

openheart Timing of pacemaker and ICD implantation in *LMNA* mutation carriers

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ABSTRACT

Aims *LMNA*-cardiomyopathy is often associated with pathology in the cardiac conduction system necessitating device implantations. The aim was to study the timing and types of device implantations and need for re-implantations in *LMNA* mutation carriers.

Methods We studied the hospital records of 60 *LMNA* mutation carriers concerning device implantations and re-implantations and their indications. Data were collected until April 2019.

Results The median follow-up time from the first ECG recording to the last clinical follow-up, transplantation, or death was 7.7 (IQR=9.1) years. Altogether 61.7% (n=37) of the *LMNA* mutation carriers received a pacemaker or an implantable cardioverter defibrillator (ICD), and of them 27.0% (n=10) needed a device upgrade. Notably, in some patients the upgrade took place very soon after the first implantation. The first device was implanted at an average age of 47.9 years (SD=9.5), whereas the upgrade took place at an average age of 50.3 years (SD=8.1). Most upgrades were ICD implantations. Male patients underwent device upgrade more often and at a younger age than women. By the end of follow-up, 35.0% (n=21) of the patients fulfilled echocardiographic criteria for dilated cardiomyopathy, and 90.5% of them (n=19) needed pacemaker implantation.

Conclusion Most *LMNA* mutation carriers underwent pacemaker implantation in this study. Due to the progressive nature of *LMNA*-cardiomyopathy, device upgrades are quite common. An ICD should be considered when the initial device implantation is planned in an *LMNA* mutation carrier.

INTRODUCTION

LMNA mutations cause a variety of phenotypes such as lipodystrophy, muscular disease, neuropathy, progeria and cardiomyopathy.¹ Cardiomyopathy caused by *LMNA* mutations, or *LMNA*-cardiomyopathy, is typically inherited in an autosomal dominant manner.² The cardiac phenotype typically first manifests as disturbances in the electrical system in early adulthood.³ An even earlier clinical abnormality seen in cardiomyopathy is an elevated level of high sensitivity troponin T.⁴ Characteristic findings include progressive atrioventricular block (AVB), and both atrial and ventricular arrhythmias.⁵ The most typical

Key questions

What is already known about this subject?

- ▶ *LMNA*-cardiomyopathy patients are at high risk for atrioventricular block, atrial and ventricular arrhythmias, and often need electrical pacing.

What does this study add?

- ▶ Due to the progressive nature of *LMNA*-cardiomyopathy, device upgrades are often indicated, sometimes soon after the initial implantation. Nearly all *LMNA* mutation carriers with dilated cardiomyopathy eventually need a pacemaker.

How might this impact on clinical practice?

- ▶ Choosing an implantable cardioverter defibrillator at the initial device implantation needs to be considered in *LMNA* mutation carriers.

macroscopic cardiomyopathy phenotype is dilated cardiomyopathy (DCM) with mainly mild dilatation of the left ventricle, although the ensuing heart failure can be severe.^{3,6} A more recently described rare phenotype is right predominant cardiomyopathy resembling arrhythmogenic right ventricular cardiomyopathy.^{7,8} Cardiac magnetic resonance studies of *LMNA* mutation carriers have shown a localisation of late gadolinium enhancement in the interventricular septum, while a similar scarring pattern was described in autopsy studies.^{9,10} Furthermore, a multi-centre study of *LMNA* mutation carriers with drug-refractory ventricular arrhythmias found that these arrhythmias typically originate from the basal septal area.¹¹ We have previously introduced an ECG entity, septal remodelling, as a simple and sensitive tool to detect pathology in the septal region in *LMNA* mutation carriers.¹²

Considering the range of electrical disturbances seen in *LMNA*-cardiomyopathy, and the progressive nature of the disease, it is not always apparent what type of cardiac pacing is appropriate, if an implantable cardioverter defibrillator (ICD) is indicated, and when the device should be upgraded. Given the increased risk of ventricular arrhythmias in



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Table 1 The *LMNA* variants, their prevalence, and the prevalence of pacemakers among the variant carriers

<i>LMNA</i> variant	Carriers (n=60)	Patients with pacemakers (n=37)
c.1086delT, p.(Leu363Trpfs*117)	6	6
c.1380G>C, p.(Glu460Asp)	12	5
c.1442dupA, p.(Tyr481*)	1	1
c.1493delG, p.(Ala499Leufs)	1	1
c.1517A>C, p.(His506Pro)	2	1
c.394G>C, p.(Ala132Pro)	4	2
c.427T>C, p.(Ser143Pro)	19	13
c.481G>A, p.(Glu161Lys)	1	1
c.497G>C, p.(Arg166Pro)	1	1
c.568C>T, p.(Arg190Trp)	6	3
c.710T>C, p.(Phe237Ser)	7	3

cardiomyopathy-causing *LMNA* mutation carriers, the European Society of Cardiology guidelines recommend considering more liberal indications than usual for ICD implantation in *LMNA* mutation carriers with additional risk factors: reduced left ventricular ejection fraction (LVEF) of $\leq 45\%$, AVB, male sex or non-missense mutations.^{13 14} It has also been suggested that when an *LMNA* mutation carrier needs a pacemaker, an ICD should be chosen. Similarly, when cardiac resynchronisation therapy (CRT) is appropriate, a CRT-D device has been proposed.⁵

The aim of this study was to review the timing and type of device implantations and need for re-implantations in a cohort of *LMNA* mutation carriers.

METHODS

This is a retrospective study based on available hospital charts. We included 60 Finnish *LMNA* mutation carriers (31 men and 29 women) identified in clinical practice or in previous studies.^{15 16} Data were collected until April 2019. The variants are listed in table 1. The most common variant was the Finnish founder mutation c.427T>C, p.(Ser143Pro).¹⁵

Table 2 The mean age at the time of the first (ECG 1) and last (ECG 2) available ECG recordings and the respective median PR intervals and QRS complex durations in ECG

	Mean age	SD	Median PR (ms)	Median QRS (ms)
ECG 1	39.4 (n=57)	12.3	200 (IQR=107) (n=43)	96 (IQR=17) (n=37)
ECG 2	45.7 (n=37)	12.3	226 (IQR=120) (n=31)	100 (IQR=25) (n=32)

PR, PR interval in ECG; QRS, QRS complex duration in ECG.

The diagnostic criteria used for DCM were left ventricular end-diastolic diameter $>27\text{ mm/m}^2$ and LVEF $<45\%$.¹⁷ Favourable response to CRT was defined as LVEF improvement of 10 units or more. More moderate improvement in LVEF, reduction in the levels of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (ProBNP), and/or QRS complex shortening in ECG were considered signs of possibly favourable response to CRT treatment.

The Shapiro-Wilk test was used to assess whether the data were normally distributed. Normally distributed continuous variables were given as mean and SD and non-parametric as median and IQR. Independent samples t-test was used to compare the means of normally distributed parameters. Frequencies were compared with the χ^2 test when appropriate, and otherwise with the Fisher's exact test. SPSS V.25 and V.27 were used for data analysis.

RESULTS

The median follow-up time from the first ECG recording to the last clinical follow-up, transplantation or death was 7.7 years (IQR=9.1 years). Of all the patients, 35.0% (n=21) fulfilled the diagnostic criteria set for DCM at some point during follow-up. Coronary artery disease was excluded using angiography or coronary CT in 41.7% of the patients; the indication for the procedure was cardiomyopathy, except in one patient with known *LMNA* mutation, where the indication was ventricular tachycardia (VT). Heart transplantation was required in 16.7% (n=10) of the patients, and seven individuals (11.7%) died during follow-up, all of them due to cardiomyopathy.

The mean patient age at the time of the first available ECG recording was 39.4 years, while the mean age at the time of the last ECG recording was 45.7 years. Table 2 shows the respective PR intervals and QRS complex durations in ECG. Table 3 shows the highest level of AVB and the mean age of the study population at the time of the detection of the conduction disorder. Figure 1A,B shows the minimum heart rate during one or more Holter monitorings in men and women prior to pacemaker implantation. Figure 1C,D shows the corresponding values in individuals, who did not have a pacemaker implanted during the follow-up. In 75.0% of the men (6/8) and 84.6% (11/13) of the women, the pacemaker implantation took place within 1 year of the preceding Holter monitoring. One female individual received a pacemaker nearly a decade after the preceding Holter recording, but the device was a CRT-D, which was implanted due to reduced LVEF. One female and two male individuals received the devices within 2 years of the preceding Holter monitoring.

Timing and type of devices

The majority of the patients, 61.7% (n=37), received a pacemaker or an ICD at some point of the follow-up. At the time of the device implantation, 11 individuals

Table 3 The presence and detection ages of AVBs

Highest AVB detected	Frequency	Per cent	Mean age, years (n)	Min age	Max age	SD
1st degree	17	28.3	44.4 (n=26)*	21.4	65.5	11.0
2nd degree	14	23.3	45.7 (n=15)*	30.5	65.6	10.7
Mobitz 1	10					
Mobitz 2	3					
Both	1					
3rd degree	5	8.3	49.1 (n=5)	41.2	61.6	8.3
Any AVB	36	60.0	44.0 (n=36)	21.4	65.5	10.6
No AVB	24	40.0	39.7† (n=24)	20.7	70.5	15.0

*Includes individuals with an initial lower level AVB followed by a higher-level block.

†At last follow-up.

AVB, atrioventricular block.

(29.7%) fulfilled the echocardiographic DCM criteria, whereas 26 individuals (70.3%) did not. On the other hand, of the 21 patients who fulfilled the DCM criteria by the end of the follow-up, 19 (90.5%) underwent device implantation at some point. The initial pacemaker types are listed in table 4. Of the patients with pacemakers, 27.0% (n=10) needed a device upgrade. The upgrades tended to be more common in men (38.9%, 7/18) than in women (15.8%, 3/19), but the difference was not statistically significant. One upgrade was performed at

the time of elective pacemaker generator replacement. Of the 13 individuals with the Ser143Pro *LMNA* variant who received a device, no one required a device upgrade. A flow chart of pacemaker implantations and upgrades is given in figure 2. The device upgrade types are listed in table 5, and the clinical characteristics of patients who did or did not undergo a device update are shown in table 6. The mean interval from the first pacemaker implantation to the upgrade was 5.1 years (SD=5.1 years), but ranged from less than a month to 14.8 years. Of note, in five cases

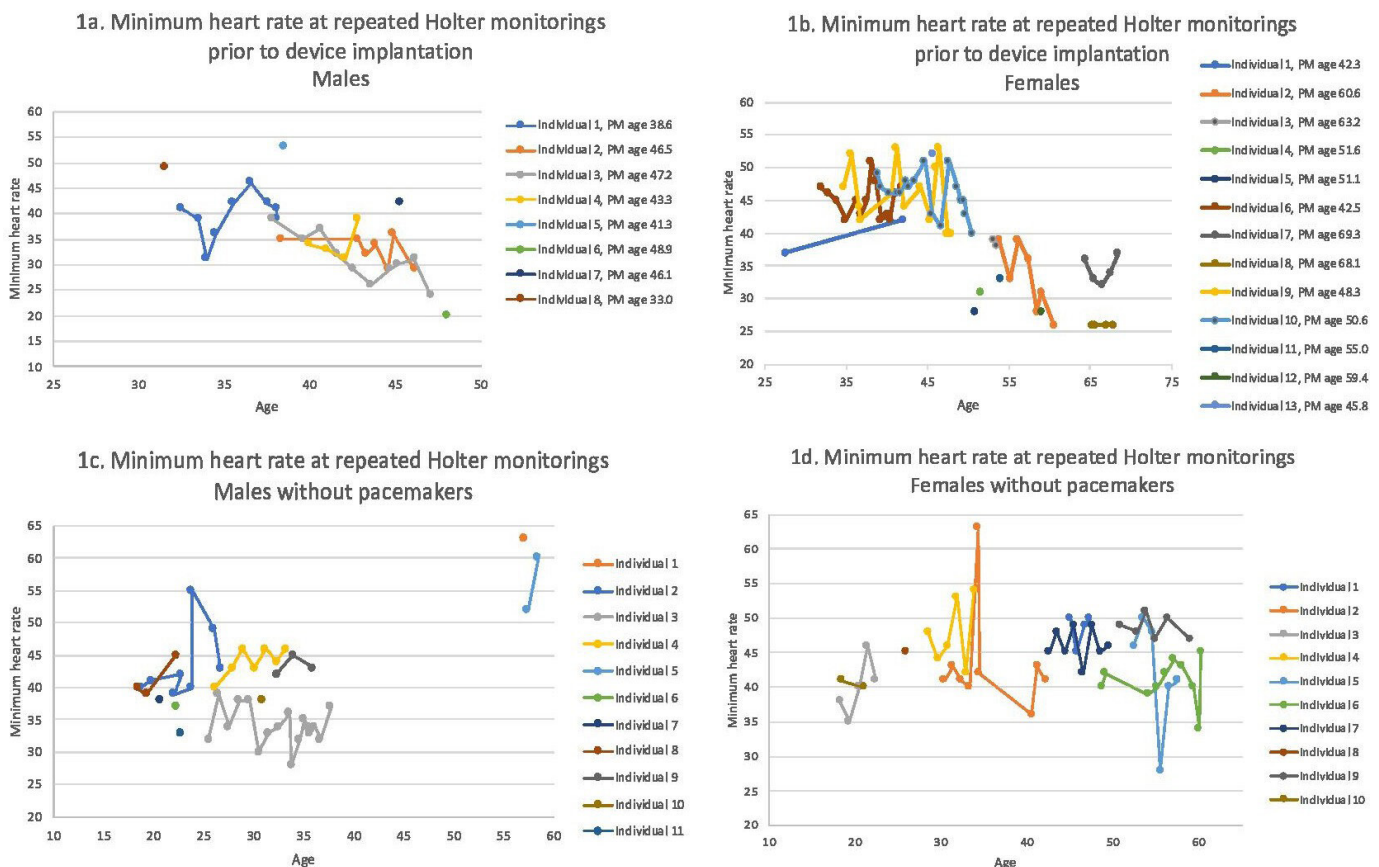
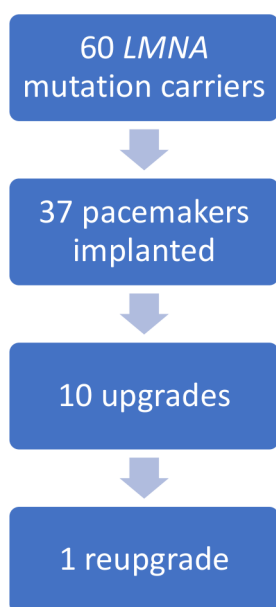


Figure 1 (A, B) The lowest heart rate at single or repeated Holter monitorings in men and women prior to pacemaker implantation. Age at pacemaker implantation is given. (C, D) The lowest heart rate at single or repeated Holter monitorings in men and women who did not have a pacemaker implanted by the end of the data collection. PM, pacemaker.

Table 4 The initial pacemaker types

AAI	1
VI	8
DDD	14
VI+ICD	6
DDD+ICD	3
CRT-P	2
CRT-D	3

the upgrade took place less than 2 years after the initial pacemaker implantation. The first device was implanted at an average age of 47.9 years (SD=9.5), whereas the upgrade took place at an average age of 50.3 years (SD=8.1). One individual received a second upgrade at age 59.2 years. By the end of data collection, 58.1% (18/31) of the men, and 65.5% (19/29) of the women (the difference was not statistically significant) had undergone device implantation. Men received the first device almost 10 years earlier (mean age 42.9 years, SD=8.1) than women (mean age 52.6 years, SD=8.4, $p=0.001$). Regarding device upgrade, the mean age for men was 48.3 (SD 9.1), and for women, 54.8 years (SD=2.5, statistically non-significant difference). Altogether 18 individuals received an ICD, 12 as the first device and 6 as an upgrade. Three of the ICDs were implanted after cardiac resuscitation, and one due to sustained VT as secondary prophylaxis, seven as primary prophylaxis, but with documented NSVT (non-sustained ventricular tachycardia), and the remaining seven as primary prophylaxis without known previous VT. At the time of the ICD implantation, 12 (66.7%) individuals fulfilled the echocardiographic DCM criteria whereas 6 (33.3%) individuals did not. Figure 3 shows the incidences of first recordings of

**Figure 2** A flow chart of pacemaker implantations and upgrades.**Table 5** Pacemaker upgrades

First PM type	Second PM type	N=10	Upgrade indication
AAI	DDD	1	DAV 3, syncope
VI	VI-ICD	2	Sustained VT, resuscitation*
VI	DDD-ICD	1	Heart failure
DDD	DDD-ICD	1	Presyncope and documented NSVT
DDD	CRT-P	1	Generator replacement, dyssynchrony and heart failure
DDD	CRT-D	2	Heart failure (n=2), symptomatic NSVT (n=1)
VI-ICD	DDD-ICD	1	Symptomatic bradycardia
VI-ICD	CRT-D	1	Heart failure

*Additionally, one individual received a second upgrade later from VI-ICD to CRT-D.

CRT, cardiac resynchronisation therapy; DAV, distal atrioventricular block; ICD, implantable cardioverter defibrillator; NSVT, non-sustained ventricular tachycardia; PM, pacemaker.

AVB, atrial fibrillation or flutter, and the timing of device implantation.

CRT response

Ten patients received a CRT-P (n=3) or a CRT-D (n=7) pacemaker, five as their initial device and five as an upgrade (see tables 4 and 5). The mean CRT implantation age was 51.6 years (SD=10.0). Seven of these patients (77.8%) had a favourable response to the device, and two were non-responders. The CRT responses are listed in table 7. Two individuals were followed up elsewhere, and data concerning CRT response was available from only one of them.

Table 6 Comparison of clinical characteristics of patients having or having not having undergone a pacemaker upgrade

	PM upgrade (n=10)	No PM upgrade (n=27)	Statistical significance
Males	7 (70%)	11 (40.7%)	ns (males vs females)
Ser143Pro	0 (0%)	13 (76.5%)	$p=0.007$
Transplantation	1 (10%)	6 (22.2%)	ns
Afib or flutter	9 (90%)	21 (77.8%)	ns
DCM by the end of follow-up	7 (70%)	12 (44.4%)	ns
Ventricular arrhythmia requiring treatment	4 (40%)	6 (22.2%)	ns

Afib, atrial fibrillation; DCM, dilated cardiomyopathy; PM, pacemaker.

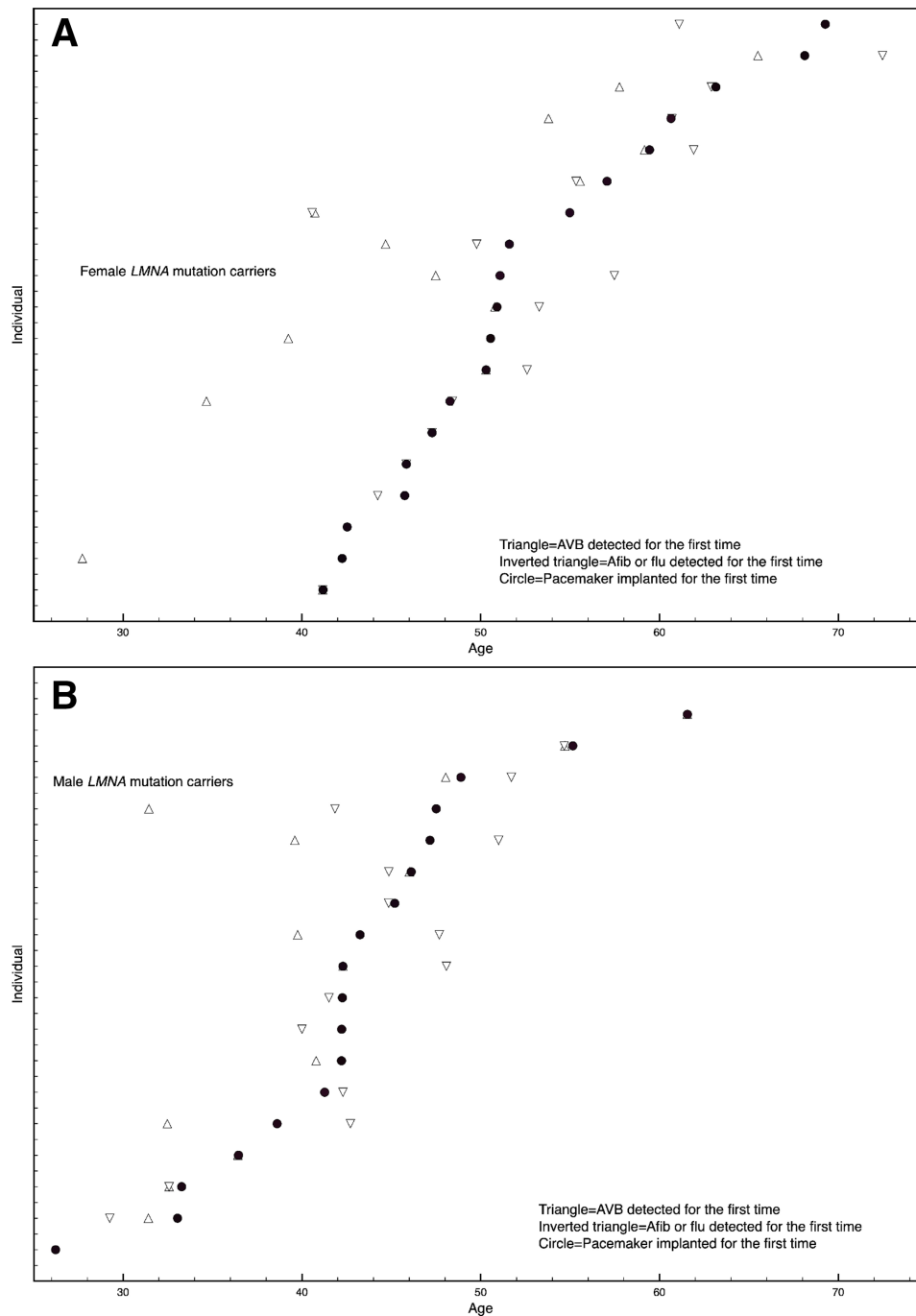


Figure 3 (A) Women (n=19) and (B) men (n=18). The incidence of a first recording of atrioventricular block (AVB), atrial fibrillation (Afib)/flutter (flu) and device implantation. Each line represents an *LMNA* mutation carrier. Each mutation carrier, who received a device is shown.

Pacemaker complications

Device-related complications occurred in 7 (18.9%) of the 37 individuals, 26.3% (5/19) of the women and 11.1% (2/18) of the men (statistically non-significant difference). As the overall number of device implantations, including the upgrades, was 48, the overall complication rate in all of the implantations was 14.6%. Five of the complications took place after the first or only pacemaker implantation and two after an upgrade. The complication rates were 13.5% for first implantations and 18.2% for upgrades. The device-related complications

included one infection leading to pacemaker removal and re-implantation, two cases of thrombosis requiring anticoagulation, one myocardial perforation, one pacemaker pocket haematoma and two cases of broken pacemaker leads leading to lead replacement.

Ventricular arrhythmias

During follow-up 16.7% (n=10) of the *LMNA* mutation carriers had ventricular arrhythmias requiring treatment; of those 33.3% (n=3) had ventricular fibrillation and 66.7% (n=7) had VT. Amiodarone treatment was

Table 7 CRT responses

Individual (M/F)	QRS shortening	LVEF improvement	Biomarker reduction (BNP or ProBNP)	Overall response
F	no	yes	yes	Favourable
M	no	Slight improvement	NA	Possibly favourable
M	NA	NA	NA	Non-responder*
F	yes	NA	NA	Possibly favourable†
F	NA	NA	NA	NA
M	yes	no	no	Possibly favourable
M	NA	yes	yes	Favourable
M	yes	yes	no	Favourable
M	no	yes	no	Favourable
F	no	no	no	Non-responder

*Patient died 3 years after the CRT implantation.

†Subjectively favourable, later follow-up elsewhere.

BNP, B-type natriuretic peptide; CRT, cardiac resynchronisation therapy; LVEF, left ventricular ejection fraction; QRS, QRS complex duration.

reported in 15.0% (n=9) of the mutation carriers, in four patients to treat ventricular arrhythmias and in six for atrial fibrillation; one patient was initially treated with amiodarone for atrial fibrillation and later on for VT.

DISCUSSION

This is a descriptive, retrospective study dealing with the need for, timing and type of pacemaker implantations in *LMNA* mutation carriers. We found that the majority (61.7%) of the 60 studied patients needed pacemaker implantation. In addition, a quarter of the patients with devices needed a device upgrade, which sometimes occurred quite soon after the initial implantation. Most upgrades were devices with a defibrillator, thus supporting the view that when a device is needed in an *LMNA* mutation carrier, the need for an ICD should always be considered.⁵ This strategy has previously been studied in a prospective manner with encouraging results.¹⁸ A significant proportion of the pacemaker implantations in this study took place before the current recommendations concerning ICD implantation in *LMNA* mutation carriers were available. This probably explains to some extent the extensive need of device upgrades that was seen.

Device upgrade tended to be more common in men, and patient age at the first device implantation was almost 10 years lower in men than in women. This is in line with the previously identified higher risk for malignant ventricular arrhythmias in men.¹⁴ At the time of device implantation, a third of the patients fulfilled the diagnostic criteria for DCM. On the other hand, 90.5% of the patients who fulfilled the DCM criteria at any point during follow-up underwent device implantation. Most of the ICD implantations were primary prophylactic, and at the time of ICD implantation two-thirds of the patients fulfilled the DCM criteria. All deaths during follow-up were related to cardiomyopathy, but none due to sudden cardiac death.

The overall complication rate related to pacemakers—18.9% of the patients with devices and 14.6% of all implantations—was rather high, compared with the rates reported in other studies. A nationwide Danish study reported complications in 9.5% of their patients.¹⁹ The same study reported a larger complication risk in females, and a larger complication rate concerning device upgrades. Similar tendencies were seen in the present study.

Our observations regarding CRT responses are not fully comprehensive, because this is a retrospective study based on hospital records, not designed to assess CRT responses. Of patients with available follow-up data after CRT implantation, 77.8% showed signs of a favourable response. This is fairly well in line with the response rates reported in CRT studies. However, it should be acknowledged that the reported response rates vary with the criteria used to assess the response.²⁰ The relatively small number of patients as well as the retrospective setting are limitations to this study particularly concerning our observations regarding CRT responses.

Typically, the first indication for device implantation in this population of *LMNA* mutation carriers was progressive bradycardia, but as shown in repeated Holter recordings both in individuals requiring a pacemaker implantation and those who had not yet needed one, the progression is sometimes very slow. The appropriate timing of pacemaker implantation is therefore still a challenge and repeated monitoring of individuals carrying disease-causing *LMNA* mutations is needed. As the majority of device upgrades involved ICDs, it is important to assess the need for an ICD when device implantation is planned for an *LMNA* mutation carrier.

Contributors LHO collected the data and participated in data analysis and interpretation, and manuscript writing. KN participated in data interpretation and manuscript writing. HP participated in planning the study, data interpretation and manuscript writing. SW participated in patient recruitment and data

collection. TH participated in planning the study, data interpretation and manuscript writing.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study patients gave written informed consent, and the study was approved by the Ethics Committee of the Helsinki University Central Hospital (HUS/24/2017 and HUS/60/1019). The data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study.

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