Archives of Cardiovascular Disease 118 (2025) 63–74

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Expert consensus

Management of conduction disease and arrhythmias in patients with cardiac amyloidosis: A position paper from the Working Group of Cardiac Pacing and Electrophysiology of the French Society of Cardiology

Nicolas Lellouche[a,*], Pascal Defaye[b], Vincent Algalarrondo[c], Estelle Gandjbakhch[d], Laurent Fauchier[e], Laure Champ-Rigot[f], Laura Delsarte[g], Fabrice Extramiana[c], Eloi Marijon[h], Raphael Martins[i], Vincent Probst[j], Rodrigue Garcia[k], Stephane Combes[l], Jerome Taieb[m], Mina Ait Said[n], Carole Mette[o], Olivier Piot[o], Serge Boveda[l,p,q], Didier Klug[r], Charles Guenancia[s], Frederic Sacher[t,u], Philippe Maury[v,w]

[a] *Cardiology Department, Hôpital Henri-Mondor, AP–HP, 94000 Créteil, France*
[b] *Cardiology Department, CHU de Grenoble-Alpes, Grenoble-Alpes University, 38043 Grenoble, France*
[c] *Cardiology Department, Hôpital Bichat, AP–HP, Université Paris Cité, 75018 Paris, France*
[d] *Cardiology Department, Pitié-Salpêtrière University Hospital, AP–HP, ICAN, Sorbonne Université, 75013 Paris, France*
[e] *Faculté de Médecine, Université François-Rabelais, 37032 Tours, France*
[f] *Cardiology Department, CHU de Caen, 14000 Caen, France*
[g] *Cardiology Department, CHU de Montpellier, 34295 Montpellier, France*
[h] *Cardiology Department, Hôpital Européen Georges-Pompidou, AP–HP, 75015 Paris, France*
[i] *Inserm, LTSI–UMR 1099, CHU de Rennes, Université de Rennes, 35000 Rennes, France*
[j] *Institut du Thorax, CHU de Nantes, Inserm, CNRS, Université de Nantes, 44000 Nantes, France*
[k] *Cardiology Department, Centre d'Investigation Clinique CIC14-02, CHU de Poitiers, 86000 Poitiers, France*
[l] *Heart Rhythm Management Department, Clinique Pasteur, 31076 Toulouse, France*
[m] *Cardiology Department, Centre Hospitalier du Pays d'Aix, 13100 Aix-en-Provence, France*
[n] *Hôpital Privé Jacques-Cartier, 91300 Massy, France*
[o] *Centre Cardiologique du Nord Saint-Denis, 93207 Saint-Denis, France*
[p] *Vrije Universiteit Brussel (VUB), 1090 Jette, Belgium*
[q] *Inserm U970, 75908 Paris, France*
[r] *Cardiology Department, CHU de Lille, 59000 Lille, France*
[s] *Cardiology Department, CHU de Dijon, 21000 Dijon, France*
[t] *Cardiac Arrhythmia Department, CHU de Bordeaux, 33000 Bordeaux, France*
[u] *Inserm U1045, IHU Liryc, CRCTB, Bordeaux University, 33000 Bordeaux, France*
[v] *Cardiology Department, Hôpital Rangueil, CHU de Toulouse, 31400 Toulouse, France*
[w] *Inserm UMR 1297, I2MC, 31432 Toulouse, France*

INFO ARTICLE

Historique de l'article :
Reçu le 8 juillet 2024
Reçu sous la forme révisée le 16 octobre 2024
Accepté le 21 octobre 2024
Disponible sur Internet le 21 November 2024

Keywords :
Cardiac amyloidosis
Arrhythmias
Cardiac implantable electronic device indication

* Corresponding author. Cardiology Department, Henri-Mondor University Hospital, AP–HP, 51, avenue du Maréchal-de-Lattre-de-Tassigny, 94000 Créteil, France.
Adresses e-mail : nicolas.lellouche@aphp.fr, nicolellouche@yahoo.com (N. Lellouche).

https://doi.org/10.1016/j.acvd.2024.10.323

1. Abbreviations

AAD	antiarrhythmic drug
AL-CA	light-chain cardiac amyloidosis
ATTR	transthyretin cardiac amyloidosis
CRT	cardiac resynchronization therapy
DCC	direct current cardioversion
ICD	implantable cardioverter-defibrillator
LAA	left atrial appendage
LVEF	left ventricular ejection fraction
NOAC	non-vitamin K antagonist oral anticoagulant
SCD	sudden cardiac death
VKA	vitamin K antagonist
vATTR-CA	hereditary (variant) transthyretin cardiac amyloidosis
wtATTR-CA	wild-type transthyretin cardiac amyloidosis

2. Background

Cardiac amyloidosis is caused by perimyocyte infiltration of amyloid deposits, which induces numerous pathophysiological mechanisms, including the inflammatory response cascade, oxidative stress and subsequent separation of myocyte fibrils. These cellular modifications can result in atrial fibrillation, which occurs very frequently in patients with cardiac amyloidosis and represents a major management issue in this population, conduction disease, such as bundle branch block, sinus node disease or atrioventricular block and ventricular arrhythmias [1]. One of the particularities of cardiac amyloidosis is the evolution of these abnormalities over time, with a faster and more unpredictable progression than in patients without cardiac amyloidosis. Finally, we describe the two main different types of cardiac amyloidosis (light-chain cardiac amyloidosis [AL-CA] and transthyretin cardiac amyloidosis [ATTR-CA; hereditary or wild type]), which have different arrhythmogenic properties [2].

Although cardiac amyloidosis is increasingly diagnosed, as a result of improvements in diagnostic tools, and despite the development of specific therapy [3], studies related to cardiac amyloidosis arrhythmias remain small in sample size, and the level of scientific evidence for arrhythmia management remains low. All the therapies currently used to treat cardiac arrhythmias are potentially applicable to patients with cardiac amyloidosis. However, the indications depend on the type of amyloidosis, the severity of the disease, patient frailty and the risk/benefit balance of the therapeutics used, with their potentially serious complications.

In this manuscript, we provide the current clinical evidence for the management of various cardiac arrhythmias in patients with cardiac amyloidosis, based on the available literature, together with potential unsolved issues that need further scientific evidence. However, we acknowledge that these data may be challenged in the near future by the very accelerated and impressive therapeutic developments in cardiac amyloidosis.

3. Atrial fibrillation and atrial arrhythmias

3.1. Rate or rhythm control

3.1.1. Prevalence, haemodynamic relevance and prognosis

Atrial amyloidosis is secondary to amyloid deposition within the atrial myocardium and cardiotoxic damage to atrial cardiomyocytes by amyloid precursors. In addition to age, elevated left ventricular filling pressures and subsequent dilation of the left atrium, atrial amyloidosis contributes to the high prevalence of atrial arrhythmias in cardiac amyloidosis [1,4]. Atrial amyloidosis can be an early manifestation of cardiac amyloidosis, explaining why atrial arrhythmias can occur before diagnosis of cardiac amyloidosis [5].

The prevalence of atrial arrhythmias in cardiac amyloidosis is quite variable, although higher than in other populations, ranging from 5% to 70%. This wide range in prevalence may be caused by differences in the timing of cardiac amyloidosis diagnosis in this fast-evolving disease [6–10]. Atrial arrhythmias appear to be more frequent in wild-type ATTR-CA (wtATTR-CA) than in hereditary ATTR-CA (vATTR-CA) and AL-CA [8–12], possibly partly because of older age [11,12]. Atrial arrhythmias often manifest as persistent or permanent atrial fibrillation at the time of cardiac amyloidosis diagnosis [12], initially usually with fast heart rates [6]. Age, abnormal P wave, conduction disturbances and left atrial size and function are predictors of incident atrial fibrillation in patients with cardiac amyloidosis [7,10].

Isolated atrial amyloidosis, caused by a local overproduction of atrial natriuretic peptide, should not be confused with ATTR-CA or AL-CA. This disease is age dependent, and is almost exclusively observed in the elderly. Relationships with atrial arrhythmia are less clear, possibly more representing a marker of atrial arrhythmia with less fibrosis [13,14].

AAs are often poorly tolerated in cardiac amyloidosis. Rapid ventricular rates, loss of atrial systole and subsequent atrioventricular mechanical synchronization in cardiac amyloidosis result in altered diastolic filling, and thus major haemodynamic impairment, usually leading rapidly to congestive heart failure [15,16]. However, paradoxically, in some instances, atrial fibrillation may have also beneficial consequences in patients with cardiac amyloidosis, because of accelerated heart rate. Indeed, some patients may have associated slow sinus rate caused by frequent sick sinus syndrome with a slow heart rate that can worsen ventricular output during diastolic dysfunction.

The apparent lack of impact of atrial arrhythmias in cardiac amyloidosis (see below) may be related to this beneficial heart rate acceleration, but also to the severity and fast progression of cardiac amyloidosis. The long-term benefits of maintaining sinus rhythm may be limited because of the evolutive restrictive diastolic dysfunction, decreasing the haemodynamic importance of atrial systole, as main ventricular filling occurs during early diastole, with negligible filling as a result of the atrial kick, as suggested by the Doppler mitral inflow velocity [11]. Also, the presence of concomitant sinus node disease can explain this lack of impact. In fact, atrial fibrillation does not seem to alter all-cause death rates [17–19] or cardiovascular death rates [12], whatever the subtype of cardiac amyloidosis [12]. Both the high recurrence rates of atrial fibrillation and the poor prognosis of cardiac amyloidosis are likely to hinder the demonstration of an additional impact of atrial fibrillation. Even if atrial arrhythmias in patients with cardiac amyloidosis have been associated with a poorer prognosis, this may simply reflect patients with a higher risk of heart failure and mortality [20], suggesting that atrial fibrillation is a marker of severity of cardiac amyloidosis.

3.1.2. Antiarrhythmic drugs in cardiac amyloidosis

Antiarrhythmic drug (AAD) therapy and drug rate control of atrial arrhythmias are challenging in cardiac amyloidosis because of the vasodilator, toxic and negative inotropic, dromotropic and especially chronotropic effects of many drugs [1,11], which are particularly deleterious in infiltrative cardiomyopathies, such as cardiac amyloidosis. This constitutes a major limitation for prescription of such drugs in patients with cardiac amyloidosis with altered diastolic filling – where heart rate is the major variable ruling cardiac output [21] – and with a high prevalence of concomitant electrical conduction disturbances.

Amiodarone is the only AAD commonly used in cardiac amyloidosis for rhythm control [19], even if the rate of sinus rhythm maintenance is lower in patients with versus without cardiac amy-

loidosis [17]. Moreover, it can be used for rate control as a last resort for patients who do not qualify for non-pharmacological techniques [18,22].

Beta-blockers are poorly tolerated, although low dosage might be useful in some patients with rapid ventricular response [22], and they are probably better tolerated than calcium channel blockers and digoxin [11]. Digoxin is traditionally contraindicated in patients with cardiac amyloidosis because of increased toxicity [23], although this has been questioned, and some propose its use at a lower dosage, with regular monitoring of drug concentration [24,25]. In fact, drug rate control is difficult, because drugs are poorly tolerated and often abandoned in cardiac amyloidosis [6].

Even if the difference in survival between drug therapy rate and rhythm control strategies is not significant, the survival curve reveals a trend towards better outcomes using rhythm control [19], which can lead to symptomatic improvement in the majority of cases [6]. Although the strategy of rhythm control does not seem to impact survival in retrospective studies, some data suggest that sinus rhythm maintenance may improve symptoms and limit the progression of heart failure. It is plausible that restoring atrial systole may improve left ventricular filling and cardiac output, at least in the initial stages of the disease. Atrial fibrillation in cardiac amyloidosis has been strongly associated with heart failure [18], and patients without atrial fibrillation are less symptomatic [12]. All of these observations rather favour rhythm control in the management of atrial arrhythmias in cardiac amyloidosis.

3.1.3. Catheter ablation

Catheter ablation is a first-line, simple and efficient, curative treatment for typical atrial flutter [6,22], and should therefore be proposed as a first-step therapy, and possibly also in case of recurrent atrial tachycardia [26]. Recurrences rates after ablation of atrial tachycardia have been evaluated at around 50% [27].

Although catheter ablation is an accepted curative therapy, leading to significant improvements in heart failure [28,29] and survival [30] in large populations of patients with atrial fibrillation and impaired left ventricular ejection fraction (LVEF), long-term efficacy of atrial fibrillation ablation in the subgroup of patients with cardiac amyloidosis is still a matter of debate [17,31–34]. Only a few studies, including a rather limited number of patients undergoing catheter ablation for atrial arrhythmia in cardiac amyloidosis, are available to date [6,17,31,32,34], although one larger series and a first meta-analysis have been published very recently [27,35,36].

In this population, in which cardiac output is initially highly dependent on both elevated heart rate and mechanical atrial systole, the benefit of rhythm control by ablation over a rate control strategy has still to be investigated. Randomized trials comparing ablation with rate control strategies in patients with cardiac amyloidosis have been lacking, but a very recent meta-analysis investigating the benefits of ablation is now available [35] (see below).

Rather modest long-term success rates have been reported, which are significantly lower than those in unselected patients with atrial fibrillation [37], probably reflecting the challenging adverse atrial remodelling in cardiac amyloidosis. Spontaneous extensive atrial scars are observed on voltage maps in investigated patients with cardiac amyloidosis [36], reflecting the presence of an unfavourable atrial substrate caused by atrial amyloidosis. After ablation of atrial arrhythmia (mainly atrial fibrillation), recurrence rates range between 25% and 85% at 1 year and 40% and 80% at 2–3 years [6,17,30–32]; these rates are significantly higher in end-stage cardiac amyloidosis (90%), and lower in patients receiving tafamidis [17]. Tafamidis seems to improve left atrial function in patients with wtATTR-CA, but only in patients in sinus rhythm [38], and it is unknown if such a treatment will really decrease the risk of atrial fibrillation. There is only one retrospective comparison, in which tafamidis use independently lowered the incidence of atrial fibrillation in patients with ATTR cardiomyopathy [39].

Atrial fibrillation ablation in patients with cardiac amyloidosis may be associated with a higher risk of acute or short-term adverse clinical events (pericardial effusions and significant bleeding) and death compared with matched patients with heart failure without cardiac amyloidosis [40], although short-term safety was found to be similar to that in a propensity score-matched cohort of dilated cardiomyopathy undergoing atrial fibrillation ablation [41].

Ablation seems to be more effective when performed in the earlier stages of the disease [17,32]. Some improvements in New York Heart Association class have been noted after ablation of atrial arrhythmias in two-thirds of patients, although the death rate was high [34]. The death rate was found to be significantly lower after ablation compared with in matched non-ablated patients (29% vs 70%), and ablation was associated with a significant reduction in the frequency of hospitalization for heart failure or arrhythmias [17]. In a recent study, including more than 30 patients with various types of cardiac amyloidosis undergoing ablation of various atrial arrhythmias [27], the long-term success rate was 70% (including AADs and redo ablations) and the death rate was 40%, with significant improvements in clinical and biological status and reduced deaths as a result of intractable heart failure when sinus rhythm could be maintained [27]. The largest series is a very recent one, including 54 patients with wild-type ATTR cardiomyopathy who underwent catheter ablation for various atrial arrhythmias [36]. The recurrence rate after multiple catheter ablations was 30% at 1 year and 56% at 5 years, with a significant reduction in deaths and heart failure hospitalization.

In addition, only one recent meta-analysis of ablation of atrial arrhythmia in cardiac amyloidosis is available, including 168 patients from eight studies; this meta-analysis found an atrial fibrillation recurrence rate of 35%, and a significant adjusted 64% reduction in deaths in patients receiving ablation for atrial arrhythmia [35]. There are currently not enough data to recommend a particular ablation technique or energy.

Thus, although data regarding the role of atrial fibrillation ablation remain scarce and sometimes controversial [42], performing early catheter ablation for atrial arrhythmia in patients with cardiac amyloidosis may be considered [43], with, in most cases, the expectation of improving rates of death and hospitalization for heart failure, based on more recent data [27,35,36].

Finally, atrioventricular node catheter ablation with pacemaker implantation may be beneficial, especially in patients with refractory rapid ventricular response or underlying conductive disorders [32], and is the only solution when both rhythm control and rate control have failed, as for other populations.

3.1.4. What is accepted?

Firstly, atrial arrhythmias are very frequent during the evolution of cardiac amyloidosis, and are usually poorly tolerated and associated with heart failure, even if not apparently linked to deaths; secondly, AADs are difficult to use in cardiac amyloidosis, with the exception of amiodarone; thirdly, the long-term results of atrial fibrillation ablation are modest, except in the earliest stages of cardiac amyloidosis, thus early catheter ablation may be considered; and lastly, in case of failure of rhythm or rate control, atrioventricular node ablation and pacemaker implantation should be discussed in this population.

3.1.5. What is still to be demonstrated?

Rhythm control can lead to better outcomes and symptomatic improvement, but the benefits of a rhythm control strategy by ablation have still to be demonstrated.

3.2. Direct current cardioversion in patients with cardiac amyloidosis

Direct current cardioversion (DCC) is the main strategy for recovering sinus rhythm acutely in patients with atrial fibrillation. Patients with cardiac amyloidosis are particularly sensitive to loss of atrial contraction and a decrease in ventricular filling and stroke volume, as observed in atrial fibrillation, because of their significant ventricular diastolic dysfunction.

The acute success rate for restoration of sinus rhythm seems to be similar in patients with cardiac amyloidosis compared with in patients without cardiac amyloidosis. El-Am et al. found a 90% DCC acute success rate compared with 94% in a control group of patients without cardiac amyloidosis ($P = 0.4$) [15]. Touboul et al. observed an 88% DCC acute success rate in 66 patients with cardiac amyloidosis [44], similar to that in the Euro Heart Survey in a general population [45]. Importantly, 64% of patients with cardiac amyloidosis were treated with amiodarone before DCC in this study. Amiodarone is known to increase the acute success rate of DCC, and can be used in cardiac amyloidosis, in contrast to most of the other AADs (digoxin and non-dihydropyridine calcium channel blockers). Thus, the use of amiodarone should be favoured before DCC in patients with cardiac amyloidosis.

Regarding the complication rate after DCC, data seem partly contradictory. El-Am et al. [15] showed that procedural complication rates were significantly higher in patients with cardiac amyloidosis than in control patients (14% vs 2%; $P = 0.007$), including ventricular tachycardia/fibrillation, bradyarrhythmia requiring pacemaker implantation, acute hypoxaemia and stroke [19]. The Euro Heart Survey reported a 4.2% incidence of major complications after cardioversion in the general atrial fibrillation population, including the occurrence of acute heart failure, in addition to rhythm and thromboembolic complications [43]. However, Touboul et al. [44] found a lower rate of complications of 1.5% in cardiac amyloidosis, probably explained by wider use of non-vitamin K antagonist oral anticoagulants (NOACs) and restricted use of some AADs (avoiding digoxin, beta-blockers and non-dihydropyridine calcium channel blockers) that could cause haemodynamic instability and conduction disorders. Also, the prevalence of cardiac implantable electronic device implantation was much higher in this study compared with in the study by El-Am et al. (68% vs 6%), eliminating bradycardia complications after DCC.

Mid- and long-term efficiency of cardioversion seems to be related to the evolution of cardiac amyloidosis. Indeed, Donnellan et al. showed that the long-term success of DCC was related to the stage of cardiac amyloidosis, particularly in patients with ATTR-CA [17]: at 1 year following DCC, 74% of patients with stage 1, 33% with stage 2 and 18% with stage 3 were still in sinus rhythm ($P < 0.0001$). However, the success rate of DCC in patients with cardiac amyloidosis seems to be similar to that in patients without cardiac amyloidosis. Touboul et al. found a relatively low arrhythmia recurrence rate of 58% after mean a follow-up of 31 ± 27 months [44]. Several studies have assessed the risk of atrial fibrillation recurrence after DCC at mid-term follow-up in general populations that were similar to patients with cardiac amyloidosis. Indeed, in a meta-analysis including 44 randomized controlled trials and 11,322 patients, Lafuente-Lafuente et al. found that pooled recurrence rates at 1 year after DCC were high: 71–84% in controls and 44–67% in patients treated with AADs [46]. Thus, DCC seems to be a safe and efficient strategy to restore sinus rhythm in patients with cardiac amyloidosis; it should be performed early in the disease course, and in patients under amiodarone, if possible, to increase the acute and long-term success rate of cardioversion.

3.2.1. What is accepted?

DCC is a safe and efficient strategy to restore sinus rhythm in patients with cardiac amyloidosis, but should be performed early in the disease course and, if possible, in patients under amiodarone.

3.3. Anticoagulation therapy during cardiac amyloidosis

3.3.1. The high prevalence of atrial thrombi in cardiac amyloidosis

The infiltration by proteinaceous deposits of amyloid is associated with a hypercoagulability state, favoured by increased oxidant stress and endothelial dysfunction [47]. Russo et al. suggested that cardiac amyloidosis was associated with a higher rate of thrombus, possibly related to endomyocardial injury secondary to amyloid infiltration, blood hypercoagulability, involving hyperviscosity and renal insufficiency, and altered haemodynamics with atrial blood stasis [48]. In addition, atrial fibrillation, a disease associated with an increased thromboembolic risk, is observed in approximately 60% of patients with cardiac amyloidosis [12].

Consistent with this, numerous studies have shown that the intracardiac thrombus rate is significantly higher in patients with versus without cardiac amyloidosis. In particular, Feng et al. found a 33% rate of intracardiac thrombus in 116 autopsies of patients with cardiac amyloidosis (AL-CA 47% and ATTR-CA 53%). Factors associated with intracardiac thrombi were left ventricular dysfunction, AL-CA and atrial fibrillation [49]. Feng et al. also reported that 27% of 156 patients with cardiac amyloidosis (AL-CA 51%, ATTR-CA 49%) had intracardiac thrombus when performing systematic transoesophageal echocardiography. Factors associated with the presence of thrombus were AL-CA, left ventricular diastolic dysfunction and low left atrial appendage (LAA) emptying velocity [50]. Martinez-Naharro et al. performed systematic cardiac magnetic resonance imaging in 324 patients with cardiac amyloidosis, and found a 6.2% rate of intracardiac thrombi, particularly in patients with left ventricular dysfunction and dilated right and left atria [51]. Interestingly, the prevalence of intracardiac thrombi in patients in sinus rhythm and with AL-CA was 4.5%, whereas it was 1.1% in patients with ATTR-CA [51].

3.3.2. The role of the CHA_2DS_2-VASc score in cardiac amyloidosis

The high rate of thrombus in patients with cardiac amyloidosis raises the problem of the clinical relevance of thromboembolic scores, such as the CHA_2DS_2-VASc score, and the indication for anticoagulation therapy for patients with cardiac amyloidosis with atrial fibrillation, and even in patients without documented atrial fibrillation. The value of the CHA_2DS_2-VASc score for predicting clinical embolism is controversial in patients with cardiac amyloidosis. Donnelan et al. found that the CHA_2DS_2-VASc score was not correlated with the presence of cardiac thrombi assessed with transoesophageal echocardiography [52]. Vilches et al. evaluated 1191 patients with ATTR-CA, and found that the annual rate of stroke in patients in sinus rhythm was 0% with and 1.3% without anticoagulation, and 1.7% with and 4.8% without anticoagulation for patients with atrial fibrillation, whereas the CHA_2DS_2-VASc score was not predictive of stroke occurrence [53]. By contrast, Capelli et al. found that a CHA_2DS_2-VASc score ≥ 3 was predictive of cardioembolic events in patients with cardiac amyloidosis in sinus rhythm, although not in those with atrial fibrillation [54]. These discrepancies may be explained by different patient profiles, consistent with different rates of atrial fibrillation and history of stroke. However, all of these studies are consistent with the fact that the CHA_2DS_2-VASc score may not be fully adapted for patients with cardiac amyloidosis.

A French study analysing a wide national public database described different factors associated with cardiac thrombus in patients with cardiac amyloidosis: left ventricular dysfunction (diastolic

and systolic); restrictive mitral profile; the absence of mitral A wave at pulsed Doppler on transthoracic echocardiography; and presence of atrial fibrillation or excessive atrial premature atrial contractions on 24-hour Holter electrocardiogram [55]. In addition, patients with cardiac amyloidosis were at higher risk of clinical haemorrhage. This study also found specific factors associated with clinical haemorrhage: AL-CA-type cardiac amyloidosis; mucocutaneous lesions; factor X deficiency for patients with ATTR-CA; history of gastrointestinal haemorrhage; and transthyretin mutation Val30Met with heart transplant.

Thus, anticoagulation therapy should be started in every patients with cardiac amyloidosis with documented atrial fibrillation, independent of the CHA_2DS_2-VASc score. Current guidelines recommend performing 24-hour Holter electrocardiography every 6 months for ATTR-CA and every 12 months for AL-CA [42]. To date, there are no data on implantable loop recorders for documenting atrial fibrillation in patients with cardiac amyloidosis, so this cannot currently be advised. In other circumstances, the clinical risk/benefit ratio of introducing anticoagulation therapy should be discussed, even in patients in sinus rhythm, particularly if the patient has a history of stroke or other arterial embolism without documented atrial fibrillation. Finally, to date, no specific bleeding risk score is available for patients with cardiac amyloidosis.

3.3.3. *Atrial thrombi before cardioversion in cardiac amyloidosis*

Systematic cardiac imaging should be proposed to exclude LAA thrombus before direct DCC. Indeed, El-Am et al. found a 28% rate of LAA thrombus on systematic cardiac imaging (transoesophageal echocardiography or computed tomography scan) before DCC in patients with cardiac amyloidosis, compared with 2.5% in a control group of patients without cardiac amyloidosis [15]. These patients were under vitamin K antagonists (VKAs), and 46% received adequate anticoagulation. In addition, Touboul et al. [44] found that 14% of patients with cardiac amyloidosis had cardiac thrombi before DCC; among them, 74% were treated with NOACs.

3.3.4. *Management of atrial thrombi in cardiac amyloidosis*

Cariou et al. compared the effect of NOACs versus VKAs in patients with cardiac amyloidosis with atrial arrhythmias [56]. In 273 patients with cardiac amyloidosis, there was a similar rate of stroke in both groups, but a higher rate of bleeding complication in the VKA group. NOACs therefore seem to be appropriate anticoagulation therapy in patients with cardiac amyloidosis. In case of contraindication to anticoagulation, LAA closure may also be proposed in patients with cardiac amyloidosis, according to European Society of Cardiology guidelines [37]. Amat-Santos et al. [57] compared 40 patients with cardiac amyloidosis with 1119 patients without cardiac amyloidosis undergoing LAA closure. The outcome was similar in the two populations, suggesting that patients with cardiac amyloidosis could also benefit from LAA closure.

Limited data suggest that the rate of resolution of atrial thrombus may be lower in patients with cardiac amyloidosis, consistent with the higher rate of thrombus observed in these patients. Touboul et al. observed a low rate of resolution of left atrial thrombi of 16% in cardiac amyloidosis [44] whereas, in the general population, Nelles et al. estimated the rate of resolution of such thrombi at 51% within 1 year in a population of patients mainly treated with oral anticoagulation at baseline [58]. A 60% rate of resolution was also observed by Niku et al. in a standard atrial fibrillation population, without difference in efficacy between NOACs and VKAs [59]. Finally, the X-TRA study showed a 60.4% rate of resolved or reduced thrombus after 6 weeks of rivaroxaban treatment in patients with initial inappropriate anticoagulation therapy [60]. In practice, according to a survey conducted in 2019 by the European Heart Rhythm Association in 54 centres, the most prevalent strategies in this setting were to switch from VKAs to NOACs or vice versa, with either a higher (2.5–3.5) or standard (2.0–3.0) target international normalized ratio. Switching to fractionated heparin was less common, and the use of unfractionated heparin or the addition of antiplatelet drugs was rare [61]. Overall, there is no consensus to favour one strategy over another, and further studies are needed to define the best antithrombotic strategies to treat left atrial thrombus, especially in patients with cardiac amyloidosis. The possible reasons explaining the variable effects of antithrombotic therapy on resolution of left atrial thrombus are not fully understood, but may include age, structure and architecture of the clot or associated co-morbidities.

Also, for patients with cardiac amyloidosis with persisting LAA thrombus despite anticoagulation therapy, LAA closure may be proposed. Sebag et al. reported that in specific clinical circumstances (stable and limited-size thrombus located deep inside the LAA) and using a specific technique to avoid thrombus mobilization, LAA closure could be safe and effective, and may possibly further facilitate proposal of DCC or atrial fibrillation ablation, for example [62].

3.3.5. *What is accepted?*

Firstly, the rate of intracardiac thrombus is important in patients with cardiac amyloidosis; secondly, the CHA_2DS_2-VASc score is not adapted for patients with cardiac amyloidosis; thirdly, anticoagulation therapy should be started in any patient with cardiac amyloidosis with atrial fibrillation, independent of the CHA_2DS_2-VASc score; and lastly, left atrial thrombus should be excluded systematically in patients with cardiac amyloidosis before DCC, even with adequate anticoagulation.

3.3.6. *What is still to be demonstrated?*

Still to be demonstrated are: firstly, the benefit of implantable loop recorders for tracking atrial fibrillation in cardiac amyloidosis; and secondly, the benefit of anticoagulation in patients with cardiac amyloidosis in stable sinus rhythm and without previous documented atrial fibrillation.

4. Cardiac conduction disturbances during cardiac amyloidosis

4.1. *Pathophysiology, epidemiology and evolution*

The spectrum of conduction disturbances during cardiac amyloidosis is broad, and may include sinus node disease, atrioventricular nodal or infranodal block, bundle branch block, intraventricular conduction disturbance and a combination of the above.

4.1.1. *Pathogenesis of conduction disturbances*

There are multiple possible factors that may be involved in the pathogenesis of conduction system disturbances in cardiac amyloidosis. First, amyloid deposition, resulting in thickening and disarrangement in myocardial architecture, may disrupt electrical impulse propagation along conduction fibres. Possible cytotoxic effects of certain amyloid precursor proteins may induce oxidative stress and apoptosis, and interfere with intracardiac conduction. For instance, infusion of light chains from patients with AL-CA into isolated mouse hearts has been shown to induce diastolic dysfunction, independent of amyloid deposit *in vitro* [63]. Transthyretin is a well-known neurotoxic agent, thus amyloid deposition within interstitial space results in sympathetic denervation that may contribute to conduction system disturbances. Data on cardiomyocyte toxicity are only emerging. In vitro studies have demonstrated that numerous ATTR variants are cytotoxic to human myocardial cell lines in a concentration-dependent manner [64]. Furthermore, the mechanism of cytotoxicity not only involves oxidative

stress and apoptosis, but also dysregulation of intracellular calcium signalling, causing action potential prolongation [65].

4.1.2. Electrocardiogram features

Typical electrocardiogram abnormalities reported during cardiac amyloidosis are low-voltage pattern and pseudoinfarction pattern in precordial leads (or poor R wave progression) [66]. Baseline electrocardiogram findings in both AL-CA and ATTR-CA have been described by Cappelli et al. [67]; wtATTR-CA showed the highest prevalence of atrioventricular block (grade 1 or greater) (41%), whereas vATTR-CA more often showed intraventricular conduction disturbance (54%). Conversely, low-voltage pattern was more common in AL-CA (49%), whereas pseudoinfarction pattern had similar prevalence among groups (around 35%). The follow-up of a large cohort of patients with AL-CA revealed that cardiac involvement was associated with significant prolongation of PQ, QRS, QT and QTc intervals, and a higher prevalence of intraventricular block. Moreover, mortality was significantly higher among patients with intraventricular delay [68].

4.1.3. Autonomic dysfunction

Autonomic dysfunction has been reported in up to 25% of patients with AL-CA, and the presence of orthostatic hypotension in patients with AL-CA is predictive of poor prognosis [69]. Autonomic dysfunction in patients with AL-CA results in abnormal baroreflex response and blood vessel control, associated with depressed heart rate variability and heart rate turbulence [70].

4.1.4. Sinoatrial node disease

Despite the high prevalence of conduction disturbances in cardiac amyloidosis, and the predisposition for amyloid to deposit in the atria, sinus node disease in cardiac amyloidosis is not well studied. Evidence of sinus node disease as an early manifestation of cardiac amyloidosis has been documented in a few case reports [71]. Most studies investigating conduction system disturbances in cardiac amyloidosis do not discuss sinus node disease; available data suggest it is rather uncommon. Reisinger et al. performed electrophysiological testing on 25 patients with AL-CA, finding that 12% had sinus node disease [72]. In a retrospective study of 369 patients with ATTR-CA followed over 28 months, sinus node disease occurred in 7% of patients, without difference between patients with vATTR-CA and those with wtATTR-CA (8% vs 6%, respectively) [73]. However, patients with cardiac amyloidosis, as already mentioned, are very sensitive to slow heart rate, and the standard definition of normal values for sinus node cardiac rate is possibly not adapted for this type of patient. Thus, the prevalence of inappropriate slow heart rate at baseline and during exercise in patients with cardiac amyloidosis is probably underestimated, and higher than mentioned in the literature, and probably may already be considered as a debutant form of sinus node disease in these patients.

4.1.5. Atrioventricular conduction disturbances

Atrioventricular block seems to be prevalent in patients with cardiac amyloidosis, and often precedes the diagnosis. Several studies have found that 2.5–13% of patients had a pacemaker implanted before the eventual diagnosis of cardiac amyloidosis. The prevalence of ATTR-CA in unselected populations of patients implanted with or needing a pacemaker for high-degree atrioventricular block is estimated at 4–9% [74,75].

In general, the prevalence of pacemaker implantation seems to be higher in patients with wtATTR-CA, followed by vATTR-CA and AL-CA. In a retrospective study including 369 patients with ATTR-CA, 9.5% of patients had a pacemaker at the time of diagnosis, and a further 11% required pacemaker implantation for high-grade atrioventricular block during a follow-up period of 28 months [73]. In an Italian study of 233 patients, Rapezzi et al. found that first-degree atrioventricular block was present in 18% of those with AL-CA, but up to 33% of those with wtATTR-CA. Moreover, 13% of patients with wtATTR-CA had pacemakers implanted before diagnosis, compared with 3% of those with vATTR-CA or AL-CA [76]. A plausible interpretation is that ATTR-CA behaves as a progressive cardiomyopathy, characterized by slow amyloid deposition within the atria, ventricles and conduction system, whereas AL-CA rather resembles an acute myocarditis, with early symptom onset and rapid disease progression to end-stage heart failure as a result of the toxic effects of AL chains, despite lesser degrees of infiltration. However, it must be noted that patients with wtATTR-CA are significantly older than those with other types of cardiac amyloidosis, and consequently are more prone to concomitant degenerative conduction disturbances [67].

Electrophysiological studies conducted in 25 patients with AL-CA reported preserved nodal atrioventricular conduction in most patients, but His-Purkinje system conduction was usually abnormal, with a prolonged HV interval, even in the presence of a narrow QRS duration on the surface electrocardiogram. In this study, HV interval prolongation was the sole independent predictor of sudden cardiac death (SCD) by multivariable analysis [72]. Similar findings were reported in electrophysiological studies on patients with both AL-CA and wtATTR-CA. In this study, almost all patients had a prolonged HV interval > 55 ms. Patients with wtATTR-CA appeared to have more prolonged His-Purkinje conduction intervals compared with patients with AL-CA [31]. Authors of both studies have suggested that HV interval prolongation with a relatively narrow QRS duration may suggest frequent widespread involvement of both right and left bundle branches in patients with cardiac amyloidosis. Atrioventricular conduction disease in cardiac amyloidosis is progressive, and develops faster than in patients without cardiac amyloidosis, leading to pacemaker dependence at 5 years in most patients implanted with some cardiac device (either a pacemaker or defibrillator) [77].

A retrospective study by Algalarrondo et al. evaluated the outcomes of prophylactic pacemaker implantation in patients with vATTR-CA in case of HV interval > 70 ms (or > 55 ms associated with intraventricular conduction delay, first-degree atrioventricular block on electrocardiogram or Wenckebach anterograde conduction $\leq$ 100/min). During 45 months of follow-up, there was a 25% incidence of high-grade atrioventricular block in the prophylactic pacemaker group, with subsequent pacemaker dependence [78]. In a cohort of 405 patients with AL-CA, Porcari et al. reported pacemaker implantation in 8.9% within 3 years after diagnosis. Predictive factors for future pacemaker implantation were PR interval > 200 ms, QRS duration > 120 ms on surface electrocardiogram and history of atrial fibrillation [79]. In the cohort of patients with ATTR-CA reported by Donnellan et al., no significant differences in the development of atrioventricular block were observed across different cardiac amyloidosis disease stages, and only a QRS duration > 120 ms was associated with an elevated risk of atrioventricular block [73]. HV interval prolongation was also reported to be associated with SCD in patients with AL-CA [72].

However, data regarding the clinical usefulness of systematic electrophysiological testing remain scarce [31,72,78], and there is no evidence that HV interval measurement in asymptomatic patients could be used to guide pacemaker implantation. The progressive conduction disturbances in cardiac amyloidosis do not necessarily imply that SCD will be related to asystole resulting from complete heart block, and may only represent the severity of myocardial infiltration [72]. In fact, if high-degree conduction disease seems to be a relevant cause of SCD in this specific population, SCD is probably also caused by lethal ventricular arrhythmia or electromechanical dissociation, resulting in pulseless electrical activity [11].

4.1.6. What is accepted?

Firstly, conduction disturbances are various, frequent and rapidly evolutive in patients with cardiac amyloidosis; secondly, HV interval may be prolonged, even with a narrow QRS duration; and thirdly, first-degree atrioventricular block and QRS duration > 120 ms are likely to predict evolution towards complete atrioventricular block.

4.1.7. What is still to be demonstrated?

It is unknown whether a systematic electrophysiological study should be performed in asymptomatic patients with or without no overt conduction disorder on their 12-lead electrocardiogram.

4.2. Accepted and potential novel indications for cardiac pacing in cardiac amyloidosis

4.2.1. What are the current official recommendations for pacing in cardiac amyloidosis?

There are currently no specific recommendations for cardiac pacing in cardiac amyloidosis, and the 2021 European Society of Cardiology guidelines on cardiac pacing and cardiac resynchronization therapy [80] recommend conventional pacing indications. Regarding cardiac amyloidosis, the 2021 position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases [42] also recommends permanent pacemaker implantation according to standard indications, although the group recognizes that the management of conduction disorders in patients with cardiac amyloidosis is an area of uncertainty, and should be investigated. Lastly, in the 2019 Heart Rhythm Society expert consensus statement on evaluation, risk stratification and management of arrhythmogenic cardiomyopathy [81], an algorithm for rhythm management of cardiac amyloidosis is proposed. However, only indications related to atrioventricular conduction disorders are mentioned, similar to the ones described previously, and without specificity regarding cardiac amyloidosis.

4.2.2. Prophylactic indications for atrioventricular conduction disorders

A French study from 2012 [78] by Algalarrondo et al. analysed the incidence of high-degree atrioventricular block in patients with prophylactically implanted pacemakers. The indication for prophylactic pacemaker implantation was HV interval $\geq$ 70 ms (or HV interval > 55 ms associated with a fascicular block, first-degree atrioventricular block or Wenckebach anterograde conduction $\leq$ 100 beats/min). The underlying spontaneous atrioventricular conduction was analysed by temporarily inhibiting the device. At 45 ± 35 months follow-up, high-degree atrioventricular block was documented in 25% of the overall population implanted prophylactically, mainly in patients with a long HV interval, first-degree atrioventricular block or Wenckebach anterograde conduction $\leq$ 100 beats/min at baseline. The risk of high-degree atrioventricular block almost reached 60% at 5 years in patients with such characteristics.

More recently, Porcari et al. [79] identified three main factors predicting the need for pacemaker implantation during follow-up: history of atrial fibrillation; PR interval > 200 ms; and QRS duration > 120 ms. At 33 months, the presence of a history of atrial fibrillation or PR interval > 200 ms led to an approximately 30% indication for pacemaker implantation, whereas the presence of a wide QRS duration exposed patients to a 41.8% risk. The accumulation of these three risk factors resulted in a 55.7% risk of high-grade conduction disorders at 33 months, whereas the absence of these three factors had a negative predictive value for pacemaker implantation of 92% at 6 months.

Both studies were retrospective but, based on their results, a careful analysis of the clinical history (history of atrial fibrillation) and of the electrocardiogram (PR interval and QRS duration) is recommended, to determine if a given patient is at risk of developing high-degree conduction disorders in the future. If an electrophysiological study is performed, pacemaker implantation could be proposed for those patients with an HV interval $\geq$ 70 ms (or an HV interval > 55 ms associated with fascicular block or Wenckebach anterograde conduction $\leq$ 100 beats/min). Whether a systematic electrophysiological study should be performed in patients with no overt conduction disorder on their 12-lead electrocardiogram is unknown, and would require further studies.

4.2.3. Sinus node dysfunction and chronotropic incompetence

The incidence of sinus node disease in cardiac amyloidosis has been documented in up to 7% of patients [82]. Chronotropic incompetence, defined as insufficient acceleration of heart rate (typically < 80% at peak exercise) is also not uncommon, limiting exercise capacity. There are currently no robust studies on the benefits of cardiac pacemaker implantation in patients with asymptomatic sinus node disease or isolated chronotropic insufficiency, although one may postulate that improving heart rate during exercise may improve exercise intolerance. However, sinus node disease is often symptomatic in patients with cardiac amyloidosis, with heart failure symptoms resulting from significant haemodynamic worsening secondary to the low cardiac rate. Further studies will be required to analyse whether systematic implantation of patients with sinus node disease or isolated chronotropic insufficiency would objectively improve exercise capacity.

However, even if there is no scientific evidence to systematically increase the baseline pacing heart rate in patients with cardiac amyloidosis who have already been implanted with a cardiac implantable electronic device, the importance of programming a minimum heart rate of 70–80 beats/min to improve left ventricular diastolic dysfunction is highly probable (unpublished data).

4.2.4. What is accepted?

Firstly, the usual indications for pacemaker implantation remain valid in patients with cardiac amyloidosis; and secondly, asymptomatic patients with prolonged HV intervals and/or QRS and/or PR intervals or atrial fibrillation will experience a high rate of high-degree atrioventricular block over a few years.

4.2.5. What is still to be demonstrated?

Still to be demonstrated are:

- whether symptomatic patients with prolonged HV intervals and/or QRS and/or PR intervals will benefit from prophylactic pacemaker implantation;
- whether asymptomatic patients with rapidly evolutive QRS and/or PR intervals will benefit from prophylactic pacemaker implantation;
- whether prophylactic pacemaker implantation of patients with asymptomatic sinus node dysfunction or isolated chronotropic insufficiency will improve patient outcome;
- and the optimal baseline pacing rate in implanted patients.

4.2.6. Pacing mode and specificities in cardiac amyloidosis

Heart infiltration by amyloid deposits may lead to elevated pacing thresholds and poor detections [83], justifying the activation of automatic threshold mode and remote monitoring.

There is no specific work studying the complication rates of device implantation in cardiac amyloidosis. However, in publications where this rate was mentioned, it was found to be similar to that in a standard population.

In cases of sinus node dysfunction, activating rate-responsive mode is highly recommended, even in patients with a low percentage of atrial pacing. Indeed, cardiac haemodynamics can be

worsened by low heart rates, and a minimum of 70 beats/min should be considered during programming.

Despite the fact that most patients with cardiac amyloidosis implanted with pacemakers do not exhibit significant reduced LVEF, which typically occurs in the later stages of the disease, maintaining ventricular synchrony with a specific available pacemaker algorithm should be favoured.

For patients with cardiac resynchronization pacemakers, progression of conduction abnormalities should be anticipated. Although not studied extensively in cardiac amyloidosis, ventricular fusion algorithms and optimizing atrioventricular delay through algorithms or echocardiography may be considered.

4.3. Indications and clinical impact of cardiac resynchronization therapy in cardiac amyloidosis

Current official recommendations for cardiac resynchronization therapy (CRT) in cardiac amyloidosis state that three main indications for CRT could be considered in cardiac amyloidosis, as in other populations with symptomatic heart failure [80]. However, these classical indications may be questioned by the pathophysiology of cardiac amyloidosis, given the infiltration of the heart, which could lead to higher pacing thresholds or lack of resynchronization as a result of conduction delays within the left ventricle. In the latest expert consensus on cardiac amyloidosis from the American College of Cardiology, CRT is mentioned in a table without any degree of recommendation ("CRT if permanent pacemaker dependent?") [43]. A European position paper in 2021 suggested to "consider CRT if high pacing burden expected", highlighting the need for studies dedicated to this topic [42].

A first study published in 2019 by Donnellan et al. suggested that in cardiac amyloidosis, compared with right ventricular-paced patients, patients with CRT had improvement in LVEF, mitral regurgitation and New York Heart Association stage [82]. In 2020, a report of two patients whose clinical and echocardiographic variables improved dramatically after upgrading from right ventricular to biventricular pacing also raised the question of the desynchronization induced by right ventricular pacing in patients with cardiac amyloidosis, even in the absence of former impairment of LVEF [84]. In the same year, Donnellan et al. published a second paper on 30 patients with cardiac amyloidosis with CRT implantation matched with 30 patients with cardiac amyloidosis not implanted with a CRT device. The authors suggested that CRT may be associated with improved survival and improvements in heart failure symptoms and LVEF [85]. Finally, in 2021, a collaborative study by nine French university hospitals included 47 patients with cardiac amyloidosis implanted with CRT devices compared with propensity-matched patients with dilated cardiomyopathy, also with CRT devices. Patients with cardiac amyloidosis had lower rates of CRT response (absolute delta LVEF $\geq$ 10%) compared with patients with dilated cardiomyopathy (36% vs 70%; $P = 0.002$). However, CRT response was the only factor predictive of major event-free survival in patients with cardiac amyloidosis (hazard ratio 0.36, 95% confidence interval 0.15–0.86; $P = 0.002$) [86].

Finally, a few reports have emerged recently on the role of left bundle branch area pacing in patients with cardiac amyloidosis [87]. This technique has gained considerable recent interest, but its feasibility and effectiveness in patients with cardiac amyloidosis could differ from in the general population because of the structural remodelling of the septum and alteration of the conduction system. In a Spanish case series, all of the three patients needing pacing and with impaired LVEF underwent successful implantation with left bundle branch area pacing. Two of these patients had an increase in LVEF after implantation [88]. Moreover, a larger Spanish series was published recently: 22 of 23 consecutive patients with cardiac amyloidosis were implanted successfully with a left bundle branch area pacing device (for CRT indication in 35%), with a significant reduction in QRS duration, without changes in LVEF or N-terminal prohormone of B-type natriuretic peptide at 6-month follow-up. The mean procedure time was 67 $\pm$ 28 minutes, and adequate stimulation variables were obtained as in classic patients with left bundle branch area pacing (R wave, lead impedance, pacing threshold, QRS morphology in V1, QRS duration and left ventricular activation time). These stimulation variables remained stable during follow-up, and no complications were recorded during implantation and during follow-up [89].

4.3.1. What is accepted?

Patients with cardiac amyloidosis with standard CRT indications should be implanted as other populations; and CRT response is less frequent in patients with cardiac amyloidosis than in those with dilated cardiomyopathy, but may be associated with improved survival.

4.3.2. What is still to be demonstrated?

The need for left bundle branch area pacing or CRT over classical right ventricular pacing in patients with preserved LVEF, and in whom a significant percentage of right ventricular pacing is expected, is unknown.

5. SCD and implantable cardioverter-defibrillators in cardiac amyloidosis

5.1. Ventricular arrhythmias and SCD in cardiac amyloidosis

Ventricular arrhythmias are common in cardiac amyloidosis, with approximately one in five patients exhibiting premature ventricular contractions on a standard electrocardiogram. Analyses of memories from pacemakers and implantable cardioverter-defibrillators (ICDs) have confirmed the high prevalence of ventricular arrhythmias (Table 1), mostly not sustained, which some authors have suggested are potentially associated with SCD, especially in AL-CA [90–92]. The management of these ventricular arrhythmias, especially the issue of ICDs, remains particularly challenging in this population with a particularly high competing risk of non-arrhythmic death.

Unexplained deaths or SCDs are not uncommon in cardiac amyloidosis, and constitute the second leading cause of cardiovascular death after end-stage progressive heart failure, accounting for 10–20% of all deaths [93]. In addition to the competing high risk of non-sudden cardiovascular death in these patients, several studies reporting in-hospital SCD or patients implanted with loop recorders have emphasized the prominent role of conduction disturbances and pulseless electrical activity, therefore challenging the usefulness of ICDs for these patients [94,95] or even pacemakers in fragile patients [93]. The precise contribution of ventricular arrhythmias to SCD in cardiac amyloidosis, and their role as a predictive factor versus other factors remain unclear, but could pave the way towards optimizing management in specific subgroups of patients.

5.2. ICDs in cardiac amyloidosis

Indications for ICDs in patients with cardiac amyloidosis have varied across studies, with some considering reduced LVEF (< 35%) and/or marked alterations in global longitudinal strain as criteria for implantation. Additionally, patient-specific factors, such as syncope and evidence of substantial ventricular hyperexcitability on Holter monitoring, may influence the decision-making process. All of the studies were retrospective and observational, and involved

Table 1
Observational studies on implantable cardioverter-defibrillators in patients with cardiac amyloidosis.

Reference	Demographics	Primary prevention	Follow-up (months)	ICD therapy	Deaths
[98]	19 AL	19 (100)	27	2 (11)	7 (37)
[99]	33 AL; 19 ATTR; 1 AA	41 (77)	23	17 (32)	32 (78)
[92]	15 AL; 4 ATTR	15 (79)	NA	5 (26)	NA
[100]	12 AL; 33 ATTR	38 (84)	17	12 (27)	12 (27)
[82]	38 ATTR	14 (37)	42	8 (21)	6 (16)
[101]	19 ATTR	17 (89)	20	2 (11)	NA
[102]	32 ATTR	32 (100)	38	8 (25)	13 (40)
[103]	19 ATTR	18 (95)	21	2 (11)	5 (28)
[104]	7 AL; 16 ATTR	20 (80)	40	5 (20)	13 (44)

Data are expressed as number (%) unless otherwise indicated. AA: atrial arrhythmia; AL: light-chain amyloidosis; ATTR: transthyretin amyloidosis; ICD: implantable cardioverter-defibrillator.

relatively small sample sizes, with a heterogeneity between studies according to the different subtypes of amyloidosis (AL-CA and ATTR-CA), which are mostly mixed, despite their known distinct natural histories. This contributes to the complexity in analysing the current literature on the topic and drawing firm conclusions (compare with Table 1).

The reported rates of appropriate ICD therapies ranged from 6% to 32%. Regarding deaths, a recent research letter gathered recent studies, and confirmed that none of the studies had demonstrated a benefit in terms of death from ICD implantation in this population [96]. Moreover, the predictive value of clinical, echocardiographic and biomarker variables in identifying patients at higher risk of ventricular arrhythmias remains uncertain. The rate of non-sudden mortality is high (approximately 30% at 18 months), and a significant proportion of sudden deaths are associated with primary pulseless electrical dissociation or are not of cardiac origin. Therefore, the extent to which an ICD may help to substantially decrease deaths overall is unclear. The place of cardiac magnetic resonance imaging to further risk stratify patients with cardiac amyloidosis also remains to be determined.

Given the lack of robust evidence supporting the use of ICDs in cardiac amyloidosis, specific recommendations cannot be provided regarding ICD implantation for the primary prevention of SCD in cardiac amyloidosis. Regarding secondary prevention, a close and comprehensive evaluation of life expectancy is recommended to achieve an individualized decision. According to the 2022 European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, an ICD should be considered in patients with AL-CA or ATTR-CA presenting with haemodynamically not tolerated ventricular tachycardia (class IIa indication) [97].

5.3. Unanswered questions and future perspectives

Several unanswered questions and areas for future research exist regarding SCD and ICDs in cardiac amyloidosis. First, the mechanisms underlying SCD in this population, including the relative contributions of ventricular arrhythmias versus other factors should be clarified. Interestingly, the type of cardiac amyloidosis could also influence ICD indications for primary prevention. Indeed, recent data suggest that ATTR-CA behaves more as a progressive cardiomyopathy characterized by slow amyloid deposition within the atria, ventricles and conduction system, whereas AL-CA rather resembles an acute myocarditis, with early symptom onset and rapid disease progression to end-stage heart failure as a result of the toxic effects of AL chains, despite lesser degrees of infiltration.

Prospective studies with larger sample sizes are needed to better understand the natural history of ventricular arrhythmias in cardiac amyloidosis, and to identify predictors of SCD. The role of ICDs in primary and secondary prevention of SCD in cardiac amyloidosis remains unclear, and warrants further study. The meticulous analysis of ICD memories, especially after SCD, may actually be helpful to better understand the true cause of sudden fatal events. Furthermore, ongoing progress in medical therapies for cardiac amyloidosis may impact the management of SCD in affected individuals. As survival rates improve and the natural history of the disease evolves, the efficacy of ICDs and other interventions in the prevention of SCD will need to be reassessed. Collaborative efforts involving multidisciplinary teams of cardiologists, electrophysiologists and researchers will be essential for advancing our understanding of SCD in cardiac amyloidosis, and optimizing clinical management strategies for affected patients.

5.4. What is accepted?

SCD constitutes the second leading cause of cardiovascular death in cardiac amyloidosis after end-stage progressive heart failure; SCD may be caused by pulseless activity or conduction disturbances in a significant part; and comprehensive evaluation of life expectancy and competing risks of death is recommended before ICD implantation for secondary prevention.

5.5. What is still to be demonstrated?

The true role of ventricular arrhythmias in sudden death in cardiac amyloidosis remains unclear; because of competing causes of death and sudden death in cardiac amyloidosis, the extent to which a prophylactic ICD may decrease deaths overall remains unclear; and it is unclear unknown whether ongoing progress in medical therapies for cardiac amyloidosis will impact the management of sudden death in the future.

Sources of funding

None.

Disclosure of interest

N.L. Expert board member for Pfizer.
P.D. Expert board member for Pfizer.
V.A. Expert board member for Pfizer.
L.F. Consultant activities for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novartis, Novo and XO; and speaker activities for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novartis and Zoll.
C.G. Research grants from MicroPort CRM; consultant for Medtronic, Abbott and Pfizer; and honoraria from AstraZeneca, Boston Scientific, BMS/Pfizer, Abbott and Novo Nordisk.
S.B. Consultant for Medtronic, Boston Scientific, Microport and Zoll.

F.S. Speaker honoraria from Abbott, Boston Scientific, Biosense Webster and Medtronic.

The other authors declare that they have no competing interest.

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