Chapter

Perspective Chapter: Lipoprotein (a), Cardiac Amyloidosis, and Aortic Stenosis - Underestimated Associations

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Abstract

This chapter aims to address two peculiar aspects of pathophysiology and clinical management of aortic valve stenosis, such as coexistence with cardiac amyloidosis and association with lipoprotein (a). Calcific aortic valve stenosis is the most common heart valve condition requiring surgical or transcatheter aortic valve replacement among adults in Western societies. Lipoprotein (a) has been shown to play an important role in the pathophysiological pathways leading to degenerative aortic stenosis, similar to that in the pathogenesis of atherosclerosis. Studies are needed to verify whether therapies that drastically reduce Lipoprotein (a) serum levels offer the possibility of a first medical treatment to arrest the progression of aortic stenosis. A large percentage of patients with aortic stenosis may have concomitant cardiac amyloidosis, commonly due to wild-type transthyretin. The challenge in this context is to differentiate aortic stenosis alone from aortic stenosis with cardiac amyloidosis, as cardiac amyloidosis shares several clinical, electrocardiographic, and echocardiographic features with the aortic stenosis phenotype. Recognition of transthyretin-related amyloidosis prior to any type of intervention is crucial for adequate risk stratification and to guide downstream management.

Keywords: aortic valve calcification, aortic valve stenosis, cardiac amyloidosis, lipoprotein (a), diagnostic imaging, drug therapy

1. Introduction

1.1 Introduction and pathophysiology

Aortic valve stenosis (AVS) represents the most common heart valve condition requiring treatment among adults in developed countries [1, 2]. The precursor and main determinant of AVS is the aortic valve calcification (AVC), characterized by thickening and calcium deposition of the aortic cusps, prevalence of which in the elderly population

is approximately 50%, of which at least 25% develops AVS during follow-up [3–5]. While the rate of execution, success, and complications of the aortic valve replacement (AVR) (surgical-SAVR or transcatheter-TAVR) are improving, pushing more and more toward the treatment even of patients with severe asymptomatic AVS as emphasized by the recent AVATAR trial [6], to date no drug therapy has been shown to be effective in altering the natural history of AVS. This would seem attributable to the fact that AVS pathogenesis is complex and does not reflect exactly that of atherosclerosis. The difference in pathobiology of valvular calcification versus vascular plaque is further emphasized by the fact that calcifications of the aortic valve appear relatively early in the disease process compared with the calcifications of atherosclerotic plaques [7].

One of the key contributors to these pathophysiological differences may be the lipoprotein (a) [Lp (a)], a low-density lipoprotein (LDL)-like particle whose plasma levels are primarily (90%) genetically determined by the LPA gene [8].

The main difference with LDL is related to an additional protein termed as apolipoprotein (a) [apo (a)] covalently bound to apolipoprotein B-100 by a single disulfide bond [9]. The extreme structural similarity between these two lipoproteins implies that the laboratory measurement of low-density lipoprotein cholesterol (LDL-C) also includes the content of Lp (a) cholesterol, even when LDL-C is measured directly and not obtained via the Friedewald formula [10]. Therefore, in clinical practice, to obtain the "real" LDL-C, the following formula should be applied: "real" LDL-C = measured LDL- C—Lp (a) mass in mg/dl x 0.3 [11].

This gimmick can prove extremely useful in the case of "non-responders" patients to statin therapy. Indeed, extremely high Lp (a) values, which are not lowered by statins, can falsely raise LDL-C. Therefore, the use of this formula could guide the choice of the most appropriate lipid-lowering therapy [11].

Very early after Lp (a) discovery in 1963 by the genetist Kaare Berg in Norway, [8] its important role in the development and progression of atherosclerosis was demonstrated. Indeed, Lp (a) levels >30 mg / dL and > 50 mg/dL, which are found in about 30 and 20% of individuals worldwide, respectively, confer an impressive 2–2.5-fold increased risk of myocardial infarction and cardiovascular disease [12]. Furthermore, a recent study [13] showed that Lp (a) is associated with accelerated progression of coronary low-attenuation plaque, a marker of necrotic core, which provides powerful prediction of future myocardial infarction outperforming clinical risk scores, severity of luminal stenosis, and computed tomography (CT) calcium scoring [14]. The European Society of Cardiology (ESC) guidelines consider hyperlipoproteinemia (a) the most widespread genetic dyslipidemia in the world and recommend that all individuals should have Lp (a) measured at least once in life, to identify subjects at significantly increased cardiovascular risk [15]. Again, the 2021 ESC guidelines on cardiovascular prevention stress the fact that Lp (a) dosage may play a role in the reclassification of global cardiovascular risk, particularly in subjects at moderate cardiovascular risk.

The possible association between Lp (a) and aortic valve sclerosis and calcification was first described only in 1995 by Gotoh et al., about 30 years after the discovery of the existence of LP (a)[16]. The landmark genome study that found that a genetic variation in the LPA locus (rs10455872), resulting in elevated Lp (a) levels, was associated with AVC across multiple ethnic groups and with incident clinical AVS and AVR surgery published only in 2013 [17]. After this cornerstone study, a rich and fervent literature has developed in support of the possible etiopathogenetic role of Lp (a) in AVS and AVR. Data from the ASTRONOMER trial demonstrated that elevated Lp (a) levels are associated with faster AVS hemodynamic progression and need for AVR in patients with mild-to-moderate AVS [18]. Two large patients' longitudinal

analyses conducted in the European Prospective Investigation into Cancer (EPIC)-Norfolk study [19] and in the Copenhagen City Heart Study and Copenhagen General Population Study [20] demonstrated that Lp (a) is not only a strong risk factor for AVS but is also associated with higher risk of hospitalization and mortality due to AVS. All these findings have been extensively replicated even in patients with heterozygous familial hypercholesterolemia [21] and in patients with established coronary artery disease (CAD) [22]. Finally, in 2019, Zheng et al. elegantly showed that AVS patients with elevated Lp (a) levels are characterized by increased valvular calcification activity, as measured with 18F-sodium fluoride (18FNaF) positron emission tomography (PET), increased AVC on CT, more rapid progression of AVS on serial Doppler echocardiography, and increased incidence of AVR and death [23].

The mechanism by which Lp (a) determines AVC and AVS is complex, and the result is of wide debate [24]. Currently, the main hypothesis foresees that Lp (a) acts simultaneously on three pathophysiological pathways:

1. *Lp (a) promotes inflammatory response within the valvular endothelium.*
Inflammation process is the principal mediator of the AVC stenosis initiation phase: within affected regions, macrophages, T-lymphocytes, and mast cells produce widespread microlesions and subsequent microcalcifications [25, 26].

2. *Lp (a) facilitates the phenotypic switch of interstitial valve cells into osteoblast-like cells capable of depositing calcium hydroxyapatite.*
Lp (a) is known to bind with proteoglycans and fibronectin on the endothelial surface and infiltrate the inner layers of the aortic valves to act locally on valvular interstitial cells (VICs) phenotype [27]. Indeed, Lp (a) is the major lipoprotein carrier of oxidized phospholipid, which is a substrate for the enzyme Lp-phospholipase 2 to produce lysophosphatidylcholine (LPC), which promotes valve mineralization [23]. Once LPC is converted into lysophosphatidic acid by the enzyme Autotaxin present on Lp (a) surface, it acts directly on VICs favoring their differentiation into osteoblasts-like cells by producing the major osteoblastic transcription factors RUNX2, BMP2, and the key inflammatory mediator IL6 [28]. To further increase calcium deposition, Lp (a) increases alkaline phosphatase activity through BMP2, which plays a crucial role in facilitating mineralization through hydrolysis of pyrophosphate and providing inorganic phosphate to fuel mineralization [29]. This osteogenic differentiation of VICs actually is believed to represent the pivotal mechanism by which Lp (a) is involved in valvular calcification and AVS development.

3. *Lp (a) promotes thrombosis.*
Apo (a), the main structural protein of Lp (a), is extremely similar to plasminogen [30], thus it may promote thrombotic apposition in the valve site by competing with plasminogen and thereby inhibiting the role of plasmin in dissolving fibrin clots [31]. Indeed, Lp (a) affects platelet activation and aggregation, increases plasminogen activator inhibitor-1 synthesis, and inhibits synthesis of the tissue factor pathway inhibitor [32].

1.2 Comparison between Lp (a) and other risk factors for aortic valve calcification

Since many epidemiologic studies have suggested an association between AVC and traditional cardiovascular risk factors for atherosclerosis, including male sex, smoking, hypertension [33], hyperlipidemia, diabetes mellitus [34], and metabolic

syndrome [35], one might think that the "pathogenetic weight" of Lp (a) is lower once adjusted for these other risk factors for aortic valve calcification.

Liu et al., analyzing 652 patients, demonstrated that even after a multivariate logistic regression analysis adjusting for traditional risk factors, such as age, sex, body mass index (BMI), hypertension, diabetes, smoking, and LDL-C, higher Lp (a) levels were an independent predictor of severe AVS, as evaluated by echocardiography (OR = 1.78,95% CI: 1.18–2.66, P = 0.006 [36]. These critical findings were soon replicated among 2412 participants from the population-based Rotterdam Study and 859 apparently healthy individuals from the Amsterdam University Medical Center cohort. The study of Kaiser et al. showed that individuals with elevated Lp (a) levels have a significantly increased prevalence of AVC, independently from age, sex, BMI, smoking, use of antihypertensive medication, and non-high-density lipoprotein cholesterol serum levels. Moreover, they found that additional adjustment for a sensitive parameter such as the coronary artery calcium, which reflects the global atherosclerotic burden, did not alter in any way the strong relationship between Lp (a) and AVC [37].

1.3 Imaging features about lipoprotein(a) involvement in aortic stenosis

Transthoracic echocardiography (TTE), which is the modality of choice to provide a comprehensive hemodynamic assessment of AS severity, yields only a qualitative assessment of AVC. CT is, indeed, a highly sensitive technique for the assessment of established macroscopic deposits of AVC. However, CT does not quantify early valve calcification (often referred to as "microcalcification").

PET/CT imaging can provide, instead, both anatomic and molecular data and is accurate and reproducible to detect and quantify inflammation (18F-fluorodeoxyglucose uptake) and develop microcalcification activity (18F-NaFuptake) into aortic valve hydroxyapatite. 18F-NaF uptake beyond macrocalcifications has been shown to predict new areas of calcium deposition and subsequent increase in AVC [19]. Thus, 18F-NaF uptake not only correlates with AS severity, but it appears to be a measure of the pathological process of ongoing calcifying activity [20].

Besides, various studies revealing increased valvular calcification activity using 18F-NaF PET confirmed faster rates of disease progression using both CT calcium scoring and echocardiography. In patients with AS, in the end, elevated Lp (a) levels were associated with increased AVC activity measured by 18F-NaF uptake on PET/CT, more rapid AS progression, and increased risks of aortic valve replacement and death [21].

1.4 Pharmacological approach to lowering Lp (a) and course of aortic valve stenosis

AVS is a progressive disease, so follow-up of patients plays a fundamental role as recommended by European and American guidelines [2, 38]. The rate of progression in patients with moderate AS is highly variable from patient to patient and mainly depends on the presence of risk factors such as advanced age, elevated leaflet calcification, and presence of aortic bicuspid valve. On average, there is an annual increase of peak aortic jet velocity (Vmax) of 0.3 m/s, of the mean pressure gradient of 7 mmHg and a decrease of functional area (AVAfx) of 0.1cm^2 [2]. When patients develop severe symptomatic AS, the risk of major adverse cardiovascular events, especially sudden cardiac death, becomes very high. The only available therapy in these cases is SAVR or TAVR, with a strong positive effect on survival, symptoms, and left ventricular (LV) systolic function. Patients with non-critical asymptomatic severe AVS (with

preserved ejection fraction (EF) (Vmax <5 m/s) instead have similar survival rates of age-matched controls, with a low risk of sudden death (<1% per year) [2].

In the field of cardiovascular diseases, increasing importance is being given to prevention of pathologies, especially for highly prevalent diseases such as AVS (2–7% of the population older than 65 years of age). Despite this, unfortunately nowadays there is no medical therapy that has proven effective in preventing the onset of AVS nor in slowing its progression. The pursuit of this goal has always been linked to the world of cholesterol-lowering therapies. The first promising results were obtained with statins. The first double-blind, placebo-controlled study was the SALTIRE trial in 2005 [39]. The study enrolled 155 patients, randomized to Atorvastatin 80 mg once daily versus placebo. To be enrolled, patients had to present AVC on TTE and a transvalvular gradient of at least 2.5 m/s; patients with LDL levels below 140 mg/dl or with statin intolerance were excluded. Primary endpoints were changes in Vmax assessed with Doppler echocardiography and calcium score (assessed with CT) after 25 months. The results of this first trial were disappointing: despite a significant reduction in LDL-C, there was no statistically significant difference not only in the primary endpoints, but also in clinical endpoints such as AVR and cardiovascular death. These results were certainly influenced by the numerous limitations of the study: a follow-up of only 2 years certainly too short to observe the effects on a slowly progressive disease; the choice of Vmax>2.5 as the cutoff may have excluded patients with initial disease in whom an early intervention could have led to greater benefits. The next trial was designed to overcome these limitations: the SEAS trial was published in 2008 [40]. Inclusion criteria were a diagnosis of asymptomatic AVS with Vmax between 2.5 and 4 but with a significantly higher sample size (1873). Patients with traditional indication for lipid-lowering therapy, such as atherosclerotic disease, hyperlipidemia, high cardiovascular risk profile and diabetes mellitus, were excluded, so placebo treatment was permitted. Patients were randomized to Simvastatin 40 mg plus Ezetimibe 10 mg versus placebo. A great novelty of this trial was the choice to use clinical and no longer parametric outcomes as primary endpoints (a composite of major cardiovascular events, including death from cardiovascular causes, AVR, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting (CABG), percutaneous coronary intervention, and non-hemorrhagic stroke) with a doubled follow-up (52 versus 25 months). Despite the substantial changes made, the results were again disappointing: no statistically significant difference between the two groups in terms of AVS progression was observed. On the other hand, significant results were obtained confirming the fundamental role that lipid-lowering therapy has in the secondary prevention of atherosclerotic disease: in the statin arm was observed a reduction in the risk of ischemic cardiovascular events [−22% ([CI] -37 -3; con P = 0.02)], especially the need for CABG [−32% ([CI] -50 -7; con P = 0.02)].The last trial published on the role of statins in AVS was the ASTRONOMER trial [41]. A small sample of patients (269) were enrolled in the study. Inclusion criteria were like SEAS' ones, but at the end of enrolment, the study population was on average 10 year younger and with less calcified valves compared with the other two studies. Patients were randomized to receive either placebo or Rosuvastatin 40 mg. the results confirm what emerged from the two previous studies: despite an excellent reduction in LDL-C, no effects were found on AS progression (as measured by aortic Vmax and AVAfx) nor on outcome events (cardiac death or AVR). Considering the results of these three well-designed and large trials, it can be stated with scientific certainty that there is no benefit in the use of statins on the progression of AVS in patients without other indications for

lipid-lowering therapy. In fact, most recent American practice guidelines on heart valve disease state: "statin therapy is not indicated for prevention of hemodynamic progression of aortic stenosis" because of no benefit class III level of evidence A [2].

Recent genetic studies have confirmed the role of some atherogenic apo-B containing lipoproteins including Lp (a). Reducing these particles can be beneficial through the inhibition of leaflet mineralization, the inhibition of macrophage infiltration, the prevention of osteoblast-like phenotype transformation, and the reduction of leaflet cholesterol accumulation. We also know that patients with high levels of Lp (a) have a more rapid progression of the disease [23]. Statins increase Lp (a), and this may be one explanation for their failure. On the other hand, Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK-9i) are effective in reducing Lp (a) by an average of 20–30% with an incompletely known mechanism [42]. In a recent study with a large sample (49,617 patients), patients with PCSK9 R46L loss of function mutation presented lower levels of LDL, Lp (a) as well as a lower risk of AVS and myocardial infarction. PCSK9 R46L carriers had an age- and sex-adjusted odds ratio of 0.64 (95% confidence interval, 0.44–0.95) for AVS, 0.77 (0.65–0.92) for myocardial infarction [43]. These innovative but preliminary data have been confirmed in a recent meta-analysis of 10 studies. This document underlines that PCSK9 is not only present in the aortic valves and is involved in the calcification process but also that there is a correlation between levels of PCSK9 and severity of calcification. Indeed, experimental in vitro studies have shown that neutralizing PCSK9 reduces the accumulation of calcium in valve cells by up to 50% [44]. Important new findings also came from an intervention study. Trial FOURIER enrolled 27,564 patients with atherosclerotic disease randomizing them to Evolocumab versus placebo. In a recent subanalysis of this important trial, the authors evaluated the safety database for aortic events [44]. the data confirmed the association between plasma levels of Lp (a) and AVS after a full multivariable adjustment; on the other hand, there was no association between AVS and Lp (a)-corrected cholesterol levels. The most interesting aspect concerns the response to Evolocumab: in fact, the patients in therapy had a lower incidence of AS with an HR of 0.66 (95% CI, 0.40–1.09), with no apparent association in the first year (HR, 1.09 [95% CI, 0.48–2.47]) but an HR of 0.48 (95% CI, 0.25–0.93) after the first year of treatment; with also a lower incidence of AVR. This may further confirm the association between Lp (a) and AS, but more importantly, it may suggest that reducing Lp (a) levels may slow the onset and progression of AVS. All this has yet to be scientifically proven; a trial with PCSK-9i is still underway to evaluate the effect on aortic leaflet calcification (NCT03051360) [45]. Another pattern under study concerns the inhibition of the renin-angiotensin-aldosterone system. Drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, in addition to the positive antihypertensive effect, could slow down the progression of the disease by reducing pro-fibrotic processes affecting the myocardium and especially the aortic leaflets. An ongoing trial is evaluating this hypothesis (NCT04913870) [46].

Studies have also been conducted regarding soluble guanylate cyclase (sGC) and nitric oxide. There is evidence on the effectiveness in preventing cardiac dysfunction and remodeling in patients with pressure overload with PDE-5 inhibitors. Moreover, the stimulation of sGC was correlated to an increase in aortic leaflet calcification [47]. A small phase 2 intervention study was also conducted with Ataciguat, obtaining a significant reduction in aortic leaflet calcification assessed by CT [48]. The calcification of the aortic leaflets is the cornerstone of the pathophysiology of AVS, leading to mechanical stress, inflammation, and further calcification. There is an association

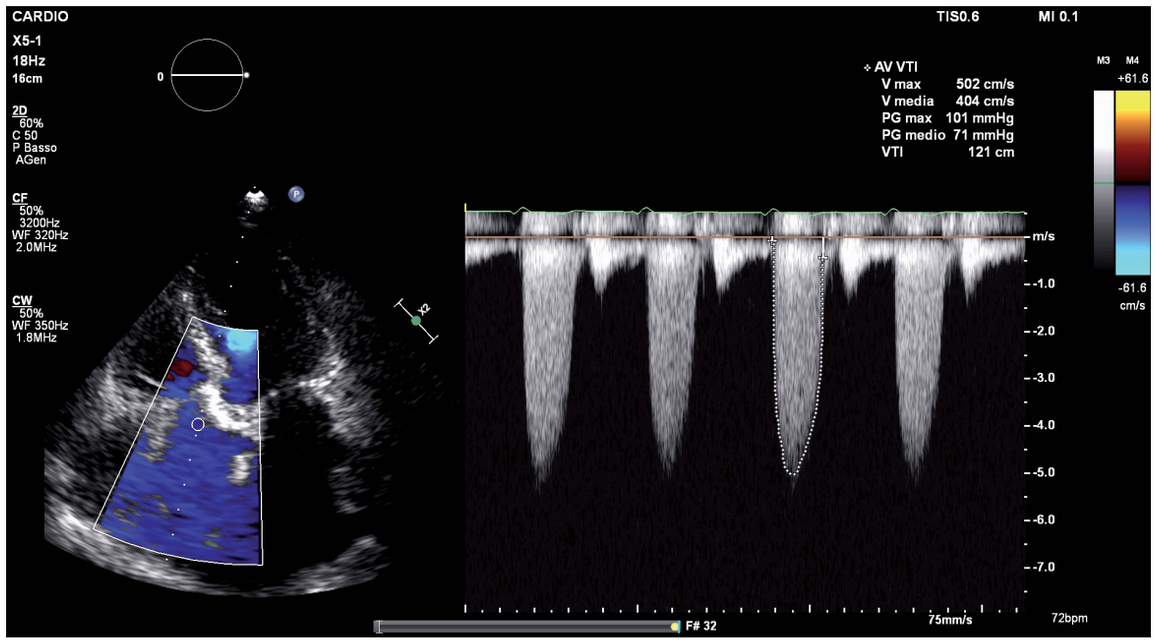

Figure 1.
Recording of the peak velocity through a stenotic aortic valve in the apical five-chamber view by continuous-wave Doppler.

between osteoporosis and increased calcification of the cardiocirculatory system. In view of this, there were hopes for osteoporosis drugs [49]. Despite these premises in the recent SALTIRE II trial, Denosumab and Alendronate failed to slow the progression of AVS, assessed by fluoride F-18 PET [50]. Vitamin K supplementation as an enhancer of the anti-calcific effects of matrix-Gla protein is currently being investigated in the BASIK2 trial.

In **Figure 1**, we show Vmax through an AVS in the apical five-chamber view by continuous-wave Doppler.

2. Aortic valve stenosis and cardiac amyloidosis

2.1 Introduction and pathophysiology

Cardiac amyloidosis (CA) refers to the deposition of amyloid fibrils in the heart. The two prevailing amyloid proteins with cardiac tropism are immunoglobulin light chain (AL) and transthyretin (ATTR) [51, 52] (**Table 1**). Describing AS and CA association has grown interest lately, as a consequence of increased facility of CA-ATTR diagnosis and novel treatments. As they share some characteristics, their discrimination still remains very challenging. Several retrospective or prospective studies have described the presence of CA, especially the ATTR form, in AS patients, with a prevalence ranging from 4–29% [53, 54]. Conversely, AL amyloidosis has rarely been described in patients with AS [55–57]. Only one group reported a majority of AL-CA in their study population [58]. Of 55 consecutive patients with CA, AS was found in 9 and 80% had AL amyloidosis. According to the authors, it is possible that a selection bias has affected the results. Thus, when describing AS-CA association, it is reasonable to consider mainly wild type (wtATTR).

The amyloidogenic process causes the aggregation and the precipitation of amyloid proteins in the extracellular space of different organs. In the heart, this results in

Acronym	Type of protein	Age of onset	M:F ratio	Organ involved
ATTRwt	Misfolded TTR	74	M> > F (90%)	Heart, bilateral carpal tunnel syndrome, spinal stenosis, spontaneous biceps tendon rupture, peripheral and/or autonomic neuropathy
ATTRv	TTR gene mutation (single amino acid mutation)	Variable, mutationdependent	M > F	Variable: cardiac and/or neurological phenotype
AL	Misfolded immunoglobulin free light chain	63	M > F (55%)	All organ except CNS: heart, kidney, liver, gastro-intestinal tract, lung, peripheral nervous system, autonomic nervous system, soft tissue (i.e., macroglossia, periorbital purpura, carpal tunnel syndrome)

AL: immunoglobulin light chain amyloidosis; ATTR: transthyretin amyloidosis; CNS: central nervous system; v: variant amyloidogenic; and wt: wild type.

Table 1.
Types of cardiac amyloidosis.

increased thickness of ventricular wall and valves, impaired myocardial contraction, and restrictive filling due to interposition of the fibrils. Moreover, amyloid fibers have a direct toxic effect, mainly dependent on the type of CA: circulating light chains have demonstrated more significant direct cardiotoxicity when compared with ATTR [59, 60]. On the other hand, the mechanical stress and atherosclerotic process affecting leaflets in AS are responsible for triggering an inflammatory response, which leads to fibrosis, thickening, sclerosis, and calcification [61]. Therefore, oxidative stress, inflammation, and extracellular remodeling play a central role in the disease process of both AS and CA [62]. To complete the circle, the increased afterload in AS may induce and accelerate amyloid fibrils deposition [54, 57].

2.2 Characteristics of the patients and red flags

Patients with concurrent AS and CA are not a minority in clinical practice [54]. AS is common in older adults, affecting more than 4% of people >75 years old [63]. Likewise, up to 25% of the octogenarians have proven CA, according to postmortem studies [64]. Thus, because of the aging of the population, the diagnosis of this dual pathology is destined to grow. Patients with concomitant AS and CA tend to be more frequently male [57, 60, 65, 66]. As much as older age [56, 67], a history of carpal tunnel syndrome, especially if bilateral, is an independent predictor of the presence of amyloid deposits of ATTR in AS [55].

Since CA is an easily missed pathological entity, the crucial aspect for diagnosing it is the "suspicious phase." In clinical practice, the rule "you find what you are looking for and you look for what you know" nearly always applies. For this reason, it is essential to know and recognize those clinical, laboratory, and imaging signs that are extremely useful to suspect the disease. These constellations of signs and symptoms

are termed "red flags" and can be cardiac or extracardiac and specific or nonspecific to a type of amyloidosis [68, 69].

Among the extracardiac red flags, the main ones include proteinuria (even mild), macroglossia, skin bruises, carpal tunnel syndrome (typically bilateral), ruptured biceps tendon, lumbar spinal stenosis, and polyneuropathy (especially in AL amyloidosis) [70, 71]. A critical clinical condition to look out for is dysautonomia, i.e., a condition in which the autonomic nervous system does not work properly, affecting the functioning of multiple organs such as the heart, bladder, intestines, sweat glands, pupils, and blood vessels [72]. A typical manifestation of the CA associated dysautonomia is the finding of hypotension or normotensive in previously hypertensive patients [73]. Three simple diagnostic techniques to objectify dysautonomia are as follows:

- A pathological Valsalva response: absence of heart rate increase in phase II of Valsalva maneuver and delayed blood pressure recovery in phase IV [74].

- A heart rate variability during deep breathing blunted or even abolished. During the deep-breathing test, the patient is asked to breathe deeply at six breaths per minute for 1 min; in healthy individuals, heart rate rises during inspiration and falls during expiration with an heart rate variability >14 b.p.m. [75].

- A nocturnal "non-dipping" or even "reverse-dipping" blood pressure pattern recorded through 24-hour ambulatory blood pressure monitoring [76].

Furthermore, CA is one cause of heart failure (HF) [77]. However, most of the studies reported more frequently a New York Heart Association (NYHA) functional class III and IV in patients with AS and CA compared with AS alone [55–58, 66, 67, 78–84]. In addition, persistently high values of N-terminal pro-brain natriuretic peptide and high-sensitivity cardiac troponin (hs-cTn) are described in patients with dual pathology when compared with AS without CA [55, 56, 67, 78, 79]. Because of very wide ranges reported, no cutoff has been proposed, although cTn may have a potential predictive role in this setting [67].

The Electrocardiogram shows two features particularly suggestive: pseudo-infarction pattern (mainly in anterior leads) and low-voltage QRS complex. The discordance between QRS voltage and LV hypertrophy on imaging may help differentiate AS-CA patients from AS alone [60]. Atrial and ventricular arrhythmias and conduction abnormalities are often found in CA [60]. In particular, wide QRS and right bundle branch block are both independent predictor of concomitant AS-CA at multivariate analysis [56, 67].

TTE is mandatory in the diagnostic process of both AS and CA. AS-CA patients tend to have lower LV EF, lower stroke volume index (SVi), and lower transaortic gradient [78–81]. All these parameters, besides high-grade diastolic dysfunction, greatly increased septal thickness and left atrial (LA) enlargement, showed predictive power on univariate analysis [67, 78]. However, only the systolic mitral annular velocity (S′) and the SVi were independent predictor of ATTR-CA in AS patients, with an area under the curve of respectively 0.95 and 0.77 [56, 78]. In particular, a cutoff value of S′ < 6 cm/s had 100% sensitivity (with a 57% specificity) in predicting a positive bone scintigraphy (17). Patients with CA and coexisting AS are more likely to present with paradoxical LFLG pattern that may be explained by LV restrictive physiology, LA remodeling and dysfunction, and right ventricular failure. This condition mainly affects individuals with the wtATTR [53].

A key aspect, in this scenario, is the evaluation of specific symptoms. The execution of a stress echocardiogram is useful when symptoms are not uniquely attributable to the valve defect, but dobutamine-induced stress, however, has proven incapable of increasing the outflow of LV in CA patients and may lead to inconclusive results.

At speckle tracking echocardiography (SPE), AS with CA has shown lower values of global longitudinal strain when compared with AS alone [55, 56, 78, 79, 82]. The typical SPE pattern of "apical sparing" is specific in CA [85]. It reflects the more preserved myocardial deformation of LV apical regions compared with mid and basal ones [60]. One study reported no significant difference in relative apical longitudinal strain in 151 patients with calcific severe AS with and without CA-ATTR [78]. Moreover, apical sparing could not predict ATTR-CA in AS because the wall stress and afterload imposed on the LV by a severely AVC may have masked the pattern. On the other hand, the apical sparing may also be observed in patients with lone AS [53]. To help clinicians in the detection of AS-CA patients, a scoring system has been recently created and validated in a cohort of 407 patients with AS undergoing TAVR [55]. The remodeling, age, injury, systemic, and electrical (RAISE) score includes five variables: LV hypertrophy and/or diastolic dysfunction, age, hs-cTn, carpal tunnel syndrome, and right bundle branch block or low QRS voltage. Scores ≥2 and ≥ 3 points had high sensitivity (93.6 and 72.3%), with adequate specificity (52.1 and 83.6%) for the presence of AS-CA. See **Figure 2**.

2.3 Cardiac amyloidosis diagnosis

Traditionally, any form of CA can be diagnosed when amyloid fibrils are found within cardiac tissue; therefore, the endomyocardial biopsy demonstrating amyloid

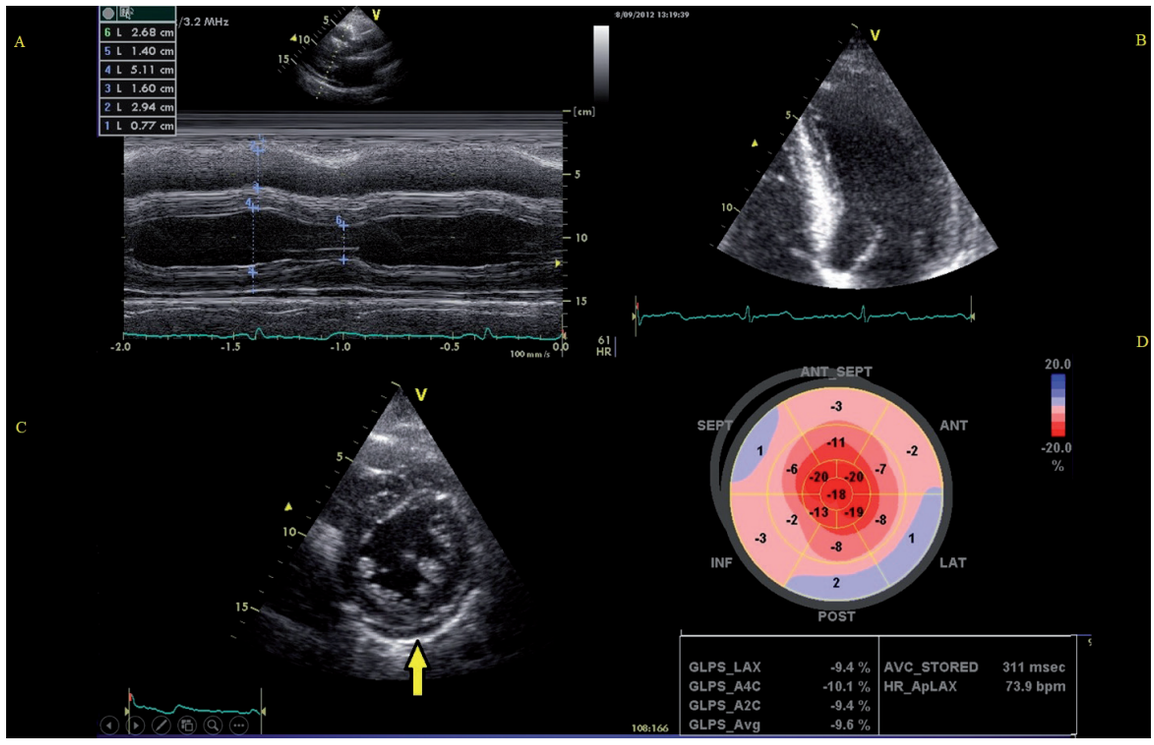

Figure 2.
Echocardiographic characteristics of a patient with amyloidosis. A: Long parasternal view, M-mode on the left ventricle, which has a thickness (> _12 mm). B: Four-chamber apical view, granular sparkling of myocardium. C: Parasternal short axis view, pericardial effusion (arrow). D: Longitudinal echocardiography strain depicted in bull's-eye map showing preserved apical strain (apical sparing) with reduction of mid and basal strain that results in hallmark "cherry on the top" pattern.

deposits with typical green refraction after Congo red staining represents the diagnostic gold standard [86]. Alternatively, the invasive diagnosis can also be confirmed if amyloid deposits within an extracardiac biopsy (e.g., of periumbilical fat) are accompanied either by characteristic features of CA by echocardiography or on cardiac magnetic resonance (CMR) [87].

Instead, noninvasive diagnostic criteria have also been proposed, the latter accepted only for ATTR forms of CA. According to the ESC 2021 myocardial working group position paper on CA, all those patients with LV wall thickness > 11 mm and at least one red flags among those mentioned above should undergo diagnostic screening [87].

As the large majority of cases of CA are AL and ATTR, the diagnostic screening algorithm proposed includes the execution of an imaging and a laboratory examination: the scintigraphy with bone-seeking tracers coupled to the assessment for monoclonal proteins by serum-free light chain (FLC) assay, serum (SPIE), and urine (UPIE) protein electrophoresis with immunofixation [88]. The combination of SPIE, UPIE, and quantification of serum FLC has a sensitivity of 99% for identifying abnormal pro-amyloidotic precursor in AL amyloidosis typically associated with clonal dyscrasias [89] while grade 2 or 3 myocardial uptake of radiotracer on scintigraphy allows the diagnosis of ATTR amyloidosis, both muted and wild-type [90].

Therefore, the results of these tests could lead to four typical scenarios [87]:

1. Positive scintigraphy and negative monoclonal proteins: in this case, the CA-ATTR is diagnosed, and it is therefore recommended to perform genetic testing to differentiate between hereditary amyloid transthyretin (vATTR) and wtATTR forms [91].

2. Negative scintigraphy and positive monoclonal proteins: in this case, AL amyloidosis has to be ruled out. Therefore, it is indicated to perform a biopsy of the periumbilical fat and perform the CMR to confirm or exclude cardiac involvement.

3. Negative scintigraphy and negative monoclonal proteins: in this case, there is a very low probability of CA and ATTR and AL amyloidosis are unlikely. Despite this, it is essential to underline that a negative scintigraphy does not completely rule out a diagnosis of CA when the clinical suspect is high [92].

4. Positive scintigraphy and positive monoclonal proteins: in this case, the overlap between a clonal dysplasia and ATTR CA is possible.

In **Figure 3**, we show an example of cardiac uptake grading in bisphosphonate scintigraphy.

Furthermore, recently, a new score that uses only data from echocardiography and/or CMR has been proposed to obtain a noninvasive diagnosis, although it has not yet been external validated [93]. Indeed, the ESC position paper considers that a score > 7 points in the presence of LV wall thickness > 11 mm in combination with amyloid deposits in an extracardiac biopsy could also be considered diagnostic of CA [87].

This suggests that, despite most of the CMR findings in CA being nonspecific, some of these may be really helpful in diagnosis. Precisely, the association of diffuse subendocardial or transmural late gadolinium enhancement and an abnormal kinetics (myocardial nulling preceding or coinciding with blood pool), eventually coupled with an extracellular volume > 0.39%, is strongly supportive for the diagnosis of CA

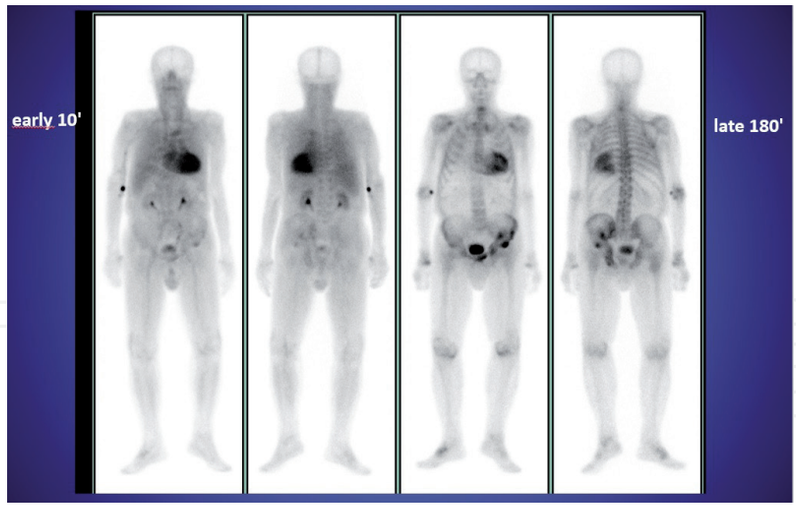

Figure 3.
Cardiac uptake grading in bisphosphonate scintigraphy shows similar myocardial and bone uptake. Courtesy of Dr. R. Giubbini.

[94]. In support of this, a recent study published in Nature Scientific Reports suggests that CMR-based T1-mapping offers superior diagnostic value compared with longitudinal strain-based assessment of relative apical sparing in CA [95].

2.4 Medical therapy

Together with a more frequent detection of CA-ATTR and thanks to a better comprehension of pathophysiology, pharmacological research has produced and tested new effective drugs with specific target.

In CA, medical therapy has two main goals: treatment of HF and the "anti-amyloid" strategy. HF treatment is not different from other etiologies and should follow the recent guidelines for treatment of acute and chronic HF, with some precautions [77]. Loop diuretics are the mainstay for congestion relief. Maintenance of euvolemia is mandatory and, at the same time, challenging, because of the restrictive nature of CA and the reduced LV capacitance [77]. Renin-angiotensin-aldosterone system antagonists and beta-blockers may be not tolerated owing to a propensity to postural hypotension [52], while calcium-channel blockers should be avoided due to their tendency to form complexes with amyloid proteins [60]. Medical therapy also includes managing arrhythmic complications [60]. Atrial fibrillation is the most common arrhythmia in CA [54]. Once it is detected, anticoagulation is mandatory irrespective of CHADs-VASc score [60]. Rate control may be hard due to a narrow window of optimal heart rate; both tachycardia and bradycardia are poorly tolerated. Amiodarone is the preferred anti-arrhythmic drug [87], while data about catheter ablation are limited, possibly having a role in the early stages of the disease. Lastly, in case of conduction abnormalities requiring pacemaker implantation, the recommendations should follow current available guidelines [96].
The "anti-amyloid" strategy is etiology-dependent. The mainstay of the treatment of AL amyloidosis is the cytoreductive, plasma-cells-directed chemotherapy and/or immunetherapy [97]. The standard of care regimen is based on the use of a combination of agents, such as cyclophosphamide, bortezomib, and dexamethasone [98]. Recently, a monoclonal antibody, called daratumumab, directly targeting plasma cells has shown effective results [99], becoming part of the standard regimen. The aim of the treatment is to achieve hematological and cardiac response with a rapid and deep reduction

of circulating free light chain. The available therapy does not directly affect amyloid deposition; thus, timing of diagnosis is of paramount importance. Novel agents are being tested in order to obtain amyloid reabsorption [97]. There are three therapeutic strategies for the treatment of ATTR amyloidosis: 1) TTR stabilization; 2) TTR mRNA silencing; and 3) amyloid fibrils disruption and/or extraction (**Table 2**) [60]. One TTR stabilizer, tafamidis, has been recently approved for use in clinical practice, thanks to the results of the ATTR-ACT trial [52, 100]. Tafamidis reduced all-cause mortality and cardiovascular hospitalization in 441 patients with CA-ATTR due to wtATTR or vATTR over a period of 30 months [100]. The effect was seen in patients in NYHA functional class I or II, while NYHA III patients had higher rates of hospitalization. Interestingly, functional improvement occurred within 6 months. Despite the improvement of mortality and morbidity, the cost of this drug still remains high. Apparently, the use of this drug does not affect outcomes after AVR [57]. The role of novel TTR tetramer stabilizer, as a concomitant or alternative treatment, has to be clarified yet. The ongoing ATTRact-AS (NCT03029026) trial will shed light on this challenging association.

2.5 Treatment options of aortic stenosis in patients with cardiac amyloidosis

CA is found to be a strong predictor of adverse outcome after SAVR, suggesting that its presence is a disease modifier in AS [82]. On the other hand, retrospective studies have shown that AS does not have an impact in terms of survival in patients

Drug	Type/effect	Administration	Side effects	Cost	Use
Tafamidis	TTR stabilizer/binds to thyroxinebinding site on TTR	Oral	No known side effects	+++	Approve d for ATTRwt and ATTRv
Diflunisal	TTR stabilizer/binds the thyroxinebinding site on TTR	Oral	Renal dysfunction; bleeding; hypertension; fluid retention	+	Off-label for ATTRwt (use with PPI)
Inotersen	TTR silencer/ antisense oligonucleotide	subcutaneous	Thrombocy topenia; glomerulon ephritis; vitamin A deficiency	++++	ATTRv with polyneur opathy
Patisiran	TTR silencer/small interfering RNA	intravenous	Infusion reactions; vitamin A deficiency	++++	ATTRv with polyneur opathy
Doxicicline/ taurodeoxy colic acid	TTR disruption/ extrac tion	Oral	NA	+	No demonstrable effects on ATTR-CA
Human antibodies (i.e., PRX004)	TTR disruption/ extrac tion	Intravenous	NA	NA	NA

CA: cardiac amyloidosis; NA: not available; PPI: proton-pump inhibitor; and TTR: transthyretin.

Table 2.
ATTR anti-amyloid drugs.

with CA, despite some individuals undergoing SAVR, concluding that mortality in these patients affected by both diseases was driven by amyloidosis [101].

Even when there is a clear component of symptomatic AS, the amyloid-induced myocardial dysfunction persists once the valve is replaced, resulting in reticence in invasive intervention.

These results are conflicting with an analysis of a cohort of individuals with CA-ATTR and AS in which patients undergoing TAVR showed a significantly longer survival. A subsequent review of this study showed the presence of population selection bias, but it is anyway suggestive that a less invasive approach with TAVR could be better tolerated by CA patients [102].

Small studies suggest a better outcome of TAVR versus SAVR in the presence of CA [79], but various procedural complications of TAVR are more frequent in these individuals due to the increased fragility of amyloid infiltrated tissues. The fundamental characteristics that favor the less invasive approach of TAVR compared with SAVR are an intermediate or high surgical risk, the presence of an LVEF of less than 50%, an SVi <30 ml/m^2, and an LV global longitudinal strain ≥ −10% [103].

The main factors of poor prognosis and usefulness of AVR in patients with AS and CA are represented by reduced LVEF, a severe reduction of LV global longitudinal strain, a grade III diastolic dysfunction, a moderate-to-severe reduction of the SVi, and a low gradient AS [79, 82]. These parameters should be considered in the assessment of risks and benefits during the multidisciplinary evaluation of the heart team, in addition to the classic criteria relating to the patient's functional condition, comorbidities, fragility, and life expectancy.

Based on the small population studies in literature, their inconclusive results, and the lack of any head-to-head comparisons, a clear recommendation on the best therapeutic strategy (SAVR vs. TAVR vs. medical therapy) cannot be given. In case the invasive approach is considered futile by the heart team, HF medical therapy is optimized [15].

3. Conclusions

High circulation Lp (a) concentration is strongly associated with degenerative AS. The importance of a therapy that can prevent AVS progression is evident, but, to date, no therapy that specifically lowers Lp (a) levels has been approved for clinical use. Furthermore, up to one-third of patients with paradoxical AS may have concomitant CA, commonly due to wtATTR. The challenge in this context is to differentiate AS alone from AS with CA. Recognition of ATTR prior to any type of intervention is crucial for adequate risk stratification and to guide downstream management.

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Appendices and Nomenclature

18FNaF	18F-sodium fluoride
AL	amyloid light chain

AF	atrial fibrillation
AS	aortic stenosis
AVAfx	aortic functional area valve
AVC	aortic valve calcification
AVR	aortic valve replacement
AVS	aortic valve stenosis
BMI	body mass index
CA	cardiac amyloidosis
CAD	coronary artery disease
CT	cardiac tomography
CMR	cardiac magnetic resonance
EF	ejection fraction
ESC	European Society of Cardiology
FLC	free light chain
GLS	global longitudinal strain
HF	heart failure
hs-cTn	high-sensitivity cardiac troponin
LA	left atrial
LDL	low-density lipoprotein
LFLG	low flow low gradient
Lp (a)	lipoprotein (a)
LPC	lysophosphatidylcholine
LV	left ventricular
PCKS9i	proprotein convertase subtilisin/kexin type 9 inhibitors
PET	positron emission tomography
SAVR	surgical aortic valve replacement
SGc	soluble guanylate cyclase
SPE	speckle tracking echocardiography
SPIE	serum protein electrophoresis with immunofixation
SVi	stroke volume index
TAVR	percutaneous aortic valve replacement
TTE	transthoracic echocardiography
UPIE	urine protein electrophoresis with immunofixation
VICs	valvular intestinal cells
vATTR	hereditary amyloid transthyretin
Vmax	peak aortic jet velocity
wtATTR	wild-type transthyretin amyloidosis

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