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ORIGINAL ARTICLE
Myocardial Disease

Prevalence and Treatment of Arrhythmias in Patients With Transthyretin and Light-Chain Cardiac Amyloidosis

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Background: Various types of arrhythmia are observed in patients with cardiac amyloidosis, but the prevalence of arrhythmia has not been fully investigated. This study investigated the prevalence and treatment of arrhythmias in patients with cardiac amyloidosis before the introduction of new agents for amyloidosis, such as tafamidis.

Methods and Results: Of 53 patients who were histologically diagnosed with cardiac amyloidosis at 10 centers in western Japan between 2009 and 2021, 43 who were diagnosed on the basis of immunohistochemical staining were evaluated in this study. Of these 43 patients, 13 had immunoglobulin light-chain (AL) amyloidosis and 30 had transthyretin (ATTR) amyloidosis; further, 27 had atrial tachyarrhythmia, 13 had ventricular tachyarrhythmia, and 17 had bradyarrhythmia. Atrial fibrillation (AF) was the most common arrhythmia in patients with cardiac amyloidosis (n=24; 55.8%), especially among those with ATTR amyloidosis (70.0% of ATTR vs. 23.1% of AL). Eleven (25.6%) patients were treated with a cardiac implantable device. All 3 patients with pacemakers were alive at the last follow-up (median 76.7 months; interquartile range [IQR] 4.8–146.4 months). Of the 8 patients who underwent AF ablation, there was no recurrence in 6 (75%) after a median of 39.3 months (IQR 19.8–59.3 months).

Conclusions: The prevalence of various arrhythmias was high in patients with cardiac amyloidosis. AF occurred most frequently in patients with cardiac amyloidosis, especially among patients with ATTR.

Key Words: Atrial fibrillation; Cardiac amyloidosis; Cardiac implantable device; Catheter ablation

Cardiac amyloidosis is a progressive disease caused by the deposition of insoluble abnormal protein fibrils in cardiac tissue.[1–4] The deposition of abnormal protein fibrils can result in heart failure associated with diastolic dysfunction and arrhythmias associated with an impaired myocardial or conduction system. Cardiac amyloidosis is strongly related to hospitalization and death, and is therefore a clinically important problem.

The incidence and prevalence rates of cardiac amyloidosis in hospitalized patients are increasing in the US and Europe.[5–7] Cardiac amyloidosis has also recently received much attention in Japan[8,9] due to development of new therapeutic agents, including tafamidis, patisiran, and daratumumab,[10–12] and advances in cardiac imaging, including nuclear cardiac scintigraphy.[13,14]

Various types of arrhythmias, including bradyarrhythmia, atrial fibrillation (AF), and ventricular arrhythmias, are more frequently observed in patients with cardiac amyloidosis than in the general population.[15–20] However, the incidence of arrhythmias in patients with cardiac amyloidosis has been investigated in only a few small studies in limited regions. The incidence of arrhythmias in patients with cardiac amyloidosis has not been fully elucidated in many countries, including Japan.

There are 2 major subtypes of cardiac amyloidosis: transthyretin (ATTR) amyloidosis and immunoglobulin light-chain (AL) amyloidosis. New drugs for the treatment of cardiac amyloidosis, including tafamidis, patisiran, and daratumumab, have recently become available in Japan.[21,22] Treatment with these drugs will become more widespread

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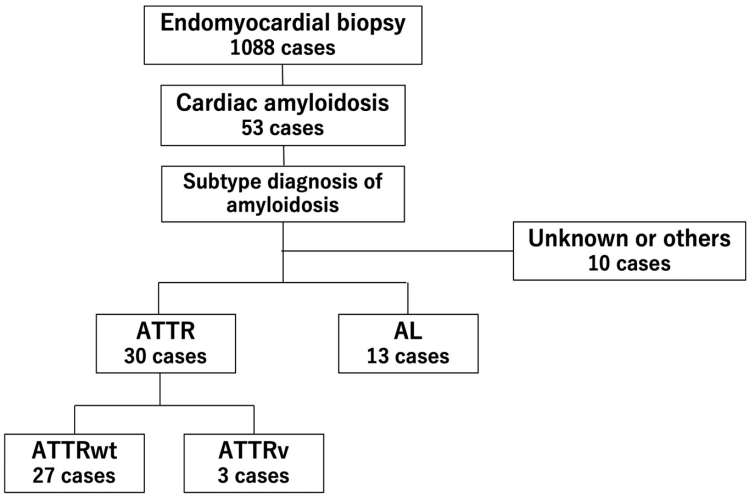

Figure 1. Study flowchart. ATTR, transthyretin; ATTRwt, wild-type transthyretin; ATTRv, variant transthyretin; AL, light-chain.

in the future, and the frequency of arrhythmias and their treatment may change. Therefore, the aim of this study was to investigate the prevalence and characteristics of arrhythmias and the treatment of arrhythmias before tafamidis, patisiran, and daratumumab became available.

Methods

Study Population

During the period December 2009–April 2021, 1,088 patients underwent endomyocardial biopsy and 53 patients were histologically diagnosed with cardiac amyloidosis in 10 centers in western Japan (Okayama University Hospital, Fukuyama City Hospital, Japanese Red Cross Society Himeji Hospital, Kagawa Rosai Hospital, Fukuyama Cardiovascular Hospital, Tsuyama Chuo Hospital, National Hospital Organization Iwakuni Clinical Center, Sumitomo Besshi Hospital, National Hospital Organization Okayama Medical Center, and Okayama Rosai Hospital). The diagnosis of cardiac amyloidosis was confirmed by myocardial biopsy when imaging studies, such as echocardiography, cardiac magnetic resonance imaging (MRI), and technetium pyrophosphate myocardial scanning, showed findings suggestive of cardiac lesions. We retrospectively reviewed the medical records of patients with a confirmed diagnosis of cardiac amyloidosis to investigate the prevalence and incidence of arrhythmic disease during the course of treatment.

An electrocardiogram (ECG) was recorded at the time of diagnosis and at each periodic medical checkup and clinic visit. Arrhythmias were confirmed by a 12-lead surface ECG, bedside monitor ECG, or intracardiac electrograms recorded by cardiovascular implantable electronic devices. Atrial arrhythmias, AF, atrial tachycardia (AT), and atrial flutter (AFL), were defined as episodes lasting more than 30 s. Ventricular tachycardia (VT) was defined as ventricular rhythm with a heart rate of ≥100 beats/min with ≥3 consecutive beats. Sustained VT was defined as a ventricular rhythm >100 beats/min lasting at least 30 s or requiring termination with cardioversion due to hemodynamic instability or appropriate implantable cardioverter defibrillator (ICD) therapy. Other arrhythmias, such as atrioventricular block (AVB) and sick sinus syndrome (SSS), were diagnosed with a 12-lead ECG, Holter ECG, or a bedside monitor ECG.

Patients with incomplete medical records were excluded from the study. This study was conducted following the ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Ethics Committee on Human Research of Okayama University (Approval no. 2107-006).

Diagnostic Definition

Histologic documentation of amyloid deposition was obtained in right ventricular endomyocardial biopsy specimens. All biopsy samples were tested for the presence of amyloid by Congo red staining and green birefringence under cross-polarized light.[23] Cardiac biopsy was performed when imaging examinations such as echocardiography, cardiac MRI, and technetium pyrophosphate myocardial scans show findings suggestive of cardiac lesions.

Differential diagnosis between ATTR amyloidosis and AL amyloidosis was based on immunohistochemistry with light chains (κ or λ) and a polyclonal antibody against transthyretin (TTR).[24] In patients with a histological diagnosis of ATTR amyloidosis, we searched for genetic abnormalities and identified pathogenic *TTR* gene mutations. Variant transthyretin amyloidosis (ATTRv) was defined as amyloidosis with a mutation in the *TTR* gene according to DNA analysis, whereas wild-type (ATTRwt) amyloidosis was defined as amyloidosis in the absence of any *TTR* mutations.[25] AL amyloidosis was defined by the presence of monoclonal plasma cells in the bone marrow plus negative immunohistochemistry for ATTR. Patients were classified as having ATTRwt, ATTRv, or AL amyloidosis. Immunohistochemical analysis was performed at Kumamoto University Amyloidosis Center (Kumamoto, Japan).

Statistical Analysis

Summary statistics are expressed as the mean±SD or median with interquartile range (IQR). Categorical variables are presented as numbers and percentages. In the contingency tables, the independence of categorical variables was

Table 1. Characteristics of Patients With Cardiac Amyloidosis

	Overall (n=43)	ATTR amyloidosis (n=30)	AL amyloidosis (n=13)	P value
Characteristics				
Age (years)	72.9±8.5	76.4±5.3	64.6±9.0	<0.0001
Male sex	34 (79.1)	26 (86.7)	8 (61.5)	0.1017
Height (cm)	159.8±7.9	159.7±7.2	160.0±9.5	0.9174
Weight (kg)	56.8±10.5	58.7±10.8	52.4±8.9	0.0724
Body mass index (kg/m^2)	22.2±3.4	22.9±3.2	20.5±3.3	0.0344
Hypertension	17 (39.5)	14 (46.7)	3 (23.1)	0.1874
Diabetes	10 (23.3)	9 (30.0)	1 (7.7)	0.2368
Ischemic heart disease	3 (7.0)	2 (6.7)	1 (7.7)	1.0000
Hemodialysis	2 (4.7)	0 (0)	2 (15.4)	0.0864
Previous HF hospitalization	19 (44.2)	14 (46.7)	5 (38.5)	0.7433
NYHA functional class ≥3	7 (16.3)	2 (6.7)	5 (38.5)	0.0190
Triggers of diagnosis				
HF	19 (41.2)	12 (40.0)	7 (53.8)	–
ECG/echocardiographic abnormality	12 (27.9)	9 (30.0)	3 (23.1)	–
Sick sinus syndrome	2 (4.7)	0 (0)	2 (15.4)	–
Atrioventricular block	1 (2.3)	1 (3.3)	0 (0)	–
Atrial fibrillation	8 (18.6)	8 (26.7)	0 (0)	–
Ventricular arrhythmia	1 (2.3)	0 (0)	1 (7.7)	–
Laboratory values				
Hemoglobin (g/dL)	12.8±1.8	13.0±1.5	12.2±2.2	0.1306
Total protein (g/dL)	6.7±0.6	6.8±0.4	6.5±0.8	0.0567
Albumin (g/dL)	3.8±0.4	3.9±0.3	3.5±0.5	0.0023
Creatinine (mg/dL)	0.98 [0.87–1.39]	1.00 [0.90–1.42]	0.96 [0.67–1.74]	0.1272
eGFR (mL/min/1.73 m^2)	51.6±21.6	50.0±17.0	55.3±30.3	0.4685
BNP (pg/mL)	428.5 [223.5–717.9]	387 [179.4–509.4]	684.2 [462.8–1,529]	0.0238
Troponin T (ng/mL)	0.054 [0.046–0.093]	0.053 [0.046–0.082]	0.094 [0.053–0.145]	0.1874
Transthoracic echocardiographic characteristics				
LVDd (mm)	43.3±6.1	43.4±6.1	43.1±6.2	0.9084
LVDs (mm)	33.1±6.8	32.9±6.8	33.6±7.0	0.7585
LVEF (%)	49.5±12.1	50.8±11.9	46.6±12.4	0.3017
IVS (mm)	13.9±3.1	13.2±2.4	15.4±4.0	0.0324
PW (mm)	13.2±2.9	12.9±2.5	14.0±3.7	0.2599
LVMI (g/m^2)	141.2±46.1	131.2±36.6	163.0±58.8	0.0392
LAVI (mL/m^2)	54.1±15.8	55.6±15.0	50.4±17.8	0.3466
Pericardial effusion	25 (58.1)	13 (43.3)	12 (92.3)	0.0030
Moderate to severe MR	10 (23.3)	6 (20.0)	4 (30.8)	0.4582

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range], or n (%). AL, amyloid light-chain; ATTR, transthyretin; BNP, B-type natriuretic peptide; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; IVS, diastolic interventricular septum thickness; LAVI, left atrial volume index; LVDd, left ventricle end diastolic diameter; LVDs, left ventricle end systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral valve regurgitation; NYHA, New York Heart Association; PW, diastolic left ventricular posterior wall thickness.

tested using Pearson's Chi-squared test. Fisher's exact test was used to compare the prevalence of arrhythmias between the ATTR and AL groups. The Wilcoxon rank-sum test was used when data were not normally distributed. Student's t-test was used to test for independence of continuous variables between 2 groups. Baseline clinical and instrumental variables that were significant (P<0.05) in univariate analysis were entered into a multivariate model to assess independent associations with the presence of AF. All statistical analyses were conducted using JMP (version 13; SAS Institute, Cary, NC, USA). All tests were 2-sided and P<0.05 was considered significant.

Results

Patient Characteristics

During the period December 2009–April 2021, 1,088 patients underwent endomyocardial biopsy and 53 patients were histologically diagnosed with cardiac amyloidosis in 10 centers in western Japan. Of these 53 patients, 10 did not undergo immunohistochemistry testing and so were excluded from this study because the amyloidosis subtype could not be determined.

Thus, 43 patients diagnosed on the basis of immunohistochemical staining were evaluated in the present study.

Table 2. Prevalence of Arrhythmias in Patients With Cardiac Amyloidosis

	Overall (n=43)	ATTR amyloidosis (n=30)	AL amyloidosis (n=13)	P value
Brady arrhythmias (n=17)				
Sick sinus syndrome	11 (25.6)	6 (20.0)	5 (38.5)	0.2619
Complete atrioventricular block	7 (16.3)	5 (16.7)	2 (15.4)	1.0000
Atrial tachyarrhythmias (n=27)				
Atrial fibrillation	24 (55.8)	21 (70.0)	3 (23.1)	0.0072
Paroxysmal (n)	9	6	3	0.0415
Non-paroxysmal (n)	15	15	0	0.0415
Atrial flutter	8 (18.6)	7 (23.3)	1 (7.7)	0.3995
Atrial tachycardia	7 (16.3)	4 (13.3)	3 (23.1)	0.6551
Paroxysmal SVT	0 (0.0)	0 (0.0)	0 (0.0)	–
Ventricular tachyarrhythmias (n=13)				
Ventricular tachycardia	13 (30.2)	9 (30.0)	4 (30.8)	1.0000
Ventricular fibrillation	3 (7.0)	0 (0.0)	3 (23.1)	0.0232

Unless indicated otherwise, data are given as n (%). SVT, supraventricular tachycardia. Other abbreviations as in Table 1.

All 43 patients were Japanese; 34 (79.1%) were men and the mean age of patients at baseline was 72.9±8.5 years. Of the 43 patients, 13 (30.2%) had AL amyloidosis and 30 (69.8%) had ATTR amyloidosis (27 with ATTRwt and 3 with ATTRv; **Figure 1**).

Patient characteristics are presented in **Table 1**. Patients with ATTR amyloidosis were significantly older and had a larger body mass index (BMI) and higher New York Heart Association (NYHA) functional class than patients with AL amyloidosis; there were no significant differences in other characteristics between the 2 groups. Blood examinations showed significantly lower albumin and higher B-type natriuretic peptide (BNP) concentrations in patients with AL amyloidosis than in patients with ATTR amyloidosis. Echocardiography showed no significant difference in left ventricular (LV) dimension or left atrial volume index (LAVI) between the 2 groups, but diastolic interventricular septum thickness and the LV mass index were significantly larger in patients with AL amyloidosis than in those with ATTR amyloidosis. A significantly higher percentage of patients with AL amyloidosis than ATTR amyloidosis had pericardial effusion.

Nine patients died during the observation period; 7 of these deaths were associated with worsening heart failure. The remaining 2 deaths were due to sudden death during chemotherapy for AL amyloidosis (n=1) and ventricular fibrillation (VF) during palliative care (n=1).

Prevalence of Arrhythmia in Patients With Cardiac Amyloidosis

The prevalence of arrhythmia in patients with cardiac amyloidosis is presented in **Table 2**. Of the 43 patients in this study, 27 (62.8%) had atrial tachyarrhythmias, 13 (30.2%) had ventricular tachyarrhythmias, and 17 (39.5%) had bradyarrhythmias.

Among the 27 patients with atrial tachyarrhythmias, 24 (55.8%) had AF, 8 (18.6%) had AFL, and 7 (16.3%) had AT. Of the 24 patients with AF, 9 had paroxysmal AF and the remaining 15 had non-paroxysmal AF. All 15 non-paroxysmal AF patients had ATTR amyloidosis. AF was already detected in 18 patients (16 ATTR amyloidosis, 2 AL amyloidosis) at the time of diagnosis of cardiac amyloidosis and developed in 6 patients (5 ATTR amyloidosis, 1 AL amyloidosis) during follow-up.

Ventricular tachyarrhythmias were diagnosed in 13 (30.2%) patients. VT was recorded in all 13 patients, and VF was also detected in 3 patients. Ventricular arrhythmias were detected in 8 patients (6 ATTR amyloidosis, 2 AL amyloidosis) at the time of diagnosis of cardiac amyloidosis, and developed in 5 patients (3 ATTR amyloidosis, 2 AL amyloidosis) during follow-up.

Seventeen (39.5%) patients had bradyarrhythmias, 11 patients with SSS and 7 patients with AVB. One of these 17 patients had both SSS and AVB. In 8 of the 11 patients with SSS (4 ATTR amyloidosis, 4 AL amyloidosis), the condition was already known at the time of cardiac amyloidosis diagnosis, whereas the remaining 3 cases (2 ATTR amyloidosis, 1 AL amyloidosis) developed during follow-up. Complete AVB was present in 4 patients (3 ATTR amyloidosis, 1 AL amyloidosis) at the time of diagnosis of cardiac amyloidosis and developed during follow-up in 3 patients (2 ATTR amyloidosis, 1 AL amyloidosis).

The prevalence of arrhythmias was also evaluated according to cardiac amyloidosis subtype. Of the 30 patients with ATTR amyloidosis, 21 (70.0% of patients with ATTR amyloidosis) had AF, 7 (23.3%) had AFL, 4 (13.3%) had AT, and 9 (30.0%) had VT. None of the patients had VF. Six (20.0%) patients had SSS and 5 (16.7%) had AVB. Of the 13 patients with AL amyloidosis, 3 had AF (23.1% of patients with AL), 1 (7.7%) had AFL, 3 (23.1%) had AT, 4 (30.8%) had VT, and 3 (23.1%) had VF. SSS was observed in 5 (38.5%) patients and AVB was observed in 2 (15.4%; **Table 2**).

Patients with cardiac amyloidosis frequently had various arrhythmia events, including AF in 70.0% of patients with ATTR amyloidosis. The prevalence of AF was significantly higher among patients with ATTR amyloidosis than among those with AL amyloidosis (P=0.0072).

Univariate analysis revealed that BMI (odds ratio [OR] 1.28, P=0.0156) and ATTR amyloidosis (OR 7.78, P=0.0039) were significant predictors of the development AF in cardiac amyloidosis (**Table 3**). Age, sex, and LAVI were not significant predictors. When multivariate analysis was performed for these 2 factors (BMI and ATTR amyloi-

Table 3. Multivariate Cox Regression Proportional-Hazard Models for the Prevalence of Atrial Fibrillation in Cardiac Amyloidosis

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.06	0.98–1.15	0.1366			
Sex (male)	1.79	0.41–7.86	0.4413			
Body mass index	1.28	1.03–1.58	0.0156	1.21	0.96–1.52	0.0912
Hypertension	1.83	0.52–6.44	0.3402			
Diabetes	1.25	0.30–5.27	0.7603			
BNP	1.00	0.99–1.00	0.1147			
LAVI	1.03	0.98–1.07	0.2335			
LVEF	0.97	0.92–1.02	0.2319			
ATTR amyloidosis	7.78	1.72–35.1	0.0039	5.84	1.21–28.1	0.00276

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

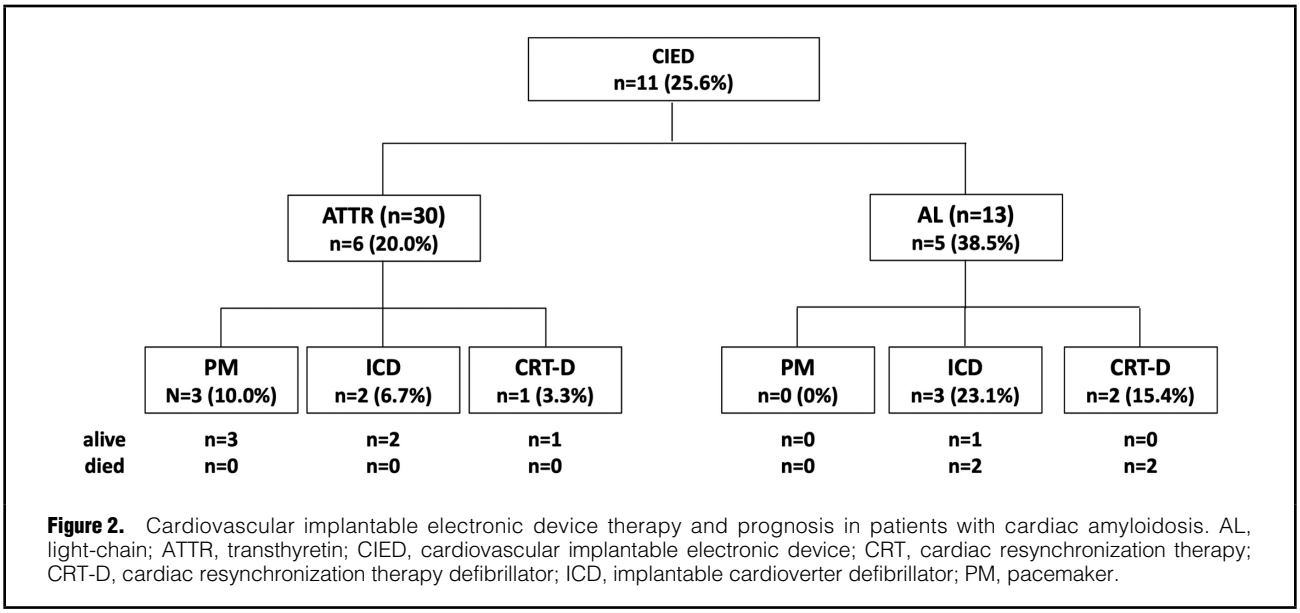

Figure 2. Cardiovascular implantable electronic device therapy and prognosis in patients with cardiac amyloidosis. AL, light-chain; ATTR, transthyretin; CIED, cardiovascular implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; PM, pacemaker.

dosis) by stepwise analysis, ATTR amyloidosis remained a significant predictor of AF in cardiac amyloidosis patients (OR 5.84, P=0.00276; **Table 3**).

Echocardiographic findings were compared among groups of atrial arrhythmias, ventricular arrhythmias, and both atrial and ventricular arrhythmias, with mean LAVI values of 51.4, 50.2, and 72.6 mL/m^2, respectively, and corresponding mean LV mass index values of 132.3, 158.0, and 148.5 g/m^2. Although the differences were not statistically significant, patients with atrial arrhythmias tended to have enlarged left atria, whereas those with ventricular arrhythmias showed a tendency toward LV hypertrophy.

Device Therapy for Arrhythmia

Of the 43 patients with ATTR or AL amyloidosis, 11 (25.6%) were treated with cardiac implantable devices: a pacemaker in 3 (6.9%), an ICD in 5 (11.6%), and a cardiac resynchronization therapy defibrillator (CRT-D) in 3 (6.9%; **Figure 2**). All 3 patients implanted with a pacemaker had ATTR amyloidosis. Of the 5 patients who underwent ICD implantation, 2 had ATTR amyloidosis and 3 had AL amyloidosis. Of the 3 patients who underwent CRT-D implantation, 1 had ATTR amyloidosis and 2 had AL amyloidosis. All 3 patients with pacemakers were alive at the last follow-up (median 76.7 months [IQR 4.8–146.4 months] after device implantation). Conversely, 2 of the 3 patients who underwent CRT-D implantation died; both these patients had AL amyloidosis. The patient with ATTR amyloidosis who underwent CRT-D implantation was still alive at the time of reporting (62.1 months after device implantation).

ICD or CRT-D implantation was performed in 8 patients with ventricular arrhythmia: 5 with AL amyloidosis and 3 with ATTR amyloidosis. Appropriate therapy was observed in 4 patients (2 with AL amyloidosis and 2 with ATTR amyloidosis) during the follow-up period (median 11.5 months; IQR 6.0–18.5 months) after ICD or CRT-D implantation. The median time from ICD or CRT-D implantation to appropriate therapy was 26 days (IQR 8.5–201 days). No inappropriate therapy following ICD implantation was observed in this study. Four of the 8 patients who received ICD or CRT-D implantation died during the follow-up period, and all those who died had

AL amyloidosis. The 4 deaths after defibrillator implantation were all associated with worsening heart failure, with none associated with ventricular arrhythmias. Conversely, all 3 ATTR amyloidosis patients were alive at the time of reporting (median 13.9 months [IQR 4.3–20.1 months] after device implantation; **Figure 2**).

Catheter Ablation for Atrial Arrhythmia

Catheter ablation was performed in 9 cardiac amyloidosis patients with atrial tachyarrhythmia (8 with AF and 1 with AFL). Extensive encircling pulmonary vein isolation (PVI) and cavotricuspid isthmus (CTI) ablation were performed in 7 of 8 patients with AF, with PVI only performed in the remaining 1 patient. CTI ablation only was performed in 1 patient with AFL. One of these 9 patients had AL amyloidosis, and the other 8 had ATTR amyloidosis. The only patient with AL amyloidosis had AF and underwent PVI and CTI ablation.

The median follow-up period after PVI ablation was 39.3 months (IQR 19.8–59.3 months), and recurrence of atrial arrhythmia was observed in only 2 ATTR amyloidosis patients, one of whom underwent PVI and CTI for paroxysmal AF and the other who underwent PVI and CTI for persistent AF. The non-recurrence rate after ablation for AF was 75% (6/8 patients).

All 9 patients who underwent ablation were alive at the time of reporting and have been well without hospitalization due to heart failure.

There were no cases of frequent appropriate therapy or VT storm after ICD implantation, and so no catheter ablation for ventricular arrhythmias was performed.

Discussion

Our study was a multicenter study that was performed to examine the prevalence of various arrhythmias in patients with cardiac amyloidosis in Japan. The prevalence of any arrhythmia was 81.4% (35/43) in the overall cohort, ranging from 69.2% (9/13) in patients with AL amyloidosis to 86.7% (26/30) in patients with ATTR amyloidosis.

As reported previously, most of the patients with cardiac amyloidosis (81%) had various arrhythmias. The most common arrhythmia was AF, which was seen in 24 (55.8%) of 43 patients. Previous studies in Europe and the US have shown that the prevalence of AF in patients with myocardial amyloidosis is 21–70%.[16,17,19] Our data show that the prevalence of AF in Japanese patients with cardiac amyloidosis is as high as in Western populations.

In the general population, the prevalence of AF is higher in men than in women, and it has been reported that the prevalence of AF increases with aging.[26,27] Inoue et al reported that the prevalence of AF in the general Japanese population aged ≥80 years was 4.4% in men and 2.2% in women.[26] In the present study, we found that the prevalence of AF in patients with cardiac amyloidosis was more than 10-fold higher than that reported in the general population. Furthermore, multivariate analysis of predictors for the development AF in cardiac amyloidosis patients revealed ATTR amyloidosis was a significant predictor of AF with a high odds ratio. However, we should also pay attention to the wide confidence intervals because they probably mean that the sample size was too small. Further studies with a larger number of patients are needed to clarify this point.

Three (23.1%) of the 13 AL amyloidosis patients and 21 (70.0%) of the 30 ATTR amyloidosis patients had AF, with the difference in the prevalence of AF between the 2 groups being significant. ATTR amyloidosis was a significant predictor of AF in cardiac amyloidosis patients.

In the present study, ATTR amyloidosis was associated with a significantly higher prevalence of AF than AL amyloidosis. Similar results have been reported previously.[28] The cardiac infiltration of ATTR amyloidosis is relatively slow, with a reported median survival of approximately 75 months.[29] In addition, chronic stress on the atrial wall due to ventricular diastolic dysfunction leads to atrial enlargement, and amyloid deposition damages the atrial muscle, resulting in a very high incidence of AF. In contrast, AL amyloidosis tends to progress more rapidly overall and develops at a younger age, with the median survival time for patients with AL amyloidosis with heart failure being reported to be approximately 4 months.[29] Therefore, it is estimated that in many patients with AL amyloidosis, the condition is fatal before the onset of AF. Therefore, patients with ATTR amyloidosis had a significantly higher incidence of AF than patients with AL amyloidosis in the present study. Further studies are needed to clarify this point.

A consensus has not been reached regarding the effectiveness of catheter ablation for AF in patients with cardiac amyloidosis. Previous retrospective studies demonstrated the effectiveness of catheter ablation for atrial arrhythmia in patients with cardiac amyloidosis, but the conclusions were different.[30,31] In the present study, catheter ablation was performed in 9 cardiac amyloidosis patients with atrial tachyarrhythmia (8 patients with AF and 1 with AFL). The non-recurrence rate after ablation for AF was 75% (6/8 cases). Furthermore, all 9 patients who underwent ablation were alive at the time of reporting and have been well without hospitalization due to heart failure. Many of the patients who underwent PVI in the present study were referred for ablation of AF and were diagnosed with amyloidosis after abnormalities were found during preoperative testing. This early detection of amyloidosis may have been one of the reasons for the good ablation results.

A study by Donnellan et al in 2020 showed that catheter ablation for AF reduces mortality in patients with ATTR cardiac amyloidosis.[32] Catheter ablation may be an effective treatment for ATTR amyloidosis patients, but there have been only a few studies on the effectiveness of catheter ablation and further studies are needed.

Many studies have reported negative conclusions regarding the effectiveness of ICD implantation for improving the prognosis of patients with cardiac amyloidosis.[33] Careful consideration should be given to ICD implantation, especially in patients with AL amyloidosis.[20]

As stated above, various arrhythmias were frequently observed in Japanese patients with cardiac amyloidosis. In Japan, tafamidis can now be used for the treatment of ATTR amyloidosis and patisiran can now be used for treatment of ATTRv, with both these drugs expected to suppress the progression of disease. These drugs also suppress the deposition of amyloid in atrial muscle, ventricular muscle, and the conduction system, and it is therefore expected that the frequency of arrhythmia complications will decrease in the future.

In the present study we investigated the prevalence of complications of arrhythmic diseases in patients with cardiac amyloidosis before new treatments, such as tafamidis, became available in Japan. Further studies after new therapeutic agents against amyloidosis became available

are needed to clarify the prevalence of arrhythmias in patients with cardiac amyloidosis.

Study Limitations

This study has several limitations. First, the sample size is too small for analysis. This study included only 43 patients with cardiac amyloidosis. Future studies with a larger number of patients are needed. New treatments for amyloidosis are now available, such as tafamidis. We hope that this study will be useful as data prior to the implementation of those new treatments. In the future, there will be large-scale studies of data collected during the use of new treatments. Second, there are limitations in detecting arrhythmias. In patients without pacemakers, ICD, or CRT-D/P, only continuous monitoring with an implantable loop recorder could potentially detect the arrhythmias. The ECGs recorded at follow-up visits or at the bedside cannot be considered sufficient. Future research also needs to incorporate means of detecting asymptomatic arrhythmias. Third, treatment was based on the arrhythmia treatment guidelines of the Japanese Circulation Society,[34] but the study appears to have resulted in aggressive device implantation and radiofrequency ablation. This may be due to the fact that the facilities enrolled in this study are those that actively treat arrhythmias. Fourth, there is a lack of information on ventricular and atrial premature beats in this study. It would be of interest to examine the association between the number of premature beats and subsequent AF or sustained ventricular tachyarrhythmias. Fifth, NYHA heart failure class was more severe and BNP was higher in patients with AL amyloidosis than in those with ATTR amyloidosis. This suggests that the patients with AL amyloidosis in the present study may have advanced cardiac amyloidosis. Thus, in the present study, echocardiographic LV wall thickness may have been greater in patients with AL amyloidosis than ATTR amyloidosis. The results may vary depending on the background of the study subjects. Sixth, because this was a retrospective observational study, clinical judgments were made by the attending physician regarding the indications for non-pharmacological therapy. Uncertainty about individual patient backgrounds and treatment criteria for non-pharmacological treatments precludes accurate interpretation of treatment effects.

Conclusions

The prevalence of various arrhythmias was high in patients with cardiac amyloidosis before new therapeutic agents against amyloidosis became available in Japan. AF occurred most frequently in patients with cardiac amyloidosis, especially in patients with ATTR amyloidosis. Implantable devices and catheter ablation were partially effective in the treatment of arrhythmias. Further studies after new amyloidosis drugs became available are needed to clarify the prevalence of arrhythmias in patients with cardiac amyloidosis.

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Author Contributions

K. Nakamura conceived the study and participated in its design and coordination. M.M. and K. Nakamura drafted the manuscript. M.M., K. Nakamura, K. Nakagawa, N.N., S.K., A.U., S.A., A.W., and H.M, acquired the data. H.I. was a supervisor. All authors read and approved the final manuscript.

IRB Information

This study was approved by the Institutional Ethics Committee on Human Research of Okayama University (Approval no. 2107-006).

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