Long Term Arrhythmic and Non-Arrhythmic Outcomes of Lamin A/C Mutation Carriers: Insights from a Multi-Centre study

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Short title: Kumar: Arrhythmic and Non-Arrhythmic Outcomes in Cardiolaminopathies

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Word count: 5206

Disclosures: Dr. Kumar is a recipient of the Neil Hamilton Fairley Overseas Research scholarship co-funded by the National Health and Medical Research Council and the National Heart Foundation of Australia; and the Bushell Travelling Fellowship funded by the Royal Australasian College of. Dr. Lakdawala receives support from the O'Hare Family Foundation directed towards research on cardiolaminopathy. The remaining authors have no disclosures.

Abstract

Background

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

Objectives

To describe the arrhythmic and non-arrhythmic outcomes of *LMNA* mutation carriers and assess the prognostic significance of the index cardiac phenotype.

Methods

The incidence of AVB, AA, sustained VA, left ventricular systolic dysfunction (LVD=LV ejection fraction ≤ 50%), and end-stage heart failure (HF) was retrospectively determined in 122 consecutive *LMNA* mutation carriers followed at 5 referral centres for a median 7 years from first clinical contact. Predictors of VA, end-stage HF/mortality 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%, LVD 44% to 57%. New cardioverter-defibrillators were implanted in 59% for new LVD or AVB. End-stage HF developed in 19% and 13% died. In patients without LVD at presentation, 24% developed new LVD and 7% developed end-stage HF. Male gender (HR 3.2, 95% CI 1.3-8, P=0.01), non-missense mutations (HR 2.5, 95% CI 1.1-6, P=0.03) and LVD at index evaluation (HR 3.4, 95% CI 1.5-8, P=0.004) were associated with development of VA, whilst LVD was associated with end-stage HF/mortality

(HR 4.8, 95% CI 1.9-12, P<0.001). Mode of presentation (with isolated or combination of clinical features) did not predict sustained VA nor end-stage HF/mortality.

Conclusions

LMNA-heart disease is associated with a high incidence of phenotypic progression and adverse arrhythmic and non-arrhythmic 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 heart failure is warranted.

Keywords: Lamin A/C; cardiomyopathy; ventricular tachycardia; atrioventricular block; complete atrioventricular block; atrial arrhythmias; atrial fibrillation; heart failure; cardiomyopathy; genetics.

Abbreviations

AA- atrial arrhythmias

AF- atrial fibrillation

AVB- atrioventricular block

CI- confidence interval

CRT- cardiac resynchronization therapy

EF- ejection fraction

HF- heart failure

HR- hazard ratio

ICD-Implanted cardioverter-defibrillator

LMNA- Gene encoding Lamin A/C

LVD- left ventricular dysfunction

ms- milliseconds

Q25-Q75- interquartile range of 25% to 75%

TE- thromboemboli

VA- ventricular arrhythmias

VT- ventricular tachycardia

VF- ventricular fibrillation

Introduction

Dominant mutations in *LMNA*, which encodes the nuclear envelope protein Lamin A/C, cause an arrhythmogenic cardiomyopathy which is characterized by age dependent penetrance that approaches 100% by the 7th decade (1), and is the culprit for ~5% of dilated cardiomyopathy cases (2). Clinical expression of pathogenic *LMNA* mutations is variable, however progressive conduction abnormalities, atrial arrhythmias (AA), and ventricular arrhythmias (VA) 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 non-arrhythmic outcomes are limited (1,4,6,7,9). Moreover, there has been a limited examination of the inter-relationship of arrhythmic and non-arrhythmic events in follow up. In this multi-center retrospective study, we sought to examine the presentation, progression and inter-relationship of arrhythmic and non-arrhythmic events and long-term outcomes of patients with pathogenic *LMNA* mutations. Furthermore, we examined if 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.

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 centres (Boston, USA; Bordeaux, Paris and Toulouse, France; Melbourne, Australia; and Leiden, The Netherlands). Genetic diagnosis was made between 1998-2015. 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 a laminopathy with possible cardiac involvement were included (6). Of 132 patients screened (92 families), 10 patients (5 families) were excluded due to incomplete follow up (7 patients), or when the *LMNA* variant was deemed benign (1 patient) or considered to be a variant of unknown significance (2 patients).

Data was collected from the first-ever clinical contact with any cardiologist to the time of last clinical contact. Baseline clinical, echocardiographic, electrocardiographic, Holter, implanted device diagnostics as well as 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: development of any form of atrioventricular block (AVB, including first degree, Mobitz II, complete AVB), AA lasting >30 seconds (including atrial fibrillation [AF], atrial flutter and atrial tachycardia), sustained VA (10) [including sustained ventricular tachycardia {VT}] lasting >30 seconds, ventricular fibrillation [VF] or cardiac arrest), heart failure (HF) or left ventricular dysfunction (LVD), type of arrhythmia device implanted (pacemaker, implanted 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 hour 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 LV ejection fraction [EF] <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, first degree, Mobitz II and complete 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 due to their family history had no clinical, electrocardiographic or echocardiographic abnormalities at first contact were categorized as phenotype negative.

DNA sequence analysis was performed through the participating institutions. *LMNA* mutation pathogenicity and type of mutation (missense versus non-missense) was confirmed by the investigators using publically available resources in 120 of 122 patients (ClinVar [www.ncbi.nlm.nih.gov/**clinvar**/] and the UMD-LMNA mutations databases

[www.umd.be/**LMNA**/]). Criteria for gene mutation pathogenicity were applied as described previously (6).

Statistical Analysis

The Statistical Package for the Social Sciences (IBM SPSS, release 23, Armonk, New York) was used for analysis and GraphPad Prism (Version 6, La Jolla, California) was used for graphical presentation. Continuous variables were expressed as mean ± standard deviation if normally distributed; median and interquartile range of 25% to 75% (Q25–Q75) were used if the data were skewed. Categorical variable were reported as counts (percentages) and compared using the Fisher's exact test, where applicable. Clinical events were described both as raw proportions (percentage of events/total number of patients; 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 if 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 $P<0.2$ at univariable analysis were included in the multivariable model. Where relevant, two-sided P value<0.05 were considered statistically significant.

Results

Patient demographics

The study cohort was comprised of 122 patients with *LMNA* mutations from 87 families (range 1-10 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 are presented in Supplemental Table 1. Median follow-up from first clinical contact until last follow up was 7 years (Q25-Q75: 3-12 years). Data for the occurrence of

arrhythmic and non-arrhythmic events was present in all patients except for AVB, which was unavailable in 5 patients.

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

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

Atrioventricular block

The prevalence of any and all forms of AVB increased from first clinical contact to last follow up (Figure 2A, B). The cumulative event estimate for AVB was 57±5% at 7 years. New complete AVB occurred in 16±5% of 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/mortality 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).

Atrial arrhythmias and thromboembolic events

The prevalence of any and all subtypes of AA increased from first clinical contact to last follow up (Figure 2). The cumulative event estimate for AA was 63±5% at 7 years. Amongst 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 form) occurred in 45% of patients. In patients who developed AF in follow up, it co-existed with HF/LVD in 57% of patients, occurred before HF/LVD in 24% of patients and occurred without future HF/LV dysfunction in 19% of patients.

Demographic features and subsequent clinical events experienced by patients who had AA on presentation are summarized Table 2, and is notable for a high incidence of subsequent AVB, VA, HF/LVD and end stage HF/mortality in follow up.

There was an increase in TE events from baseline to follow up (Figure 2A, C) which included 10 strokes. Two of the 10 patients with strokes had no documented AA at any point in follow up. At last follow up, 56% of patients were taking oral anticoagulation.

Ventricular arrhythmias

The prevalence of any and all forms of sustained VA increased from presentation to last follow up (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 (Q25-Q75: 0-9 years).

At the time of sustained VA, some form of AVB was present in 75% of patients (complete AVB in 34%). At least one episode of AA was experienced by 60% of patients with VA. Mean LVEF at time of sustained VA was 42±15% (range 19-66%). Amongst patients with VA, 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 anti-arrhythmic drugs or beta-blockers. Twenty-two patients (18%) experienced arrhythmic storm (VT: 21 patients, VF: 1 patient) that was managed with catheter ablation (17 patients), anti-arrhythmic drugs (4 patients) or urgent cardiac transplantation after failing multiple ablations (1 patient).

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 heart failure/LV dysfunction and complete AVB events (Figure 3). Notably, 59/122 patients (48%) received a new implant (n=39 patients) or required device upgrade (n=20). In follow up, an ICD was implanted was for primary prevention of sudden cardiac death in 46 patients, for sustained VA in 8 patients. Three patients received a new pacemaker for sinus node dysfunction or AV block with preserved ventricular function and 2 patients received a device upgrade from a secondary prevention ICD to a CRT-defibrillator for new HF/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 ventricular arrhythmias and 1 patient in whom sudden death was the initial disease presentation. There were 58 patients with a primary prevention ICD (12 implanted shortly after presentation and 46 in follow up); 29 of the 58 primary prevention ICD patients (50%) experienced an appropriate ICD intervention for sustained VA.

Data on device complications and inappropriate shocks was available in 24 patients. None received inappropriate shocks for AA nor experienced device infection. Two patients received inappropriate shocks due to lead malfunction.

Heart failure, left ventricular dysfunction and mortality

Heart failure/LV dysfunction 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 heart failure; cumulative event estimate was 19±4% at 7 years. Of these, 10 patients underwent cardiac transplant, 8 had ventricular assist device implants; additionally, 6 were awaiting transplant without ventricular devices and 3 were receiving chronic inotrope infusions because they were declined for other advanced heart failure therapies.

In patients who had preserved LV function (EF >50%) and no HF at presentation, new HF/LVD events occurred in 24±6% and end stage HF occurred in 7±4% of patients at 7 years (Figure 2C).

Demographic features and subsequent clinical events experienced by patients who had HF on presentation are summarized Table 2, and is notable for a high incidence of subsequent AVB, AA, VA and end stage HF/mortality.

During follow up, 22 patients had died (18%), predominantly from HF (8 patients) or complications related to transplantation or ventricular assist device (9 patients), sudden death (4 patients), and stroke (1 patient; Supplemental Table 2). Cumulative estimate for mortality was 13±4% at 7 years.

Predictors of adverse events

Male gender (Hazard ratio [HR] 3.2, 95% confidence interval [CI] 1.3-8, P=0.01), LVEF ≤50% at first clinical contact (HR 3.4, 95% CI 1.5-8.1, P=0.004) and non-missense mutations (HR 2.5, 95% CI 1.1-6, P=0.03) were independently associated with new sustained VA in follow up

(Supplemental Table 3). Amongst 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 in follow up (HR 4.8, 95% CI 1.9-12.1, P=0.001; Supplemental Table 4). In addition to LVEF≤50% at first clinical contact (HR 3.1, 95% CI 1.1-8.5), non-missense mutation (HR 3.7, 95% CI 1.4-10.1, P=0.009) and male gender (HR 2.7, 95%CI 0.9-7.8, P=0.07) were factors independently associated with mortality in follow up (Supplemental Table 5). Mode of presentation (with isolated clinical finding versus a combination of findings) did not independently predict new sustained VA, or composite endpoint of end stage heart failure/mortality or mortality alone (Supplemental Table 3-5). Patients with rapid disease progression from first clinical contact to end stage HF/death within 5 years (n=20) could not be differentiated from patients with long interval to end stage HF/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 (Supplemental Table 6). Phenotype negative relatives were younger (31±16 years) compared to phenotype positive relatives (44±12 years, p=0.009) and probands (43±14 years, p=0.002) with a shorter duration of follow up (median 1.5 years). However, 3 (17%) of initially phenotype negative relatives experienced phenotypic expression with follow up (AA at 5 years, first degree AVB at 8 years, complete AVB at 17 years). Event rates in phenotype positive relatives (new complete AVB: 21%, new AA: 24%; new VA 24%, end stage HF/mortality 24%) were comparable to what was observed in probands (new complete AVB: 27%, new AA 28%; new VA 32%; end stage HF/mortality 31%; Supplemental Table 6).

Discussion

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

We confirm the proclivity of *LMNA* mutation carriers to malignant VAs (1,4,9,14). Cumulative event estimate for VA was 34% at 7 years. In patients who did not present with VA, 22% experienced new sustained VA by 7 years' 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 (~3-7%/year) are higher or comparable to appropriate ICD interventions experienced by high risk patients without a prior history of VA who receive a prophylactic ICD for non-ischemic dilated cardiomyopathy with severe systolic dysfunction (LVEF~25%) and symptomatic heart failure [~2%/year] (15), arrhythmogenic right ventricular cardiomyopathy [~5%/year] (16), hypertrophic cardiomyopathy ~2%/year (17), and high risk patients with ischemic cardiomyopathy [~7-8%/year] (18).

Moreover, as previously recognized (3,19), up to 1/3rd of *LMNA*-mutation carriers who manifested sustained VA had preserved ventricular function (LVEF>50%) and 56% did not meet conventional criteria for ICD implantation as they had LVEF >35% at the time they first experienced sustained VA. This emphasizes the limitations of traditional risk stratification based on systolic function and heart failure amongst 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 in pacemaker recipients), which were lower than that reported in prior studies [31-46% of patients] (9,20). It is plausible that fewer sudden deaths reflects increasing tendency for implantation of an ICD rather than permanent pacemaker in *LMNA*-related heart disease as physicians recognize the VA risk; that 59% of patients underwent a new ICD implant or a ICD upgrade from a pacemaker supports this point (21,22). The common coexistence of AV conduction disease with atrial arrhythmias in *LMNA*-related heart disease may reduce the risk of inappropriate shocks (23). Indeed, no patient reported here experienced inappropriate shocks for AA, which is in marked contrast to other inherited cardiomyopathies and arrhythmia syndromes where inappropriate shocks outnumber appropriate shocks (21). As previously reported, male gender and non-missense mutations were associated with sustained VA (6). Nevertheless, the high VA event rate, occurrence of VA with preserved ventricular function, lack of robust predictive factors to identify a truly low risk cohort, and the low rate of inappropriate shocks suggests decisions regarding ICD utilization may be a matter of timing of implantation, rather than patient selection.

Another important finding of this study is the inexorable progression to end stage HF (57% at 7 years). Indeed, amongst patients *without* LV dysfunction or heart failure at presentation, 24% developed new heart failure/LV dysfunction and 7% reached end stage HF at a median of 7 years' 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 mortality. Indeed only 21% of patients with any clinical manifestations at the index evaluation were at low risk of VA, HF/LV dysfunction or mortality.

The final important message from this study is the ubiquitous presence of atrial arrhythmias 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 under-recognized burden of disease morbidity in *LMNA*-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 need careful longitudinal follow up for detection and management of phenotypic expression.

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Limitations

The sample size is modest due to 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, as patients were drawn from academic centers with expertise in complex arrhythmia management.

Conclusions

LMNA heart disease has a malignant course with the majority of patients experiencing atrial and ventricular arrhythmias, heart block, embolic events or heart failure 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 enabling careful surveillance and prevention of complications.

Perspectives

Competency in Medical Knowledge: Patients with LMNA mutations have a high incidence of progression to AVB, atrial arrhythmias, sustained ventricular arrhythmias, heart failure and ventricular dysfunction, device upgrade to a defibrillator or a cardiac re-synchronization device over long term follow up. Although individual factors such as male gender, non-missense mutations and presence of left ventricular dysfunction predicted adverse outcomes in follow up, the index cardiac phenotype (presence of single or multiple clinical features) does not predict future risk of adverse outcomes.

Competency in patient care: For patients with a cardiac phenotype suggesting of LMNA mutations, genetic diagnosis and rigorous subsequent follow-up, including anticipatory planning for therapies to prevent sudden death and manage heart failure are critical.

Translational outlook: Larger studies are needed to identify a truly low risk cohort. Trials of novel drugs such as mitogen-activated protein kinase inhibitors to slow disease progression are critical in an attempt to reduce the high mortality associated with this condition.

Central Illustration

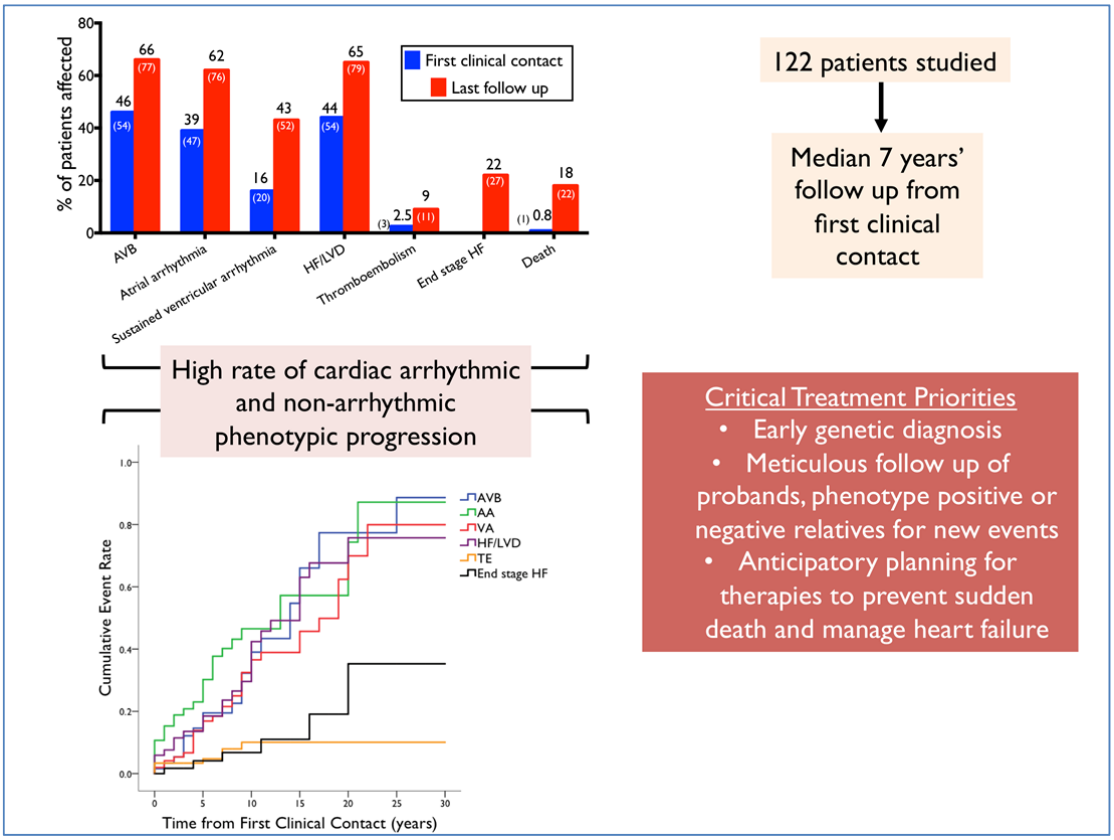

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Figure Legends

Central Illustration: Long-term arrhythmic and non-arrhythmic outcomes of cardiolaminopathies from a multi-centre cohort.

Shown are the event-rates at presentation and over follow up demonstrating the high rate of phenotypic progression over time and highlighting the critical treatment priorities in patients with Lamin A/C mutations.

Abbreviations: AA-atrial arrhythmias, AVB-atrioventricular block, HF/LVD-heart failure/left ventricular dysfunction, VA-ventricular arrhythmia, TE-thromboembolism.

Figure 1: Clinical events in patients in the cohort.

Age at which clinical events occurred (information on date of event missing in 5 patients for AVB).

Abbreviations: AA-atrial arrhythmia, AVB-atrioventricular block, HF-heart failure, LV-left ventricular, Q25-Q75-interquartile range 25%-75%, TE-thromboembolism, VA-sustained ventricular arrhythmia

Figure 2: Prevalence of clinical events at first clinical contact and at last follow up.

Panel A shows the prevalence of clinical events at first clinical contact (blue bars) and at last follow up (red bars) as a proportion of total patients (n=122) in the study cohort. Numbers in brackets below represent number of patients with the clinical event. Panel B further characterizes the prevalence of arrhythmia events. Note information for AVB missing for 5 patients. Patients may have experienced more than one subtype of atrial or ventricular arrhythmia (see Supplemental Figure 1, 2). Panel C is a Kaplan-Meier curve for new clinical events after exclusion of patients who presented with that particular clinical event. Patients with HF/LVD at presentation were excluded from the new end stage HF event curve.

Abbreviations: AF-atrial fibrillation, AVB-atrioventricular block, HF -heart failure, LV-left ventricular, VF-ventricular fibrillation, VT-ventricular tachycardia.

Figure 3: Arrhythmia device implantation.

Summary of devices implanted immediately after presentation (left) and at the end of follow up (right).

Abbreviations: CRT-D- cardiac resynchronization therapy defibrillator, ICD- implanted defibrillator.

Figures

Figure 1

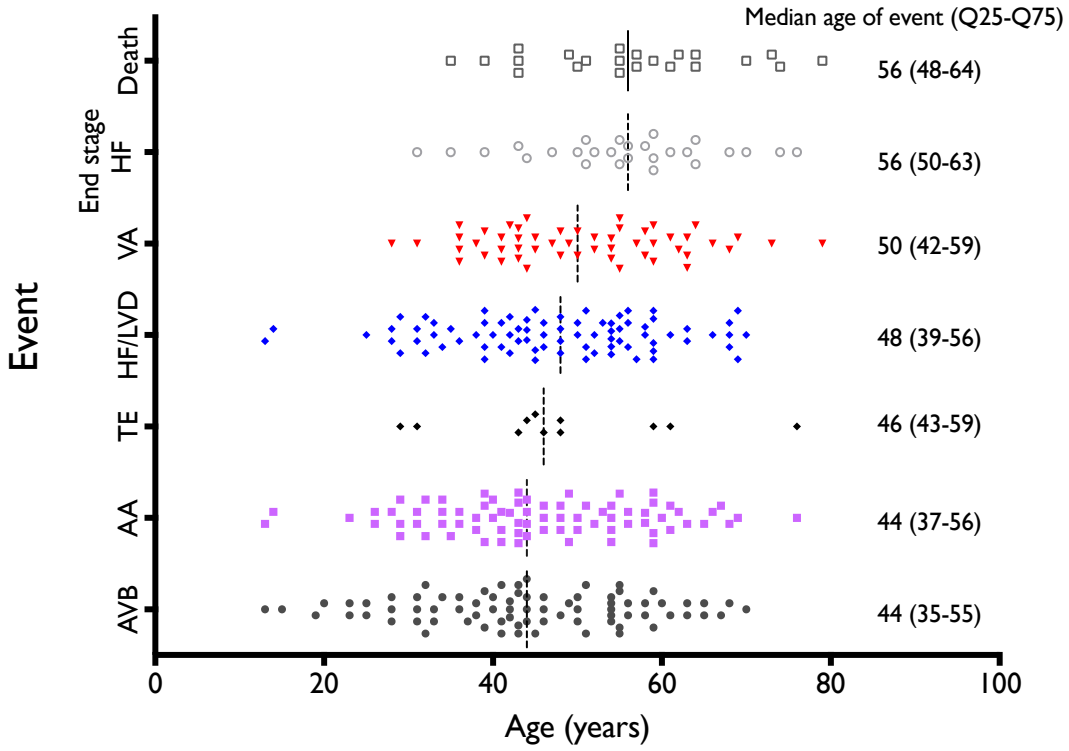
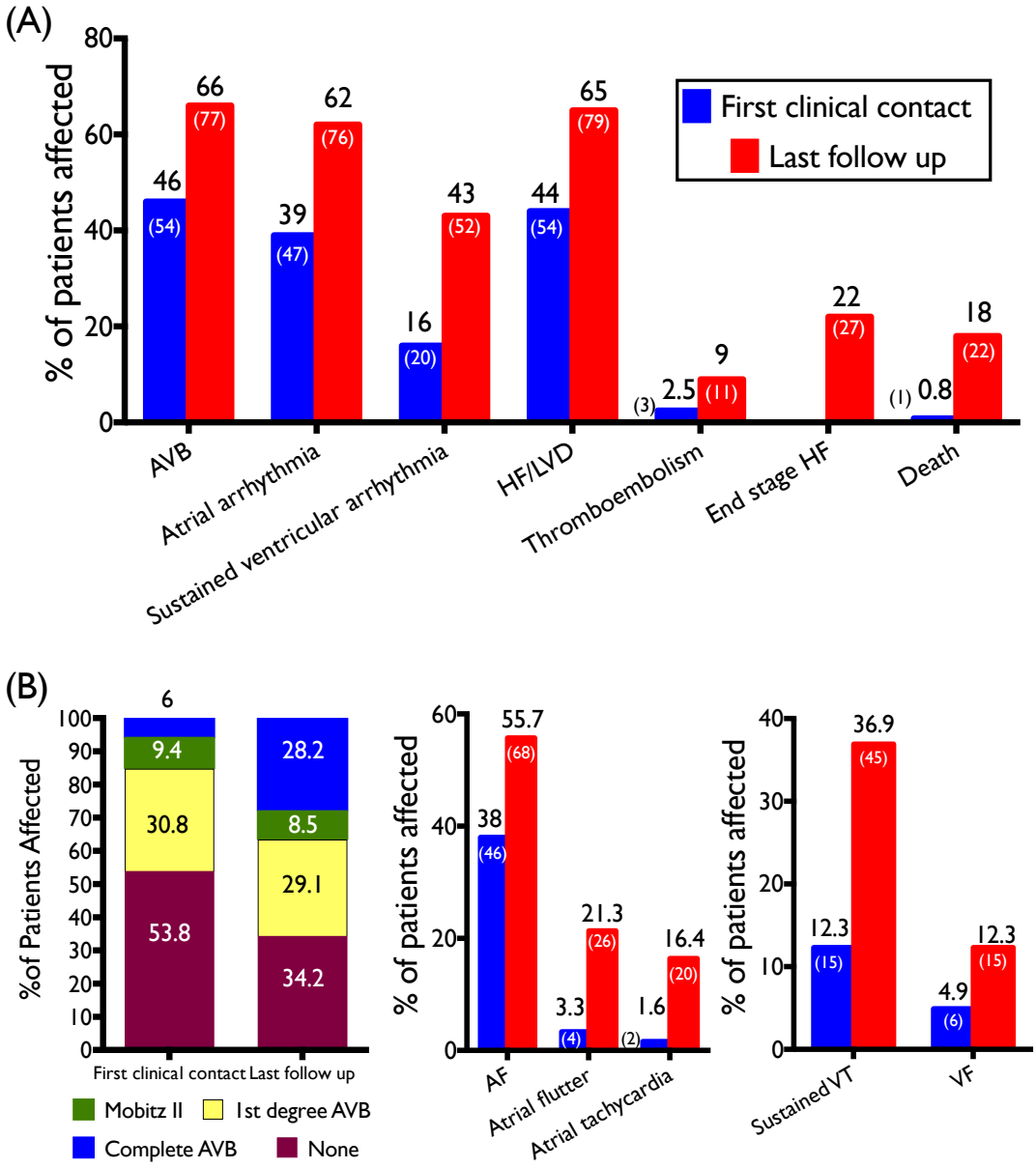
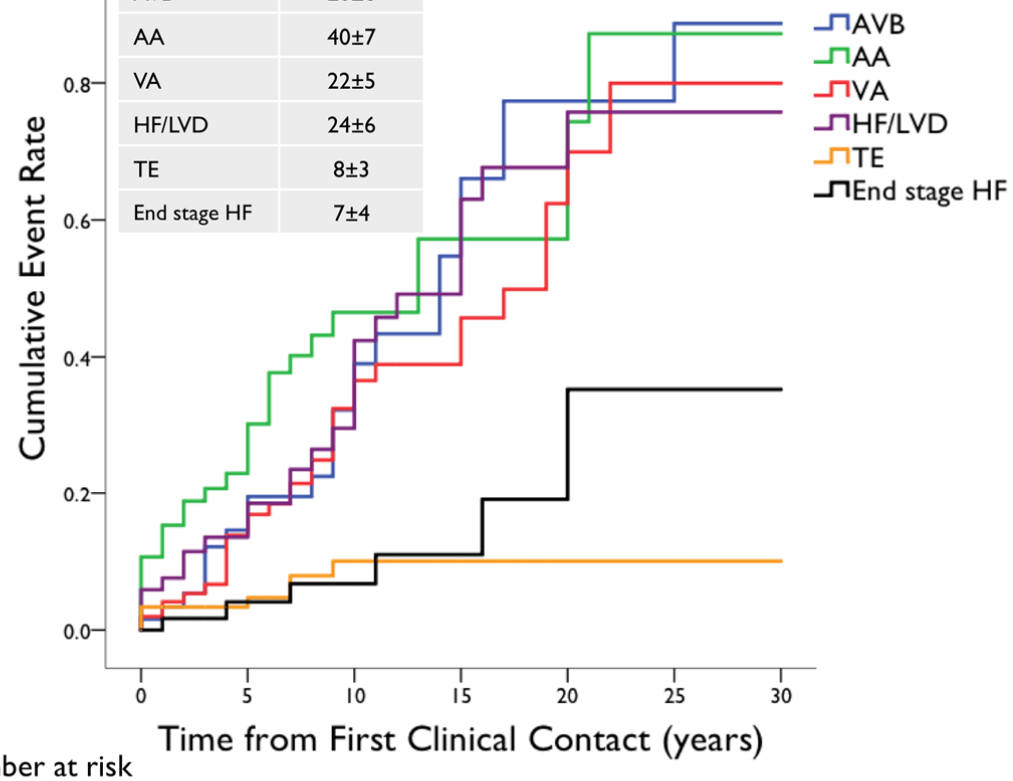


Figure 2


(A)
% of patients affected
First clinical contact
Last follow up
AVB
Atrial arrhythmia
Sustained ventricular arrhythmia
HF/LVD
Thromboembolism
End stage HF
Death
(B)
%of Patients Affected
First clinical contact
Last follow up
Mobitz II
1st degree AVB
Complete AVB
None
% of patients affected
AF
Atrial flutter
Atrial tachycardia
% of patients affected
Sustained VT
VF

(C)

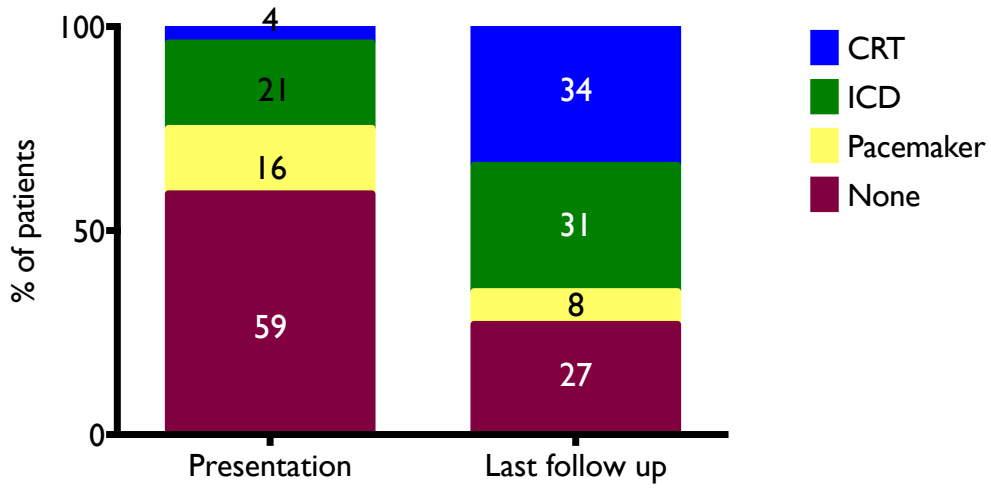
Event	Estimate at 7 years (%)
AVB	20±6
AA	40±7
VA	22±5
HF/LVD	24±6
TE	8±3
End stage HF	7±4



Number at risk

AVB	68	32	14	6	2	1	0
AA	75	28	11	8	2	2	0
VA	102	54	27	16	3	1	0
HF/LVD	68	32	17	8	3	2	0
TE	119	64	31	16	4	2	0
End stage HF	68	37	22	11	4	2	0

Figure 3


100
50
0
% of patients
4
21
16
59
34
31
8
27
Presentation
Last follow up
CRT
ICD
Pacemaker
None

Table

Table 1: Baseline characteristics

	n=122
Number of families (median number of members/family; range of members/family)	87 (1; 1-10)
Number of probands/relatives	87/35
Asymptomatic relatives (families)	18 (9 families)
Symptomatic relatives (families)	17 (12 families)
Age at first clinical contact, years, mean ± SD, (range)	41±14 (13-71)
Female, n (%)	52 (43)
Time from first clinical contact to gene diagnosis, years, median (Q25-Q75)	3 (0-9)
Type of mutation, n (%)	
Missense	69 (58)
Non-missense	51 (42)
LVEF at first clinical contact, %, mean±SD	53±14
% of patients with LVEF >50% (%)	53
Left ventricular end diastolic diameter at first clinical contact, mm, mean±SD	52±9
Neuromuscular manifestations, n (%)	18 (15)
Emery-Dreifuss muscular dystrophy	10
Limb-Girdle muscular dystrophy	6
Unclassified	2
Follow up duration, years, median (Q25-Q75)	7 (3-12)

Abbreviations: LVEF-left ventricular ejection fraction, n-number, Q25-Q75- interquartile range 25%-75%, SD-standard deviation

Table 2

Demographic features and subsequent clinical events in patients based on mode of presentation. Note patients could be represented more than once or not at all.

	AVB on presentation (n=54)	**AA on presentation (n=47)**	**HF on presentation (n=54)**
Age at first clinical contact, mean ± SD, years	43 ± 14	44 ± 12	45 ± 13
Female gender (%)	43	49	24
LVEF at first clinical contact, mean ± SD, %	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 mortality by last follow up (%)	24	30	43

Abbreviations as per text.

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

Date:
2016-11-29

Citation:
Kumar, S., Baldinger, S. H., Gandjbakhch, E., Maury, P., Sellal, J. -M., Androulakis, A. F. A., Waintraub, X., Charron, P., Rollin, A., Richard, P., Stevenson, W. G., Macintyre, C. J., Ho, C. Y., Thompson, T., Vohra, J. K., Kalman, J. M., Zeppenfeld, K., Sacher, F., Tedrow, U. B. & Lakdawala, N. K. (2016). Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 68 (21), pp.2299-2307. https://doi.org/10.1016/j.jacc.2016.08.058.