Cardiac Amyloidosis in Clinical Practice:

Comparison and Critical Assessment of Documents by Scientific Societies

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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 non-invasive diagnosis with the combined use of bone scintigraphy and the exclusion of a monoclonal protein; 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 "grey zones" requiring further investigation.
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Condensed 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 thus facilitate diagnosis and management of CA. These 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 "grey zones" requiring further investigation.
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Abbreviations

AHA, American Heart Association

AL-CA, amyloid light-chain cardiac amyloidosis

ATTR-CA, amyloid transthyretin cardiac amyloidosis (v, variant; wt, wild-type)

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

Bullet points

- Several documents have been recently published on the diagnosis and management of cardiac amyloidosis (CA).
- These documents diverge on specific details of diagnosis, risk stratification and treatment.
- A comparison of these documents highlights “grey zones” requiring further investigation.

Keywords: cardiac amyloidosis; guidelines; scientific societies; recommendations; diagnosis; management.

Over the last year, five 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 guidelines (2); a position statement by the **German Cardiac Society (*Deutsche Gesellschaft für Kardiologie,* DGK)** (3); a position statement and an update on tafamidis by the **Canadian Cardiovascular Society/Canadian Heart Failure Society (CCS/CHFS)** (4,5); a scientific statement focused on 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 workup for CA. These "red flags" consist of clinical evidence of extra-cardiac 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). Differ red flags noted are listed in the five 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 one 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: an understanding of 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 report the steps of diagnostic algorithms in specific flow-charts that combine the search for a monoclonal protein and bone scintigraphy. These algorithms may lead to a final diagnosis of ATTRv-CA, ATTRwt-CA, AL-CA, ATTRv or ATTRwt and MGUS, 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 workup for CA, has not been formally investigated and its positive predictive value could be low when prevalence is low, which is often seen 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. published a multicenter, international study establishing the accuracy of non-biopsy diagnosis of transthyretin 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 evaluation for monoclonal proteins with immunofixation of the serum and urine 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 exams 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 (6). (4) 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, where 4 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- 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 two echocardiographic scores to facilitate the diagnosis of cardiac involvement in patients with known AL amyloidosis, or in patients with unexplained hypertrophy and other red flags (1,13) (**Supplemental Figure 1**). These scores 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 NT-proBNP and hs-troponin might aid the diagnosis of CA (class IIa, level of evidence C) (8). The **JCS** guideline 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 non-amyloid HF, although no diagnostic cut-off 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 workup?

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 where

CMR can be important for diagnosis: 1) when bone scintigraphy is negative and no monoclonal protein is found, but the clinical suspicion is high, 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 (if there is a monoclonal protein present) 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 wt 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 (e.g., 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 still asymptomatic should be treated.

How can we stratify patient risk?

Only some documents provide some details about risk prediction. Specifically, the **ESC** statement lists 2 scores for AL-CA, 1 for ATTRwt-CA, and 2 for ATTRv- or ATTRwt-CA (1), and the **JCS** guideline reminds that NT-proBNP and hs-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 heart failure drugs?

Recommendations for neurohormonal blockade are summarized in **Table 3**. Treatment with tolerated doses of angiotensin-converting enzyme inhibitors/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/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 allow 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 through observational evidence suggests 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 biding 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 or equivalent 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, three 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 patient with CA and sinus rhythm is another unmet need in management.

When is ambulatory electrocardiogram (ECG) indicated?

Patients with CA are at high risk for atrial arrhythmias and conduction disease. Ambulatory 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- 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 then 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 [i.e., 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 towards 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 CRT were established in patients with non-amyloidotic 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 indications for and contraindications to advanced heart failure therapies in CA is then another unmet need.

How should we choose between disease-modifying therapies?

<u>AL-CA</u>

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) class, as summarized in **Table 5**. Specifically, tafamidis is variably indicated regardless of NYHA class (**ESC**) (1), from NYHA class I to III (**AHA**) (6), preferably in NYHA 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 class I-II than for NYHA 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 class I or II, without explicitly addressing the issue of patients in NYHA class III (2).

The Food and Drugs 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, two important unmet needs in the use of tafamidis are its role in patients with NYHA class III symptoms (who experienced an increase in frequency of hospitalizations in a subgroup analysis of the ATTR-ACT 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 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), 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 echo or CMR, and patients have symptoms that can be attributed to cardiac disease. A significant knowledge gap, not addressed in any of the documents, concerns two challenging scenarios, namely: 1) cardiac involvement in asymptomatic patients, or 2) positive bone scintigraphy without clear echo or CMR findings, in patients who may be either symptomatic or asymptomatic.

Can age or advanced heart failure be exclusion criteria for treatment?

According to the **ESC** document, a physiological age >70 years and advanced heart failure contraindicate autologous stem cell transplantation (1). The other documents do not mention any contraindications to treatment based on age or heart failure severity except for NYHA class IV or III-IV contraindicating tafamidis (see above).

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 "grey zone" and an area of active investigation.

CONCLUSIONS

In the past few years, 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 non-invasive diagnosis with

the combined use of bone scintigraphy and the exclusion of a monoclonal protein; 3) a treatment algorithm describing indications for novel disease-modifying therapies for symptomatic CA with and without neurological involvement. The documents diverge with respect to other points, most notably: 1) the optimal sequence of monoclonal light chain screen and bone scintigraphy in the diagnostic algorithm; 2) the role of echocardiogram, biomarkers, and CMR for diagnosis; 3) the recommendations for use of guideline-directed medical therapy for heart failure with reduced ejection fraction. An integrated analysis of the five documents shows many grey 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** and **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.

Figure legends

Figure 1. Diagnostic algorithms for cardiac amyloidosis proposed by national and international scientific societies: an overview.

For details, see the original documents (1,3,4,6,8). AHA, American Heart Association; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; DGK, *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ESC, European Society of Cardiology; JSC, Japanese Society of Cardiology; MP, monoclonal protein; NPs, cardiac natriuretic peptides (B-type natriuretic peptide, N-terminal B-Type natriuretic peptide); Tn, high sensitivity troponins.

Central Illustration. Areas of uncertainty in cardiac amyloidosis and level of agreement between guidelines.

The main open issues about the diagnosis and management of patients with cardiac amyloidosis are summarized. The corresponding donut sectors are colored in green (when guidelines agree on the specific point), yellow (when mild disagreement exists), or orange (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; MCS, mechanical circulatory support; RAAS, renin-angiotensin-aldosterone system.

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Tables

Table 1. Red flags for cardiac amyloidosis.

ESC (1)	DGK (2)	CCS/CHFS (3)	AHA (5)	JCS (6)
• HF ≥65 years • Aortic stenosis ≥65 years • Hypotension or normotensive when previously hypertensive • Sensory involvement, autonomic dysfunction • Peripheral polyneuropathy • Proteinuria • Skin bruising • Bilateral carpal tunnel syndrome • Ruptured biceps tendon • Subendocardial/transmural	• Age >60 years, 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	• Unexplained increased LV wall thickness • LFLG aortic stenosis with preserved LVEF (> 60 years of age) • Carpal tunnel syndrome (bilateral) • Established AL or ATTR in noncardiac organ/system (ie, renal AL amyloidosis causing nephrotic syndrome) • Peripheral sensorimotor neuropathy and/or	• 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	• Symptoms of HF (e.g., shortness of breath, edema), dizziness, and syncope • Atrial fibrillation • Conduction system disorder (e.g., AV block, bundle branch block, intraventricular conduction disorder) • Ventricular arrhythmia • Low voltage in limb leads • QS pattern in V1–3 • Ventricular wall thickening (including RV)

LGE or increased ECV • Decreased QRS voltage to mass ratio • Pseudo Q waves • AV conduction disease • Possible family history	• Periorbital purpura • Atraumatic biceps tendon rupture • Sensorimotor polyneuropathy • Spinal stenosis • Autonomic dysfunction • Vitreous opacity, pupillary changes	dysautonomia	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,	• 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

			or atrial wall thickening • Family history of cardiomyopathy	fraction in T1 mapping

AHA, American Heart Association; AV, atrio-ventricular; 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.

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 hours	Perugini score ≥2 on a ^{99m}Tc-DPD or ^{99m}Tc-HMDP scan after 3 hours	Perugini score ≥2 and/or a H/CL ratio ≥1.5 on a ^{99m}Tc-PYP scan after 1 or 3 hours	Perugini score ≥2 and/or a H/CL ratio >1.5 on a ^{99m}Tc-PYP scan after 1 or 3 hours	Perugini score ≥2 and/or a H/CL >1.5 on a 1-hour scan or >1.3 on a 3-hour scan

A "positive bone scintigraphy" allows to diagnose amyloid transthyretin cardiac amyloidosis when no monoclonal protein is found. AHA, American Heart Association; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; DGK, *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); DPD, 3,3-diphosphono-1,2-propanodicarboxylate; ESC, European Society of Cardiology; H/CL, heart/contralateral chest; HMDP, hydroxymethylene; PYP, pyrophosphate; JCS, Japanese Circulation Society.

Table 3. Drug therapies for heart failure and atrial fibrillation.

Setting	Drug	ESC (1)	DGK (2)	CCS/CHFS (3)	AHA (5)	JCS (6)
HF	**Loop or thiazide diuretics**	Recommended ***	Recommended ***	Recommended ***	Recommended, but avoid underfilling and worsening renal function from restrictive physiology ***	Recommended ***
	Nitrates or carperitide (AHF)	*No recommendation*	*No recommendation*	*No recommendation*	*No recommendation*	Might be considered ***
	Catecholamines, PDEi (AHF)	*No recommendation*	*No recommendation*	*No recommendation*	*No recommendation*	Might be considered ***

	Beta-blockers	Not recommended, deprescribe ***	Avoid or very cautious use ***	Avoid or very cautious use ***	No data for benefit; may not be tolerated given fixed stroke volume ***	Tolerated dosing might be considered ***
	ACEi/ARB	Not recommended ***	Avoid or very cautious use ***	Avoid or very cautious use ***	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction ***	Tolerated dosing might be considered ***
	Sacubitril/valsartan	*No recommendation*	*No recommendation*	*No recommendation*	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction ***	*No recommendation*

	MRA	*No recommendation*	*No recommendation*	Recommended ***	Might be considered in conjunction with loop diuretics if adequate blood pressure and renal function ***	Tolerated dosing might be considered ***
AF/flutter/ tachycardia	**Digoxin**	Might be considered **	Avoid or very cautious use **	Avoid or very cautious use **	Might be considered; use cautiously **	Not recommended **
	Amiodarone	Might be considered (1^{st} choice) ***	*No recommendation*	Might be considered (1^{st} choice) ***	Might be considered (1^{st} choice) ***	*No recommendation*
	Beta-blockers	Not recommended ***	Avoid or very cautious use ***	Avoid or very cautious use ***	Might be considered ***	Case-by-case decision ***

	Non-DHP CCB: ATTR-CA, preserved LV function	*No recommendation*	Avoid or very cautious use ***	Avoid or very cautious use ***	Avoid whenever possible ***	Case-by-case decision ***
	Non-DHP CCB: ATTR-CA, reduced LV function					Not recommended ***
	Non-DHP CCB: AL-CA				Not recommended ***	Not recommended ***
	Anticoagulation regardless of CHA_2DS_2-VASc score?	Yes ***	*No recommendation*	Yes ***	Yes ***	*No recommendation*
	Anticoagulation in SR?	Might be considered ***	*No recommendation*	*No recommendation*	Might be considered ***	*No recommendation*

Recommended treatments are highlighted in green, those that may be considered in yellow, and those that should be avoided in red. The levels of evidence are classified as: *, evidence from a clinical trial in this specific population; **, evidence from a subgroup analysis, retrospective studies or case series; ***, expert consensus opinion.

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; AHA, American Heart Association; AHF, acute heart failure; AT, atrial tachycardia; AL-CA, amyloid light-chain cardiac amyloidosis; ATTR-CA, amyloid transthyretin cardiac amyloidosis; CCB, calcium channel blocker; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; DHP, dihydropyridine; DOAC, direct oral anticoagulant; DGK, *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ESC, European Society of Cardiology; JCS, Japanese Circulation Society; LOE, level of evidence; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; PDEi, phosphodiesterase inhibitor; SR, sinus rhythm; VKA, vitamin K antagonist.

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 **	Might be considered in patients with paroxysmal AF without LA dilatation or LV hypertrophy **
					Is contraindicated for patients with AL amyloidosis, poor prognosis and severe LA dilatation, and LV hypertrophy ***
PM	Might be considered according to standard	Might be considered according to standard indications **	Might be considered according to standard indications **	Might be considered according to standard indications **	Might be considered in patients with risk factors (1st degree block, Wenckebach rate <100

	indications **	Is contraindicated in patients with a median life expectancy <1 year ***			bpm, AH >70 ms, HV >55 ms, bundle branch block), symptomatic sinus sick syndrome or bradycardic AF **
ICD	Is recommended for secondary prevention **	Is recommended for secondary prevention **	Is recommended for secondary prevention **	Is recommended for secondary prevention (aborted SCD with expected survival >1 year or significant ventricular arrhythmias) **	Might be considered in patients with mild hypertrophy preserved systolic/diastolic function, a good prognosis after adequate therapy **
	Is usually not recommended for primary prevention **	Might be considered in primary prevention (especially with an increased mortality risk according to serum or imaging parameters and/or	An individualized approach should be used for primary prevention **	Questionable benefit for primary prevention **	

		documented nsVTs) **			
		Is contraindicated in patients with a median life expectancy <1 year ***			Is contraindicated in patients with a poor prognosis (<1 year) ***
CRT	Might be considered if high pacing burden expected ***	Might be considered according to the general indications ***	No specific evidence	Might be considered in PM-dependent patients ***	Might be considered in patients with LBBB and an expected survival >1 year ***
					Is contraindicated for patients with a poor prognosis (<1 year), QRS <150 ms, conduction disturbances other than LBBB ***
Heart transplantation	Might be considered in	*No recommendation*	Might be considered for select patients with	Might be considered in patients with stage D HF	*No recommendation*

	selected cases **		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 **	**	
MCS	LVAD not suitable for most patients **	*No recommendation*	Uncertain role	Limited data	*No recommendation*

Recommended treatments are highlighted in green, those that may be considered in yellow, and those that should be avoided in red. The levels of evidence are classified as: *, evidence from a clinical trial in this specific population; **, evidence from a subgroup analysis, retrospective studies or case series; ***, expert consensus opinion. AHA, American heart Association; AL, amyloid light-chain; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; CRT, cardiac resynchronization therapy; DGK, *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ESC, European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter defibrillator; JCS, Japanese Circulation Society; LA, left atrial; LV, left ventricular; LBBB, left bundle branch block; LOE, level of evidence; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PM, pacemaker; SCD, sudden cardiac death.

Table 5. Recommendations about disease-modifying drugs for variant or wild-type amyloid transthyretin (ATTRv/wt) amyloidosis.

Drug	ESC (1)	DGK (2)	CCS/CHFS (3)	AHA (5)	JSC (6)
Tafamidis	ATTRwt- or ATTRv-CA * ATTRv-CA + PN (stage 1) ATTRv PN (stage 1) ** 	ATTRwt- or ATTRv-CA *	Recommended for patients with ATTR-CA and NYHA class I-III symptoms *	Patients with predominantly cardiac disease from ATTRv or ATTRwt, NYHA class I to III symptoms *	• ATTRwt-CA with NYHA I-II symptoms • ATTRwt-CA with NYHA III symptoms • ATTRv-PN and CA with NYHA I-II symptoms • ATTRv-PN and CA with NYHA III symptoms **
Notes	ESC HF guidelines recommendations: • ATTRwt-CA with NYHA I-II symptoms (class I, LOE B) • ATTRwt-CA with NYHA I-II symptoms	ATTR-ACT inclusion and exclusion criteria should be met Case-by-case decision is needed when NYHA III symptoms	ATTR-ACT inclusion (NT-proBNP >600 ng/L) and exclusion criteria (NYHA IV, severe functional disability, 6MWD <100 m) should be considered when determining eligibility for	Benefit of tafamidis not observed in patients with NYHA 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

	(class I, LOE B) Reasonable expected survival		treatment. The expected benefit is greater in patients with NYHA I-II symptoms		
Patisiran	ATTRv PN (stage 1-2) *	ATTRv PN (stage 1-2) *	ATTRv with ambulatory PN *	ATTRv PN (stage 1-2) *	ATTRv PN (stage 1-2) *
	ATTRv PN (stage 1-2) + CA **	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) *	ATTRv PN (stage 1-2) *	ATTRv with ambulatory polyneuropathy *	ATTRv PN (stage 1-2) *	Not approved in Japan

Recommended treatments are highlighted in green, those that may be considered in yellow, and those that should be avoided in red. The levels of evidence are classified as: *, evidence from a clinical trial in this specific population; **, evidence from a subgroup analysis, retrospective studies or case series; ***, expert consensus opinion. 6MWD, 6-minute walking distance; AHA, American heart Association; CA, cardiac amyloidosis; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; DGK, *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ESC, European Society of Cardiology; JCS, Japanese Circulation Society; LOE, level of evidence; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PN, polyneuropathy.

Table 6. Proposed follow-up protocols for patients with cardiac amyloidosis.

ESC (1)	DGK (2)	CCS/CHFS (3)	AHA (5)	JCS (6)
<u>AL-CA</u> *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 months (after completing initial haematological treatment):* • Complete blood count, basic biochemistry, NT-proBNP	<u>AL-CA</u> *During specific drug therapy* Every 3 months (or after every 2 further therapy cycles): • NT-proBNP • Troponin T or I Every 6 months: • 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*	• Serial imaging with echocardiography or CMR in addition to measuring BNP/NT-proBNP • Echo or CMR repeated every 6 to 48 months 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)	-

and troponin • Serum free light-chain quantification • Clinical evaluation by Hematology *Every 6 months:* • ECG • Echocardiography/CMR • Evaluation by Cardiology *Every 12months:* • 24 h Holter ECG <u>ATTR-CA</u> Every 6 months: • ECG • Blood tests including NT-proBNP and troponin • Neurological evaluation (if ATTRv)	*therapy* Every 6 months: • Resting ECG • NT-proBNP • Troponin T or I • Transthoracic echocardiography including strain measurements Every 12 months: • Holter ECG • Additional CMR including LGE and T1 mapping in case of suspected disease progression due to serum biomarkers and/or echocardiographic findings <u>ATTR-CA</u> *During specific drug therapy* Every 3–6 months:			

• 6MWD (optional) • KCCQ (optional) Every 12months: • Echocardiography/CMR • 24 h Holter ECG • Ophthalmological evaluation (if ATTRv)	• NT-proBNP • Troponin T or I Every 12 months: • 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 months: • Resting ECG • NT-proBNP • Troponin T or I • Transthoracic echocardiography including strain measurements			

	Every 12 months: • Holter ECG Every 12 to 24 months: • Additional CMR including LGE and T1 mapping in case of suspected disease progression due to serum biomarkers and/or echocardiographic findings.			

6MWD, 6-minute walking distance; AHA, American Heart Association; AL-CA, amyloid light-chain cardiac amyloidosis; ATTR(v)-CA, (variant) amyloid transthyretin cardiac amyloidosis; 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; ESC, European Society of Cardiology; JCS, Japanese Circulation Society; KCCQ, Kansas City Cardiomyopathy Questionnaire; LGE, late gadolinium enhancement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 7. Main topics evaluated in the five documents and level of agreement or disagreement between them.

	ESC (1)	DGK (2)	CCS/CHFS (3)	AHA (5)	JSC (6)
DIAGNOSIS					
General approach to diagnosis					
Sequence of scintigraphy and monoclonal protein assessment					
Echocardiographic scores					
Biomarkers					
Tracer for bone scintigraphy					
SPECT					
CMR recommended					
Tissue biopsy					
Genetic testing					
RISK PREDICTION AND MANAGEMENT					
Gene screening in family members					
Follow-up of mutation carriers					
Risk stratification in CA					
HF drugs					
ACEi/ARB					

ARNI					
Beta-blockers					
MRA					
Loop diuretics					
Digoxin					
Anticoagulation for AF					
Anticoagulation in sinus rhythm					
LA appendage occlusion Pulmonary veins isolation					
Ambulatory ECG					
PM					
ICD for secondary prevention					
ICD for primary prevention					
CRT					
Heart transplantation					
Mechanical circulatory support					
Disease-modifying therapies					
AL-CA					
ATTR-CA without neurologic involvement					

ATTR-CA plus polyneuropathy					
Minimal degree of cardiac disease for treatment					
Age or advanced HF as exclusion criteria for treatment					
Treatment of asymptomatic carriers					
Monitoring disease progression and response to treatment					
Costs of disease modifying therapy					

Legend

Considered with substantial agreement with all other documents	Considered with substantial agreement with ≥1 other document	Considered with a specific position, not found in any other document	Not considered

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; AHA, American Heart Association; AL-CA, amyloid light-chain cardiac amyloidosis; ATTR-CA, amyloid transthyretin cardiac amyloidosis; CA, cardiac amyloidosis; CCS/CHFS, Canadian Cardiovascular Society/Canadian Heart Failure Society; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; DGK, *Deutsche Gesellschaft für Kardiologie* (German Cardiac Society); ECG, electrocardiogram; ESC, European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter defibrillator; JCS, Japanese Circulation Society; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; SPECT, single photon emission computed tomography.