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THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Aortic Stenosis and Cardiac Amyloidosis

JACC Review Topic of the Week

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ABSTRACT

The prevalence of calcific aortic stenosis (AS) and of cardiac amyloidosis (CA) increases with age, and their association is not uncommon in the elderly. The identification of CA is particularly challenging in patients with AS because these 2 conditions share several features. It is estimated that ≤15% of the AS population and ≤30% of the subset with low-flow, low-gradient pattern may have CA. In patients with AS, CA is associated with increased risk of heart failure, mortality, and treatment futility with aortic valve replacement. In case of suspicion of CA, it is thus crucial to confirm the diagnosis to guide therapeutic management of AS and eventually implement recently developed pharmacological treatment dedicated to transthyretin amyloidosis. Given the high surgical risk of patients with AS and concomitant CA, transcatheter aortic valve replacement may be preferred to surgery in these patients. (J Am Coll Cardiol 2019;74:2638–51)

Aortic stenosis (AS) is the most common valvular heart disease (VHD), with a prevalence >4% in octogenarians. The pressure overload associated with AS leads to development of left ventricular (LV) concentric hypertrophy, impairment of LV diastolic and systolic function, and ultimately, heart failure (HF). In the absence of treatment, symptomatic severe AS is associated with poor prognosis. However, aortic valve replacement may change the natural history of AS and restore a patient's life expectancy close to that of the age- and sex-matched general population.

Cardiac amyloidosis (CA) is characterized by extracellular deposit of amyloid fibrils within the myocardium and other cardiac structures; this condition afflicts ≤25% of octogenarians (1,2). CA shares several common features with AS, but its prognosis generally is worse than severe AS alone (3). Recent studies suggest that the coexistence of AS and CA is more common than previously anticipated (4,5). The

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HIGHLIGHTS

- CA may be present in ≤15% of patients with AS.
- Clinical and imaging "red flags" for CA should be systematically searched in patients with AS.
- Transcatheter rather than surgical AVR may be preferred in patients with CA.
- Recently developed pharmacological treatment for transthyretin CA should be instituted as soon as diagnosis is confirmed.

combination of AS and CA complicates the diagnosis and therapeutic management of both conditions. Recently, effective pharmacotherapies have been developed to halt and reverse the course of transthyretin (TTR) CA (6). There is thus an urgent need to standardize and optimize the diagnostic evaluation and therapeutic management of CA in AS, and vice versa (7,8). The aim of this review is to provide an overview of current knowledge on: 1) the pathophysiology and prevalence of CA in the AS population; 2) the diagnostic and therapeutic management of CA in patients with AS; and 3) the diagnostic and therapeutic management of AS in patients with concomitant CA.

PATHOPHYSIOLOGY OF CA

Amyloidosis corresponds to the extracellular accumulation of amyloid fibrils within otherwise normal organs (**Figure 1**). The 2 more prevalent proteins involved in CA are transthyretin (TTR-CA) and the immunoglobulin light chain (or AL-CA) (9). There are 2 types of systemic TTR-CA: senile or wild-type transthyretin (wtTTR) and hereditary transthyretin (hTTR). Senile or wtTTR-CA is more prevalent in patients age >80 years (1) and is related to the deposition of genetically unaltered transthyretin. The mechanism of this dysregulation is unknown, but it is likely more complex and multifaceted than solely the aging process. Hereditary TTR-CA is a genetic disease with an autosomal dominant pattern and is observed in younger patients than those with wtTTR-CA (10). Among the 120 mutations, some variants are more prevalent in CA such as the ATTR pVal142Ile mutation also called the Afro-American mutation (11). Depending on the mutation, the main phenotypic expression can be cardiovascular or neurological (12,13). Overall, TTR is the most prevalent type of CA associated with AS, especially in men age >70 years (4,5). Patients with AS rarely have the AL-CA type, which is related to the accumulation of an amyloidogenic light chain variant (κ- or λ-) produced by plasma cell dyscrasia.

Cardiac deposition of amyloid substance can infiltrate any cardiovascular structure (**Figure 1**). Infiltration of myocardium and valves is frequent and often becomes the "red flag" that raises the suspicion of CA (**Table 1**) (14-16). LV myocardial amyloid infiltration starts from the base to the apex and results in increased biventricular wall thickness and stiffness, which ultimately leads to hypertrophic restrictive cardiomyopathy with severe impairment of LV diastolic function and longitudinal systolic function (**Figures 1 and 2**) (10). The most prevalent type of HF associated with CA is diastolic HF with preserved left ventricular ejection fraction (LVEF), but nearly one-third of patients present with reduced ejection fraction (17). These features are also common in patients with severe AS, which may mask the presence of a concomitant CA. Aortic valve infiltration by amyloid substance may contribute to the initiation and progression of AS (14,18). Infiltration of amyloid within the atria walls contributes to the high prevalence of supraventricular arrhythmia and leads to atrioventricular electromechanical dissociation, which is associated with increased risk of thromboembolic events and HF decompensation (19,20). Microvascular amyloid infiltration contributes to the myocardial dysfunction and ischemia, therefore explaining the frequent dissociation between the absence of epicardial coronary lesion and the elevated troponin levels (21,22). The conduction disorders caused by amyloid infiltration of conduction tissue often occurs early in the course of the disease (23). Pericardial effusion is also a common feature of CA.

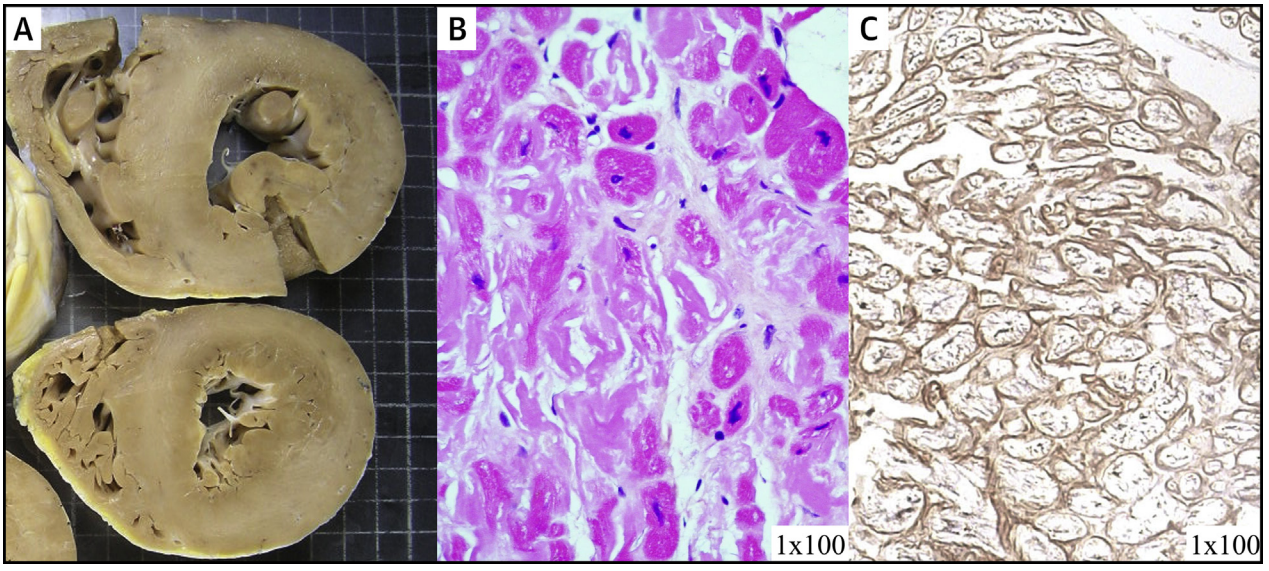
ABBREVIATIONS AND ACRONYMS

AL = light-chain amyloidosis
AS = aortic stenosis
AVR = aortic valve replacement
CA = cardiac amyloidosis
hTTR = hereditary transthyretin
LV = left ventricle
LVEF = left ventricular ejection fraction
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement
TTR = transthyretin
wtTTR = wild-type transthyretin

PREVALENCE OF CA

The exact prevalence of CA in the general population as well as in patients with AS is likely underestimated because of the absence of systematic screening, the complexity of diagnosis confirmation, and the overlap with other cardiac disease phenotypes. The prevalence of CA reported in previous studies for the general population ranges from 5% to 74% (1,2,14,17). This wide interstudy variability is related to differences in population selection criteria and diagnostic modality. The rate of detection of myocardial amyloid at endomyocardial biopsy or autopsy in the general population increases markedly with age: 25% age >85

FIGURE 1 Cardiac Amyloidosis Pathology



(A) Severe biventricular thickening. **(B)** Typical aspect of amyloid extracellular deposition within the myocardium using Congo Red staining. **(C)** Immunofixation confirms transthyretin deposition.

years, 32% age >95 years, and 63% age >100 years (1,2).

With increased information about the prevalence of CA and how to use noninvasive diagnostic tools (7), the identification of TTR-CA in patients with AS became easier. In a retrospective analysis of patients with proven wtTTR-CA, 16% had moderate or severe AS. Studies conducted in patients with AS reported a prevalence of TTR-CA ranging from 4% to 29% (**Table 2**) (5,24–26). Hence, AS and CA frequently coexist in the elderly population.

SCREENING AND DIAGNOSIS OF CA IN PATIENTS WITH AS

Until now, there is no recommendation or consensus on whether patients with AS should be systematically screened for CA. The TTR-CA screening and diagnosis protocol is similar in AS versus in the general population, but it is more challenging because AS and CA share several features (**Figures 2 and 3, Central Illustration**). CA diagnostic tests should be considered in AS patients presenting with suspicion criteria or "Red Flags" for CA (**Table 1**).

SUSPICION CRITERIA FOR CA. In the AS population, TTR-CA occurs more frequently in men than in women (**Tables 2 and 3**). A clinical history of carpal tunnel syndrome (27,28), lumbar spinal stenosis (29), deafness (30), premature pacemaker implantation, disproportionate HF symptoms despite nonsevere AS, and predominant signs of right ventricular (RV) failure should raise the suspicion of TTR-CA. Macroglossia and other soft-tissue manifestations associated with CA are less frequent in TTR-CA than in AL-CA. Electrocardiogram findings in CA patients are not specific, but conduction abnormalities, low voltage despite LV wall thickening, and Q waves without history of myocardial infarction can be observed (**Table 1, Figure 2**, Online Videos 1, 2, and 3) (23).

Biological findings such as elevated N-terminal pro-brain natriuretic peptide levels despite the absence of significant LV systolic dysfunction, or elevated troponin levels without history of coronary artery disease, are also suggestive of CA.

Imaging features mainly observed by transthoracic echocardiography in subjects with CA include (**Table 1, Central Illustration**): disproportionate LV wall thickening and LV diastolic dysfunction relative to AS severity, RV wall thickening, pericardial effusion, bilateral atrial dilatation, myocardial granular sparkling, and impaired LV longitudinal systolic function. A mitral annulus S′ velocity ≤6 cm/s has been shown to be useful to screen for CA in patients with AS and preserved LVEF (5). LV global longitudinal strain measured by speckle tracking is also often markedly

TABLE 1 Demographic, Clinical, Electrocardiogram, Biomarker, and Imaging Criteria to Suspect and Confirm Cardiac Amyloidosis in Patients With Aortic Stenosis

Suspicion criteria—"red flags"	
Demographics	Elderly age ≥65 yrs
	Male
	African origins
Clinical	Heart failure with preserved left ventricular ejection fraction
	Disproportionate heart failure symptoms
	Predominant right ventricular heart failure (edema, ascites)*
	Premature severe conduction abnormalities
	Bilateral/unilateral carpal tunnel syndrome
	Lumbar spinal stenosis
	Deafness
ECG	Discordance between low-voltage and LV wall thickness*
	Pseudo-infarction pattern (Q waves) without history of myocardial infarction*
Blood biomarkers	Chronic elevation of troponin without significant coronary artery disease or chronic renal failure
	Disproportionate NT-proBNP/BNP elevation with aortic stenosis severity in the absence of renal failure
	Severe LV concentric remodeling (RWT >0.5)
	Disproportionate LV wall thickening (≥15 mm) relative to AS severity*
Echocardiography	Disproportionate severity of LV diastolic dysfunction (Grade ≥ 2; E/e'>16) relative to extent of LV hypertrophy
	Moderate/severe pulmonary hypertension
	Severe LV longitudinal systolic dysfunction with apical sparing Mitral S' ≤6 cm/s LV global longitudinal strain ≥−12% Apex/basal longitudinal strain ratio >2*
	RV wall thickening (≥5 mm)*
	Myocardial granular sparkling*
	Atrial septal thickening and biatrial dilatation*
	Atrioventricular valve thickening (>2 mm)*
CMR	Circumferential and extensive late gadolinium enhancement which starts from the subendocardium and predominates at the basal segments*
	Reverse order of T_1 inversion scout sequences*
	Elevated native T_1 mapping (>1,080 ms with 1.5-T scanner) and ECV (>0.58)*
Confirmation criteria	
Bone scintigraphy (for TTR-CA)	Strong cardiac uptake at bone scintigraphy*
	Extracardiac fixation: lung or soft tissue*
Serum/urine monoclonal free light chain protein (for AL-CA)	Monoclonal free light chain in blood and/or urine*
Histology on endomyocardial and/or extracardiac biopsies	Positive Congo red staining*
	Apple-green birefringence when viewed under polarizing microscopy*

*Criteria that are more specific to CA and generally not observed in AS.

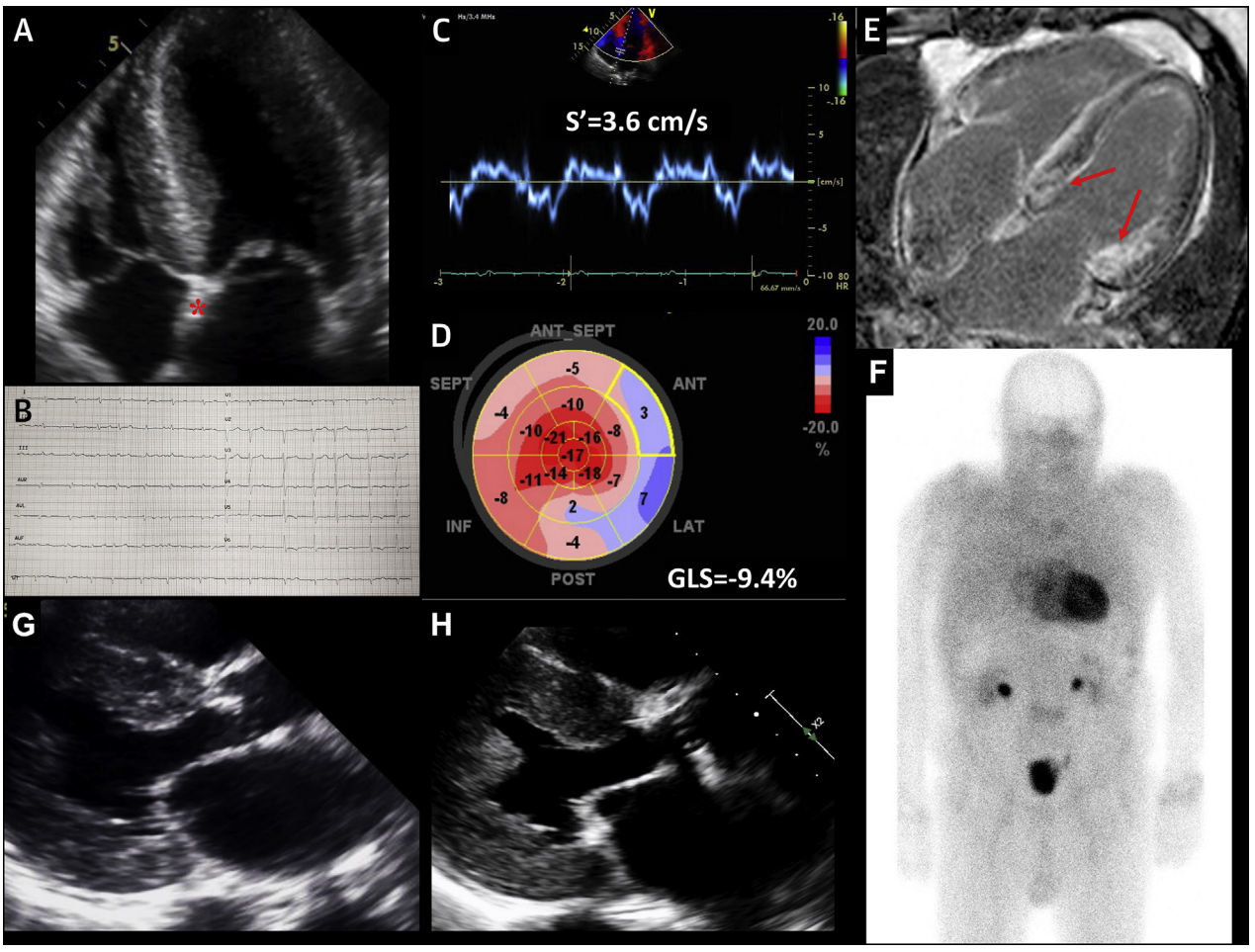
AS = aortic stenosis; BNP = brain natriuretic peptide; CA = cardiac amyloidosis; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ECV = extracellular volume; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; TTR-CA = transthyretin cardiac amyloidosis.

reduced (≥−12%) in patients with CA and is a powerful prognostic maker (10). The LV longitudinal strain is often preserved at the apex in CA, but the apical sparing may also be observed in patients with AS and no CA (**Figures 2 and 3**). The presence of a paradoxical (i.e. preserved LVEF) low-flow, low-gradient AS pattern should raise the suspicion of CA (4,5,25,31).

Cardiac magnetic resonance (CMR) has an incremental value for CA diagnosis and prognosis using late gadolinium enhancement (LGE), native T_1 mapping, and extracellular volume (ECV) sequences (9), but 15% of CMR examinations may be normal in patients with CA (**Table 1**) (32). Typical findings are circumferential LGE within the entire LV subendocardium with a various degree of myocardial extension (**Figure 2**) and a base-to-apex gradient (10,33) as well as elevated native T_1 and ECV values (32,34,35). CMR is useful to distinguish: 1) myocardial extracellular amyloid deposition from diffuse fibrosis in AS patients (**Figures 2 and 3**) (34); and 2) TTR- from AL-CA (36).

CONFIRMATION CRITERIA FOR CA. All the aforementioned findings (**Table 1**) are suggestive of CA but are not sufficient to confirm the diagnosis. The next step is to perform a bone scintigraphy with 99m technetium-labeled bisphosphonates combined with

FIGURE 2 Multimodality Imaging of Typical Features of Cardiac Amyloidosis in a Patient With Severe Aortic Stenosis



(A) Transthoracic echocardiographic (TTE) apical 4-chamber view showing severe left ventricular (LV) hypertrophy with myocardial granular sparkling, atrial septal thickening **(red asterisk)**, and right ventricular hypertrophy (Online Video 1). **(B)** Electrocardiogram showing low voltage despite severe LV hypertrophy. **(C and D)** Severely impaired longitudinal systolic function with apical sparing despite preserved LV ejection fraction (60%). **(E)** Cardiac magnetic resonance showing basal subendocardium late gadolinium enhancement, which extends to the epicardium and to the apex **(red arrows)**. **(F)** Technetium-labeled (^{99m}Tc) hydroxymethylene diphosphonate scintigraphy showing strong cardiac uptake (Grade 3). **(G and H)** TTE parasternal long-axis views prior **(G,** Online Video 2**)** and 1-year post **(H,** Online Video 3**)** transcatheter aortic valve replacement, showing no regression of LV hypertrophy. ANT = anterior; GLS = global longitudinal strain; INF = inferior; LAT = lateral; POST = posterior; SEPT = septal.

search for monoclonal light chain in blood and urine (**Figures 2 and 4, Central Illustration**) (7). An early cardiac to mediastinum retention ratio above 1.21 (37) or a late cardiac uptake grade ≥2 using the Perugini score (38) on bone scintigraphy combined with the absence of monoclonal protein in blood and urine confirm the TTR-CA diagnosis (**Figures 2 and 4**). Genotyping is required to distinguish wtTTR from hTTR (4). The absence of both cardiac uptake on scintigraphy and monoclonal protein in serum/urine analysis make the presence of AL- or TTR-CA very unlikely. All other situations require further evaluation (**Figure 4**). A positive extracardiac biopsy is not sufficient to confirm diagnosis of CA in patients without typical CA features on imaging. Conversely, a negative extracardiac biopsy is not sufficient to exclude the diagnosis in patients with typical CA features on imaging. Within the AS population, the vast majority of CA cases are of TTR type and could thus be diagnosed using bone scintigraphy only. However, given its very poor prognosis in the absence of chemotherapy, AL-CA should be systematically

TABLE 2 Prevalence and Demographic Characteristics of Cardiac Amyloidosis in Series of Patients With Aortic Stenosis Series

Author or Study Name, Year (Ref. #)	Study Context	Diagnosis Modality	N	Prevalence of CA (%)	Male (%)	Mean Age (yrs)	Lower Age Limit (yrs)
Nietlispach et al., 2012 (48)	Autopsy after TAVR	Histology	17	29.0	33	85	76
Longhi et al., 2016 (25)	AS patients referred for AVR (surgical or transcatheter)	Bone scintigraphy when echocardiographic suspicion ("red flags")	43	11.6	80	84	76
Treibel et al., 2016 (24)	AS patients referred for SAVR	Histology: intraoperative biopsy	146	4.1 in whole cohort 6.0% in age >65 yrs	67	75	69
Castaño et al., 2017 (5)	AS patients referred for TAVR	Bone scintigraphy	151	16.0	92	86	≥65*
Cavalcante et al., 2018 (31)	Patients with moderate-severe AS referred to CMR	LGE pattern on CMR	113	8.0 in whole cohort 16.0 in age >74 yrs	89	88	>80
Scully et al., 2018 (26)	Patients with AS referred for TAVR	Bone scintigraphy	101	13.9	50	88	≥75*
ATTRact-AS, 2019 (NCT03029026)	Patients with AS considered for AVR (surgical or transcatheter)	Echocardiography, bone scintigraphy, cardiac CT, CMR, EMB	250	Study is ongoing	NA	NA	≥75*
Amylo-CARTESIAN, 2020 (NCT02260466)	Patients with AS referred for AVR (surgical or transcatheter)	Echocardiography, bone scintigraphy and CMR	180	Study is ongoing	NA	NA	≥70*

*Study inclusion criteria.

AVR = aortic valve replacement; CT = computed tomography; EMB = endomyocardial biopsy; LGE = late gadolinium enhancement; ND = not done; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

screened using serum/urine light chain protein analyses.

ASSESSMENT OF AS SEVERITY IN PATIENTS WITH CA

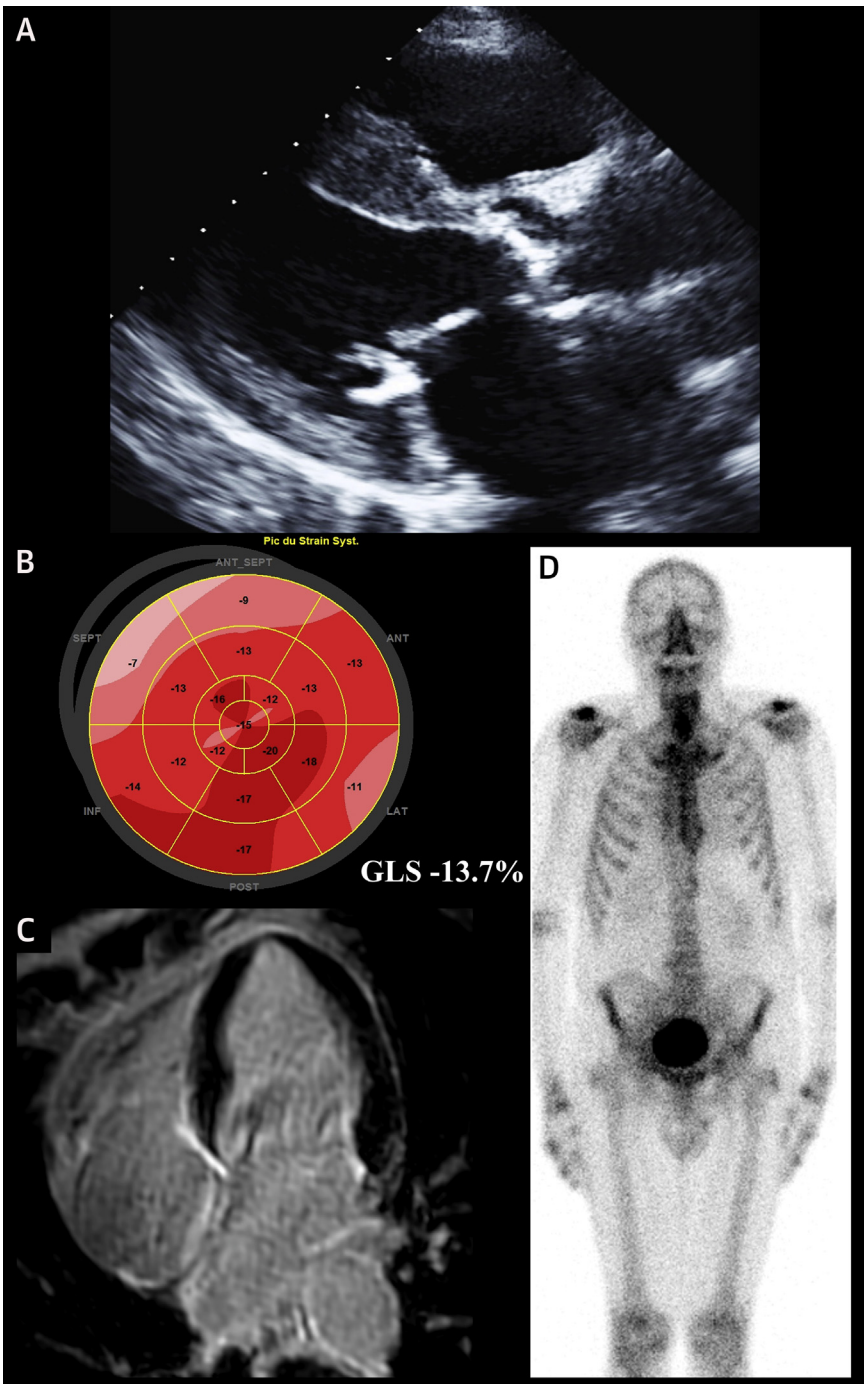
In patients with coexisting CA, AS severity should be assessed according to current guidelines (39,40). AS is graded severe if transthoracic echocardiography shows a high peak aortic jet velocity (≥4 m/s) and/or mean transvalvular pressure gradient (≥40 mm Hg). However, patients with AS and concomitant CA are more likely to present with a low-flow, low-gradient pattern (i.e., AVA ≤1.0 cm^2, mean gradient <40 mm Hg, and stroke volume index <35 ml/m^2) compared with those without CA (30% to 80% vs. <30%) (**Figure 5**) (4,5,25,31). Approximately 50% of patients with CA and low-flow, low-gradient have preserved LVEF, that is, a paradoxical low-flow, low-gradient pattern (4,25). The high prevalence of low-flow state in patients with CA may be explained by the following factors: severe LV concentric remodeling, impairment of diastolic filling, LA remodeling and dysfunction, markedly reduced LV longitudinal systolic function (LV global longitudinal strain ≥−12%), and RV remodeling and dysfunction (4,24). The assessment of AS severity is more challenging in patients with low-flow, low-gradient AS, and additional imaging tests are required to differentiate a true-severe versus a pseudo-severe AS (**Figures 5 and 6**). Dobutamine stress echocardiography may be used to confirm AS severity (peak stress mean gradient ≥40 mm Hg) in patients with low-flow, low-gradient AS and reduced LVEF. However, in patients with CA, dobutamine stress often fails to significantly increase LV outflow and thus provides inconclusive results. Hence, regardless of the levels of LVEF or flow, the quantitation of aortic valve calcium burden using noncontrast CT appears to be the most appropriate imaging modality to confirm AS severity in patients with CA (**Figures 5 and 6, Central Illustration**) (41).

THERAPEUTIC MANAGEMENT OF CA IN PATIENTS WITH AS

Until now, there is no randomized trial and no expert consensus that determines the best management of CA in patients with AS. Management of CA includes general (CHAD-STOP: Conduction and rhythm disorders prevention, High heart rate maintenance, Anticoagulation, Diuretic agents, and STOP ß-receptor and calcium-channel blockers, digoxin, RAA inhibitors) and targeted therapeutic measures (**Figure 6**).

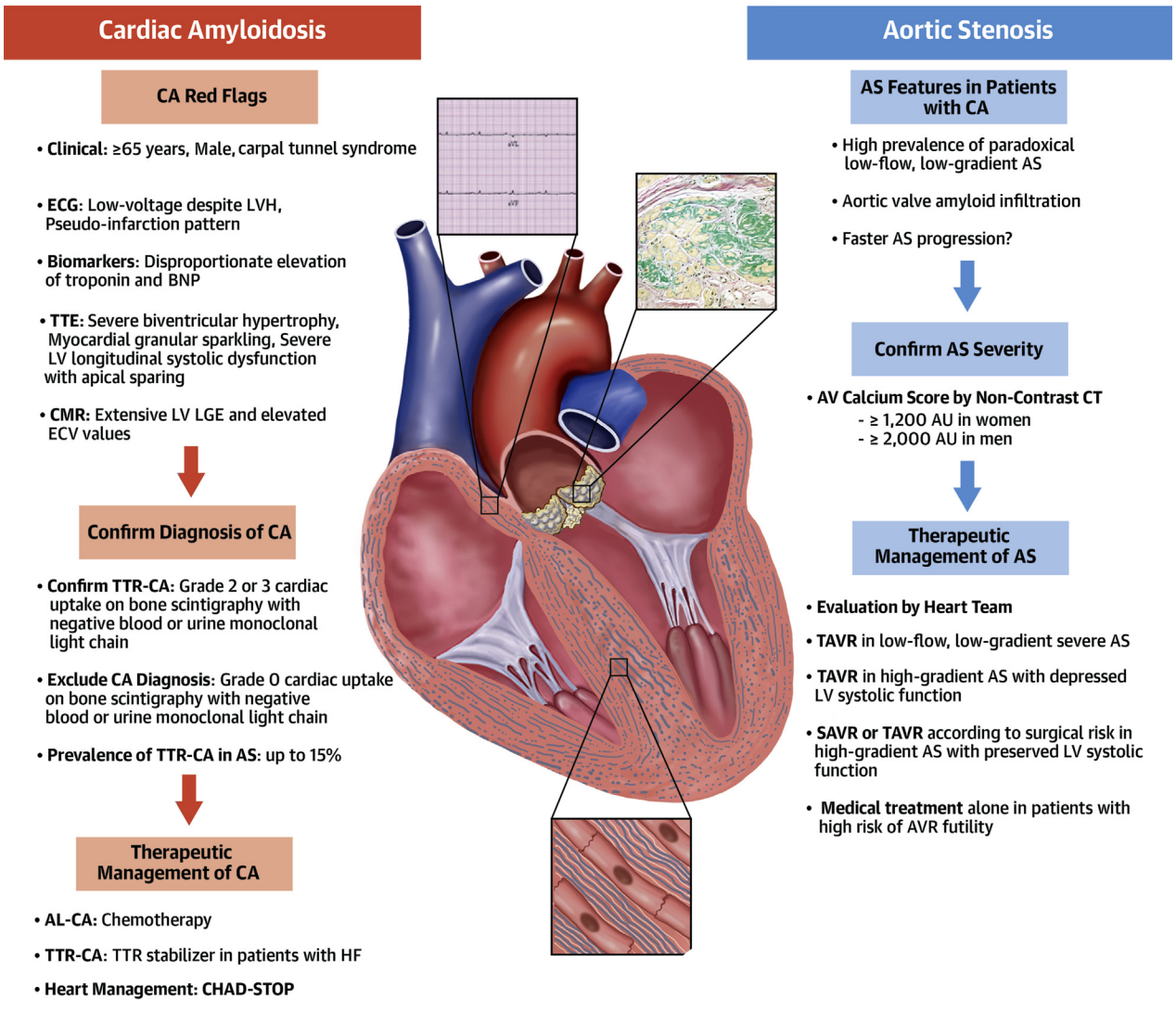
General principles aim to control the consequences of the disease and avoid iatrogenic effects. Medications recommended by the current HF guidelines must be adapted. The amyloid myocardial infiltration often leads to a restrictive cardiomyopathy with severe impairment of LV filling. The ability to increase preload is thus limited, and acceleration of heart rate becomes the sole mechanism to increase cardiac output. Hence, β-receptor and calcium-channel blockers should be stopped to prevent any deleterious negative chronotropic effect. Renin-angiotensin-aldosterone inhibitors should be used with caution because of the risk of severe

FIGURE 3 Multimodality Imaging of a Patient With Severe Aortic Stenosis and No Cardiac Amyloidosis



(A) TTE parasternal long-axis view showing severe LV hypertrophy. **(B)** Speckle tracking imaging showing a moderately depressed LV global longitudinal strain, which predominates in basal segments. **(C)** Cardiac magnetic resonance showing LV hypertrophy without late gadolinium enhancement. **(D)** ^{99m}Tc-hydroxymethylene diphosphonate scintigraphy showing no cardiac uptake. Abbreviations as in Figure 2.

CENTRAL ILLUSTRATION **Diagnostic Confirmations and Therapeutic Managements in Severe Aortic Stenosis Patients With Cardiac Amyloidosis**



Ternacle, J. et al. J Am Coll Cardiol. 2019;74(21):2638–51.

AL = light-chain; AS = aortic stenosis; AV = aortic valve; AVR = aortic valve replacement; BNP = brain natriuretic peptide; CA = cardiac amyloidosis; CHAD-STOP = Conduction and rhythm disorders prevention, High heart rate maintenance, Anticoagulation, Diuretics, and STOP ß-receptor and calcium-channel blockers, digoxin, renin-angiotensin-aldosterone inhibitors; CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiogram; ECV = extracellular volume; GLS = global longitudinal strain; HF = heart failure; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve implantation; TTE = transthoracic echocardiography; TTR = transthyretin.

hypotension, especially in the presence of autonomic nervous system involvement. Diuretic agents are essential to decrease volume overload in symptomatic patients or during HF decompensation, but the dose should be adjusted with caution because an excessive depletion can severely affect cardiac output. Amiodarone can be used in case of arrhythmia, while digoxin should be monitored because of the risk of accumulation in the amyloid fibrils (42). CA patients exhibit a high risk of thromboembolic complications, even in sinus rhythm (20). Anticoagulant therapy should be administered in case of supraventricular arrhythmia, history of systemic embolism, or intracardiac thrombosis. Systematic administration of anticoagulants in all patients with CAS is currently not recommended because of the risk

TABLE 3 Outcome of Patients With Moderate or Severe Aortic Stenosis and Concomitant Cardiac Amyloidosis

First Author, Year (Ref. #)	N	Lower Age Limit (yrs)	Male (%)	Type of Amyloidosis	Type of AVR (n)	Medical Treatment (%)	30-Day Mortality (%)	Late Mortality (%)	Follow-Up Duration
Cavalcante et al., 2018 (31)	9	>80	89	NM	SAVR: 0 TAVR: 4	55.0	TAVR: 50	56	1 yr
Galat et al., 2016 (4)	16	70	81	TTR	SAVR: 9 TAVR: 1	37.5	SAVR: 33 TAVR: 0	44	33 months
Treibel et al., 2016 (24)	6	69	67	TTR	SAVR: 6 TAVR: 0	0.0	SAVR: NM	50	2.3 yrs
Sperry et al., 2016 (49)	27	NM	71	TTR	SAVR: 11 TAVR: 0	59.0	SAVR: NM	37	2 yrs

NM = not mentioned; TTR = transthyretin amyloidosis; other abbreviations as in Table 2.

of bleeding. Because of the high risk of conduction disturbance, pacemaker implantation should be extended to patients with first-degree atrioventricular block, unexplained syncope, and abnormal infra-Hisian conduction. Pacemaker implantation may also be considered before aortic valve replacement (AVR), especially before transcatheter aortic valve replacement (TAVR). Indications for intracardiac defibrillator implantation are still debated (43).

Targeted pharmacotherapies aim at treating the amyloid deposition and are specific to the CA type. AL-CA is a hematological disease with a cardiac tropism and requires chemotherapy associated with a close cardiovascular monitoring because of the high risk of acute HF. In young patients with advanced but stable HF at high risk of unfavorable evolution and without extracardiac comorbidities, cardiac transplantation should be considered (3). However, unlike TTR-CA, AL-CA is rare in patients with AS.

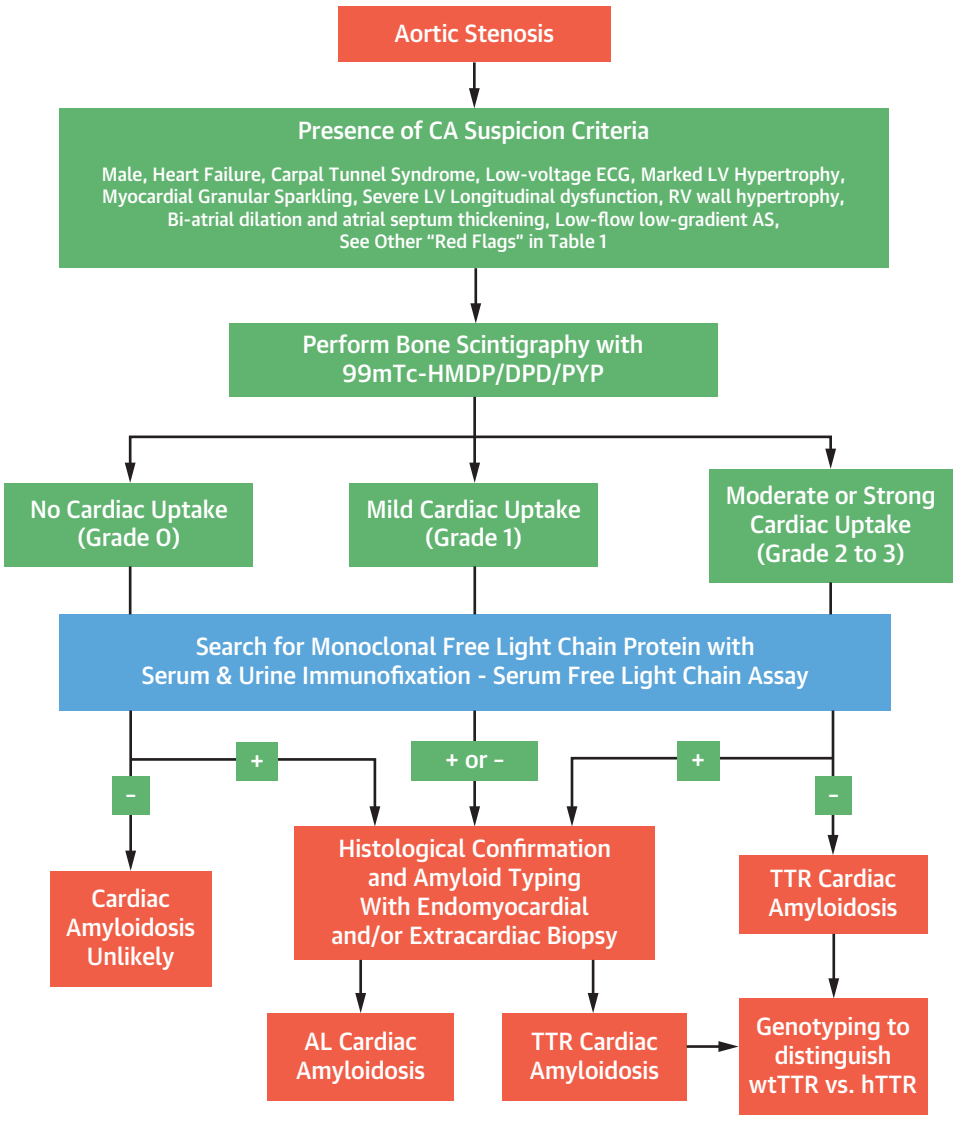
Treatment of TTR-CA has long been limited to double transplantation (heart and liver) in young ATTR-h patients with severe cardiac involvement, whereas no treatment was available in older wtTTR-CA patients. Recently, 2 randomized controlled trials demonstrated the efficacy and safety of new targeted medications, which represent a major advance for the management of TTR-CA (6,44). The ATTR-ACT study investigated the administration of tafamidis, a drug that prevents the tetramer dissociation by a selective and affine binding with transthyretin (6). The protein stabilization avoids misfolding and facilitates its elimination. This study demonstrated a reduction in all-cause mortality and cardiovascular-related hospitalizations at 30 months and improvement in functional status at 6 months with tafamidis compared to placebo in patients with severe CA with wtTTR (75% of patients) or hTTR (25%) (6). The clinical benefit of tafamidis became significant after 18 months and was more pronounced when administered early in the course of the CA disease (New York Heart Association functional class I and II).

The APOLLO study using Patisiran, a small interfering ribonucleic acid that blocks the liver production of transthyretin (normal and mutated), showed interesting results in patients with hTTR neuropathy (45). A subanalysis in the CA subset showed a reverse cardiac remodeling with an improvement in cardiac output and decrease in N-terminal pro-brain natriuretic peptide levels, but without significant reduction in mortality or rehospitalization (44).

THERAPEUTIC MANAGEMENT OF AS IN PATIENTS WITH CA

There are very few data on the outcome and therapeutic management of patients with AS and concomitant CA (**Table 3**). Most studies reported a high risk of mortality and nonimprovement in functional status following AVR in patients with severe AS and CA (4,24,31,46–50). Studies in small number of patients (n <30) suggest that outcome of patients with AS and CA may be better with TAVR versus surgical aortic valve replacement (SAVR) (4). Patients with CA may be at higher risk for several procedural complications during or early after TAVR due to the fragility of amyloid infiltrated tissue (46,51). Screening for CA should also be performed in patients with nonsevere AS and unexplained HF symptoms to adjust HF therapy and institute TTR stabilizer treatment in case of confirmed CA diagnosis. Once the presence of severe AS is confirmed in a patient with CA, the different therapeutic options (i.e. SAVR, TAVR, or medical treatment) should be discussed by a multidisciplinary heart team including geriatricians and cardiomyopathy specialists (**Figure 6, Central Illustration**). The factors that were associated with poor prognosis in patients with CA and with futility of

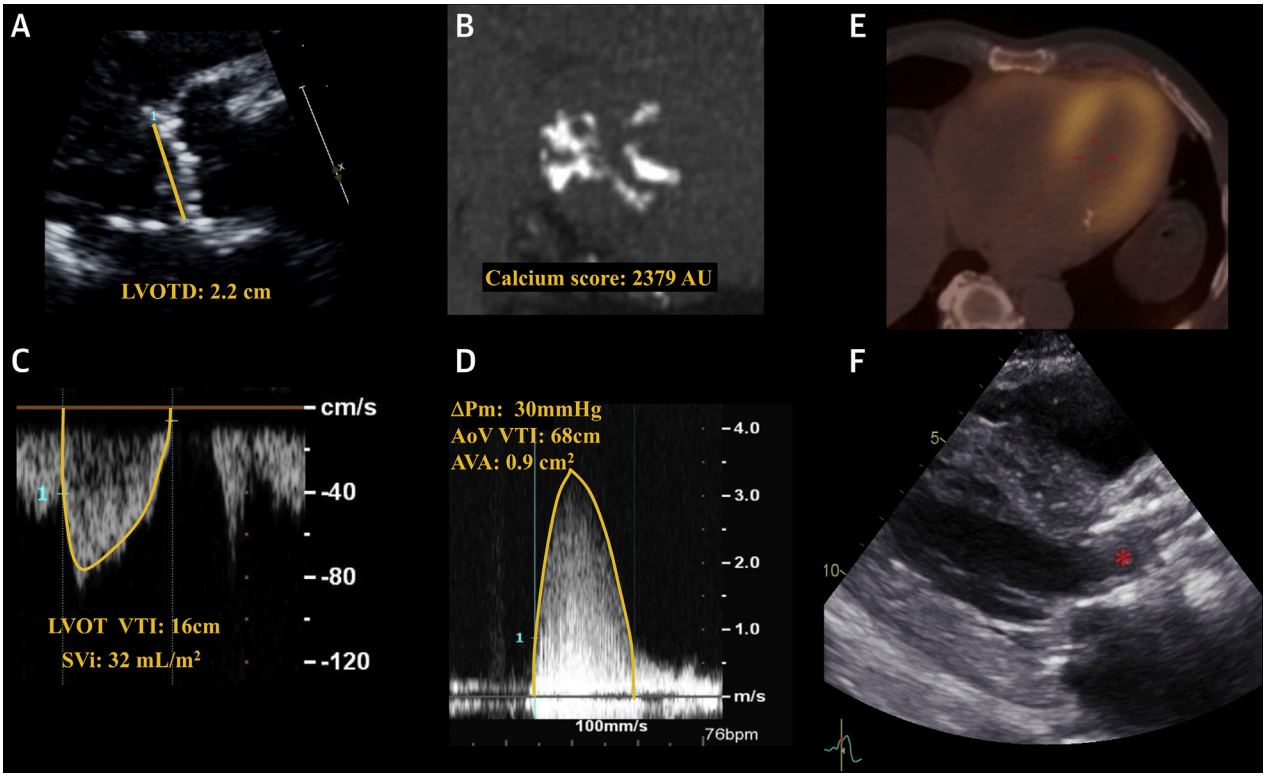
FIGURE 4 Proposed Algorithm for the Diagnosis of Cardiac Amyloidosis in Patients With Aortic Stenosis



^{99m}Tc-HMDP/DPD/PYP = technetium-labeled hydroxymethylene diphosphonate/3,3-diphosphono-1,2-propanodicarboxylic acid/pyrophosphate; AL = light-chain; AS = aortic stenosis; CA = cardiac amyloidosis; ECG = electrocardiogram; hTTR = hereditary transthyretin; LV = left ventricle; RV = right ventricular; TTR = transthyretin; wtTTR = wild-type transthyretin.

AVR (especially SAVR) in patients with AS and CA include: depressed LVEF (<50%), severely reduced global longitudinal strain (≥-10%), restrictive pattern (Grade III diastolic dysfunction), moderate-to-severe low-flow state (stroke volume index <30 ml/m^2), and low-gradient AS (4,24). The heart team should take into account these factors as well as the comorbidities, the patient's functional status, frailty, and life expectancy to select the best therapeutic option (**Figure 6**). If the heart team considers that AVR is very likely to be futile, HF therapy should be optimized and pharmacotherapy with tafamidis should be instituted. Otherwise, AVR should be considered in patients with severe AS and CA, and TAVR may be preferred in those with intermediate or high surgical risk, low-flow, low-gradient AS, depressed LVEF, markedly reduced global longitudinal strain, and/or severe low-flow state (**Figure 6**). TTR stabilization (e.g., tafamidis) therapy should be instituted as soon as a diagnosis of TTR-CA is confirmed.

FIGURE 5 Low-Flow, Low-Gradient Aortic Stenosis in a Patient With Transthyretin Cardiac Amyloidosis



Calcium scoring assessment using transthoracic echocardiography **(A)** and cardiac computed tomography **(B)**. Hemodynamic assessment of aortic stenosis by transthoracic echocardiography **(C and D)**. Transthyretin cardiac amyloidosis confirmation using ^{99m}Tc-HMDP scintigraphy **(E)**. Transthoracic echocardiography evaluation after transcatheter aortic valve replacement **(red asterisk, F)**. AoV = aortic valve; AVA = aortic valve area; LVOTD = left ventricular outflow tract diameter; SVi = stroke volume index; VTI = velocity time integral; ΔPm = mean transaortic pressure gradient.

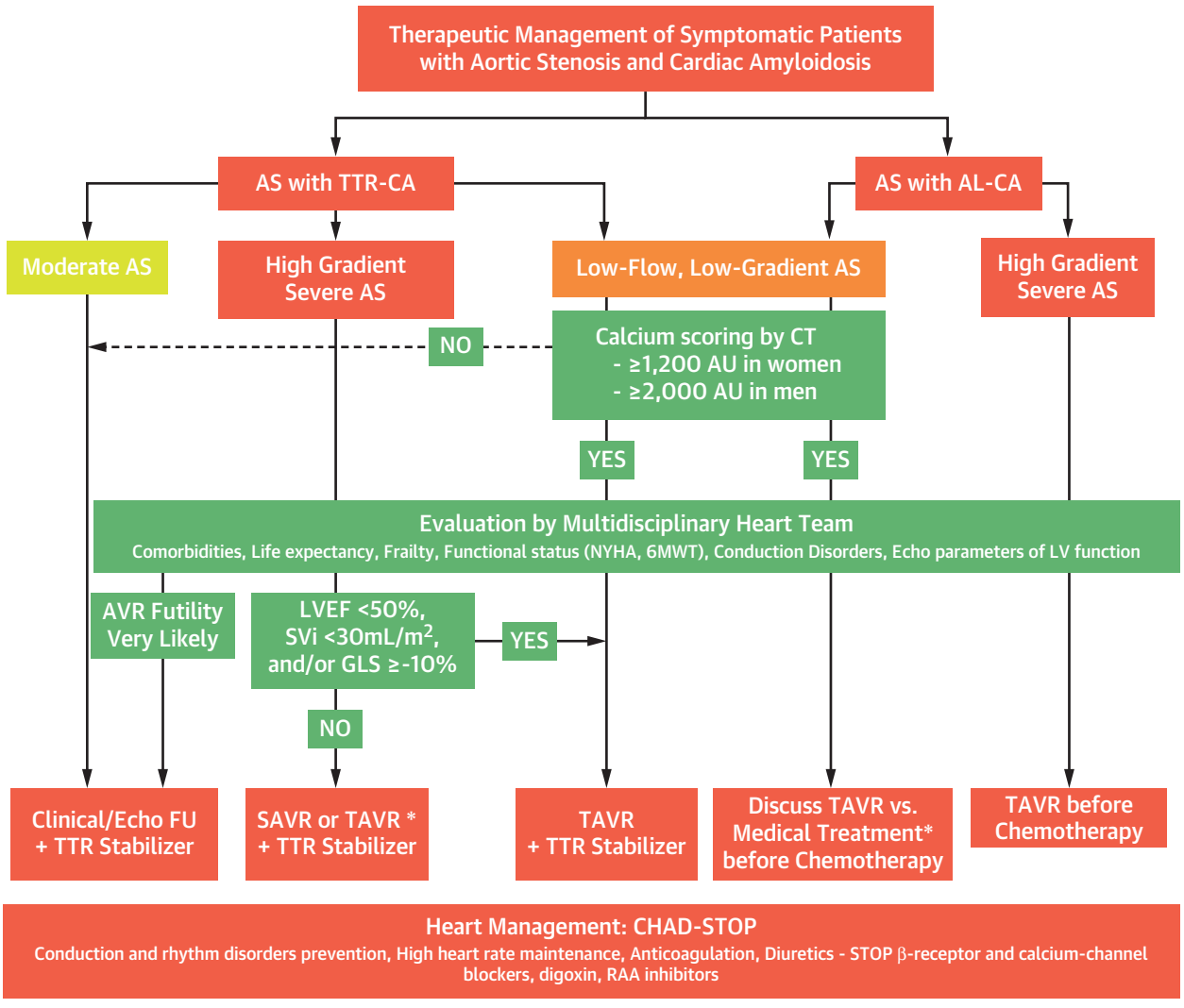
FUTURE PERSPECTIVES AND UNSOLVED QUESTIONS

Given that noninvasive diagnostic methods and pharmacotherapies have recently become available for CA, there is now an urgent need to conduct studies to determine the optimal approaches for the screening and treatment of CA in patients with AS. Ultimately, specific guidelines should be developed to guide the heart team in the decision making for the type (SAVR, TAVR, tafamidis, chemotherapy, and so on) and timing of treatment in symptomatic patients with severe AS and concomitant CA. The ongoing prospective Amylo-CARTESIAN (Prevalence and Post-surgical Outcomes of CARdiac Wild-type TransthyrEtin amyloidoSIs in Elderly Patients With Aortic steNosis Referred for Valvular Replacement) (NCT02260466) and ATTRact-AS (The Role of Occult Cardiac Amyloid in the Elderly With Aortic Stenosis) (NCT03029026) studies will provide a comprehensive and contemporary portrait of the prevalence, management, and outcome of CA in AS patients referred for an AVR (Table 2). Further studies are needed to determine if patients with CA are at higher risk for structural valve deterioration following biological AVR. Future approaches based on artificial intelligence and machine-learning could improve and facilitate the systematic screening of CA in patients with AS by the automatic detection of CA red flags (Table 1) (52). Pharmacotherapies using small interfering ribonucleic acid could potentially be more efficient than protein stabilization therapies in patients with advanced CA. However, the efficacy and safety of such therapies remain to be demonstrated.

CONCLUSIONS

Up to 15% of patients with AS may have TTR-CA. The presence of red flags should raise the suspicion of CA and trigger additional tests, including bone scintigraphy and serum free light chain assay to confirm the diagnosis of CA (Central Illustration). Patients with

FIGURE 6 Proposed Algorithm for the Management of Patients with Symptomatic Aortic Stenosis and Cardiac Amyloidosis



This algorithm is based on the limited published data on patients with AS and/or CA, is not supported by current guidelines, and will need to be further validated in future studies. *Choice between SAVR and TAVR according to the surgical risk stratification proposed in the current valvular heart disease guidelines. *Medical treatment should be discussed in patients with severe comorbidities to avoid futility. 6MWT = 6-minute walk test; AL = light chain; AS = aortic stenosis; AVR = aortic valve replacement; CA = cardiac amyloidosis; CT = computed tomography; FU = follow-up; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; NYHA = New-York Heart Association; RAA = renin-angiotensin-aldosterone; SAVR = surgical aortic valve replacement; SVi = stroke volume index; TAVR = transcatheter aortic valve replacement; TTR = transthyretin.

AS and CA frequently harbor a low-flow, low-gradient pattern and thus require calcium scoring by CT to confirm AS severity. Symptomatic patients with severe AS and concomitant CA should be carefully evaluated by the Heart Team. TAVR is often preferred to SAVR in patients with AS and CA given that they are generally at high surgical risk. The recent emergence of targeted therapies for TTR-CA may dramatically transform the therapeutic management and outcome of patients with AS and CA.

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KEY WORDS aortic stenosis, cardiac amyloidosis, Doppler echocardiography, heart failure, surgical aortic valve replacement, tafamidis, transcatheter aortic valve replacement, transthyretin

APPENDIX For supplemental videos, please see the online version of this paper.