J'implante? Je n'implante pas?

La place de la cardiogénétique dans le raisonnement clinique et thérapeutique

ELECTRA & RHYTHM

18-21 MAY 2022

Golden Tulip Villa Massalia
Marseille, France

Centre Hospitalier du Pays d'Aix

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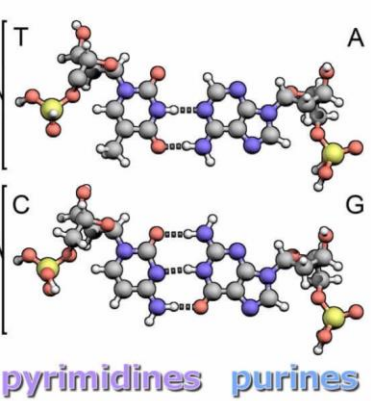
Dr DANG Duc
Praticien hospitalier

Je n’ai pas de conflit d’intérêt

Cas clinique

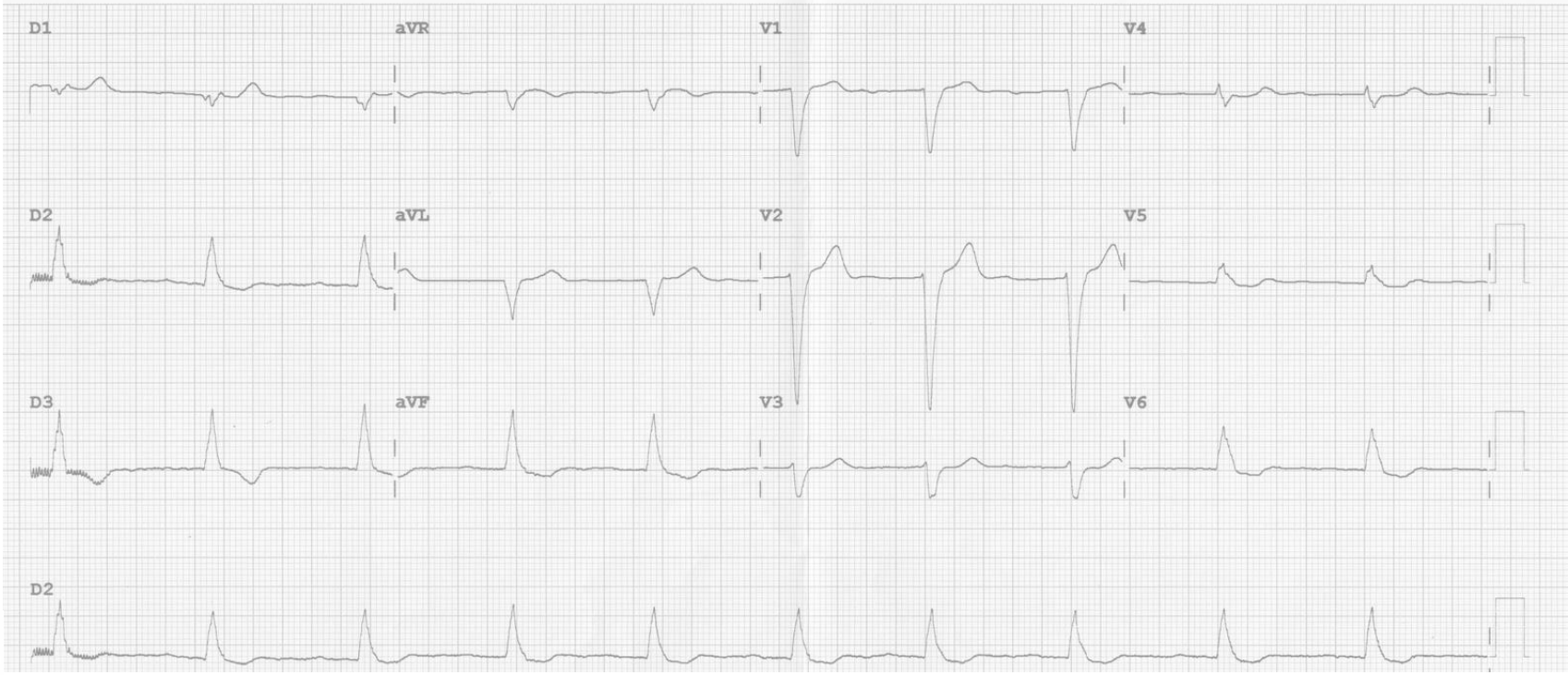
- Homme 49 ans, asymptomatique
- **ATCD médical**: ablation de FA (veines pulmonaires/ ICT)
- **ATCD familiaux**:
  - Père porteur d'un DAI en prévention primaire: CEI approprié
  - Deux apparentés du premier degré décédés de MS avant 50 ans
- **ETT** normale
- **Génétique**: mutation hétérozygote non sens LMNA



ECG

PR 289
QRSD 154
QT 444
QTc 444

--AXES--
P 0
QRS 97
T -41
12 dériv. ; position standard



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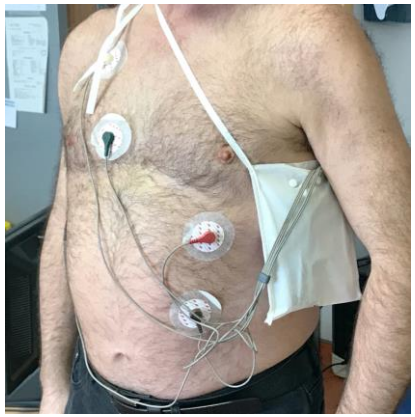
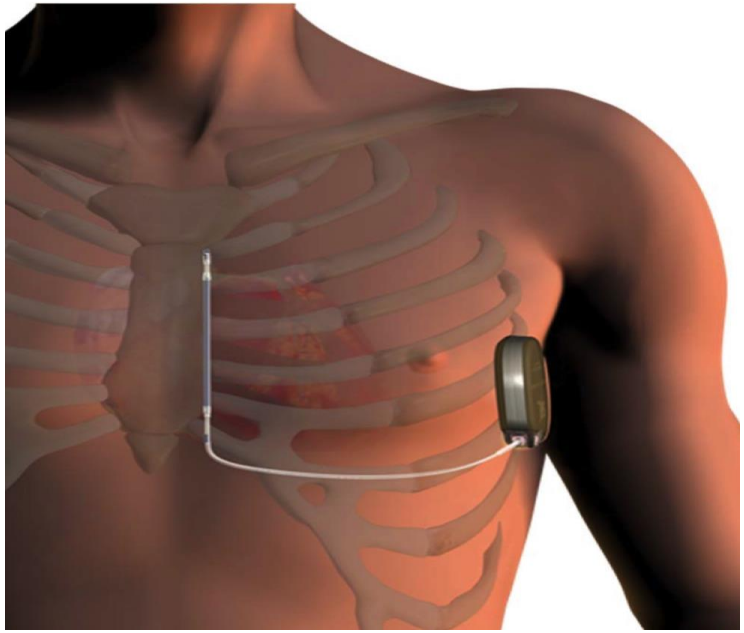
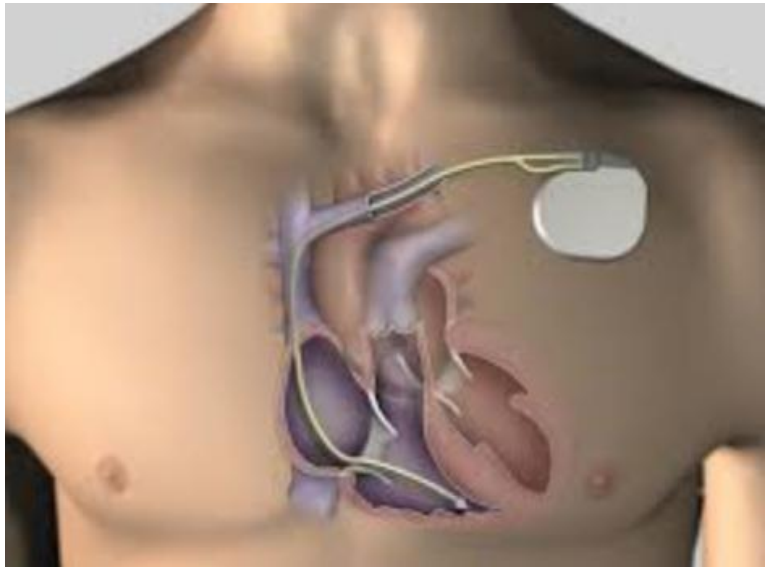


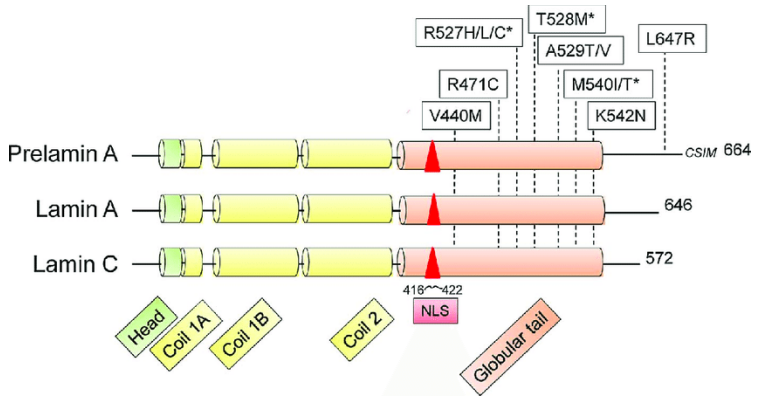




letter

Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy

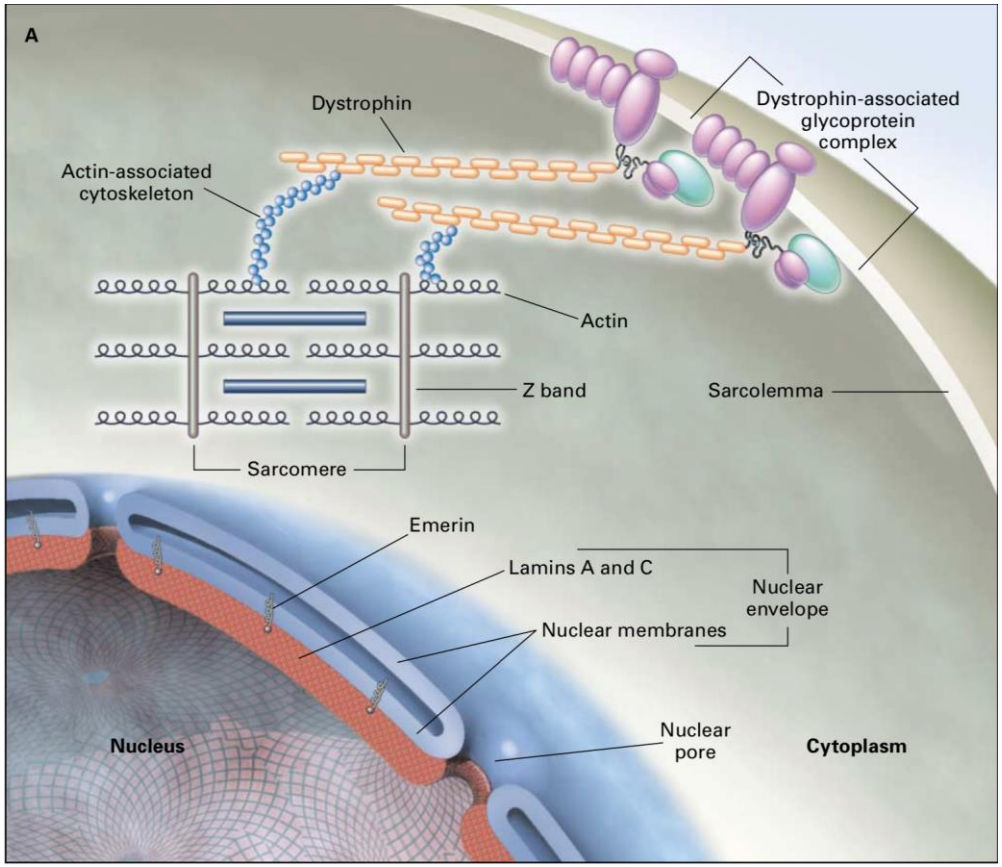
Gisèle Bonne[1], Marina Raffaele Di Barletta[1,3], Shaida Varnous[1], Henri-Marc Bécane[2], El-Hadi Hammouda[2], Luciano Merlini[4], Francesco Muntoni[5], Cheryl R. Greenberg[6], Françoise Gary[7], Jon-Andoni Urtizberea[2], Denis Duboc[2,8], Michel Fardeau[1,2], Daniela Toniolo[3] & Ketty Schwartz[1]

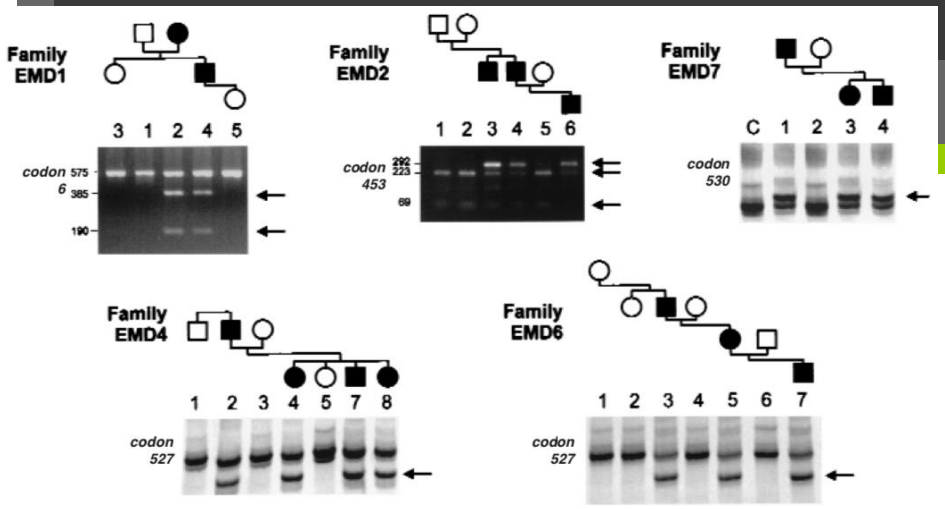


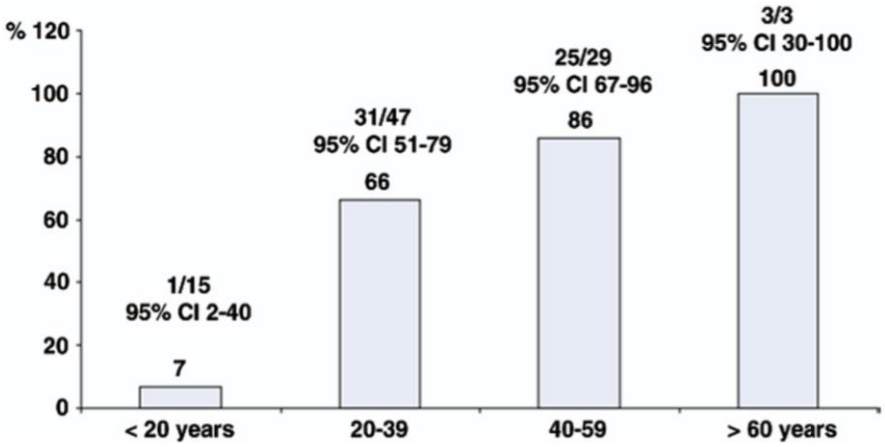
MISSENSE MUTATIONS IN THE ROD DOMAIN OF THE LAMIN A/C GENE AS CAUSES OF DILATED CARDIOMYOPATHY AND CONDUCTION-SYSTEM DISEASE

Diane Fatkin, M.D., Calum MacRae, M.D., Takeshi Sasaki, M.D., Matthew R. Wolff, M.D., Maurizio Porcu, M.D., Michael Frenneaux, M.D., John Atherton, M.B., B.S., Humberto J. Vidaillet, Jr., M.D., Serena Spudich, M.D., Umberto De Girolami, M.D., J.G. Seidman, Ph.D., and Christine E. Seidman, M.D.

N Engl J Med, 1999;341:1715–1724







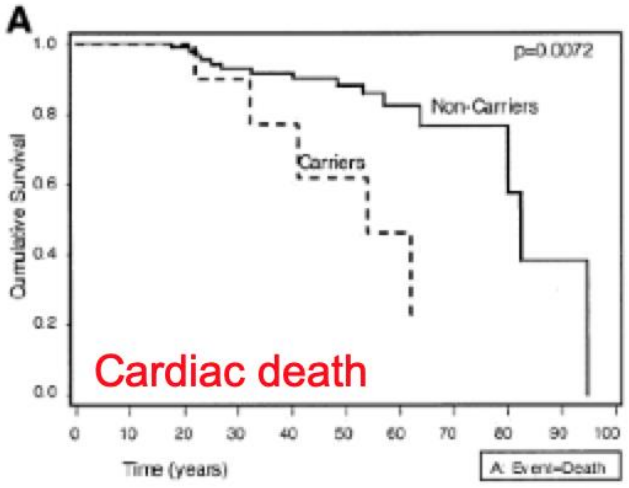
- Autosomique dominante
- Pénétrance complète

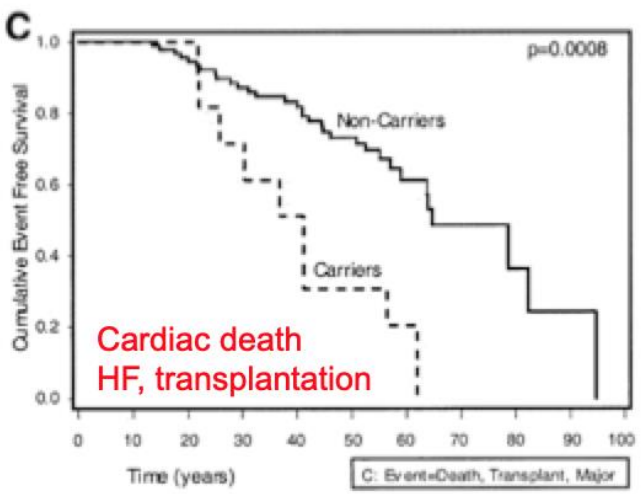
Bonne G, Di Barletta MR, Varnous S et al. Nat Genet, 1999;21:285–288.

Pasotti M, Klersy C, Pilotto A, et al. J Am Coll cardiol 2008;52:1250-1260.

Natural History of Dilated Cardiomyopathy Due to Lamin A/C Gene Mutations

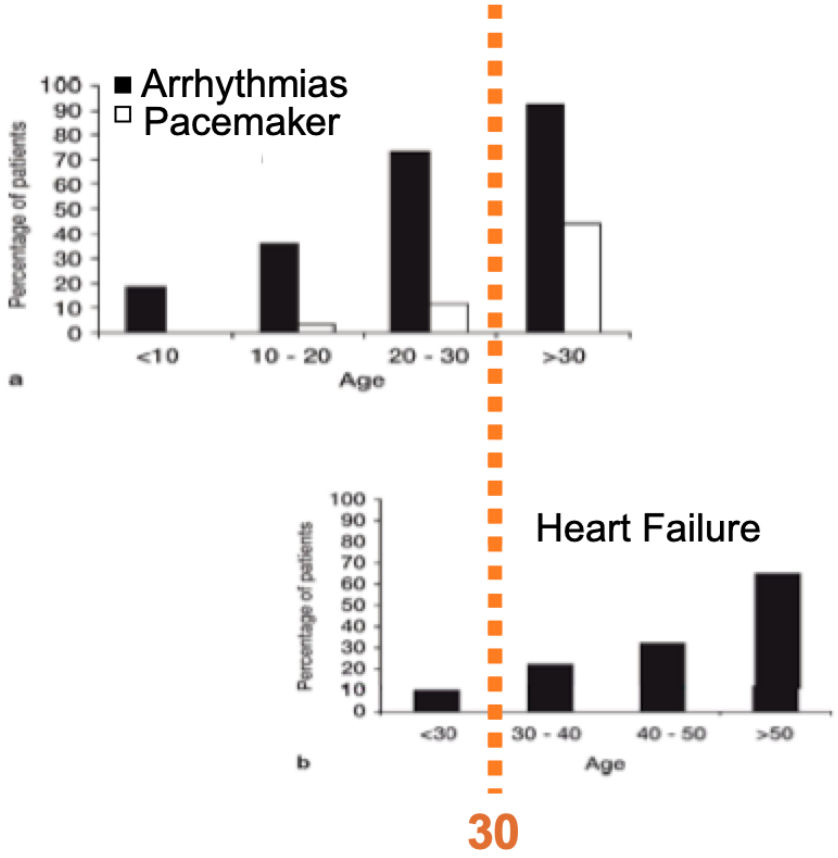
Matthew R. G. Taylor, MD,* Pamela R. Fain, PHD,*†‡ Gianfranco Sinagra, MD, FESC,§
Misi L. Robinson,‖ Alastair D. Robertson, PHD,* Elisa Carniel, MD,§ Andrea Di Lenarda, MD, FESC,§
Teresa J. Bohlmeyer, MD,* Debra A. Ferguson, MS,* Gary L. Brodsky, PHD,* Mark M. Boucek, MD,*¶
Jean Lascor, MS,¶ Andrew C. Moss, BA,* Wai-Lun P. Li, BS,*† Gary L. Stetler, PHD,†
Francesco Muntoni, MD, FRCPCH,# Michael R. Bristow, MD, PHD, FACC,*
Luisa Mestroni, MD, FACC, FESC,* Familial Dilated Cardiomyopathy Registry Research Group
Denver, Colorado; Trieste, Italy; Omaha, Nebraska; and London, United Kingdom





Taylor et al. J Am Coll Cardiol 2003;41:771-80.

La mort subite cause principale de décès chez les laminopathies



Meta-analysis

233 patients

- Death =76
- Sudden death=35 (11.7%, 46% of all deaths)
- Pacemaker recipients (84 patients)

→ **SD=16 (19%)**

van Berlo JH, de Voogt WG, van der Kooi AJ, et al. J Mol Med. 2005;83:79-83.

Primary Prevention of Sudden Death in Patients with Lamin A/C Gene Mutations

N ENGL J MED 354;2 WWW.NEJM.ORG JANUARY 12, 2006

- Primary prevention: patients with an indication for pacemaker implantation 1999 – 2004
- N=19 patients (age=41.7±13.4 years) were implanted with an ICD
- LVEF>45%

Follow-up : 33.9±21.0 months

Malignant arrhythmias: n=8 patients 42%

(6 ventricular fibrillations, 2 sustained ventricular tachycardias)

Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. N Engl J Med. 2006 ;354:209-10

Table 1 Baseline patient characteristics (n = 47)

Age (y)	38 ± 11
Sex: male	26 (55%)
Prior syncope	15 (32%)
Family history of sudden death	10 (21%)
Family history of syncope	33 (70%)
Atrial fibrillation or flutter	12 (26%)
Significant conductive disorders	21 (45%)
Nonsustained ventricular tachycardia	31 (66%)
Left ventricular ejection fraction (%)	56 ± 11
Left ventricular ejection fraction <45%	6 (13%)
Left ventricular end-diastolic diameter (mm)	53 ± 6
Left ventricular end-diastolic diameter >56 mm	13 (28%)
Medical treatment	
Beta-blockers	8 (17%)
ACE inhibitors/angiotensin receptor blockers	12 (26%)
Amiodarone	7 (15%)
Class I antiarrhythmic drugs	4 (9%)
Vitamin K antagonists	11 (23%)
Phenotype	
Isolated skeletal muscular involvement	18 (38%)
Dilated cardiomyopathy	16 (34%)
Gene mutation	
Missense mutations	18 (38%)
R377H	4
R482C	1
L530P	1
R482 [R,Q]	1
R335W	4
R377C	4
R50P	1
R249P	1
L379F	1
Non-missense mutations	29 (62%)
Nucleotide A insertion in 444	21
Q6 stop	7
IVS6-1 G ->A	1

Data are expressed as mean ± SD or as n (%).
ACE = angiotensin-converting enzyme.

N= 21 pts

No Sudden death

52% Appropriate ICD therapy

FU = 62 months

Implantable cardiac defibrillators (rather than pacemakers)

Anselme F, Moubarak G, Savoure A, Godin B, Borz B, Drouin-Garraud V, Gay A. Heart Rhythm 2013;10:1492 1498.

La stratification du risque de mort subite

European registry

Cardiology tertiary centers
n=269 patients

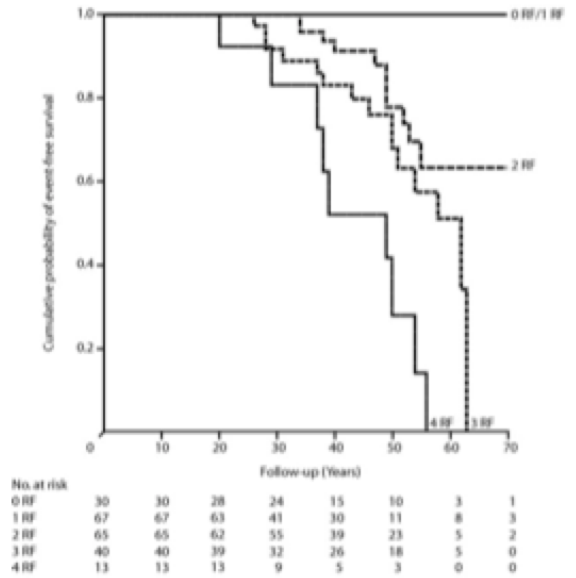
Dilated cardiomyopathy: n=89 (37%)
Muscular dystrophy: n=41/198 (21%)
Age=36 years [27-45]

Follow up = 43 months [17-101]

Malignant ventricular arrhythmia
N=48 (17% = 4.7%/year)

Multivariate analysis: 4 risk factors

(1) NSVT (2) LVEF<45%
(3) Male (4) Non missense mutation



van Rijsingen IA, Arbustini E, Elliott PM, et al. J Am Coll Cardiol. 2012;59:493-500.

Circulation

ORIGINAL RESEARCH ARTICLE

Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

BACKGROUND: An accurate estimation of the risk of life-threatening (LT) ventricular tachyarrhythmia (VTA) in patients with *LMNA* mutations is crucial to select candidates for implantable cardioverter-defibrillator

Karim Wahbi, MD, PhD
et al

Circulation. 2019;140:293-302.

Derivation cohort
France

OPALE: Nationwide Registry on Laminopathies

660 Patients diagnosed with pathogenic *LMNA* mutations between January 2000 and Nov 2016

Study population of 444 patients with adult-onset laminopathies

Validation cohort
International

Tertiary cardiology referral centers

Saint Bartholomew's Hospital (London); Brigham and Women's Hospital (Boston); University Hospital in Bern; the University Medical Centre in Leiden; the Royal Melbourne Hospital

179 Patients diagnosed with pathogenic *LMNA* mutations between 2000 and June 2017

Study population of 145 patients with adult-onset laminopathies

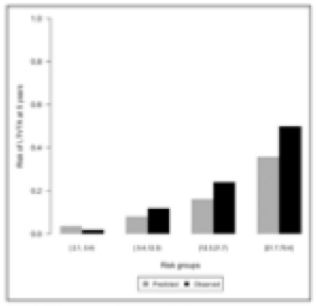
Modèle et validation du score LMNA

	Coefficients	HR [95% CI]	P-value
Male	0.47548428	1.61 [1.04-2.48]	0.031
1st degree AV block	1.023349	2.78 [1.51-5.13]	0.001
3rd degree AV block	1.16058109	3.19 [1.69-6.03]	<0.001
Non sustained VT	0.92153979	2.51 [1.59-3.98]	<0.001
Nonmissense mutation	0.50987848	1.67 [1.09-2.55]	0.019
LV ejection fraction (%)	-0.03773161	0.96 [0.95-0.98]	<0.001

$$1 - 0.8884505^{exp\,(0.51573542*male + 0.85513823*1st\ degree\ AV\ block + 1.05127326*higher\ AV\ block + 0.76692653*NSVT + 0.56318475*non\text{-}missense\ mutation - 0.01949484*LVEF\ (\%))}$$

https://lmna-risk-vta.fr

	Internal (derivation cohort)	External (validation cohort)
C-index [95%IC]	0.787 [0.74-0.834]	0.769 [0.669-0.869]
Calibration slope	0.924	0.888 [0.552-1.224]



2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Recommendations	Class[a]	Level[b]	Ref.[c]
Optimal medical therapy (ACE inhibitors, beta-blockers and MRA) is recommended in patients with DCM to reduce the risk of sudden death and progressive HF.	I	A	8
Prompt identification and treatment of arrhythmogenic factors (e.g. pro-arrhythmic drugs, hypokalaemia) and co-morbidities (e.g. thyroid disease)	I	C	8
An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B	71

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3427–3520
doi:10.1093/eurheartj/ehab364

ESC GUIDELINES

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC)

With the special contribution of the European Heart Rhythm Association (EHRA)

Recommendation for patients with LMNA gene mutations (for references, see *Supplementary Table 18*)

Recommendation	Class[a]	Level[b]
In patients with LMNA gene mutations, including Emery–Dreifuss and limb-girdle muscular dystrophies who fulfil conventional criteria for pacemaker implantation or who have prolonged PR interval with LBBB, ICD implantation with pacing capabilities should be considered if at least 1-year survival is expected.[616]	IIa	C

ICD = implantable cardioverter-defibrillator; LBBB, left bundle branch block.
[a]Class of recommendation.
[b]Level of evidence.

Au total

- FDR: sexe masculin, BAV 1, mutation non sens
- LMNA score : 24.8%
- Décision d'implanter un DAI endocavitaire simple chambre VDD en prévention primaire