Manifestations cardiaques des myopathies

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SMHP 2015

Plan

- **Myopathies / cardiomyopathies**

  →génétiques

- **Prévention**

1. Mort subite par troubles conductifs → **Steinert**
2. Mort subite par troubles du rythme ventriculaires → **Laminopathies**
3. Insuffisance cardiaque terminale → **Duchenne**

Nosologie
myopathies - cardiomyopathies

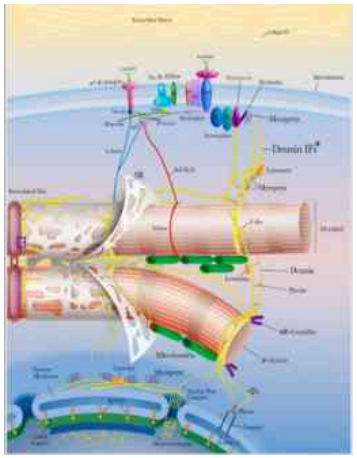
Génétiques

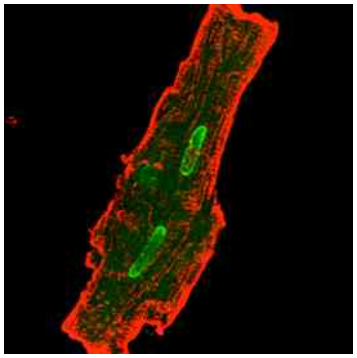
Dystrophies musculaires

Myopathies métaboliques

Syndromes myotoniques

Myopathies congénitales





Acquises

Myopathies inflammatoires

Myopathies endocriniennes

Myopathies toxiques et iatrogènes

Syndromes myasthéniques

Striated muscle
skeletal and cardiac - similarities

Gene mutation

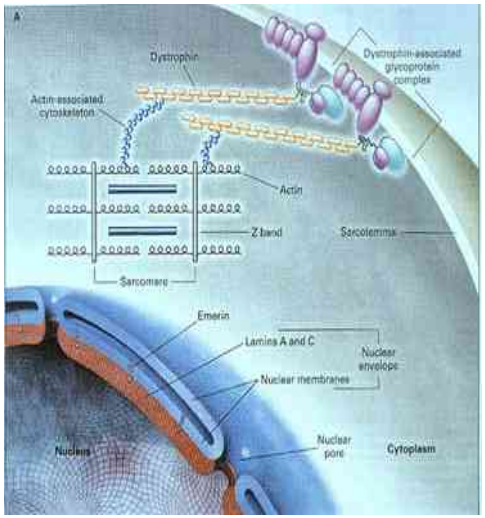
↓

Abnormal protein expression

↙ ↓ ↘

Myopathy | Cardiomyopathy | Other targets

- Great similarities between cardiac and skeletal muscles structure, genetics and protein expression: dystrophinopathies, LGMDs



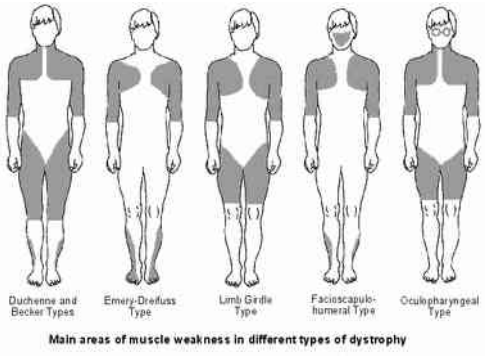
- Or different pathways: myotonic dystrophies (missplicing)

Cardiomyopathies et maladies musculaires

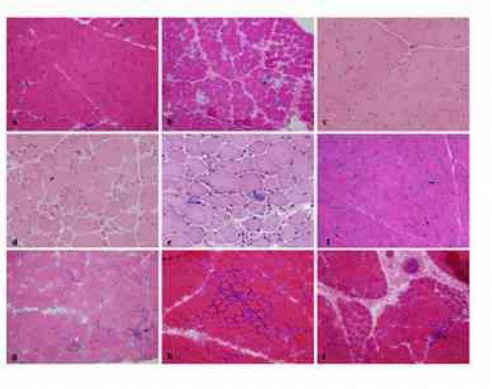
- **Population française : 50.000 patients**

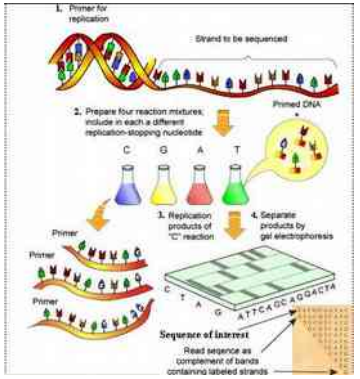
- **Un nombre important d'entités cliniques – plus de 300 gènes**

Duchenne (DMD)	Steinert (DM1)	Laminopathies (LMNA)	Mitochondriales	Becker (DMD)	Desminopathies (DES)	Distales (MYH7)	M. ceintures (FKRP, sarco,…)	…



Main areas of muscle weakness in different types of dystrophy





Dystrophies musculaires congénitales (DMC) dites "classiques"

(sans retard mental)

- Dystrophie musculaire congénitale de type 1A (MDC1A)

- Syndrome d'Ullrich

- Syndrome de la colonne raide (RSMD1)

- Dystrophie musculaire congénitale de type 1B (MDC1B)

- Dystrophie musculaire congénitale de type 1C (MDC1C)

- Dystrophie musculaire congénitale avec déficit en intégrine alpha-7

Dystrophies musculaires congénitales (DMC) avec atteinte du système nerveux central (ou alpha-dystroglycanopathies)

- Dystrophie musculaire de Fukuyama

- Syndrome muscle-oei

- Syndro

- DMC avec mutation du gene *LARGE* (MDC1D)

Dystrophies musculaires d'Emery-Dreifuss (DMED) .

Dystrophies musculaires des ceintures (LGMD pour "*Limb Girdle*

***Muscular Dystrophy*")**

- Calpaïnopathie (LGMD2A)

- Sarcoglycanopathies (σ-sarcoglycanopathie ou LGMD2C, ν-sarcoglycanopathie ou LGMD2D, ω-sarcoglycanopathie ou LGMD2E, ρ-sarcoglycanopathie ou LGMD2F)

- Dysferlinopathie (LGMD2B)

- Dystrophie musculaire des ceintures LGMD2G

- Dystrophie musculaire des ceintures LGMD2H

- Dystrophie musculaire des ceintures LGMD 2I

- Dystrophie musculaire des ceintures LGMD2J

- Dystrophie musculaire des ceintures LGMD2K

Dystrophies myotoniques

- Dystrophie myotonique de Steinert ou type 1

- Dystrophie myotonique de type 2 (dite aussi PROMM)

Dystrophinopathies

- Dystrophie musculaire de Duchenne (DMD)

- Dystrophie musculaire de Becker (DMB)

- Formes mineures de dystrophinopathies

Fibrodysplasie ossifiante progressive (FOP)

Glycogénoses musculaires

- Maladie de Pompe ou glycogénose de type II

- Maladie de Cori (ou maladie de Forbes) ou glycogénose de type III

- Maladie de McArdle ou glycogénose de type V

- Déficit en carnitine-palmitoyl transférase de type II (CPT II)

- Déficit en acyl CoA déshydrogénase

- Déficit en VLCAD (*Very Long Chain Acyl-CoA Dehydrogenase*)

Myopathies mitochondriales

Myopathies congénitales

- Myopathies congénitales à bâtonnets ou némaline myopathies

- Myopathie congénitale à central cores

- Myopathie congénitale myotubulaire

- Myopathie congénitale centronucléaire

- Myopathie congénitale à multi-minicores

Myopathies distales .

- Myopathie de Miyoshi

- Dystrophie musculaire tibiale de type Udd

- Myopathie de Nonaka

Amyotrophies spinales proximales

(ou SMA pour "*Spinal Muscular Atrophy*")

- Amyotrophie spinale infantile type I (maladie de Werdnig-Hoffman)

- Amyotrophie spinale infantile type II

- Amyotrophie spinale infantile type III (maladie de Kugelberg-Welander)

- Amyotrophie spinale de l'adulte type IV

Canalopathies

- Adynamie épisodique de Gamstorp (paralysie périodique hyperkaliémique), paralysie périodique hypokaliémique de type II et maladie de Westphal (paralysie périodique hypokaliémique)

- Paramyotonie d'Eulenburg

Myotonies congénitales

de Becker

e Thomsen

- Myotonie chondrodystrophique ou syndrome de Schwartz-Jampel

Maladies de Charcot-Marie-Tooth (CMT) .

- Maladies de Charcot-Marie-Tooth de type 1 (CMT1)

- Maladies de Charcot-Marie-Tooth de type 4 (CMT4)

- Maladies de Charcot-Marie-Tooth de type 2 (CMT2)

- Maladies de Charcot-Marie-Tooth intermédiaires dominantes liées à l'X

(CMTX)

- Maladies de Charcot-Marie-Tooth de type intermédiaires autosomiques

dominantes (DI-CMT)

Maladies inflammatoires du muscle

- Dermatomyosites

- Polymyosites

- Myosite à inclusions

Plusieurs centaines de pathologies

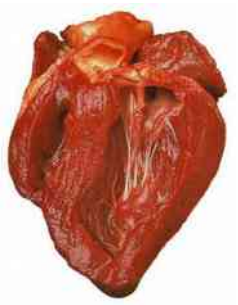
Cardiac involvement in myopathies

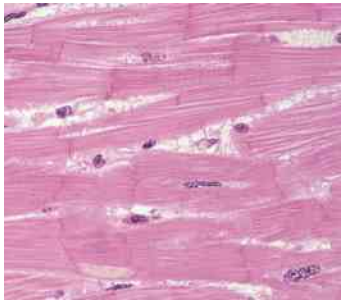
Very different cardiac patterns from a disease to another

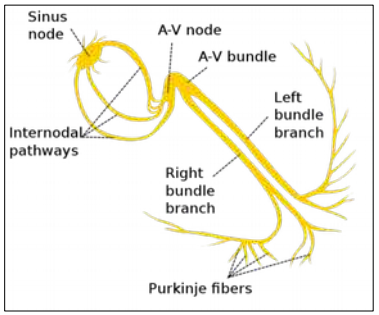
Myocardial and/or **Electrical disease**

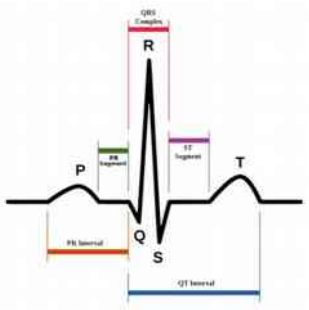
Dilated	Hypertrophic	Restrictive

Conduction	Ventricular arrhythmias	SV arrhythmias





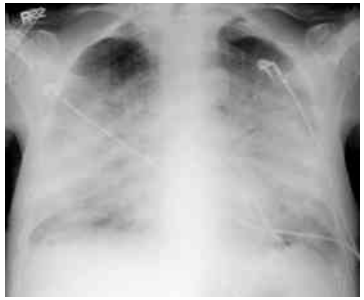


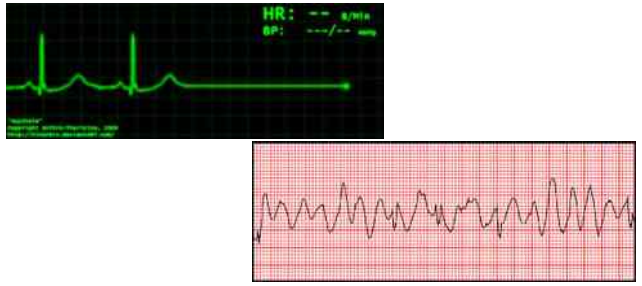


Heart failure | **Sudden death** | **Stroke**

Disease specific cardiac patterns

	Heart failure	Conduction	VA	SVA
DM1	+	+++	+	++
Duchenne Becker	+++	+	±	±
LMNA	++	++	+++	++
DES	+++	+++	++	+++
Mitochondrial	+++	+++	+	±





Manifestations cardiaques des mitochondriopathies

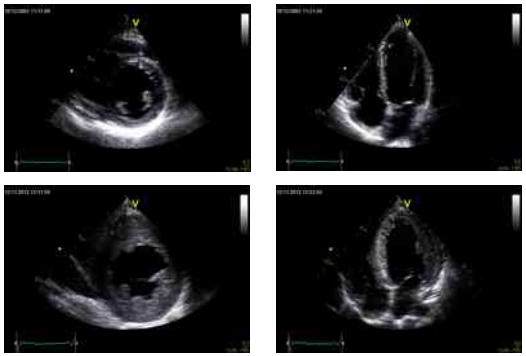
Atteinte myocardique - ventriculaire

- Hypertrophie
- Dilatation
- Dysfonction systolique

Insuffisance cardiaque

Hospitalisations pour IC décompensée

Décès



MELAS - MERRF

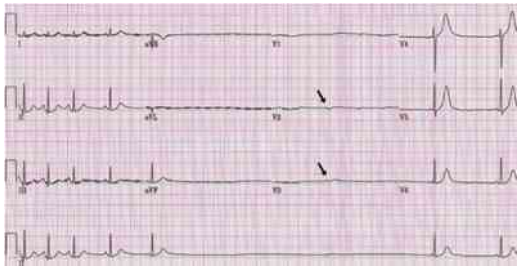
Anomalies « électriques »

- Troubles conductifs
- Troubles du rythme auriculaire
- Troubles du rythme ventriculaire

Syncopes

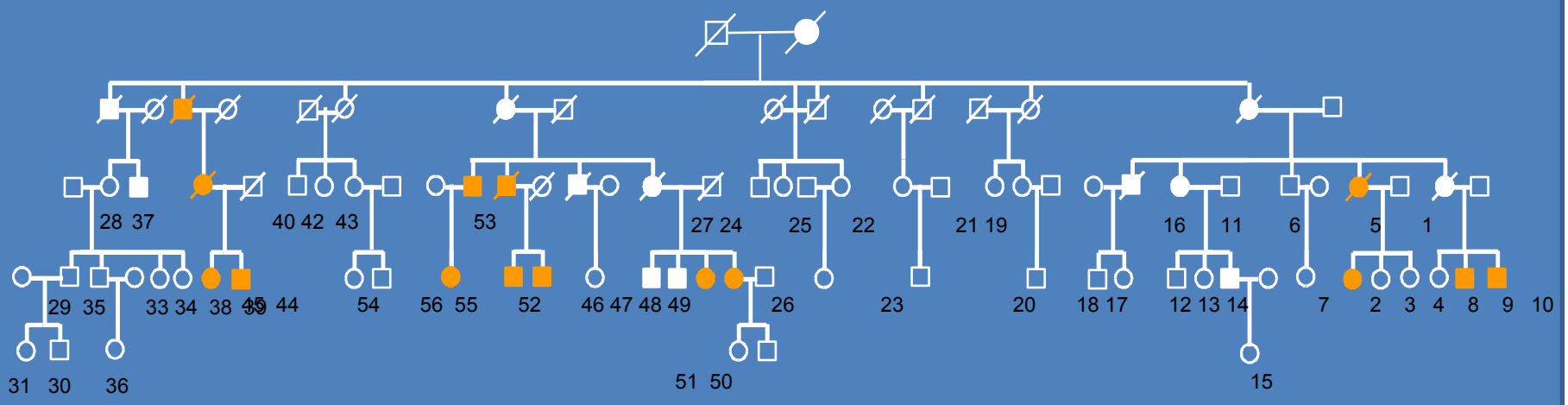
Blocs sévères (BAV 3)

Mort subite



Délétions simples - KSS

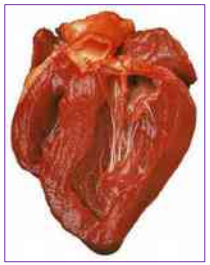
Pénétrance des atteintes squelettique et cardiaque - *LMNA*



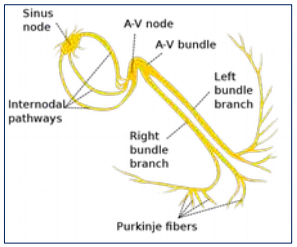
Bonne et al., Nat. Genetics, 1999
Bécane et al, PACE, 2000

Early stages of the disease → Prevention

Gene mutation Abnormal protein expression	Subclinical abnormalities	Overt cardiac involvement	Life threatening manifestations

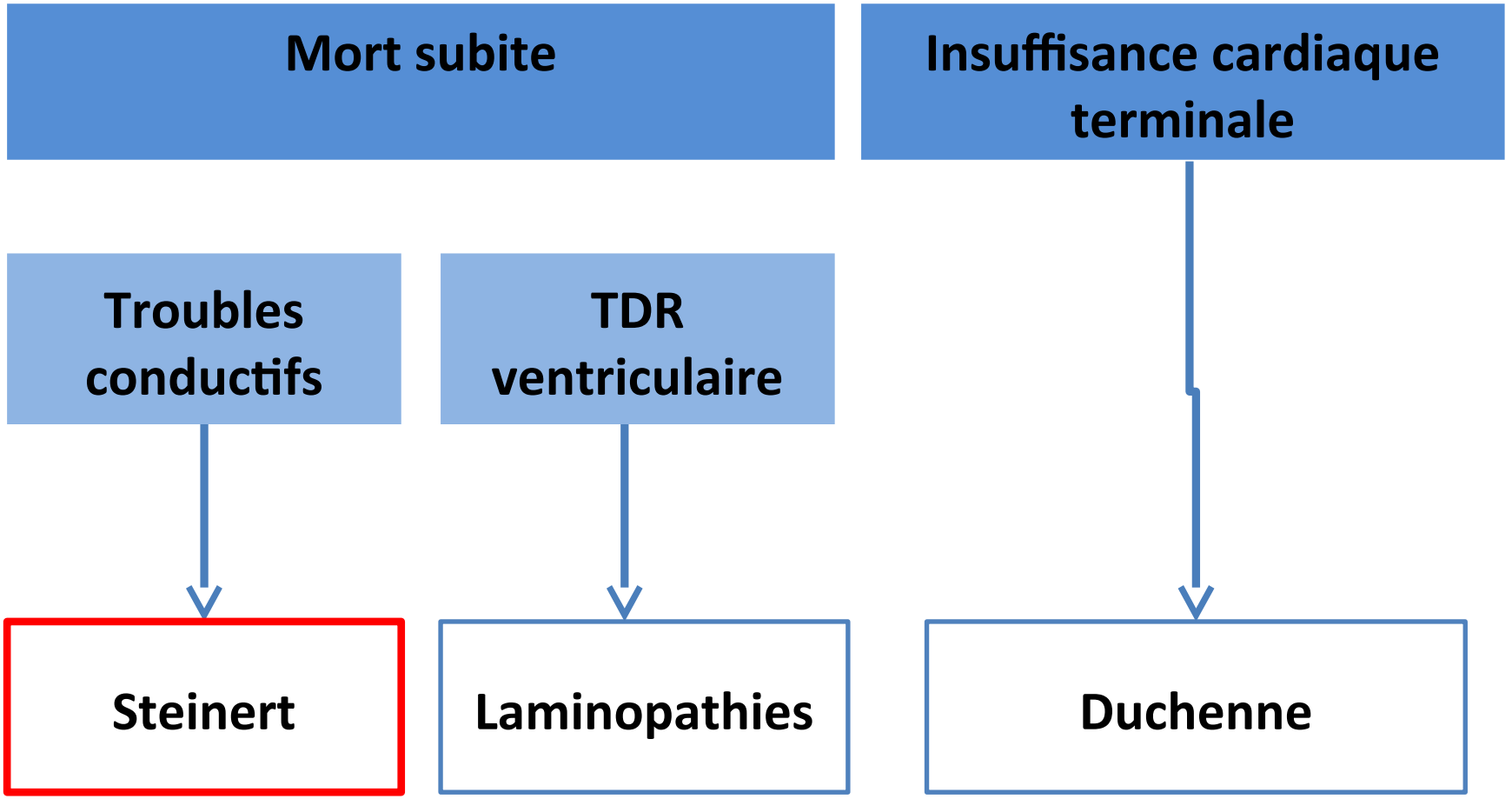


Mild ventricular dysfunction → Severe dysfunction Heart failure → Terminal HF

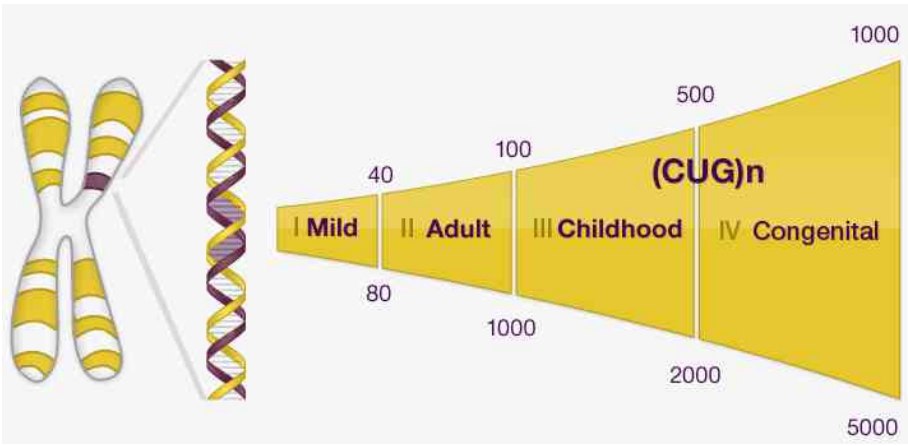


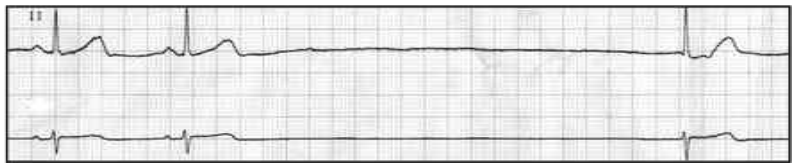
Mild conduction defects - arrhythmias → Severe conduction defects - VT → Cardiac arrest Sudden death

Prévention


Mort subite
Insuffisance cardiaque terminale
Troubles conductifs
TDR ventriculaire
Steinert
Laminopathies
Duchenne

Cardiac involvement in DM1



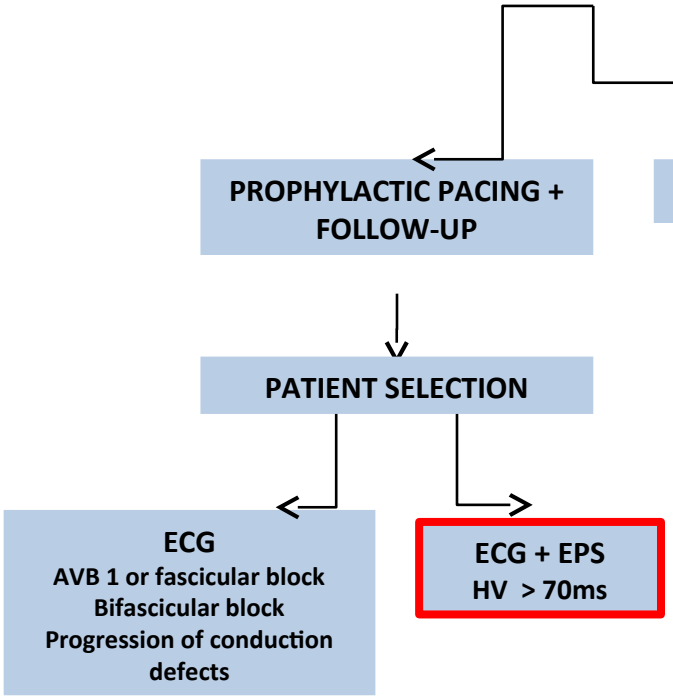


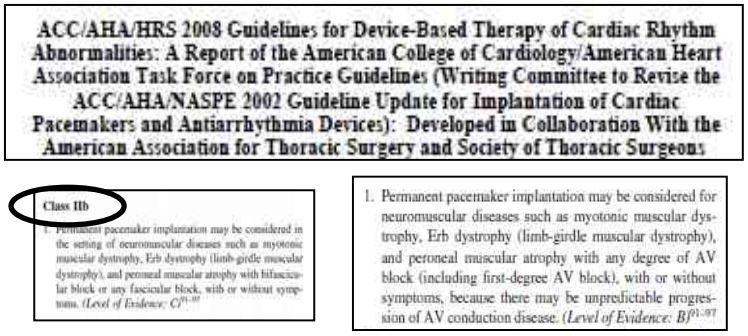
DM1 – sudden death

Cardiac manifestations of the disease	Petri N=1828 Int JC 11	Groh N=406 NEJM 08	Breton N=428 Can JC 09	Wahbi N=914 JAMA 12
Conduction system disease				
- AVB1	**28.2%**	**45.0%**	**-**	**34.1%**
- QRS>120ms	**19.9%**	**16.5%**	**-**	**18.4%**
Atrial fibrillation/flutter	5.0%	12.8%	-	7.6%
Sustained ventricular tachyarrhythmias	-	1.9%	-	1.0%
Left ventricular dysfunction	7.2%	11.3%	-	8.4%
SUDDEN DEATH (annual)	**0.56%**	**1.16%**	**0.25%**	**0.53%**
		PR>240ms QRS>120ms AF	**PR>200ms QTc>450ms**	

Petri H, Vissing J, Witting N. Cardiac manifestations of myotonic dystrophy type 1. Int J Cardiol. 2012 Oct 4;160(2):82-8.
Wahbi K, Meune C, Porcher R. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. JAMA. 2012 Mar 28;307(12):1292-301.
Breton R, Mathieu J. Usefulness of clinical and electrocardiographic data for predicting adverse cardiac events in patients with myotonic dystrophy. Can J Cardiol. 2009 Feb;25(2):e23-7.
Groh WJ, Groh MR, Saha C. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med. 2008 Jun 19;358(25):2688-97.

DM1 – conduction system disease





ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons

Class IIb

1. Permanent pacemaker implantation may be considered in the setting of neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with or without symptoms. (*Level of Evidence: C*[01-07])

1. Permanent pacemaker implantation may be considered for neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease. (*Level of Evidence: B*[01-07])

Gagnon C, Chouinard MC, Laberge L, Veillette S, Bégin P, Breton R, Jean S, Brisson D, Gaudet D, Mathieu J; DMI Expert Panel. Health supervision and anticipatory guidance in adult myotonic dystrophy type 1. Neuromuscul Disord. 2010 Dec;20(12):847-51

DM1 - conduction system disease

EPS for risk stratification: pilot study

Patients with prophylactic permanent pacing for HV prolongation >70ms on EPS (primary prevention)

N=49 patients (45.5±8.9 years old)

Symptoms:

- palpitations (n=11)
- syncope or fainting episodes (n=16)
- asymptomatic (n=25)

ECG:

- PR>200ms and/or QRS>100ms (n=47)
- PR interval=223±36ms

1. ECG (PR>200, QRS>100ms)

⇩

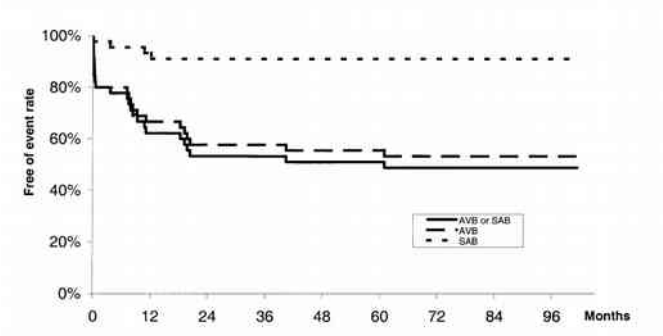
2. EPS (HV>70ms)

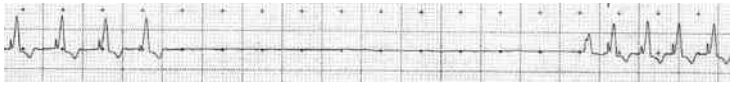
⇩

3. Pacemaker

Follow-up duration=53.5±27.2 months

- Complete AV block: n=21
- Sino atrial block: n= **50%**
- Ventricular tachycardia: n=1
- Sudden death: n=4 (arrhythmia excluded in 3)

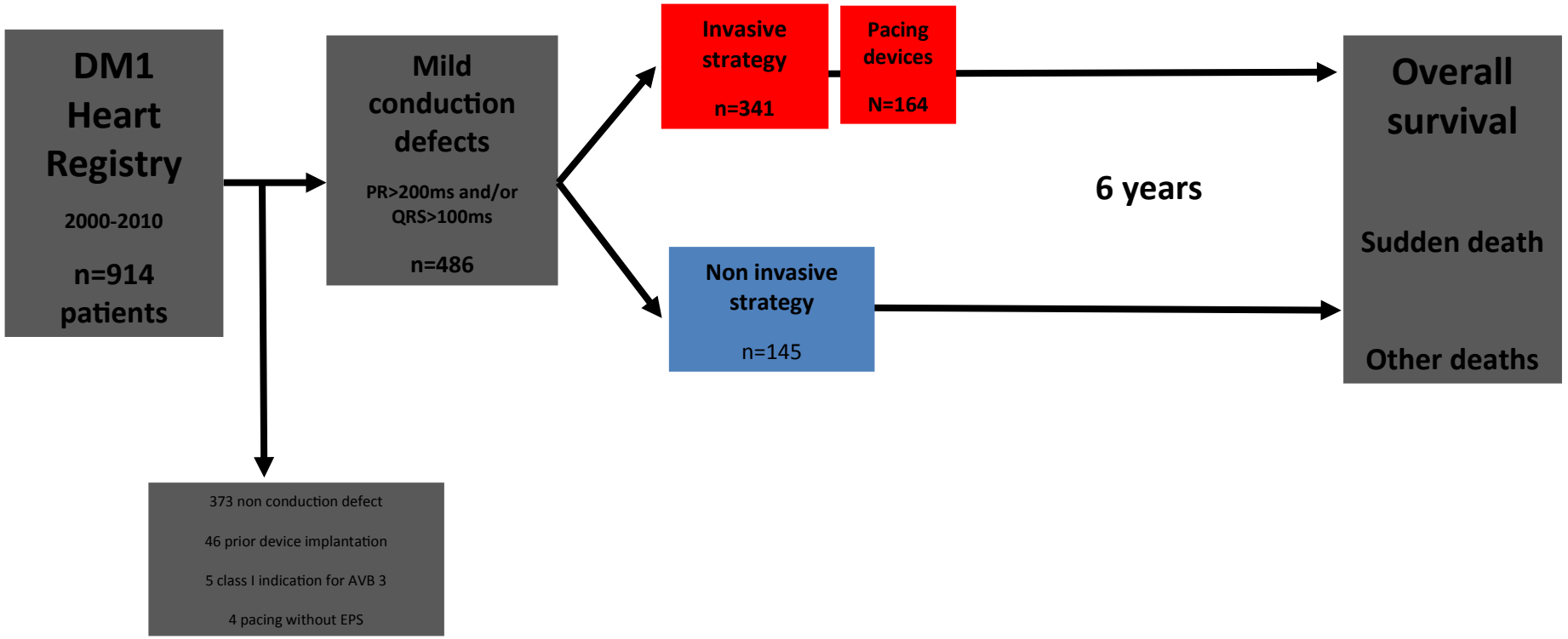




Update of the ACC/AHA guidelines

Lazarus A, Varin J, Babuty D, Anselme F, Coste J, Duboc D. Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: a multicenter diagnostic pacemaker study. J Am Coll Cardiol. 2002;40(9):1645-1652.

DM1 - conduction system disease
Prophylactic pacing: the impact on survival



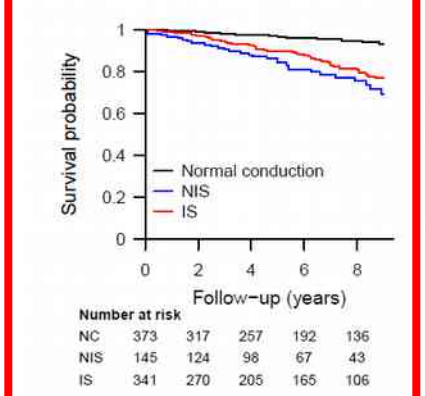
Wahbi K, Meune C, Porcher R, Bécane HM, Lazarus A, Laforêt P, Stojkovic T, Béhin A, Radvanyi-Hoffmann H, Eymard B, Duboc D. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. ***JAMA****. 2012 Mar 28;307(12):1292-301.*

DM1 - conduction system disease
Prophylactic pacing: the impact on survival

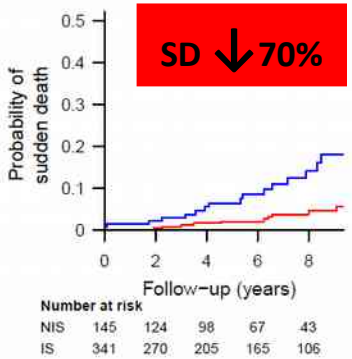
IS

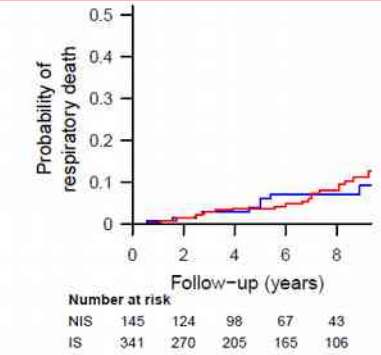
NIS

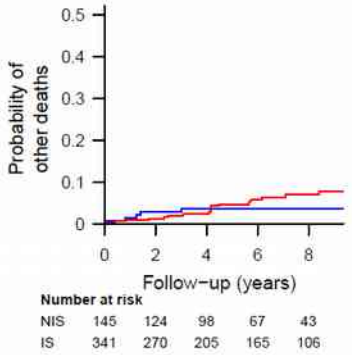
SURVIVAL



SD ↓70%







SURVIVAL

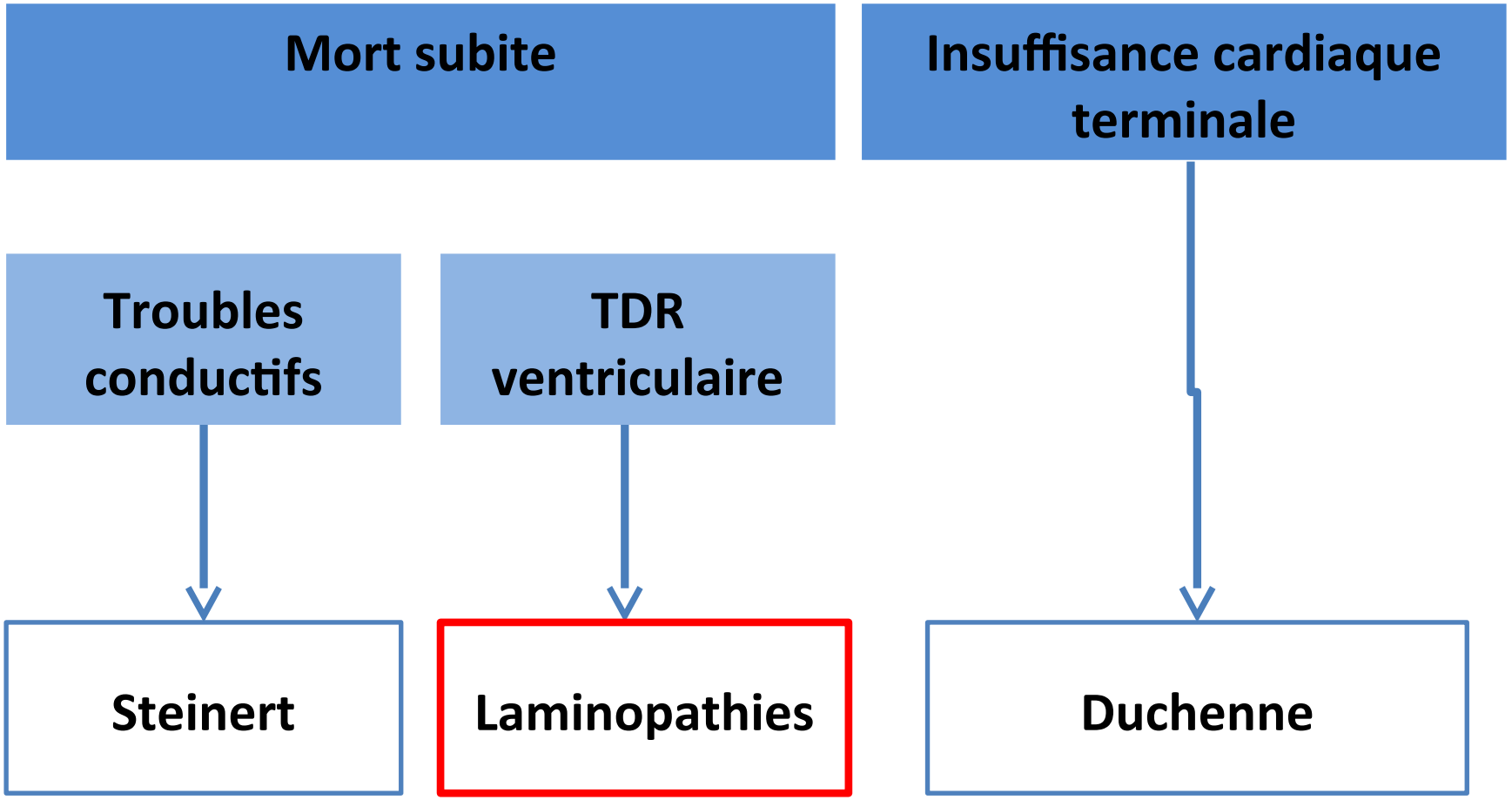
Analysis method	Events/patients NIS	Events/patients IS	HR (95% CI)
Unadjusted	30/145	50/341	0.74 (0.47 to 1.16)
Adjusted	30/145	50/341	0.61 (0.38 to 0.98)
Propensity quintile	30/145	50/341	0.61 (0.38 to 0.99)
Propensity quintile + covariates	30/145	50/341	0.55 (0.33 to 0.92)
Propensity matched	27/113	27/226	0.55 (0.31 to 0.96)
Propensity matched + covariates	27/113	27/226	0.47 (0.26 to 0.84)

Overall survival: HR 0.47 (95% CI, 0.26-0.84; P=.01) to 0.61 (95% CI, 0.38-0.99; P=.047) – Sudden death: HR 0.24 (95% CI, 0.10-0.56; P=.001) to 0.28 (95% CI, 0.13-0.61; P=.001)

70% reduction of sudden death in the invasive strategy group

Wahbi K, Meune C, Porcher R, Bécane HM, Lazarus A, Laforêt P, Stojkovic T, Béhin A, Radvanyi-Hoffmann H, Eymard B, Duboc D. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. ***JAMA****. 2012 Mar 28;307(12):1292-301.*

Prévention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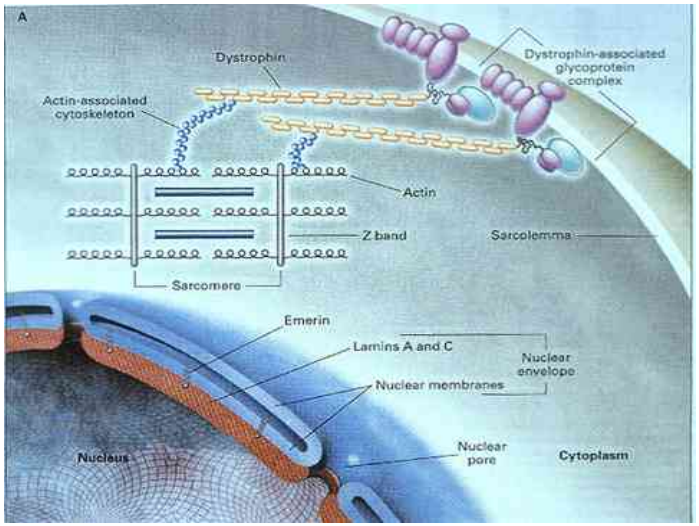
Insuffisance cardiaque terminale
Troubles conductifs
TDR ventriculaire
Steinert
Laminopathies
Duchenne

Laminopathies



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

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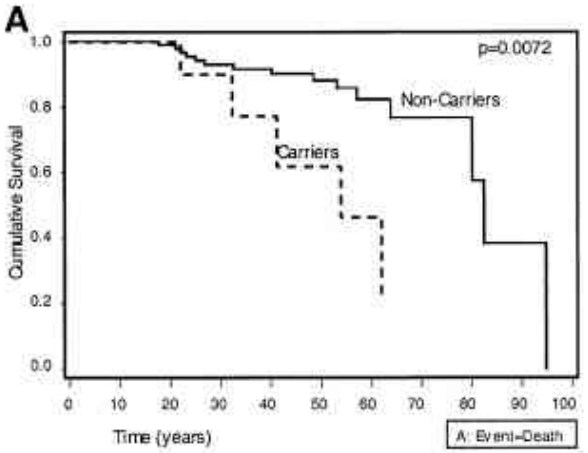
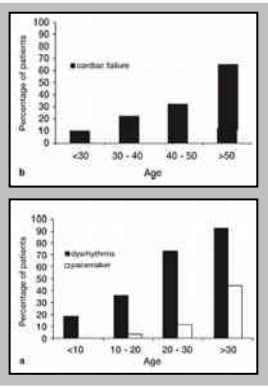


Prevention of sudden death in laminopathies

Meta analysis - *Van Berlo. J Mol Med 2005*
n=299 patients (mean age=31 years)

- **Supraventricular arrhythmias**
- **Conduction disease**
- **Ventricular arrhythmias**
- **Dilated cardiomyopathy**



Sudden death

Total population: 11.7%
Pacemaker recipients: 19%

Electrophysiological studies
Meune et al. N Engl J Med 2006 ; 354 : 209-210

- Primary prevention: patients with infrahissien blocks (HV > 70ms)
- 1999 – 2004
- N=19 patients (Age=41.7±13.4 years) with an ICD

Follow-up = 34 months

Malignant arrhythmias: 42%

European registry – Cardiology tertiary centers
N=269 patients - Age=36 years [27-45]

- dilated cardiomyopathy: n=89 (37%)
- muscular dystrophy: n=41/198 (21%)

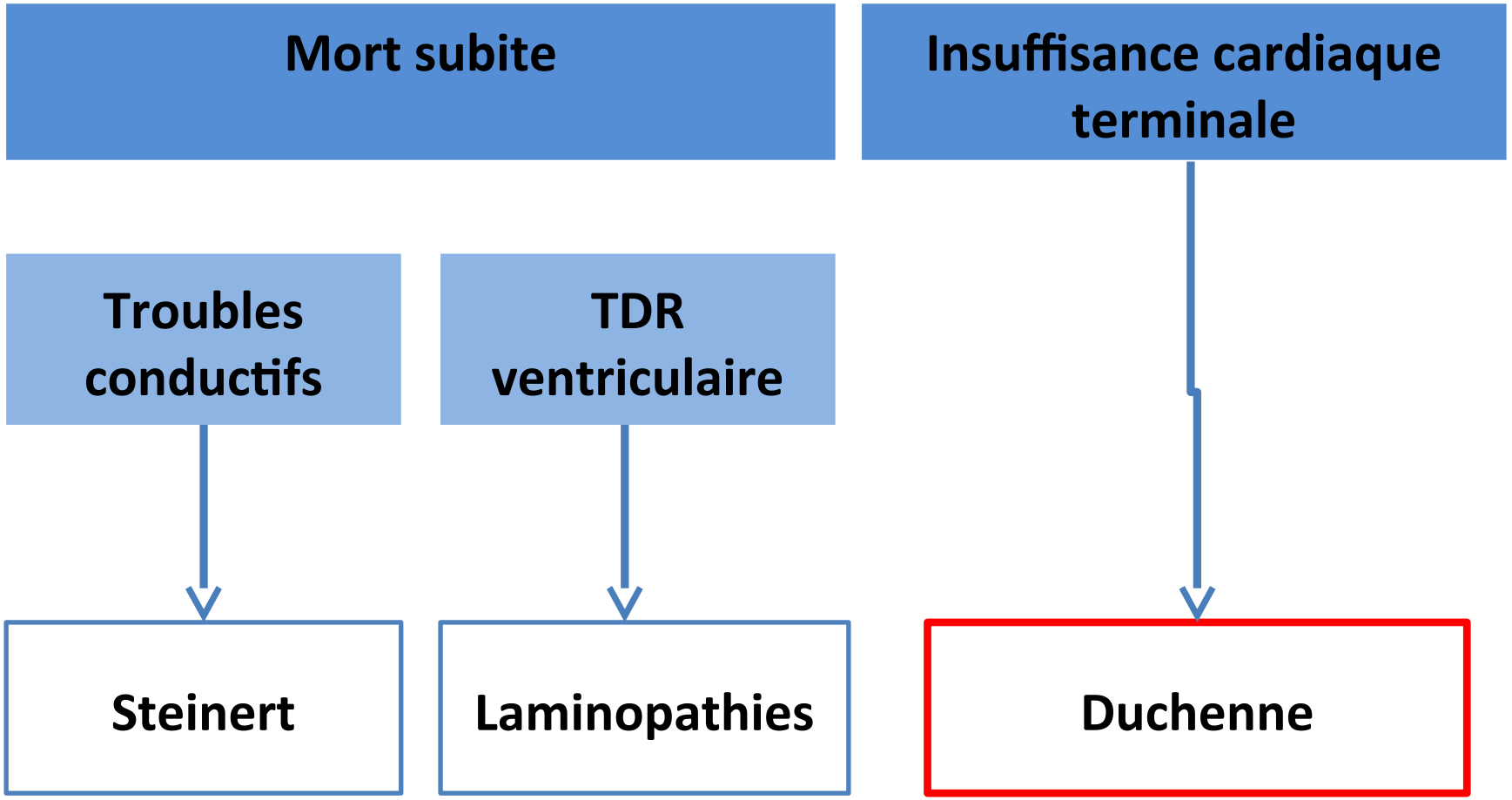
Follow up = 43 months

Malignant arrhythmia: 17%

4 risk factors: NSVT, LVEF<45%, male, non missense mutation

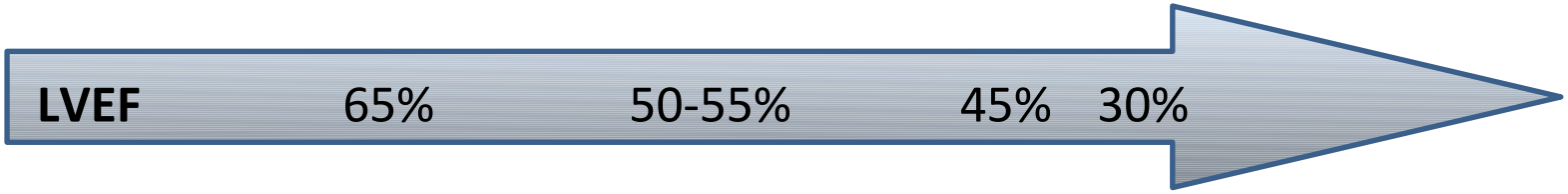
Cardiac defibrillators - no pacemakers

Prévention


Mort subite
Insuffisance cardiaque terminale
Troubles conductifs
TDR ventriculaire
Steinert
Laminopathies
Duchenne

Dilated cardiomyopathies

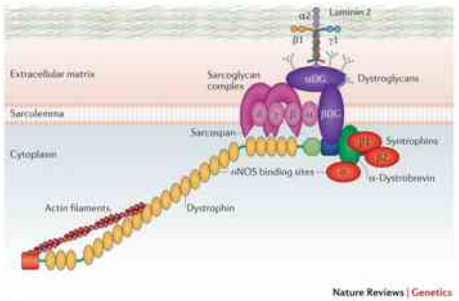
Prevention: when and how?



Treatment?

HF medical treatment

Duchenne muscular dystrophy



Terminal heart failure

40% of deaths

Engel AG Myology ; De Kermadec JM, Am Heart J 1994;127:618-23

Age (years)	Normal	ECG	DCM	Conduction defects
<6	74%	26%	0	0
6-10	38.5%	61.5%	0	0
10-14	18.8%	41.6%	25.7%	8.9%
14-18	5.3%	28.9%	44.7%	13.1%
>18	0%	2.2%	**71.7%**	0

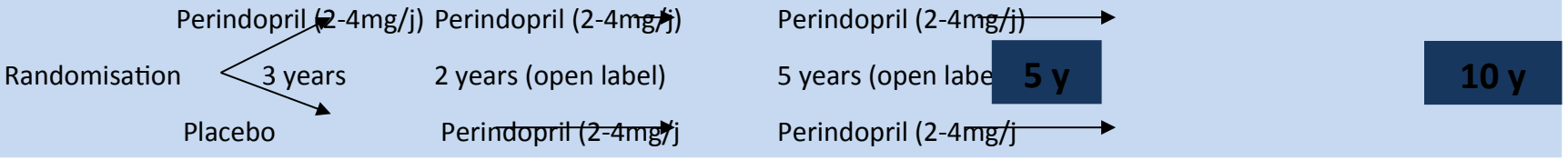
PREVENTION

Nigro G, Int J Cardiol 1990;26:271-7

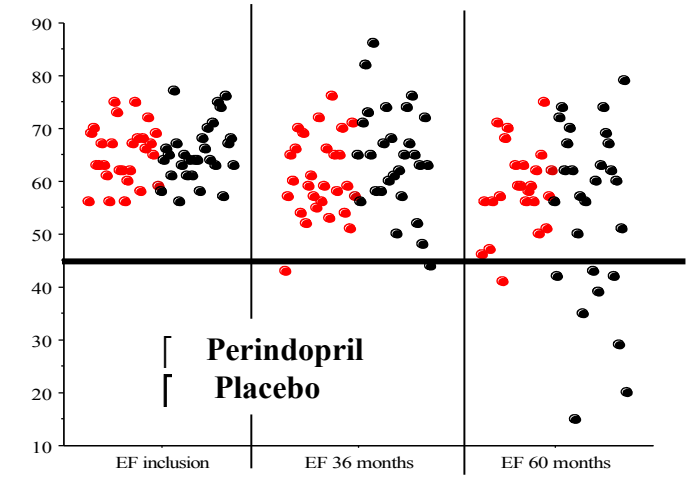
Duchenne MD
ACE inhibitors

57 patients
Age = 9.5-13 years
LVEF>55%

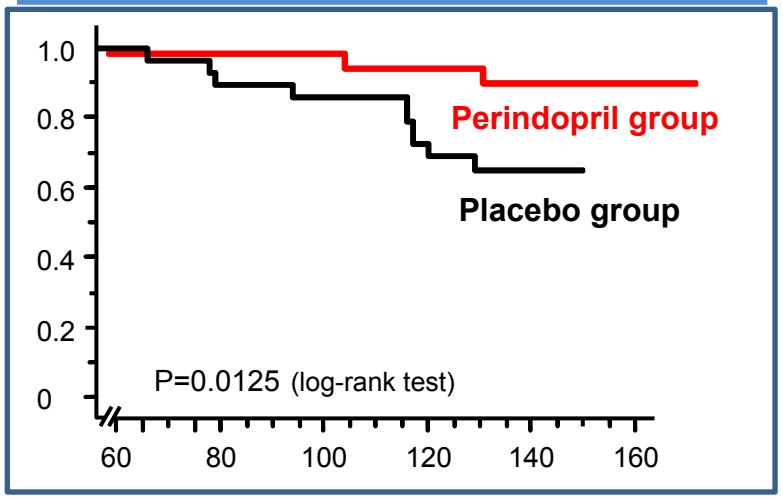
Prospective multicenter randomized trial: perindopril vs. placebo



5 years: 1 vs 8 patients with EF<45%



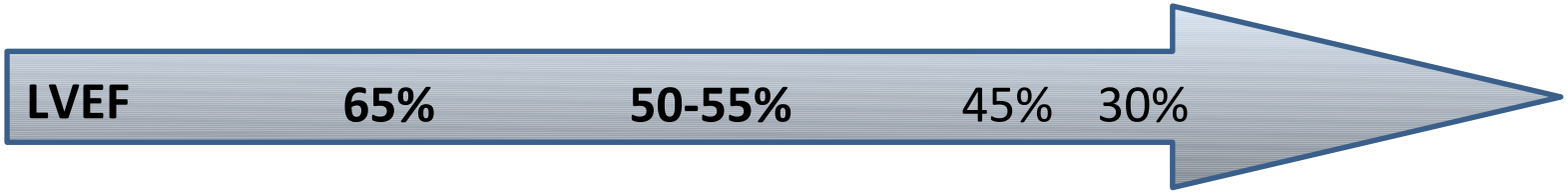
10 years: 27% mortality reduction



Duboc D, J Am Coll Cardiol 2005;45:855-7

Dilated cardiomyopathies

Prevention: when and how?



Cardiac MRI…… **Fibrosis?**

Echo – TDI, *Speckle tracking*…… **Myocardial strain?**

Biomarkers…… **HF, fibrosis, miRNAs?**

Genetic markers…… **SNPs,…**

Treatment?

Medical treatment

Conclusion

Proximité muscles striés squelettique et cardiaque

- Physiologie
- Pathologies acquises et génétiques
- Mêmes gènes

Prises en charges cardiomyopathies génétiques

- Spécifiques ++
- Intérêt des mesures préventives (ins. cardiaque, mort subite)

Manifestations cardiaques des mitochondriopathies

- Délétions ADNm
- Mutation MELAS
- Mutation MERRF
- Autres mutations

Revue de la littérature

Suivi cohorte patients de la Pitié Salpêtrière :

- 2000 – 2013
- 250 patients porteurs de mutations
- Del (102), MELAS (57), MERRF (22), POLG (21), Twinkle (10), autres mtDNA (28), autres nucléaires (9)

Manifestations cardiaques des mitochondriopathies

Atteinte myocardique - ventriculaire

- Hypertrophie
- Dilatation
- Dysfonction systolique

Insuffisance cardiaque

Hospitalisations pour IC décompensée

Décès

Anomalies « électriques »

- Troubles conductifs
- Troubles du rythme auriculaire
- Troubles du rythme ventriculaire

Syncopes

Blocs sévères (BAV 3)

Mort subite

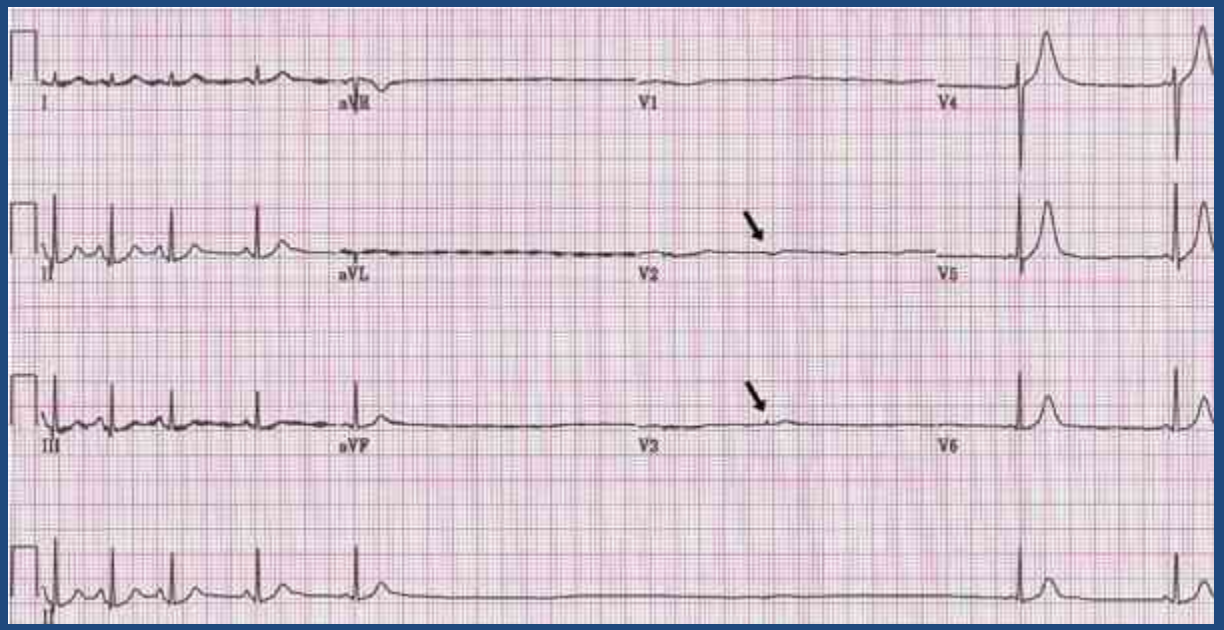
Causes de décès

- *Klopstock et al. Neurology 1999* : 16 décès (MELAS=9, PEO=7) - 5 décès « cardiorespiratoires »
- Pitié Salpêtrière : 41 décès (17% des patients)

  - **décès cardiaques = 11 (30% - 8 insuffisances cardiaques, 3 morts subites)**

Délétions ADN mitochondrial
Manifestations cardiaques

1/ <u>Troubles conductifs, principalement auriculo-ventriculaires</u>



2/ <u>Cardiomyopathie dilatée</u>

Hirano et al. Molecular genetics 2001
Auré et al. Brain 2007

Délétions ADN mitochondrial

Continuum : PEO isolées – KSS « incomplet » – KSS

- *Auré et al. Brain 2007*

	Trouble conductif	Pacemaker	Cardiomyopathie dilatée
CPEO/+N (N=29)	58%	73%	17%
CPEO/-N (N=40)	32%	5%	0%

- *Hirano et al. Molecular genetics 2001*

KSS - Troubles conductifs : 84% des patients (61/73)

- *Pitié Salpêtrière* : pacemaker 18 patients (17%)
  - 13 patients avec troubles conductifs sévère symptomatique
  - 5 patients appareillés

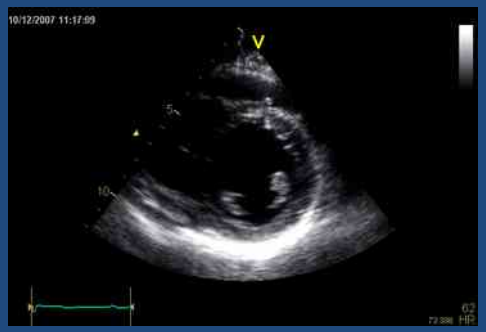
Suivi : ECG – échographie cardiaque

Indications d'implantation d'un stimulateur cardiaque

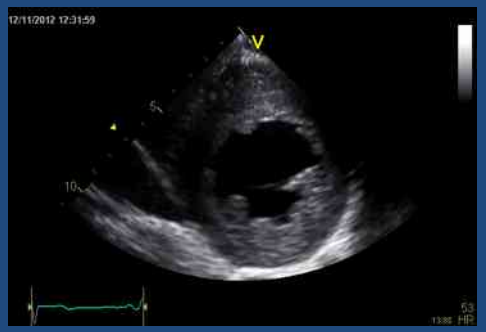
MELAS – m.3243A>G

Manifestations cardiaques

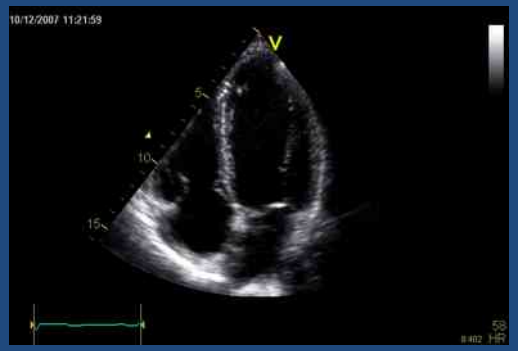
1/ **<u>Atteinte myocardique</u> :** hypertrophie ventriculaire G (27-37%) – dysfonction systolique (18-35%)

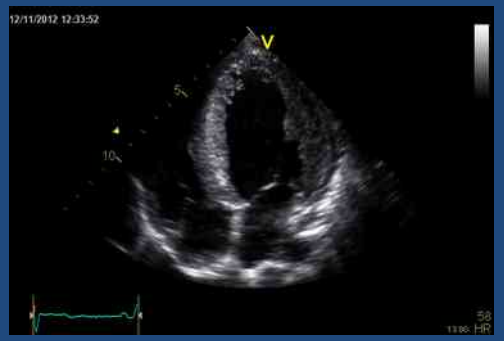


TEMOIN



MELAS





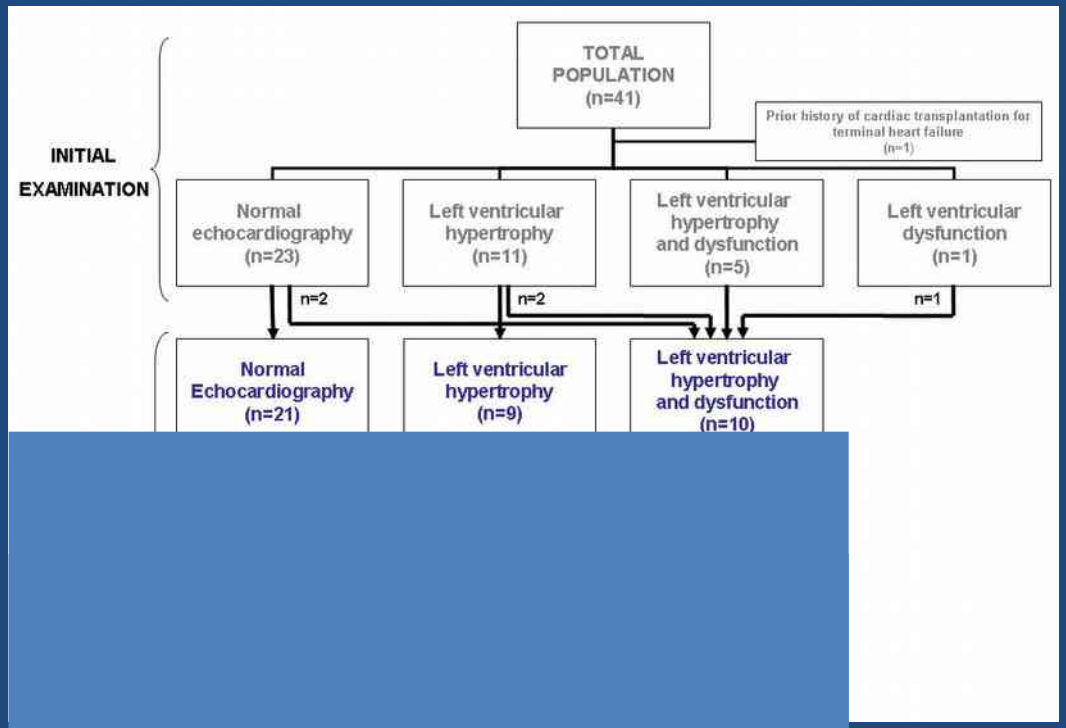
2/ Syndrome de Wolff Parkinson White (9-14%)

3/ Troubles conductifs (6%)

Hirano et al. Molecular genetics 2001, Majamaa-Voltti et al, BMJ 2002, Majamaa-Voltti et al, Neurology 2006, Wortmann et al, Acta Predicts 2007, Okajima et al, Heart 2008, Sproule et al, Arch Neurol 2009

MELAS – m.3243A>G

Manifestations cardiaques



Hypertrophie VG

Dysfonction VG

ou

Décès = 11
- neurologiques = 4
- cardiologiques = 3

Malfatti et al. Neurology 2013