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REVIEW

Management of complications of cardiac amyloidosis: 10 questions and answers

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Amyloidosis is a systemic disorder characterized by extracellular deposition of insoluble fibrils. The most common forms are amyloid light chain and amyloid transthyretin (ATTR) amyloidoses. Cardiac involvement may be found in both these forms, and is an important cause of morbidity and mortality. The clinical presentation of cardiac amyloidosis (CA) may be represented by congestive heart failure (HF), possibly progressing to end-stage HF, as well as atrial fibrillation with possible thromboembolic events, and also conduction disturbances related to amyloid infiltration of conduction fibres. Beyond therapies targeting the blood dyscrasia or the ATTR amyloidogenic cascade, a careful choice of drug therapies, need for device implantation, and possibly treatments for advanced HF is then warranted. In the present review, we try to provide a useful guide to clinicians treating patients with CA by enucleating 10 main questions and answering them based on the evidence available as well as expert opinion and our clinical experience.

Keywords Amyloidosis • cardiac disease • therapy

Amyloidosis is a systemic disorder characterized by extracellular deposition of insoluble fibrils. The most common form is amyloid light chain (AL) amyloidosis, affecting around 10 people per million per year, where these fibrils are composed of monoclonal light chains.[1] Another form is amyloid transthyretin (ATTR) amyloidosis, where the amyloid constituent is a carrier for thyroxine and retinol-binding protein.[1] ATTR amyloidosis can be caused by accumulation of either normal (wild-type (ATTRwt)) or mutated (variant (ATTRv)) transthyretin molecules.

Cardiac involvement may be found in both AL and ATTR amyloidosis. In the latter case, it can be either an isolated disease manifestation (in ATTRwt and some forms of ATTRv), or be associated with polyneuropathy (in other cases of ATTRv).[2] The main features of cardiac amyloidosis (CA) on echocardiographic examination are increased left ventricular (LV) wall thickness (pseudohypertrophy), diastolic dysfunction, depressed LV systolic function with relative preservation of the apex (apical sparing), left atrial (LA) dilation, and possibly pericardial effusion.[2,3] The clinical presentation of CA may be represented by congestive heart failure (HF), possibly progressing to end-stage HF, as well as atrial fibrillation (AF) with possible thromboembolic events, and also conduction disturbances related to amyloid infiltration of conduction fibres. Patients with clinical and imaging features suggestive of or compatible with CA should undergo a diagnostic workup including diphosphonate scintigraphy, then the search for a monoclonal protein. ATTR cardiomyopathy can be diagnosed when there is evidence of intense transthyretin deposition in the heart (Perugini score 2–3) and no monoclonal protein is present (which excludes AL amyloidosis). In all other cases, amyloid deposition must be searched in the heart or other sites, most commonly the periumbilical fat.[4,5]

Therapies for the blood dyscrasia or targeting transthyretin production or tissue accumulation are now available,[5,6] and may modify the natural history of the disease, albeit only after a period of latency following treatment initiation (for example, around 18 months for tafamidis).[7] In the meantime, cardiac disease remains a crucial determinant of morbidity and mortality, with an evolution that is partially independent from that of the underlying disorder. The careful choice of drug therapies, need for device implantation, and possibly treatments for advanced HF is then warranted.[8]

In the present review, we try to provide a useful guide to clinicians treating patients with CA by enucleating 10 main questions and answering them based on the evidence available, mostly limited to retrospective analyses or case series, integrated with expert opinion and our clinical experience.

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HF

(1) Are beta-blockers and drugs acting on the renin–angiotensin–aldosterone system contraindicated in patients with HF?

The guideline-recommended therapeutic algorithms for HF cannot be applicated to cardiac AL or ATTR amyloidosis because therapies targeting cardiac damage and its direct consequences may yield limited benefit, mostly limited to dyspnoea relief through diuretics. Beta-blockers may be poorly tolerated or contraindicated – for example, because of hypotension, conduction disturbances, or impossibility of adequately increasing cardiac output, especially in cases with overt restrictive pathophysiology – when cardiac output becomes critically dependent on heart rate.[9] Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs) may be poorly tolerated as well, particularly in hypotensive patients. Nonetheless, almost 30% of patients in the phase 3 ATTRACT trial were on beta-blockers or ACEi/ARBs.[7] Because of the lack of evidence on their prognostic impact in cardiac ATTR, no specific recommendation can be made, and these drugs might be considered in the absence of clear contraindications, starting from low doses, with slow up-titration and close monitoring.[5] Mineralocorticoid receptor antagonists (MRAs) are frequently and safely used in patients with CA.[5,10]

(2) How do these patients respond to diuretic and inotropic therapy?

Diuretics (loop diuretics and MRAs) are the predominant supportive therapies.[11] They are essential for dyspnoea relief and are often needed in high doses to reduce pulmonary and peripheral congestion, particularly in patients with severe diastolic dysfunction.[10] Combination therapy – for example, with torsemide and spironolactone – is feasible.[10] Care should be taken to avoid worsening renal function, electrolyte disturbances, and excessive preload reduction.[10] The combination of a loop diuretic, such as torsemide, and spironolactone has been proposed.[10]

In a single-centre, retrospective study, 26 patients with CA were admitted to the intensive care unit because of cardiogenic shock. Dobutamine was administered to 21 patients, with norepinephrine added in 10 patients, with progressive increase in infusion doses over the first 48 hours; two patients were switched from dobutamine to levosimendan.[12] The response to inotrope therapy was poor, with 17 patients (81%) dying during hospitalization, and the other four (15%) within three months.[12] Therefore, inotrope therapy does not seem to be able to improve the dismal prognosis of cardiogenic shock in CA.

(3) When should patients receive an implantable cardioverter defibrillator (ICD) for primary prevention?

Sudden cardiac death ranks among the most common forms of deaths in patients with CA, but results from pulseless electric activity (PEA) or non-defibrillable rhythms much more often than tachyarrhythmias.[13] We may add that ICD testing after implantation is deemed dangerous because of a risk of electromechanical dissociation,[14] defibrillation thresholds and complication rates are higher than in other patients, and appropriate ICD shocks were not found to translate into a survival benefit.[15] Therefore, the indications and benefit of ICD implantation for primary prevention are at best uncertain. A decisional algorithm has been proposed by the Stanford Amyloid Center based on a retrospective analysis of data from 31 patients (15 with AL amyloidosis, two with ATTRwt, and two with ATTRv). According to these authors, ICD for primary prevention might be considered in patients with New York Heart Association class lower than IV and life expectancy longer than one year when history of exertional syncope or documentation of ventricular tachycardia (either non-sustained or sustained) on ambulatory Holter monitoring are present.[14]

(4) Are LV assist device implantation and heart transplantation (HT) feasible?

LV assist device implantation is usually feasible, as demonstrated by a case series from the Mayo Clinic, but in-hospital mortality is quite high, and overall prognosis is poor.[16]

HT is an option for patients with ATTRv (either as a stand-alone procedure or combined with liver transplantation), for the few patients with ATTRw who are younger than 65 years, and for selected patients with AL amyloidosis. High mortality while on the waiting list (up to 40% in AL amyloidosis), and suboptimal post-transplant outcomes are major issues[17] and, thus a rational choice of decisional threshold for patient selection is desirable.

In ATTRv, a multidisciplinary team including cardiologists, hepatologists, and neurologists is recommended to assess the need for combined heart and liver transplantation (class IIA, level of evidence B in the International Society for Heart and Lung Transplantation guidelines).[18] The Stanford Cardiac Transplantation Evaluation guidelines may be usefully considered for screening candidates to HT[19] (Supplemental *Table 1*).

In the case of AL amyloidosis, HT should be considered only after initial chemotherapy has led to the successful control of the blood dyscrasia; in selected cases when disease-specific treatments are contraindicated because of HF, autologous stem cell transplantation should be planned as soon as clinically feasible (class IIA, level of recommendation B).[18] Severe extracardiac amyloid organ dysfunction is a contraindication to HT (class IIA, level of evidence B).[18] Even in this case, the Stanford evaluation guidelines may help screen candidates to HT.[19] (Supplemental *Table 1*).

AF

(5) What are the indications to anticoagulant therapy? Which drugs should be chosen?

Amyloid accumulation in the atrial wall predisposes to arrhythmias (AF, but also flutter and tachycardia). It also promotes mechanical dysfunction, and then blood stasis in the atria, and represents by itself a procoagulant mechanism. Intracardiac thrombosis (most commonly in the left or right atrial appendages) was reported to be more frequent in patients with AL amyloidosis than other patients with CA (35% versus 18%; $p = 0.02$), although patients with AL amyloidosis

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were younger and had less often AF. The independent predictors of intracardiac thrombosis were AF, poor LV diastolic function, and lower LA appendage emptying velocity. Anticoagulation therapy was associated with a significantly lower risk of intracardiac thrombosis.[20] Based on these premises, we may conclude that anticoagulation should be prescribed for any atrial arrhythmia, also regardless of the CHA_2DS_2-VASc score,[21] and may be considered also for some patients in sinus rhythm, when the atria are enlarged and dysfunctional, and the bleeding risk is low.

In the absence of any specific evidence about the relative safety and efficacy of the possible anticoagulation strategies in patients with CA, both vitamin K antagonists (VKAs) or the oral non-vitamin K antagonist anticoagulants (NOACs) can be prescribed, taking into account the same contraindications and criteria for dose reductions as the other disease settings. An interaction between dexamethasone, a drug frequently used in patients with AL amyloidosis, and VKAs has been reported, with prolongation of the international normalized ratio.[22] In patients receiving NOACs, particular attention should be paid to renal function. Dabigatran and edoxaban are excreted by 80% and 50% by kidneys, respectively, and cannot be prescribed when creatinine clearance (CrCl) is <30 mL/min.[23] Rivaroxaban must be prescribed at a lower dose (15 mg once per day(including those on dialysis) unless there are at least two criteria for dose reduction: creatinine ≥1.5 mg/dL, age ≥80 years, weight <60 kg.[23] Nonetheless, therapy with VKA is the most common approach to anticoagulation when CrCl is <30 mL/min or the patient is on dialysis.[23]

(6) Should a rhythm control or a rate control strategy be pursued? When should transoesophageal echocardiography be performed before elective cardioversion? Is cardioversion effective?

Because of the lack of specific studies, no recommendations can be made regarding the importance of re-establishing a sinus rhythm (rhythm control strategy) as opposed to the pharmacological control of mean heart rate (rate control strategy).

In a retrospective analysis of the Mayo Clinic registries, all patients with CA ($n = 58$) referred for elective direct-current cardioversion (DCCV) for atrial arrhythmias (AF in 58%, atrial flutter in 41%, and atrial tachycardia in 1%) and 114 matched controls were examined. A trans-oesophageal echocardiogram (TOE) was performed in 79% of patients with CA and 69% of controls. Patients with CA had significantly lower LA appendage emptying velocities than controls (20.6 ± 14.1 cm/s vs 33.9 ± 18.4 cm/s; $p < 0.001$), and more often a thrombus in the LA or the LA appendage (28% vs 3%; $p < 0.001$). As a result, the CA group had a much higher cancellation rate (28% vs 7%; $p < 0.001$). Notably, among the CA patients with an intracardiac thrombus, 15% had AF from less than 48 hours, and 29% had an international normalized ratio in the therapeutic range for ≥3 weeks. Cancellation rates were similar between patients with AL or ATTR amyloidosis, and those with AF versus atrial flutter. It is then advisable that patients with CA undergo a TOE examination before an elective DCCV, including patients on therapeutic anticoagulation.[24]

In the same study, among patients with CA proceeding to DCCV, the success rate (90%), the proportion of patients requiring >1 shock (33%), and median energy required (110 J) were not significantly different than the other patients; no differences in the same parameters were noted also when comparing patients with CA and AF versus flutter.[24] Complications of DCCV in patients with CA included ventricular tachycardia/fibrillation (5%), severe bradyarrhythmia requiring pacemaker implantation (5%), acute hypoxemia (2%), and stroke (2%).[24] Overall, elective DCCV performed after TOE seems to be an effective and safe procedure.

(7) Which antiarrhythmic can be used? Is catheter ablation for atrial arrhythmias effective?

If antiarrhythmic agents are needed for rhythm or rate control, drugs with a negative inotropic or chronotropic effect should be avoided or used with caution because of the risk to precipitate HF decompensation. Amiodarone is the preferred antiarrhythmic agent because of its favourable safety profile in cardiomyopathies, and its use has been advocated in both AL and ATTR amyloidosis.[10,21]

Digoxin has been traditionally contraindicated because of old reports of increased toxicity in patients with amyloid cardiomyopathy,[25,26] related to the accumulation of digoxin into amyloid deposits. Nonetheless, a retrospective series of 107 patients with AL amyloidosis receiving digoxin between 2000 and 2015 suggested that digoxin may be cautiously utilized in these patients, and a flowchart for digoxin therapy was proposed.[27] Risk factors for digoxin toxicity (kidney or thyroid dysfunction, drug interactions) should be searched, and digoxin should be started at low doses (0.125 mg daily in the absence of risk factors, or 0.0625 mg every 24–48 hours when ≥1 risk factor are present); patients on haemodialysis should receive 0.0625 mg every 48 hours or as recommended by nephrologist. Serum through levels should be monitored after 5–7 days, and digoxin dose should be adjusted to keep drug level between 0.5 and 0.8 ng/mL. Renal function, electrolytes, and serum digoxin should be monitored every 1–2 weeks during the first three months, then monthly for the next three months, and thyroid function should be monitored monthly. Potential adverse effects and the continuing need for digoxin therapy should be reassessed periodically.[27] In the absence of specific data, the same algorithm could be followed even to treat patients with ATTR amyloidosis.

Catheter ablation for atrial arrhythmias may target the mechanism of atrial arrhythmia, or aim to control the heart rate through atrioventricular node (AVN) ablation. Data on the outcomes of catheter ablation are limited. In early stage patients, ablation may help maintain sinus rhythm, especially in the setting of atrial flutter. Nevertheless, the rates of long-term success of ablation therapies other than AVN ablation are likely lower in these patients than in patients without CA.[21]

(8) Are calcium channel blockers safe?

According to European Society of Cardiology HF guidelines, verapamil and diltiazem should not be prescribed to patients with HF and reduced ejection fraction (LV ejection fraction (LVEF) <40%),[28] and should be administered with great caution to those with LVEF ≥40% due to the risk of precipitating systolic dysfunction. Since the risk of HF is usually higher in AL amyloidosis, therapy with verapamil and diltiazem is strongly discouraged in these patients.[10] Dihydropyridines

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can be prescribed, although they are not frequently needed given that patients with CA tend to have low blood pressure levels.

Conduction disturbances

(9) What are the indications and responses to pacemaker implantation?

A significant percentage of patients with CA develop conduction disturbances, related to the infiltration of myocardial tissue by amyloid fibres, but also (in ATTRv) to abnormal autonomic innervation of the heart. A recent review on ATTR amyloidosis has advised for ECG Holter monitoring when symptoms of syncope, presyncope, or palpitations are reported, and has suggested that a pacemaker be implanted following the indications of the American College of Cardiology/American Heart Association/Heart Rhythm Society, with indications for pacing including sinus node dysfunction, high-degree atrioventricular (AV) block, and AF with a slow ventricular response. On the other hand, patients with ATTRv often receive a prophylactic pacemaker implantation when they have a first-degree AV block, which is interpreted as a risk factor for high-degree AV block. For example, in a retrospective analysis of 258 patients with ATTRv-related polyneuropathy undergoing liver transplantation between 1992 and 2012, as many as 57% of patients received a pacemaker, either before or after liver transplantation, and the most common indication was first-degree AV block.[29] A demonstration that first-degree AV block predisposes to high-degree AV block is available. In a study on 262 patients with ATTRv-related polyneuropathy undergoing a cardiac

Table 1 Questions and answers about the management of cardiac amyloidosis.

Heart failure	
1) Are beta-blockers and drugs acting on the RAAS contraindicated?	Beta-blockers and ACEi/ARB should be administered with caution. MRAs are better tolerated.
2) How do these patients respond to diuretic and inotropic therapy?	Diuretic therapy relieves congestion and is rather safe; volume depletion and electrolyte disturbances must be avoided. The response to inotropes is usually poor.
3) When should patients receive an ICD for primary prevention?	An ICD might be considered in patients with NYHA class <IV, life expectancy >1 year when history of exertional syncope or non-sustained or sustained VT.
4) Are LVAD implantation and heart transplantation feasible?	LVAD is technically feasible, but the outcome is poor. Heart transplantation is an option for patients with ATTRv (either alone or with liver transplantation), ATTRw <65 years, and selected patients with AL amyloidosis.
Atrial fibrillation	
5) What are the indications to anticoagulant therapy? Which drugs should be chosen?	Anticoagulation should be given for any atrial arrhythmia, and might be considered in patients in sinus rhythm but an enlarged and dysfunctional LA. Both VKA and NOACs can be prescribed, with the same contraindications and criteria for dose reductions as other settings.
6) Should a rhythm control or a rate control strategy be pursued? When should transoesophageal echocardiography be performed before elective cardioversion? Is cardioversion effective?	No recommendations can be made regarding rhythm vs rate control. Patients should always undergo transoesophageal echocardiography before an elective cardioversion. Direct-current cardioversion seems effective and safe.
7) Which antiarrhythmic can be used? Is catheter ablation for atrial arrhythmias effective?	Drugs with negative inotropic or chronotropic effects and digoxin should be avoided or administered with great caution. Catheter ablation of the substrate of atrial fibrillation, flutter, or tachycardia does not seem particularly effective.
8) Are calcium channel blockers safe?	Diltiazem and verapamil should be avoided.
Conduction disturbances	
9) What are the indications and responses to pacemaker implantation?	A pacemaker should be implanted when "classical" indications exist, and might be considered in patients with ATTRv and polyneuropathy and first-degree AV block.
Orthostatic hypotension	
10) How can orthostatic hypotension be managed?	In addition to cautious increase in salt and water intake, physical counter-manoeuvres, etc., therapy with midodrine might prove useful.

ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AL: amyloid light chain; ATTR: amyloid transthyretin amyloidosis (ATTRv: variant form; ATTRwt: wild-type form); AV: atrioventricular; HF: heart failure; ICD: implantable cardioverter defibrillator; LA: left atrium; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NOAC: non-vitamin K antagonists; NYHA: New York Heart Association; RAAS: renin-angiotensin-aldosterone system; VKA: vitamin-K antagonist; VT: ventricular tachycardia.

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assessment including electrophysiological testing, the risk of high-degree AV block was higher in patients with first-degree AV block at baseline or Wenckebach anterograde point ≤100 beats/min.[30] On the other hand, the efficacy and cost-effectiveness of prophylactic pacemaker implantation in patients with ATTRv and first-degree AV block have never been established. We are not aware of any study on ATTRwt. Finally, the only evidence on AL amyloidosis comes from a single-centre study on 20 consecutive patients with AL amyloidosis receiving an implantable loop recorder because of syncope or presyncope.[13] Over a median follow-up of 308 days, 13 patients died; among the eight evaluable cases, death was heralded by profound bradycardia, usually associated with third-degree AV block, and followed by PEA after a median interval of one hour (range 0.1–48 hours). Pacemaker implantation following symptomatic complete AV block did not prevent a rapid decompensation and death.[13]

Overall, we may suggest that conduction disturbances be searched in patients with CA, especially when symptoms (syncope, etc.) are present. A pacemaker should be implanted when "classical" indications exist (high-degree AV block, etc.), and might be considered in patients with ATTRv and polyneuropathy and first-degree AV block.

Orthostatic hypotension

(10) How can orthostatic hypotension be managed?

The most common cause of orthostatic hypotension in AL and ATTRv is autonomic neuropathy. A cautious increase in salt and water intake (avoiding HF decompensation), physical exercise, specific physical counter-manoeuvres, compression stockings, smaller and more frequent meals, and reduced alcohol intake may all prove useful.[31] When additional pharmacological management is needed, the oral α1-adrenoreceptor agonist midodrine has been advocated in both AL[10] and ATTRv amyloidosis,[31] despite the absence of dedicated studies. It has been reported that patients with AL amyloidosis do not develop supine hypertension in response to midodrine; thus, the drug can be used even at high doses.[10] Conversely, supine hypertension is common in patients with ATTRv on midodrine; therefore, they should take this drug more than 3–4 hours before bedtime.[31] Patients with CA can also develop hypotension during exercise, which should be distinguished from light-headedness during exercise despite normal supine and standing blood pressures, possibly because of a fixed cardiac output.[10] Treadmill testing might aid in the differential diagnosis; the first condition often responds to pre-exercise midodrine.[10]

The synthetic mineralocorticoid fludrocortisone should be preferably avoided in patients with cardiac involvement.[31] Droxidopa, an oral synthetic amino acid that is converted to norepinephrine, has been proposed as an approach to orthostatic hypotension in ATTRv, but is not approved in Europe.[31]

Conclusions

CA requires a tailored treatment that is no less important than therapies targeting the amyloid cascade. We have tried to provide the answers to some of the most common challenges facing clinicians who treat patients with CA (*Table 1*). Nonetheless, basically all answers do not rely on a solid body of evidence or are necessarily incomplete, and must then be implemented by careful assessment of each individual phenotype, multidisciplinary evaluation, request of advice from specialized centres, and even active engagement of patients and their families in therapeutic choices.

Supplemental material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Author contribution

AA, CR, and ME contributed to the conception of the review. AA and GV drafted the manuscript. CR, AG, VS, CP, and ME critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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