Contribution of genetics for sudden death risk stratification in dilated cardiomyopathy

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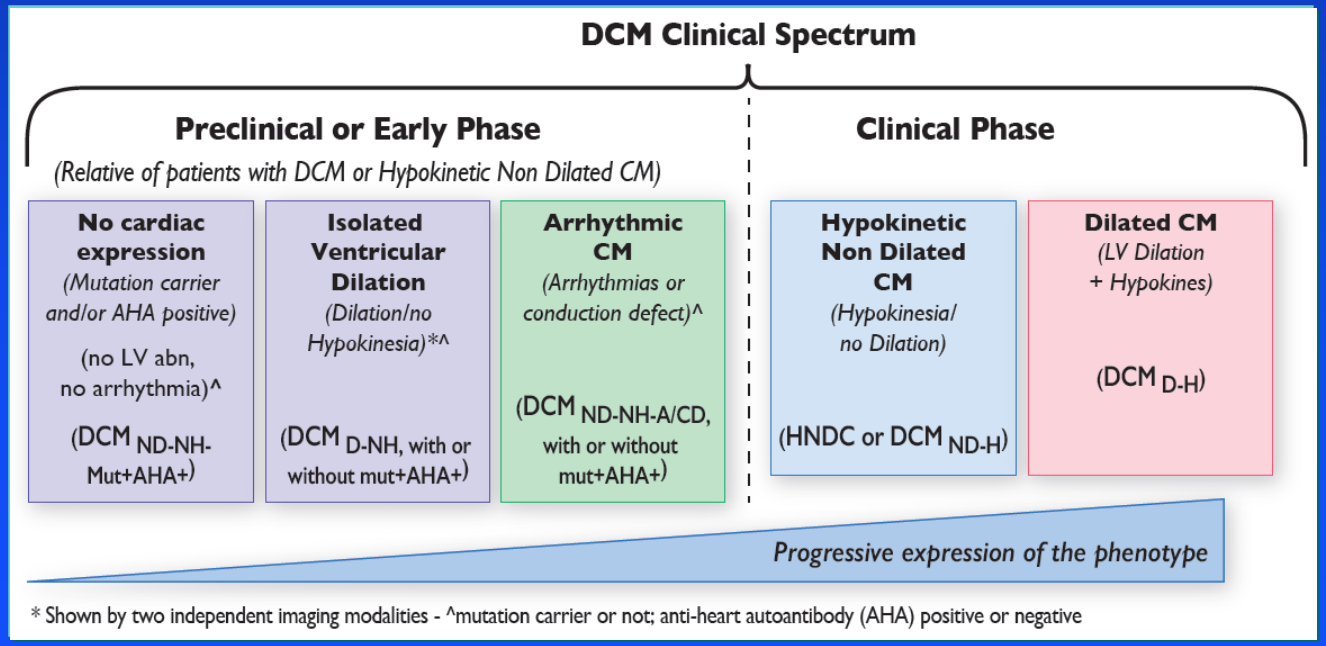
ESC REPORT

Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases

Yigal M. Pinto[1*], Perry M. Elliott[2], Eloisa Arbustini[3], Yehuda Adler[4], Aris Anastasakis[5], Michael Böhm[6], Denis Duboc[7], Juan Gimeno[8], Pascal de Groote[9,10], Massimo Imazio[11], Stephane Heymans[12,13], Karin Klingel[14], Michel Komajda[15], Giuseppe Limongelli[16], Ales Linhart[17], Jens Mogensen[18], James Moon[19], Petronella G. Pieper[20], Petar M. Seferovic[21], Stephan Schueler[22], Jose L. Zamorano[23], Alida L.P. Caforio[24], and Philippe Charron[25,26]

Left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease.

Pinto et al. EHJ, 2016
Jun 14;37(23):1850-8



Familial / genetic origin of DCM has been underestimated for a long time…

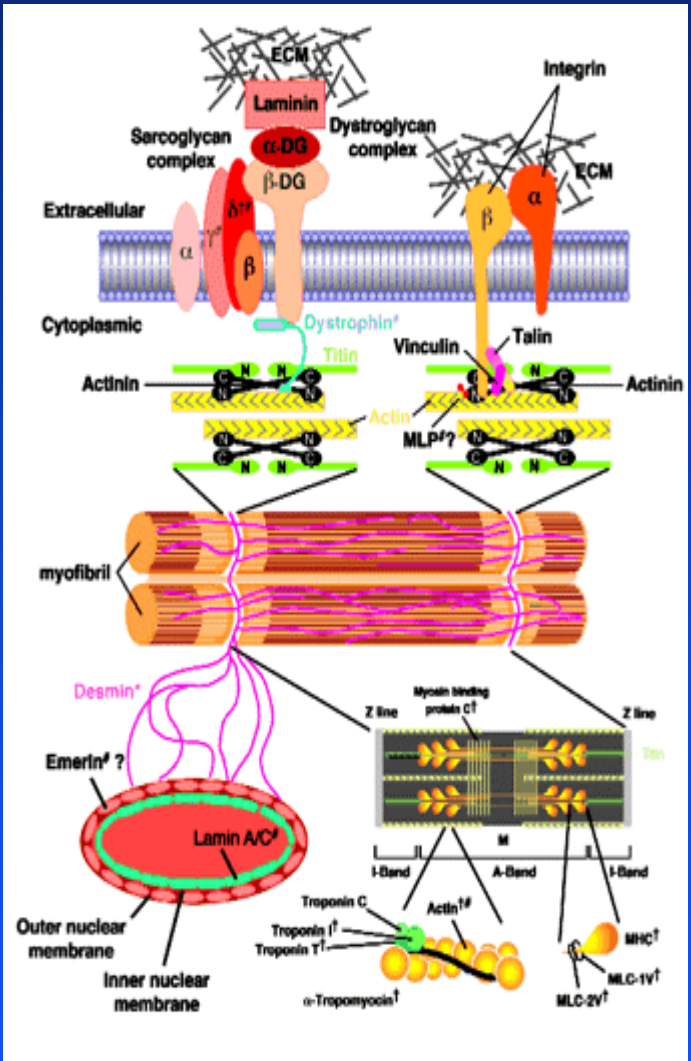
*Familial DCM forms after **echo** screening*

- 6%, retrospective study,
Michels et al. AJC 1985
- 8,5% retrospective study (HTx),
Valentine et al., AJC 1989
- 20% prospective study, (59 index, 315 relatives),
Michels et al., NEJM 1992
- 25% prospective study, (40 index patients)
Keeling et al., BHJ, 1995
- 35% prospective study, (445 index)
Grünig et al., JACC 1998
- 65% prospective study, (60 index)
Mestroni et al. JACC 1999

*Yield of **mutation** screening in DCM*

- 6%, analysis of 4 genes in 95 DCM pts,
Villard et al. EHJ 2005
- 11%, analysis of 6 genes in 313 pts,
Hersberger et al. Clin Transl Sci 2008
- 25-30% analysis of 19 genes in 73 pts,
Zimmerman et al., Genet Med 2010
- +18-25%, analysis of titin (TTN) gene in 312 pts, Herman et al., NEJM 2012
- 35% analysis of 101 genes in 145 pts,
Akinrinade et al., EHJ 2015
- 46-73% analysis of 84 genes in 639 pts,
Haas et al., EHJ, 2015

Global view of genes responsible for DCM



Chen J, Chien KR. J Clin Invest 1999

>50 genes, variable inheritance but usually AD, proteins:

- Cytosqueleton (i.e. dystrophin):
  - **force transmission?**
- Nuclear membrane (i.e. lamin A/C):
  - **membrane stabilization?**
  - **transcriptional factors?**
- Sarcomere (i.e. bêta-myosin, titin):
  - **force production?**
- Z Band (i.e. Muscle LIM Protein):
  - **strech sensor?**
- Ca^{2+} metabolism (i.e. phospholamban):
  - **contraction-relaxation cycle?**
- **Other**

Table 2 Genes associated with DCMs

Gene		Estimated prevalence (%)
TTN	(titin)	20
MYH7	(beta myosin)	4–7
LMNA	(lamin A/C)	2–6
SCN5A		2–3
TNNI3		2–3
LDB3		1–3
PLN		1–3
TNNT2		1–3
TNNC1		Rare
TAZ		Rare
CSRP3		Rare
DES		Rare
ACTN2		Rare
ANKRD1		Rare
ABCC9		Rare
TPM1		Rare
DMD		Rare
VCL		Rare
EMD		Rare
MYOZ1		Rare
MYBPC3		Rare
BAG3		Rare
ABCC9		Rare
LAMP2		Rare
EYA4		Rare
TMPO		Rare
PSEN1		Rare
PSEN2		Rare
SGCD		Rare

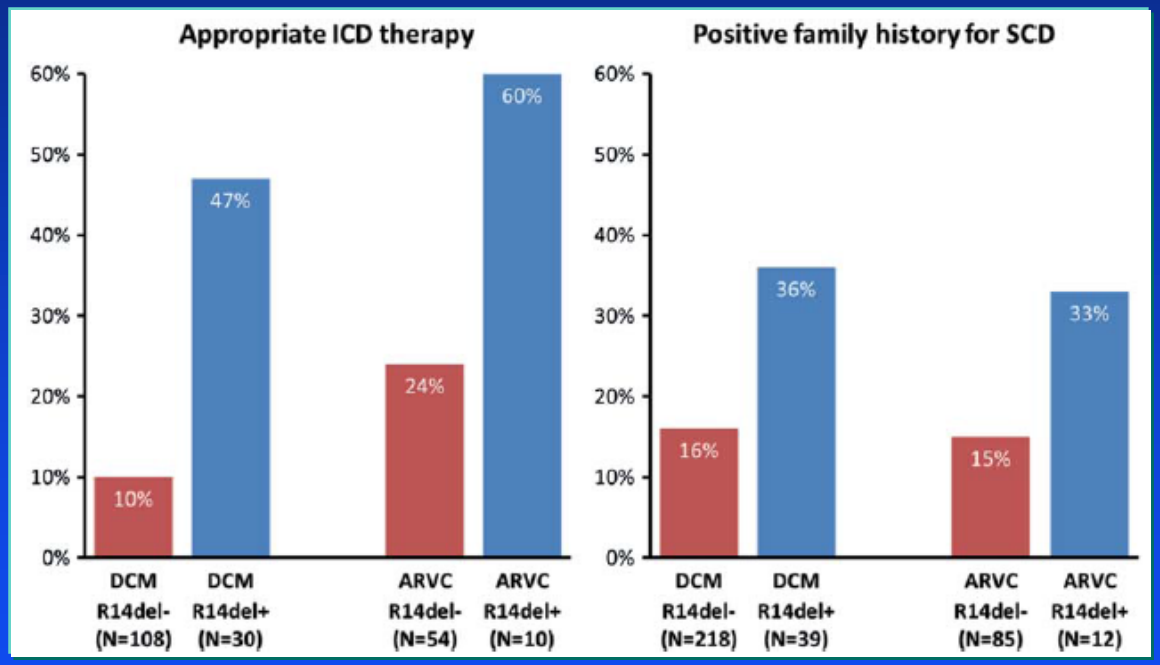
Ho C, Charron et al. Circ Res 2015;105(4):397

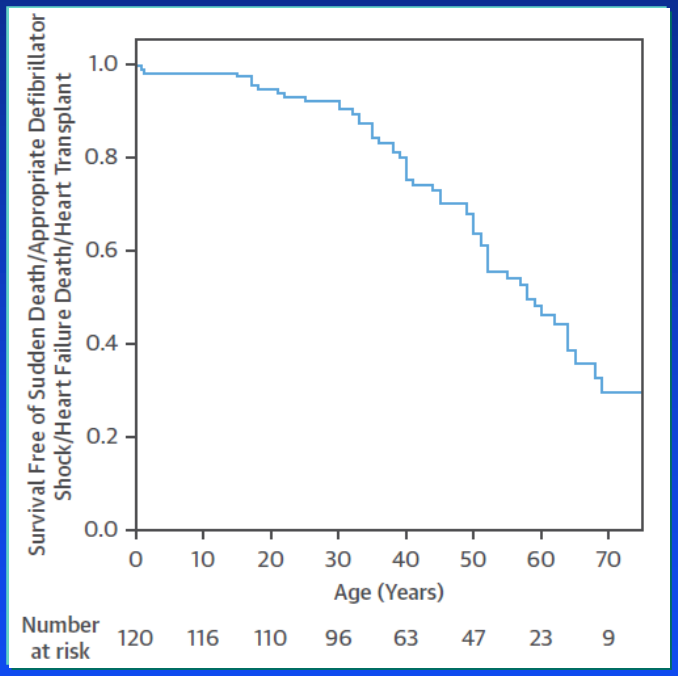
Impact of genetic knowledge in risk stratification of DCM

Revised concept on familial DCM

Prognosis and phenotype-genotype correlations

High risk of sudden cardiac death / ventricular arrhythmia for some genes





High risk of SCD / VA associated with **Phospholamban** (PLB) mutations

Van der Zwaag, EJHF 2012;14(11):1199

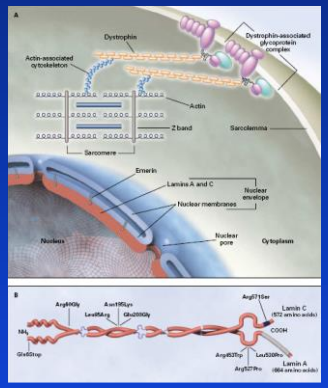
High risk of SCD / VA associated with **Filamin C** (FLNC) mutations

Ortiz-Genga, JACC 2016;68(22):2440-2451

Revised concept on DCM

Prognosis and phenotype-genotype correlations

prognosis of DCM related to Lamin A/C mutation



- LMNA (lamin A/C) gene mutations
- Autosomal dominant inheritance

Specific phenotype :

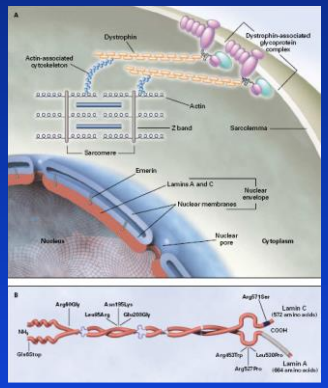
- early AV block / sinus dysfunction and/or SV or V arrhythmia
- DCM
- +/- skeletal myopathy

Fatkin et al., NEJM 1999;341:1715

Revised concept on DCM

Prognosis and phenotype-genotype correlations

*prognosis of DCM related to **Lamin A/C mutation***



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Specific phenotype :

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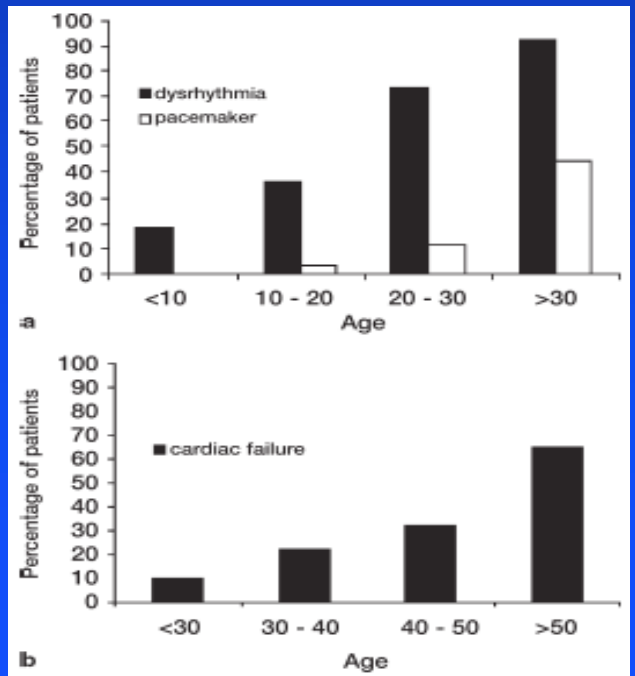
Fatkin et al., NEJM 1999;341:1715

- Meta-analysis of 299 LMNA mutation carriers
- Progressive ↑ dysrhythmia (CD or arrhythmia): 92% after 30 y.
- ↑ PM implantation: 44% after 30 y.
- ↑ Heart Failure: 64% after 50 y.



Van Berlo et al., J Mol Med 2005;83:79

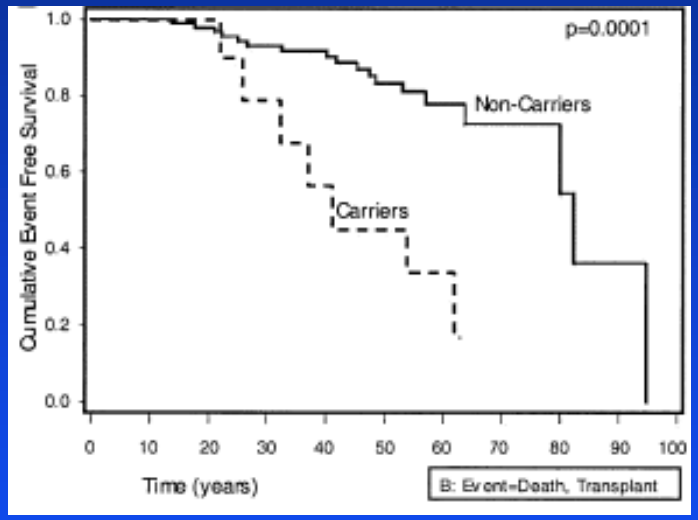
Revised concept on DCM

Prognosis and phenotype-genotype correlations

prognosis of DCM related to Lamin A/C mutation

Natural history of DCM patients

(12 LMNA mutations vs 93 pts) Taylor JACC 2003;41:771



↗mortality
- AVB
- VT/FV

- Analysis of survival in DCM patients
  - LMNA mutation carriers (N = 12)
  - DCM without LMNA mutation (N=93)
- Event free (D+Htx) survival at 45 y.: 45% vs 89%

Genotype-phenotype in 8000 DCM patients

Kayvanpour Clin Res Cardiol 2017 Feb;106(2):127

LMNA gene associated with:
- Highest rate of conduction disease (73%)
- Highest rate of ventricular arrhythmia (50%)
- Highest rate of heart transplant (27%)

Lamin A/C gene mutation: → specific FU → early PM and ICD

Prediction of ventricular arrhythmia in LMNA carriers and management

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

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Anneke J. van der Kooi, MD, PhD,‡ J. Peter van Tintelen, MD, PhD,***
Maarten P. van den Berg, MD, PhD,*†† Andrea Pilotto, BS,‖ Michele Pasotti, MD, PhD,‖
Sharon Jenkins, MS,¶ Camilla Rowland, MD,¶ Uzma Aslam, MS,‡‡
Arthur A. M. Wilde, MD, PhD,*† Andreas Perrot, MS,§§ Sabine Pankuweit, PhD,‖‖
Aeilko H. Zwinderman, MS, PhD,§ Philippe Charron, MD, PhD,‡‡ Yigal M. Pinto, MD, PhD*†

269 *LMNA* mutation carriers
FU 43 months

- MVA (n=48): 11 resuscitations, 28 appropriate ICD therapy (8%/y in PP), 14 SCD
- **4 Predictors of MVA** (multivariate analysis):
  - nsVT HR 4,4 (95% CI: 1,9-10.4)
  - LV EF < 45% HR 4,4 (95% CI: 2.0-8.0)
  - Male gender HR 2.9 (95% CI: 1,2-7.0)
  - Ins/del/nonsense/splice site mutation HR 2.5 (95% CI: 1.4-4.5)

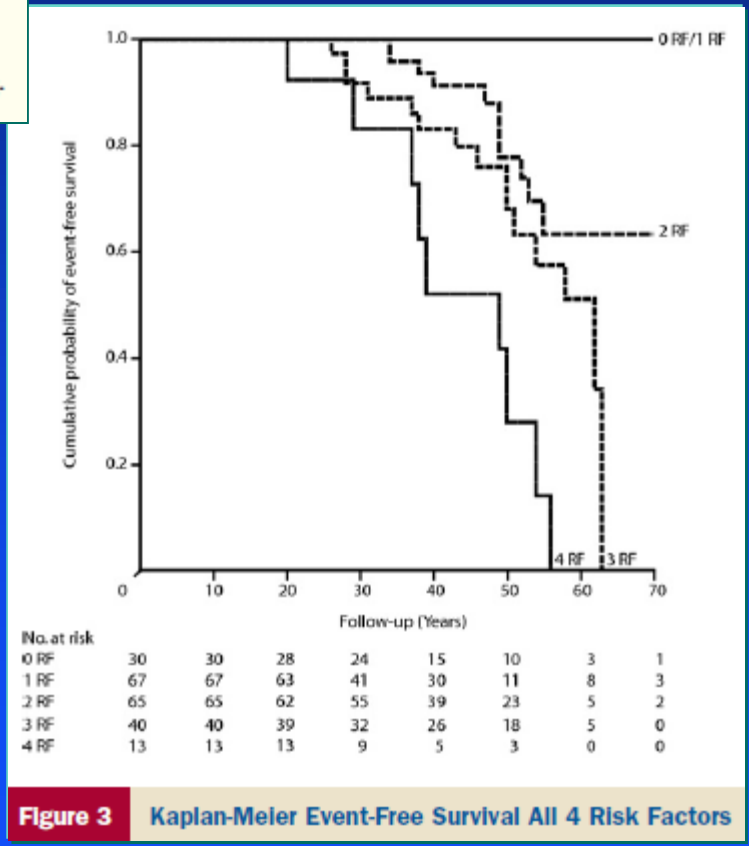


Figure 3 Kaplan-Meier Event-Free Survival All 4 Risk Factors

≥ 2 RF → propose ICD

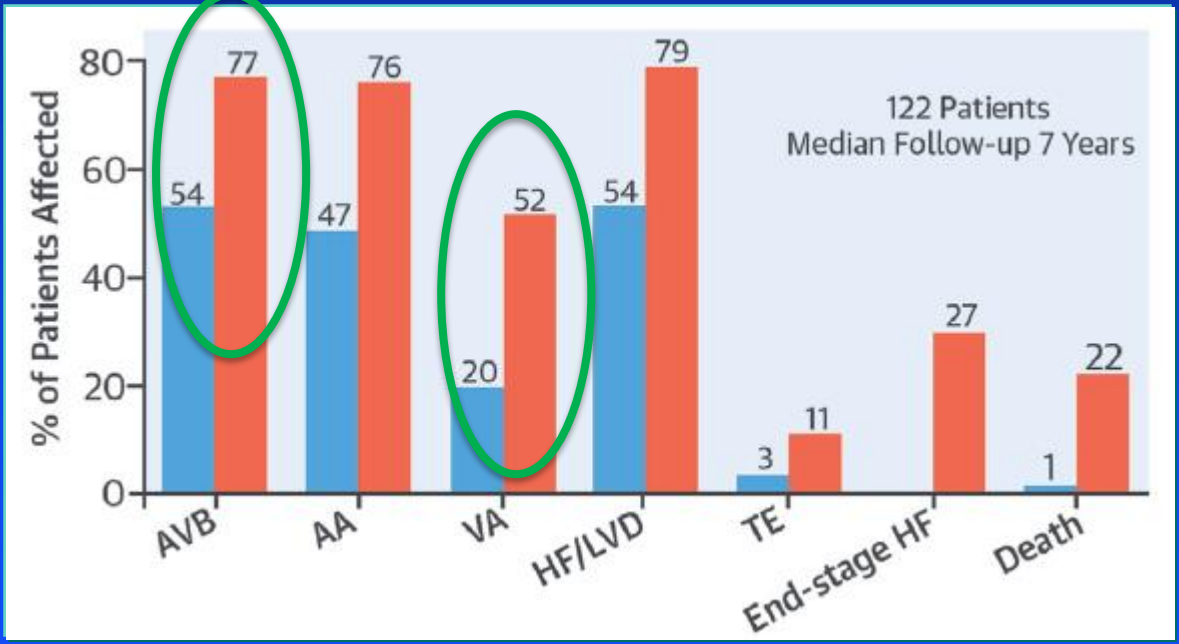
van Rijsingen J Am Coll Cardiol 2012

DCM & LMNA mutations

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

Saurabh Kumar, BSc(Med)/MBBS, PhD,[a] Samuel H. Baldinger, MD,[b] Estelle Gandjbakhch, MD, PhD,[c] Philippe Maury, MD,[d] Jean-Marc Sellal, MD,[e,f,g,h] Alexander F.A. Androulakis, MD,[i] Xavier Waintraub, MD,[c] Philippe Charron, PhD,[c,j,k] Anne Rollin, MD,[d] Pascale Richard, PhD,[l] William G. Stevenson, MD,[a] Ciorsti J. Macintyre, MD,[a] Carolyn Y. Ho, MD,[a] Tina Thompson, RN,[m] Jitendra K. Vohra, MD,[n] Jonathan M. Kalman, MBBS, PhD,[n] Katja Zeppenfeld, MD,[i] Frederic Sacher, MD,[e,f,g] Usha B. Tedrow, MD, MSc,[a] Neal K. Lakdawala, MD[a]

Kumar, JACC 2016;68:2290



- N= 122 LMNA carriers
- Predictors of sVA (multivariate):
  - Male sex (HR 3.1, p=0.01)
  - Non missense mutation (HR 2.5, p=0.03)
  - LVEF<50% (HR 3.4, p=0.004)

- **Ventricular arrhythmia (sVT/VF): 34 ±5% at 7 years**
- **Device implanted in 48% during FY (7 y.)**

→ Early ICD & PM

Other predictors of VA in LMNA carriers

- 94 Italian mutation carriers, FU: 57 months
  - 2 independent RF for sudden death:
    - type of mutation (splice site mutations)
    - history of competitive sports
      - Pasotti et al. J Am Coll Cardiol 2008;52:1250
- 47 French mutations carriers
  - 1 RF for sudden death:
    - significant conduction disorders

    (hazard ratio 5.20; 95% confidence interval 1.14-23.53; P = 0.03)
      - Anselme et al. Heart Rhythm 2013 Oct;10(10):1492

Implications for practical management of DCM in daily practice

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Diagnostic work up in DCM :

(6) Cardiac screening with echocardiography and ECG is recommended in all first degree-relatives of an index patient with DCM, irrespective of family history.

(7) Genetic testing is recommended in the presence of a familial form of DCM OR in sporadic DCM with clinical clues suggestive of a particular/rare genetic disease (such as atrio-ventricular block or CK elevation).

Aetiology directed management:

Recommendation 6:

- When a definite causative LMNA mutation is identified, early indication for primary prevention by ICD implantation should be considered (guided by the risk factors as detailed elsewhere)[43,44].

Pinto et al. EHJ, 2016 Jun 14;37(23):1850

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Conclusions

- Familial/genetic origin is frequent in DCM
  - At least 1/3 of DCM are familial forms
  - Yield of mutation screening: 20-30% with Sanger → 45-75% with NGS
  - Genetic testing is recommended in the presence of a familial form of DCM OR in sporadic DCM with clinical clues suggestive of a particular/rare genetic disease

- Some genes are associated with higher risk of SCD in DCM, especially LMNA gene (lamin A/C)
  - When should you suspect Lamin A/C gene mutations? If a particular phenotype (including conduction defect, SV and V arrhythmia, dilated cardiomyopathy, sometimes muscular dystrophy)
  - Why should you identify LMNA mutations? Because of high mortality, particular cardiac expression, early sport restriction, early PM and ICD implantation (LVEF <45 %, nsVT, male gender and non-missense *LMNA* mutation), genetic counselling

Sources d'information

- **Centre de référence Maladies rares** (Paris),
  label Plan Maladies rares n°1:
  - Centre de référence pour les **maladies cardiaques héréditaires**, Paris, **www.cardiogen.aphp.fr**

    Coordinateur du centre: philippe.charron@aphp.fr

    Paris multi-site: A. Paré, Bichat, HEGP, Necker, R. Debré, Pitié-Salpêtrière
  - 22 Centres de compétence en région

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Paris

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- **Filière nationale de santé CARDIOGEN**,
  label Plan Maladies rares n°2, coordinateur: Ph Charron

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