. Ac-al: cardiac light chain amyloidosis. Attrh: cardiac amyloidosis due to hereditary transthyretin

Diagnostic Algorithm

In a patient with severe AS, routine studies to categorize this pathology, combined with relevant clinical findings, may lead us to suspect the presence of CA [7].

The next step should be a cardiac scintigraphy. If the result is Perugini grade 2 or 3 myocardial uptakes, the diagnosis of CA is confirmed. The next step is to search for the presence of monoclonal gammopathy in serum or urine, or serum immunofixation to classify the type of amyloid. If positive, the diagnosis is likely CA-AL, and therefore, confirmation by extracardiac or endomyocardial biopsy is required. Otherwise, a diagnosis of ATTR is reached without the need for a biopsy. Therefore, a positive cardiac scintigraphy for AC, combined with the absence of monoclonal protein in serum, allows for the diagnosis of ATTR with 100% specificity. [2,14,28,36,39,49,50].

Finally, only genotyping can distinguish between hereditary and wild-type ATTR. Therefore, it should always be performed, regardless of age, since within the population with amyloidosis, 5% of men >70 years of age and 10% of women have ATTRh and will therefore benefit from various treatments (Figure 4) [3,12,25,26,37,39,50].

Natural Course of the Disease

ATTRwt appears to be the most benign type of amyloidosis due to its slow progression. Survival varies depending on the time of diagnosis and the degree of cardiac involvement. This disease progresses slowly toward refractory HF with fewer therapeutic options, with a median survival of 3.5 years from diagnosis [3,17,33,36,39].

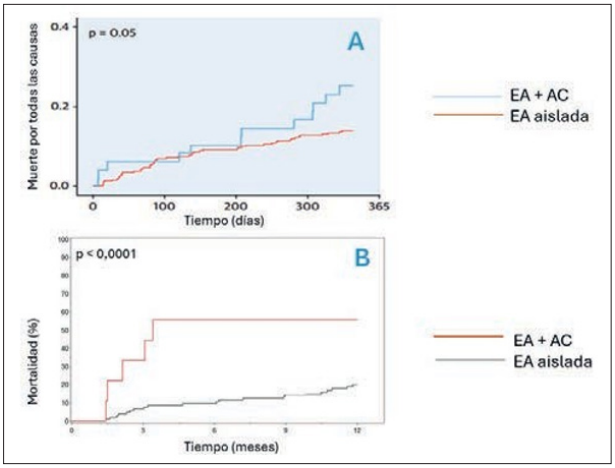

Figure 5: AS mortality with and without CA [13, 16].
a) One-year all-cause mortality in patients with aortic stenosis referred for transcatheter aortic valve replacement with and without amyloidosis according to Nitsche et al.
b) All-cause mortality in patients with AS with and without CA

AS represents a pathology whose survival rate drops dramatically in the presence of HF. Interventional treatment favorably modified the course of the disease, with mortality comparable to that of the general population [6,14,18,28,60].

In patients with dual pathology, most studies show a significant increase in all-cause mortality compared to AS alone, which almost doubles (24.5% vs. 13.9%; p=0.05) (Figure 5) [8,11-13,16,18-22].

There are Some Indicators of Poor Prognosis in this Group of Patients

The Following Stand Out

- Elevated NYHA functional class 3.
- Increased mean LV thickness 3.
- Systolic dysfunction measured by LVEF 3.
- Diastolic dysfunction 3.
- Systolic dysfunction and increased RV thickness.3
- Low-flow, low-gradient AE.13
- Decreased serum albumin (hazard ratio [HR] = 0.70; 95% CI: 0.57-0.85; p = 0.001).13
- Elevated NT-proBNP (HR = 1.40; 95% CI: 1.12-1.76; p = 0.003).13
- Increased serum creatinine (HR = 1.20; 95% CI: 1.04-1.38; p = 0.015).13
- Decreased body mass index (HR = 0.77; 95% CI: 0.61-0.97; p = 0.018).13

Therapeutic Approach

Most authors agree that the presence of both pathologies implies a worse prognosis. The establishment of medical treatment for isolated AC modifies the course of the disease, improves survival, and improves quality of life, although these benefits have not been proven when associated with AD. On the other hand, the indication for interventional treatment, well established for the resolution of Isolated AD could be extrapolated to dual pathology (AD+CA), although there are no specific recommendations in this setting [4,12,13,16,19,42].

The Therapeutic Options Available in the Literature are Described below

Medical Treatment

When a diagnosis of severe symptomatic AS is made, medical treatment should be initiated for risk factors, underlying arrhythmias, and HF, according to the recommendations of diagnostic and treatment guidelines. These include angiotensin-converting enzyme inhibitors or angiotensin receptor neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and gliflozins. All of these are indicated for AI when a reduced LVEF is found. None of these strategies improves the course of the disease or has any curative connotation. [1,5,13,35,13].

In contrast, in the presence of CA, specific treatments are proposed to slow the progression of the disease. Regarding the management of HF symptoms, typical drugs are often poorly tolerated when associated with hypotension due to autonomic dysfunction and compromised ventricular filling, which requires an elevated heart rate to maintain an already reduced cardiac output. Furthermore, there is no evidence of their usefulness in the treatment of amyloid infiltration [7,28,33,36,41,53].

Regarding the medical management of AS+CA, there are no specific indications. For the management of HF in these patients, although no recommendations are made, drugs recognized as the mainstay of heart failure treatment could be used if tolerated. On the other hand, diuretics are not first-line therapeutic drugs. However, they may be required to relieve HF symptoms. [1,2,5,6,27,28,33,39,50].

Regarding the management and prevention of supraventricular arrhythmias, rhythm control could be a strategy, especially in patients with early-stage CA, although there is no clear benefit to survival. Pharmacological or electrical cardioversion could be an option in selected patients after ruling out thrombus by transoesophageal echocardiogram due to its high prevalence, even in patients receiving anticoagulation. A similar success rate was observed in patients without CA, but a higher rate of recurrence at discharge [33,36]. If pharmacological cardioversion is chosen, amiodarone is the most commonly used drug in this group [2,28,33,36,37].

Ablation could be an option, although with less success in patients with amyloidosis and without improved survival in AS. 36,42 Although the decision is not to use beta-blockers for the management of HF in CAD, their use at low doses may be necessary to control the frequency of arrhythmias. For most authors, calcium channel blockers and digoxin are contraindicated in patients with CAD [26,33,35,39] In the presence of AF, anticoagulation is recommended. 5,6,39 The indications for permanent pacing are the same as for patients without CAD. Even in patients with a high pacing load, cardiac resynchronization therapy implantation may be beneficial [33,36,37].

Regarding the use of implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden cardiac death, there is no evidence of its benefit. tion, treatment should be individualized according to life expectancy, although it has not shown improvements in survival [26,33,36,37].

Regarding the treatment of AC, there are various drugs, many of them still under review, that modify the process of synthesis, deposition, and elimination of amyloid material. These can be grouped into three types, which are described below.

Transthyretin Stabilizers

Diflunisal is a drug from the nonsteroidal anti-inflammatory drug group that has been used as a TTR stabilizer, binding to thyroxine binding sites, preventing the dissociation of the amyloid protein and its folding. Although it has shown improvement in polyneuropathy, evidence is still lacking to consolidate its use. In trials, it was associated with a high percentage of adverse effects, especially renal failure that led to drug discontinuation [25,28,36,53].

Tafamidis is another stabilizer with a mechanism similar to diflunisal by binding to thyroxine binding sites, but without an anti-inflammatory effect. This drug reduced all-cause mortality and decreased hospitalizations for HF ($p<0.001$), without significant adverse effects. It is the drug with the greatest evidence (class I, level B), endorsed by guidelines for improving symptoms and reducing hospitalizations for HF [3,11,25,28,33,37,50,54].

Gene Silencers

The messenger RNA responsible for the formation of TTR is the target of this group.

Inotersen stabilizes polyneuropathy and improves quality of life. Although it has a high rate of major adverse effects, it is not recommended as a first-line drug. Patisiran showed a slowing of neuropathy progression and a reduction in mean LV thickness, global longitudinal strain, and NT-proBNP at 18 months. It also showed a decrease in mortality, all-cause hospitalizations, and a reduction in ECV on MRI compared to untreated patients. However, its use is approved for ATTRh and not currently recommended for ATTRwt [33,37,53].

Removal of Amyloid Deposits

Tetracyclines disaggregate amyloid fibers and may slow infiltration. Doxycycline and ursodeoxycholic acid could be considered if another drug with a low quality of evidence is unavailable [25,36,53].

Invasive Treatment

An invasive treatment to suppress TTR synthesis is liver transplantation. It could be considered an option in ATTRh, but is not indicated in ATTRwt. Regarding heart transplantation, it could be an option for any ATTR subtype, although it is not usually feasible in our setting. The lack of organ availability, the requirement for lifelong immunosuppression, and patient frailty at the time of diagnosis make this option difficult to pursue [25,36,37].

Valve replacement surgery (VRS) and TAVR are the interventions with IA indications for the treatment of severe symptomatic AS, except in patients with a life expectancy of <1 year.

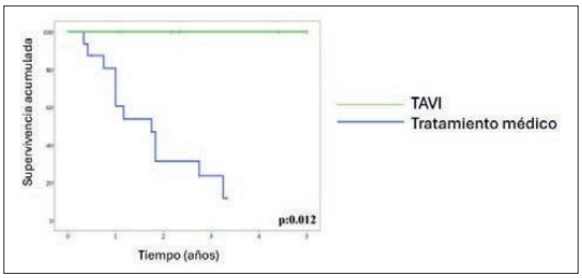

Figure 6: Mortality in patients with AS and CA undergoing transcatheter valve replacement and medical treatment. TAVI: transcatheter aortic valve implantation. Extracted from: Chacko L, Martone R, Bandera F, Lane T, Naharro N, Boldrini M, et al. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. Eur Heart J. 2020;41 [40].

Risk scores such as the EuroSCORE II, ArgenSCORE, and STS-Score have been validated to predict postoperative outcomes in valve surgery. However, they do not assess fragility or anatomical aspects related to TAVI, so treatment is limited to individualized assessment of each patient [1,2,5-7].

The PARTNER 3 and Evolut Low Risk studies demonstrated that TAVI is considered superior to medical treatment, and not inferior to CVS. Additionally, European and American guidelines recommend the use of TAVI in patients aged 75 years or older, and in younger patients defined as inoperable or at high surgical risk. It is important to mention that patients with AS with low flow and low gradient are not assessed, nor is CA considered as a poor prognostic factor [5,55,56].

The 2020 American valvular heart disease guidelines establish that TAVI produces adverse outcomes in patients with decreased LVEF, which would be comparable to a large proportion of the study population [6].

Despite the high prevalence of AS+CA, the relevance of interventional therapies for this valvular heart disease in the presence of infiltrative cardiomyopathy is currently unknown. The lack of recommendations for this group leads to ignoring the presence of CA and addressing only AS [2,3,57].

The interventional therapies described in the literature for patients with dual pathology are reviewed below.

Balloon Valvuloplasty

This procedure has a Class IIb indication for severe AS, as palliative treatment in symptomatic patients with a life expectancy of <1 year. In the case of AS+CA, some believe it is reasonable to opt for this less invasive intervention than valve replacement, due to the high surgical mortality rate in these patients, especially given a life expectancy of <1 year [3,58].

Transcatheter Aortic Valve Implantation

For many authors, TAVI reduces mortality in patients with both concomitant pathologies, with results comparable to those of isolated valve disease (Figure 6) [10,13,18,21,23,30-32,34,37,57]. A few associate this procedure with increased mortality [3,44]. Nietlispach et al. establish that, although there are no differences in intraprocedural mortality in patients with dual pathology compared to solitary AS, infiltrative pathology. It carries a worse prognosis and non-procedure-related mortality [29].

A systematic review including 7 observational studies establishes that TAVI reduces mortality compared to non-operative patients (OR=0.23; 95% CI: 0.07-0.73; p=0.001, number needed to treat=3), and with adverse effects similar to those of patients with solitary AS [57]. The systematic review by Sin-Ying Ho et al. establishes that there will be more procedure-related complications and a greater need for post-TAVI MCP implantation, although without statistical significance. Other authors support this increase in complications [8,21].

Cannata et al., in a 2022 meta-analysis, established the same risks as the population without CA, although with a greater tendency for post-TAVI MCP implantation (p=0.08) [23]. However, for Rosenblum et al. In a prospective study of 204 patients with severe AS undergoing TAVI, CA patients had similar rates of MCP implantation [31].

Regarding hospitalizations for HF, some studies report a reduction in patients undergoing TAVI compared to pharmacological treatment (3.8% vs. 19.4%; HR = 0.22; 95% CI: 0.07–0.68; p = 0.008) [37,57]. Other authors report more hospitalizations during follow-up compared to patients with isolated AS [23,31]. Compared with VRS, TAVI appears to result in fewer postprocedural hospitalizations [34,52].

It should be noted that not all studies specify the access route for this procedure. However, transapical access could be detrimental in the case of friable myocardium, potentially leading to a higher risk of rupture, bleeding, or pseudoaneurysm. 59.

Valve Replacement Surgery

In a single study, this intervention showed increased mortality with a high rate of periprocedural complications at the expense of a modest improvement in symptoms [3]. For others, one-year mortality is similar to that of patients with isolated AS [21,34]. Compared with TAVI, open surgery was associated with higher mortality. VRS compared with medical treatment showed improvements in survival [10,13,22].

LVEF <50%, severe reduction in SL, restrictive relaxation pattern, advanced age, left atrial dilation, and reduced aortic valve gradient are considered poor prognostic factors for patients undergoing VRS (p=0.02) [2,7,31,60]. Postprocedural hospitalization was higher compared to TAVR [34].

Postprocedural Treatment

There is no evidence for the use of tafamidis after aortic valve surgery, but it is recommended regardless of whether the procedure is performed. If valve replacement is performed, whether open or percutaneous, it is suggested to start it early, although this drug has not been shown to reduce postprocedural mortality [2,3,13,18,52].

Discussion

The Problem of Screening an Underdiagnosed Pathology

When addressing symptomatic AS, we must remember that a considerable percentage of these patients concomitantly present with CA. The prevalence is not accurately described and is likely underdiagnosed [2-4,7]. As we mentioned throughout this study, knowing the “red flags” and generating an initial suspicion is crucial to diagnosing this infiltrative cardiomyopathy, a condition that is often hidden by the signs and symptoms of AS and therefore goes untreated [2,3,11-17]. However, to date, there are gaps in knowledge that contribute to perpetuating this situation.

Among the demographic factors that differentiate dual pathology from isolated AS, advanced age represents a relevant indicator. Despite this, there is no consensus on a cutoff point to establish the need to suspect CA. Among the clinical aspects, many authors mention carpal tunnel syndrome as one of the most characteristic findings. It is even a variable in the RAISE score for screening for CAD in patients with AS. However, it constitutes a condition with low sensitivity for CAD, as most patients do not present with it, and the most common presentation is HF [2,8,12,13,20,26,39-41].

Despite representing expected clinical and demographic elements in any patient with severe AS, it would seem prudent to investigate the presence of combined pathology in elderly patients with HF and valvular heart disease. Consequently, routine complementary studies performed for their evaluation, along with clinical findings, could suggest amyloid infiltration. It is of particular interest to identify these findings regardless of the availability of nuclear imaging. [1,5,6,35].

There are many tools that allow us to screen for the presence of this pathology in the population of patients with severe AS. As mentioned above, an electrocardiogram with a pseudoinfarct pattern, associated with an echocardiogram showing bright, heterogeneous left ventricular wall enlargement associated with pericardial effusion, with low-flow, low-gradient AS, in an elderly patient with disproportionate HF, should lead us to consider something more than the repetitive evaluation of a formula that appears to be, at the very least, insufficient. Red flags are described in many articles, but they are not used in the clinical cardiology office. Screening for carpal tunnel syndrome or measuring biomarkers in this population is not routine, and much less frequent [2,3,11-17,37].

Finally, when CAD is highly suspected, we have highly specific studies available to detect it. A scintigraphy, plus a test to rule out monoclonal gammopathy, would provide the necessary diagnostic information to differentiate this population [14,28,36,39,49,50].

Cardiac Amyloidosis: A Higher-Risk Population

Several studies have shown that patients with dual pathology have a poorer prognosis when compared to patients with isolated AD [8,11-13,16,18-22].

On the other hand, patients diagnosed with CA differ from the population.

General population with HF due to poor tolerance to conventional treatment. However, traditional drugs could be used with caution if tolerated. Regarding the management of arrhythmias, it seems to have a similar approach to isolated AS [7,28,33,36,41,53].

Among the specific drugs for the treatment of CAD, tafamidis is the drug that has shown the best results, with the advantages of its oral administration and its availability in our setting. However, experts still do not agree that its use may be beneficial in patients with AS+CAD. [2,3,13,18,52].

The futility of valve intervention is another controversial issue. For most studies, aortic valve intervention should have the same indications with or without amyloid infiltration [10,13,22,31]. Severe AS leads to a clinical picture of HF with a rapid deterioration in functional class and increased mortality if valve intervention is not performed, leading many authors to suggest early treatment of this valvular disease. The diagnosis of CA should not delay valve replacement if feasible, since relieving wall tension would reduce amyloid deposition, which is favorable for both pathological conditions [8,13,31]. Regarding the preferable intervention strategy, the authors agree on a percutaneous approach over surgical valve replacement. Once the valve is replaced, these patients are likely to benefit from CA-modifying therapy [10,29]. However, there is wide variability in the published results. This is probably due to population differences among the patients included, associated comorbidities, the stages of dual disease at the time of intervention, and the experience of the operators. Further studies are needed to establish a definitive therapeutic approach for these patients [3].

The poorer prognosis of patients with dual disease does not preclude them from interventional treatment for valvular disease, but knowing the stage of amyloidosis is important. For most authors, invasive treatment for It would reduce mortality compared to medical treatment. Additionally, diagnosing the presence of AC is possible without the need for invasive testing, and specific treatment is currently available that can modify the course of the disease. [10,13,18,21,23,30-32,34,37,57].

Conclusions

The coexistence of severe AD and AC is relatively common, affecting populations with similar demographic characteristics and clinical manifestations. Furthermore, their association worsens the prognosis in these patients. This problem requires awareness among the medical community in order to detect it early. A growing number of studies support the need to establish initial suspicion parameters through AC screening in patients with symptomatic severe AD. The RAISE score is the only score available that would allow for its detection in these patients. However, it has not been validated by any scientific association, nor is it recommended by national and international diagnostic and treatment guidelines as a mandatory tool for this population.

Once suspected, CA is diagnosed without major difficulties using well-established noninvasive studies. The problem again arises when choosing a therapeutic strategy. Much of the scientific community agrees that improved survival can be achieved with the resolution of valvular disease, regardless of pharmacological treatment, with greater benefits if initiated early. TAVI would be preferable over CVS in patients with a certain degree of frailty. Regarding specific medical treatment, tafamidis is the drug of choice for ATTRwt, but its efficacy in patients with concomitant AS is unknown.

Many questions remain. However, recognition of this associated pathology and the incorporation of tools for its management constitute the first step to modify the prognosis of our patients.

References

1. Aquieri A, Agatiello C, Avegliano G, Baratta S, Battellini R, Bermann A, et al. (2015) Consensus de Valvulopatías. Rev Argent Cardiol 83: 1-44.
2. Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, et al. (2019) Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol 74: 2638-2651.
3. Balciunaite G, Rimkus A, Zurauskas E, Zaremba T, Palionis D, Valeviciene N, et al. (2020) Transthyretin cardiac amyloidosis in aortic stenosis: Prevalence, diagnostic challenges, and clinical implications. Hell J Cardiol 61: 92-98.
4. Florio L (2021) Amyloidosis and aortic stenosis. Epidemiological association and common pathological bases. Rev Urug Cardiol https://www.redalyc.org/journal/4797/479771193003/479771193003.pdf .
5. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. (2022) ESC/EACTS 2021 guide on the diagnosis and treatment of valve disease. Rev Española Cardiol 43: 561-632.
6. Otto CM, Nishimura RA, Bonow RO, Carabello B, Erwin J, 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 143: e72 - e227.
7. Jaiswal V, Agrawal V, Khulbe Y, Hanif M, Huang H, et al. (2023) Cardiac Amyloidosis and Aortic Stenosis: A State-of-the-art review. Eur Heart J Open 3 :1-15.
8. Galat A, Guellich A, Bodez D, Slama M, Dijos M, Zeitoun D, et al. (2016) Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg?. Eur Heart J 37: 3525-3531.
9. Kristen AV, Schnabel PA, Winter B, Helmke B, Longerich T, Hardt S, et al. (2010) High prevalence of amyloid in 150 surgically removed heart valves a comparison of histological and clinical data reveals a correlation to atheroinflammatory

conditions. Cardiovasc Pathol 19: 228-235.

10. Fabbri G, Serenelli M, Cantone A, Sanguettoli F, Rapezzi C (2021) Transthyretin amyloidosis in aortic stenosis: clinical and therapeutic implications. Eur Heart J Suppl 230: 128-132.
11. Arshad S, Goldberg YH, Bhopalwala H, Dewaswala N, Miceli N, et al. (2022) High Prevalence of Cardiac Amyloidosis in Clinically Significant Aortic Stenosis: A Meta-Analysis. Cardiol Res 13: 357-371.
12. Treibel TA, Fontana M, Gilbertson JA, Castelleti S, White S, Scully P, et al. (2016) Occult Trans-thyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis. Circulation 9: e005066.
13. Nitsche C, Scully PR, Patel KP, Kammerlander A, Koschutnik M, et al. (2021) Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. J Am Coll Cardiol 77: 128-139.
14. Castaño A, Narotsky DL, Hamid N, Khalike O, Morgenstern R, DeLuca A, et al. (2017) Un-veiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 38: 2879-2887.
15. Singal AK, Bansal R, Singh A, Dorbala S, Sharma G, Gupta K, et al. (2021) Concomitant Transthyretin Amyloidosis and Severe Aortic Stenosis in Elderly Indian Population. JACC 3: 565-576.
16. Cavalcante JL, Rijal S, Abdelkarim I, Althouse A, Sharbaugh M, Fridman Y, et al. (2017) Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson 19: 98.
17. Sperry BW, Jones BM, Vranian MN, Hanna M, Jaber WA (2016) Recognizing Transthyretin Cardiac Amyloidosis in Patients with Aortic Stenosis: Impact on Prognosis. JACC 9: 904-906.
18. Scully PR, Patel KP, Treibel TA, Thornton G, Hudges R, et al. (2020) Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. Eur Heart J 41: 2759-2767.
19. Longhi S, Lorenzini M, Gagliardi C, Milandri A, Marzocchi A, Marrozzini C, et al. (2016) Coexistence of Degenerative Aortic Stenosis and Wild-Type Transthyretin-Related Cardiac Amyloidosis. JACC 9: 325-327.
20. Peskó G, Jenei Z, Varga G, Apor A, Vago H, et al. (2019) Coexistence of aortic valve stenosis and cardiac amyloidosis: echocardiographic and clinical significance. Cardiovasc Ultrasound 17: 32.
21. Ho JS, Kor Q, Kong WK, Lim Y, Syn N, et al. (2022) Prevalence and outcomes of concomitant cardiac amyloidosis and aortic stenosis: A systematic review and meta-analysis. Hell J Cardiol 64: 67-76.
22. Myasoedova VA, Conte M, Valerio V, Moschettta D, Massaiu I, et al. (2022) Red Flags, Prognostic Impact, and Management of Patients with Cardiac Amyloidosis and Aortic Valve Stenosis: A Systematic Review and Meta-Analysis. Front Med 9: 858281.
23. Cannata F, Chiarito M, Pinto G, Villaschi A, Sanz J, et al. (2022) Transcatheter aortic valve replacement in aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis. ESC Heart Fail 9: 3188-3197.
24. Tanskanen M, Peuralinna T, Polvikoski T Notkola I, Sulkava R, et al. (2008) Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: A population-based autopsy study. Ann Med 40: 232-239.
25. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C (2017) Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation 135: 1357-1377.
26. González-López E, Gagliardi C, Dominguez F, Quarta C, Del Moral J, Milandri A, et al. (2017) Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. Eur Heart J 38: 1895-1904.
27. Gorcsan J, Delgado-Montero A (2015) Improving the determination of cardiac involvement in amyloidosis using three-dimensional speckle tracking echocardiography. Rev Española Cardiol 68: 647-648.
28. McDonagh TA, Metra M, Adamo M, Gardner R, Baumbach A, Bohm M, et al. (2022) ESC 2021 Guide on the diagnosis and treatment of acute and chronic heart failure. Rev Española Cardiol 24: 4-131.
29. Nietlispach F, Webb JG, Ye J, Cheung A, Lichtenstein S, et al. (2012) Pathology of Transcatheter Valve Therapy. JACC 5: 582-590.
30. Nitsche C, Aschauer S, Kammerlander AA, Schneider M, Poschner T, et al. (2020) Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. Eur J Heart Fail 22: 1852-1862.
31. Rosenblum H, Masri A, Narotsky DL, Goldsmith J, Hamid N, et al. (2020) Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. Eur J Heart Fail 23: 250-258.
32. Dobner S, Pilgrim T, Hagemeyer D, Heg D, Lanz J, Reusser N, et al. (2023) Amyloid Trans-thyretin Cardiomyopathy in Elderly Patients with Aortic Stenosis Undergoing Transcatheter Aortic Valve Implantation. J Am Heart Assoc 12: e030271.
33. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK (2021) ATTR Amyloidosis: Current and Emerging Management Strategies. JACC 3: 488-505.
34. Java AP, Greason KL, Dispenzieri A, Grogan M, King K, et al. (2018) Aortic valve replacement in patients with amyloidosis. J Thorac Cardiovasc Surg 156: 98-103.
35. Mann D, Zipes D, Libby B, Bonnow R (2016) Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 10th ed Braunwald Tratado de Cardiología https://books.google.co.in/books/about/Braunwald_s_Heart_Disease_E_Book.html?id=1R44BAAAQBAJ&redir_esc=y .
36. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS (2019) Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol 73: 2872-2891.
37. Combarro-Eiriz M, González-López E, Martínez-Naharro A, Barge-Caballero G (2022) Update on the diagnostic and therapeutic approach to transthyretin cardiac amyloidosis. Rev méd sinerg 9: e1150.
38. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk R, Ferrari V, et al. (2019) ASNC/AHA/ASE/ EANM/HFSA/ ISA/SCMR/SNMMI Expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2-evidence base and standardized methods of imaging. J Nucl Cardiol 26: 2065-2123.
39. Arbelo E, Prothonotarios A, Gimeno JR, Arbustini E, Villa R, Basso C, et al. (2023) 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J 44: 3503-3626.
40. Chacko L, Martone R, Bandera F, Lane T, Naharro N, et al. (2020) Echocardiography- ic phenotype and prognosis in transthyretin cardiac amyloidosis. Eur Heart J 41: 1439-1447.
41. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman B, Fontana M, et al. (2019) Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circulation 12: e006075.
42. Rapezzi C, Tinuper AL, Lorenzini M (2017) Broadening the Phenotypic Spectrum and the Diagnostic Needs of TTR-

Related Cardiac Amyloidosis. J Am Coll Cardiol 70: 478-480.
43. Baumgartner H, Hung J, Bermejo J, Chambers J, Evangelista A, Griffin B, et al. (2009) Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice. J Am Soc Echocardiogr 22: 1-23.
44. Porat A, Gordon M, Perlman G, Planer D, Danenberg H, Alcalai R, et al. (2022) Mass to voltage-age ratio index predicts mortality following TAVI. Catheter Cardiovasc Interv 99: 1918-1924.
45. Mora V, Roldán I, Romero E, Saad A, Gil C, et al. (2022) Myocardial wringing and rigid rotation in cardiac amyloidosis. CJC Open 5: 128-135.
46. Vitarelli A, Lai S, Petrucci MT, Capotoso L, Mangieri E, Ricci S, et al. (2018) Biventricular assessment of light-chain amyloidosis using 3D speckle tracking echocardiography: Differentiation from other forms of myocardial hypertrophy. Int J Cardiol 271: 371-377.
47. Oda S, Kidoh M, Takashio S, Inoue T, Nagayama Y, et al. (2020) Quantification of Myocardial Extracellular Volume with Planning Computed Tomography for Transcatheter Aortic Valve Replacement to Identify Occult Cardiac Amyloidosis in Patients with Severe Aortic Stenosis. Circulation 13: e010358.
48. Rodriguez Granillo G, Gomez E, Gorka B, Cademartiti F (2014) Cardiovascular CT and MRI 237-241.
49. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, et al. (2016) Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 133: 2404-2412.
50. Heidenreich PA, Bozkurt B, Aguilar D, Allen A, Byunt J, Colvin M, et al. (2022) AHA/ACC/ HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 952-954.
51. Perugini E, Guidalotti PL, Salvi F, Robin M, Cooke T, Pettinato C, et al. (2005) Noninva- sive Etiologic Diagnosis of Cardiac Amyloidosis Using 99m Tc-3,3-Diphospho- no-1,2-Propanodicarboxylic Acid Scintigraphy. J Am Coll Cardiol 46: 1076-1084.
52. Pibarot P, Lancellotti P, Narula J (2020) Concomitant Cardiac Amyloidosis in Severe Aor- tic Stenosis: The Trojan Horse?. J Am Coll Cardiol 77: 140-143.
53. Italian Hospital of Buenos Aires (HIBA), Medical Clinic Service, Internal Medicine In- vestigation Area, Amyloidosis Study Group (GEA) (2022) Clinical practice guideline for the treatment of patients with systemic amyloidosis. Trovare Institutional Repository 78: 74-82.
54. Maurer MS, Schwartz JH, Gundapaneni B, Elliott P, Merlini G, et al. (2018) Tafa- midis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. New Engl J Med Rev 379: 1007-1016.
55. Leon MB, Smith CR, Mack M, Miller C, Moses J, Svensson L, et al. (2010) Transcatheter Aortic Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. New Engl J Med 363: 1597-1607.
56. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, et al. (2019) Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. New Engl J Med Rev 380: 1706-1715.
57. Khawaja T, Jaswaney R, Arora S, Jain A, Arora N, et al. (2022) Transcatheter aortic valve replacement in patients with aortic stenosis and cardiac amyloidosis. IJC Heart Amp Vasc 40: 101008.
58. Yoshida S, Tada H, Nishikawa T, Kamiya T, Nakahashi T, et al. (2020) Ante- grade Balloon Aortic Valvuloplasty for the Highly Frail Patient of Severe Aortic Stenosis Complicated by Transthyretin-Type Cardiac Amyloidosis. Intern Med Rev 59: 1053-1057.
59. Monticelli FC, Kunz SN, Keller T, Bleiziffer S (2014) Cardiac Amyloidosis as a Potential Risk Factor for Transapical Transcatheter Aortic Valve Implantation. J Card Surg 29: 623-624.
60. Flowers-Marin A, Gomez-Doblas JJ, Knight-Borrego J, Cabrera F, Rodriguez I, et al. (2010) Predictors of long-term mortality and functional recovery in valvular replacement for severe aortic stenosis with ventricular dysfunction. Rev Spanish Cardiol 63: 36-45.
61. Rodriguez Granillo G, Gomez E, Gorka B, Cademartiti F (2014) Cardiovascular CT and MRI. Radiology 271: 237-241.