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Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers

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ABSTRACT

BACKGROUND Mutations in *LMNA* are variably expressed and may cause cardiomyopathy, atrioventricular block (AVB), or atrial arrhythmias (AAs) and ventricular arrhythmias (VA). Detailed natural history studies of *LMNA*-associated arrhythmic and nonarrhythmic outcomes are limited, and the prognostic significance of the index cardiac phenotype remains uncertain.

OBJECTIVES This study sought to describe the arrhythmic and nonarrhythmic outcomes of *LMNA* mutation carriers and to assess the prognostic significance of the index cardiac phenotype.

METHODS The incidence of AVB, AA, sustained VA, left ventricular systolic dysfunction (LVD) (= left ventricular ejection fraction ≤50%), and end-stage heart failure (HF) was retrospectively determined in 122 consecutive *LMNA* mutation carriers followed at 5 referral centers for a median of 7 years from first clinical contact. Predictors of VA and end-stage HF or death were determined.

RESULTS The prevalence of clinical manifestations increased broadly from index evaluation to median follow-up: AVB, 46% to 57%; AA, 39% to 63%; VA, 16% to 34%; and LVD, 44% to 57%. Implantable cardioverter-defibrillators were placed in 59% of patients for new LVD or AVB. End-stage HF developed in 19% of patients, and 13% died. In patients without LVD at presentation, 24% developed new LVD, and 7% developed end-stage HF. Male sex ($p = 0.01$), non-missense mutations ($p = 0.03$), and LVD at index evaluation ($p = 0.004$) were associated with development of VA, whereas LVD was associated with end-stage HF or death ($p < 0.001$). Mode of presentation (with isolated or combination of clinical features) did not predict sustained VA or end-stage HF or death.

CONCLUSIONS *LMNA*-related heart disease was associated with a high incidence of phenotypic progression and adverse arrhythmic and nonarrhythmic events over long-term follow-up. The index cardiac phenotype did not predict adverse events. Genetic diagnosis and subsequent follow-up, including anticipatory planning for therapies to prevent sudden death and manage HF, is warranted. (J Am Coll Cardiol 2016;68:2299–307) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AA = atrial arrhythmia

AF = atrial fibrillation

AVB = atrioventricular block

CRT = cardiac resynchronization therapy

ICD = implantable cardioverter-defibrillator

LMNA = gene-encoding lamin A/C

LVD = left ventricular systolic dysfunction

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Dominant mutations in *LMNA*, which encodes the nuclear envelope protein lamin A/C, cause a type of arrhythmogenic cardiomyopathy characterized by age-dependent penetrance that approaches 100% by the seventh decade (1), and it is the culprit for ~5% of dilated cardiomyopathy cases (2). Clinical expression of pathogenic *LMNA* mutations is variable; however, progressive conduction abnormalities, atrial arrhythmias (AAs), and ventricular arrhythmias (VAs) are highly prevalent and may precede or supersede systolic dysfunction, with associated risks for stroke and sudden death (1,3–8). Detailed natural history studies of *LMNA*-associated arrhythmic and nonarrhythmic outcomes are limited (1,4,6,7,9). Moreover, there has been a limited examination of the interrelationship of arrhythmic and nonarrhythmic events in follow-up. In this multicenter retrospective study, we sought to examine the presentation, progression, and interrelationship of arrhythmic and nonarrhythmic events and long-term outcomes of patients with pathogenic *LMNA* mutations. Furthermore, we examined whether the mode of clinical presentation (with either isolated or combination of clinical features) as a marker of mutation expression and disease severity was associated with adverse outcomes.

SEE PAGE 2308

METHODS

A chart review was performed in all patients (probands and available relatives) with a pathogenic or likely pathogenic *LMNA* mutation followed by cardiovascular genetics clinics of 5 international referral centers (in Boston, Massachusetts; Bordeaux, Paris, and Toulouse, France; Melbourne, Australia; and Leiden, the Netherlands). Genetic diagnosis was made between 1998 and 2015. Persons with a previously published pathogenic *LMNA* mutation with cardiac involvement and persons with a newly identified *LMNA* mutation with clinical or family evidence of laminopathy with possible cardiac involvement were included (6). Of 132 patients screened (92 families), 10 patients (5 families) were excluded because of incomplete follow-up (n = 7) or when the *LMNA* variant was deemed benign (n = 1) or was considered to be a variant of unknown significance (n = 2).

Data were collected from the patient's first-ever clinical contact with any cardiologist to the time of last clinical contact. Baseline clinical, echocardiographic, electrocardiographic, Holter, implanted device diagnostic, and genetic data were collected. Details of clinical events occurring at first clinical contact and in follow-up (including the timing of events) were collected. Events characterized were as follows: development of any form of atrioventricular block ([AVB] including first degree, Mobitz II, and complete AVB); AA lasting >30 s (including atrial fibrillation [AF], atrial flutter, and atrial tachycardia); sustained VA (10) (including sustained ventricular tachycardia [VT] lasting >30 s, ventricular fibrillation [VF], or cardiac arrest); heart failure (HF) or left ventricular systolic dysfunction (LVD); type of arrhythmia device implanted (pacemaker, implantable cardioverter-defibrillator [ICD], or cardiac resynchronization therapy [CRT]), thromboemboli ([TE] arterial and/or venous); end-stage HF; and overall mortality.

Cardiac arrest was defined as witnessed sudden cardiac death with or without documented VF or death within 1 h of acute symptoms or nocturnal deaths with no antecedent history of worsening symptoms (11). HF was defined according to published guidelines (12). LVD was defined as left ventricular ejection fraction (LVEF) <50%. End-stage HF was defined as treatment with continuous inotropic infusion, mechanical circulatory support, or cardiac transplantation. Where possible, both composite and individual subtypes of clinical events (e.g., any form of AVB) were reported. Mode of presentation was defined as a phenotype with isolated clinical features (e.g., AVB alone, AA alone) or a combination of clinical features (e.g., AVB and AA) at first clinical contact. A subset of subjects with *LMNA* mutations who were evaluated because of their family history had no clinical, electrocardiographic, or echocardiographic abnormalities at first contact, and thus these subjects were categorized as phenotype negative.

Deoxyribonucleic acid sequence analysis was performed through the participating institutions. *LMNA* mutation pathogenicity and type of mutation (missense vs. nonmissense) was confirmed by the

received consultant fees from Sorin, Medtronic, Boston Scientific, and Bayer. Dr. Stevenson has intellectual property and a patent for needle ablation consigned to Brigham and Women's Hospital. Dr. Sacher has received speaker honoraria from St. Jude Medical. Dr. Tedrow is on the faculty of St. Jude Medical and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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investigators using publicly available resources in 120 of 122 patients (ClinVar and the UMD-LMNA mutations databases). Criteria for gene mutation pathogenicity were applied as described previously (6).

STATISTICAL ANALYSIS. SPSS Version 23 (IBM Corp., Armonk, New York) was used for analysis, and Prism Version 6 (GraphPad Software Inc., La Jolla, California) was used for graphic presentation. Continuous variables were expressed as mean ± SD if normally distributed; median and interquartile range (IQR) of 25% to 75% were used if the data were skewed. Categorical variables were reported as counts (percentages) and were compared using the Fisher exact test, where applicable. Clinical events were described both as raw number of events and percentages (percentage of events/total number of patients × 100; reported as prevalence) and as cumulative event rates using the Kaplan-Meier method. Follow-up started at first-ever clinical contact and ended at the last available physician visit.

Cox regression analysis was used to identify whether independent clinical factors at presentation (including mode of presentation) predicted sustained VA and a composite endpoint of end-stage HF and overall mortality in follow-up. Variables reaching $p < 0.20$ at univariable analysis were included in the multivariable model. Where relevant, 2-sided p values <0.05 were considered statistically significant.

RESULTS

The study cohort comprised 122 patients with *LMNA* mutations from 87 families (range 1 to 10 subjects per family) with 87 probands and 35 relatives. At first evaluation, 18 relatives were phenotype negative and 17 were phenotype positive. Baseline characteristics are shown in **Table 1**, and a list of mutations is presented in Online Table 1. Median follow-up from first clinical contact until last follow-up was 7 years (IQR: 3 to 12 years). Data for the occurrence of arrhythmic and nonarrhythmic events were present in all patients except for AVB, which were unavailable in 5 patients.

At first clinical contact, 104 patients were phenotypically affected (including electrocardiographic manifestations such as first-degree AVB). Of these patients, 42% presented with an isolated clinical finding and 58% with a combination of clinical findings. Isolated clinical findings included AA (11.5%), AVB (13.5%), HF or LVD (10.6%), neuromuscular manifestation (4.8%), or VA alone (1.9%). Patients with a combination of clinical findings could be broadly grouped into the following categories: those with AVB in addition to 1 or more of AA, VA, HF or LVD, or neuromuscular symptoms (38.5%); or HF in addition to 1 or more of AA, VA, or neuromuscular symptoms (17.3%); or AA in addition to neuromuscular manifestations (1.9%).

TABLE 1 Baseline Characteristics (N = 122)

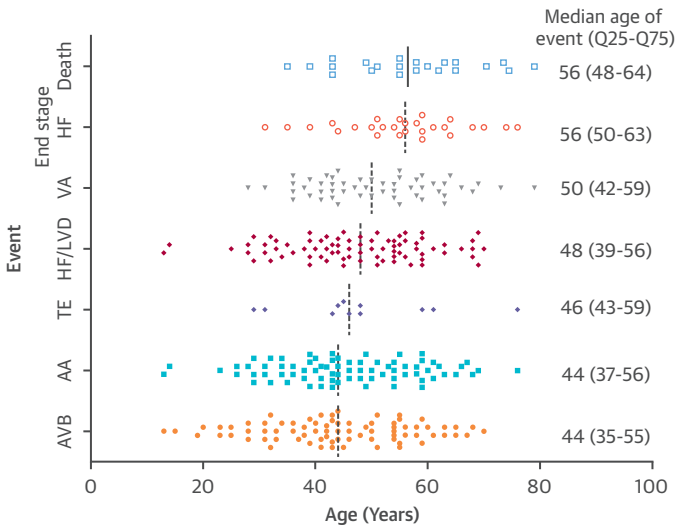
Number of families	87
Median number of members per family	1
Range of members per family	1–10
Number of probands	87
Number of relatives	35
Asymptomatic relatives (families)	18 (9)
Symptomatic relatives (families)	17 (12)
Age at first clinical contact, yrs	41 ± 14
Range, yrs	13–71
Female	52 (43)
Time from first clinical contact to gene diagnosis, yrs	3 (0–9)
Type of mutation	
Missense	69 (58)
Nonmissense	51 (42)
LVEF at first clinical contact, %	53 ± 14
Patients with LVEF >50%	53%
LV end-diastolic diameter at first clinical contact, mm	52 ± 9
Neuromuscular manifestations	18 (15)
Emery-Dreifuss muscular dystrophy	10
Limb-girdle muscular dystrophy	6
Unclassified	2
Follow-up duration, yrs	7 (3–12)

Values are n (%), mean ± SD, median (interquartile range), or n, unless otherwise indicated.
LVEF = left ventricular ejection fraction.

Figure 1 shows the age at which arrhythmic and nonarrhythmic clinical events occurred during follow-up. Notably, the median age of patients with clinical events exhibited a stepwise increment from AVB, AA, and TE events (44 to 46 years) to HF or LVD and sustained VA (48 to 50 years) to end-stage HF and death (56 years). The **Central Illustration** and **Figure 2** summarize the prevalence of arrhythmic and nonarrhythmic events at presentation and at last follow-up. Any clinical event (arrhythmic or nonarrhythmic) was experienced by 82 ± 4% by median follow-up of 7 years. The **Central Illustration** (panel B) summarizes the rate of new clinical events (incident) after excluding patients who had experienced these events at presentation. Notably, among patients with any clinical manifestations on presentation, only 17% remained free of VA, HF or LVD, or death.

ARRHYTHMIAS, CONDUCTION DISORDERS, AND THROMBOEMBOLIC EVENTS. The prevalence of any and all forms of AVB increased from first clinical contact to last follow-up (**Central Illustration**, **Figure 2**). The cumulative event estimate for AVB was 57 ± 5% at 7 years. New complete AVB occurred in 16 ± 5% of

FIGURE 1 Clinical Events



The median age at which clinical events occurred demonstrated a stepwise increment as disease intensified. AA = atrial arrhythmia; AVB = atrioventricular block; HF = heart failure; LVD = left ventricular dysfunction; TE = thromboembolism; VA = ventricular arrhythmia.

patients at 7 years. Demographic features and subsequent clinical events experienced by patients who had AVB on presentation are summarized **Table 2** and are notable for a substantial incidence of subsequent AA, VA, and end-stage HF or death events in follow-up. In patients with AVB (excluding patients with second- or third-degree AVB), mean PR interval on presentation increased from 261 ± 50 ms at first clinical contact to 309 ± 55 ms at last follow-up ($p = 0.03$).

The prevalence of any and all subtypes of AA increased from first clinical contact to last follow-up (**Figure 2**, Online Figure 1). The cumulative event estimate for AA was 63 ± 5% at 7 years. Among patients without AA at first evaluation, new AF, atrial flutter, and atrial tachycardia occurred in 33 ± 7%, 14 ± 5%, and 14 ± 5% of patients, respectively.

Of patients with AF on presentation, progression of AF (e.g., paroxysmal to persistent or persistent to permanent) occurred in 45% of patients. In patients with AF that developed during follow-up, AF coexisted with HF or LVD in 57% of patients, occurred before HF or LVD in 24% of patients, and occurred without future HF or LVD in 19% of patients.

Demographic features and subsequent clinical events experienced by patients who had AA on presentation are summarized in **Table 2** and are notable for the high incidence of subsequent AVB, VA, HF or LVD, and end-stage HF or death in follow-up.

There was an increase in TE events from baseline to follow-up (**Central Illustration**, **Figure 2**), and these events included 10 strokes. Two of the 10 patients with strokes had no documented AAs at any point in follow-up. At last follow-up, 56% of patients were receiving oral anticoagulant therapy.

The prevalence of any and all forms of sustained VA increased from presentation to last follow-up (**Figure 2**, Online Figure 2). The cumulative event estimate for VA was 34 ± 5% at 7 years. New sustained VT occurred in 19 ± 5% of patients, and VF occurred in 8 ± 3% of patients at median follow-up. Median time from first clinical contact to sustained VA was 4 years (IQR: 0 to 9 years).

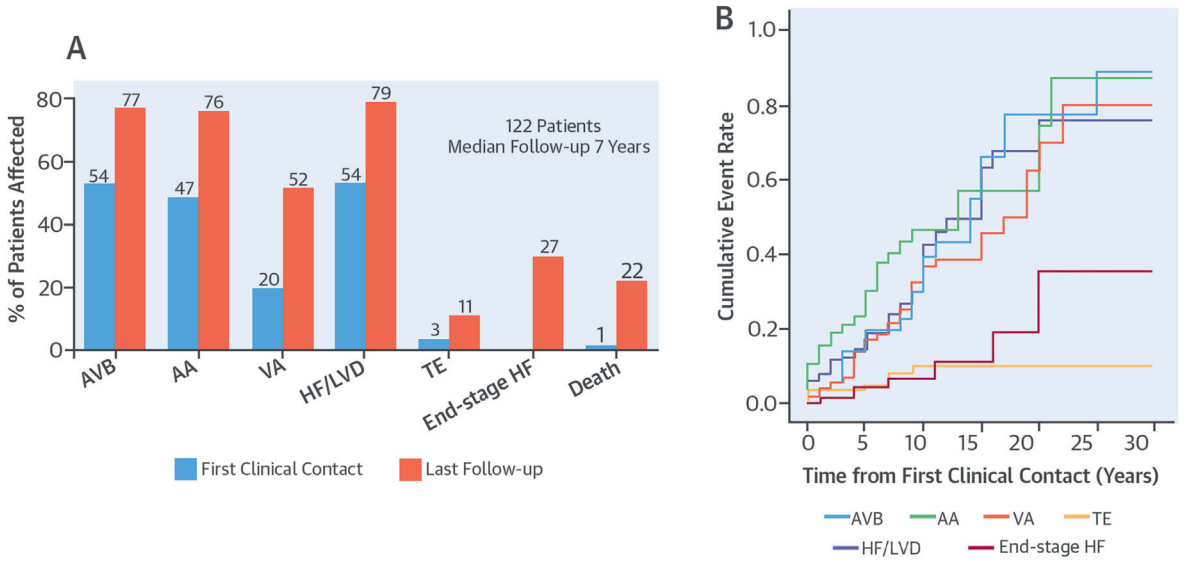
At the time of sustained VA, some form of AVB was present in 75% of patients (complete AVB in 34%). At least 1 episode of AA was experienced by 60% of patients with VA. Mean LVEF at time of sustained VA was 42 ± 15% (range 19% to 66%). Among patients with VAs, 27% of patients had preserved systolic function (LVEF >50%), and 56% had an LVEF >35%.

Of the 52 patients experiencing sustained VA, 25 patients were managed with catheter ablation, and 27 patients were managed with antiarrhythmic drugs or beta-blockers. Twenty-two patients (18%) experienced arrhythmic storm (VT, n = 21; VF, n = 1) that was managed with catheter ablation (n = 17), antiarrhythmic drugs (n = 4), or urgent cardiac transplantation after multiple ablations failed (n = 1).

IMPLANTED ARRHYTHMIA DEVICES. The presence of an arrhythmia device increased from 41% of patients at presentation to 73% in follow-up (**Figure 3**). The most notable increase was in the proportion of ICDs and CRTs, paralleling the increasing incidence of new HF or LVD and complete AVB events (**Figure 3**). Notably, 59 of 122 patients (48%) received a new implant (n = 39) or required a device upgrade (n = 20). In follow-up, an ICD was placed for primary prevention of sudden cardiac death in 46 patients and for sustained VA in 8 patients. Three patients received a new pacemaker for sinus node dysfunction or AVB with preserved ventricular function, and 2 patients received a device upgrade from a secondary preventive ICD to a CRT-defibrillator for new HF or LVD.

There were no sudden deaths in the 20 patients with a pacemaker. Sudden death occurred in 3 patients who had CRT-defibrillators but developed refractory VAs and in 1 patient whose sudden death was the initial disease presentation. There were 58 patients with primary preventive ICDs (12 implanted shortly after presentation and 46 during follow-up); 29 (50%) of

CENTRAL ILLUSTRATION **High Rate of Cardiac Arrhythmic and Nonarrhythmic Phenotypic Progression**



Kumar, S. et al. J Am Coll Cardiol. 2016;68(21):2299–307.

Early genetic diagnosis and anticipatory planning to prevent stroke or death from arrhythmia or heart failure (HF) are recommended because of the adverse natural history of heart disease caused by *LMNA* mutations. **(A)** A comparison of event rates at presentation and last contact demonstrated a high rate of phenotypic progression over time. **Bars** represent % of patients affected; number of patients affected shown by text on each bar. **(B)** In patients free of these events at first clinical contact, the incidence of new events rose over time. AA = atrial arrhythmia; AVB = atrioventricular block; LVD = left ventricular dysfunction; TE = thromboembolism; VA = ventricular arrhythmia (ventricular fibrillation or sustained ventricular tachycardia).

these patients experienced an appropriate ICD intervention for sustained VAs.

Data on device complications and inappropriate shocks were available in 24 patients. No patients received inappropriate shocks for AA or experienced device infection. Two patients received inappropriate shocks caused by lead malfunction.

HF, LVD, AND MORTALITY. HF or LVD increased from presentation to last follow-up (Figure 2A). The cumulative event estimate was 57 ± 5% at 7 years. At last follow-up, 27 patients (22%) had end-stage HF; the cumulative event estimate was 19 ± 4% at 7 years. Of these, 10 patients underwent cardiac transplantation, and 8 underwent ventricular assist device implantation; additionally, 6 patients were awaiting cardiac transplants without ventricular devices, and 3 patients were receiving long-term inotrope infusions because they were declined for other advanced HF therapies.

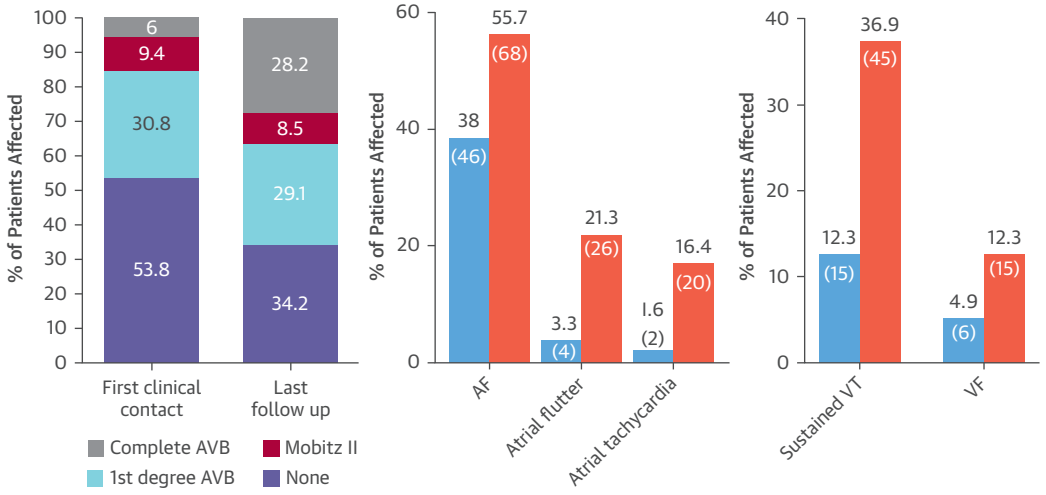
In patients who had preserved LV function (LVEF >50%) and no HF at presentation, new HF or LVD events occurred in 24 ± 6%, and end-stage HF occurred in 7 ± 4% of patients at 7 years (Central Illustration, panel B).

Demographic features and subsequent clinical events experienced by patients who had HF on presentation are summarized Table 2; there is a notably high incidence of subsequent AVB, AA, VA, and end-stage HF or death.

During follow-up, 22 patients died (18%), predominantly of HF (n = 8) or of complications related to cardiac transplantation or ventricular assist devices (n = 9), sudden death (n = 4), and stroke (n = 1) (Online Table 2). The cumulative estimate for mortality was 13 ± 4% at 7 years.

PREDICTORS OF ADVERSE EVENTS. Male sex (hazard ratio [HR]: 3.2; 95% confidence interval [CI]: 1.3 to 8.0; p = 0.01), LVEF ≤50% at first clinical contact (HR: 3.4; 95% CI: 1.5 to 8.1; p = 0.004), and nonmissense mutations (HR: 2.5; 95% CI: 1.1 to 6.0; p = 0.03) were independently associated with new sustained VA in follow-up (Online Table 3). Among patients with none, 1, 2, or 3 of these features at first clinical contact, event rates for VA at median follow-up were 9 ± 6%, 28 ± 8%, 47 ± 9%, and 69 ± 16%, respectively. LVEF ≤50% at first clinical contact was the only factor independently associated with a composite endpoint of new end-stage HF or death

FIGURE 2 Event Prevalence at First Clinical Contact and Last Follow-Up



Over time, the prevalence of specific arrhythmia events rose. Patients may have experienced >1 subtype of atrial or ventricular arrhythmia. After excluding patients who initially presented with a particular clinical event, new clinical events for patients with lamin A/C mutations rose over time. AF = atrial fibrillation; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Figure 1.

during follow-up (HR: 4.8; 95% CI: 1.9 to 12.1; p = 0.001) (Online Table 4). In addition to LVEF ≤50% at first clinical contact (HR: 3.1; 95% CI: 1.1 to 8.5), nonmissense mutation (HR: 3.7; 95% CI: 1.4 to 10.1; p = 0.009) and male sex (HR: 2.7; 95% CI: 0.9 to 7.8; p = 0.07) were factors independently associated with death in follow-up (Online Table 5). Mode of presentation (with isolated clinical finding versus a combination of findings) did not independently predict new sustained VA or the composite endpoint of end-stage HF or death or death alone (Online Tables 3 to 5). Patients with rapid disease progression from first clinical contact to end-stage HF or death within 5 years (n = 20) could not be differentiated from patients with long interval to end-stage HF or death (n = 11) on the basis of clinical or genetic factors.

CHARACTERISTICS AND OUTCOMES OF RELATIVES VERSUS PROBANDS. Phenotypic expression was absent (phenotype negative) in 18 of the 35 mutation-positive relatives at initial evaluation (Online Table 6). Phenotype-negative relatives were younger (age 31 ± 16 years) compared with phenotype-positive relatives (age 44 ± 12 years; p = 0.009) and probands (age 43 ± 14 years; p = 0.002), with a shorter duration of follow-up (median 1.5 years). However, 3 (17%) initially phenotype-negative relatives experienced phenotypic expression during follow-up (AA at 5 years, first degree AVB at 8 years, and complete AVB at 17 years). Event rates in phenotype-positive relatives (new complete AVB, 21%; new AA, 24%; new VA, 24%; and end-stage HF or death, 24%) were comparable to those observed in probands (new complete AVB, 27%; new AA, 28%; new VA, 32%; and end-stage HF or death, 31%) (Online Table 6).

DISCUSSION

Mutations in *LMNA* are relatively rare but important causes of arrhythmogenic cardiomyopathy (**Central Illustration**). This multicenter study adds to the existing literature highlighting the adverse outcomes associated with this disease and emphasizes the value of a gene-based diagnosis. Here we have catalogued the spectrum of arrhythmic and nonarrhythmic disease manifestations among 122 *LMNA* mutation carriers with detail and a robust duration of follow-up (median 7 years). Furthermore, our dataset was comprehensive, with complete data on event rates present for all patients except for AVB (94% complete). Previous studies provided critical insights into natural history but included limited numbers of affected persons (4,5,7), had a shorter or comparable duration of follow-up (1,13), lacked a detailed assessment of specific nonarrhythmic or arrhythmic events (e.g., limited to VA), or focused principally on identifying risk factors of malignant VAs (1,4–6).

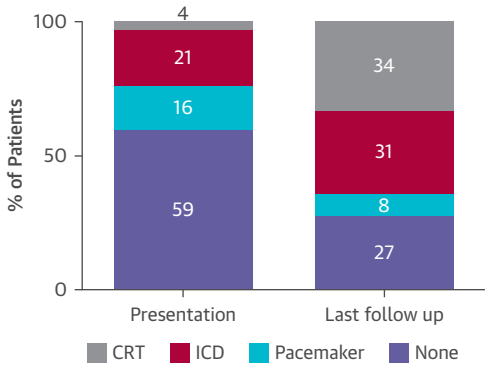
TABLE 2 Demographic Features and Subsequent Clinical Events*

	AVB on Presentation (n = 54)	AA on Presentation (n = 47)	HF on Presentation (n = 54)
Age at first clinical contact, yrs	43 ± 14	44 ± 12	45 ± 13
Female	43	49	24
LVEF at first clinical contact, %	52 ± 12	53 ± 14	41 ± 11
Concurrent presentation with AVB at first clinical contact	–	47	50
New AVB events by last follow-up	–	36	22
Concurrent presentation with AA at first clinical contact	39	–	41
New AA events by last follow-up	33	–	32
Concurrent presentation with HF/LV dysfunction at first clinical contact	46	47	–
New HF/LV dysfunction events by follow-up	24	38	–
Concurrent presentation with sustained VA at first clinical contact	20	9	26
New VA events by last follow-up	32	30	35
New TE events by last follow-up	9.3	9	11
End-stage HF or death by last follow-up	24	30	43

Values are mean ± SD or %. *Patients could be represented more than once or not at all.

AA = atrial arrhythmia; AVB = atrioventricular block; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; TE = thromboembolism; VA = ventricular arrhythmia.

FIGURE 3 Arrhythmia Device Implantation



The percentage of patients with implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy (CRT) defibrillators increased substantially at follow-up.

We confirm the proclivity of *LMNA* mutation carriers to malignant VAs (1,4,9,14). The cumulative event estimate for VA was 34% at 7 years. In patients who did not present with VA, 22% experienced new sustained VAs by 7-year follow-up. Moreover, 50% of patients with an ICD implanted for the primary prevention of sudden cardiac death experienced an appropriate ICD intervention by last follow-up. These event rates (~3% to 7%/year) are higher than or comparable to appropriate ICD interventions experienced by high-risk patients without a previous history of VA who received a prophylactic ICD for the following indications: nonischemic dilated cardiomyopathy with severe systolic-dysunction (LVEF ~25%) and symptomatic HF (~2% per year) (15); arrhythmogenic right ventricular cardiomyopathy (~5% per year) (16); hypertrophic cardiomyopathy ~2% per year (17); and high-risk patients with ischemic cardiomyopathy (~7% to 8% per year) (18).

Moreover, as previously recognized (3,19), up to one-third of *LMNA* mutation carriers who manifested sustained VA had preserved ventricular function (LVEF >50%), and 56% did not meet conventional criteria for ICD implantation because they had LVEF >35% at the time of first sustained VA. This finding emphasizes the limitations of traditional risk stratification on the basis of systolic function and HF among patients with *LMNA* mutations and the value of a gene-based diagnosis in clinical management. Notably, malignant VA and sudden death events in the absence of an ICD occurred in 7% of patients (1 sudden death, 8 sustained VA episodes in pacemaker recipients), which was a lower rate than that reported in previous studies of 31% to 46% of patients (9,20). It is plausible that fewer sudden deaths reflected increasing tendencies to implant an ICD rather than a permanent pacemaker in *LMNA*-related heart disease because physicians recognize the VA risk; that 59% of patients underwent implantation of a new ICD or had an ICD upgrade from a pacemaker supports this point (21,22). The common coexistence of AV conduction disease with AAs in *LMNA*-related heart disease may reduce the risk of inappropriate shocks (23). Indeed, no patient reported here experienced inappropriate shocks for AA, in marked contrast to patients with other inherited cardiomyopathies and arrhythmia syndromes in which inappropriate shocks outnumber appropriate shocks (21). As previously reported, male sex and nonmissense mutations were associated with sustained VA (6). Nevertheless, the high VA event rate, the occurrence of VA with preserved ventricular function, the

lack of robust predictive factors to identify a truly low-risk cohort, and the low rate of inappropriate shocks suggested that decisions regarding ICD use could be a matter of timing of implantation, rather than patient selection.

Another important finding of this study was the inexorable progression to end-stage HF (57% at 7 years). Indeed, among patients without LVD or HF at presentation, 24% developed new HF or LVD, and 7% reached end-stage HF at a median of 7 years of follow-up. Critically, the mode of clinical presentation (whether isolated or a combination of clinical manifestations) did not predict subsequent VA, end-stage HF, or death. Indeed, only 21% of patients with any clinical manifestations at the index evaluation were at low risk of VA, HF or LVD, or death.

The final important message from this study was the ubiquitous presence of AAs in *LMNA*-related heart disease (63% at 7 years), the high rate of AF progression from paroxysmal to persistent or permanent forms (45%), and the accompanying high incidence of TE events (10% at 7 years). AA likely contributes to an underrecognized burden of disease morbidity in *LMNA*-related heart disease. Further work is needed to elucidate the mechanism of *LMNA*-related atriopathy.

These findings have important implications. We believe that early recognition of lamin-related heart disease with a high index of clinical suspicion and early use of genetic testing is critical. Our findings also highlight the need to maintain heightened vigilance for disease progression with early consideration of adjunctive therapies such as CRT and support the need for trials of novel drugs, such as mitogen-activated protein kinase inhibitors to slow disease progression (24). Furthermore, at-risk relatives require careful longitudinal follow-up for detection and management of phenotypic expression.

STUDY LIMITATIONS. The sample size was modest because of the seeming rarity of the disease, which likely reflects the incomplete use of genetic testing in contemporary practice beyond select referral centers. Similarly, there is the potential for referral bias toward more severely affected patients, given that patients were drawn from academic centers with expertise in complex arrhythmia management.

CONCLUSIONS

LMNA heart disease has a malignant course; most patients experience AAs and VAs, heart block, embolic events, or HF within 7 years of diagnosis. Although the disease is rare, the malignant course warrants a high index of suspicion in patients with familial cardiomyopathy and cardiomyopathies characterized by prominent arrhythmias and conduction disease to enable careful surveillance and prevention of complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: During long-term follow-up, patients with *LMNA* mutations exhibit high rates of atrioventricular conduction block, AAs, sustained VAs, ventricular dysfunction, and HF and frequently require upgrade of implanted cardiac electrical devices to provide defibrillation or resynchronization functionality.

TRANSLATIONAL OUTLOOK: Larger studies are needed to identify lower- or higher-risk subsets of patients with *LMNA* mutations and assess the therapeutic impact of drugs such as mitogen-activated protein kinase inhibitors on disease progression and related clinical outcomes.

REFERENCES

1. Pasotti M, Klersy C, Pilotto A, et al. Long-term outcome and risk stratification in dilated cardiolaminopathies. J Am Coll Cardiol 2008;52:1250–60.

2. Lakdawala NK, Funke BH, Baxter S, et al. Genetic testing for dilated cardiomyopathy in clinical practice. J Card Fail 2012;18:296–303.

3. Anselme F, Moubarak G, Savoure A, et al. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm 2013;10:1492–8.

4. Arbustini E, Pilotto A, Repetto A, et al. Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease. J Am Coll Cardiol 2002;39:981–90.

5. Taylor MR, Fain PR, Sinagra G, et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol 2003;41:771–80.

6. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol 2012;59:493–500.

7. Fatkin D, MacRae C, Sasaki T, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and

conduction-system disease. N Engl J Med 1999; 341:1715–24.

8. van Tintelen JP, Hofstra RM, Katerberg H, et al. High yield of LMNA mutations in patients with dilated cardiomyopathy and/or conduction disease referred to cardiogenetics outpatient clinics. Am Heart J 2007;154:1130–9.

9. van Berlo JH, de Voogt WG, van der Kooi AJ, et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl) 2005;83:79–83.

10. Aliot EM, Stevenson WG, Almendral-Garrote JM, et al. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm 2009;6:886–933.

11. Hinkle LE Jr., Thaler HT. Clinical classification of cardiac deaths. Circulation 1982;65:457–64.

12. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013;62:1495–539.

13. van Rijsingen IA, Bakker A, Azim D, et al. Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. Int J Cardiol 2013;168:472–7.

14. van Rijsingen IA, Nannenberg EA, Arbustini E, et al. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. Eur J Heart Fail 2013;15:376–84.

15. Sedlacek K, Ruwald AC, Kutyifa V, et al. The effect of ICD programming on inappropriate and appropriate ICD therapies in ischemic and non-ischemic cardiomyopathy: the MADIT-RIT trial. J Cardiovasc Electrophysiol 2015;26:424–33.

16. Corrado D, Calkins H, Link MS, et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. Circulation 2010;122:1144–52.

17. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405–12.

18. Gracieux J, Sanders GD, Pokorney SD, et al. Incidence and predictors of appropriate therapies delivered by the implantable cardioverter defibrillator in patients with ischemic cardiomyopathy: a systematic review. Int J Cardiol 2014;177:990–4.

19. Meune C, Van Berlo JH, Anselme F, et al. Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 2006; 354:209–10.

20. van der Kooi AJ, Bonne G, Eymard B, et al. Lamin A/C mutations with lipodystrophy, cardiac abnormalities, and muscular dystrophy. Neurology 2002;59:620–3.

21. Becane HM, Bonne G, Varnous S, et al. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. Pacing Clin Electrophysiol 2000;23: 1661–6.

22. van Berlo JH, Duboc D, Pinto YM. Often seen but rarely recognised: cardiac complications of lamin A/C mutations. Eur Heart J 2004;25: 812–4.

23. Olde Nordkamp LR, Postema PG, Knops RE, et al. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: a systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm 2016;13:443–54.

24. Wu W, Muchir A, Shan J, et al. Mitogen-activated protein kinase inhibitors improve heart function and prevent fibrosis in cardiomyopathy caused by mutation in lamin A/C gene. Circulation 2011;123:53–61.

KEY WORDS atrial fibrillation, cardiomyopathy, complete atrioventricular block, genetics, heart failure, ventricular tachycardia

APPENDIX For supplemental figures and tables, please see the online version of this article.