Acta Cardiol Sin 2023;39:511–543
Consensus
doi: 10.6515/ACS.202307_39(4).20230610A

2023 Expert Consensus of the Taiwan Society of Cardiology on the Diagnosis and Treatment of Cardiac Amyloidosis

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Cardiac amyloidosis is one form of systemic amyloidosis caused by abnormal amyloid fibrils deposited in the extracellular space of the myocardium causing heart failure because of restrictive cardiomyopathy and conduction disturbances. The incidence and prevalence of cardiac amyloidosis are higher than previously noted, particularly among special populations. The most common forms of cardiac amyloidosis are light chain and transthyretin amyloid cardiomyopathy. Even though more than 70% of patients with systemic amyloidosis have cardiac amyloidosis, the diagnosis is often delayed, suggesting significant gaps in the knowledge of cardiac amyloidosis and a lack of multidisciplinary teamwork in our daily practice.

The Taiwan Society of Cardiology Heart Failure Committee organized experts to draft the "Expert Consensus on the diagnosis and treatment of cardiac amyloidosis." This statement aims to help clinicians and healthcare professionals improve early diagnosis and management of cardiac amyloidosis in Taiwan. The expert panel met virtually to review the data and discuss the consensus statements. Our review provided practical information about diagnostic methods and algorithms, clinical clues and red-flag signs, cardiac amyloidosis per se and its comorbidities treatment modalities, and follow-up plans for asymptomatic transthyretin gene carriers.

We especially innovate two acronyms, "HFpEF MUTED CALL" and "HFmrEF MUST COUNT", to help in the early diagnosis and screening of transthyretin amyloid cardiomyopathy as shown in the Central Illustration.

Key Words: Amyloidosis • Cardiac • Heart failure • Hypertrophic cardiomyopathy

Received: February 15, 2023 Accepted: June 10, 2023

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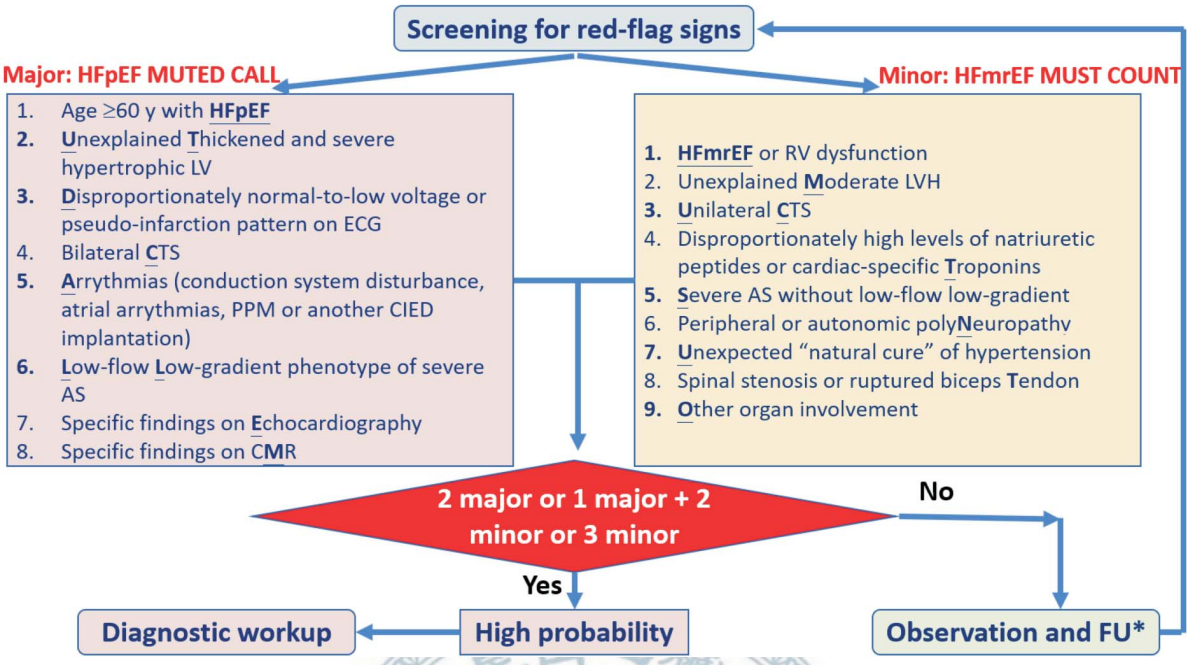

Central Illustration. *"HFpEF MUTED CALL" and "HFmrEF MUST COUNT" algorithm to help in the early diagnosis and screening of transthyretin amyloid cardiomyopathy. * Further diagnostic workup may still be considered at the physician's discretion. AS, aortic stenosis; CIED, cardiovascular implantable electronic device; CMR, cardiac magnetic resonance; CTS, carpal tunnel syndrome; ECG, electrocardiogram; FU, follow-up; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; PPM, permanent pacemaker; RV, right ventricular.*

Abbreviations

^{123}I-MIBG	^{123}Iodine-metaiodobenzylguanidine
^{99m}Tc-DPD	^{99m}Technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid
^{99m}Tc-PYP	^{99m}Technetium-labeled pyrophosphate
AF	Atrial fibrillation
AL-CM	Immunoglobulin light chain amyloid cardiomyopathy
AS	Aortic stenosis
ATTR	Transthyretin
ATTR-ACT	Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRm	Mutant transthyretin amyloidosis
ATTRv	Variant transthyretin amyloidosis; hereditary transthyretin amyloidosis
ATTRwt	Wild-type transthyretin amyloidosis
BNP	B-type natriuretic peptide
CA	Cardiac amyloidosis
CMR	Cardiac magnetic resonance imaging
CTS	Carpal tunnel syndrome
ECG	Electrocardiogram
ECV	Extracellular volume
EF	Ejection fraction
FLC	Free light chain
H/CL	Heart/contralateral lung
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HMDP	Hydroxymethylene diphosphonate
LGE	Late gadolinium enhancement
LV	Left ventricular
NT-proBNP	N-terminal pro-B-type natriuretic peptide
ROI	Region of interest
β2M	β2-microglobulin

INTRODUCTION

Amyloidosis comprises a group of progressive infiltrative disorders characterized by the localized or systemic deposition of insoluble amyloid fibrils in the extracellular spaces of various tissues and organs. Cardiac amyloidosis (CA) is one form of systemic amyloidosis caused by abnormal amyloid fibrils deposited in the extracellular space of the myocardium causing heart failure (HF) because of restrictive cardiomyopathy and conduction disturbances. The most common forms of CA are light chain amyloid cardiomyopathy (AL-CM) and

transthyretin amyloid cardiomyopathy (ATTR-CM). Even though more than 70% of patients with systemic amyloidosis have CA, cardiologists often delay the diagnosis, suggesting significant knowledge gaps in CA and a lack of multidisciplinary teamwork in our daily practice.

Therefore, the Taiwan Society of Cardiology Heart Failure Committee organized experts to draft the "Expert Consensus on the diagnosis and treatment of cardiac amyloidosis." This consensus aims to aid clinicians and healthcare professionals in familiarizing themselves with CA's epidemiology, diagnosis, and management.

DEFINITION AND CLASSIFICATION OF CARDIAC AMYLOIDOSIS

Given non-specific clinical presentations and lacking optimal diagnostic tools, cardiac amyloidosis is a rare disease frequently underdiagnosed or misdiagnosed.[1] With the improvement of nuclear images and the diagnostic platform of "myocardial biopsy free" to date, we have a chance to explore the detailed pathophysiology, prevalence, and management of cardiac amyloidosis.[2]

Definition of cardiac amyloidosis

Amyloidosis is caused by misfolding proteins from β-sheet structured amyloid fibrils, resulting in multiple organ dysfunction.[2,3] Despite more than 30 proteins capable of aggregating amyloid in vivo, only nine amyloidogenic proteins accumulate in the myocardium and cause significant cardiac disease (Figure 1).[3]

Classification of cardiac amyloidosis

In contrast to some forms of misfolded proteins, including AApoAI, AApoAII, AApoAIV, and AGel, most plasma cell dyscrasia-induced monoclonal immunoglobulin light chains or liver-synthesized transthyretin (ATTR), either in autosomal dominant hereditary (variants in the transthyretin gene *TTR*; ATTRv) or acquired (wild-type transthyretin protein;ATTRwt) form are frequently depositing in the myocardium and results in cardiac hypertrophy, dysfunction, and conduction abnormalities (Table 1).[2-4] ATTR amyloid protein, previously termed prealbumin, includes transportation of the hormone thyroxine and retinol-binding protein.[5] In addition to myocardial involvement, ATTR amyloid proteins frequently infiltrate nerve systems, contributing to autonomic dysfunction and peripheral neuropathy.[6,7] Different from

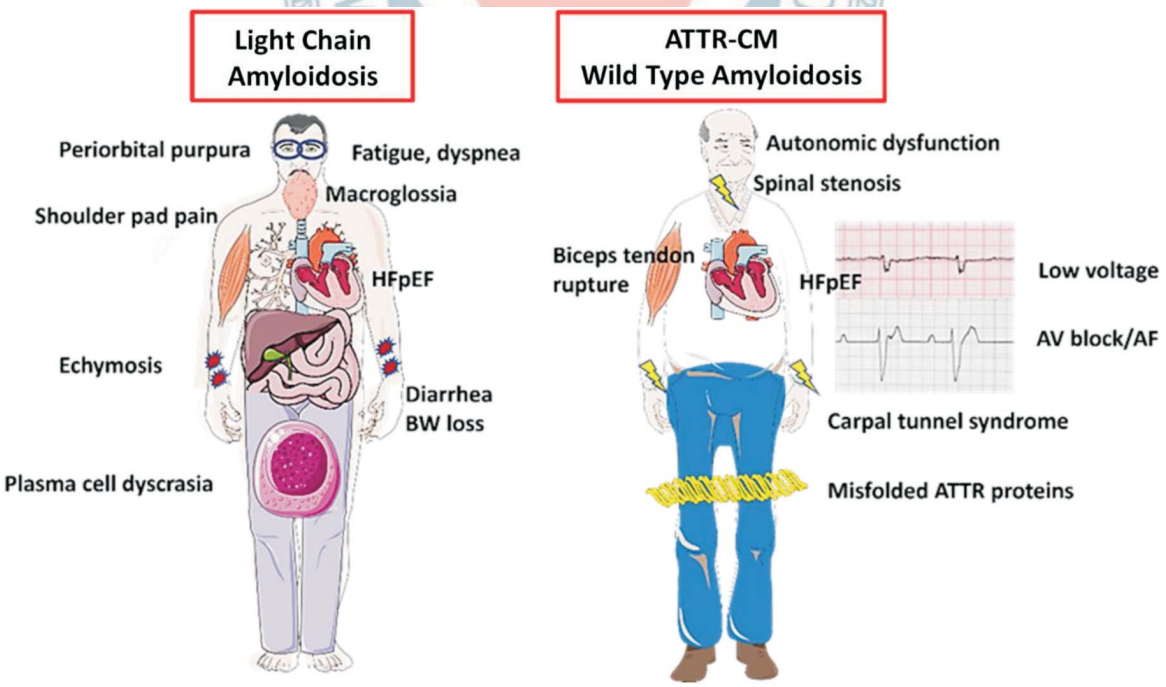

Figure 1. *Definition of cardiac amyloidosis. AF, atrial fibrillation; ATTR, transthyretin; ATTR-CM, transthyretin amyloid cardiomyopathy; AV, atrioventricular; BW, body weight; HFpEF, heart failure with preserved ejection fraction.*

Table 1. Classification of amyloidosis with cardiac involvement

	Main disorders	Amyloidogenic proteins	Main organ involvement	Extra-cardiac presentations	Outcomes and management
AL	Plasma cell dyscrasia	Light chain (Plasma cell dyscrasia)	Heart (~70%), kidney (~70%), liver (~40%), nerve (~20%)	Fatigue, ecchymosis, shoulder pad pain, Macroglossia, diarrhea	Chemotherapy, ASCT
ATTRv	Inherited ATTR gene mutation	Transthyretin	Nerve (major, ~70%), heart (30~100%), kidney (~20%)	Autonomic dysfunction, Spinal stenosis, CTS	TTR stabilizer, oligonucleotide therapy, liver transplantation
ATTRwt	Aging	Transthyretin	Heart (100%), kidney (~20%), nerve (~20%)	Spinal stenosis, CTS, Biceps tendon rupture	TTR stabilizer
AA	Systemic or inflammatory diseases	Serum amyloid A	Kidney (major, ~70%), heart (~5%), liver (~20%)	Nephropathy, hepatomegaly	Control of inflammatory disease
Aβ2M	Hemodialysis	β2-microglobulin	Heart (~80%), nerve (~16%),	CTS	No specific therapy
HGA	AD inherited form	Gelsolin	Nerve (~70%), eyes (~80%), skin (~80%), heart (~5%)	Cranial and peripheral neuropathy, corneal lattice dystrophy, cutis laxa (loose skin)	No specific therapy (similar life scan)

AA, serum amyloid A amyloidosis; AD, autosomal dominant; AL, amyloid light-chain; ASCT, autologous stem cell transplant; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; Aβ2M, β2-microglobulin; CTS, carpal tunnel syndrome; HGA, hereditary gelsolin amyloidosis; TTR, transthyretin.

the inherited nature, serum amyloid A (AA) amyloidosis is related to chronic inflammatory diseases such as rheumatoid arthritis, vasculitis syndrome, and other autoimmune diseases. At the same time, instead of the heart, the kidney is the most common organ system involved in this form.[7,8] Also, among patients under long-term hemodialysis or peritoneal dialysis, myocardial accumulation of amyloid fibrils from β2-microglobulin (β2M).[7,9] In addition to cardiac hypertrophy, patients with β2M amyloidosis frequently presented with carpal tunnel syndrome (CTS).[9] Lastly, hereditary gelsolin amyloidosis causes various ophthalmologic, neurologic, and cutaneous symptoms.[10] Given that renal and cardiac manifestations are rare, patients with hereditary gelsolin amyloidosis have a similar lifespan to those free from amyloidosis.[10]

DIAGNOSIS OF ATTR CARDIAC AMYLOIDOSIS

ATTR-CM is an important but relatively rare cause of HF. However, its true incidence is frequently under-recognized. Its prevalence could be high – up to 16% in special populations such as those with HF with preserved ejection fraction (HFpEF) and aortic stenosis (AS).[11,12] The most crucial step in diagnosing the disease is to suspect it based on the patient's clinical presentation and use proper diagnostic tools to confirm the diagnosis. Since disease-modifying medication has been developed and approved for the treatment of ATTR-CM, the clinician should be aware of this disease and facilitate recognition of it. Once CA is suspected, a further diagnosis could be reached through either noninvasive methods such as nuclear scintigraphy, the free light chain (FLC) test,[7,13,14] and genetic testing, or invasive methods such as endomyocardial biopsy, which is considered to be the gold standard for the diagnosis of ATTR-CM.[15]

Special populations that may be affected

The deposition of misfolded protein fragments in different organs is the picture of amyloidosis. Various systemic symptoms/signs depend on the organs involved. Patients with typical systemic conditions such as nephrotic syndrome, peripheral neuropathy, plasma cell dys-

crasia, or a chronic systemic inflammatory condition present with cardiac symptoms may have CA. CA can be identified in 70% of light chain amyloidosis patients, almost all ATTRwt patients, and variable frequencies of ATTRv patients, depending on the underlying mutation.[7,16,17]

There are special populations that may be affected by CA.[17,18]

All patients with established or suspected non-cardiac amyloidosis

These include:

- Patients presenting with measurable paraprotein.
- Patients with established or suspected light chain amyloidosis.
- Patients with established or suspected amyloid-related nephropathy.
- Patients with established or suspected amyloid-related polyneuropathy or autonomic dysfunction.
- Patients with bilateral CTS, lumbar spinal stenosis, and/or spontaneous biceps tendon rupture.

Light chain amyloidosis is the most common type, with a prevalence of = 0.3 per 100,000 of the general population; it primarily affects the heart, kidneys, bone marrow, skin, and liver. It occurs predominantly in males, with an age peak of 60-69 years. CA can be identified in 70% of patients with light chain amyloidosis. The substantial mortality rate is 50% yearly after the first cardiac decompensation.[17]Patients with AL-CM commonly present with HF and multiorgan involvement, such as hepatomegaly, peripheral and autonomic neuropathy, nephrotic syndrome, macroglossia, and periorbital purpura.[19]

Wild-type ATTR-CM (ATTRwt-CM) is seen predominantly in males and older adults, with an average age of 74 years; however, rare individuals are diagnosed in their 40s.[2] Bilateral CTS, lumbar spinal stenosis, and spontaneous biceps tendon rupture are more frequently associated with ATTRwt-CM than other CAs (Figure 2). CTS is a common initial manifestation, involving ~ 50% of ATTRwt-CM patients and often preceding overt ATTR-CM by an average of 5-10 years.[2] Spontaneous biceps tendon rupture has been reported in 33% of ATTRwt-CM patients. Transthyretin amyloid deposits in the ligamen-

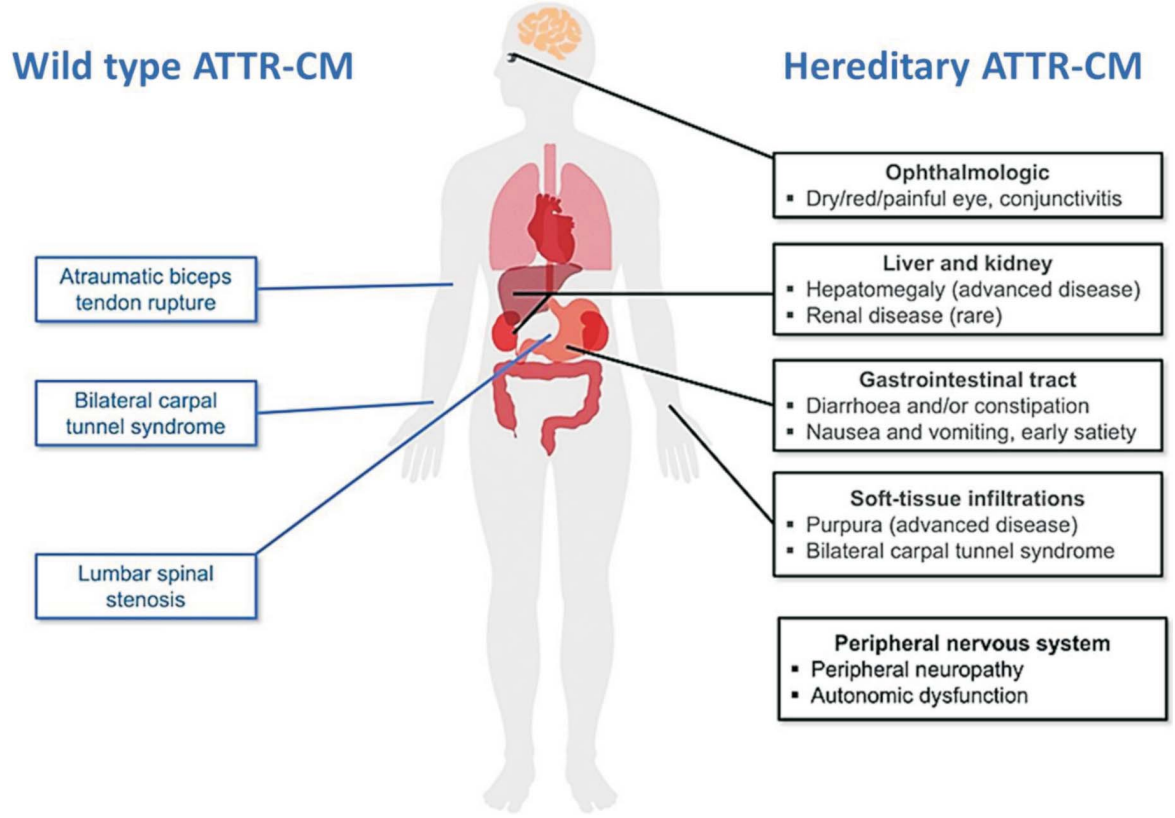

Figure 2. *Non-cardiac manifestations of transthyretin amyloid cardiomyopathy. ATTR-CM, transthyretin amyloid cardiomyopathy.*

tum flavum may be related to the pathogenesis of lumbar spinal stenosis in elderly patients, with incidence increasing with age.[20-22] However, ATTRv-CM patients commonly show peripheral sensorimotor neuropathy with motor impairment and neuropathic pain, and autonomic dysfunction includes gastrointestinal dysautonomia followed by weight loss and orthostatic hypotension.[17]

Patients with hypertrophic cardiomyopathy (HCM) phenotype of unknown origin

This particularly applies to HCM patients with:

- Old age (> 65 years).
- HFpEF and an HCM phenotype.
- AS, particularly with (paradoxical) low-flow/low-gradient pattern.
- Electrocardiogram (ECG) with atrial fibrillation (AF), atrioventricular block, discordant low QRS voltage, pseudo-infarction pattern.

Concentric left ventricular hypertrophy (LVH) is a prominent characteristic of cardiac amyloidosis. Further evaluation should be considered when it is found in elderly patients with common cardiac syndromes like HFpEF, HCM, or severe AS, particularly among those undergoing transcatheter aortic valve replacement.[18] In several autopsy studies, increasing prevalence of ATTRwt myocardial deposits with age was noted, as high as 20-25% in octogenarians and 37% in those > 95 years of age.[2] In an autopsy study of 109 patients with an antemortem diagnosis of HFpEF, 17% had ATTRwt myocardial deposits, with 5% having moderate to severe interstitial deposition consistent with HF due to senile systemic amyloidosis.[23] Furthermore, the incidence of ATTRwt deposits dramatically increased to 40% in patients aged > 80, with male predominance. Left ventricular (LV) ATTRwt deposition was not observed at autopsy in patients diagnosed with HFpEF before 65 years of age; but was very common at autopsy in those who were ≥ 80 years of age at the time of HFpEF diagnosis. One study in the United Kingdom showed that in 211 Afro-Caribbean patients presenting with HF, this was due to cardiac amyloidosis in 11.4% of the patients. The ATTRv V122I variant was a relatively common cause (8.5%) of HF in Afro-Caribbean patients presenting to the general HF clinic and was the worst prognosis compared with the other causes of HF in Afro-Caribbean and Caucasian patients.[24] The prevalence of CA among patients with severe AS undergoing surgical valve replacement ranged from 6% to 12%;[2] in patients undergoing transcatheter aortic valve replacement, it was 8-16%; and in patients with HFpEF, it was 13-17%.[17] Furthermore, it was estimated that up to 16% of the degenerative AS population and up to 30% of the subset with (paradoxical) low-flow, low-gradient pattern may have cardiac amyloidosis.[25,26] A report also revealed that 5% of patients diagnosed with HCM have ATTRv-related familial CA in France.[27] This study did not assess the presence of ATTRwt-CM, likely the most common phenocopy of HCM in older adults. In addition, a retrospective analysis in a large cohort of ATTRwt patients revealed an asymmetric hypertrophy pattern was 23%.[21] Table 2 summarizes the reported prevalence of cardiac

Table 2. The reported prevalence of cardiac amyloidosis with different presentations

Conditions	Any CA	ATTRwt	ATTRv
HFpEF	13-17%	17% ATTR deposits (autopsy); 5% moderate to severe deposits; > 80 y 40%, male predominant; < 65 y 0%	Varying levels of cardiac involvement by different TTR variants
HF	11.4% in Afro-Caribbean patients, UK		8.5% (V122I) in Afro-Caribbean patients, UK
Severe AS for surgical valve replacement	6-12%		
TAVR	8-16%		
Degenerative AS	16%		
Low-flow, low-gradient pattern AS	30%		
HCM			5%, France

AS, aortic stenosis; ATTRv, hereditary transthyretin amyloid cardiomyopathy; ATTRwt, wild type transthyretin amyloid cardiomyopathy; CA, cardiac amyloidosis; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; TAVR, transcatheter aortic valve replacement; TTR, transthyretin; UK, United Kingdom; y, year.

amyloidosis with different presentations. Conduction system disturbances, such as atrioventricular block and AF, are more frequently observed in patients with ATTRwt than those with AL-CM.[7] It has been shown that AF (≤ 67%) and a pseudo-infarct pattern (≤ 71%) were the most common ECG findings.[7,28] However, atrial arrhythmias and a progressive decline in effort tolerance are difficult to definitively attribute to amyloidosis because they also occur commonly with advancing age.[29] About half the patients with CA present a low voltage ECG pattern, but there is a lower prevalence (~ 13-40%) in those with ATTR-CM.[7,28,30] Low QRS voltage is only observed in the later stages of amyloidosis. Light chain toxicity might be attributable to the higher prevalence of low voltage in AL-CM compared with ATTR-CM.[31] In ATTRv, different *TTR* variants are associated with varying levels of cardiac involvement.[4]

Clinical clues and red-flag signs of ATTR-cardiomyopathy

ATTR-CM is commonly underdiagnosed or misdiagnosed because it poses nonspecific symptoms and clinical presentations and is usually considered a rare disease.[2,4] Nevertheless, some clinical clues should be considered to trigger a further evaluation for ATTR-CM (Table 3).

Clinical clues

1. **HFpEF:** patients with HFpEF, particularly men aged ≥ 60 years, according to the results of a retrospective analysis of 67 patients (77.6% male; 85% with preserved left ventricular ejection fraction [LVEF]) with ATTRv A97S polymorphism amyloidosis in Taiwan; mean age at diagnosis is 65.1 ± 6.2 years and 25 patients (37.3%) develop HF symptoms during follow-up.[28] A retrospective analysis of 360 patients in the United States diagnosed with ATTRwt-CM with a median age of 75.5 years, 91% were male, and the median LVEF was 51%, revealed that presenting signs and symptoms suggestive of HF were found in 67% of patients.[32] Another retrospective analysis of 99 patients with ATTRwt-CM in the United Kingdom showed that 57% of patients were found to have HF functional class ≥ 2.[33] The median age of diagnosis was 73 years, 88.8% was male, and mean LVEF was 46.6 ± 12.8%.[33] A prospective study conducted in Spain screening all consecutive patients (age ≥ 60 years) admitted with HFpEF demonstrated that ATTRwt-CM was underdiagnosed and accounted for a significant number of patients with HFpEF (13%).[11] Although the elderly are prone to have HFpEF, ATTR-CM should always be included on the differential diagnosis list for HFpEF, especially when other clinical clues and red-flag signs are present.
2. **Unexplained LVH:** LVH is commonly observed in patients with ATTR-CM, owing to deposits of amyloid fibrils in the heart. Lai et al. found 82% of Taiwan patients with ATTRv A97S polymorphism amyloidosis met LVH criteria.[28] In addition, in a small Taiwanese study, all patients with ATTRv A97S polymorphism amyloidosis manifested LVH and mimicked HCM without other causes.[34] Results from an earlier analysis of five patients with ATTRv A97S polyneuropathy in Taiwan revealed that 60% of patients presented with LVH.[35] Recent analysis of 57 patients with ATTRv amyloidosis from Taiwan, among whom 80% had ATTR-CM, showed thickening of the interventricular septum (mean 14.1 mm) and posterior wall (mean 13 mm).[36] Furthermore, the prevalence of ATTR-CM cannot be ignored in patients initially diagnosed with HCM (5%).[27] Yang et al. analyzed a Japanese database and found that 34% of patients initially diagnosed with HCM had ATTR-CM.[37] Therefore, patients with LVH without identified causes should be carefully evaluated for possible ATTR-CM.
3. **Disproportionately low voltage and pseudo-infarction patterns on ECG:** QRS voltage is often normal or low on ECG, which is disproportionate to LVH found on echocardiography, owing to abundant amyloid fibril infiltrations rather than hypertrophic sarcomere. According to the results of two retrospective analyses of Taiwanese ATTRv amyloidosis, approximately 31.3%[28] to 100%[34] of patients have low-to-normal voltage, and 64.2% of patients have pseudo-infarction patterns on ECG.[28] In Western reports, low-voltage QRS complex is found in 13-33% of patients with wtATTR-CM.[28,30,38] A large-scale registry, including 425 patients with ATTR-CM, revealed that ECG showed low voltage in 39% of patients with a moderate interventricular septal thickness and 30% with severe interventricular septal thickness; and pseudo-infarction patterns in 31% of patients with moderate interventricular septal

Table 3. Clinical clues and red-flag signs suggestive of transthyretin amyloid cardiomyopathy

Acronym	Clinical clue and red-flag sign	Description	Major or minor red-flag sign
Major red-flag signs: **HFpEF MUTED CALL**			
	Patients at age of ≥ 60 with **HFpEF**	HF with LVEF: ≥ 50% (especially male gender)	Major
	Unexplained **T**hickened and hypertrophic LV	IVST or PWT: ≥ 1.4 cm	Major
	Disproportionately normal-to-low voltage or pseudo-infarction pattern on ECG	Especially combined with moderate and severe LVH	Major
	Bilateral **C**TS	Typical form; more prevalent in ATTRwt-CM	Major
	Arrythmias (conduction system disturbance, atrial arrythmias, PPM or another CIED implantation)	Conduction system disturbance: AV block, BBB, and fascicular block; more prevalent in ATTRwt-CM	Major
	Low-flow **L**ow-gradient phenotype of severe AS	-	Major
	Specific findings on **E**chocardiography*	Reduced LV strain rate (especially GLS) with apical sparing; or interventricular/interatrial septal thickening with granular sparkling echo density	Major
	Specific findings on C**M**R	Increased extracellular volume fraction, an inability to suppress or "null" the myocardial signal, increased myocardial native T1 or diffuse late gadolinium enhancement (transmural or subendocardial)	Major
Minor red-flag signs: **HFmrEF MUST COUNT**			
	HFmrEF or RV dysfunction	HF with LVEF: ≥ 40% and < 50%; RV dysfunction: RV S' < 12 cm/s or TAPSE < 16 mm	Minor
	Unexplained **M**oderate LVH	IVST or PWT: ≥ 1.2 cm and < 1.4 cm	Minor
	Unilateral **C**TS	Atypical form	Minor
	Disproportionately high levels of natriuretic peptides or cardiac-specific **T**roponins	-	Minor
	Severe AS without low-flow low-gradient	-	Minor
	Peripheral or autonomic poly**N**europathy	More prevalent in ATTRv-CM; paresthesia, limb weakness, diarrhea/constipation, impotence, postural hypotension, etc	Minor
	Unexpected "natural cure" of hypertension	-	Minor
	Spinal stenosis or ruptured biceps **T**endon	More prevalent in ATTRwt-CM	Minor
	Other organ involvement	Kidney, liver, vitreous opacity, etc	Minor

AS, aortic stenosis; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, hereditary transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild type transthyretin amyloid cardiomyopathy; AV, atrioventricular; BBB, bundle branch block; CIED, cardiovascular implantable electronic device; CMR, cardiac magnetic resonance; CTS, carpal tunnel syndrome; ECG, electrocardiogram; GLS, global longitudinal strain; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IVST, interventricular septal thickness; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; PPM, permanent pacemaker; PWT, posterior wall thickness; RV, right ventricular; RV S', tricuspid lateral annular peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion.
* Please refer to echocardiography section for details.

thickness and 41% with severe interventricular septal thickness.[39]

4. **History of carpal tunnel syndrome:** ATTR amyloidosis can cause nerve entrapment due to amyloid fibrils deposited in relevant soft tissues.[2] The most common form is CTS, typically presenting with bilateral symptoms,[2,40] which is often the initial manifestation of ATTR amyloidosis.[2,41] From the surgeon's perspective, amyloid deposits can be found in 10.2% of patients undergoing carpal tunnel release.[42] A prospec-

tive study including 233 patients undergoing surgery for CTS showed that 1.2% of patients were further diagnosed as ATTR-CM; of these, 100% had bilateral CTS.[43] Among patients with LVH and bilateral CTS, the prevalence rate of ATTR-CM was increased to 5.5% and 13.6%, respectively, if occupational factors were excluded.[43] The prevalence rate of ATTR-CM was increased from 4% to 33% if the combination of LVH and bilateral CTS was used for screening 83 male patients undergoing surgery for bilateral CTS, according to the results of a recently published study.[44] Approximately 50% of patients with ATTRwt-CM have a history of CTS,[33,38] usually occurring before diagnosing ATTR amyloidosis by 5-10 years.[41] Lai et al. found that approximately 31.3% of patients with ATTRv amyloidosis in Taiwan underwent surgical treatment for previously diagnosed CTS.[28] Earlier data from an analysis of five patients with ATTRv A97S polyneuropathy in Taiwan revealed that 80% of patients presented with CTS.[35] Taken together, the history of CTS, with classically bilateral symptoms, is one of the most important clinical clues in searching for ATTR-CM.

5. **Disproportionately high levels of natriuretic peptides or cardiac-specific troponins:** N-terminal pro B type natriuretic peptide (NT-proBNP) is usually elevated early in patients with mutant transthyretin amyloidosis (ATTRm) amyloidosis before the presentation of cardiac symptoms.[4,45] Disproportionately high plasma levels of NT-proBNP compared with the degree of HF and elevated troponin levels in a patient with LVH should prompt the diagnostic workup of ATTR-CM.
6. **Conduction system disturbance and atrial arrhythmias:** Conduction system disturbance is more commonly seen in patients with ATTRwt-CM than ATTRv-CM, with up to one-third needing permanent pacemaker implantation.[2] Atrial arrhythmias are also more common in patients with ATTRwt-CM than ATTRv-CM, 40-70% of patients diagnosed with ATTR-CM.[30,32,33,46] In Taiwan, Lai et al. found that AF was present in 11.9% of patients, first-degree atrioventricular block in 22.4% of patients, conduction block (including left bundle branch block, right bundle branch block, left anterior fascicular block, and left posterior fascicular block) in 35.8% of patients with ATTRv amyloidosis.[28] Approximately 10.4% of patients with ATTRv amyloidosis needed permanent pacemaker implantation.[28] Hsu et al. and Liu et al. reported that up to 70% of patients with ATTRv amyloidosis had conduction disturbance in Taiwan.[34,35] Conversely, amyloid was detected in 46% of patients undergoing surgically resected atrial appendage due to AF.[47] Although old age is a well-known risk factor for AF or conduction system disturbance requiring permanent pacemaker implantation, the combination of conduction system disturbance/AF and other clinical clues and red-flag signs should trigger further diagnostic workup of ATTR-CM.
7. History of peripheral or autonomic polyneuropathy: Peripheral or autonomic polyneuropathy is more commonly seen in patients with ATTRv-CM than ATTRwt-CM.[2] According to the results of a global case series of ATTRv polyneuropathy, 77% of patients had autonomic neuropathy, 71% of patients had peripheral sensory neuropathy, and 57% had peripheral motor neuropathy in 35 patients with A97V polymorphism, mainly from a Taiwanese database.[48] At the time of diagnosing ATTRm polyneuropathy, only 11% of patients presented with ATTRv-CM.[48] Hsu et al. and Liu et al. also reported that in Taiwan, 100% of patients with ATTRv amyloidosis had autonomic and sensory peripheral neuropathy.[34,35] However, autonomic neuropathy was found in only 12% of patients with ATTRwt-CM[38] and 3-9% of patients with peripheral neuropathy.[33,38] The most common symptoms of autonomic neuropathy were gastrointestinal symptoms, such as diarrhea or constipation, followed by impotence and postural hypotension.[48] The most common sensory peripheral neuropathy is paresthesia, while the distal nerve is commonly involved in motor neuropathy.[35,48]
8. **Unexpected "natural cure" of hypertension:** If we need down-titration or discontinuation of antihypertensive treatment without identified causes responsible for the normalization of blood pressure should prompt consideration of amyloidosis.[2]
9. **History of spinal stenosis or ruptured biceps tendon:** Deposition of amyloid fibrils can result in thickening of the ligamentum flavum, which leads to narrowing or compression of the spinal canal with resultant spinal stenosis.[2] Westermark et al. reported that amyloid deposition in the ligamentum flavum could be

found in 96.2% of patients undergoing surgery for spinal stenosis, although ATTR-CM was not further confirmed.[49] They also found that ATTR was demonstrated immunohistochemically in 5 out of 15 studied resected tissues; however, none had definite signs of CA.[49] A case series study showed that 33.3% of 111 patients with ATTRwt-CM had a history of the ruptured distal biceps tendon.[20]

10. **Presence of aortic valve stenosis, particularly low-grade and low-flow pattern:** Severe AS will cause LVH and HFpEF. However, ATTR-CM presenting with LVH and HFpEF can be associated with valvular thickness and AS. Therefore, it is a great challenge to differentiate one from the other. Castaño et al. found that 16% of 151 patients with severe calcified AS undergoing transcatheter aortic valve replacement were diagnosed with ATTR-CM and had a 3-fold increase in the risk of low-flow, low-gradient phenotype with mildly reduced LVEF than those without ATTR-CM.[12] A similar study including more participants showed that 11.8% of 407 patients with severe AS undergoing transcatheter aortic valve replacement were found to have positive ^{99m}Technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) bone scintigraphy, suggestive of ATTR-CM.[50] Some clinical parameters, including LV remodeling (LVH/diastolic dysfunction), age, high-sensitivity cardiac troponin T, systemic involvement (CTS), and electrical abnormality (bundle branch block or low voltage), were identified to be independently associated with ATTR-CM in this clinical setting.[50] Accordingly, to identify concomitant ATTR-CM in patients with severe AS, we should pay more attention to a severe AS phenotype of low-flow, low-gradient, or combination of severe AS and other clinical clues suggestive of ATTR-CM.
11. **Specific findings on echocardiography and cardiac magnetic resonance (CMR) imaging:** These have been discussed in detail in this consensus previously. In summary, reduced LV strain rate, particularly global longitudinal strain, with apical sparing and interventricular/interatrial septal thickening with granular sparkling echo density, are specific clues for ATTR-CM.[2,51] Increased extracellular volume fraction, an inability to suppress or "null" the myocardial signal, increased myocardial native T1, or diffuse late gadolinium enhancement (LGE) (transmural or subendocardial) on CMR imaging is also suggestive of ATTR-CM.[2,51] The detailed echocardiographic and CMR imaging findings can be found in the related sections.

Proposed screening algorithm with red-flag signs

So far, few studies evaluate the sensitivity and specificity of red-flag signs,[52] except for echocardiography and CMR imaging, for diagnosing ATTR-CM owing to the rarity of this disease entity and nonspecific symptoms and clinical presentations. Setting up a screening algorithm with red-flag signs remains a big challenge. Heterogeneous inclusions of relevant parameters into analysis for different types of CA in different study populations/ethnicity would result in different results and challenging clinical applications. Besides, the prevalence of clinical clues is diverse among the three categories of CA. To avoid over- or under-screening, we categorized red-flag signs into major or minor criteria (Table 3) and proposed a screening algorithm with red-flag signs, shown in Central Illustration.

Moreover, ATTRwt-CM is much more prevalent than ATTRv-CM;[2] however, the precise distribution regarding both in Taiwan is poorly understood. Nevertheless, some clinical clues are more prevalent and theoretically more specific, which may be considered as major criteria, e.g., patients aged > 60 years with HFpEF, unexplained severe LVH, the disproportionately normal-to-low voltage on ECG, history of bilateral CTS, and specific finding on echocardiography or CMR imaging suggestive of ATTR-CM. Remember, the acronym "HFpEF MUTED CALL" denotes all major red-flag signs, and "HFmEF MUST COUNT" represents all minor red-flag signs. Patients who fulfill two major red-flag signs, one major plus two minor, or three minor red-flag signs are highly suspected of having ATTR-CM and should prompt further diagnostic workup. Otherwise, we may keep observation with regular clinical follow-up.

The role of echocardiography in the diagnosis of ATTR-CM

As a mainstay of initial HF evaluation and a standard imaging modality for daily use, echocardiography in the diagnosis of CA has several advantages, although nonspecific, and is cost-effective, including bedside feasibility, high temporal resolution, radiation-free process, and the ability to identify other relevant findings (e.g., AS).[53]

Although echocardiography alone is not diagnostic of CA, a comprehensive echocardiography study also aids in identification (in conditions where CA may exist) and differentiation of other nonamyloid etiologies of LV wall thickening:[16] AS, HCM, or Fabry disease. By using the American Heart Association scientific statement, the existence of discordance between moderate to severe wall thickening (especially when the wall thickness is ≥ 14 mm) on echocardiography and QRS voltage on ECG should raise the suspicion and clinical consideration of ATTR-CM.[16,54]

Concentric and symmetric LVH typically features the morphologic finding of CA from accumulating amyloid fibrils, although asymmetric hypertrophy does not exclude the possibility of CA. As part of a critical noninvasive diagnostic component in CA, the presence of LV wall thickness ≥ 12 mm combined with at least one red flag of clinical scenario raised the suspicion of CA according to the position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases (Table 4).[18] Other findings may include normal or decreased LV cavity size, thickened cardiac valve leaflets, and pericardial or pleural effusion.[53,55] The presence of right ventricular hypertrophy and bilateral atrial enlargement signifies a higher specificity for CA in those patients manifesting LVH.[56,57] Hereditary ATTR-CM has been reported to be prevalent (> 10%) with very thickened LV (≥ 15 mm) in the elderly population (> 65 years) from a cohort of predominantly male Caucasian patients (76%) according to the American College of Cardiology/American Heart Association guidelines for HCM definition.[27,58] Severely impaired LV diastolic function is common (elevated E/e'), which likely parallels deteriorated systolic index as assessed by strain measure.[18] If LV wall thickness ≥ 12 mm combined with amyloid deposits in an extracardiac biopsy, a multiparametric echocardiographic score could also be considered diagnostic of CA if the score is ≥ 8 points (Table 4).[18] Except for those mentioned above, systolic longitudinal strain apex-to-base ratio, a pattern of apical sparing by objective and quantitative strain measure using the index of "relative apical longitudinal strain" (RALS = [average apical LS] / [average basal LS + average mid LS]) alone, may also provide additive diagnostic value for CA.[59] RALS > 1 had a sensitivity > 90% and specificity > 80% for CA compared with LVH from other etiologies. A

Table 4. Clinical diagnostic utilization of echocardiography for transthyretin amyloid cardiomyopathy

Different cut-offs of LV wall thickness measure	References
≥ 12 mm	Position statement of the ESC Working Group on Myocardial and Pericardial Diseases[18]
≥ 14 mm	Scientific statement from the AHA[16]
≥ 15 mm	French multicenter cross-sectional study[27]/2020 AHA/ACC guideline for HCM[58]
Echocardiographic criteria for non-invasive diagnosis of cardiac amyloidosis (ESC Working Group on Myocardial and Pericardial Diseases)[18]	
Unexplained LV wall thickness (≥ 12 mm) plus 1 or 2:[1]	
1. Characteristic echocardiography findings (≥ 2 of a, b, and c have to be present):	2. Multiparametric echocardiographic score (IWT) ≥ 8 points: Scores
a. Grade 2 or worse diastolic dysfunction	a. Relative LV wall thickness (IVS + PWT)/LVEDD > 0.6 3 points
b. Reduced tissue Doppler s', e' and a' waves velocities (< 5 cm/s)	b. Doppler E wave/e' wave velocities > 11 1 point
c. Decreased global longitudinal LV strain (absolute value < -15%).	c. TAPSE ≤ 19 mm 2 points
	d. LV global longitudinal strain absolute value ≥ -13% 1 point
	e. Systolic longitudinal strain apex to base ratio > 2.9 3 points

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; IVS, interventricular septum; IWT, increased wall thickness; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; PWT, posterior wall thickness; TAPSE, tricuspid annular plane systolic excursion.

higher LVEF to global longitudinal strain ratio (EFSR: > 4.1) has also shown sensitivity and specificity of 90% as an alternative index in differentiating CA from other causes of LVH.[60]

The role of ^{99m}Technetium-labeled pyrophosphate (^{99m}Tc-PYP) scintigraphy in the diagnosis of ATTR-CM

This hereditary form of ATTR manifests predominantly as polyneuropathy, cardiomyopathy, or mixed phenotype.[61] The Transthyretin Amyloidosis Outcomes Survey (THAOS) found that approximately half of the symptomatic patients with transthyretin (TTR) mutations have neurologic manifestations as their primary symptom, followed by cardiac abnormalities and mixed phenotype, each constituting approximately a quarter, respectively.[61] Because there are no large-scale screening and registration studies, the prevalence of ATTR-CM in Taiwan remains unclear. The Ala97Ser mutation is the most common cause of ATTRm in Taiwan.[28,36] It is considered a mixed type of cardiomyopathy and a polyneuropathic syndrome.[28]

Once CA is suspected, a further diagnosis could be reached through either non-invasive methods such as nuclear scintigraphy, the FLC test,[7,13,14] and genetic testing, or invasive methods such as endomyocardial biopsy, which is considered the gold standard for the diagnosis of ATTR-CM.[15]

Bone-avid radiotracers, including ^{99m}Tc-PYP, have been reported to help detect CA.[7,13-15,21,22,29,62-66] The exact mechanism is not fully understood. It may be related to amyloid microcalcification. ^{99m}Tc-PYP scintigraphy is a feasible and objective tool for assessing the burden of CA in diagnosing ATTR-CM.[67,68] A joint expert consensus has been reached by the Taiwan Society of Cardiology and the Society of Nuclear Medicine of the Republic of China to advocate for the application of ^{99m}Tc-PYP scintigraphy in the diagnosis of ATTR-CM and highlight the recommendations on standardization of image acquisition parameters, qualitative and quantitative assessments of cardiac ^{99m}Tc-PYP uptake, reporting format and facilitate earlier therapeutic intervention and clinical research.[69]

Standard planar images for the anterior, left anterior oblique, and lateral views are obtained 1 and 3 hours after tracer injection. One-hour imaging has higher detection sensitivity, whereas 3-hour imaging results improve specificity because the delayed clearance of blood pool activity is not uncommon in patients with poor renal function or low cardiac output. Patients' HF severity, LVEF, recent myocardial infarction history, and renal function should be considered to interpret the image correctly. In our recommendation, 3-hour planar images are recommended for visual scoring and semiquantitation, and 1-hour images are optional. Further delayed imaging may be considered if background or blood pool activity remains high. Single-photon emission computed tomography is necessary to distinguish blood pool activity from myocardial activity. Single-photon emission computed tomography/computed tomography is preferred for attenuation correction and anatomical localization to distinguish blood pool or rib activity.[69]

Semiquantitative analyses are based on the radiotracer uptake in the heart and surrounding ribs. A visual grading scale is used to interpret the imaging results, as follows: Grade 0: absence of myocardial tracer uptake and normal bone uptake; Grade 1: myocardial uptake in a lower degree than at bone level; Grade 2: similar myocardial and bone uptake; and Grade 3: myocardial uptake greater than bone with reduced/absent bone uptake (Figure 3 and Table 5). If myocardial uptake patterns are focal or focal on diffuse, using the maximal uptake for visual grading is recommended.

A heart-to-contralateral lung (H/CL) ratio on the planar anterior view is used for semiquantitation. A circular or elliptical region of interest (ROI) is drawn to maximize the left ventricle while cautiously avoiding the sternal region and the adjacent lung. The ROI is mirrored to the contralateral chest, carefully excluding any right heart or mediastinal activity and avoiding the subdiaphragmatic organs. A H/CL ratio is calculated as the fraction of heart ROI mean counts to contralateral chest ROI mean counts (Figure 4).

Interpretation of ^{99m}Tc-PYP scintigraphy should include a visual evaluation of planar and single-photon emission computed tomography images for any radiotracer uptake, visual grading, and the semiquantitative H/CL ratio (Table 5). For 1-hour images, a H/CL ratio > 1.5 is used to identify ATTR-CM. For 3-hour images, a H/CL ratio $\geq$ 1.3 is used to identify ATTR-CM if plasma cell dyscrasia was excluded. Although different H/CL ratios and cut-off values for 1 or 3 hours have been reported,[7,13,14,26] our consensus upholds the criteria of the 2019 American Society of Nuclear Cardiology recom-

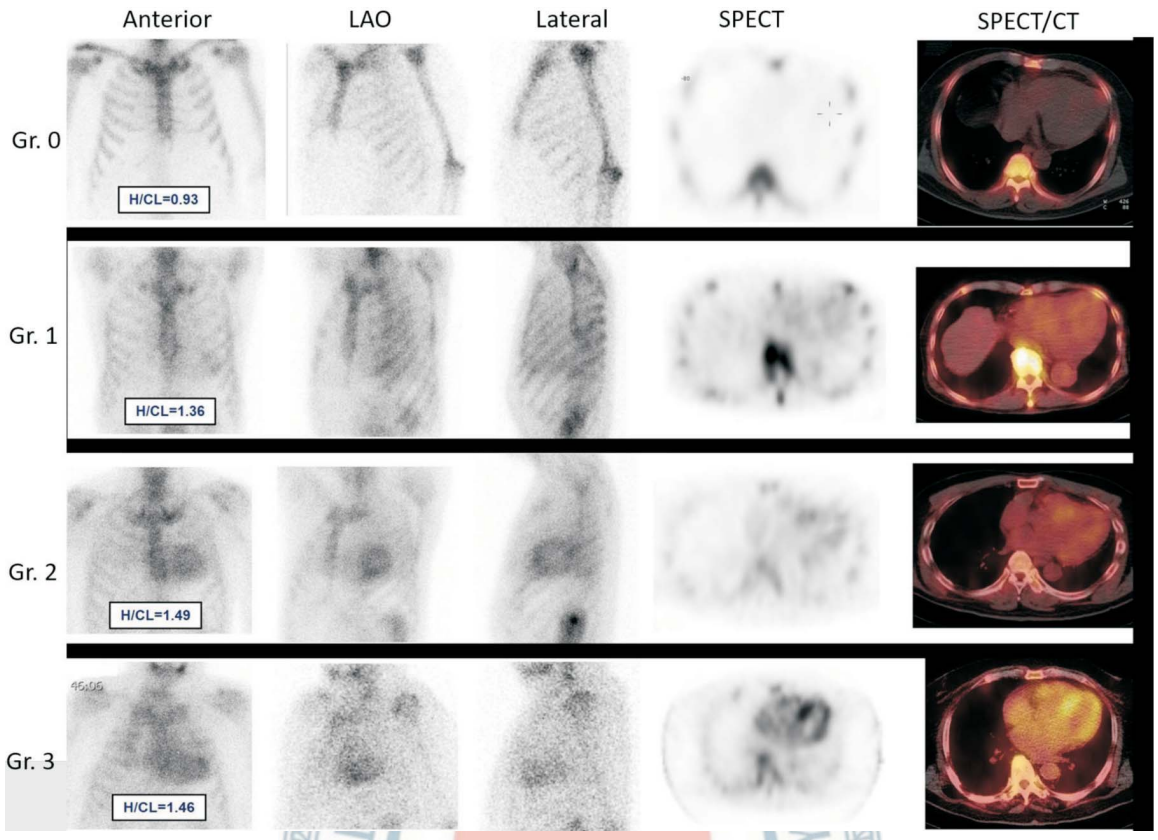

Figure 3. *Visual scores from 0 to 3 based on ^{99m}Tc-PYP planar, SPECT, fused SPECT/CT images*. ^{99m}Tc-PYP, ^{99m}Technetium-labeled pyrophosphate; CT, computed tomography; Gr., Grade; LAO, left anterior oblique; ROI, region of interest; SPECT, single-photon emission computed tomography. * Modified with permission from Huang YH, Lin YH, Yen RF, et al. 2021 advocacy statements for the role of 99mTc-pyrophosphate scintigraphy in the diagnosis of transthyretin cardiac amyloidosis: a report of the Taiwan Society of Cardiology and the Society of Nuclear Medicine of the Republic of China. Acta Cardiol Sin 2021;37:221.*

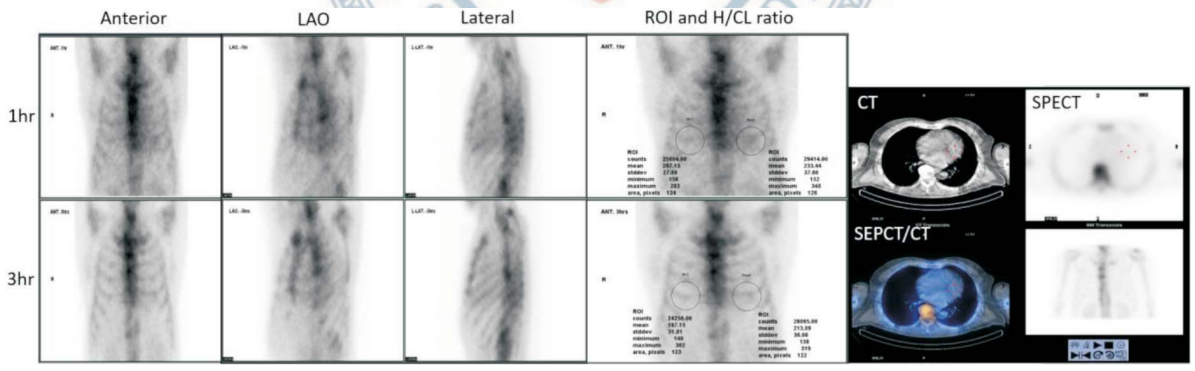

Figure 4. *Standard planar images and H/CL quantitation of cardiac ^{99m}Tc-PYP uptake*. ^{99m}Tc-PYP, ^{99m}Technetium-labeled pyrophosphate; CT, computed tomography; H/CL, heart/contralateral lung; hr, hour; LAO, left anterior oblique; ROI, region of interest; SPECT, single-photon emission computed tomography. * Modified with permission from Huang YH, Lin YH, Yen RF, et al. 2021 advocacy statements for the role of 99mTc-pyrophosphate scintigraphy in the diagnosis of transthyretin cardiac amyloidosis: a report of the Taiwan Society of Cardiology and the Society of Nuclear Medicine of the Republic of China. Acta Cardiol Sin 2021;37:221.*

mendations[13,14] and the 2020 Japanese Circulation Society guideline.[7]

An overall interpretation of the findings separates patients into three categories — not suggestive, strongly suggestive, or equivocal — for ATTR-CM (Table 5). If ATTR-CM is strongly suggestive, proceed with genetic

Table 5. Interpretation of ^{99m}Tc-pyrophosphate scintigraphy

Visual grading			
The relative tracer uptake in the myocardium to ribs seen on planar and SPECT images is graded on the following scale:			
• Grade 0	No myocardial uptake and normal bone uptake		
• Grade 1	Myocardial uptake less than rib uptake		
• Grade 2	Myocardial uptake equal to rib uptake		
• Grade 3	Myocardial uptake greater than rib uptake with mild/absent rib uptake		
H/CL ratio interpretation			
• 1-hour images	H/CL ratio > 1.5		
• 3-hour images	H/CL ratio ≥ 1.3		
Conclusions	Components		
	Visual Score (Grade)	H/CL ratio at 1-hour	H/CL ratio at 3-hour
Not suggestive	0	< 1	< 1.3
Strongly suggestive	2 or 3	> 1.5	≥ 1.3
Equivocal	1	1-1.5	

H/CL ratio, heart to contralateral lung ratio; SPECT, single-photon emission computed tomography. (Adapted and modified from reference 4, 5, 57).

testing to differentiate between ATTRm and ATTRwt forms. Equivocal results on ^{99m}Tc-PYP scintigraphy could represent either AL-CM or early ATTR-CM, which could be correlated with other diagnostic modalities such as CMR imaging or histologic confirmation. In addition, false positives on ^{99m}Tc-PYP scans may arise from AL-CM, blood pool uptake, rib fractures, myocardial infarction, quinine drug toxicity, or other rare forms of CA. False negatives may be due to the specific type of ATTRm, minimal myocardial infiltration (early-stage disease), and scar tissue formation after myocardial infarction. Because of this, carefully reviewing clinical data and even histologic confirmation of amyloid deposits should be considered.[7,13,14,16,18,70,71]

In a study enrolling 1217 patients, after excluding light chain amyloidosis with suspected CA and using ^{99m}Tc-PYP scan grades 2-3 as criteria, the specificity and positive predictive values were as high as 100%.[72] Owing to high sensitivity and specificity, it is considered a suitable alternative to endomyocardial biopsy in some patients suspected of ATTR-CM after excluding light chain amyloidosis.[73-75] On the other hand, if the FLC test is positive and visual grade 2-3 for ^{99m}Tc-PYP scintigraphy, histologic confirmation is always necessary.[18] Therefore, we suggest checking monoclonal proteins in serum and urine before or simultaneously with the ^{99m}Tc-PYP scintigraphy study.

Scintigraphy using another bone-seeking tracer might detect CA, and an incidental finding is not uncommon,[76] and further workup could be considered. However, owing to a lack of standardization of regional scan acquisition and semiquantitative H/CL ratios, we still recommend ^{99m}Tc-PYP scintigraphy in the diagnostic algorithm for CA.

Recent advances in therapeutic strategies shown to be most beneficial in the early stages of the disease have determined a paradigm shift in the screening, diagnostic algorithm, and risk classification of patients with ATTR-CM.[77] Besides the bone scintigraphy, positron-emission tomography with ^{18}F-sodium fluoride has been reported,[78] with inconsistent results in diagnostic performance. Other nuclear imaging, including amyloid and ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy, have been reported to diagnose ATTR-CM.[79-82] Assessment of myocardial sympathetic nerve function with ^{123}I-MIBG scintigraphy may reflect autonomic dysfunction, which may detect cardiac denervation in ATTR-CM patients before signs of amyloidosis are evident on echocardiography,[79] the severity may link to amyloid deposition,[80] severity of neuropathy,[81] arrhythmia, HF, and possible cardiovascular events.[82,83] Amyloid-targeted positron-emission tomography tracers can detect amyloid deposition in AL-CM and ATTR-CM, including the myocardium and extracardiac organs.[84-86] Amyloid posi-

tron-emission tomography is quantitative and provides a measure of whole-heart and whole-body amyloid load and can be repeated, making it a potentially promising tool to evaluate response to therapy. Some discrepancies between ^{123}I-MIBG, and amyloid positron-emission tomography, compared with ^{99m}Tc-PYP in CA, are reported,[83-88] and a complementary role in the specific ATTRm has been reported. Only the 2020 Japanese Circulation Society guideline included these two imaging modalities,[7] partly due to scarce evidence and diversity of genetic mutation and clinical presentations. The role of these functional imaging modalities remains to be explored.

The role of cardiac magnetic resonance imaging in the diagnosis of ATTR cardiomyopathy

CMR imaging is a valuable and non-invasive tool in detecting and differentiating the etiologies of cardiomyopathy, such as HCM and Fabry disease.[89] It can provide tissue characterization and cardiac structural and functional assessment. The commonly applied CMR imaging techniques for detecting and differentiating CA include the patterns of LGE, native T1 mapping (non-contrast), and extracellular volume (ECV) measurement (Table 6).

LGE can detect myocardial fibrosis and be used in the differentiation of CA.[90] The pattern of LGE in CA could be transmural or subendocardial; both are present in AL-CM and ATTR-CM. Dark blood pool is also a typical LGE pattern that originates from the abnormal gadolinium kinetics to amyloidosis.[91] LGE mainly occurs in the left ventricle, especially the basal segments, right ventricle, left atrium, and atrial septum.[7,92] The subendocardial LGE is more prevalent in AL-CM, and transmural LGE is more prevalent in ATTR-CM.[93] However, LGE is difficult to quantify in CA, and the atypical LGE pattern is often seen.[89,93] In addition, the diagnostic value of LGE is limited in patients with diffuse fibrosis because of the absence of normal reference myocardium and in patients with microscopic interstitial fibrosis.[89,94] Compared with LGE, T1 mapping and ECV can directly measure the amyloid burden and be used in the disease course follow-up. Both native T mapping and ECV are associated with clinical outcomes.[95]

Native T1 mapping can directly measure the intrinsic signal from the myocardium. It is advantageous when the administration of contrast is contraindicated. Native T1 mapping values are the summation of intracellular and extracellular space signals.[89] However, the native T1 result is easily affected by the systems' imaging sequences and magnetic field strength. Because of this, the reference values should be established for each system and imaging sequence.[96] Compared with native T1, ECV reflects changes only in the extracellular space. ECV can demonstrate the percentage of extracellular space, which is easily quantified and less likely to be affected by magnetic field strength or imaging sequences. CA should be suspected when ECV is $\geq$ 40%.[97] Compared with LGE and native T1, ECV can accurately measure the degree of infiltration of the extracellular space, resulting in a more

Table 6. Cardiac magnetic resonance imaging findings in cardiac amyloidosis

Imaging	Findings
Cine CMR and myocardial strain	1. Left ventricular hypertrophy, symmetric or asymmetric
	2. Right ventricular hypertrophy
	3. Thicken atrial septum ($\geq$ 6 mm)
	4. Abnormal longitudinal and circumferential strains
Late gadolinium enhancement (LGE) imaging	1. Diffuse transmural or subendocardial LGE
	2. LGE mainly occurs in the basal segments of left ventricle, right ventricle, left atrium, and atrial septum
	3. Dark blood pool pattern
T1 mapping (non-contrast)	1. Non-contrast imaging
	2. Significantly elevated T1 value
Extracellular volume (ECV)	1. Contrast is needed for this imaging
	2. Significantly elevated ECV
	3. ECV $\geq$ 40%

CMR, cardiac magnetic resonance; ECV, extracellular volume; LGE, late gadolinium enhancement.

accurate marker of infiltration, and it can be used as a tool to predict outcomes and monitor treatment response.[95,98,99] Other CMR imaging techniques, such as T2 mapping, the indicator of myocardial edema, and myocardial strain analysis, can also potentially be used in diagnosing CA and predicting outcomes.[100,101]

The CMR imaging should be combined with clinical symptoms, electrocardiographic and biochemical parameters, and other imaging modalities to maximize diagnostic accuracy. Currently, none of these CMR imaging techniques can be used to differentiate between the AL-CM and ATTR-CM. However, in cases with suspected ATTR-CM but with equivocal results on ^{99m}Tc-PYP scintigraphy, CMR imaging is a valuable tool to help us identify the amyloid disposition and to guide the need for further histologic confirmation.

The role of endomyocardial biopsy in the diagnosis of ATTR cardiomyopathy

Currently, there is no understanding of how amyloid precursor proteins misfold, aggregate, and form precipitates[102] or how powder-like substances are deposited in tissues and interact with the extracellular matrix and cell function, leading to cell apoptosis and death. The mechanisms of amyloid deposits in the heart are still unclear.[103]

Scientists have identified 36 proteins that produce amyloid in the human body, the deposits of which may be localized or systemic.[104] About 22 of these proteins have only localized amyloid deposition, whereas about 12 proteins are deposited systemically, and two (AL/AH) are deposited locally or systemically.[105]

Amyloidosis can be diagnosed by tissue biopsy of involved organs or by testing for amyloid protein in blood or urine. Correct amyloid typing is crucial because some are treatable, and others are untreatable. The increase in newly diagnosed cases is due to increased awareness of these diseases in recent years.

Both light chain and ATTR amyloidosis are the leading causes of most CA. Endomyocardial biopsy remains the gold standard for ATTR-CM diagnosis, with nearly 100% sensitivity and specificity.[106] Biopsy specimens were suggested to collect from multiple sites of the endocardium (≥ four are recommended). Endomyocardial biopsy is suitable to differentiate from other hypertrophy cardiomyopathies, including Fabry disease. Serious complication rates related to endomyocardial biopsy are < 1%. Other tissue biopsies from various parts, such as abdominal fat or low gastrointestinal tract, have varying sensitivity; in the case of wild-type disease, the sensitivity of fat aspirate is relatively low.[103]

Light microscopy and stains

The amyloid appears as a homogeneous, eosinophilic interstitial substance in hematoxylin-eosin stained under the light microscope, with a similar location to other extracellular proteins in the heart. Congo red dye binds to the amyloid beta-pleated sheet structure, which produces apple-green birefringence under polarized light and is usually used as a definitive diagnostic procedure.[7]

Immunohistochemical analysis and mass spectrometry

Once amyloid is detected, specific antibody immunohistochemical analysis should be used to identify the amyloid subtype. The subtypes of the light chain and ATTR amyloidosis are the most common, and the diagnosis is essential. Commercialized immunohistochemical antibodies are now available, including anti-transthyretin, anti-kappa, and anti-lambda light chains.[107] Tissue-specific sampling by laser microdissection followed by liquid chromatography to separate amyloid compounds from the sample, then combined with mass spectrometry, is an alternative approach for diagnosing and typing amyloidosis.[7]

Diagnostic algorithm for ATTR-CM

For patients with suspected ATTR-CM, we propose a diagnostic algorithm to identify the subtypes of CA with the ^{99m}Tc-PYP scintigraphy and the FLC test (Figure 5). In this diagnostic algorithm, we suggest simultaneously checking monoclonal proteins in serum and urine as in the ^{99m}Tc-PYP scintigraphy study. The FLC tests include the measurement of serum immunofixation electrophoresis, urine immunofixation electrophoresis, and serum FLC, which has > 99% sensitivity for light chain amyloidosis.[108] In patients with suggestive ^{99m}Tc-PYP scintigraphy who have a negative FLC test, the diagnosis of ATTR-CM is confirmed. ATTR-CM diagnosis could not be excluded entirely in patients with a positive FLC test, especially in patients with ^{99m}Tc-PYP scintigraphy Grade ≥ 1. Monoclonal gammopathy of undetermined significance (MGUS) is frequently associated with ATTR-CM, espe-

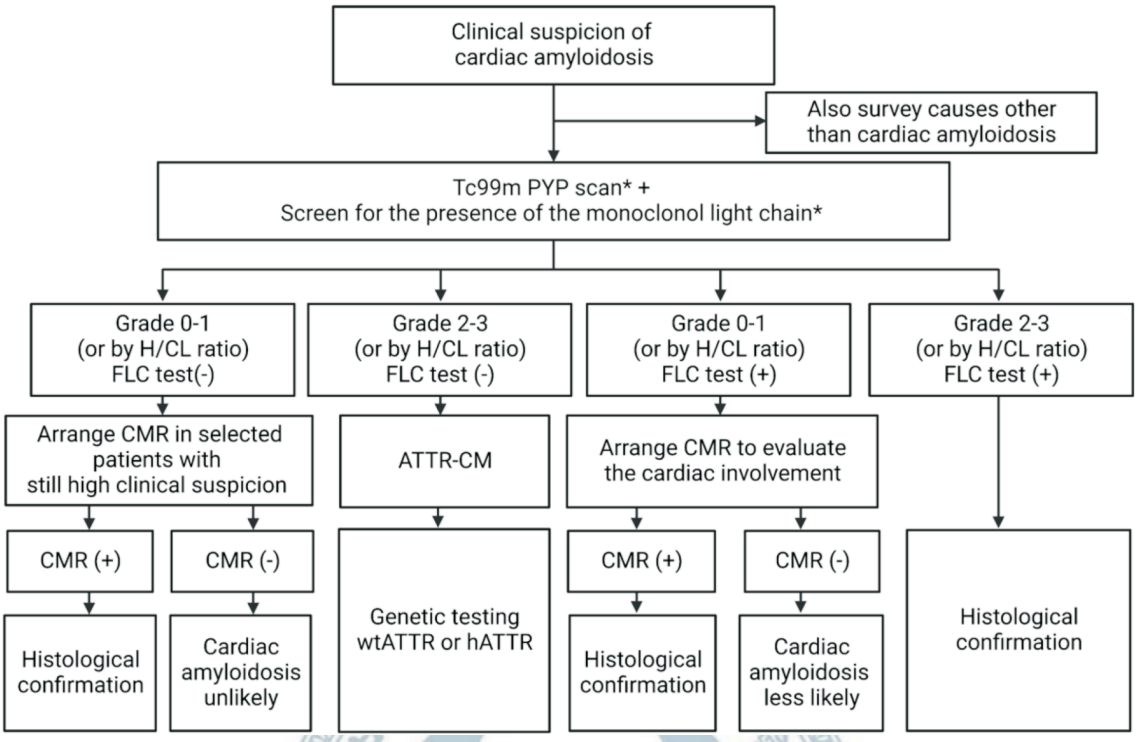

Figure 5. *Diagnostic algorithm for transthyretin amyloid cardiomyopathy. ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance; FLC, free light chain; hATTR, hereditary transthyretin amyloid cardiomyopathy; H/CL, heart/contralateral lung; Tc99m PYP, ^{99m}Technetium-labeled pyrophosphate; wtATTR, wild type transthyretin amyloid cardiomyopathy.*

cially in ATTRwt. Up to 39% of patients with the ATTRwt cohort had the diagnosis of MGUS, which indicated abnormal FLC test results.[109] Because of that, a different diagnostic approach is still needed in patients with a positive FLC test with high clinical suspicion of ATTR-CM. CMR imaging is a useful noninvasive tool for equivocal cases with ^{99m}Tc-PYP scintigraphy Grades 0-1 to evaluate the amyloid burden. CMR imaging can also help us differentiate other infiltrative cardiac diseases.[110] However, CMR imaging is not diagnostic for AL-CM and ATTR-CM; therefore, histologic confirmation is needed for equivocal cases with positive CMR imaging results to confirm the subtypes of amyloidosis. Because of that, we use ^{99m}Tc-PYP scintigraphy grade results, FLC tests, and CMR imaging in the current diagnostic algorithm to help the clinician make the diagnosis.

In patients with ^{99m}Tc-PYP scintigraphy Grade 2-3 and negative FLC tests, the ATTR-CM was confirmed, and further genetic testing can help us to identify the subtypes such as ATTRm or ATTRwt. ATTR CM is unlikely in patients with ^{99m}Tc-PYP scintigraphy Grade 0-1 and negative FLC tests, especially those with Grade 0. However, we can use CMR imaging to identify the amyloid disposition before the invasive histology confirmation in those with high clinical suspicion. If the CMR imaging suggests CA, histologic confirmation is needed for the final diagnosis.

In patients with ^{99m}Tc-PYP scintigraphy Grade 2-3 and positive FLC tests, histologic confirmation is needed to confirm the diagnosis, owing to the high prevalence of MGUS in ATTR-CM patients.[109] In patients with ^{99m}Tc-PYP scintigraphy Grade 1-2 and positive FLC tests, we can also use CMR imaging to evaluate the amyloid disposition in the myocardium. If positive CMR imaging results were obtained, histologic confirmation could be considered to confirm the diagnosis.

The role of genetic testing in the diagnosis of ATTR-CM

TTR sequencing is recommended and a prerequisite for accurate clinical classification of ATTR-CM as ATTRwt-CM or ATTRv-CM. According to a recent scientific statement from the American Heart Association, it may prompt confirmation of ATTRv and trigger genetic counseling and

potential screening of family members.[4,16,70] Furthermore, consensus recommendations for genetic workup in highly suspected ATTR-CM have also been proposed as part of HF management from guidelines. More than 100 different *TTR* mutations have been identified,[111] with some tending to predominantly neurologic features, some belonging to predominantly cardiac features, and others with mixed clinical phenotypes. Although, in general, ATTRwt-CM tended to be diagnosed with more advanced age accompanied by multiple comorbid conditions with a high frequency of cardiac involvement (~100%),[18] differences between ATTRv-CM and ATTRwt-CM may also be observed according to the degree of LVH on echocardiography/CMR imaging.[53] In general, ATTRwt-CM may have higher LVMI and wall thickness and may occasionally present with a more thickened interatrial septum, partly explained by the more elderly demographic and longer asymptomatic disease status before clinical diagnosis.

Among 186 patients diagnosed as diverse ATTR variants, exclusively or predominantly cardiac variants (Val122Ile, Thr60Ala, Leu111Met, and Ile68Leu) occupied (n = 31; 17%), compared with exclusively neurologic (n = 46; 25%) and mixed cardiac/neurologic (n = 109; 58%) in a Caucasian-based multicenter survey.[112] Several important or common forms of genetic variants, including the worldwide most common *TTR* variant of Val122Ile (or pV142I, in ~ 3-4% of African Americans) manifesting primarily as CM;[4,113] another common *TTR* variant of Thr60Ala (in ~ 1% of people in northwest Ireland);[114] the Val30Met variant is the most common cause of hereditary ATTR with peripheral neuropathy, with late-onset Val30Met variant typically manifesting as CM.[112,115] Details about these *TTR* sequences are listed in Table 7. In Taiwan, six common missense *TTR* mutations were identified, including Ala45Thr (c.193G>A), Thr60Ala (c.238A>G), Ile73Val (c.277A>G), Ser77Try (c.290C>A), Glu89Asp

Table 7. Common forms of transthyretin amyloid cardiomyopathy

Hereditary ATTR-CM	Age at onset, y	Sex distribution	National/ethnic predominance	Cardic involvement	Other organ involvement
Val30Met (V30M) or pV50M	< 30 in early onset > 60 in late onset	Slight F > M	Portuguese, Swedish, and Japanese	Conduction disease more common than heart failure	Peripheral neuropathy Autonomic neuropathy
Val122Ile (V122I) or pV142I	60-65 (older age at onset in women)	Slight M > F	Afro-American Afro-Caribbean	Common	Peripheral neuropathy likely Bilateral carpal tunnel syndrome
Thr60Ala (T60A) or pT80A	> 60	Unknown	Irish	Common	Autonomic and peripheral neuropathy
Ala97Ser	> 50	Slight M > F	Taiwanese	Common	Sensory-motor Autonomic and peripheral neuropathy
Wild ATTR-CM	**Age at onset, y**	**Sex distribution**	**National/ethnic predominance**	**Cardic involvement**	**Other organ involvement**
TTRwt	70-75	80%-90% male	None	Common	Bilateral carpal tunnel syndrome, spinal stenosis, biceps tendon rupture

ATTR-CM, transthyretin amyloid cardiomyopathy; F, female; M, male; TTRwt, wild-type transthyretin amyloid cardiomyopathy; y, year.

Data extracted and modified from "Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement from the American Heart Association.[16]"

(c.327G>T), and Ala97Ser (c.349G>T) (Table 7).[115] In particular, a common *TTR* hot-spot on Ala97Ser (≥ 90%) was observed[36] with predominant neurologic manifestations (e.g., familial amyloid polyneuropathy) along with frequently cardiac involvement, presenting primarily phenotypic LVH (~ 80%),[28,116] followed by cardiac arrhythmias.

OUTCOME AND PROGNOSIS OF CARDIAC AMYLOIDOSIS

Prognosis

ATTR-CM has a progressive course, resulting in HF, arrhythmia, and conduction abnormalities.[30] Although the natural history differs among AL-CM, ATTRv-CM, and ATTRwt-CM, the contemporary concept of prognosis prediction is based on multiparametric biomarkers. There are currently five staging systems, which include a scoring system for light chain amyloidosis,[117,118] ATTRwt, and ATTRv,[119,120] and ATTRwt.[32] These scoring systems are summarized in Table 8. The most frequently used parameters are NT-proBNP or B-type natriuretic peptide (BNP), followed by troponin (I or T) and estimated glomerular filtration rate. Because these scores were obtained during the presentation, the impact during follow-up has not yet been established. A recent publication from Law et al. has shown that the increase in National Amyloidosis Center (NAC) score can predict mortality throughout follow-up.[121] Indeed, more data are needed to address this issue.

AL-CM is more aggressive than ATTR-CM, and its prevalence increases gradually as more patients survive with advanced diagnostic tools and treatment.[7] The difference can be attributed to more direct cardiotoxicity of FLCs with pre-fibrillar aggregation than ATTR-CM. Previous studies also suggest that AL-CM is not a simple disease of infiltrative disorder but toxic-infiltrative cardiomyopathy.[122,123] The Mayo Clinic scoring system used the difference between involved and uninvolved FLC ≥ 18 mg/dL, troponin T ≥ 0.025 ng/mL, and NT-proBNP ≥ 1800 pg/mL as the prognostic factors. Four stages were defined: Stage I: no parameters, Stage II: one parameter, Stage III: two parameters, and Stage IV: three parameters. The 5-year survival rates were 68%, 60%, 28%, and 14%, respectively. Lilleness et al.[118] changed two parameters in the Mayo Clinic scoring scheme using troponin I > 0.1 ng/mL and BNP > 81 pg/mL in this modified system. They defined the four stages as Stage I: no parameters, stage II: one parameter, Stage III: two parameters, and Stage IIIb: two parameters plus BNP > 700 pg/mL. The median survival months were 112.8 months in Stage I, 51.6 months in Stage II, and 12 months in Stage IIIb.

ATTR-CM is a relatively "chronic" disease compared with AL-CM. Although HF occurs in the disease course, conduction system disease seems to precede HF development over several years.[2] Patients usually stay relatively stable, then develop a suddenly declined and refractory HF. When comparing ATTRv with ATTRwt, the presentation of ATTRv is much more variable. ATTRv can present as primary cardiomyopathy, peripheral autonomic polyneuropathy, or, not uncommonly, both. The variability of the age of onset, phenotype, and clinical course derives from the mutation and fibril type within families.[124] Higher rates of mortality and cardiovascular hospitalization have been reported in ATTRv carrying the Val122Ile mutation compared with ATTRwt in African American patients.[125]

The ATTRwt, on the other hand, has a more consistent course of the disease and tends to develop conduction system diseases more frequently than ATTRv, according to previous studies.[32] Up to 30% of patients require permanent pacemaker implantation, and 40-60% develop atrial arrhythmias.[33,38] Grogan et al.[32] (Mayo Clinic score) used thresholds of troponin T and NT-proBNP (> 0.05 ng/ml and > 3000 pg/mL, respectively) as prognostic staging indicators for patients with ATTRwt. The three stages were defined as Stage I: no parameters; Stage II: one parameter; and Stage III: two parameters. These three stages had a median survival of 66, 42, and 20 months, respectively.[32] While Gillmore et al. (NAC score) used NT-proBNP (> 3000 pg/mL) and estimated glomerular filtration rate (< 45 mL/min/1.73 m^2) as prognostic parameters for both ATTRwt and ATTRv with a median survival of 69.2, 46.7, and 24.1 months, respectively, for the 3-stage system.[119] A recent study found that a staging system using NT-proBNP and estimated glomerular filtration rate had better prognostic accuracy for 175 patients with ATTR-CM (133 wild-type and 42 hereditary) compared with the one using NT-proBNP and troponin I.[126] Based on the two scoring systems (Mayo Clinic and NAC scores), Cheng et al. included New York

Table 8. Imaging in prognosis

	Light chain amyloidosis	Hereditary transthyretin amyloidosis (ATTRv)	Wild type transthyretin amyloidosis (ATTRwt)
Clinical course	Rapid progression of HF, especially cardiac involvement Worse than ATTR-CM	More variable, depends on the mutation Presented with primary cardiomyopathy or peripheral autonomic polyneuropathy Worse outcome and EF than ATTRwt, especially in Val22Ile	Conduction system disease present before HF Conduction system disease more common than ATTRv One-third requires PPM More common with atrial arrhythmias (40-60%)
Staging system	Kumar et al.[117] (Mayo Clinic)	Gillmore et al.[119] (NAC) (ATTRv and ATTRwt)	Grogan et al.[32] (Mayo Clinic) (ATTRwt)
	FLC-diff ≥ 18 mg/dL TnT ≥ 0.025 ng/mL NT-proBNP ≥ 1800 pg/mL	eGFR < 45 mL/min/1.73 m^2 NT-proBNP > 3000 pg/mL	TnT > 0.05 ng/mL NT-proBNP > 3000 pg/mL
	5-year survival	Median survival	4-year survival, median survival
	Stage I (0 parameters) 68% Stage II (1 parameter) 60% Stage III (2 parameters) 28% Stage IV (3 parameters) 14%	Stage I (0 parameters) 69.2 months Stage II (1 parameter) 46.7 months Stage III (2 parameters) 24.1 months	Stage I (0 parameters) 57%, 66 months Stage II (1 parameter) 42%, 40 months Stage III (2 parameters) 18%, 20 months
	Lilleness et al.[118] (Boston University)	Cheng et al.[120] (Columbia University) (ATTRv and ATTRwt)	
	TnI > 0.1 ng/mL BNP > 81 pg/mL	Mayo or NAC score (0-2 points) Daily dose of furosemide or equivalent: 0 mg/kg (0 points); > 0-0.5 mg/kg (2 points); > 1 mg/kg (3 points) NYHA class (I-IV) (1 to 4 points)	
	Median survival	Median survival	
	Stage I (0 parameters) Not reached Stage II (1 parameter) 112.8 months Stage III (2 parameters) 51.6 months Stage IIIb (2 parameters)* 12 months	1-3 points 90.5 months 4-6 points 38.5 months (Mayo Clinic) 36.0 months (NAC) 7-9 points 20.3 months (Mayo Clinic) 19.8 months (NAC)	

* TnI > 0.1 ng/mL and BNP > 700 pg/mL.

ATTRv, hereditary transthyretin amyloid cardiomyopathy; ATTRwt, wild type transthyretin amyloid cardiomyopathy; BNP, B-type natriuretic peptide; EF, ejection fraction; eGFR, estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula; FLC-diff, difference between involved and uninvolved free light chains; HF, heart failure; NAC, National Amyloidosis Center; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PPM, permanent pacemaker; TnI, troponin I; TnT, troponin T.

Adapted from Table 6 of "Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases."[18]

Heart Association functional class and diuretic use into the scoring system. They found that the area under the receiver operating characteristic curve can be further increased from 0.693 to 0.798 and 0.711 to 0.816 for the Mayo Clinic and NAC scores, respectively.[120] ATTR-CM has increasingly been diagnosed in recent years because of the development of effective disease-specific treatment. Therefore, accurate risk stratification requires identifying those who could benefit the most from the treatment.

Imaging in prognosis

Cardiac involvement is common in the light chain and ATTR amyloidosis. Imaging has a specific role in risk stratifying AL-CM and ATTR-CM and may add value to the existing clinical and biomarker-based risk stratification.[13]

Echocardiography

Numerous studies have investigated the prognostic value of echocardiographic parameters such as global longitudinal strain, early mitral inflow, deceleration time, myocardial performance index, and stroke volume index as predictors in cardiac amyloidosis. Although most of these parameters failed to demonstrate the prognostic value, Liu et al. reported that the Tei index or deformation parameters could predict 1-year mortality risk in patients with AL-CM.127 Other investigators found LV thickness progression was a potent risk predictor in AL-CM.[128,129] Currently, echocardiographic parameters alone are not used to stratify patients' risk with ATTRv-CM, ATTRwt-CM, or AL-CM, and further studies are required to evaluate the incremental value of echocardiographic parameters in prognostic staging.[97,129-133]

Cardiac magnetic resonance imaging

Multiple CMR imaging parameters have prognostic significance, including the presence and pattern of LGE, native T1, post-contrast T1, and multiple morphologic parameters.[134] Despite the excellent discriminative capacity of LGE, results are conflicting due to the non-standardized acquisition of CMR imaging.[91,135] After the transition to a phase-sensitive inversion recovery sequence, more evidence supports that the LGE pattern can show the progression of AL-CM and ATTR-CM.[93,136,137] Several studies also pointed out that the LGE pattern can be an independent prognosis-predicting factor for AL-CM and ATTR-CM after adjusting for echocardiographic parameters and biomarkers.[137] Additionally, the native T1 and ECV, as a surrogate of infiltration, are useful diagnostic markers in cardiac amyloidosis. Studies demonstrated that high native T1 indicates a worse prognosis in AL-CM but not ATTR-CM.[95,138] On the other hand, T1-derived ECV is an independent predicting factor for AL and ATTR-CM after adjusting for other risk factors.[26,95] T2 image, an indicator of tissue edema, is also an independent factor in AL-CM.[100] Incorporating CMR imaging parameters into the scoring system requires further investigation.

Radionuclide imaging

^{99m}Tc-PYP/DPD/hydroxymethylene diphosphonate (HMDP) scintigraphy and ^{123}I-MIBG have been shown to have prognostic value in several studies. ^{99m}Tc-PYP/DPD/HMDP cardiac uptake positively correlates with LV wall thickness and mass, troponin T, NT-proBNP, and ECV, and a negative correlation with LVEF.[26,139,140] Furthermore, some studies have shown that, in ^{99m}Tc-PYP scintigraphy, the H/CL ratio of > 1.5 was associated with worse survival in ATTR-CM.[26,140] It has been reported that cardiac sympathetic denervation is associated with decreased survival in ATTRv.[82,141] A late decreased heart-to-mediastinum ratio (HMR) measured by ^{123}I-MIBG scintigraphy indicates poor prognosis in ATTRv patients who underwent liver transplantation.[82] Nevertheless, the prognostic value of late-HMR reduction is still less clear in AL-CM and ATTRwt.[142-144] Although nuclear imaging is not formally incorporated into current risk-assessment algorithms, whether it should be combined with electrocardiographic, clinical, biomarker, and other imaging findings to develop an optimal prognostication scheme requires more studies.

TREATMENT OF CARDIAC AMYLOIDOSIS

The treatment of cardiac amyloidosis consists of two aspects: (1) Modify its underlying disease to suppress new amyloid formation, and (2) manage cardiac-related complications due to amyloid involvement (Figure 6).

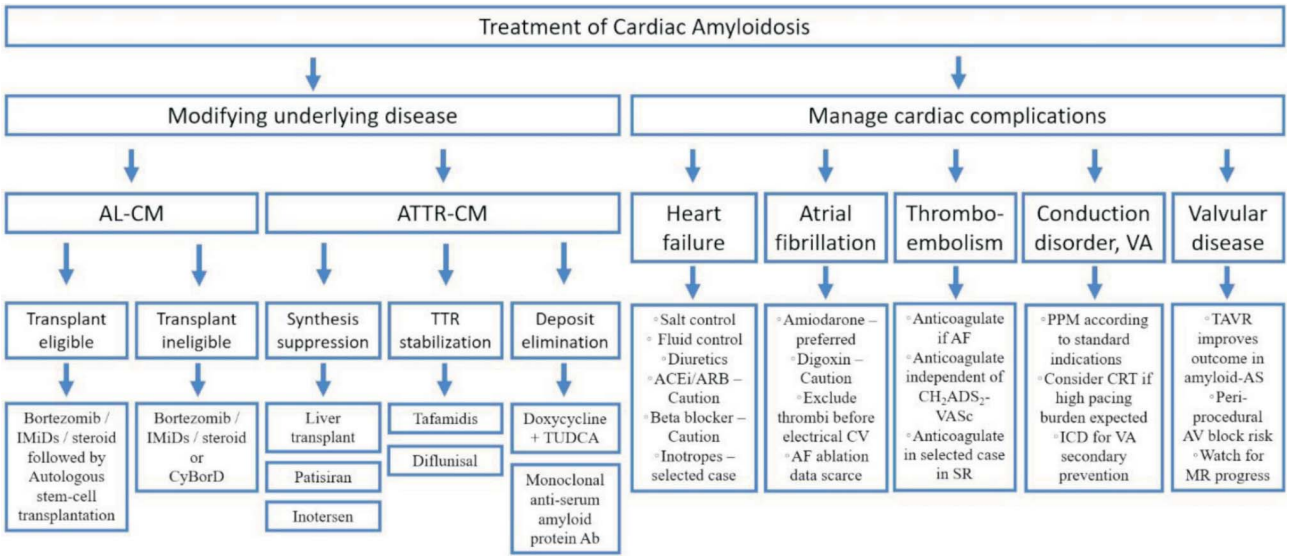

Figure 6. *Treatment of cardiac amyloidosis*. Ab, antibody; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AL-CM, immunoglobulin light chain amyloid cardiomyopathy; ARB, angiotensin receptor blocker; AS, aortic stenosis; ATTR-CM, transthyretin amyloid cardiomyopathy; AV, atrioventricular; CRT, cardiac resynchronization therapy; CV, cardioversion; ICD, implantable cardioverter defibrillator; MR, mitral regurgitation; PPM, permanent pacemaker; SR, sinus rhythm; TAVR, transcatheter aortic valve replacement; TTR, transthyretin; TUDCA, tauroursodeoxycholic acid; VA, ventricular arrhythmia. * Tafamidis is the only Taiwan Food and Drug Administration-approved medication for the treatment of transthyretin amyloid cardiomyopathy.*

Modify underlying disease

Two primary forms of amyloidosis could significantly affect the heart, and the treatments for their underlying disorders are discussed below:

Immunoglobulin light chain amyloid cardiomyopathy (AL-CM)

Plasma cell dyscrasia, which produces immunoglobin light chains, would probably cause light chain amyloidosis. Referral to hematology is mandatory for these patients. In general, patients would be classified into "transplant-eligible" and "transplant-ineligible" considering the patient's age, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, and baseline characteristics. Bortezomib (Proteasome inhibitor), IMiDs (Thalidomide or Lenalidomide), and steroids as triplet therapy is currently front-line therapy before autologous stem-cell transplantation in transplant-eligible patients. In contrast, the combination of bortezomib/IMiDs/steroid (VTD or VRD) and CyBorD (cyclophosphamide, bortezomib, and dexamethasone) are usually prescribed triplets for transplant-ineligible patients. Although melphalan/lenalidomide/prednisone (MPR) triplets proved effective in transplant-ineligible patients as first-line therapy, the chemotherapy-containing regimen is less used in contemporary clinical practice. Instead, many upcoming novel agents such as Daratumumab (anti-CD38 monoclonal antibody) showed encouraging results when used upfront with therapies mentioned above in newly diagnosed myeloma patients in transplant-eligible or ineligible settings. In relapse/refractory setting, plenty of novel agents are under investigation for future treatment of plasma cell dyscrasia, such as anti-SLAMF7 mAb (Elotuzumab), XPO1 inhibitor (Selinexor), monoclonal/bispecific anti-BCMA mAbs, CAR-T cells, and antibody-drug conjugates.

Transthyretin amyloid cardiomyopathy (ATTR-CM)

ATTR amyloidosis is derived from transthyretin. The liver produces most serum transthyretin; therefore, liver transplantation has been shown to reduce the serum concentration of transthyretin rapidly. According to data from the Familial Amyloidotic Polyneuropathy World Transplant Registry and Domino Liver Transplant Registry, 5-year and 20-year survival rates of liver transplantations for ATTR amyloidosis were 77% and 55%, respectively. However, the progression of amyloid deposition is often observed in the heart even after liver transplantation and the primary cause of death is still cardiovascular.

Suppression of transthyretin synthesis is another

way to modify the disease progression of ATTR amyloidosis. Patisiran, a small interfering RNA therapeutic agent targeting transthyretin mRNA, had been proven to reduce the serum transthyretin level by 80% from baseline. It could also inhibit the deterioration of LV wall thickness, global longitudinal strain, cardiac output, and NT-proBNP compared to the placebo group in the APOLLO study. Patisiran had been approved for ATTRv polyneuropathy by the EU and the USA. Inotersen, an antisense oligonucleotide therapeutic agent targeting transthyretin mRNA, has been proven to prevent the synthesis of transthyretin protein in the liver. Subcutaneous administration of inotersen significantly reduced neurological progression and improved health-related quality of life in patients with ATTRv amyloidosis and polyneuropathy in a phase III trial. Inotersen was approved in the EU and the USA but not in Japan, concerning its serious adverse effects on glomerulonephritis and thrombocytopenia.

The tetrameric structure of transthyretin is thought to be destabilized by gene mutations or aging and dissociated into monomers, causing misfolding and polymerization. Transthyretin tetramer stabilizer, tafamidis, has been shown to inhibit disease progression and decrease all-cause mortality and cardiovascular-related hospitalizations in the Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT) trial.[151] Details on tafamidis were described in another section.

Diflunisal, a nonsteroidal anti-inflammatory drug, can stabilize the TTR tetramer in vitro and may prevent misfolding monomers and dimers from forming amyloid deposits in the heart.[145,146] Diflunisal has been shown to reduce disease progression and preserve the quality of life of ATTRv polyneuropathy in a small randomized placebo-controlled trial.[145] Small retrospective studies showed that diflunisal stabilized cardiac function and was associated with improved survival in ATTR cardiomyopathy.[146,147] However, there is no large-scale randomized control trial to verify the effectiveness of diflunisal in ATTR cardiomyopathy. Although diflunisal is an off-label therapy for ATTR-CM, it may be a reasonable alternative in patients with financial restrictions with tafamidis (Table 9).

Eliminating amyloid deposits is a therapeutic goal anticipated to translate into restoring cardiac function and improving patient survival. Some data showed that doxycycline could destroy preformed amyloid. Doxycycline combined with tauroursodeoxycholic acid (ursodiol) improved cardiac outcomes in transthyretin amyloidosis. A recent multicenter randomized controlled trial demonstrated that doxycycline combined with CyBorD failed to prolong survival compared with CyBorD alone in AL-CM. New trials using ATTR antibodies (such as NI006) to remove amyloid fibrils from the heart are ongoing.

TAFAMIDIS AND ATTR-STABILIZERS IN THE TREATMENT OF ATTR CARDIOMYOPATHY (TABLE 9)

Tafamidis

Tafamidis was discovered by using a structure-based drug design strategy to inhibit transthyretin fibril formation in 1990.[148] The effectiveness of tafamidis is based on the ATTR-ACT trial, a randomized, double-blind, placebo-controlled study to evaluate the effect of tafamidis on all-cause mortality and cardiovascular hospitalization in ATTR-CM.[149] Tafamidis was significantly associated with reductions in all-cause mortality and cardiovascular hospitalizations in ATTRv and ATTRwt in this study. Tafamidis also significantly preserved the functional status evaluated by the 6-minute walk distance and quality of life measured by the Kansas City Cardiomyopathy Ques-

Table 9. ATTR stabilizers for the treatment of transthyretin amyloid cardiomyopathy

	Tafamidis	Diflunisal	AG10
Evidence	FDA, EMA, and TFDA approved	Off-label use	Under investigation
Dose	61 mg (tafamidis meglumine) QD	250 mg BID	N/A
Side effect	No	Fluid retention Renal dysfunction GI bleeding	N/A

ATTR, transthyretin; BID, twice per day; EMA, European Medicines Agency; FDA, Food and Drug Administration; GI, gastrointestinal; N/A, not applicable; QD, once per day; TFDA, Taiwan Food and Drug Administration.

tionnaire during the 30-month follow-up. The effectiveness of tafamidis, especially the high-dose regimen, was also confirmed in two long-term extension studies.[150,151] Tafamidis was well-tolerated in the study. Tafamidis is currently the only drug recommended for ATTR-CM by the European Society of Cardiology and the American Heart Association.[16,18]

Other ATTR stabilizers

Another approach to discovering ATTR stabilizers is based on the finding of the super-stabilizing mutation (T119M).[152] This mutation protects carriers from disease.[153] AG 10 is a selective ATTR stabilizer designed to mimic the structural influence of the protective T119M mutation. The phase II clinical trial was promising,[154] and it is now under phase III study (ATTRIBUTE-CM [Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy]; ClinicalTrials.gov. unique identifier: NCT03860935).

TREATMENT OF COMORBIDITIES

Heart failure

ATTR-CM results in progressive restrictive physiology, causing decreased compliance, reduced stroke volume, and compromised cardiac output. The roles of traditional HF medications remain restrained.

Loop diuretics have been prescribed to relieve congestion and maintain fluid balance.[16] Furosemide is a first-line diuretic; torsemide or bumetanide are good alternatives if patients respond poorly to furosemide because torsemide or bumetanide provides better potency and bioavailability. However, intravascular volume depletion might cause organ hypoperfusion, such as acute kidney injury, and lead to diuretic resistance. Tolvaptan may be an alternative therapy.[155] Aldosterone antagonists can synergize potassium-sparing when ATTR-CM patients have appropriate blood pressure and renal function. However, the hastening need for diuretics is a surrogate for disease progression.[120]

Pulmonary artery pressure monitoring has proved beneficial for HF with reduced EF hospitalization,[2,156] although the evidence in ATTR-CM patients is lacking.

Standard HF medications in ATTR-CM are not recommended by expert consensus. Beta-blockers may harm patients with ATTR-CM by reducing cardiac output because patients with ATTR-CM are heart rate dependent, owing to a relatively fixed low stroke volume.[16] The left ventricle cannot perform work as standard due to abnormal ventricular filling and altered ventricular-vascular coupling.[157] This leads to a lower stroke volume index. Patients with ATTR-CM have lower stroke volume. Hence beta-blockers should be prescribed carefully in those with symptomatic hypotension and slow heart rates. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin-receptor-neprilysin inhibitors might lead to symptomatic hypotension and are not recommended for ATTR-CM with HF with reduced EF. Data on using sodium-glucose cotransporter-2 inhibitors are still lacking. Postural hypotension usually occurs with autonomic neuropathy, especially in ATTRv,[160] and the symptom might be improved by midodrine, droxidopa, or compression stockings.[161] Reduced myocardial reserve may deteriorate the symptoms. For ATTR-CM with advanced HF, inotropic agents, such as catecholamines and phosphodiesterase inhibitors, can treat lower perfusion in the acute phase temporally. However, data on using inotropes in ATTR-CM are lacking.

Arrhythmia

AF

Amyloid fibers infiltrate the myocardial interstitial matrix, causing LVH with resultant diastolic dysfunction, increased left atrial pressure, and conduction disturbances in the atrium. Atrial dysfunction may be observed by decreased A-wave amplitude and left atrial appendage velocities. AF is more frequently encountered in ATTRwt than in ATTRv, and the prevalence is about 70%.[158] The prognosis of AF patients was worse than those without AF.[159] Anticoagulation is essential due to the high prevalence of intracardiac thrombus. The CHA_2DS_2-VASc risk score is not associated with the intracardiac thrombus.[160] Anticoagulation in ATTR-CM patients with AF is recommended regardless of the $CHAD_2DS_2$-VASc risk score and TEE-guided direct current cardioversion (DCCV).[160] However, recurrence is common.

Data is lacking on the antithromboembolic efficacy of vitamin K antagonists and direct oral anticoagulants. Given the known increased risk of intracardiac thrombus, the left atrial appendage is not recommended due

to concerns for potential device thrombosis. Using bisoprolol fumarate and carvedilol is reasonable in persistent AF for rate control. Careful monitoring while using carvedilol is needed as it consists of an alpha-blocker that could worsen postural hypotension. Non-dihydropyridine calcium channel blockers should not be used in CA[16,161] to avoid the negative inotropic effect, amyloid fibril biding, blunting of heart rate response, and hypotension. Amiodarone is preferred for rhythm and rate control because of its safety profile in cardiomyopathy, although limited information is available on ATTR-CM.[162] Digoxin remains controversial in managing ATTR-CM. There were concerns about digoxin binding with amyloid fibrils, which may result in toxicity in AL-CM.[163] On the other hand, a Cleveland Clinic single-center retrospective study revealed digoxin-related toxicity or arrhythmias that occurred in 12% of CA patients.[164] Low-dose digoxin with careful monitoring is an alternative for rate control, especially for those with hypotension. Mints et al. found no difference in survival between patients treated with rate or rhythm control.[162] TEE-guided DCCV may be considered in symptomatic AF patients with ATTR-CM.[165] Data in catheter ablation for AF in CA is not well-established. Some suggest that ablation is better than medical management in reducing clinical events when performed earlier during the disease process.[166] However, the recurrence rate of AF was still as high as 58%. Patients with ATTR-CM and paroxysmal AF, without LVH or left atrial dilatation, may consider receiving pulmonary vein isolation.[167]

Bradycardia

Patients with ATTR-CM frequently have atrioventricular conduction abnormalities.[33,168] This might be associated with loss of autonomic nervous control of cardiac function. Ambulatory electrocardiographic monitoring is suggested for those with syncope, pre-syncope, or palpitation. Standard indications for pacing are recommended. However, cardiac resynchronization therapy is recommended if a high pacing burden is expected since it is related to better survival.[169]

Ventricular arrhythmias are common, mainly asymptomatic non-sustained ventricular tachycardia. Several studies demonstrated appropriate implantable cardioverter-defibrillator therapy for ventricular arrhythmia but failed to show better survival than patients without implantable cardioverter-defibrillator.[158,170-173] Primary-prevention implantable cardioverter-defibrillator implantation in ATTR-CM is not recommended in the 2015 European Society of Cardiology guidelines,[174] and individualized decision-making for both primary and secondary prevention is recommended in the 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines.[175]

Valvular heart disease

Aortic stenosis (AS): 15% undergoing transcatheter aortic valve replacement has ATTR-CM,[50,176-178] which resembles a worse prognosis. Patients with ATTR-CM and severe AS tend to be older, male, and with increased interventricular septal wall thickness. They usually have a history of CTS and present with low flow-low gradient AS with mildly reduced LVEF.[12,50,179] Data from several studies demonstrate that transcatheter aortic valve replacement is preferred over surgical aortic valve replacement, and studies show that medical therapy is inferior for preventing death compared with aortic valve replacement.[50]

FOLLOW-UP PLAN IN CARDIAC AMYLOIDOSIS AND ASYMPTOMATIC *TTR* VARIANT CARRIERS

Because treatment for ATTR-CM is most effective when the cardiac function has not deteriorated significantly, establishing guidelines for medical care for the asymptomatic ATTRv carriers is essential, including an early diagnosis for ATTR-CM with readily available non-invasive tests and initiation of prompt treatment. However, the natural history of subclinical ATTR-CM and the test and diagnosis performance in this period are not yet well recognized, which would later lead to the controversial issues of the pros and cons of early treatment for asymptomatic ATTRv carriers.

Preclinical course

ATTR is a heterogeneous disorder with multiorgan involvement, and a relatively high prevalence of ATTR seen at cardiology sites in the general population is p.V142I variant.[180] Several epidemiologic cohort studies of p.V142I ATTRm carriers provided a few clues for subclinical ATTR-CM phenotypes. However, cohort studies

on other less frequent *TTR* genetic variants are still scant. As the clinical penetrance of pathogenic alleles is not 100%, data from the Cardiovascular Health Studies cohorts and the Atherosclerosis Risk In Communities have shown that p.V142I *TTR* carriers at a median age of 52 years have a 45% higher lifetime risk to develop HF than the non-carriers.[181] Clinical penetrance is age-dependent, and HF commonly manifests after the seventh and eighth decades of life;[182] carriers of pathogenic *TTR* variants likely manifest with subclinical forms of the disease at a much younger age.

Screening tools

Imaging- or biomarker-based screening criteria for ATTR-CM for asymptomatic *TTR* variant carriers are not yet provided. Low sensitivity and specificity for diagnosing ATTR-CM are found when screening is performed with electrocardiography, echocardiography, and other biomarkers such as NT-proBNP and cardiac troponin. Furthermore, the subtle cardiac abnormalities observed by these imaging modalities in asymptomatic *TTR* variant carriers are not verified to be associated with myocardial amyloid infiltration on pathologic examinations, and these results might not be specific for ATTR-CM.

Genetic testing

Genetic testing is capable of identifying *TTR* variant carriers and estimating the potential risk in the pre-penetrant phase and is recommended for the relatives of patients with hereditary ATTR-CM to mitigate underdiagnosis in the *TTR* variant carriers.[183] Importantly, genetic testing should be provided with genetic counseling to both patients and their families and could be offered during young adulthood to provide valuable genetic information to guide professional treatment choices and reproductive plans. Genetic testing for minors is not suggested, as all hereditary amyloidosis occurs later in adulthood.

Once an individual's pathologic *TTR* genetic variant is identified, the predicted age of disease onset should be determined. Several factors should be considered when defining the predicted age of disease onset, which include the specific variant, the typical age at disease onset, and disease severity in family members.[184]

Biomarkers

Some cardiac biomarkers, such as troponin and NT-proBNP, are known to be associated with the development of HF. However, they might fall in normal ranges for asymptomatic *TTR* variant carriers and do not distinguish asymptomatic carriers of pathogenic *TTR* variants from noncarriers well, although these biomarker levels might increase over time for asymptomatic *TTR* variant carriers.[185,186] Several ATTR-specific biomarkers might be promising to reflect ATTR kinetic stability and the degree of amyloidogenesis, which include circulating misfolded ATTR oligomers,[187,188] retinol-binding protein 4,[189,190] and neurofilament light chains.[191] However, tests for these circulating biomarkers are not commonly available in the clinical laboratories in hospitals, and whether they provide incremental diagnostic insight to uncover subclinical ATTR-CM is unknown.

Echocardiography

The Coronary Artery Risk Development in Young Adults (CARDIA) study results have demonstrated that the p.V142I *TTR* carriers would have a relatively lower absolute LV systolic circumferential strain and greater LV mass indexed to body surface area at the mean age of 54 years compared with race-matched non-carriers.[192] IThe echocardiography with strain-based imaging monitored the development of ATTR-CM phenotypic penetrance over time, although these p.V142I *TTR* carriers manifested with subtle cardiac abnormalities.[185] Echocardiography is helpful for the early detection of cardiac structural change in asymptomatic *TTR* variant carriers in these studies.

^{99m}Tc-PYP scintigraphy

A total of 40 patients received ^{99m}Tc-PYP imaging to evaluate for ATTR-CM in a single-center retrospective study, and myocardial uptake with an average heart/contralateral lung ratio of 1.5 ± 0.4 was found in 10 out of 12 asymptomatic carriers of pathogenic *TTR* variants, despite their relatively low levels of BNP and normal thickness of interventricular septal on echocardiography.[193] From the study results, detecting subclinical ATTR-CM with ^{99m}Tc-PYP scans is feasible.

Cardiac magnetic resonance imaging

Imaging with CMR imaging can exert tissue characterization and quantify myocardial amyloid infiltration from subclinical ATTR-CM. Although the performance

estimates (approximately 80-93% sensitivity and specificity) of CMR imaging are well accepted for the diagnoses of cardiac amyloidosis for individuals with a reasonable index of suspicion for the disease,[194] the application of CMR imaging to subclinical ATTR-CM has not been systematically examined.

Screening timing and follow-up interval

No consensus is obtained and validated for the timing of screening for subclinical ATTR-CM in asymptomatic *TTR* variant carriers. Generally, for the asymptotic *TTR* variant carriers, it is recommended to start monitoring for ATTR-CM 10 years before the predicted age of disease onset.[195] Furthermore, once the red-flag symptoms and/or abnormal findings for amyloidosis are recognized during this follow-up period, more specific imaging studies and biopsies to detect amyloid deposits should be considered to confirm the diagnosis of ATTR-CM. These recommendations are especially pertinent for the age-similar siblings of a proband at higher risk for developing ATTR-CM.

No optimal follow-up scheme for asymptomatic ATTRv carriers has yet been addressed in any study; however, annual follow-up with increasing frequency is recommended, especially for those approaching the predicted age of disease onset and genotypes well known to have rapidly progressive courses. A standard scheme is recommended to consist of every 6-month visits with ECG and serum biomarker tests (including serum creatinine, NT-proBNP, and cardiac troponin) and an annual echocardiogram with 24-hour Holter ECG. These recommendations warrant further studies on larger scales to prove their efficacy and cost-effectiveness.

DECLARATION OF CONFLICT OF INTEREST

All authors declare no conflict of interest.

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