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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Critical Comparison of Documents From Scientific Societies on Cardiac Amyloidosis

JACC State-of-the-Art Review

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ABSTRACT

Over the last year, 5 national or international scientific societies have issued documents regarding cardiac amyloidosis (CA) to highlight the emerging clinical science, raise awareness, and facilitate diagnosis and management of CA. These documents provide useful guidance for clinicians managing patients with CA, and all include: 1) an algorithm to establish a diagnosis; 2) an emphasis on noninvasive diagnosis with the combined use of bone scintigraphy and the exclusion of a monoclonal protein; and 3) indications for novel disease-modifying therapies for symptomatic CA, either with or without peripheral neuropathy. Nonetheless, the documents diverge on specific details of diagnosis, risk stratification, and treatment. Highlighting the similarities and differences of the documents by the 5 scientific societies with respect to diagnosis, risk stratification, and treatment offers useful insight into the knowledge gaps and unmet needs in the management of CA. An analysis of these documents, therefore, highlights "gray zones" requiring further investigation. (J Am Coll Cardiol 2022;79:1288-1303) © 2022 by the American College of Cardiology Foundation.

Over the last year, 5 national or international scientific societies have issued documents regarding cardiac amyloidosis (CA): a position statement by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases[1] implemented into the latest ESC heart failure (HF) guidelines[2]; a position statement by the German Cardiac Society (*Deutsche Gesellschaft für Kardiologie* [German Cardiac Society] [DGK])[3]; a position statement and an update on tafamidis by the

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HIGHLIGHTS

- Clinical guidance documents on CA have been issued by 5 professional societies during the past year.
- These are generally aligned on a diagnostic algorithm, noninvasive diagnosis based on combining bone scintigraphy and exclusion of a monoclonal proteins, and indications for disease-modifying therapies for symptomatic patients.
- Divergence on certain aspects of diagnosis, risk stratification, and clinical management highlights areas requiring further investigation.

Canadian Cardiovascular Society/Canadian Heart Failure Society (CCS/CHFS)[4,5]; a scientific statement focused on amyloid transthyretin CA (ATTR-CA) by the American Heart Association (AHA) followed by an addendum on tafamidis dose[6,7]; and a guideline by the Japanese Circulation Society (JCS).[8] Interest in CA has grown as a result of multiple recent areas of advancement. First, imaging techniques allow accurate noninvasive diagnosis of ATTR-CA without the need for a confirmatory endomyocardial biopsy. Second, observational studies indicate that CA may be underrecognized in a significant proportion of patients with HF. Third, novel and expensive medications may effectively treat the cardiac and neurologic sequelae of CA, so clear criteria for prescription and reimbursement are required.[9]

This review paper highlights the similarities and differences between documents by scientific societies with respect to diagnosis, risk stratification, and treatment of cardiac complications. We do not wish to endorse, discard, or replace specific recommendations by existing documents. On the contrary, we present the different recommendations about specific topics together with our assessment of their level of evidence, using a simple system (evidence from a clinical trial in this specific population; evidence from a subgroup analysis, retrospective studies or case series; expert consensus opinion). By doing so, our goal is to encourage further amyloidosis research and to promote the standardization of diagnostic and therapeutic algorithms.

DIAGNOSIS

WHICH IS THE GENERAL APPROACH TO THE DIAGNOSIS OF CA? Four out of 5 documents propose a single diagnostic flow chart that can be schematically articulated into 3 steps: suspicion, definite diagnosis of CA, and identification of the CA subtype.[4,6,8,10] The 2 main decisional nodes consist in the search of the monoclonal protein and bone scintigraphy with diphosphonate or pyrophosphate tracers, with the possible need for further histological exams. The DGK statement diverges from the others because it contemplates multiple diagnostic pathways, one of them based on cardiac magnetic resonance (CMR); this last pathway mandatorily requires an endomyocardial biopsy to allow a definite diagnosis and to distinguish the CA subtype.[2] The diagnostic algorithms are summarized in **Figure 1**.

The need for early diagnosis is stressed by all documents, which list several findings that may prompt a diagnostic work-up for CA. These "red flags" consist of clinical evidence of extracardiac disease (with frequent involvement of tendons, peripheral nerves, and kidneys) and low QRS voltages despite increased left ventricular increased wall thickness on echocardiogram, preserved apical strain despite depressed basal strain on echocardiogram, or Q waves on electrocardiogram without evidence of a previous infarction.[11] Different red flags noted are listed in the 5 documents (**Table 1**). Furthermore, the ESC[1] and DGK[3] documents recommend evaluation for CA in patients with left ventricular wall thickness 12 mm or higher in the presence of at least 1 red flag, while the CCS/CHFS and AHA documents basically recommend a diagnostic evaluation for CA if red flags are present.[4,6] Finally, the JCS guideline notes that some red flags are mandatory for diagnosis.[8] The variation between statements highlights the first unmet need: understanding how the red flags should be utilized, prioritized, and combined when deciding on the timing of a diagnostic evaluation for CA in a population with a low prevalence of disease.

All documents propose diagnostic algorithms that combine the search for a monoclonal protein and bone scintigraphy. These algorithms may lead to a final diagnosis of variant ATTR-CA (ATTRv-CA), wild-type ATTR-CA (ATTRwt-CA), amyloid light-chain CA (AL-CA), ATTRv or ATTRwt and monoclonal gammopathy of undetermined significance, rarer CA forms, or other cardiomyopathies. The approach proposed by the ESC and DGK documents, namely the referral of patients with an increased wall thickness and a single red flag to a diagnostic work-up for CA, has not been formally investigated, and its positive

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

AL-CA = amyloid light-chain cardiac amyloidosis

ATTR-CA = amyloid transthyretin cardiac amyloidosis

ATTRv-CA = variant amyloid transthyretin cardiac amyloidosis

ATTRwt-CA = wild-type amyloid transthyretin cardiac amyloidosis

CCS/CHFS = Canadian Cardiovascular Society/Canadian Heart Failure Society

CMR = cardiac magnetic resonance

DGK = *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society)

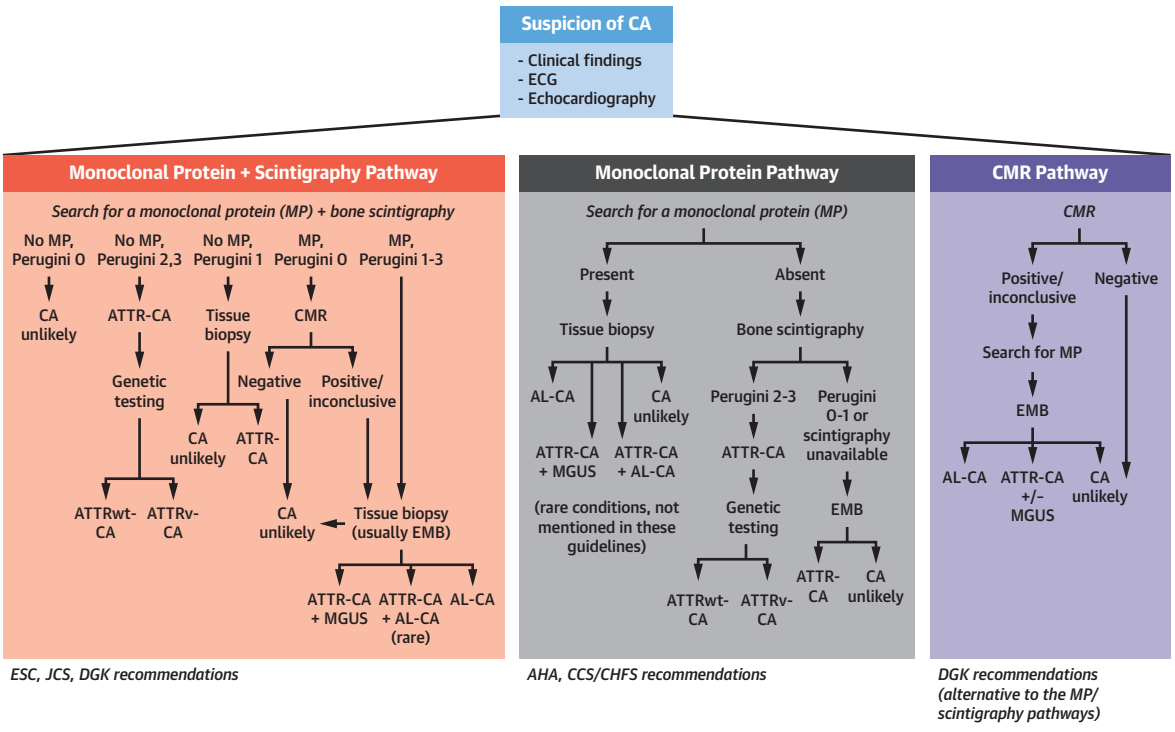
ECG = electrocardiogram

ESC = European Society of Cardiology

JCS = Japanese Circulation Society

NYHA = New York Heart Association

FIGURE 1 **Overview of Diagnostic Algorithms for CA**



For details, see the original documents.[1,3,4,6,8] AHA = American Heart Association; AL-CA = amyloid light-chain cardiac amyloidosis; ATTR-CA = amyloid transthyretin cardiac amyloidosis; ATTRv-CA = variant amyloid transthyretin cardiac amyloidosis; ATTRwt-CA = wild-type amyloid transthyretin cardiac amyloidosis; CA = cardiac amyloidosis; CCS/CHFS = Canadian Cardiovascular Society/Canadian Heart Failure Society; CMR = cardiac magnetic resonance; DGK = *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ECG = electrocardiography; EMB = endomyocardial biopsy; ESC = European Society of Cardiology; MGUS = monoclonal gammopathy of undetermined significance; JSC = Japanese Society of Cardiology; MP = monoclonal protein; NP = cardiac natriuretic peptide (B-type natriuretic peptide, N-terminal B-type natriuretic peptide); Tn = high-sensitivity troponins.

predictive value could be low outside of tertiary referral centers. Furthermore, the relative diagnostic yield of single red flags or combinations of red flags is currently unclear and should be explored in dedicated studies.

BONE TRACER SCINTIGRAPHY AND MONOCLONAL PROTEIN SEARCH: WHICH IS THE RIGHT SEQUENCE? In 2016, Gillmore et al[12] published a multicenter, international study establishing the accuracy of nonbiopsy diagnosis of TTR CA. In the proposed algorithm, patients with clinical, electrocardiographic, echocardiographic, and possibly also CMR features compatible with CA were recommended to have bone scintigraphy and the search for a monoclonal protein with serum or urine immunofixation and assessment of serum-free light chains (which must also be interpreted in relation to renal function, given the normal polyclonal rise in ratio with advancing chronic kidney disease). The chronological order of bone scintigraphy and the search for a monoclonal protein was not specified, implicitly suggesting that both examinations must be performed.[12] The AHA and CCS/CSHFS documents note that while both bone scintigraphy and monoclonal light chain screens may be performed simultaneously for convenience, the monoclonal light chain screen takes priority, as bone scintigraphy findings must be interpreted on the light of the presence or absence of a monoclonal protein, and also because AL-CA should be promptly recognized and treated. When no monoclonal protein is found, the patient should undergo a bone scintigraphy or (when scintigraphy is not available) an endomyocardial biopsy.[4,6] The DGK statement also recommends that the search for a monoclonal protein precedes imaging in patients with suspected AL amyloidosis.[3] Conversely, the ESC document explicitly states that the search for a monoclonal protein and bone scintigraphy should be performed together.[1] The notion of performing both exams in a single step emerges also from the JCS document, in which 4

TABLE 1 Red Flags for Cardiac Amyloidosis

ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
• HF ≥65 y • Aortic stenosis ≥65 y • Hypotension or normotensive when previously hypertensive • Sensory involvement, autonomic dysfunction • Peripheral polyneuropathy • Proteinuria • Skin bruising • Bilateral carpal tunnel syndrome • Ruptured biceps tendon • Subendocardial/transmural LGE or increased ECV • Decreased QRS voltage-to-mass ratio • Pseudo Q waves • AV conduction disease • Possible family history	• Age >60 y, HF symptoms, normal-sized ventricles • Low voltages or detection of an AV block in the resting ECG • Pericardial effusion, interatrial thickening, granular sparkling appearance, RV wall thickening, apical sparing • Macroglossia with notches in the lateral portions of the tongue • Periorbital purpura • Atraumatic biceps tendon rupture • Sensorimotor polyneuropathy • Spinal stenosis • Autonomic dysfunction • Vitreous opacity, pupillary changes	• Unexplained increased LV wall thickness • LFLG aortic stenosis with preserved LVEF (age >60 y) • Carpal tunnel syndrome (bilateral) • Established AL or ATTR in noncardiac organ/system (ie, renal AL amyloidosis causing nephrotic syndrome) • Peripheral sensorimotor neuropathy and/or dysautonomia	• Intolerance to antihypertensive or HF medications because of symptomatic hypotension or orthostasis • Neurological: sensorimotor polyneuropathy (paresthesias and weakness), autonomic dysfunction (orthostatic hypotension, postprandial diarrhea alternating with constipation, gastroparesis, urinary retention, and incontinence) • Persistent low-level elevation in serum troponin • Orthopedic: carpal tunnel syndrome, lumbar spinal stenosis, unprovoked biceps tendon rupture, hip and knee arthroplasty • Discordance between QRS voltage on an ECG and wall thickness on imaging • Black race • Unexplained AV block or prior pacemaker implantation • Family history of polyneuropathy • Unexplained LV wall thickening, RV thickening, or atrial wall thickening • Family history of cardiomyopathy	• Symptoms of HF (eg, shortness of breath, edema), dizziness, and syncope • Atrial fibrillation • Conduction system disorder (eg, AV block, bundle branch block, intraventricular conduction disorder) • Ventricular arrhythmia • Low voltage in limb leads • QS pattern in V_1-V_3 • Ventricular wall thickening (including RV) • Atrial septal thickening • Ventricular diastolic dysfunction (restrictive) • Granular sparkling appearance • Pericardial effusion • Valve thickening • Reduction in longitudinal strain at the base of left ventricle (apical sparing) • Elevated BNP and NT-proBNP • Elevated cardiac troponin T/I • Global diffuse myocardial LGE in the subendocardial layers on CMR imaging • Elevated native T1 and ECV fraction in T1 mapping

AHA = American Heart Association; AL = amyloid light chain; ATTR = amyloid transthyretin; AV = atrioventricular; BNP = B-type natriuretic peptide; CCS/CHFS = Canadian Cardiovascular Society/Canadian Heart Failure Society; CMR = cardiac magnetic resonance; DGK = *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ECG = electrocardiogram; ECV = extracellular volume; ESC = European Society of Cardiology; JCS = Japanese Circulation Society; LFLG = low-flow, low-gradient; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RV = right ventricular.

possible combinations of positive or negative results are considered.[8] When these exams are not performed in the same step, there is a risk of missing the coexistence of ATTR-CA and monoclonal gammopathy of unknown significance. Indeed, this combination is not specifically mentioned in the AHA and CCS/CHFS algorithms,[4,6] while it is contemplated in the ESC statement: "[In patients with both a positive scintigraphy scan and a monoclonal protein,] ATTR amyloidosis with concomitant [monoclonal gammopathy of unknown significance], AL amyloidosis or coexistence of both AL and ATTR amyloidosis are possible."[1]

Overall, the divergence of the diagnostic pathways on the timing of bone scintigraphy and monoclonal light chain screens in patients with suspected CA highlights another unresolved issue regarding the optimal diagnostic approach.

WHICH ARE THE ECHOCARDIOGRAPHIC CLUES TO THE DIAGNOSIS OF CA? Transthoracic echocardiography is the primary and most widely available diagnostic imaging tool for patients with suspected CA[3] and may provide many "red flags" for this condition.[1] The AHA document stresses that echocardiography is useful to distinguish CA from cardiomyopathies with a hypertrophic phenotype, while it cannot differentiate AL-CA from ATTR-CA.[6] The CCS/CHFS statement,[4] JCS guideline,[8] and DGK statement[3] recommend the use of all available echocardiographic techniques, including speckle-tracking analysis, to diagnose CA. The ESC document uniquely proposes an echocardiographic score (the IWT score) as a diagnostic tool, stating that score values of 8 or higher could be diagnostic of ATTR-CA when no monoclonal protein is found, bone scintigraphy is positive (Perugini score 2-3), and a peripheral tissue biopsy shows ATTR amyloid,[1,13] (Supplemental Figure 1). This proposal may be seen as the first attempt to standardize the echocardiographic evaluation of patients with suspected CA.

HOW SHOULD WE USE CIRCULATING BIOMARKERS? B-type natriuretic peptides and troponins within the normal range virtually exclude CA. Conversely, elevated biomarkers may indicate cardiac involvement in amyloidosis but are not specific for CA. Only the JCS guideline provides formal recommendations about biomarkers, stating that both N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin might aid the diagnosis of CA (Class IIa, Level of Evidence: C).[8] The JCS guideline

TABLE 2 Criteria for Positive Scintigraphy With Bone Tracers

ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
Perugini score ≥2 on a ^{99m}Tc-DPD or ^{99m}Tc-HMDP scan after 3 h	Perugini score ≥2 on a ^{99m}Tc-DPD or ^{99m}Tc-HMDP scan after 3 h	Perugini score ≥2 and/or an H/CL ratio ≥1.5 on a ^{99m}Tc-PYP scan after 1 or 3 h	Perugini score ≥2 and/or an H/CL ratio >1.5 on a ^{99m}Tc-PYP scan after 1 or 3 h	Perugini score ≥2 and/or an H/CL >1.5 on a 1-h scan or >1.3 on a 3-h scan

A positive bone scintigraphy allows to diagnose ATTR cardiac amyloidosis when no monoclonal protein is found.
DPD = 3,3-diphosphono-1,2-propanodicarboxylate; H/CL = heart/contralateral chest; HMDP = hydroxymethylene; PYP = pyrophosphate; other abbreviations as in Table 1.

also mentions the possible utility of retinol binding protein 4, which binds to TTR and could stabilize the tetramer, for identifying subjects with ATTRv.[8] Indeed, it has been reported that patients with Val122Ile ATTRv have significantly lower RBP4 than patients with nonamyloid HF, although no diagnostic cutoff was identified.[14] The diagnostic value of RBP4 is being investigated in elderly Black and Hispanic patients with HF (NCT03812172).

The dearth of specific recommendations for use of biomarkers in the diagnosis or prognostic stratification of CA in these 5 documents denotes our lack of understanding on how to best incorporate biomarkers into the CA management algorithm.

WHICH TRACER SHOULD BE USED FOR BONE SCINTIGRAPHY? WHEN IS SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY NEEDED? The ^{99m}Tc phosphates currently most often used in Europe are ^{99m}Tc-DPD (3,3-diphosphono-1,2-propanodicarboxylate) and ^{99m}Tc-HMDP (hydroxymethylene). By contrast, ^{99m}Tc-PYP (pyrophosphate) is the only tracer available in the United States, Canada, and Japan. The diagnostic criteria for positive planar scintigraphy are shown in Table 2. Single-photon emission computed tomography imaging enables a more accurate assessment of tracer uptake in the myocardium and blood pool and is recommended by all societies. While there is uniformity among society documents,[15,16] whether the 3 current isotopes perform equally well and whether tomographic imaging adds to planar scintigraphy remain unanswered questions.

WHICH IS THE ROLE OF CMR IMAGING IN THE DIAGNOSTIC WORK-UP? CMR is highly sensitive in detecting cardiac involvement in CA but cannot be used to distinguish amyloid subtypes.[17] In the AHA,[6] CCS/CHFS,[4] and JCS[8] documents, CMR is not an essential part of the diagnostic algorithm. The ESC statement identifies specific instances in which CMR can be important for diagnosis: 1) when bone scintigraphy is negative and no monoclonal protein is found, but the clinical suspicion is high; and 2) when bone scintigraphy is negative and a monoclonal protein is found. In the latter case, a negative CMR scan makes CA unlikely, possibly allowing to avoid tissue biopsy.[1] Moreover, CMR may be indicated in case of inconclusive results, as bone scintigraphy could be negative in some ATTRv mutations (p.Phe84Leu, p.Ser97Tyr) and in rare subtypes of CA.[1] Finally, the DGK statement is the only one to explicitly include a CMR-based diagnostic pathway that parallels the "scintigraphy-based" path and the "laboratory-based (monoclonal protein) path"[3] and requires an endomyocardial biopsy to reach a definite diagnosis of CA.

WHEN IS A HISTOLOGY EVALUATION REQUIRED? WHICH ORGAN OR TISSUE SHOULD BE BIOPSIED? The documents all note that histologic diagnosis is required for AL amyloidosis (when a monoclonal protein is found) or if there is high clinical suspicion for CA despite negative or equivocal bone scintigraphy. The ESC document also emphasizes the role of histologic diagnosis if there are borderline findings on bone scintigraphy (Perugini score 1).[1] Uniquely, the JCS guideline recommends a possible biopsy even if there is a positive bone scintigraphy scan and no monoclonal protein to make a definitive diagnosis of ATTR-CA.[8]

Regarding the choice of biopsy site, all documents note that possible alternatives to endomyocardial biopsy are fat pad biopsy, renal biopsy (in patients with suspected renal amyloidosis),[4,6] or bone marrow biopsy.[4] The JCS guideline proposes several additional sites for minimally invasive biopsy: abdominal wall liposuction biopsy, skin biopsy, lip biopsy, or digestive tract biopsy.[8] Importantly, a fat pad biopsy has low sensitivity, and a negative fat pad biopsy is not sufficient to exclude CA.[6]

WHO SHOULD UNDERGO A GENETIC TEST? All documents agree that patients with a definite diagnosis of ATTR-CA should undergo a search for *TTR* gene mutations to distinguish wild-type from hereditary (variant) forms.[1,3,4,6,8] Genetic testing should be performed regardless of age.[1,6] The DGK document adds

that "In selected cases, an extended genetic diagnosis of further amyloidosis genes (eg, if AApoA1 is suspected) may also be considered."[3]

RISK PREDICTION AND MANAGEMENT

WHEN SHOULD WE SEARCH FOR A GENE MUTATION IN FAMILY MEMBERS? HOW SHOULD WE FOLLOW MUTATION CARRIERS? "First-degree relatives"[3] and possibly other biologically related relatives of patients with ATTRv-CA[1,3,4,6,8] should undergo a genetic screening to determine their mutation carrier status. Genetic testing should not be proposed to minors,[1,8] while it could be offered to young adults when results could guide lifestyle choices or reproductive planning.[1]

There is little guidance regarding monitoring of *TTR* mutation carriers. The ESC document advises to "search for disease manifestations [starting] around 10 years before the age of disease onset in affected family members or as soon as symptoms compatible with amyloidosis develop."[1] The JCS guideline states that "the carrier should be followed on a periodic basis […] and psychological support and screening tests for the onset of amyloidosis should be provided."[8] The AHA document notes that "what methods (imaging or biomarkers) should be used to monitor disease progression, the timing of initiation of therapy in ATTRv carriers remains an area of uncertainty."[6]

This lack of clear guidance and empiric data highlights another unmet need in CA: how to follow asymptomatic gene carriers. Another important point, not touched by current guidelines, is how mutation carriers with signs of disease but who are still asymptomatic should be treated.

HOW CAN WE STRATIFY PATIENT RISK? Only some documents discuss specifically risk prediction. Specifically, the ESC statement lists 2 scores for AL-CA, 1 for ATTRwt-CA, and 2 for ATTRv-CA or ATTRwt-CA,[1] and the JCS guideline reminds that NT-proBNP and high-sensitivity troponin can help refine risk stratification in patients with ATTRwt.[8] The choice between different scores and the ways to tailor the therapeutic strategy is not described, highlighting another knowledge gap in the management of patients with CA.

CAN WE USE HF DRUGS? Recommendations for neurohormonal blockade are summarized in **Table 3**. Treatment with tolerated doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and mineralocorticoid receptor antagonists has a weak recommendation by the JCS guideline (Class IIb, Level of Evidence: C),[8] while the DGK and AHA statements advise for "considerable caution."[3,6] Conversely, the ESC statement declares that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be avoided.[1]

Beta-blockers are traditionally contraindicated in patients with CA because of concerns of hypotension, coronary hypoperfusion, decreasing cardiac output, and conduction disturbances, in the absence of a demonstrated benefit on patient survival or quality of life.[3] The JCS guideline allows treatment with tolerated doses of beta-blocker in heart failure patients (Class IIb, Level of Evidence: C) or for heart rate control in patients with atrial fibrillation, following a case-by-case discussion (Class IIb, Level of Evidence: C).[8] The DGK and AHA documents stress the possible complications of beta-blockers; the AHA document notes that beta-blockers are often poorly tolerated, even at low doses, because patients with ATTR-CA "rely on heart rate response to maintain cardiac output given a fixed stroke volume."[3,6] Similarly, the CCS/CHFS statement recommends "considerable caution" when beta-blockers are prescribed for indications other than CA.[4] The ESC document instead recommends discontinuing them regardless of their indication or tolerability.[1]

A better understanding of the role of neurohormonal blockade in patients with CA remains an unmet need, though observational evidence suggests that there may be no survival benefit in these patients and that deprescribing beta-blockers in ATTR-CA was associated with improved survival.[18]

CAN WE USE DIGOXIN? Digoxin therapy is a possible option for rate control in patients with atrial fibrillation. The notion that digoxin should be avoided in patients with CA derives from old case reports reporting toxic effects attributed to the binding of digoxin to amyloid fibrils.[19,20] Recent retrospective cohorts suggest that digoxin is safe when started at low doses and patients are closely monitored.[21] The JCS guideline advises against digoxin treatment (Class III, Level of Evidence: C).[8] The CCS/CHFS statement recommend to avoid digoxin or use it with caution,[4] the DGK,[3] ESC,[1] and AHA statements[6] that digoxin "may be used cautiously."

WHICH PATIENTS WITH ATRIAL FIBRILLATION SHOULD RECEIVE ANTICOAGULANTS? Atrial fibrillation is common in patients with CA, particularly those with ATTR-CA.[22,23] Patients with CA and atrial fibrillation have a very high risk of left atrial thrombosis that is not adequately captured by the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category) or equivalent

TABLE 3 Drug Therapies for HF and AF

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
HF setting					
Loop or thiazide diuretics	Recommended[a]	Recommended[a]	Recommended[a]	Recommended, but avoid underfilling and worsening renal function from restrictive physiology[a]	Recommended[a]
Nitrates or carperitide (AHF)	No recommendation	No recommendation	No recommendation	No recommendation	Might be considered[a]
Catecholamines, PDE inhibitor (AHF)	No recommendation	No recommendation	No recommendation	No recommendation	Might be considered[a]
Beta-blockers	Not recommended, deprescribe (should be avoided)[a]	Avoid or very cautious use[a]	Avoid or very cautious use[a]	No data for benefit; may not be tolerated given fixed stroke volume (should be avoided)[a]	Tolerated dosing might be considered[a]
ACE inhibitor/ARB	Not recommended (should be avoided)[a]	Avoid or very cautious use[a]	Avoid or very cautious use[a]	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction (should be avoided)[a]	Tolerated dosing might be considered[a]
Sacubitril/valsartan	No recommendation	No recommendation	No recommendation	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction (should be avoided)[a]	No recommendation
MRA	No recommendation	No recommendation	Recommended[a]	Might be considered in conjunction with loop diuretics if adequate blood pressure and renal function[a]	Tolerated dosing might be considered[a]
AF/flutter/tachycardia setting					
Digoxin	Might be considered[b]	Avoid or very cautious use[a]	Avoid or very cautious use[a]	Might be considered; use cautiously[b]	Not recommended (should be avoided)[a]
Amiodarone	Might be considered (first choice)[a]	No recommendation	Might be considered (first choice)[a]	Might be considered (first choice)[a]	No recommendation
Beta-blockers	Not recommended (should be avoided)[a]	Avoid or very cautious use[a]	Avoid or very cautious use[a]	Might be considered[a]	Case-by-case decision (may be considered)[a]
Non-DHP CCB: ATTR-CA, preserved LV function	No recommendation	Avoid or very cautious use[a]	Avoid or very cautious use[a]	Avoid whenever possible[a]	Case-by-case decision (may be considered)[a]
Non-DHP CCB: ATTR-CA, reduced LV function					Not recommended (should be avoided)[a]
Non-DHP CCB: AL-CA				Not recommended (should be avoided)[a]	Not recommended (should be avoided)[a]
Anticoagulation regardless of CHA_2DS_2-VASc score?	Yes (recommended)[a]	No recommendation	Yes (recommended)[a]	Yes (recommended)[a]	No recommendation
Anticoagulation in SR?	Might be considered[a]	No recommendation	No recommendation	Might be considered[a]	No recommendation

[a]Expert consensus opinion. [b]Evidence from a subgroup analysis, retrospective studies, or case series. green = considered with substantial agreement with all other documents; yellow = considered with substantial agreement with ≥1 other document; red = considered with a specific position, not found in any other document; white = not considered.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AHF = acute heart failure; AL-CA = amyloid light-chain cardiac amyloidosis; ARB = angiotensin receptor blocker; AT = atrial tachycardia; ATTR-CA = amyloid transthyretin cardiac amyloidosis; CCB = calcium-channel blocker; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; DHP = dihydropyridine; DOAC = direct oral anticoagulant; LOE = Level of Evidence; MRA = mineralocorticoid receptor antagonist; PDE = phosphodiesterase; SR = sinus rhythm; VKA = vitamin K antagonist; other abbreviations as in Table 1.

scores. The 5 documents uniformly agree that all patients with CA and history of atrial fibrillation or flutter should be anticoagulated.[1,3,4,6,8] As for the choice between anticoagulants, the only indication comes from the CCS/CHFS statement, which recommends to prefer direct oral anticoagulants in the absence of contraindications,[4] despite the lack of specific evidence. Left atrial appendage closure is mentioned just in the AHA document, stating that it may be considered when the bleeding risk is prohibitive.[6] Finally, 3 documents remind that transesophageal echocardiogram to exclude left atrial

thrombosis should be either considered[3,4] or systematically performed[1] in all patients referred to elective electric cardioversion.

ARE THERE PATIENTS WITHOUT ATRIAL FIBRILLATION WHO MAY NEED ANTICOAGULATION? The JCS guideline states that "Patients with atrial tachycardia and systolic/diastolic dysfunction should also receive anticoagulant therapy."[8] Patients with CA have a high risk of left atrial thrombosis even when in sinus rhythm,[24] prompting the ESC statement to recommend "to consider [anticoagulation] in selected cases in sinus rhythm."[1] Based on the AHA document, "decreased A-wave amplitude and left atrial appendage velocities on echocardiography" may warrant empirical anticoagulation even in sinus rhythm.[6] The role of anticoagulation in patients with CA and sinus rhythm is another unmet need in management.

WHEN IS AMBULATORY ELECTROCARDIOGRAPHY INDICATED? Patients with CA are at high risk for atrial arrhythmias and conduction disease. Ambulatory electrocardiography (ECG) may detect atrioventricular blocks and bradycardia, atrial fibrillation episodes, or ventricular arrhythmias,[3] and investigate the relationship between symptoms and bradycardic atrial fibrillation.[8] Despite these possible applications, the CCS/CHFS,[4] AHA,[6] and JSC[8] documents do not discuss the role of ambulatory ECG. The ESC statement advises for a yearly ambulatory ECG in patients with either AL-CA or ATTR-CA, regardless of clinical stability or therapy.[1] The DGK document advises for ambulatory ECG every 6 months in AL-CA, or every 12 months when remission or clinical stability is achieved, and every 12 months in ATTR-CA.[3] Ambulatory ECG should also be repeated when patients develop symptoms such as vertigo, syncope, or palpitations.[3]

WHICH PATIENTS SHOULD RECEIVE A PACEMAKER? Recommendations for device therapy are summarized in **Table 4**. The JCS guideline identifies 2 possible scenarios warranting pacemaker implantation: 1) atrioventricular block; and 2) sick sinus syndrome or atrial fibrillation with bradycardia.[8] The indications for pacemaker implantation for atrioventricular blocks are the same as in patients without CA. Atrial fibrillation with bradycardia warrants pacemaker implantation only when symptomatic, and the causal relationship between the arrhythmia and symptoms should be documented.[8] The DGK statement is the only one to state that "in principle, device therapy [ie, pacing or defibrillation] is only considered if a median life expectancy of at least 1 year is to be expected."[3] According to the ESC and AHA statements, a pacemaker should be implanted according to standard indications,[1,6] without mentioning expected survival.

WHEN IS AN IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR INDICATED? All documents agree that an implantable cardioverter-defibrillator should be offered to patients with standard indications for secondary prevention, with the partial exception of the JCS guideline, which does not give a Class I indication for secondary prevention because of the lack of demonstrated prognostic benefit and the frequency of pulseless electric activity as the ultimate cause of death.[8] The attitude toward implantable cardioverter-defibrillator for primary prevention ranges from the "rather generous (primary prophylactic) indication" (DGK)[3] to the "usually not recommended" (ESC).[1]

WHEN IS CARDIAC RESYNCHRONIZATION THERAPY INDICATED? All documents refer to the recommendations by the corresponding national and international societies, in the absence of any specific evidence about CA.[1,3,6,8] Nonetheless, the indications to cardiac resynchronization therapy were established in patients with nonamyloidotic HF, then in a pathophysiological model different from CA, which warrants further investigations in the specific setting of CA. The ESC statement is the only one to recommend considering cardiac resynchronization therapy in patients requiring pacemaker implantation if the paced burden is predicted to be high.[1]

WHICH PATIENTS ARE CANDIDATE TO HEART TRANSPLANTATION? In patients with ATTR-CA, candidates to heart transplantation must not have significant extracardiac disease.[3,4] In patients with AL-CA, heart transplantation can be considered to allow a strategy of autologous stem cell transplantation despite a severe cardiac dysfunction, or after the eradication of the plasma cell clone in patients with persisting severe cardiac dysfunction.[4] No document specifies the role of disease-modifying therapy after heart transplantation, either alone or together with liver transplantation, or in a recipient of a transplanted heart after a domino transplantation.

WHEN CAN WE CONSIDER MECHANICAL CIRCULATORY SUPPORT? The small left ventricular cavity size and restrictive physiology make CA patients poor candidates for left ventricular assist device implantation.[4] Furthermore, there is evidence from retrospective cohort studies of the feasibility of intra-aortic balloon pump as a bridge to transplantation and total artificial heart implantation.[25] A better understanding of the

TABLE 4 Summary of Statements About Catheter Ablation, Device Therapies, and Heart Transplantation

Strategy	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
AF ablation	Scarce and controversial data	No recommendation	Uncertain efficacy	Might be considered in selected cases[a]	Might be considered in patients with paroxysmal AF without LA dilatation or LV hypertrophy[a]
					Is contraindicated for patients with AL amyloidosis, poor prognosis and severe LA dilatation, and LV hypertrophy (should be avoided)[b]
PM	Might be considered according to standard indications[a]	Might be considered according to standard indications[a]	Might be considered according to standard indications[a]	Might be considered according to standard indications[a]	Might be considered in patients with risk factors (first degree block, Wenckebach rate <100 bpm, AH >70 ms, HV >55 ms, bundle branch block), symptomatic sinus sick syndrome or bradycardic AF[a]
		Is contraindicated in patients with a median life expectancy <1 y (should be avoided)[b]			
ICD	Is recommended for secondary prevention[a]	Is recommended for secondary prevention[a]	Is recommended for secondary prevention[a]	Is recommended for secondary prevention (aborted SCD with expected survival >1 y or significant ventricular arrhythmias)[a]	Might be considered in patients with mild hypertrophy preserved systolic/diastolic function, a good prognosis after adequate therapy[a]
	Is usually not recommended for primary prevention (should be avoided)[a]	Might be considered in primary prevention (especially with an increased mortality risk according to serum or imaging parameters and/or documented nsVTs)[a]	An individualized approach should be used for primary prevention (may be considered)[a]	Questionable benefit for primary prevention (may be considered)[a]	
		Is contraindicated in patients with a median life expectancy <1 y (should be avoided)[b]			Is contraindicated in patients with a poor prognosis (<1 y) (should be avoided)[b]
CRT	Might be considered if high pacing burden expected[b]	Might be considered according to the general indications[b]	No specific evidence	Might be considered in PM-dependent patients[b]	Might be considered in patients with LBBB and an expected survival >1 y[b]
					Is contraindicated for patients with a poor prognosis (<1 y), QRS <150 ms, conduction disturbances other than LBBB (should be avoided)[b]
Heart transplantation	Might be considered in selected cases[a]	No recommendation	Might be considered for select patients with advanced HF, in whom significant extracardiac manifestations are absent and the risk of disease progression is considered low and/or amenable to disease-modifying therapy[a]	Might be considered in patients with stage D HF[a]	No recommendation
MCS	LVAD not suitable for most patients (should be avoided)[a]	No recommendation	Uncertain role	Limited data	No recommendation

[a]Evidence from a subgroup analysis, retrospective studies or case series. [b]Expert consensus opinion. green = considered with substantial agreement with all other documents; yellow = considered with substantial agreement with ≥1 other document; red = considered with a specific position, not found in any other document; white = not considered.

CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LA = left atrial; LBBB = left bundle branch block; LVAD = left ventricular assist device; MCS = mechanical circulatory support; nsVT = nonsustained ventricular tachycardia; PM = pacemaker; SCD = sudden cardiac death; other abbreviations as in Tables 1 and 3.

TABLE 5 Recommendations About Disease-Modifying Drugs for ATTRv or ATTRwt Amyloidosis

Drug	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
Tafamidis	ATTRwt-CA or ATTRv-CA (recommended)[a] ATTRv-CA + PN (stage 1) (recommended) ATTRv PN (stage 1) (recommended)[b]	ATTRwt-CA or ATTRv-CA (recommended)[a]	Recommended for patients with ATTR-CA and NYHA functional class I-III symptoms[a]	Patients with predominantly cardiac disease from ATTRv or ATTRwt, NYHA functional class I to III symptoms (recommended)[a]	• ATTRwt-CA with NYHA functional class I-II symptoms (recommended) • ATTRwt-CA with NYHA functional class III symptoms (recommended) • ATTRv-PN and CA with NYHA functional class I-II symptoms (recommended) • ATTRv-PN and CA with NYHA functional class III symptoms (recommended)[b]
Notes	ESC HF guidelines recommendations: • ATTRwt-CA with NYHA functional class I-II symptoms (Class I, LOE B) • ATTRwt-CA with NYHA functional class I-II symptoms (Class I, LOE B) Reasonable expected survival	ATTR-ACT inclusion and exclusion criteria should be met Case-by-case decision is needed when NYHA functional class III symptoms	ATTR-ACT inclusion (NT-proBNP >600 ng/L) and exclusion criteria (NYHA functional class IV, severe functional disability, 6MWD <100 m) should be considered when determining eligibility for treatment The expected benefit is greater in patients with NYHA functional class I-II symptoms	Benefit of tafamidis not observed in patients with NYHA functional class IV, severe aortic stenosis, or eGFR <25 mL/min/1.73 m^2	Need for histological documentation of ATTR amyloid deposits in the heart or peripheral tissue Tafamidis doses: 20 mg PN, 80 mg CA
Patisiran	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv with ambulatory PN (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]
	ATTRv PN (stage 1-2) + CA (recommended)[b]	No sufficient data about ATTRv PN (stage 1-2) + CA	No sufficient data about ATTRv PN + CA	—	No sufficient data about ATTRv PN + CA
Inotersen	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	ATTRv with ambulatory PN (recommended)[a]	ATTRv PN (stage 1-2) (recommended)[a]	Not approved in Japan

[a]Evidence from a clinical trial in this specific population. [b]Evidence from a subgroup analysis, retrospective studies or case series. green = considered with substantial agreement with all other documents; white = not considered.

6MWD = 6-minute walking distance; ATTR-CA = amyloid transthyretin cardiac amyloidosis; ATTRv-CA = variant amyloid transthyretin cardiac amyloidosis; ATTRwt-CA = wild-type amyloid transthyretin cardiac amyloidosis; CA = cardiac amyloidosis; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; PN = polyneuropathy; other abbreviations as in Tables 1, 3, and 4.

indications for and contraindications to advanced heart failure therapies in CA is then another unmet need.

HOW SHOULD WE CHOOSE BETWEEN DISEASE-MODIFYING THERAPIES? Amyloid light-chain CA. Disease-modifying therapies block or delay amyloid deposition. Regarding AL-CA, all documents broadly recommend collaboration between cardiologists and hematologists with no further details.[1,3,4,6,8]

ATTR-CA without neurologic involvement. Tafamidis is currently the only approved treatment for patients with ATTRwt-CA or ATTRv-CA without polyneuropathy.[1,3,4,6,8] The documents offer varied indications for use based on New York Heart Association (NYHA) functional class, as summarized in Table 5. Specifically, tafamidis is variably indicated regardless of NYHA functional class (ESC),[1] from NYHA functional class I-III (AHA),[6] preferably in NYHA functional class I-II (CCS/CHFS and DGK).[3,4] Furhermore, the JCS guideline provides a stronger (Class IIa, Level of Evidence: B) recommendation for NYHA functional class I-II than for NYHA functional class III (Class IIb, Level of Evidence: B).[8] We may add that ESC heart failure guidelines includes a Class I, Level of Evidence: B recommendation for tafamidis in patients with NYHA functional class I or II, without explicitly addressing the issue of patients in NYHA functional class III.[2]

The U.S. Food and Drug Administration approved either the 80-mg dose (as four 20 capsules) or a single 61-mg capsule. According to an addendum to the AHA document, "Although the 20-mg dose is not approved, it may be considered by clinicians for patients who have issues with affordability, as there is evidence of benefit from the 20-mg dose."[7]

To summarize, 2 important unmet needs in the use of tafamidis are its role in patients with NYHA functional class III symptoms (who experienced an increase in frequency of hospitalizations in a subgroup analysis of the ATTR-ACT [Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial]),[26] and the role of varying doses of tafamidis when patients face financial toxicity from this therapy.

ATTR-CA plus polyneuropathy. The indications for disease-modifying therapies in patients with a

TABLE 6 Proposed Follow-Up Protocols for Patients With Cardiac Amyloidosis

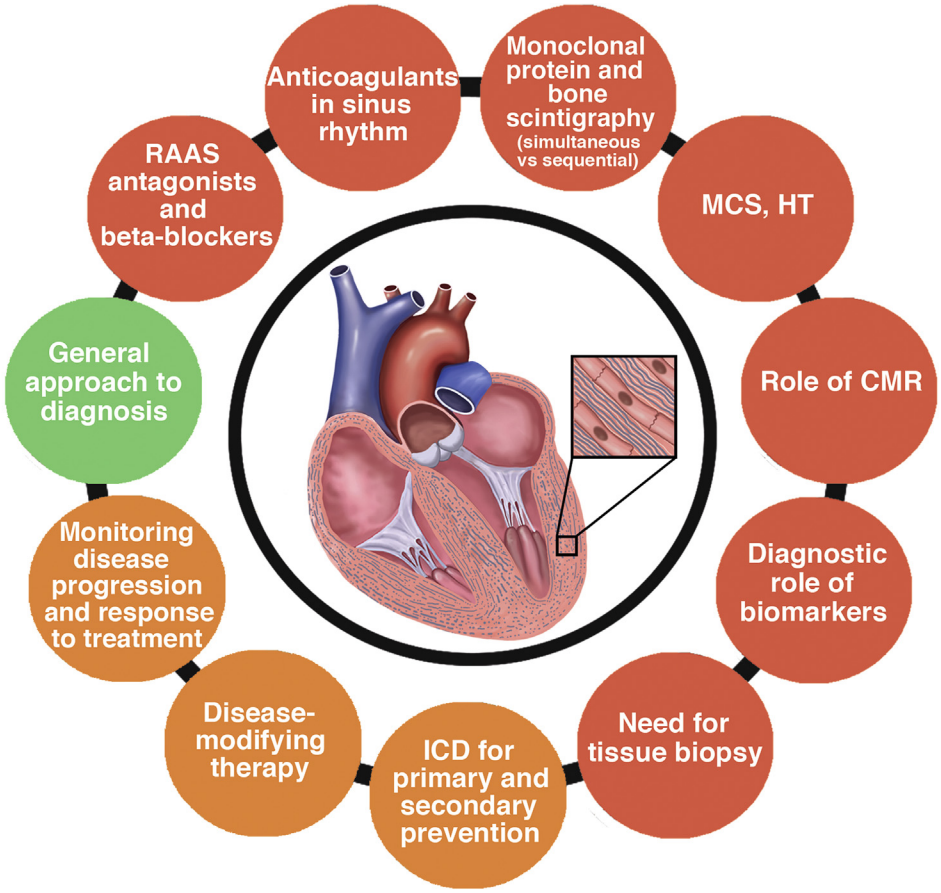
ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
AL-CA Every month (during initial hematological treatment): • Complete blood count, basic biochemistry, NT-proBNP, and troponin • Serum-free light-chain quantification • Clinical evaluation by hematology • Evaluation by cardiology if clinically indicated Every 3-4 mo (after completing initial hematological treatment): • Complete blood count, basic biochemistry, NT-proBNP and troponin • Serum-free light-chain quantification • Clinical evaluation by hematology Every 6 mo: • ECG • Echocardiography/CMR • Evaluation by cardiology Every 12 mo: • 24-h Holter ECG ATTR-CA Every 6 mo: • ECG • Blood tests including NT-proBNP and troponin • Neurological evaluation (if ATTRv) • 6MWD (optional) • KCCQ (optional) Every 12 mo: • Echocardiography/CMR • 24-h Holter ECG • Ophthalmological evaluation (if ATTRv)	AL-CA During specific drug therapy Every 3 mo (or after every 2 further therapy cycles): • NT-proBNP • Troponin T or I Every 6 mo: • Resting ECG + Holter ECG • Transthoracic echocardiography including strain measurements • If available: CMR including LGE and T1 mapping After remission or in stable condition without specific therapy Every 6 mo: • Resting ECG • NT-proBNP • Troponin T or I • Transthoracic echocardiography including strain measurements Every 12 mo: • Holter ECG • Additional CMR including LGE and T1 mapping in case of suspected disease progression due to serum biomarkers and/or echocardiographic findings ATTR-CA During specific drug therapy Every 3-6 mo: • NT-proBNP • Troponin T or I Every 12 mo: • Resting ECG + Holter ECG • Transthoracic echocardiography including strain measurements • If available: CMR including LGE and T1 mapping After remission or in stable condition without specific therapy Every 6 mo: • Resting ECG • NT-proBNP • Troponin T or I • Transthoracic echocardiography including strain measurements Every 12 mo: • Holter ECG Every 12-24 mo: • Additional CMR including LGE and T1 mapping in case of suspected disease progression due to serum biomarkers and/or echocardiographic findings	• Serial imaging with echocardiography or CMR in addition to measuring BNP/NT-proBNP • Echo or CMR repeated every 6-48 mo or when the clinical picture deteriorates • Integration of imaging and laboratory findings indicated • No role for bone scintigraphy to monitor the response to treatment	— (no accepted definition of progression or response to therapy)	—

KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Table 1 and 5.

mixed cardiac and neurologic phenotype are summarized in Table 5. The ESC statement is the only one to include a clear algorithm for drug choice in these patients. Tafamidis should be prescribed to patients with stage 1 polyneuropathy, and patisiran to those with stage 1 or 2 polyneuropathy.[1] Other documents broadly suggest a choice based on drug "accessibility and side-effect profile,"[6] considering just tafamidis and patisiran (JCS),[8] or also other agents such as inotersen (AHA),[6] diflunisal (CCS/CHFS, AHA),[4,8] and epigallocatechin gallate and doxycycline (DGK, CCS/CHFS).[3,4]

WHICH IS THE MINIMAL DEGREE OF CARDIAC DISEASE THAT JUSTIFIES A TREATMENT? According to all documents, treatment is indicated when there is clear evidence of cardiac disease on echocardiogram or CMR and when patients have symptoms that can be attributed to cardiac disease. A significant knowledge gap, not addressed in any of the documents, concerns 2 challenging scenarios, namely: 1) cardiac involvement in asymptomatic patients; or 2) positive bone scintigraphy without clear echocardiogram or CMR findings in patients who may be either symptomatic or asymptomatic.

CENTRAL ILLUSTRATION **Agreement Between Guidelines and Areas of Uncertainty**



Gray zones that highlighted unmet needs in the management of CA

- Incorporation of "red flags" into the diagnostic algorithm
- Timing of bone scintigraphy vs monoclonal light-chain screen for diagnosis
- Use of CMR for diagnosis
- Role of biomarkers for diagnosis and surveillance
- Screening of asymptomatic gene carriers
- Anticoagulation in the absence of atrial fibrillation
- Neurohormonal blockade in the setting of reduced ejection fraction
- Gene stablizers vs gene silencers for treatment of ATTRv-CA
- Monitoring response to disease-modifying therapies
- Extra-cardiac manifestations contraindicating advanced HF therapies

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The main open issues about the diagnosis and management of patients with cardiac amyloidosis (CA) are summarized. The corresponding donut sectors are colored in **green** (when guidelines agree on the specific point), **orange** (when mild disagreement exists), or **red** (when a moderate degree of disagreement among guidelines is found). AL-CA = amyloid light-chain cardiac amyloidosis; ATTRv-CA = variant amyloid transthyretin cardiac amyloidosis; CMR = cardiac magnetic resonance; HF = heart failure; HT = heart transplantation; ICD = implantable cardioverter-defibrillator; MCS = mechanical circulatory support; RAAS = renin-angiotensin-aldosterone system.

TABLE 7 Main Topics Evaluated in the 5 Documents and Level of Agreement or Disagreement Between Them

	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
Diagnosis					
General approach to diagnosis	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
Sequence of scintigraphy and monoclonal protein assessment	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
Echocardiographic scores	Considered with a specific position, not found in any other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
Biomarkers	Not considered	Not considered	Not considered	Not considered	Considered with a specific position, not found in any other document
Tracer for bone scintigraphy	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
SPECT	Not considered	Not considered	Not considered	Not considered	Not considered
CMR recommended	Considered with substantial agreement with ≥1 other document	Considered with a specific position, not found in any other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
Tissue biopsy	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with a specific position, not found in any other document
Genetic testing	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
Risk prediction and management					
Gene screening in family members	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
Follow-up of mutation carriers	Considered with a specific position, not found in any other document	Not considered	Not considered	Considered with a specific position, not found in any other document	Considered with a specific position, not found in any other document
Risk stratification in CA	Considered with a specific position, not found in any other document	Not considered	Not considered	Not considered	Considered with a specific position, not found in any other document
HF drugs					
ACE inhibitor/ARB	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
ARNI	Not considered	Not considered	Not considered	Not considered	Not considered
Beta-blockers	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
MRA	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
Loop diuretics	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
Digoxin	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document

Continued on the next page

TABLE 7 Continued

	ESC[1]	DGK[2]	CCS/CHFS[3]	AHA[5]	JCS[6]
Anticoagulation for AF	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
Anticoagulation in SR	Considered with substantial agreement with ≥1 other document	Not considered	Not considered	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
LA appendage occlusion	Not considered	Not considered	Not considered	Not considered	Not considered
Pulmonary veins isolation					
Ambulatory ECG	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Not considered	Not considered	Not considered
PM	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Not considered	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
ICD for secondary prevention	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with a specific position, not found in any other document
ICD for primary prevention	Considered with a specific position, not found in any other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
CRT	Considered with a specific position, not found in any other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
Heart transplantation	Considered with substantial agreement with ≥1 other document	Not considered	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Not considered
Mechanical circulatory support	Considered with a specific position, not found in any other document	Not considered	Not considered	Not considered	Not considered
Disease-modifying therapies					
AL-CA	Not considered	Not considered	Not considered	Not considered	Not considered
ATTR-CA without neurologic involvement	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents	Considered with substantial agreement with all other documents
ATTR-CA plus PN	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document
Minimal degree of cardiac disease for treatment	Not considered	Not considered	Not considered	Not considered	Not considered
Age or advanced HF as exclusion criteria for treatment	Not considered	Not considered	Not considered	Not considered	Not considered
Treatment of asymptomatic carriers	Not considered	Not considered	Not considered	Not considered	Not considered
Monitoring disease progression and response to treatment	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Considered with substantial agreement with ≥1 other document	Not considered	Not considered
Costs of disease-modifying therapy	Not considered	Not considered	Not considered	Not considered	Not considered

green = considered with substantial agreement with all other documents; yellow = considered with substantial agreement with ≥1 other document; red = considered with a specific position, not found in any other document; white = not considered.

ARNI = angiotensin receptor-neprilysin inhibitor; SPECT = single-photon emission computed tomography; other abbreviations as in Tables 1, 3, and 4.

CAN AGE OR ADVANCED HF BE EXCLUSION CRITERIA FOR TREATMENT? According to the ESC document, a physiological age >70 years and advanced HF contraindicate autologous stem cell transplantation.[1] The other documents do not mention any contraindications to treatment based on age or HF severity except for NYHA functional class IV or functional class III-IV contraindicating tafamidis.

HOW CAN WE ASSESS DISEASE PROGRESSION AND RESPONSE TO TREATMENT? Recommendations regarding evaluation of disease progression and response to treatment are highly variable across documents (**Table 6**), denoting the lack of specific evidence. Clearly, disease progression is a major "gray zone" and an area of active investigation.

CONCLUSIONS

The ESC,[1] DGK,[3] CCS/CHFS,[4,5] AHA,[6] and JSC[8] have provided guidance regarding the diagnosis and management of CA. These documents provide useful guidance for clinicians managing patients with CA, and all include: 1) a diagnostic algorithm to establish a definitive, etiological diagnosis; 2) an emphasis on the noninvasive diagnosis with the combined use of bone scintigraphy and the exclusion of a monoclonal protein; and 3) a treatment algorithm describing indications for novel disease-modifying therapies for symptomatic CA with or without neurological involvement. The documents diverge with respect to other points, most notably: 1) the optimal sequence of monoclonal protein screen and bone scintigraphy in the diagnostic algorithm; 2) the role of echocardiogram, biomarkers, and CMR for diagnosis; and 3) the recommendations for use of guideline-directed medical therapy for HF with reduced ejection fraction. An integrated analysis of the 5 documents shows many gray zones or knowledge gaps, including several issues pertaining to diagnosis (the role of biomarkers and CMR, the timing of search for a monoclonal protein and bone scintigraphy), risk stratification and treatment tailoring, the initiation of treatment in carriers of pathogenic mutations, the prescription of anticoagulants to patients in sinus rhythm and heart failure drugs, the criteria for response (or lack of) to disease-modifying therapies, and the role of defibrillator implantation for primary prevention (**Table 7, Central Illustration**). A better understanding of the knowledge gaps and unmet needs highlights areas for future investigation of the diagnostic and management strategies of CA.

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APPENDIX For expanded Methods, Results, and references as well as supplemental tables, please see the online version of this paper.

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