Troubles du Rythme Ventriculaire Héréditaires

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Filière Cardiogen
DEIU 15 Janvier 2019

Centre de Référence des Maladies Cardiaques Héréditaires

cardiogen
filière nationale de santé
maladies cardiaques héréditaires

Causes de mort subite

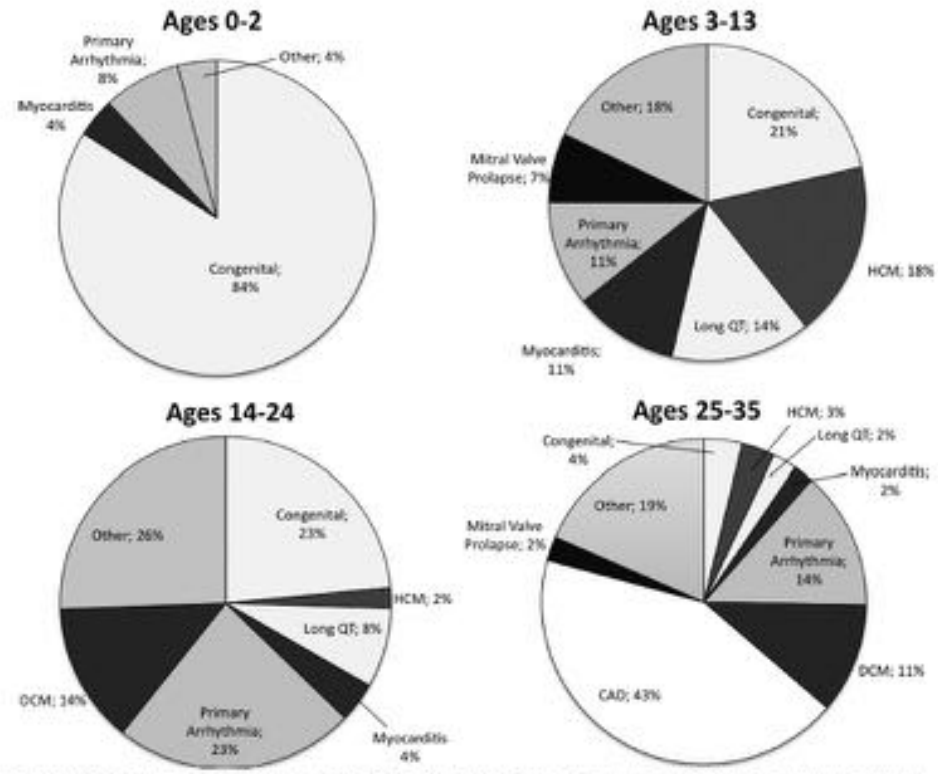
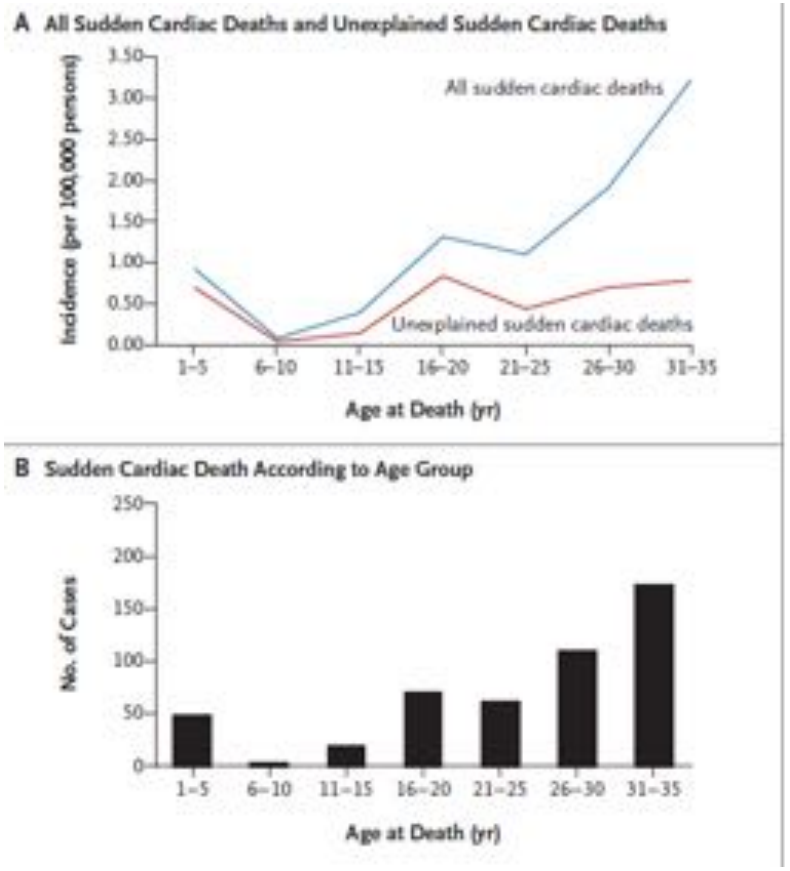


Figure 2. Detailed causes of arrest by age group. HCM indicates hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; and CAD, coronary artery disease. Other corresponds to all other causes.

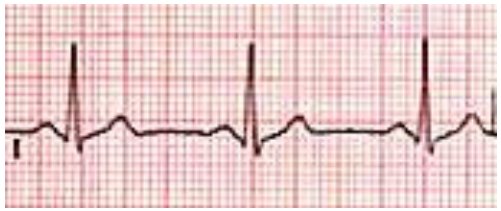


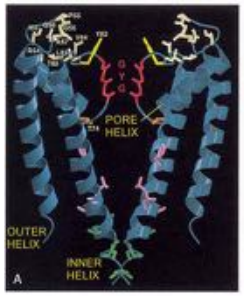
R.D. Bagnall,

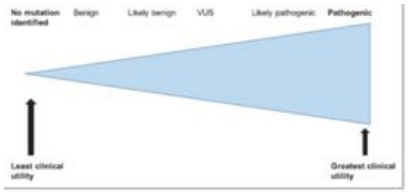
Canalopathies cardiaques

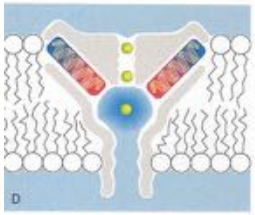
- Anomalie de fonctionnement d'un type de canal ionique cardiaque
- Survenue de troubles du rythme ventriculaire avec coeur « sain »
- Pronostic vital en jeu = > mort subite
- Origine génétique => maladie familiale transmissible

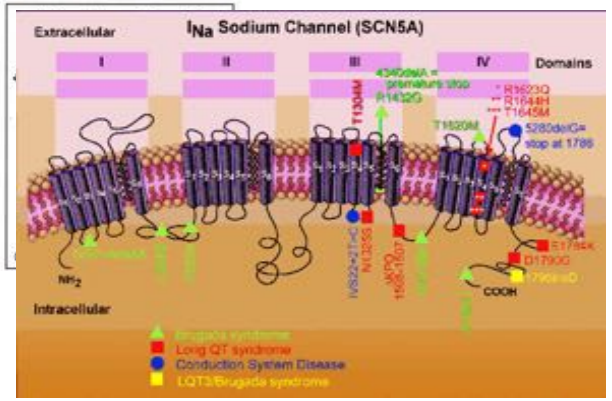
Maladies électriques

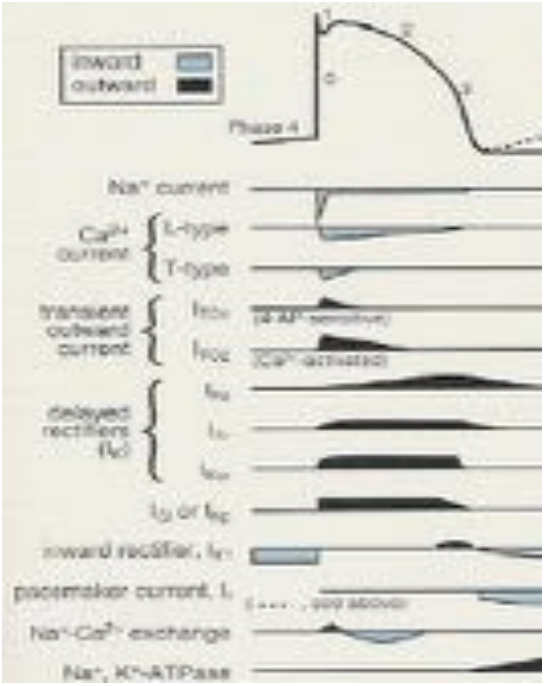


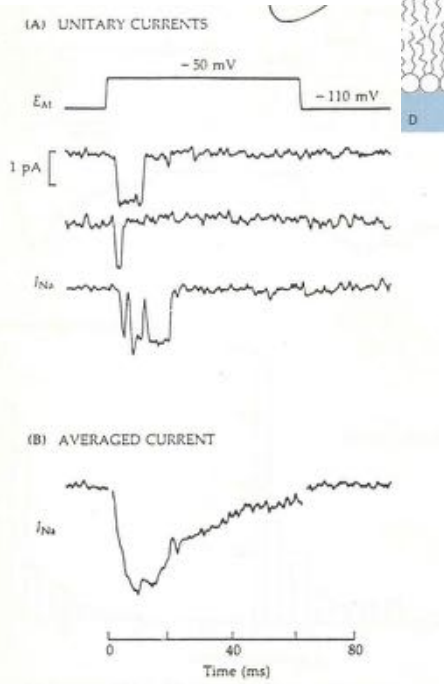


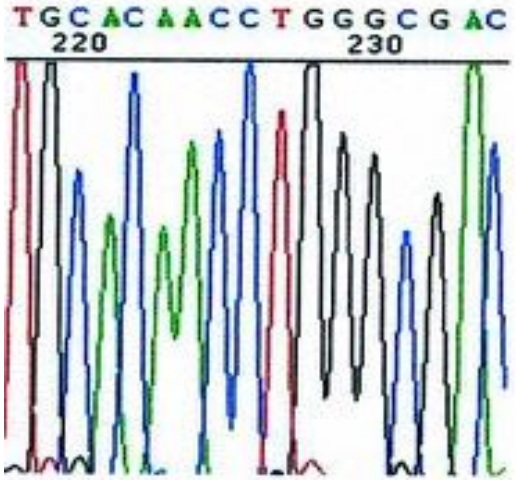












« Canalopathies »

Quand penser à une canalopathie chez l'enfant?

- Syncope
- Arrêt cardiaque
- Noyade
- Symptomatologie neurologique (comitialité)
- Circonstances : effort - émotion - fièvre
- Histoire familiale de MS ou de PC
- Absence d'ATCD cardiaques personnels
- Cœur normal ou Autopsie négative

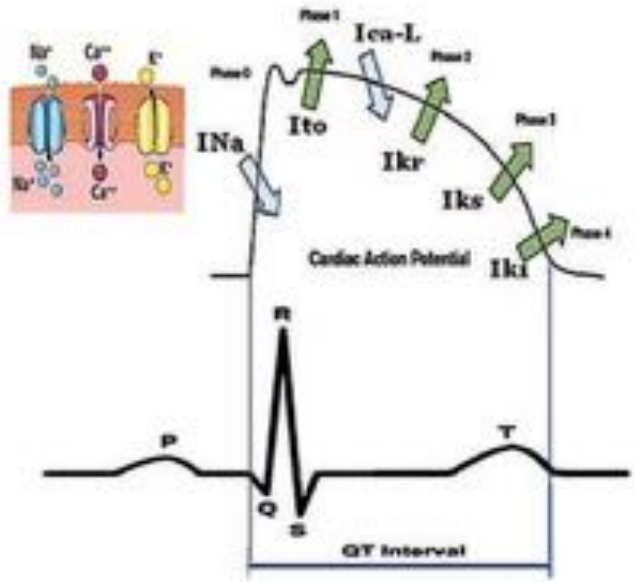
Syndromes en cause

- Syndrome du QT Long congénital
- Tachycardies Ventriculaires Catécholergiques
- Syndrome de Brugada
- Syndrome du QT court
- Syndrome de repolarisation précoce

Syndrome du QT Long

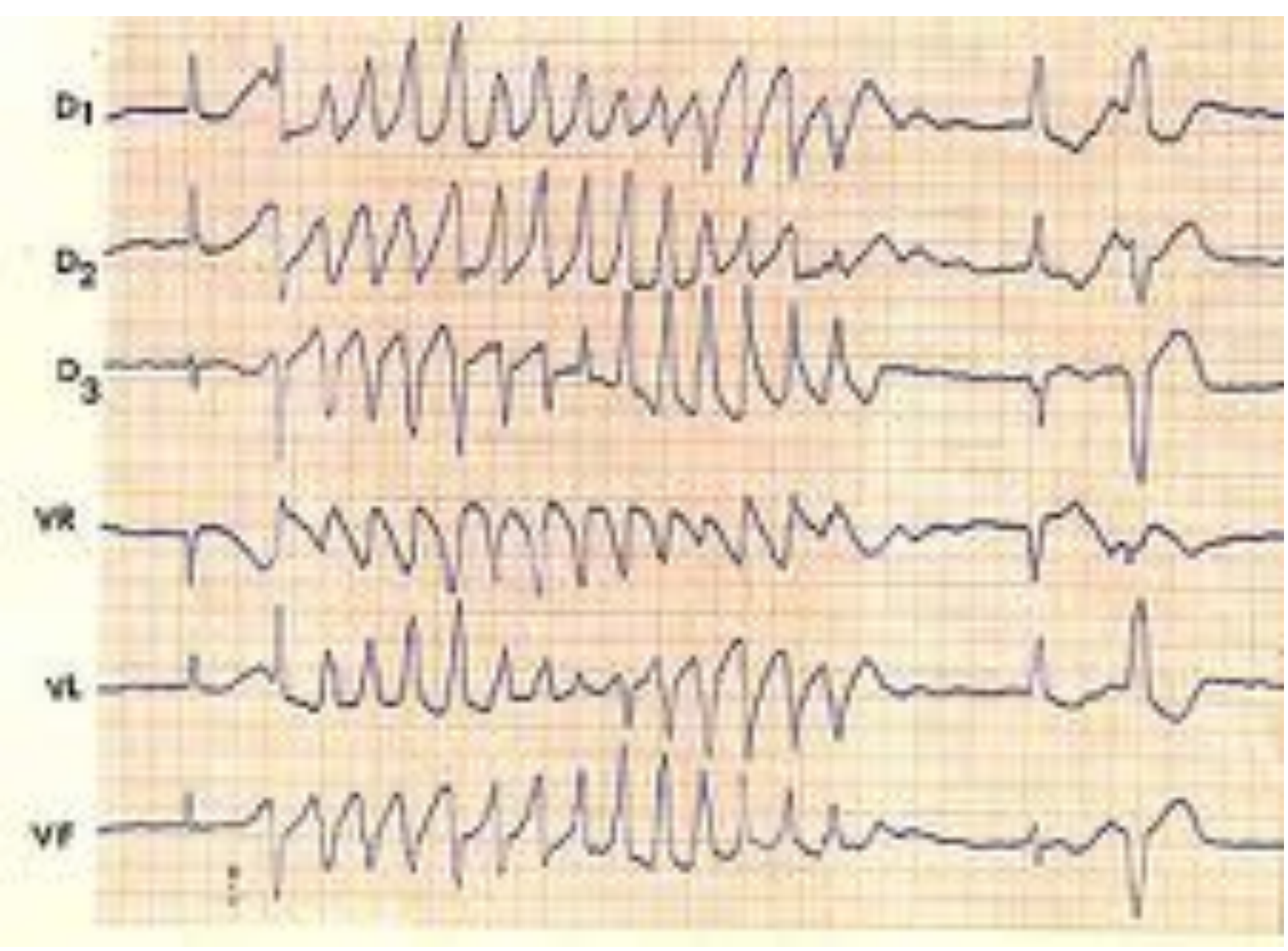
- Maladie génétique (1/2500) : 17 gènes connus
- Transmission autosomale dominante (95%)
- Pénétrance 70 % (7 à 90%)
- ECG : intervalle QTc allongé (> 440 ms)
- Torsade de pointes, TV
- Syncope, Arrêt cardiaque/ MS chez enfants et adultes jeunes (30%)
- Facteurs favorisants : stimulation adrénergique (effort, émotions), médicaments QT↗

Allongement du potentiel d'action => QT ↑



Cardiogenetics 2011; 1(s1):e2
doi:10.4081/cardiogenetics.2011.s1.e2

LQTS Type	Gene	Protein	Current	Frequency
LQT1	*KCNQ1*	Kv7.1	IKs↓	40%–45%
LQT2	*KCNH2*	KV11.1	IKr↓	30%–35%
LQT3	*SCN5A*	Nav1.5	INa↑	10%
LQT4	*ANK2*	Ankyrin-B	Na+/K+↓	1%
LQT5	*KCNE1*	MinK	IKs↓	1%
LQT6	*KCNE2*	MiRP1	IKr↓	Rare
LQT7	*KCNJ2*	Kir2.1	IK1↓	Rare
LQT8	*CACNA1C*	CaV1.2	ICa-L↑	Rare
LQT9	*CAV3*	Caveolin 3	INa↑	Rare
LQT10	*SCN4B*	SCNβ4 subunit	INa↑	Rare
LQT11	*AKAP9*	Yotiao	IKs↓	Rare
LQT12	*SNTA1*	Syntrophin-α1	INa↓	Rare
LQT13	*KCNJ5*	Kir3.4	IKACH↓	Rare
LQT14	*CALM1*	Calmodulin 1	Calcium signalling	Rare
LQT15	*CALM2*	Calmodulin 2	Calcium signalling	Rare
LQT16	*TRDN*	Triadin	ICa-L↑	Rare
Jervell and Lange-Nielsen syndrome (autosomal recessive)				
JLN1	*KCNQ1*	Kv7.1	IKs↓	Rare
JLN2	*KCNE1*	MinK	IKs↓	Rare


D1
D2
D3
VR
VL
VF

Diagnostic

1. a: score ≥ 3.5
1. c: QTc ≥ 500 ms

1. Le SQTL est diagnostiqué :
   a. En présence d'un score de risque > 3 en l'absence d'une cause secondaire à l'allongement du QT, et/ou
   b. En présence d'une mutation pathogène dans un des gènes du SQTL quelle que soit la valeur du QTc, ou
   c. En présence d'un QTc ≥ 480 ms sur l'ECG 12 dérivations et en l'absence d'une cause secondaire d'allongement du QT.

2. Le SQTL peut être diagnostiqué en présence d'un QTc ≥ 460 ms sur l'ECG 12 dérivations chez un patient ayant présenté une syncope inexpliquée en l'absence de cause secondaire à l'allongement du QT et en l'absence d'une mutation pathogène.

2 . QTc entre 480 et 499 ms

ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

1993–2011 LQTS Diagnostic Criteria

	Points
Electrocardiographic findings #	
A QTc*	
≥480 ms	3
460–479 ms	2
450–459 ms (in males)	1
B QTc* 4th minute of recovery from exercise stress test ≥480 ms	1
C Torsade de pointes"	2
D T wave alternans	1
E Notched T wave in 3 leads	1
F Low heart rate for age@	0.5
Clinical history	
A Syncope"	
With stress	2
Without stress	1
B Congenital deafness	0.5
Family history	
A Family members with definite LQTS$	1
B Unexplained sudden cardiac death below age 30 among immediate family members$	0.5

#In the absence of medications or disorders known to affect these electrocardiographic features.
*QTc calculated by Bazett's formula where QTc=QT/$\sqrt{RR}$.
"Mutually exclusive.
@Resting heart rate below the 2nd percentile for age.
$The same family member cannot be counted in A and B.

SCORE

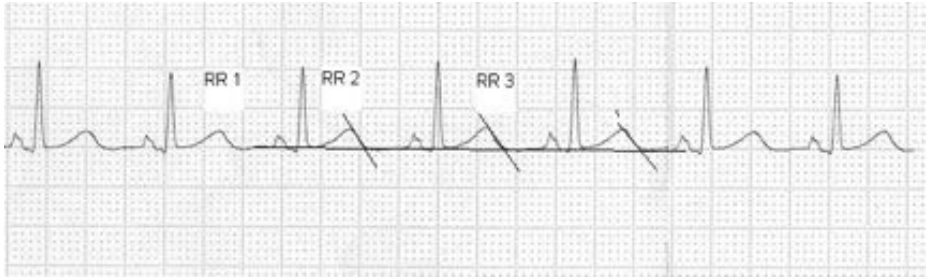
≤ 1 point: faible probabilité de SQTL.

1.5 à 2.5 points: probabilité intermédiaire de SQTL.

>3 points: probabilité élevée.

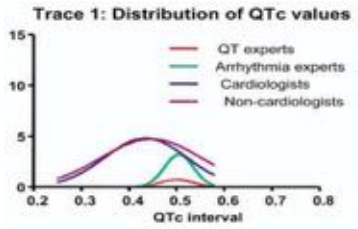
PJ Schwartz & L Crotti
Circulation 2011;124: 2181-4

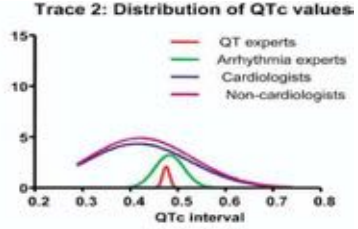
QT interval measurement

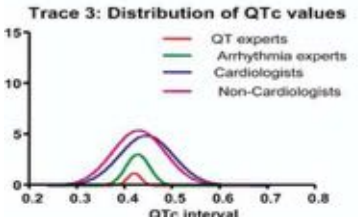


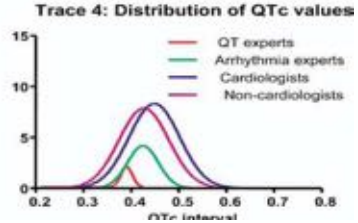
Corrected QT interval (Bazett's formula)

$$QTc = \frac{(QT1/\sqrt{RR1}) + (QT2/\sqrt{RR2}) + (QT3/\sqrt{RR3})}{3}$$

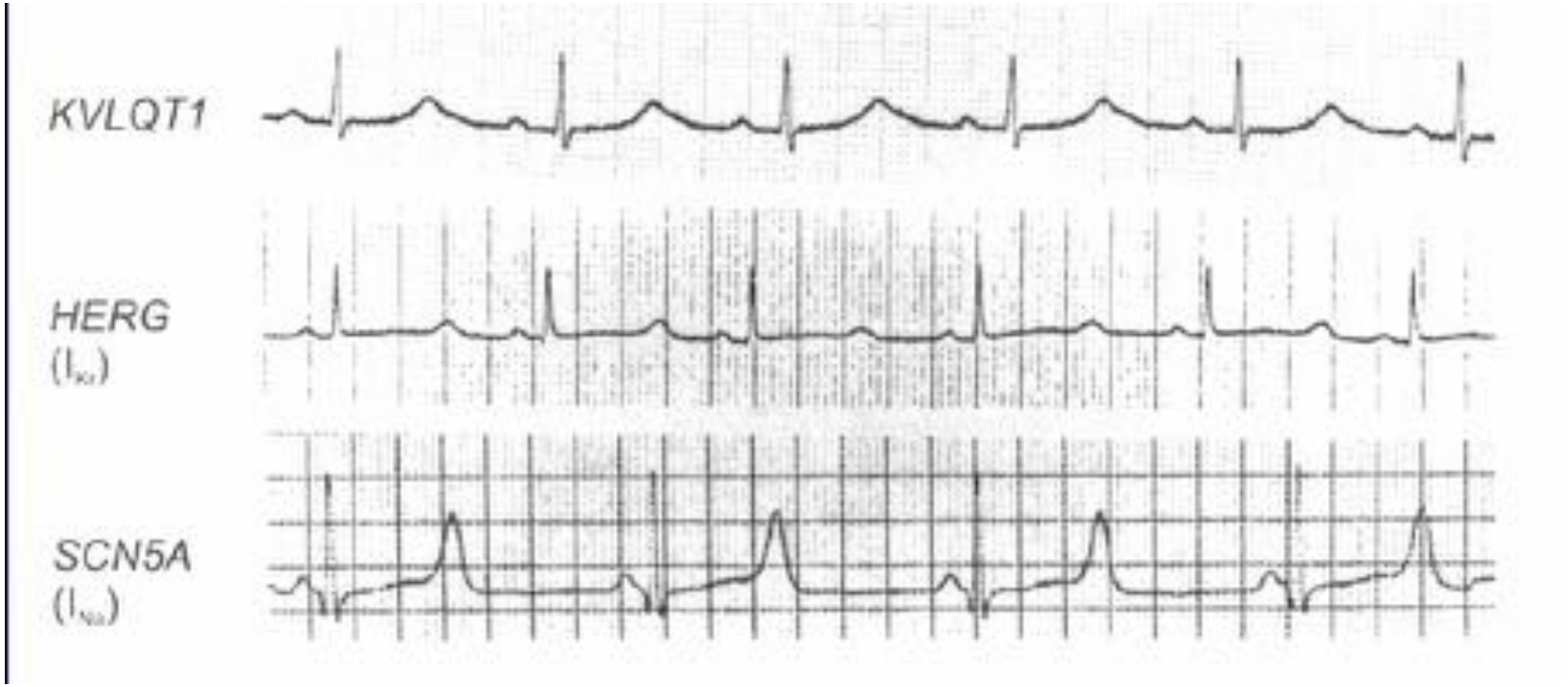






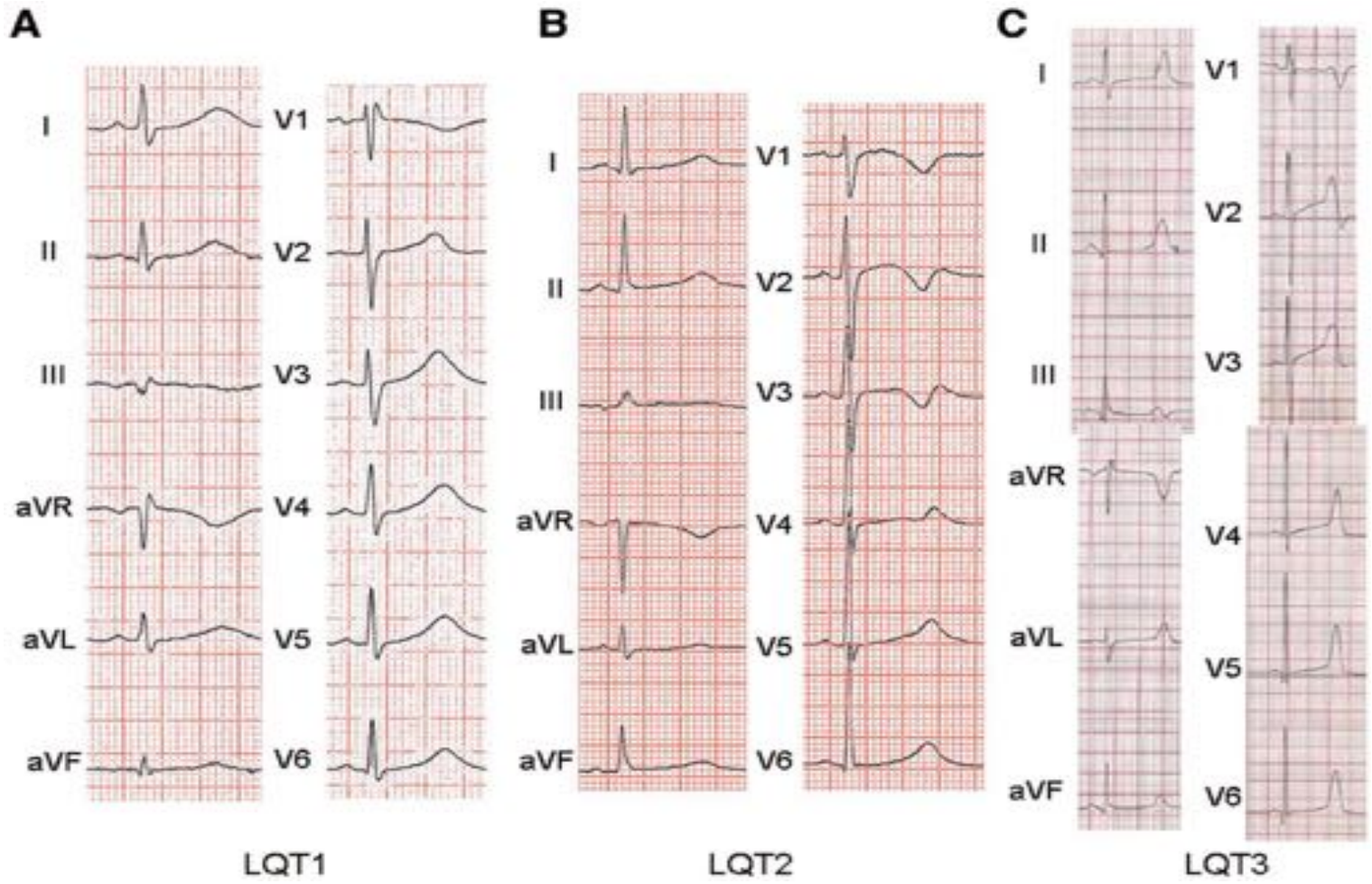


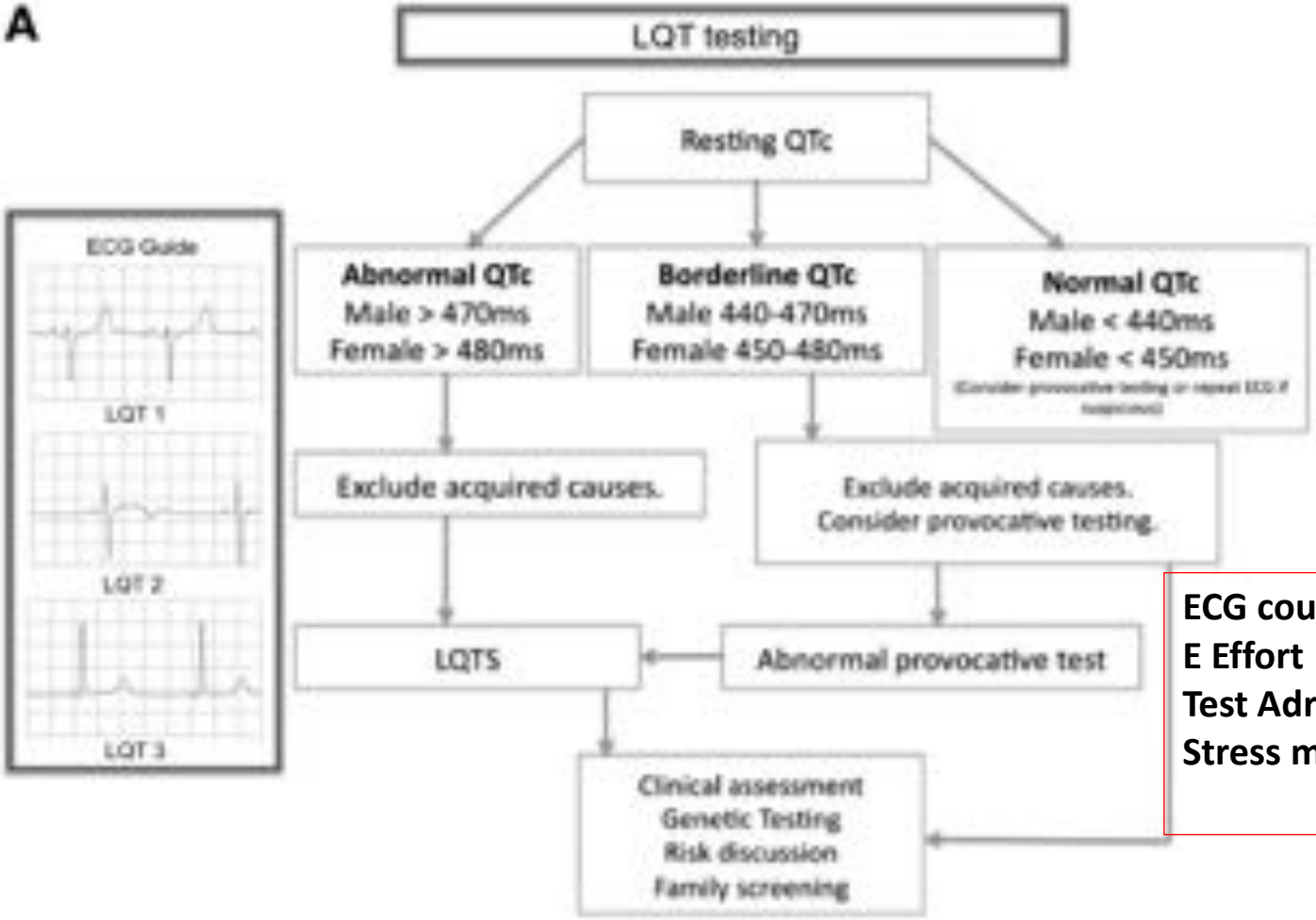
Aspects ECG du SQTL



Lupoglazoff et al Arch Mal Cœur 2003; 96:539-47

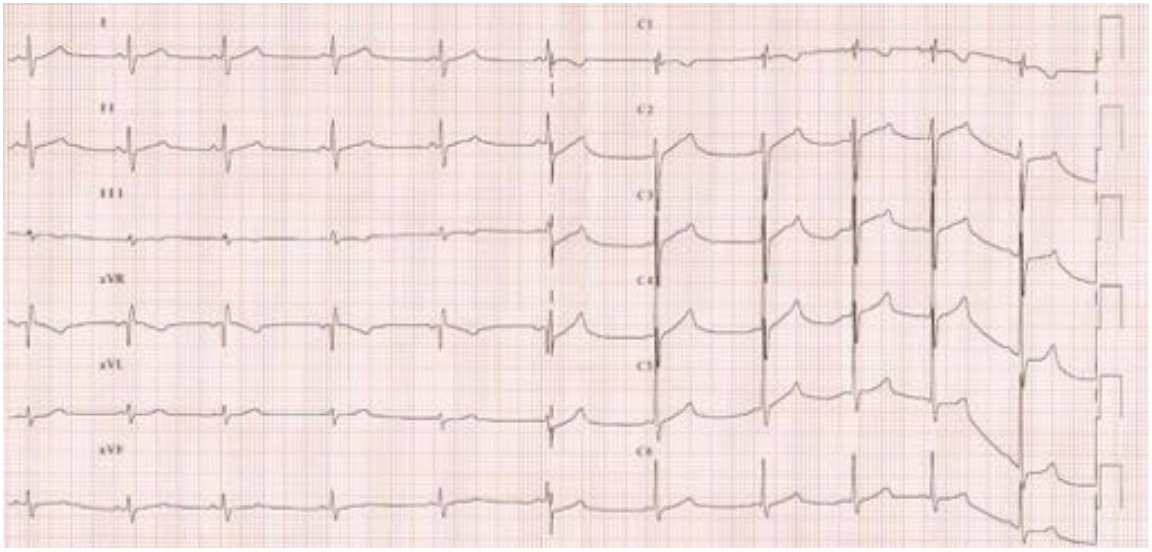
T Wave morphology





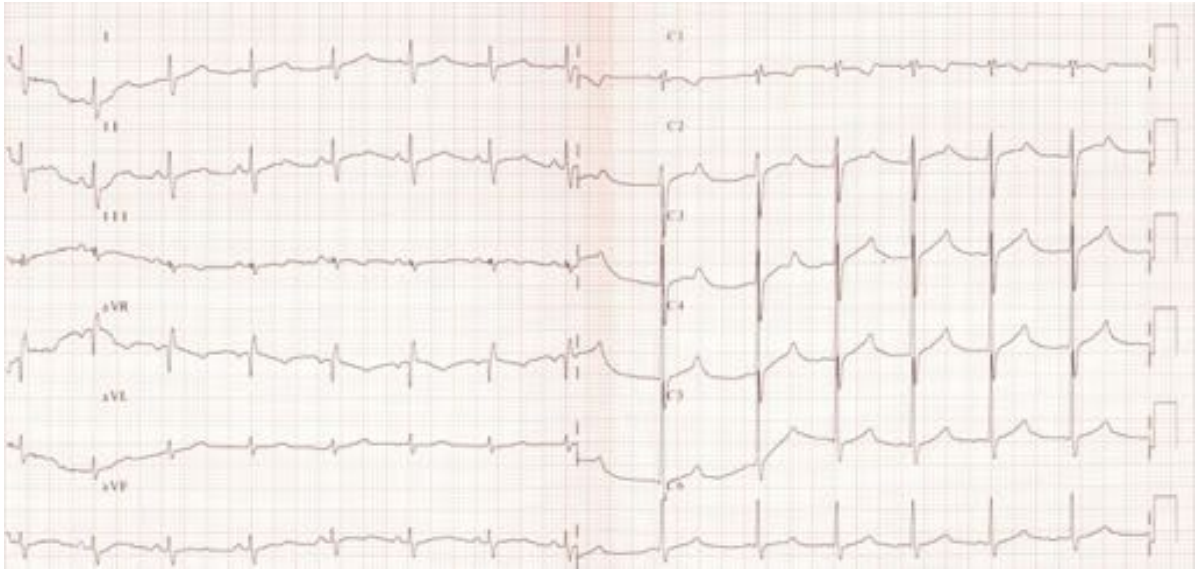
ECG couché/debout
E Effort : 4ème mn récup
Test Adrénaline
Stress mental

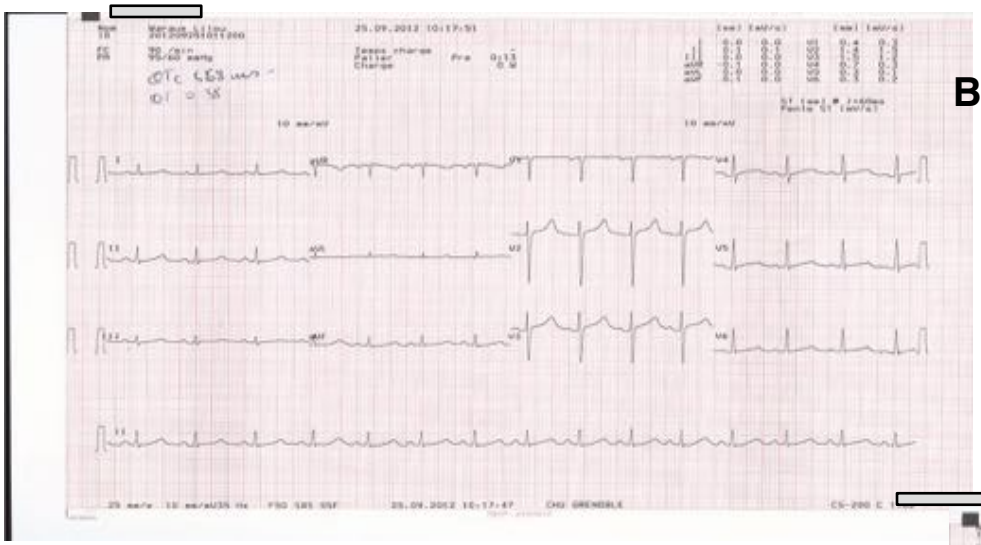
Obeyesekere M et al. Circ Arrhythm Electroph 2011; 4 : 958-964



ECG allongé : QTc 440ms

ECG debout : QTc 470ms

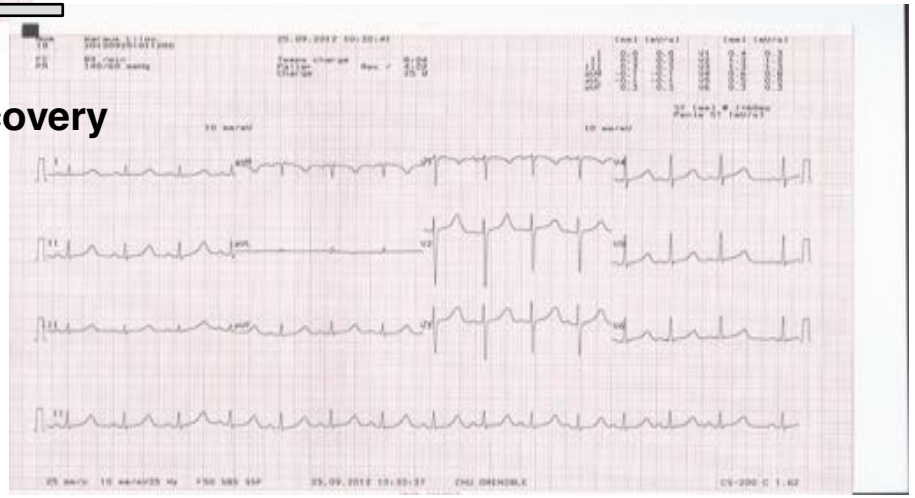




Baseline

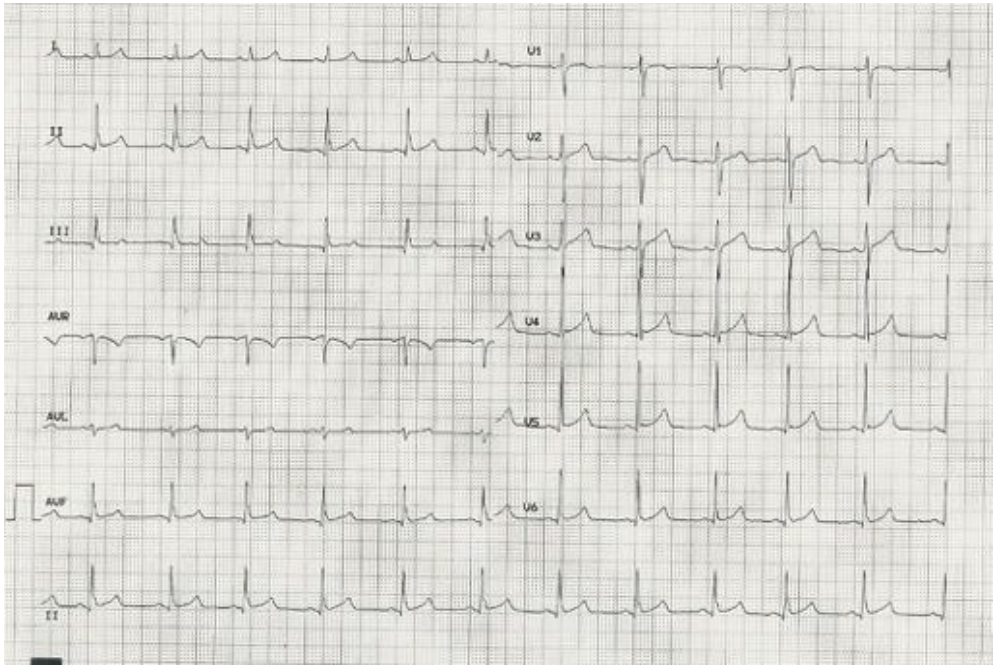
Sensitivity 94%
Specificity 90%

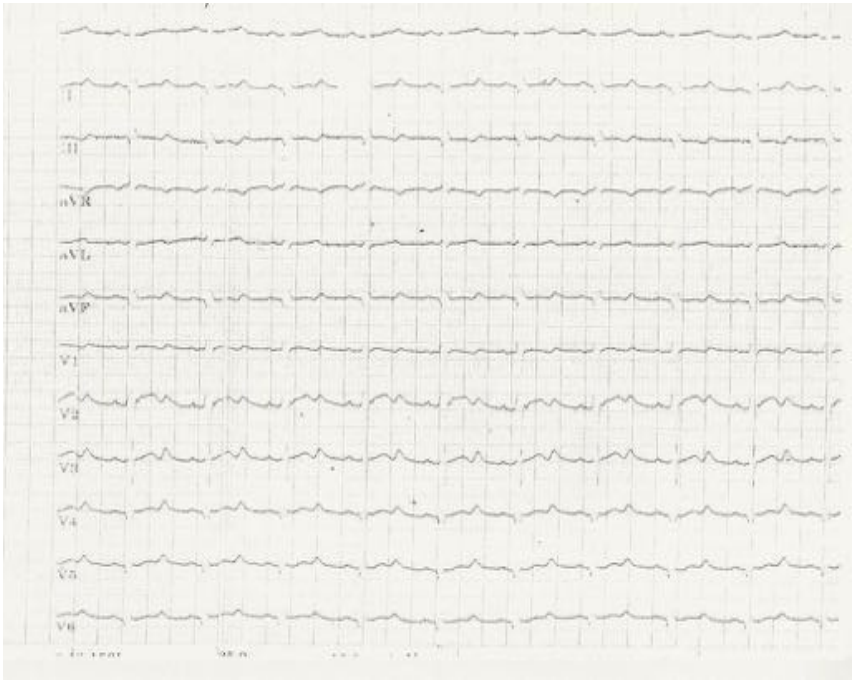
4th mn recovery



RW Sy et al. Circulation 2011; 124: 2187-94

Syncope in a 12 year old girl



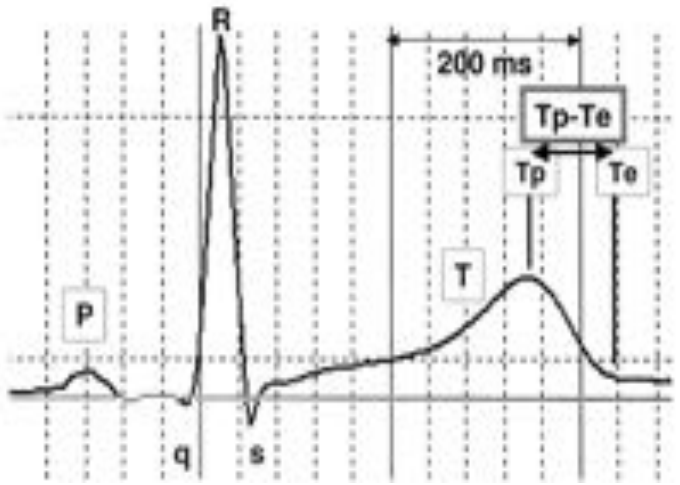


Baseline ECG : QTc 450 ms

Adrenaline challenge : QTc 530 ms

Rechercher les anomalies de la repolarisation

- **Dynamique :**
  - Pentes QT/RR jour < nuit (Holter)
    - Merri et al, Circulation 1992
    - Neyroud et al, Eur Heart J, 1998
  - QTp/QTe ↗
    - Extramiana et al, Am J Cardiol 2005
    - Viitasalo et al, JACC 2006



- **Morphologie :**
  - ECG de surface
    - Moss et al, Circulation 1995
    - Zangh et al, Circulation 2001
  - Moyennage en fct FC (Holter)
    - Lupoglazoff et al, Circulation 2001

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

STATE OF GENETIC TESTING FOR LONG QT SYNDROME (LQTS)

Class I (is recommended)

Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.

Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing **is recommended** for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults).

Mutation-specific genetic testing **is recommended** for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

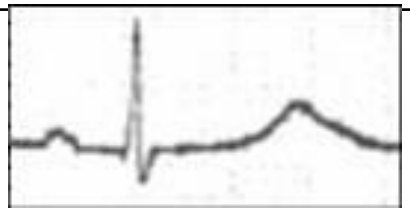
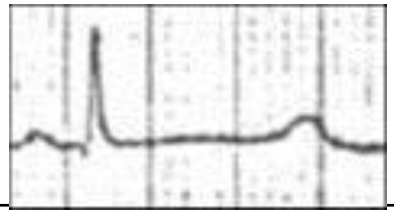
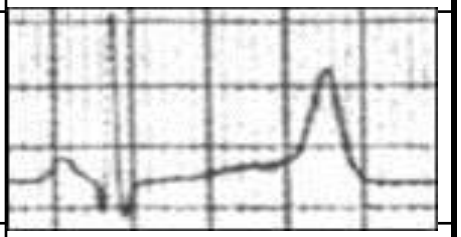
Class IIb (may be considered)

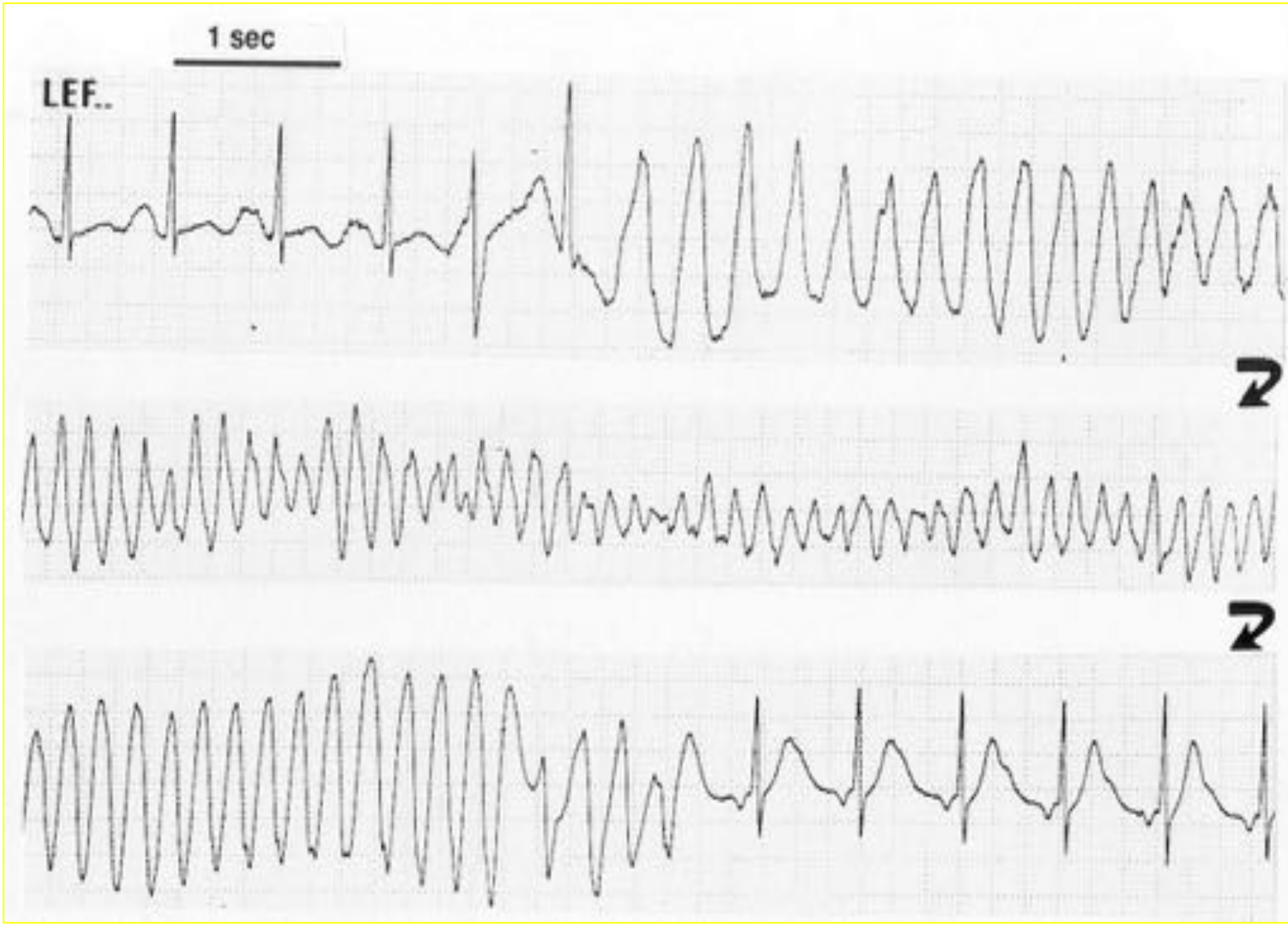
Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing **may be considered** for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs.

Positif 50%

Heart Rhythm 2011;8:1308-39

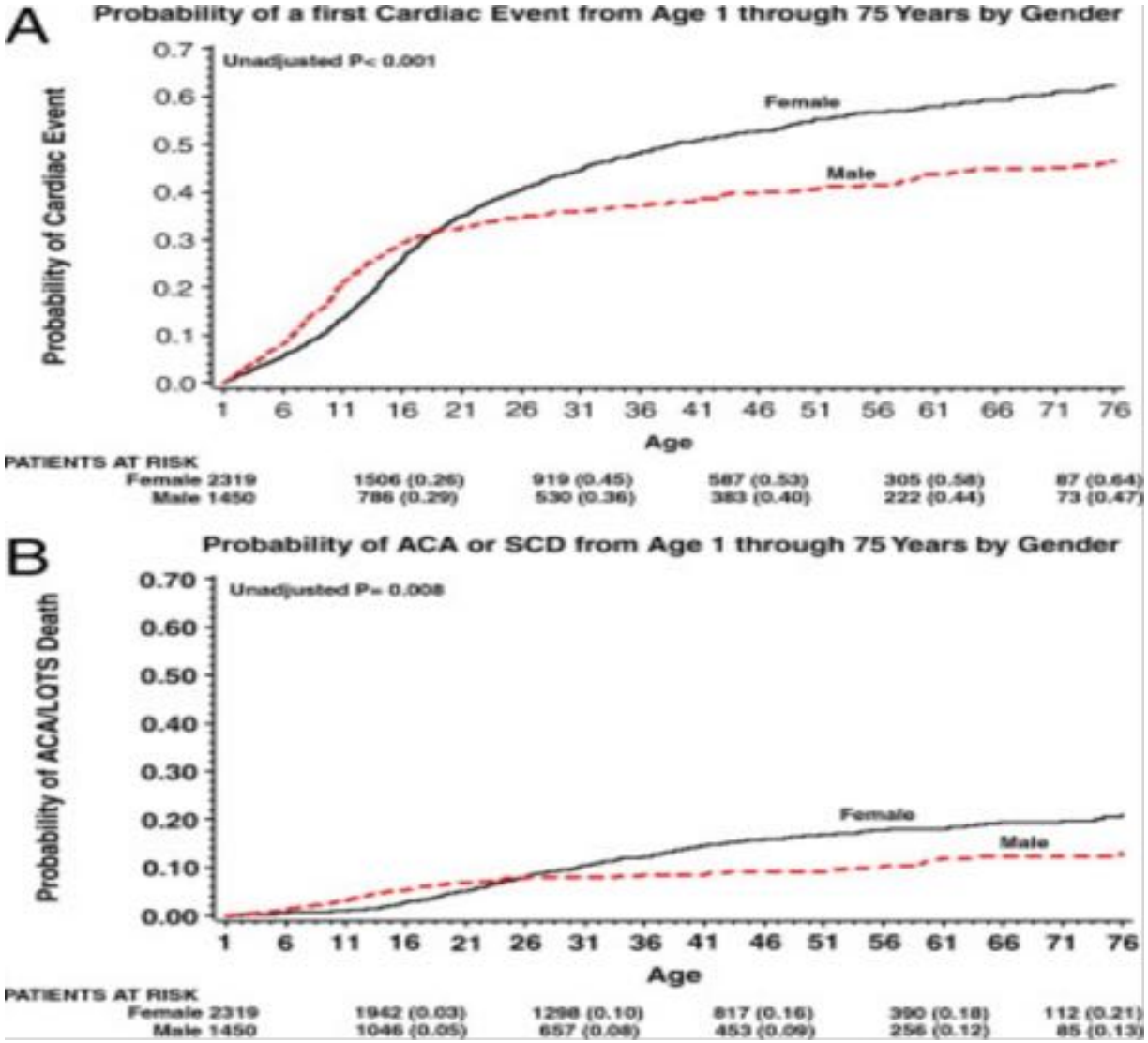
Syndrome du QT Long : QTc > 440 ms

	LQT1	**LQT2**	**LQT3**
Gènes	KCNQ1	KCNH2	SCN5A
Proportion	50%	46%	4%
Morphologie onde T			
F déclenchant	Sports, drogues QT↗	Emotion, drogues QT↗	Repos, drogues QT↗


1 sec
LEF..

QTL et risque d'évènements cardiaques

- **Pas de symptômes pour 50 % des patients QTL (génétique + clinique)**
- **Syncopes 40% ; Mort subite 4% (Stimulation adrénergique +++)**
- **Facteur de risque majeur : durée de QTc**
-
- **30 % des patients mutés ont un QTc compris entre 400 et 460 ms**
- **10% entre 400 et 440ms**

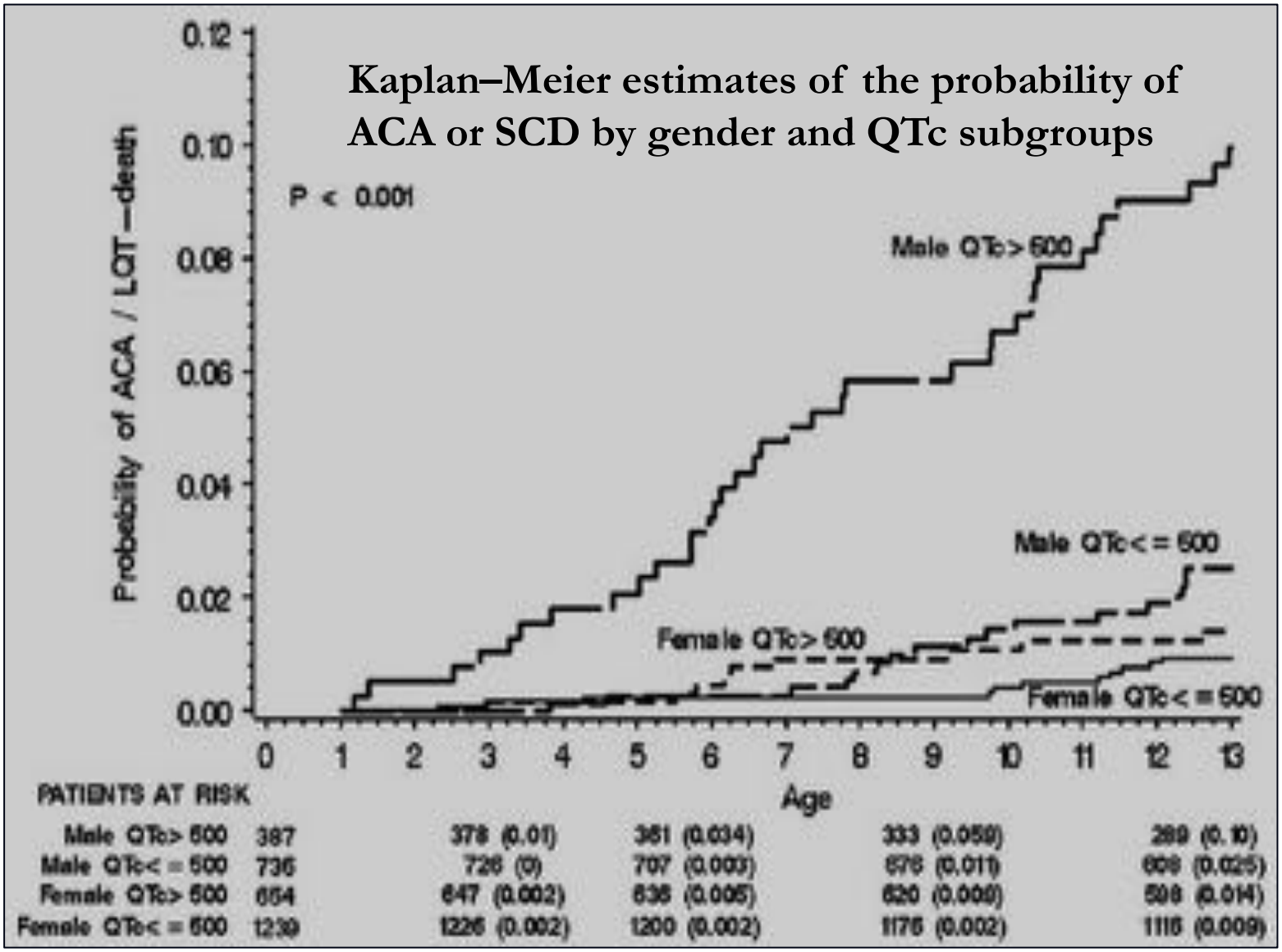


Probability of LQTS-Related Events by Gender

Kaplan-Meier estimates of the cumulative probability of (A) a first cardiac event (syncope, aborted cardiac arrest [ACA], or sudden cardiac death [SCD]) and (B) a first life-threatening cardiac event (ACA or SCD) from age 1 through 75 years by gender in 3,779 long QT syndrome (LQTS) patients from the International LQTS Registry. Reprinted, with permission, from Goldenberg et al. (30).

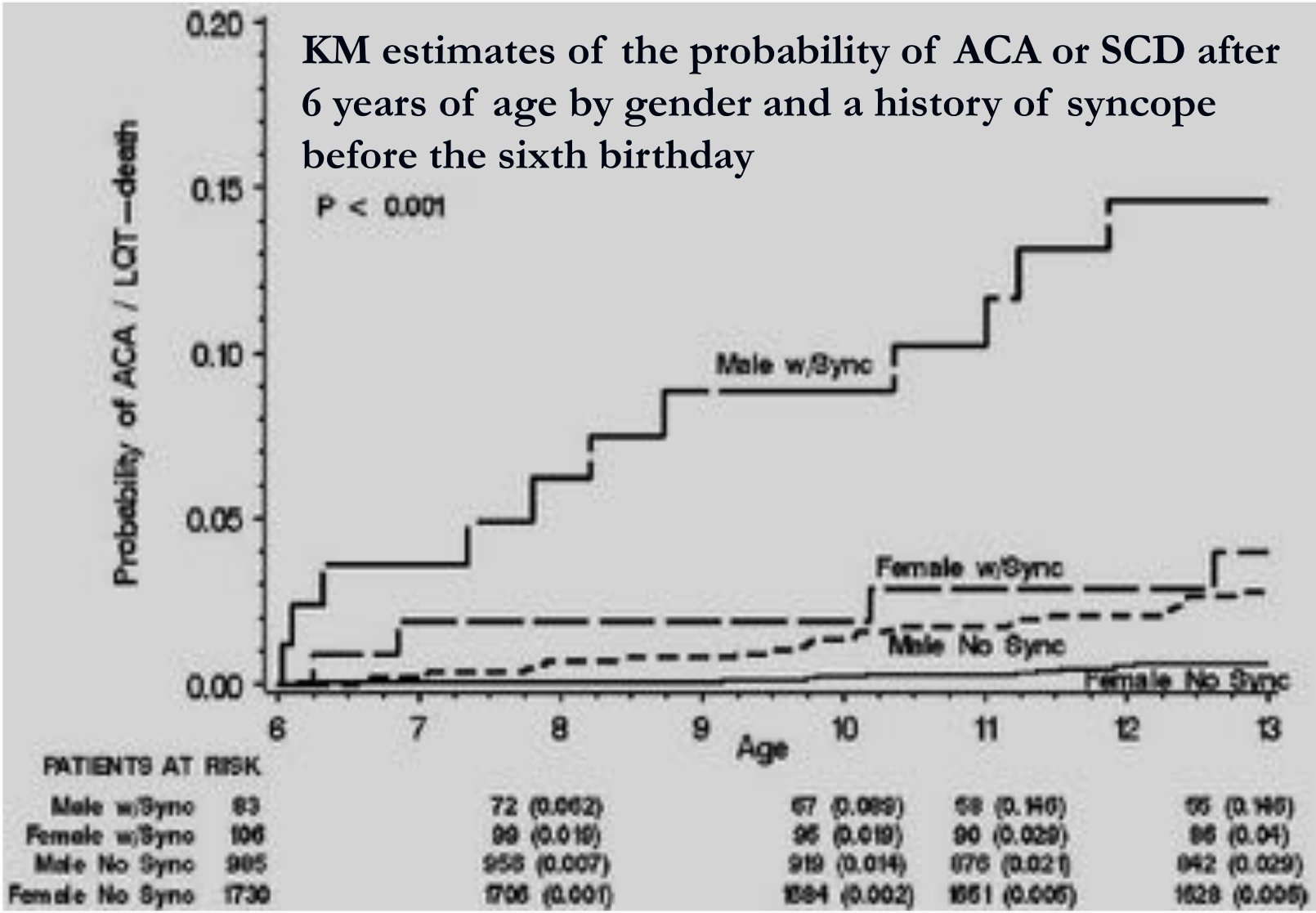
J Am Coll Cardiol. 2008;51(24):2291-2300.

QTL : Risque de MS chez l'enfant

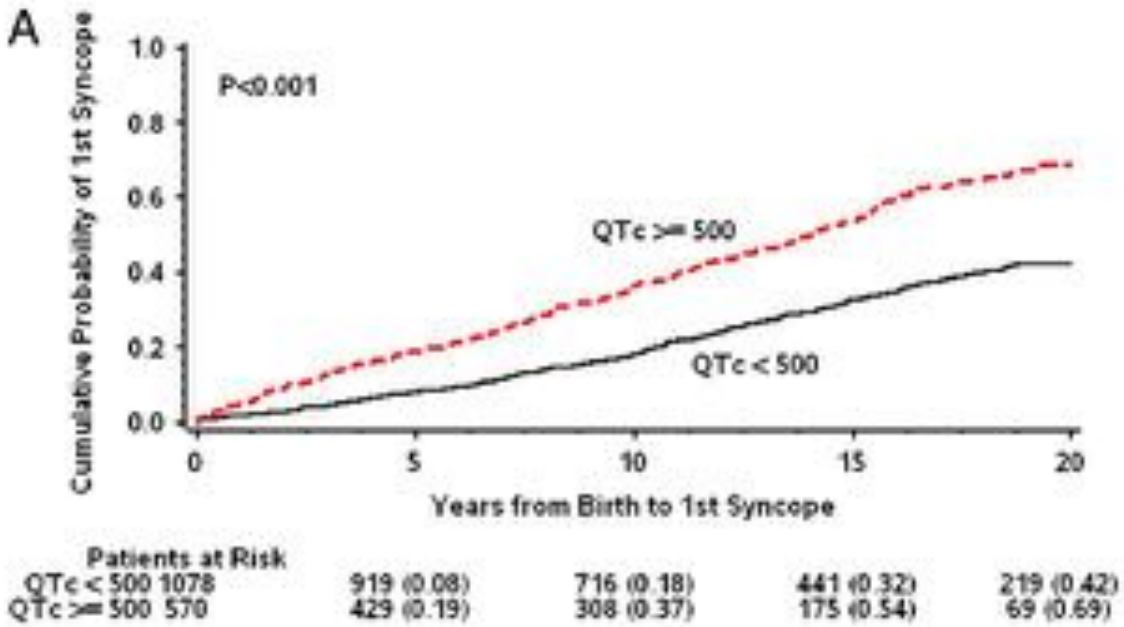


I Goldenberg et al. Circulation. 2008; 117: 2184-91

QTL : Risque de MS chez l'enfant



I Goldenberg et al. Circulation. 2008; 117: 2184-91



Suivi	0 à 20 ans
Population	1648 (827 G; 821 F)
Génotype positif	738 (QT1 51%;QT2 34%; QT3 13%)
Syncope	40%
Age 1ère syncope	9 ± 6 ans

Liu et al, JACC 2011; 57 : 911 - 50

Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

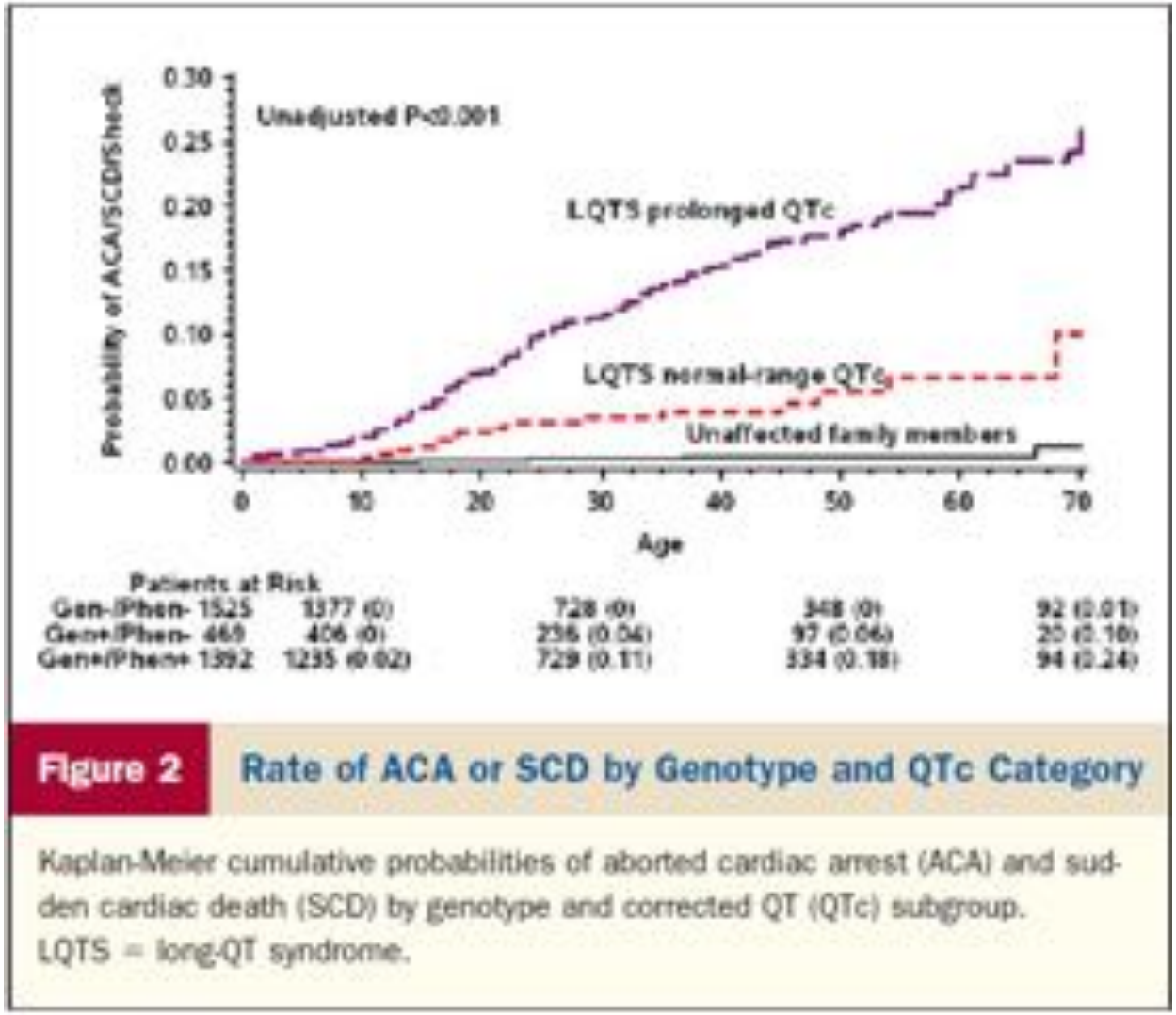


Figure 2 **Rate of ACA or SCD by Genotype and QTc Category**

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by genotype and corrected QT (QTc) subgroup.
LQTS = long-QT syndrome.

Goldenberg et al, JACC 2011; 57 : 51-9

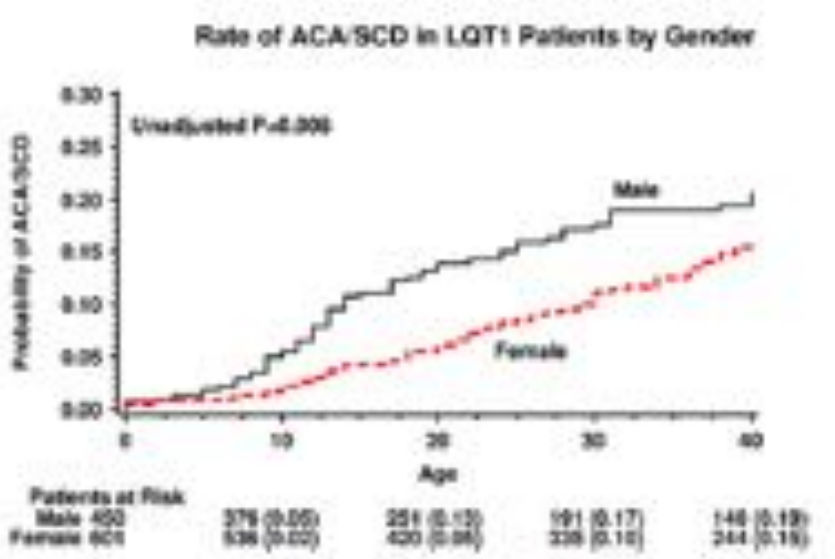


Figure 2 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in patients with LQT1 by sex. ACA = aborted cardiac arrest; LQT1 = long QT syndrome type 1; SCD = sudden cardiac death.

ACA or SD : 137 pts (13%)
Syncope 35%

Table 2 Multivariate analysis: Risk factors for ACA/SCD among all patients with LQT1*

Risk factor	Relative risk		
	Hazard ratio	95% Confidence interval	P
Sex			
Men vs women ≤ 13 y	2.31	1.41–3.92	.003
Men vs women >13 y	0.92	0.61–1.51	.72
Mutation location (vs nonmissense mutations)			
Cytoplasmic loop (S2–S3/S4–S5 linkers)	1.93	1.37–2.75	.005
MS (S1, S2, S3, S4, S5, P-loop, S6)	1.02	0.71–1.85	.51
N/C terminus	0.96	0.52–1.57	.72
QTc duration (ms)			
≥550 vs <500	4.18	2.06–8.46	<.001
500–550 vs <500	3.35	1.83–6.11	<.001
Time-dependent syncope			
Syncope vs no syncope	3.40	2.22–5.21	<.001

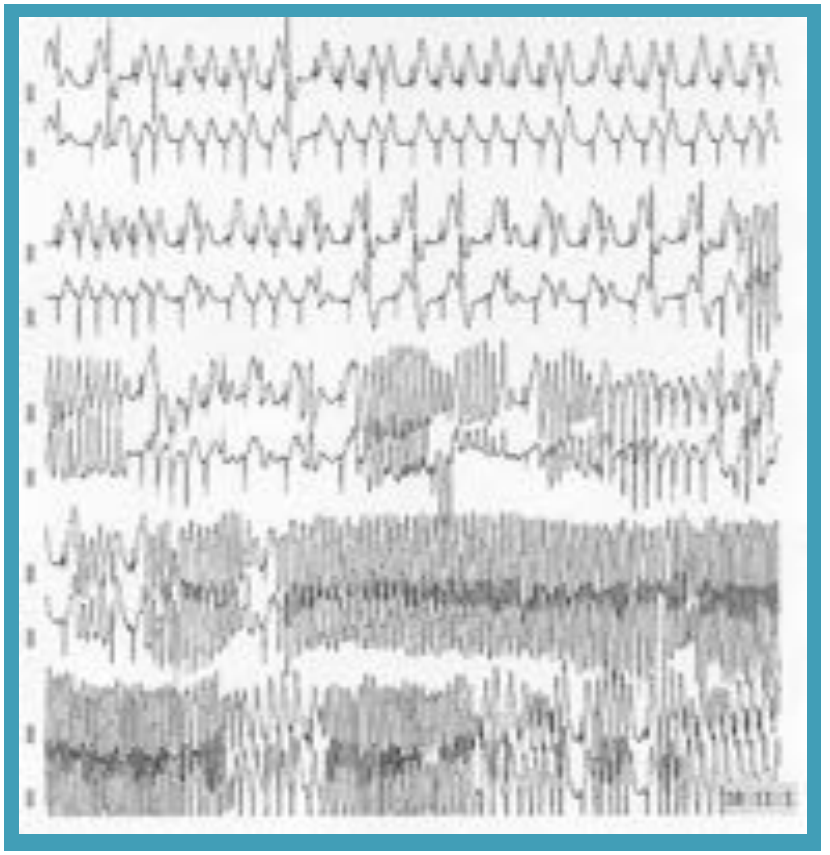
ACA = aborted cardiac arrest; LQT1 = long QT syndrome type 1; MS = membrane spanning; QTc = corrected QT interval; SCD = sudden cardiac death.
*Models were further adjusted for missing QTc values, time-dependent beta-blocker therapy.

βB : Reduction risk 61% for ACA or SD , equal effect M/F

Costa et al, Heart Rhythm 2012; 9 : 892-898

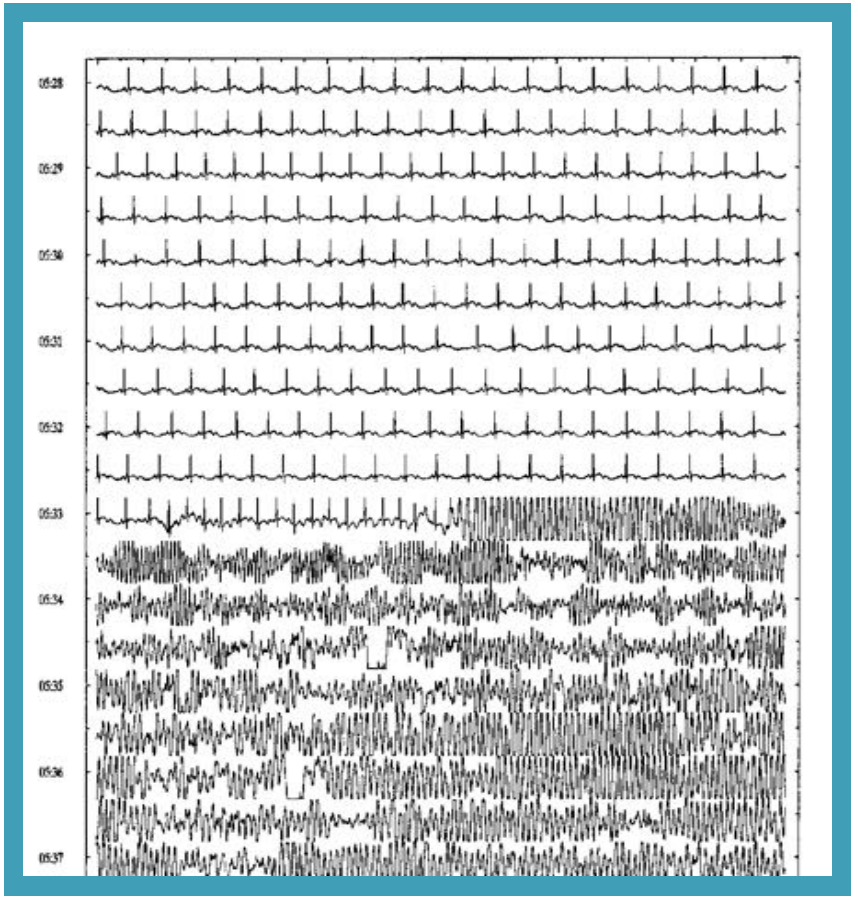
Syncope

- 40 % patients :
  - QT1 > QT2 > QT3
- Risk factors:
  - QTc > 500ms
  - Male < 13 yrs
  - Female > 13 yrs
  - TM Mutations
- Bβ effect:
  - ↓ 20 à 80%

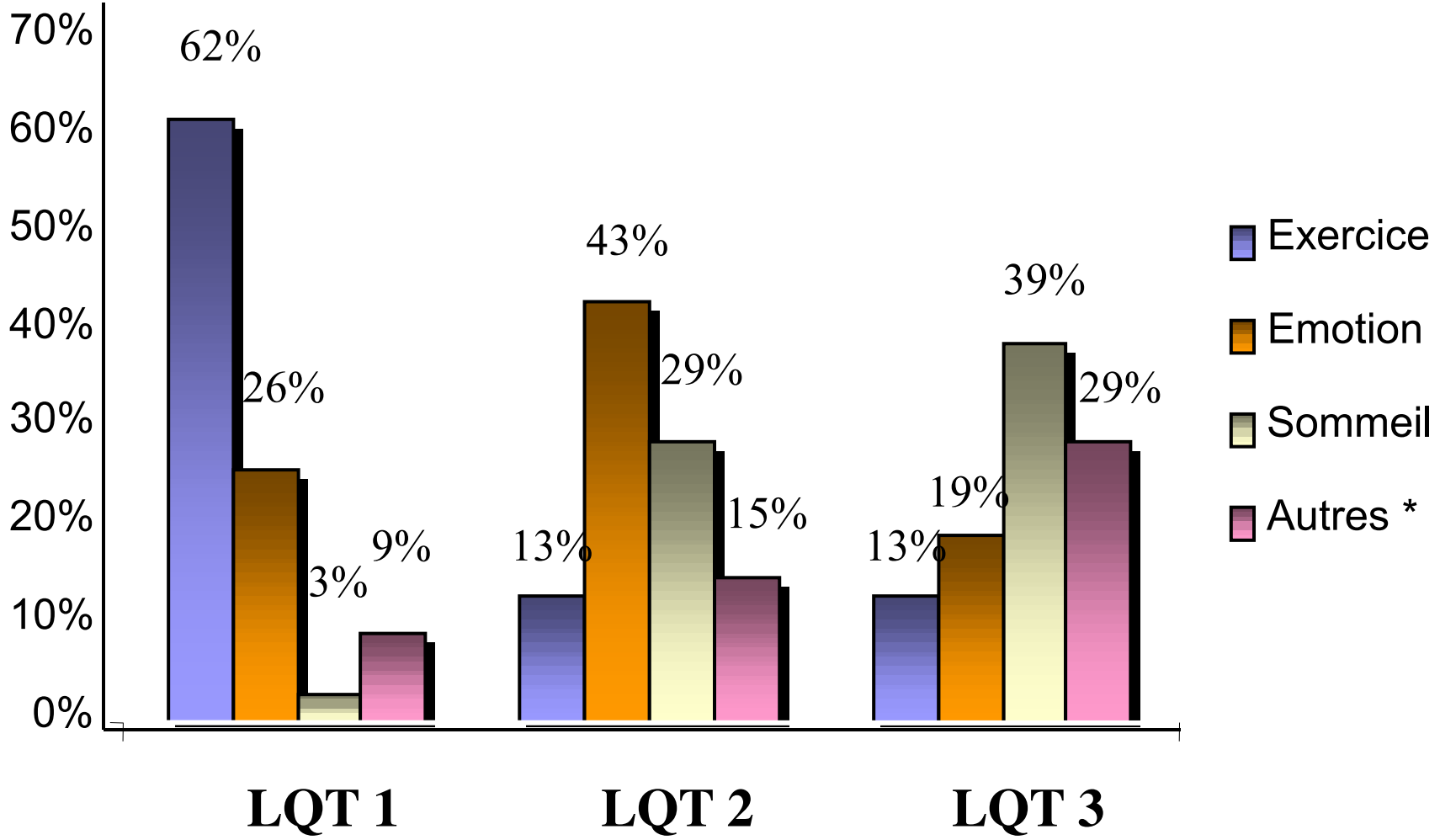


CA or SD

- 2 - 10 % patients:
  - QT3 > QT2 > QT1
- Risk factors:
  - Prior Syncope
  - QTc > 500ms
  - TM mutations
- Bβ effect: ±



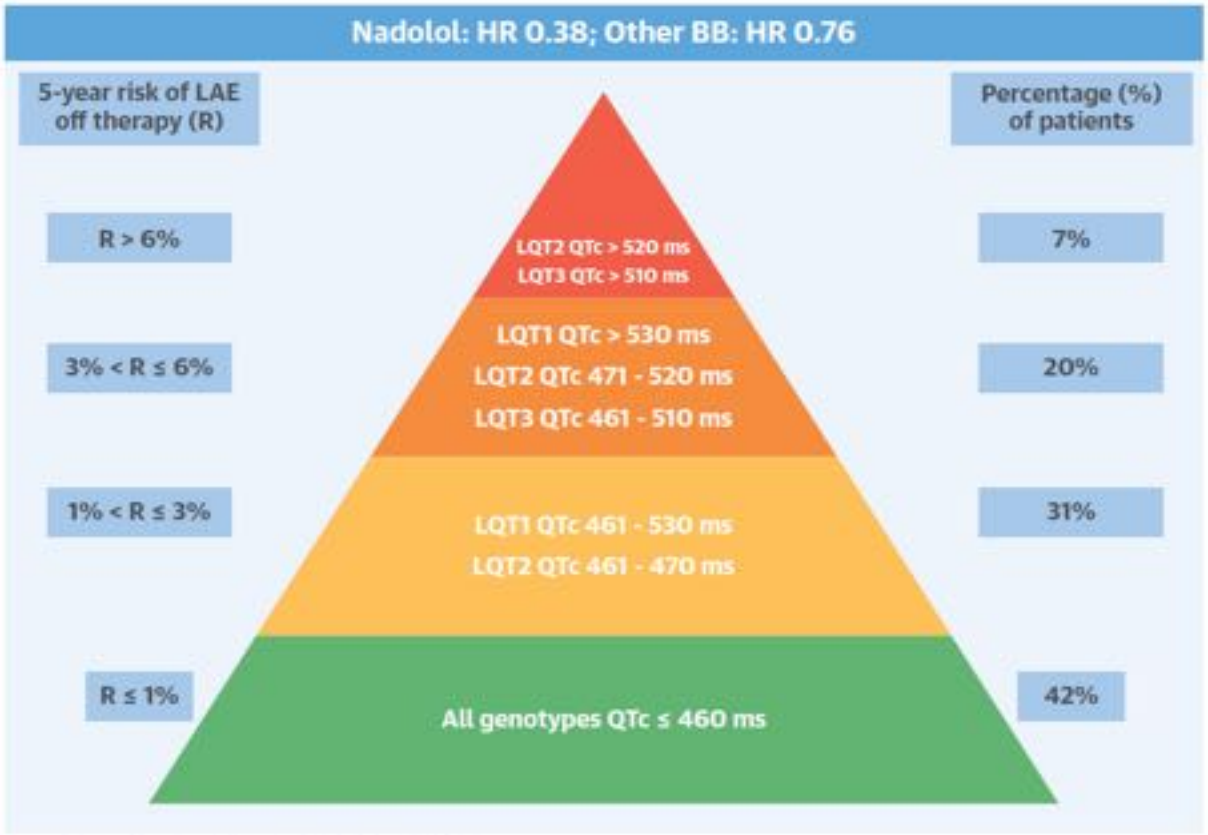
Syncope /Mort subite selon le génotype



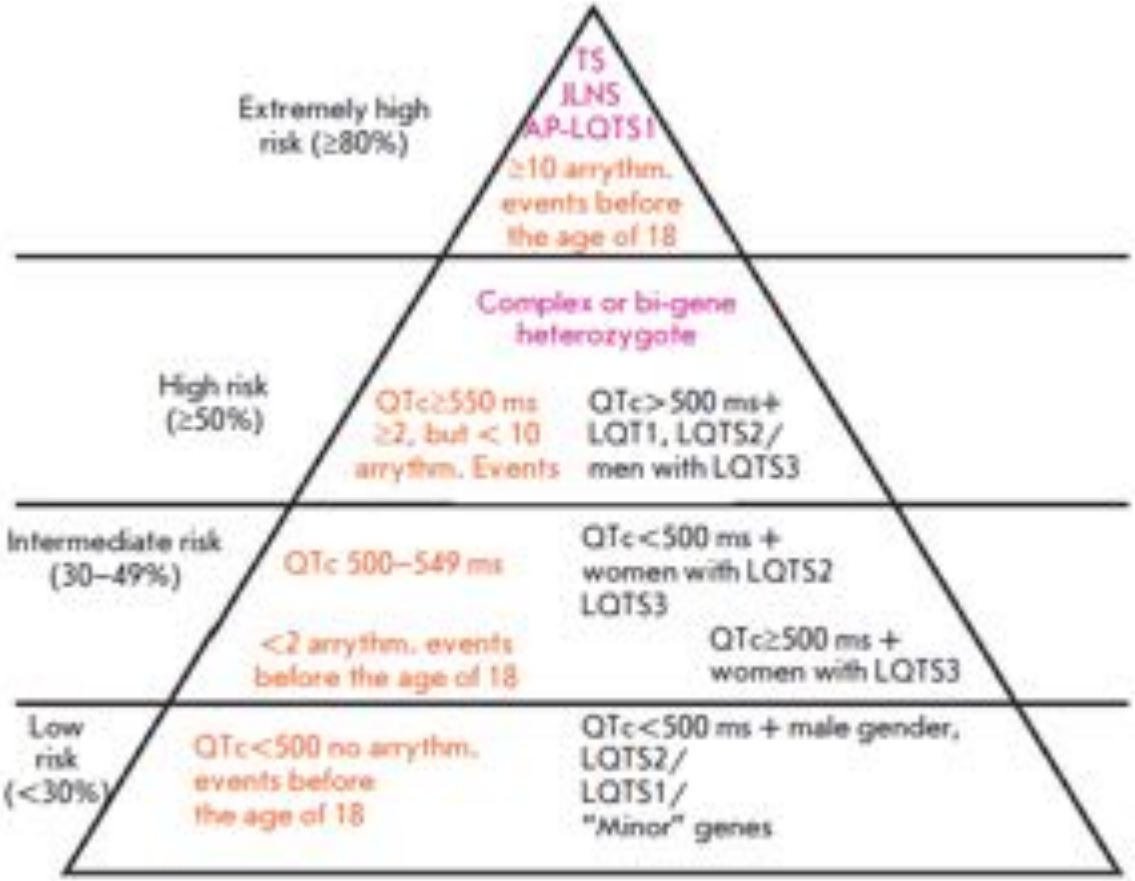
Autres : anésthesie, fièvre, règles, grossesse

PJ Schwartz et al Circulation 2001; 103: 89-95.

CENTRAL ILLUSTRATION 5-Year Risk of LAEs by Genotype and QTc Interval Before Therapy and Effect of BBs



Mazzanti, A. et al. J Am Coll Cardiol. 2018;71(15):1663-71.



Golubkhova et al

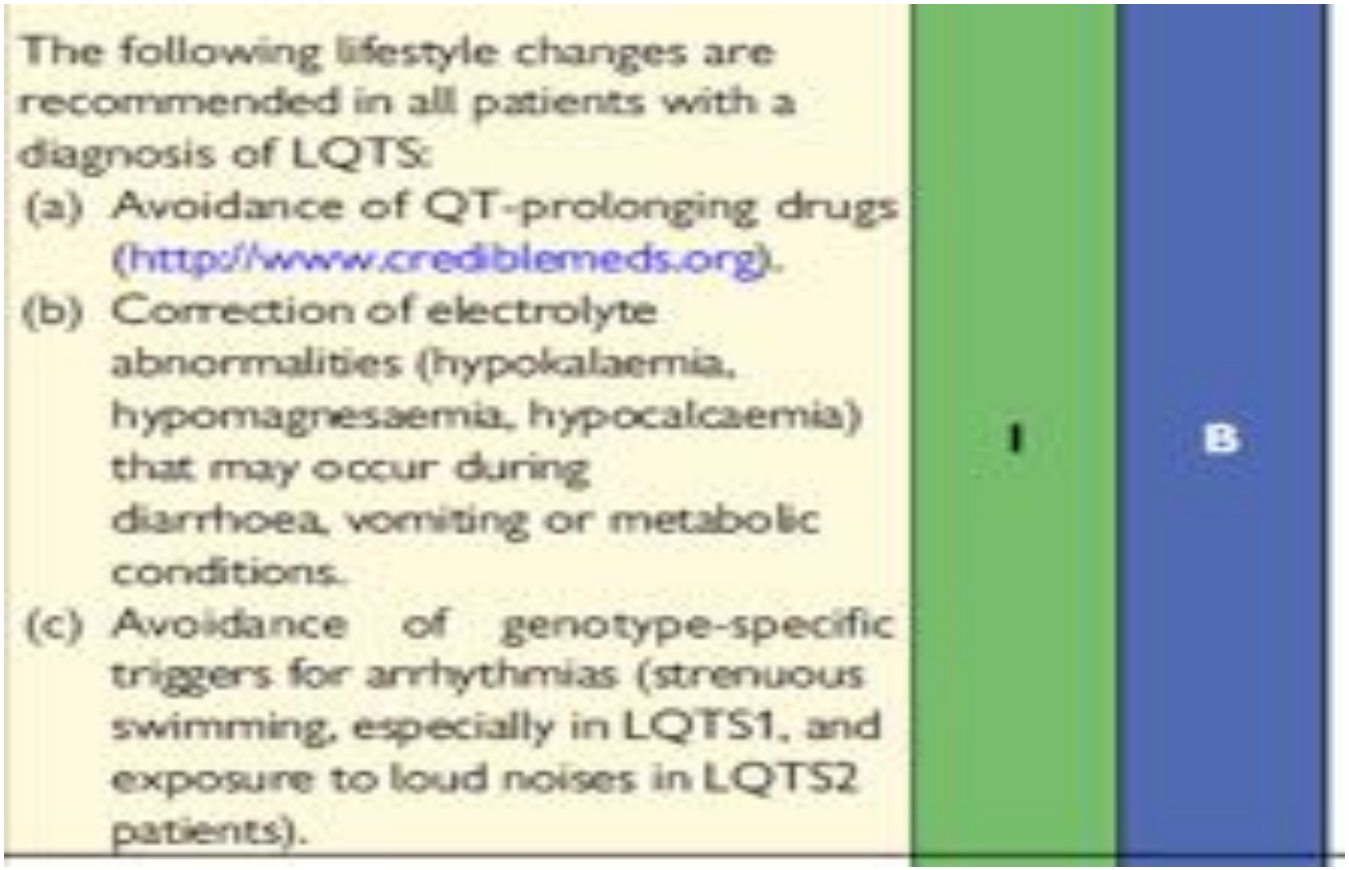
Prise en charge

Expert Consensus Recommendations on ***LQTS Therapeutic Interventions***

Class I	1. The following lifestyle changes **are recommended** in all patients with a diagnosis of LQTS: a) Avoidance of QT prolonging drugs (www.qtdrugs.org) b) Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss. 2. Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are: *a)* Asymptomatic with QTc ≥ 470 ms, *and/or* b) Symptomatic for syncope or documented VT/VF. 3. Left cardiac sympathetic denervation (LCSD) **is recommended** for high-risk patients with a diagnosis of LQTS in whom: a) ICD therapy is contraindicated or refused, *and/or* b) Beta-blockers are either not effective in preventing syncope/ arrhythmias, not tolerated, not accepted or contraindicated. 4. ICD implantation **is recommended** for patients with a diagnosis of LQTS who are survivors of a cardiac arrest. 5. All LQTS patients who wish to engage in competitive sports **should be** referred to a clinical expert for evaluation of risk.
Class IIa	6. Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470ms.

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes 2013-

Le mode de vie



ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015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pointes. Additionally, we maintain a comprehensive list of drugs that are a concern for a special population-- those with inherited prolongation of the QT interval and torsades de pointes
To view QT-prolonging drugs grouped by risk of torsades, possible risk of torsades, and conditional risk of torsades, Click Here
To view a comprehensive list of drugs to be avoided by patients with Congenital Long QT Syndrome (CLQTS), Click Here
Click Here to Browse all QT-prolonging Drug Lists by Drug Name
Click Here for drugs to be avoided by Brugada Syndrome patients

Athlètes et sports de compétition

- Evaluation par un expert canalopathies (CDR/CDC) (I; C)
- Athlète QTL symptomatique ou QTc > 470ms H, QTc > 480 ms F :
  - **Participation possible avec un traitement approprié (BB-; DAI) et > 3 mois SF=0 (IIb;C)**
  - Précautions +++ (liste, déshydratation, hyperthermie)
  - **PEC en cas d'évènement : DAS, équipe prévenue**
  - **Natation interdite pour LQT1**
- Athlète QTL asymptomatique QTc normal/GA
  - **Participation possible avec un traitement approprié (BB-) (IIa; C)**
  - **Précautions +++ (liste, déshydratation, hyperthermie)**
  - **PEC en cas d'évènement : DAS, équipe prévenue**

Ackerman JA et al, Task Force 10 : The cardiac channelopathies : JACC 2015 / 66(21). 2424-28

QT Long et activités sportives

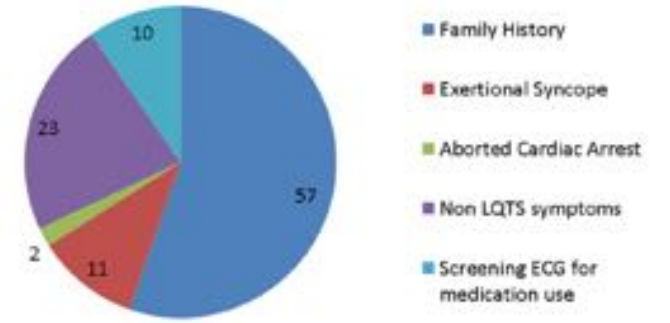
TABLE 1 Patient Demographics

	Total Participants	Competitive Sports	Recreational Sports	Physical Education
n	103	26	77	84
Age at diagnosis, yrs	8.4 ± 5.6	9.3 ± 4.5	8.0 ± 5.6	7.4 ± 4.8
Age at follow-up, yrs	15.4 ± 5.1	16.2 ± 3.0	15.4 ± 5.5	14.0 ± 3.7
Percent female	51	58	45	50
Average QTc, ms	468 ± 42	461 ± 35	470 ± 43	466 ± 42
QTc 25th percentile, ms	442	436	449	440
QTc 75th percentile, ms	484	481	484	483
Genotype positive, phenotype negative	43 (42)	13 (50)	46 (45)	36 (44)
Gene mutations	105	26	79	84
KCNQ1	60 (58)	15 (58)	46 (58)	48 (57)
KCNH2	36 (35)	8 (31)	25 (32)	31 (37)
SCN5A	6 (6)	1 (4)	5 (6)	3 (4)
KCNE1	1 (1)	1 (4)	1 (1)	0 (0)
KCNE2	2 (2)	1 (4)	2 (3)	2 (2)
>1 genotype (included above)	2 (2)	0	2 (3)	2 (2)
Beta-blockers	101 (98)	26 (100)	75 (97)	82 (100)
Personal AED	36 (36)	15 (58)	21 (27)	30 (36)
ICD	6 (6)	2 (8)	5 (6)	6 (7)
Noncompliance	3 (3)	2 (8)	2 (3)	2 (2)
Known follow-up, yrs	7.1 ± 4.0	6.9 ± 4.1	7.3 ± 3.9	6.6 ± 4.0
LQTS cardiac events during participation	0 (0)*	0 (0)	0 (0)	0 (0)

Values are mean ± SD or n (%). *There were no long QT syndrome (LQTS) cardiac events during sports participation. However 1 patient had an appropriate implantable cardioverter-defibrillator (ICD) shock while running casually in the backyard when she was noncompliant with beta-blockers.

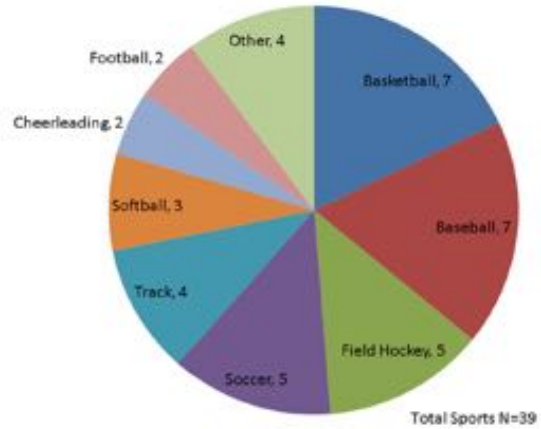
AED = automated external defibrillator.

FIGURE 1 Athlete Presentation



Athlete presentation is categorized for all sports participants. The majority of patients were identified through familial electrocardiogram (ECG) screening. LQTS = long QT syndrome.

FIGURE 2 Competitive Sports Participation



A total of 39 sports are depicted by type in this pie chart. The most frequently participated sports were basketball, baseball, soccer, and field hockey.

Aziz P et al; JACC EP 2015; 1-2 : 62-70

Le traitement médical

Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B
Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	IIa	B
Sodium channel blockers (mexiletine, flecainide or ranolazine) may be considered as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms.	IIb	C

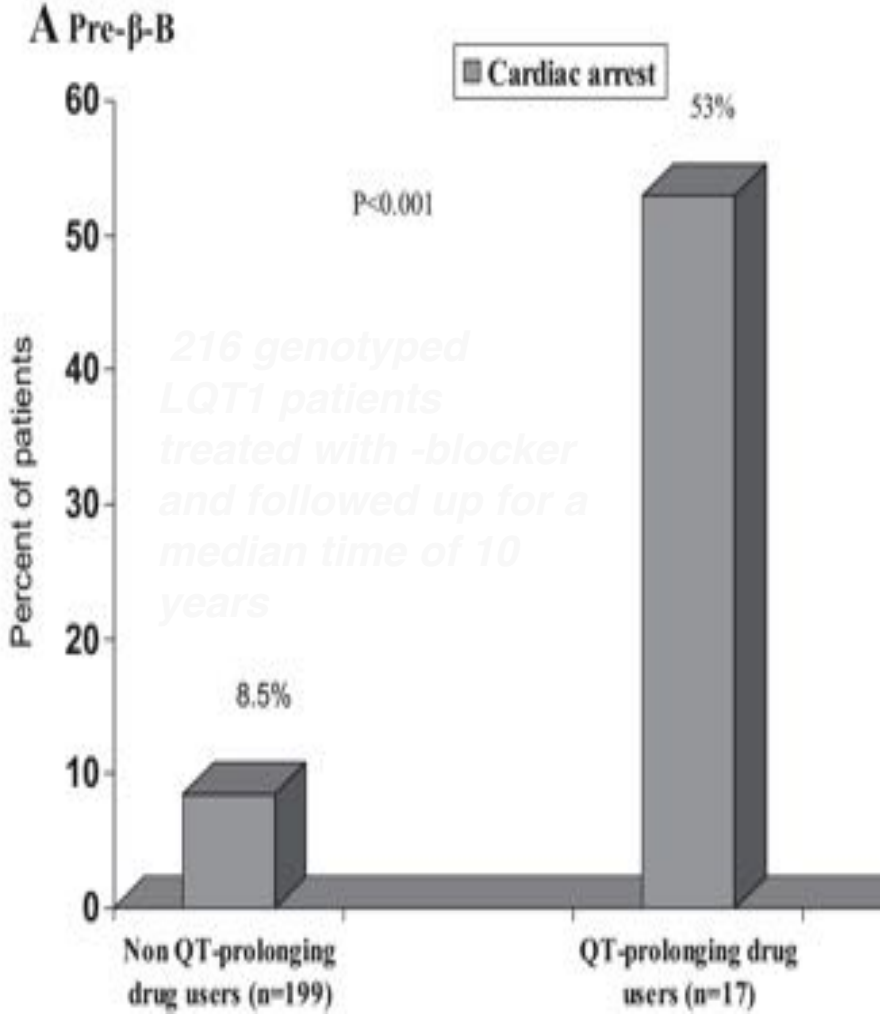
ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

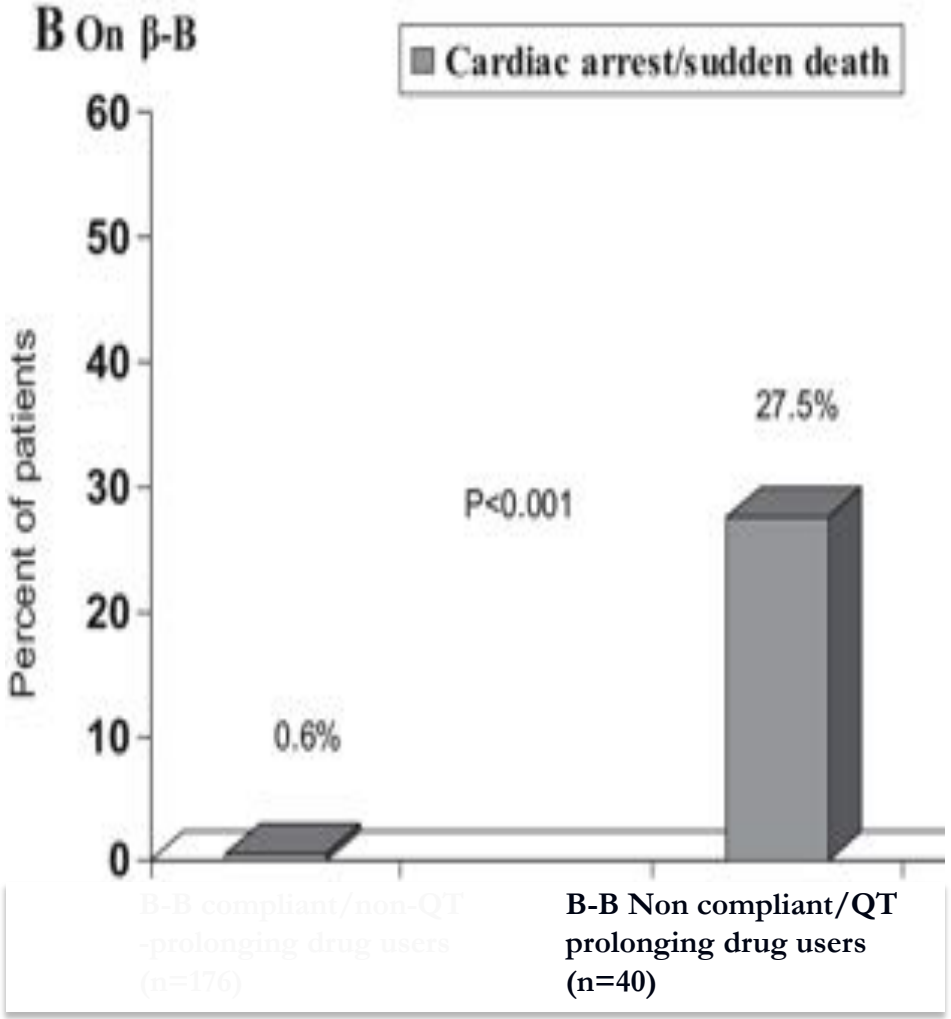
Effet des β-bloquants dans le QTL

- Diminution de l'incidence des évènements cardiaques
  - 0.97±1.42 à 0.31±0.86 EC/an chez proband
  - 0.26±0.84 à 0.15 ±0.69 EC/an fratrie atteinte
- Diminution significative des syncopes
- Diminution du taux de MS chez les probands
- LQT1 et LQT2 : bénéfice plus marqué des ß-
- LQT3 : bénéfice moins net des ß-

Moss et al. Circulation 2000; 101:616-623

Non compliance et médicaments torsadogènes dans l'échec des BB chez LQT1





GM Vincent et al. Circulation. 2009;119:215-21.

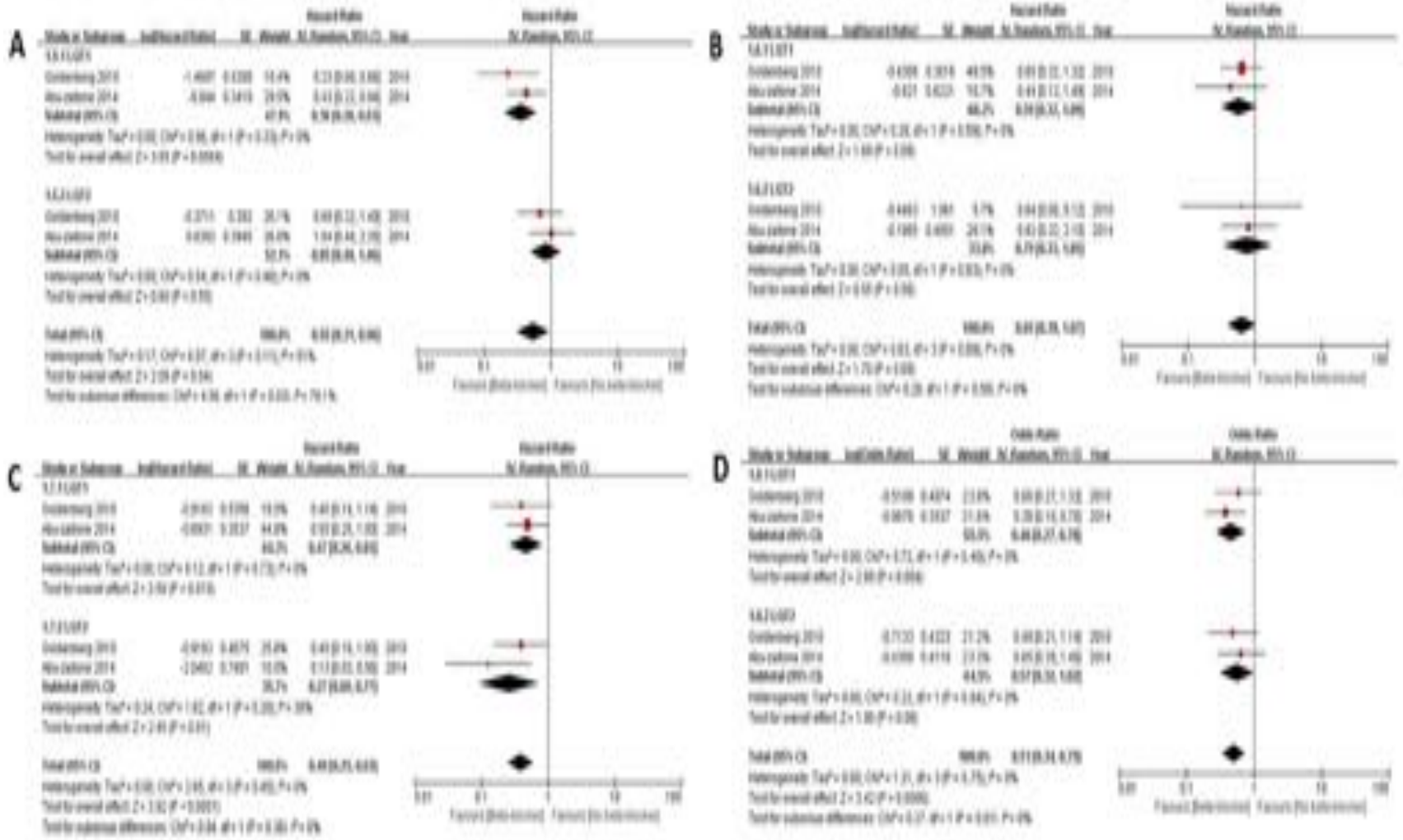


Fig 4. Comparison of effectiveness of beta-blockers on reduction of cardiac events between long-QT syndrome type 1 (LQT1) and 2 (LQT2). A. atenolol; B. metoprolol; C. nadolol; D. propranolol.

Ahn et al, PLOS One, oct 2017

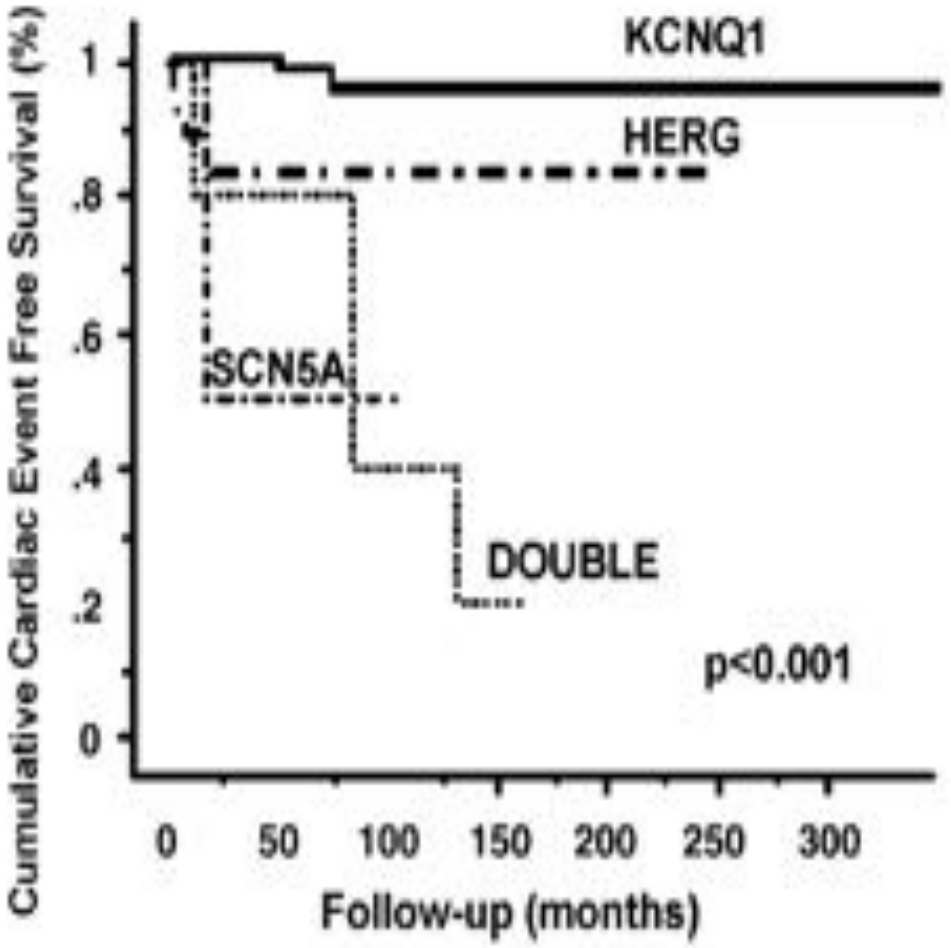


Fig. 3 Kaplan Maier estimates of survival free of cardiac events among 104 genotyped children with LQT syndrome.

Age = 6.4 ± 3.7 ans

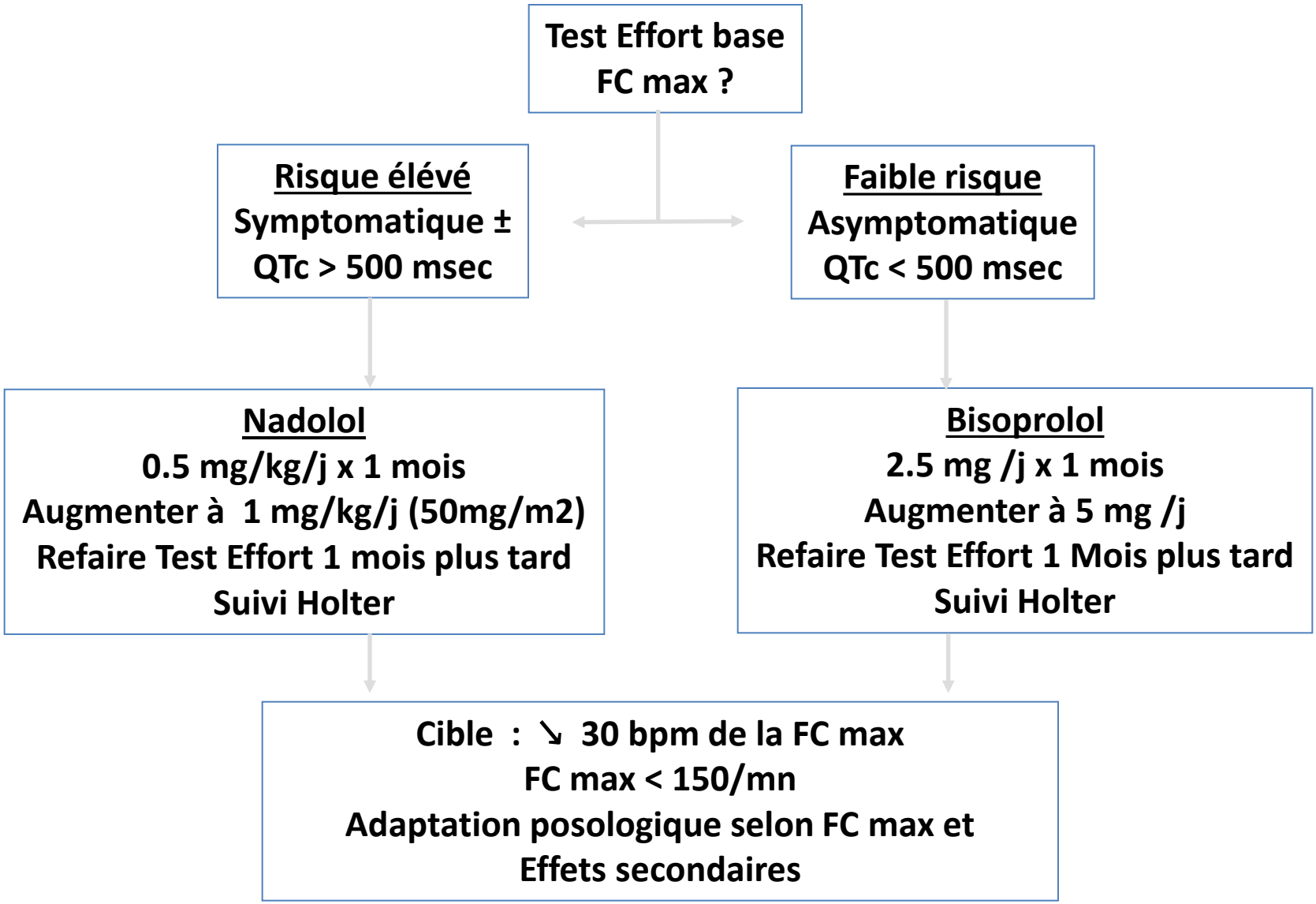
KCNQ1 = 52%

KCNH2= 31%

Suivi = 7.5 ± 5.3 yrs

Villain et al. *Eur Heart J*. 2004;25:1405-11.

Beta Bloquants et QT Long

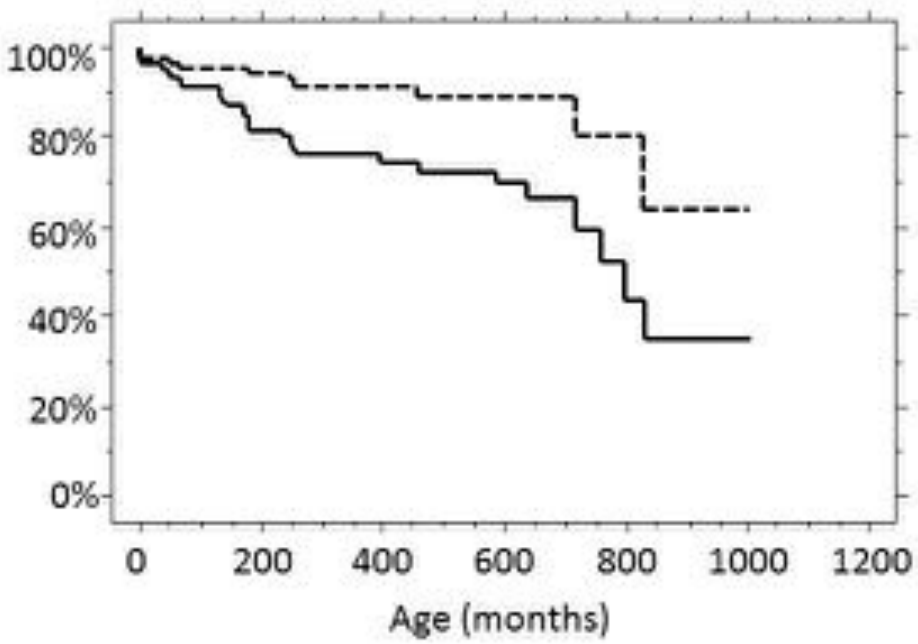


LQT3 risk factors

- N= 391 (82 probands)
- 118 pts 1st cardiac event (30%)
  - 38% Syncope/ACA/SD
  - 20% ACA/SCD
  - 14% SD
- Treatment :BB 28%; DAI 18%
- BB- : 83 % risk reduction of cardiac events in females
- Risk factor : QTc > 500ms, prior syncope

Wilde A, et Al, ESC 2012

Série française : 117 patients - 44 familles - 23 variants



Number of patients at risk							
Cardiac Events	117	96	66	44	24	5	1
Severe CE	117	96	69	46	24	5	1

—— Cardiac Event

---- Severe Cardiac Event

From birth to diagnosis

The rate of cardiac event:

- 5.1% at 2 years,
- 10.3% at 10 years and
- 20.4% at age 20

The rate of severe CE:

- 4.3% at 2 years,
- 6.0% at 10 years and
- 8.0% at 20 years

DAI

ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B
ICD implantation in addition to beta-blockers should be considered in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers.	IIa	B
Implant of an ICD may be considered in addition to beta-blocker therapy in asymptomatic carriers of a pathogenic mutation in *KCNH2* or *SCN5A* when QTc is >500 ms.	IIb	C

ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

Age à l'implantation

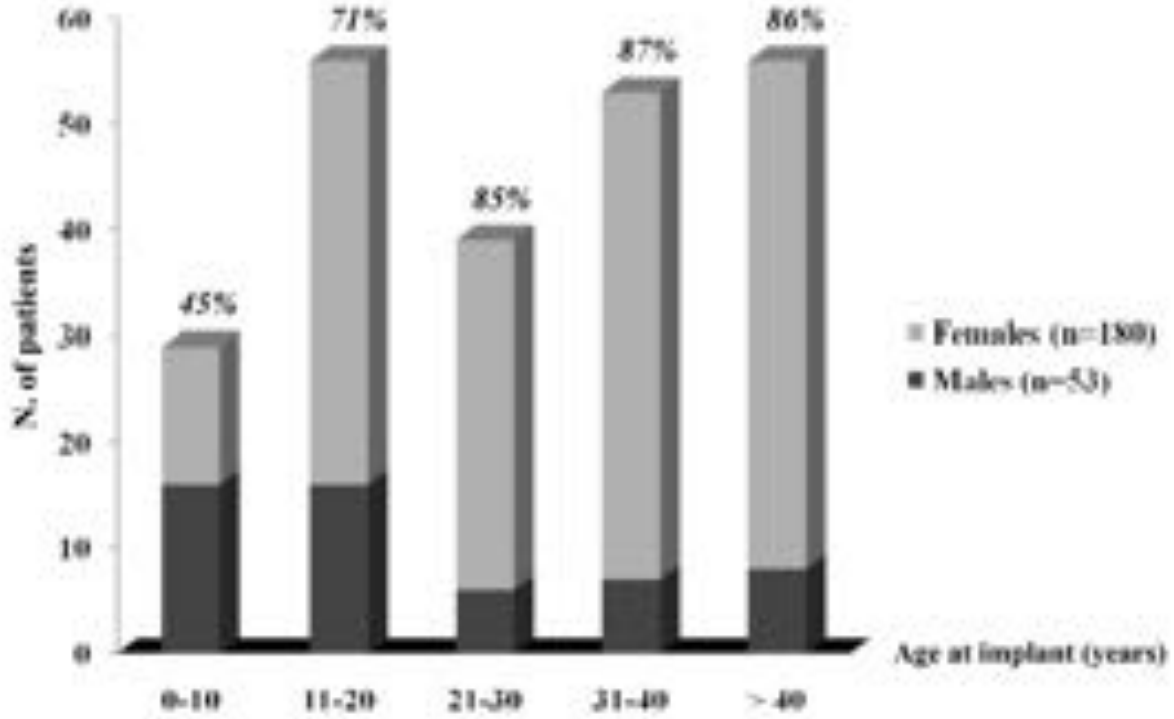


Figure 2. Distribution of patients at implantation by age and gender. Numbers above the histograms represent the percentages of female patients.

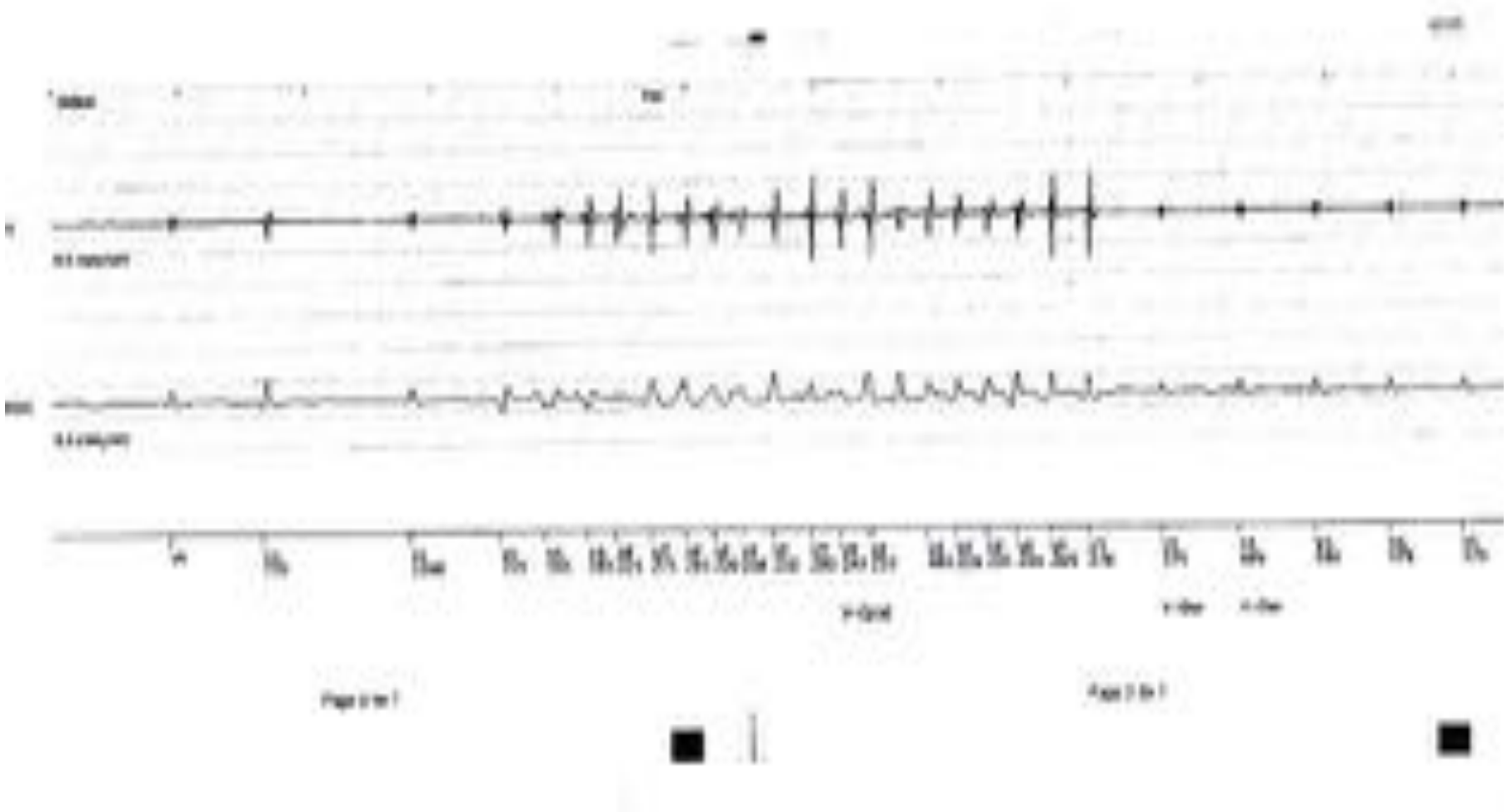
Critères prédictifs des chocs appropriés

Variables cliniques	OR (95% IC)	*p*
ATCD AC	1.81 (1.09-3.0)	0,023
Evènements sous TTT	1.81 (1.08-3.0)	0,025
Age implantation < 20 ans	2.3 (1.38-3.8)	0,001
QTc > 500ms	1.41 (1.03-1.92)	0,03

Période d'observation de 7 ans :

Pas de choc approprié chez les patients n'ayant aucun de ces facteurs

Chocs appropriés chez 70% des patients ayant au – moins 1 de ces facteurs



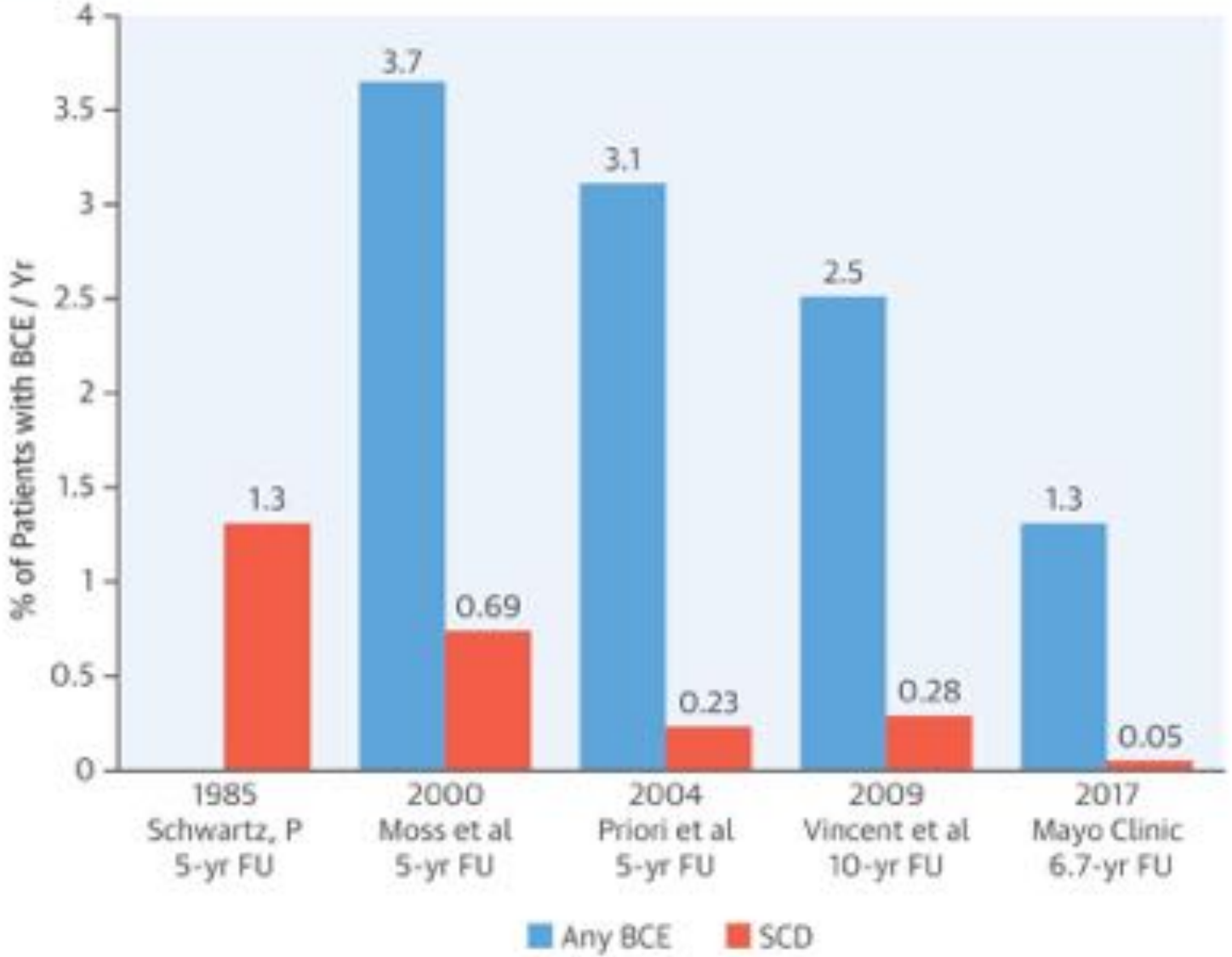
Fille de 15 ans . LQT3. ATCD DE PC => DAI.
Malaise bref sous nadolol
TDP enregistrée mémoire du DAI

La sympathectomie

Left cardiac sympathetic denervation should be considered in patients with symptomatic LQTS when (a) Beta-blockers are either not effective, not tolerated or contraindicated; (b) ICD therapy is contraindicated or refused; (c) Patients on beta-blockers with an ICD experience multiple shocks.	IIa	C

ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

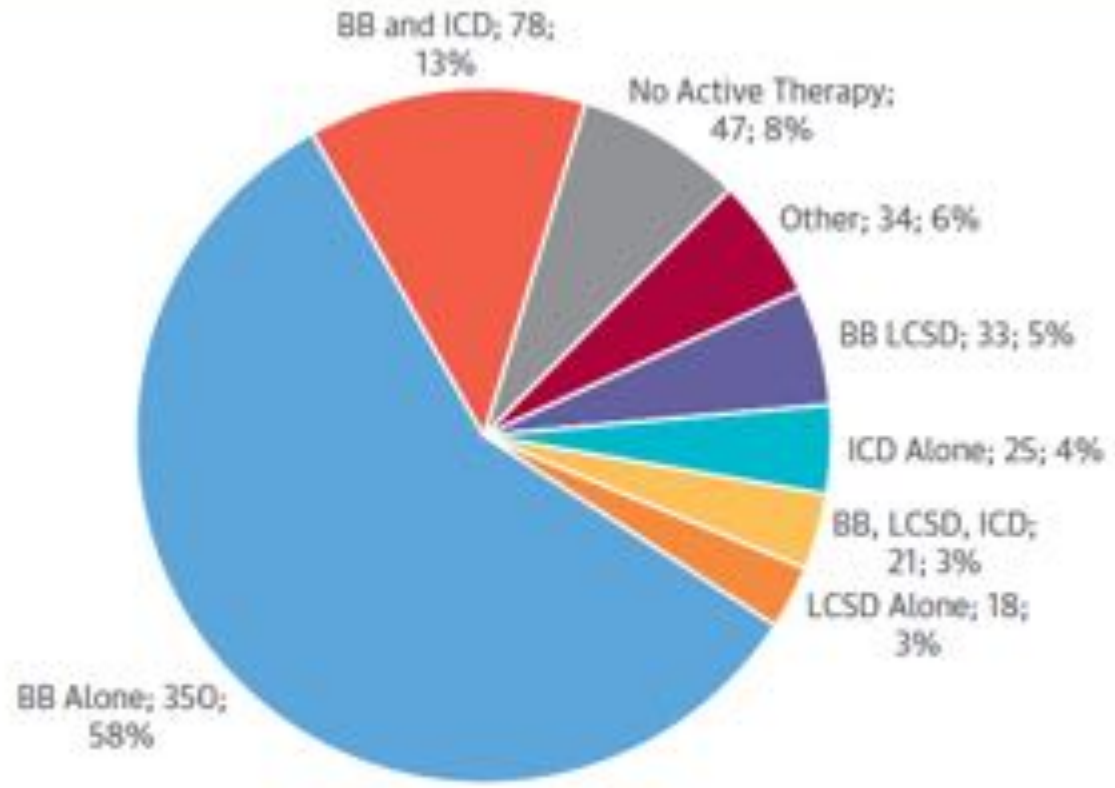
CENTRAL ILLUSTRATION: Trends in Rates of BCEs Among Treated LQTS Patients



Rohatgi, R.K. et al. J Am Coll Cardiol. 2017;70(4):453-62.

Traitement

FIGURE 1 Treatment Summary



Summary of long QT syndrome–directed therapy after being evaluated and risk stratified at the Mayo Clinic. BB = beta-blocker; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation.

Rohatgi RK et al, Jacc 2017

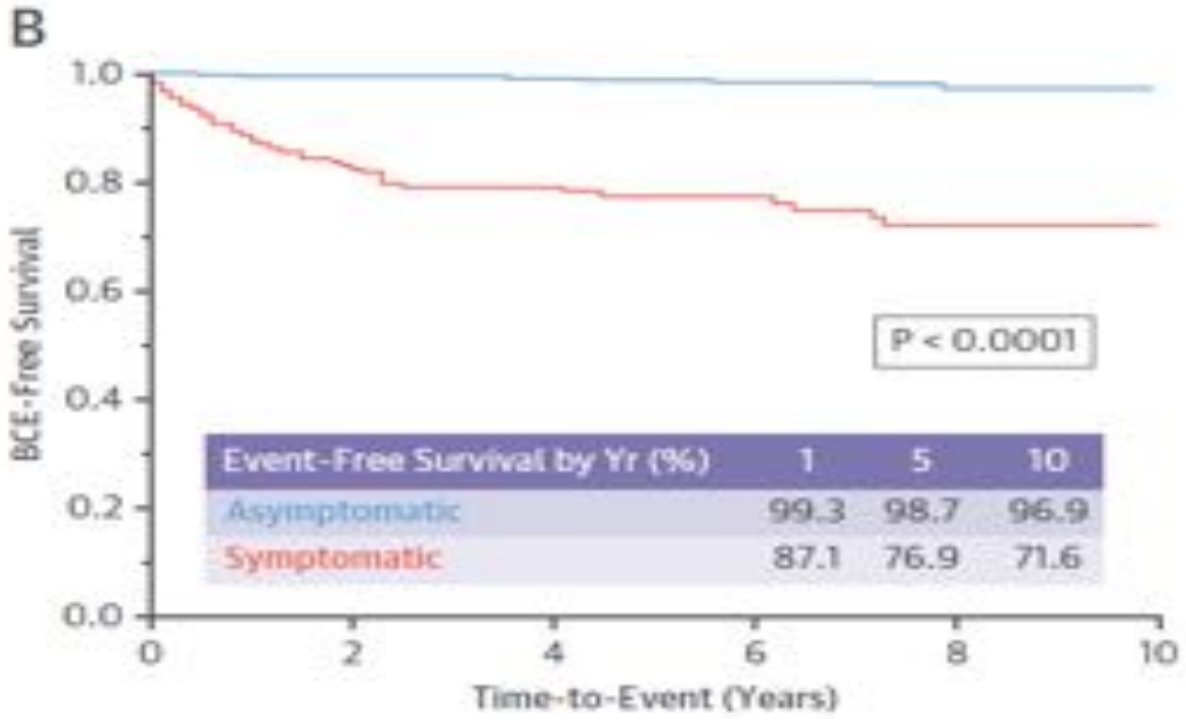
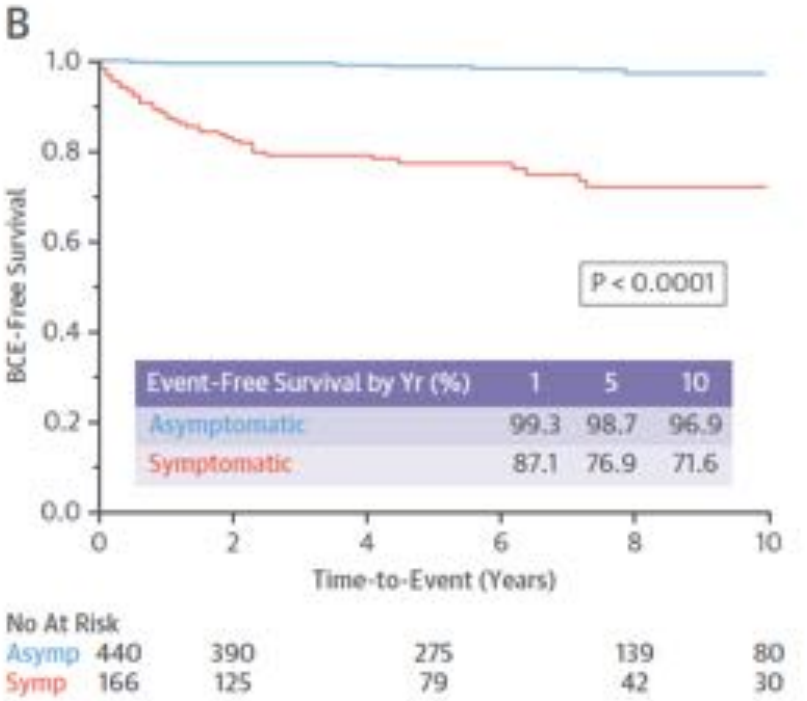


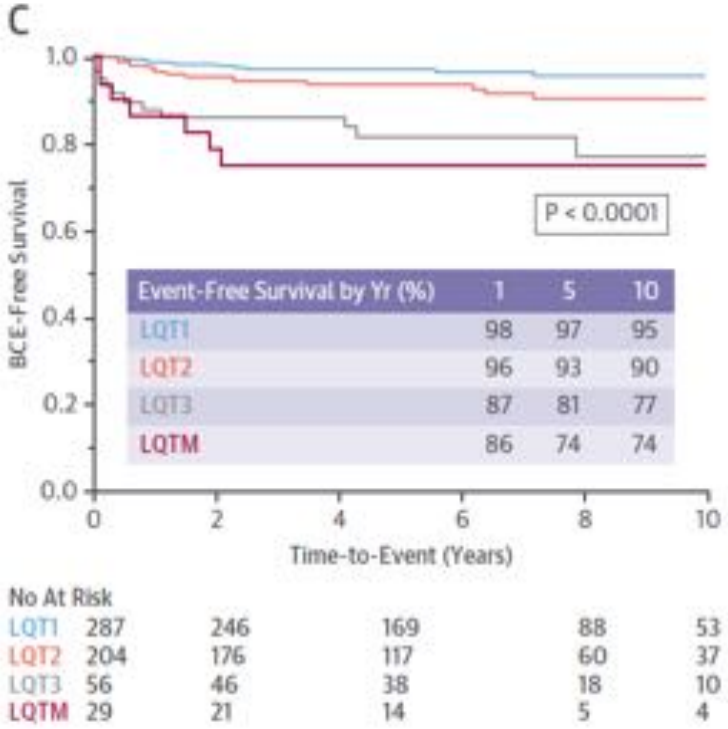
TABLE 4 Treatment Outcomes and Comparison by Symptomatic Status

	Entire Cohort (N = 606)	Asymptomatic (n = 440)	Symptomatic (n = 166)	p Value
Follow-up, yrs	6.7 (3.9-9.8)	6.7 (3.9-9.8)	6.8 (3.7-10.1)	NS
Event/total	50/606 (8)	8/440 (2)	42/166 (25)	0.0001
Annual event rate, %/yr*	1.2	0.3	3.7	0.0001
Event burden				NA
0 BCE	556 (92)	431 (98)	125 (75)	
1 BCE	20 (3)	8 (2)	12 (7)	
2-5 BCEs	21 (3)	–	21 (13)	
6-10 BCEs	6 (1)	–	6 (3)	
>10 BCEs	3 (<1)	–	3 (2)	

Rohatgi RK et al, Jacc 2017

Pronostic





Rohatgi RK et al, Jacc 2017

Génétique SQTL et MSIN, Mort In Utero

	KCNQ1	KCNH2	SCN5A	CAV3	KCNE1	KCNE2
MSIN 19/ 201	2 (10,5%)	2 (10,5%)	13 (68%)	1 (5%)	0	1 (5%)
MIU 12/ 45	0	2 (17%)	6 (50%)	2 (17%)	1 (8%)	1 (8%)

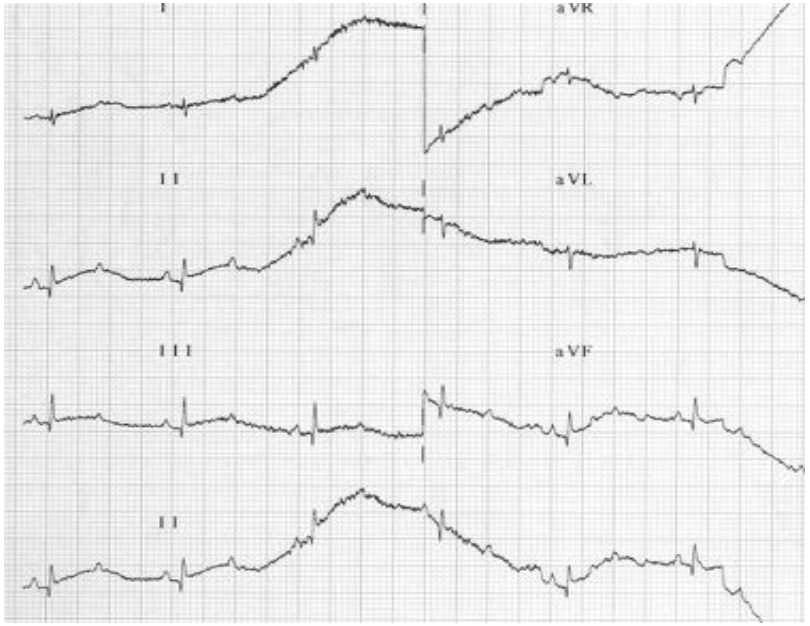
Crotti et al, Circulation 2007, Esc 2010

QTL chez les nouveau-nés : Résultats génétiques

- ADN chez 18/23 cas
- Génotype positif dans 17/18 cas
- Mutations dans HERG (n = 8)
- Mutations dans KCNQ1 (n = 8)
- 1 cas avec 3 mutations (KCNQ1 + HERG + SCN5A)
- Toutes les mutations dans HERG chez nourrissons avec BAV 2:1
- Toutes les mutations dans KCNQ1 chez nourrissons avec bradycardie sinusale

Lupoglazoff et al. J Am Coll Cardiol 2004; 43: 826-30

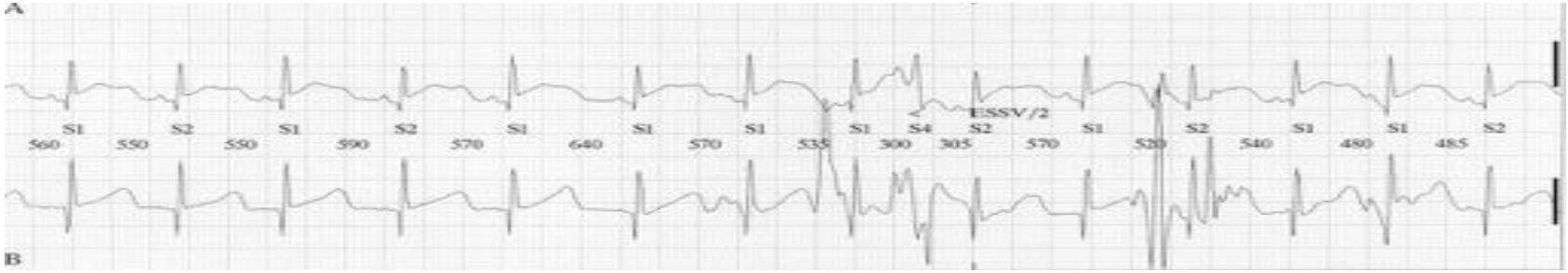
BAV 2:1 chez un nouveau-né



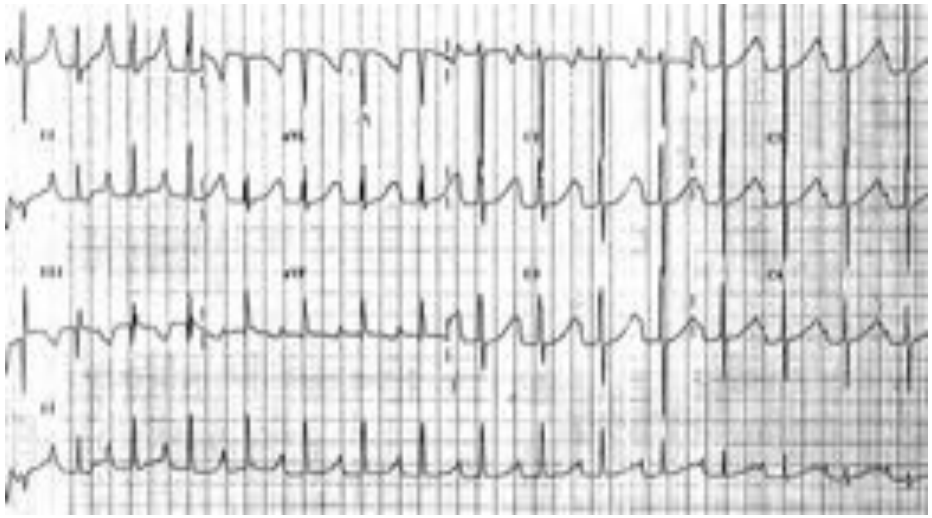
-BAV 2:1 sur ECG

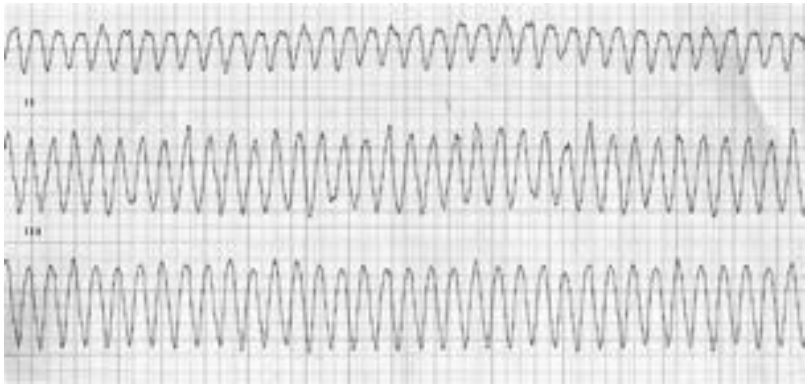
- Conduction en 1:1 avec ondes T bifides sur le Holter

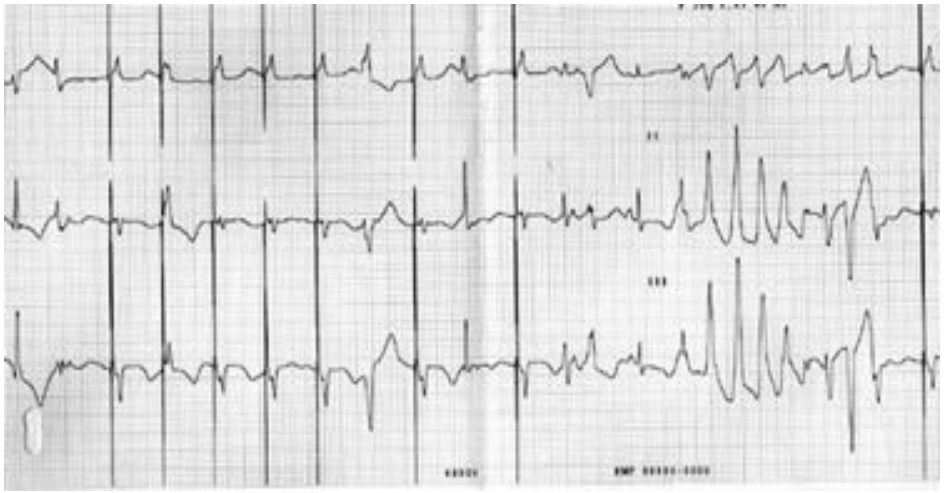
- Mutation dans HERG

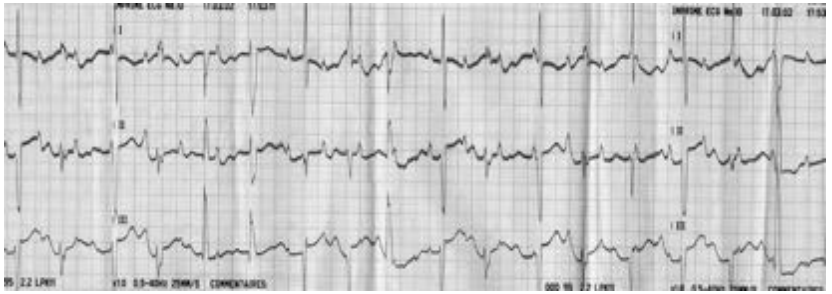


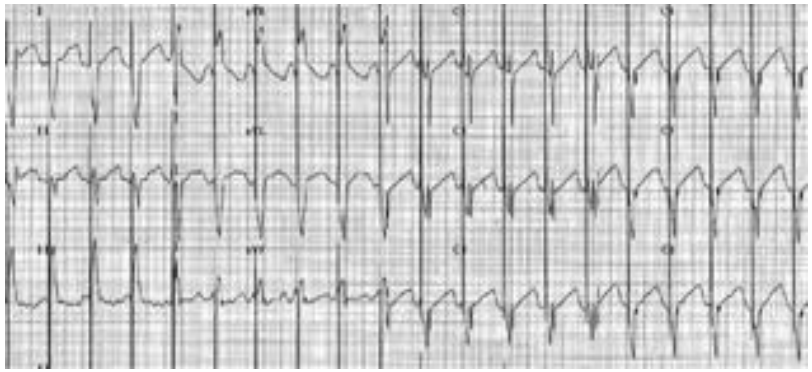
Lupoglazoff et al. *J Am Coll Cardiol 2004; 43: 826-30*





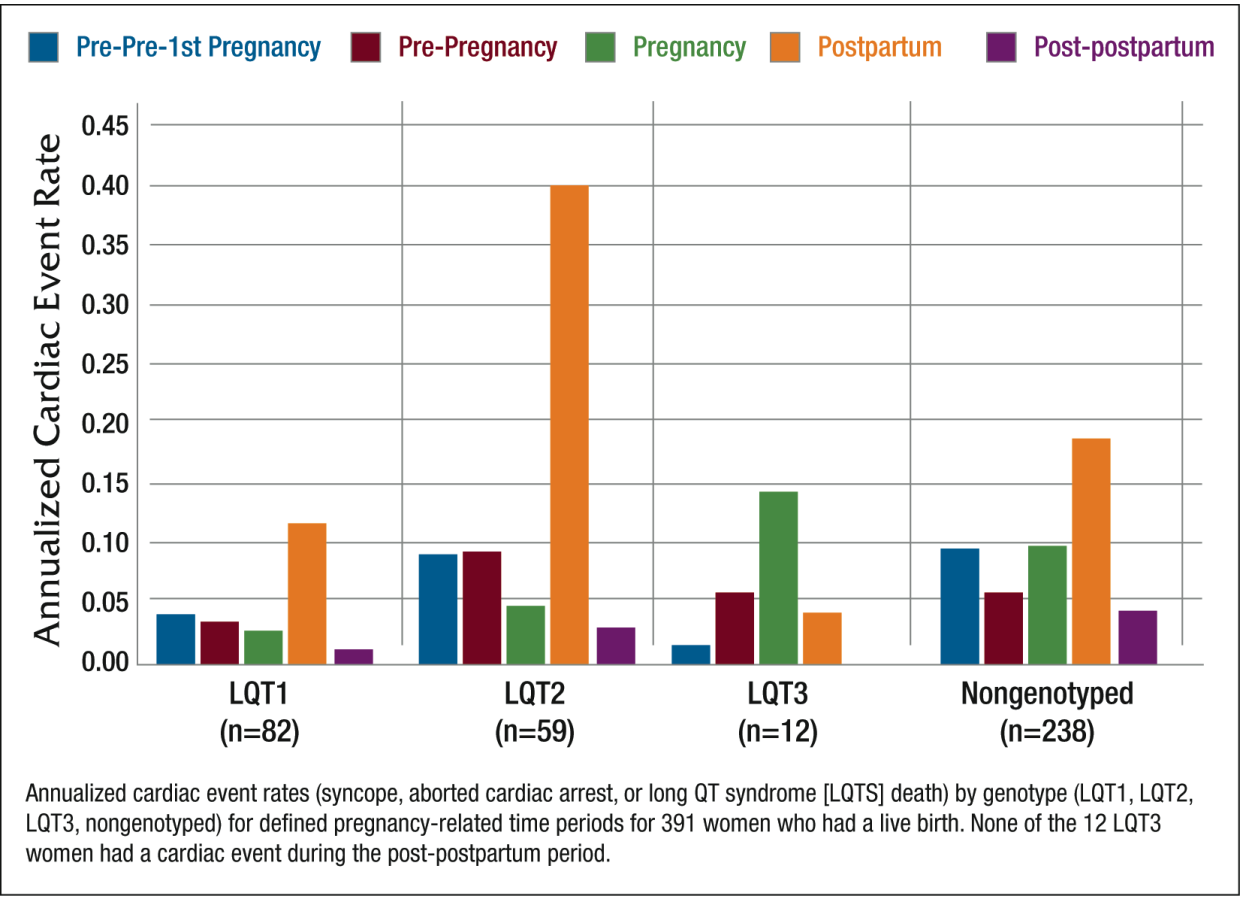






Neonatal LQTS (HERG)

SQTL et grossesse : évènements cardiaques



Annualized cardiac event rates (syncope, aborted cardiac arrest, or long QT syndrome [LQTS] death) by genotype (LQT1, LQT2, LQT3, nongenotyped) for defined pregnancy-related time periods for 391 women who had a live birth. None of the 12 LQT3 women had a cardiac event during the post-postpartum period.

N = 391 (1980-2003)

QTc = 500 ± 50 ms

EC < 15 ans = 28%

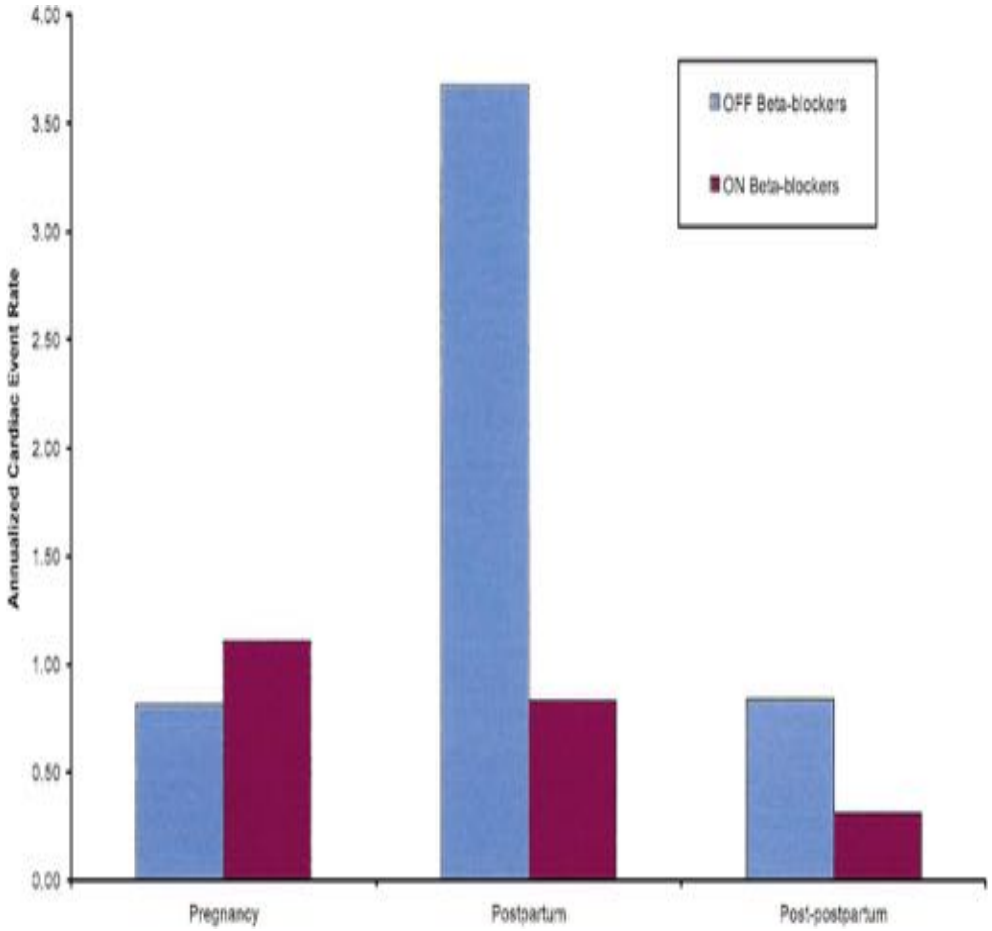
EC > 15 ans = 55%

Genotype

- Inconnu 61%
- LQT1 21%
- LQT2 15%
- LQT3 3%

Seth, R. et al. J Am Coll Cardiol 2007;49:1092-1098

SQTL et grossesse : BB-



Béta-Bloquants :

A la conception 27 % (104/391)

A la naissance 30 % (116/391)

Post-partum 33% (128/391)

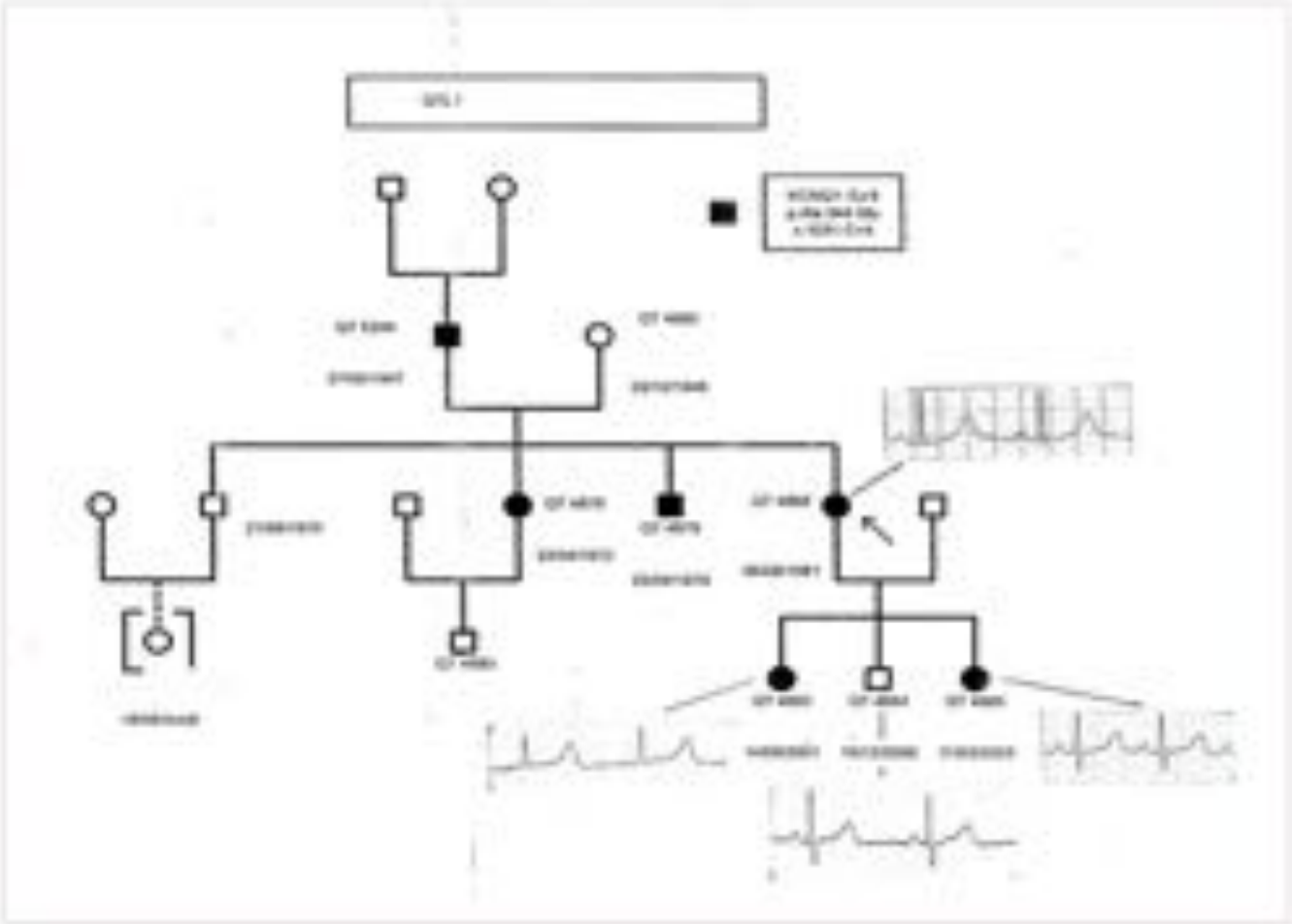
Seth, R. et al. J Am Coll Cardiol 2007;49:1092-1098

LQTS and pregnancy

- Don’t stop BB during pregnancy and post partum
- Materny level 2 (neonatalogy + adult cardiology LQT2)
- Monitoring of the fetus :
  - In Utero Growth Retardation
  - Hypoglycemia at birth
- Baby : 50% risk having LQTS
  - LQT1 (bradycardia) : low risk
  - LQT2 & LQT3 (conduction +TDP) : high risk

Lupoglazoff et al. J Am Coll Cardiol 2004; 43: 826-30

Etude familiale



Family screening : parents, sibling, 1st degree relatives

Tests	LQTS
When ?	From birth
ECG	QTc ↑ , morphology, supine/standing
Holter	QTc ↑, morphology, slope
Stress test	QTc ↑ 4mn
Pharmacologic challenge	Adrenaline
EPS	No
Genetic	Yes +++

Syndrome du QT long

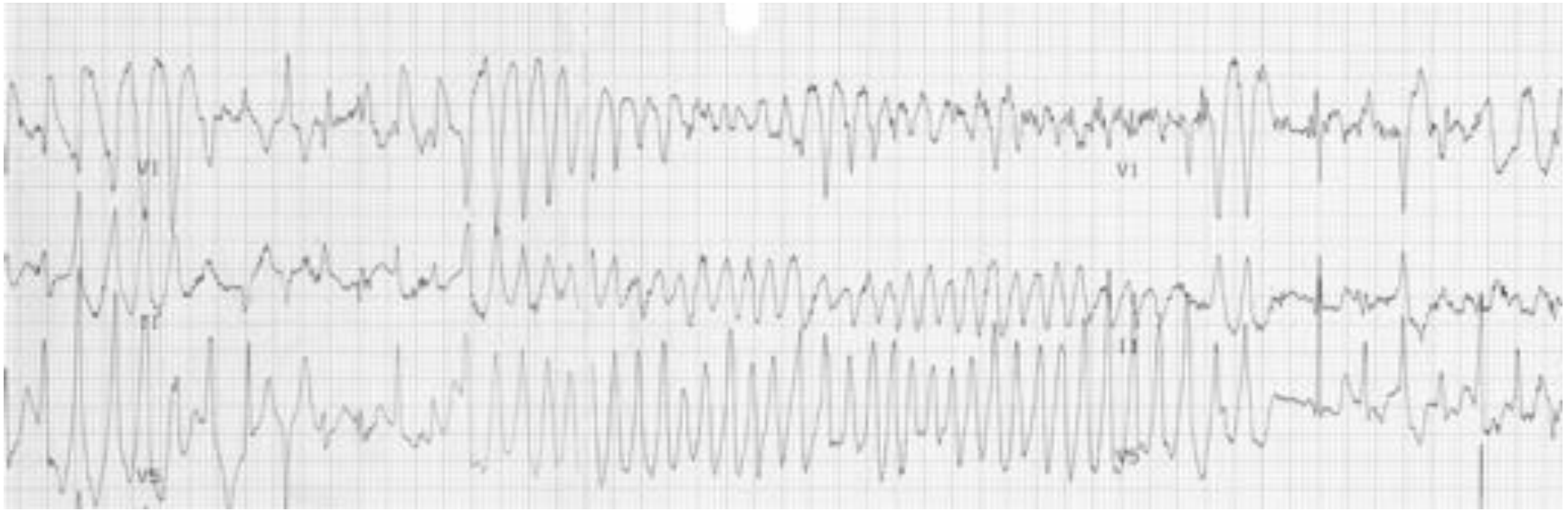
- **Diagnostic :**
  - ECG : QTc ↑, morphologie
  - Holter : QTc ↑, morphologie, pente QT/RR
  - (Adrenaline : QTc ↑, ESV)
  - Epreuve d'effort > 8 ans : QTc ↑ 4ème mn récupération

- **Tests génétiques** (KCNQ1, KCNH2, SCN5A) : les apparentés 1er degré au moment du bilan familial + enfants

- **Traitement** : dès le diagnostic clinique
  - Béta-bloquants
  - Liste médicaments
  - Activité sportive restreinte adaptée

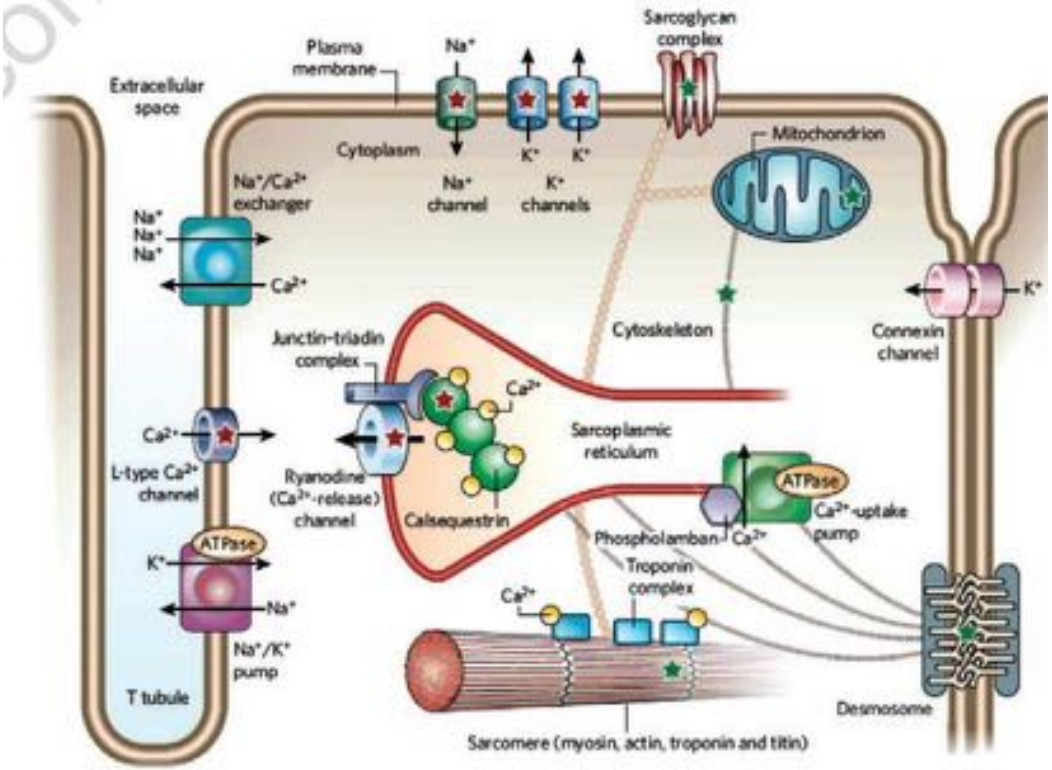
www.crediblemeds.org

Tachycardie ventriculaire catécholergique



- ECG de base souvent normal (QTc normal)
- Enfants avec syncopes/mort subite à l'**EFFORT**
  - A partir de 2 ans, rare après 40 ans
- Prévalence :1/10 000
- Génétique : **RyR2**, CASQ2, Triadin (calcium)
- Pénétrance 65 à 80% (variable avec l'âge)

Name	Gene	Protein	Frequency
CPVT1	*RYR2*	Cardiac ryanodine receptor 2	50%–60%
CPVT2	*CASQ2*	Cardiac calsequestrin	≈5%
CPVT3	*TECLR*	Originally mapped to chromosome 7 p14-p22, now reallocated to chromosome 4	Rare
CPVT4	*CALM1*	Calmodulin	Rare
CPVT5	*TRDN*	Triadin	Rare
? LQT4 overlap	*ANK2*	Ankyrin B	Rare
? LQT7 overlap	*KCNJ2*	Potassium inwardly rectifying channel Kir2.1	Rare



Name	Gene	Protein	Frequency
CPVT1	*RYR2*	Cardiac ryanodine receptor 2	50%–60%
CPVT2	*CASQ2*	Cardiac calsequestrin	~5%
CPVT3	*TECLR*	Originally mapped to chromosome 7 p14-p22, now reallocated to chromosome 4	Rare
CPVT4	*CALM1*	Calmodulin	Rare
CPVT5	*TRDN*	Triadin	Rare
? LQT4 overlap	*ANK2*	Ankyrin B	Rare
? LQT7 overlap	*KCNJ2*	Potassium inwardly rectifying channel Kir2.1	Rare

Tachycardie Ventriculaire Polymorphe

- Syncopes ± arrêt cardiaque (**emotion, exercice, noyade**) vers 10 ans (exceptionnel < 2 ans)
- Syncope + convulsions => **Attention Dic ≠ épilepsie**

- ESV polymorphes à l'effort-bigéminisme-salves polymorphes : reproductibles
  - **Holter, Epreuve d'effort, Isoprénaline, Adrénaline**
- Arythmie atriale adrénergique

- ECG de repos normal : QTc normal

- Mortalité ++ en l'absence de traitement (30 % à l'âge de 20-30 ans)

Diagnosis

Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Expert Consensus Recommendations on ***CPVT Diagnosis***

1. CPVT ***is diagnosed*** in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats (VPBs) or VT in an individual younger than 40 years.
2. CPVT ***is diagnosed*** in patients (index case or family member) who have a pathogenic mutation.
3. CPVT ***is diagnosed*** in family members of a CPVT index case with a normal heart who manifest exercise-induced premature ventricular contractions or bidirectional/ polymorphic VT.
4. CPVT ***can be diagnosed*** in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in an individual older than 40 years.

Europace. 2013;13:1389-1406

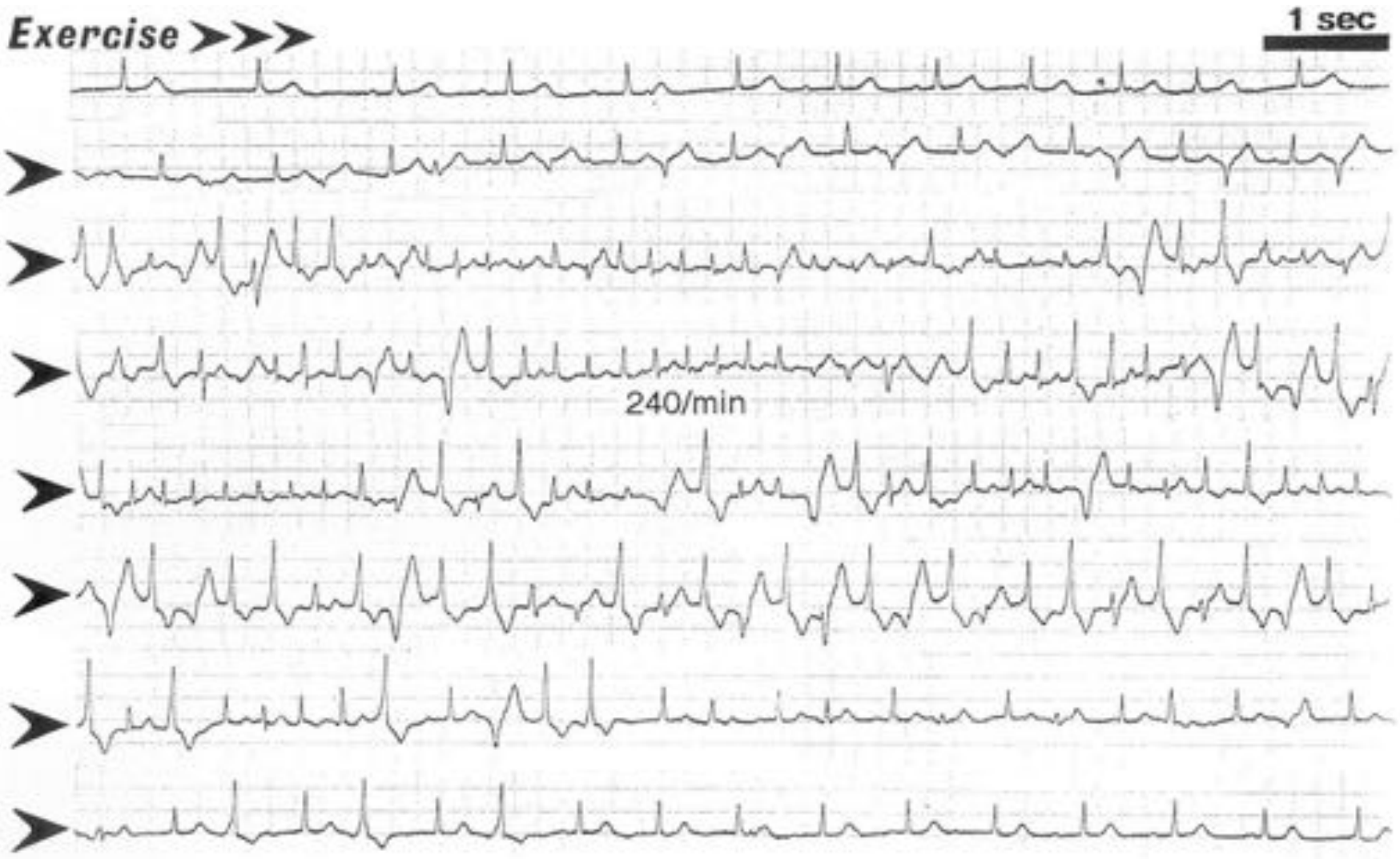
2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

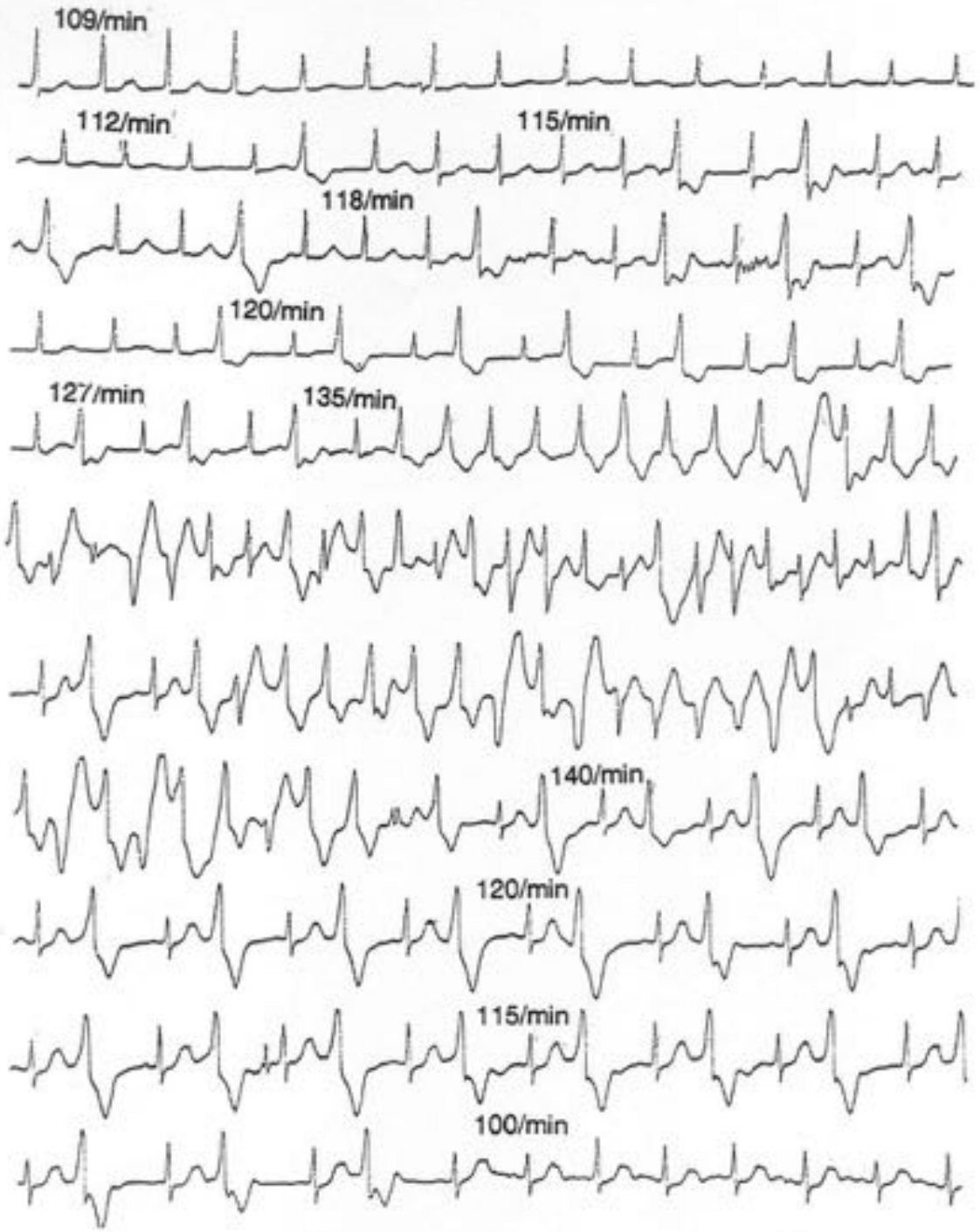
Diagnosis of catecholaminergic polymorphic ventricular tachycardia

Recommendations	Class[a]	Level[b]
CPVT is diagnosed in the presence of a structurally normal heart, normal ECG and exercise- or emotion-induced bidirectional or polymorphic VT.	I	C
CPVT is diagnosed in patients who are carriers of a pathogenic mutation(s) in the genes *RyR2* or *CASQ2*.	I	C

Europace. 2015;17:1601-

TVC

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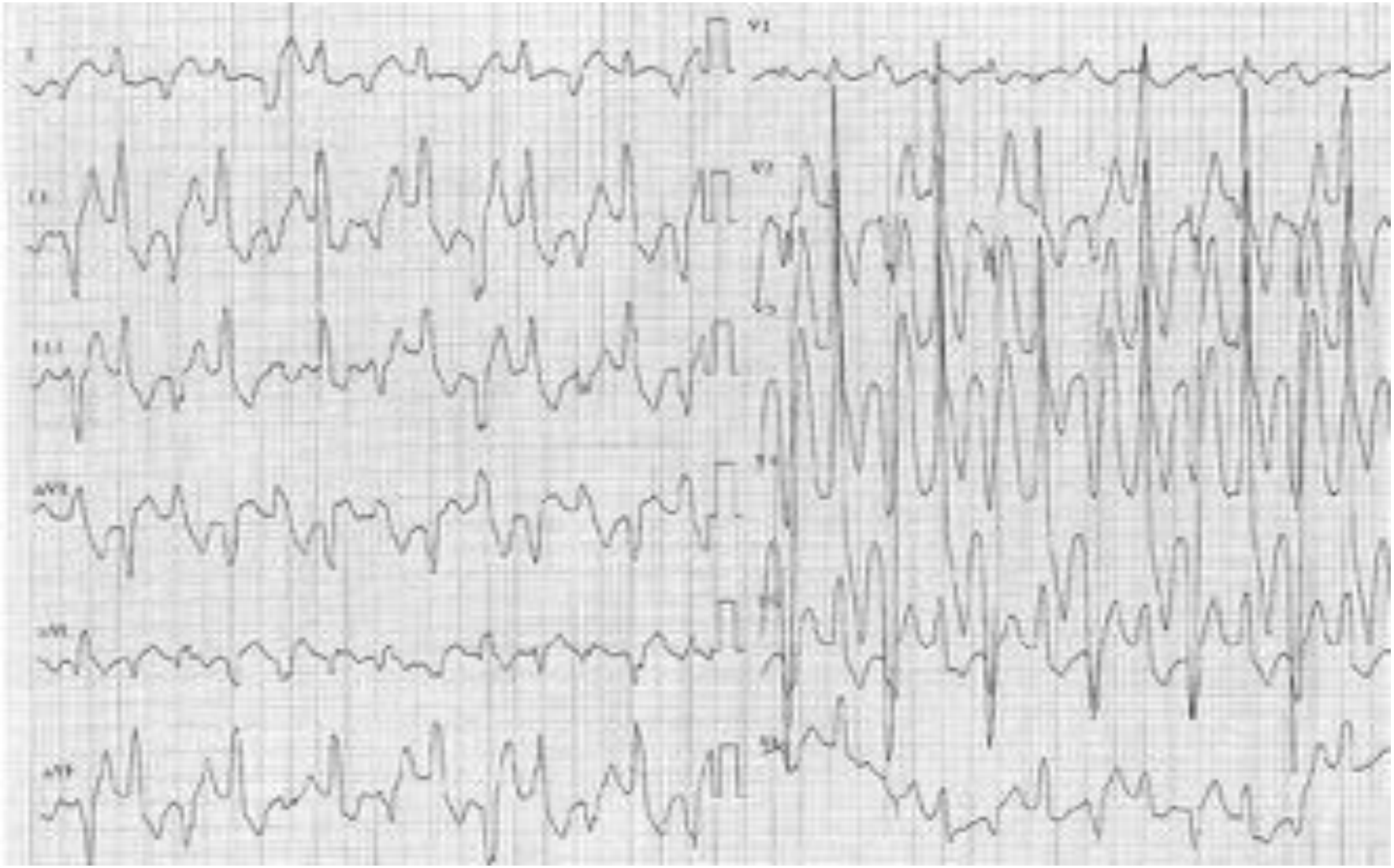
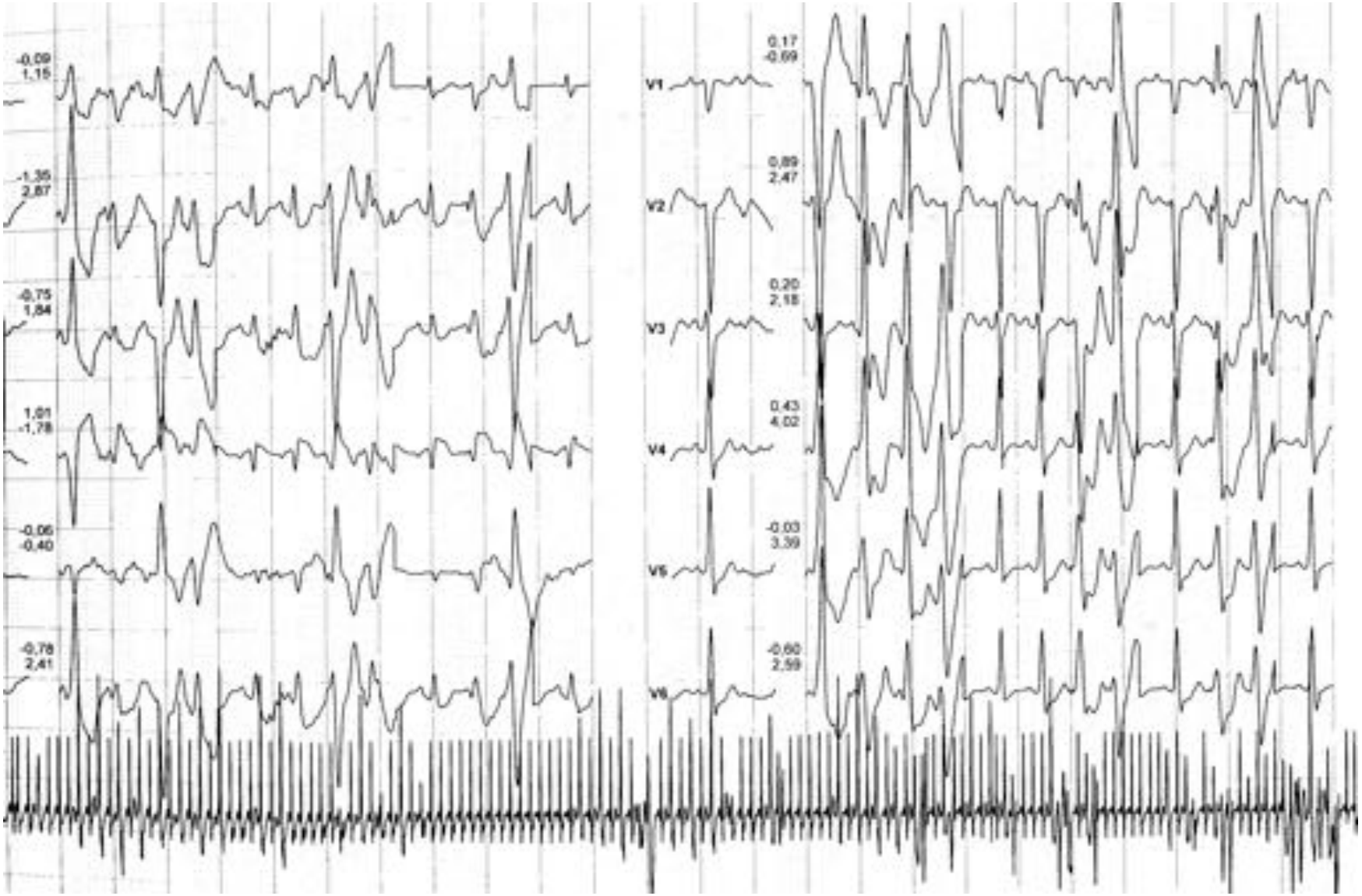
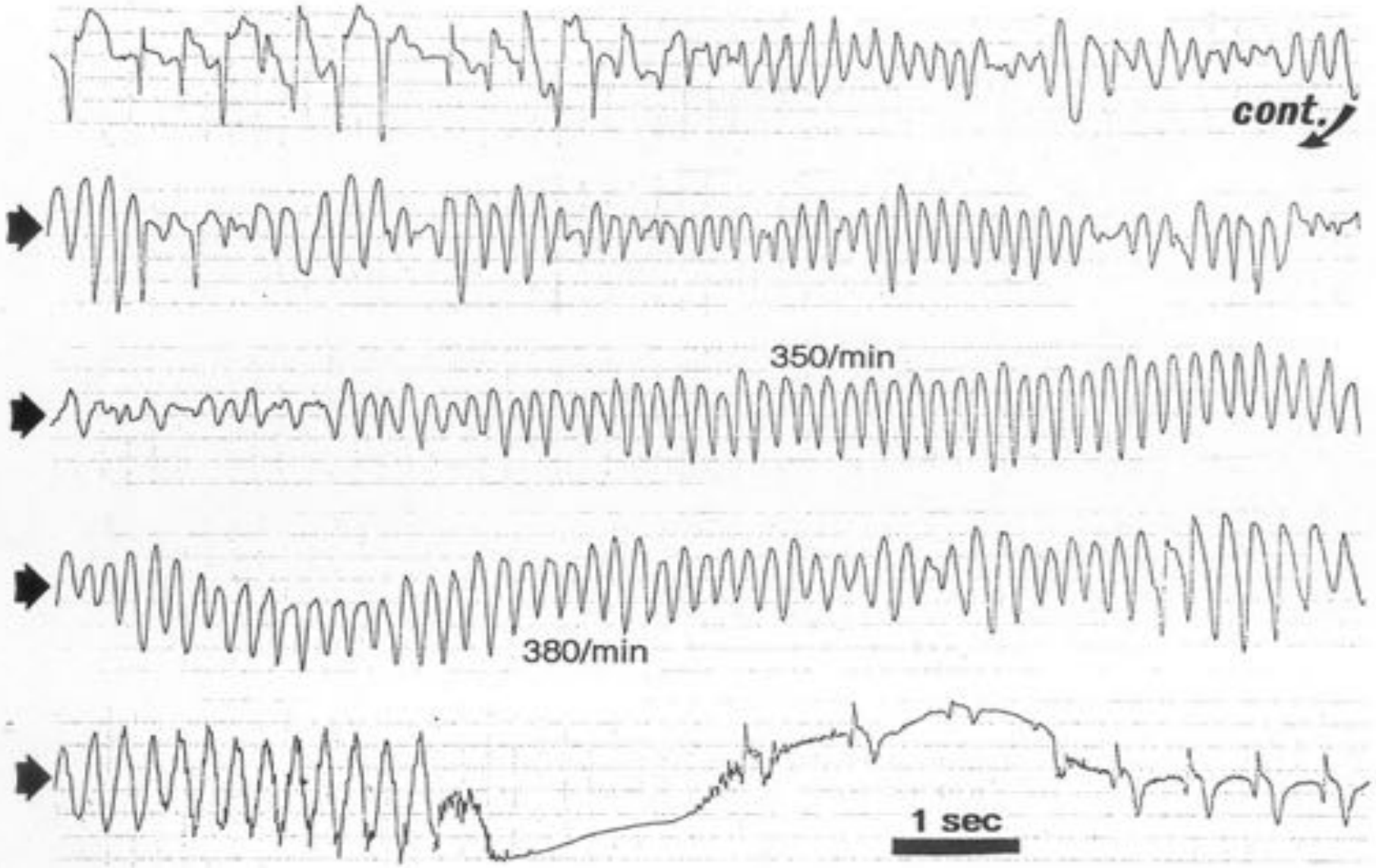
112/min
115/min
118/min
120/min
127/min
135/min
140/min
120/min
115/min
100/min

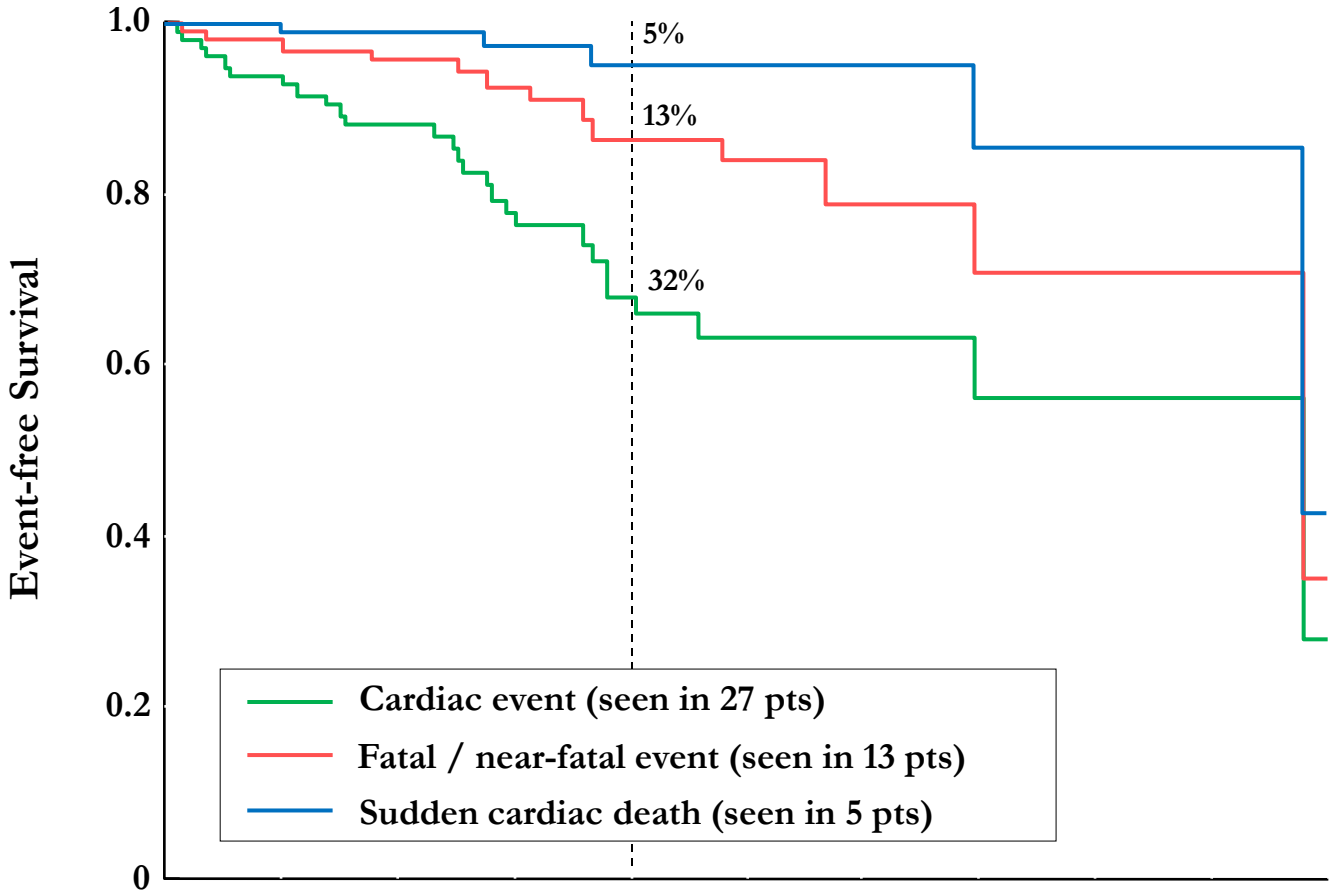


Leenhardt A. et al. Circ Arrhythm Electrophysiol. 2012; 5:1044-52.


-0,09
1,15
-1,35
2,87
-0,75
1,84
1,01
-1,78
-0,06
-0,40
-0,78
2,41
V1
V2
V3
V4
V5
V6
0,17
-0,69
0,89
2,47
0,20
2,18
0,43
4,02
-0,03
3,39
-0,60
2,59


cont.
350/min
380/min
1 sec

Event rates during the follow-up



Time from the diagnosis (years)

No. at risk											
Cardiac event	101	84	67	49	32	23	12	7	6	3	1
	101	88	69	56	39	30	14	8	6	3	1
Sudden cardiac death	101	91	72	59	44	36	15	8	6	3	1

Hayashi M, et al. Circulation 2009; 119: 2426-34

Expert Consensus Recommendations on CPVT
Therapeutic Interventions

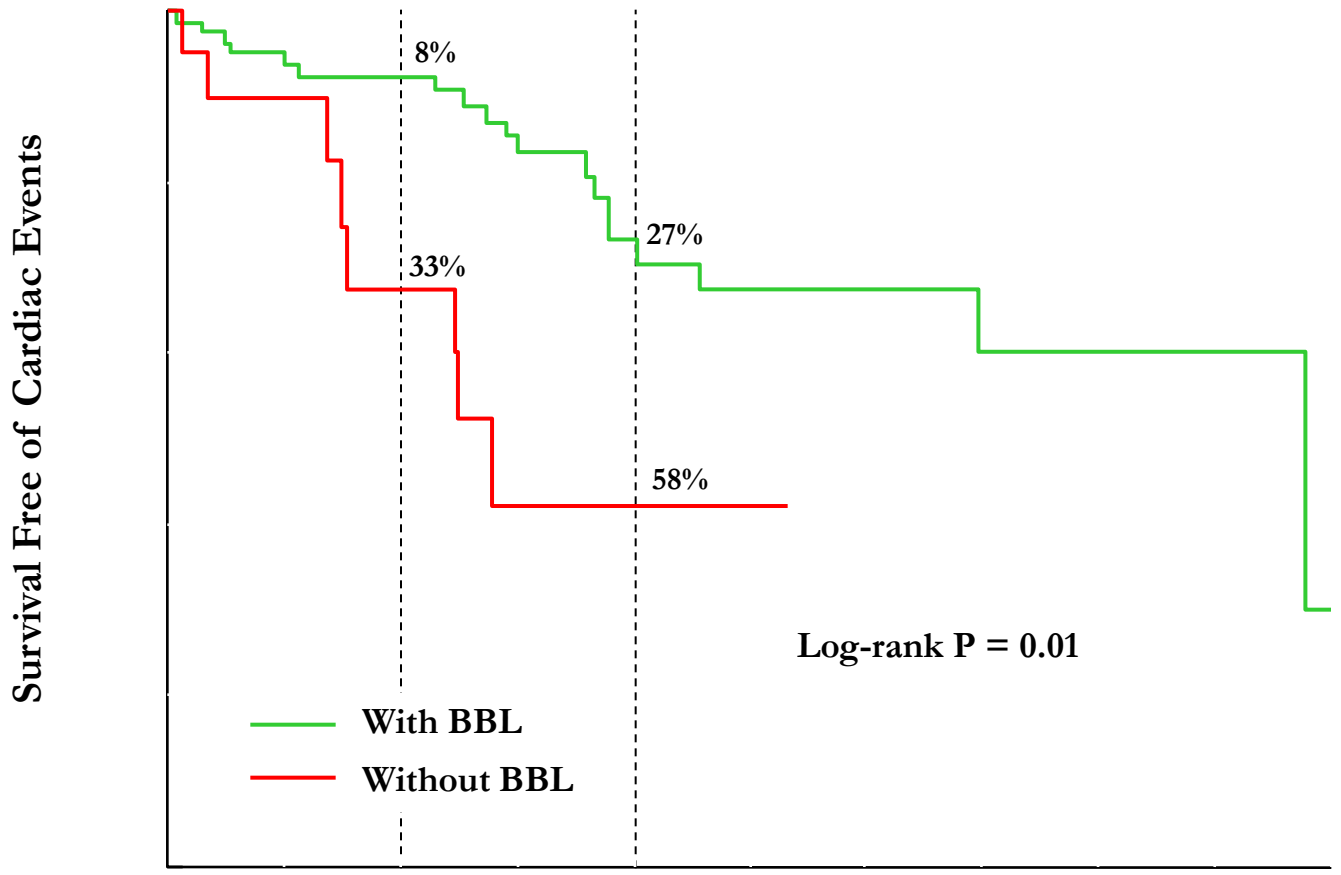
Class	Beta-blockers Recommendations
Class I	Beta-blockers ***are recommended*** in all symptomatic patients with a diagnosis of CPVT.
Class IIa	Beta-blockers ***can be useful*** in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (concealed mutation-positive patients).

Tachycardie Ventriculaire Polymorphe

Efficacité du traitement béta bloquant

- Disparition des syncopes
- Holter et test effort :
  - FC max HR < 130 bpm pendant effort
  - Diminution significative ou disparition des ESVs répétitives
  - Persistence d'ESV isolées
- Peu d'effet sur la FC seuil de déclenchement des ESV

Cardiac events in patients with or without BBL



No. at risk

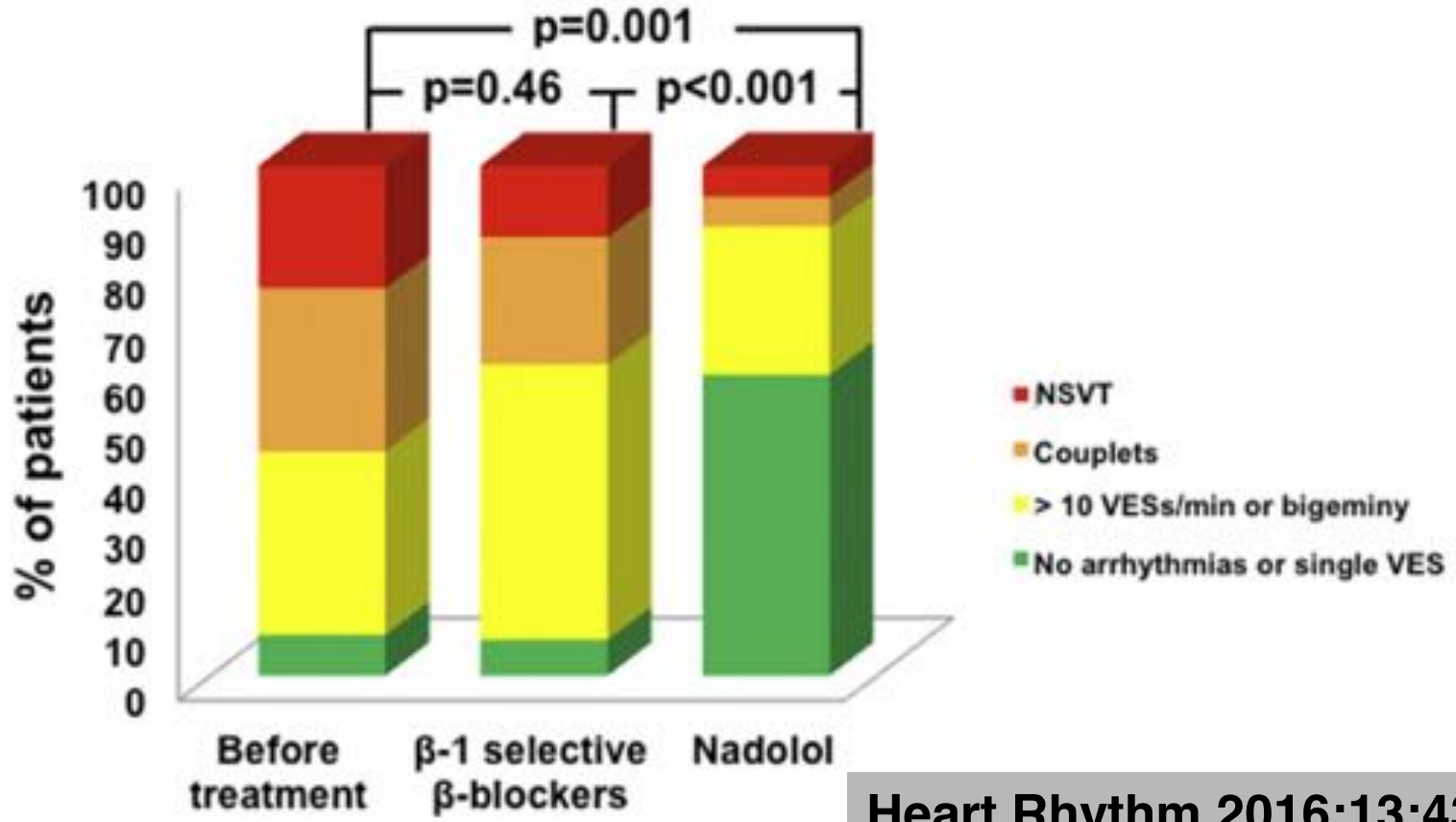
Time from the diagnosis (years)

With BBL	81	69	58	45	28	20	12	7	6	3	1
	20	15	9	4	4	3					

Hayashi M, et al. Circulation 2009; 119: 2426-34

Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with β_1-selective β-blockers in patients with catecholaminergic polymorphic ventricular tachycardia

Ida S. Leren, MD,[*†‡] Jørg Saberniak, MD,[*†‡§] Eman Majid,[‡] Trine F. Haland, MD,[*†‡§] Thor Edvardsen, MD, PhD,[*†‡§] Kristina H. Haugaa, MD, PhD[*†‡§]



Heart Rhythm 2016;13:433-440

Expert Consensus Recommendations on CPVT
Therapeutic Interventions

Class	Flecainide Recommendations
Class IIa	Flecainide ***can be a useful*** addition to beta- blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT while on beta-blockers.

JAMA Cardiology | Original Investigation

Efficacy of Flecainide in the Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia

A Randomized Clinical Trial

Prince J. Kannankeril, MD, MSCI; Jeremy P. Moore, MD, MS; Marina Cerrone, MD; Silvia G. Priori, MD, PhD; Naomi J. Kertesz, MD; Pamela S. Ro, MD; Anjan S. Batra, MD; Elizabeth S. Kaufman, MD; David L. Fairbrother, MD; Elizabeth V. Saarel, MD; Susan P. Etheridge, MD; Ronald J. Kanter, MD; Michael P. Carboni, MD; Matthew V. Dzurik, MD, MSCI; Darlene Fountain, RN; Heidi Chen, PhD; E. Wesley Ely, MD, MPH; Dan M. Roden, MD; Bjorn C. Knollmann, MD, PhD

Key Points

Question Is flecainide acetate more effective than placebo when used in addition to maximally tolerated β-blocker therapy for the prevention of exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia?

Findings This randomized clinical trial in 14 patients with catecholaminergic polymorphic ventricular tachycardia using maximally tolerated β-blockers demonstrated that ventricular arrhythmias during exercise were significantly reduced by flecainide, with complete suppression observed in 11 of 13 patients, compared with placebo. Overall and serious adverse events did not differ between the flecainide and placebo arms.

Meaning Flecainide is efficacious in reducing ventricular arrhythmias associated with exercise in patients with catecholaminergic polymorphic ventricular tachycardia and persistent exercise-induced ectopy despite a maximally tolerated β-blocker dosage.

Table 1. Baseline Characteristics of the Study Cohort

Characteristic	Patient Data (n = 13)[a]
Age, median (IQR), y	16 (15.0-22.5)
Male	7 (54)
White	12 (92)
Hispanic	1 (8)
Putative pathogenic mutation	11 (85)
RYR2	10 (77)
CASQ2	1 (8)
Weight, median (IQR), kg	74.5 (54-86)
Height, median (IQR), cm	168 (157-180)
β-Blocker use[b]	13 (100)
Nadolol	9 (69)
Atenolol	2 (15)
Metoprolol succinate	1 (8)
Propranolol hydrochloride	1 (8)
Exercise score at baseline[c]	
0	3 (23)
1	0 (0)
2	1 (8)
3	6 (46)
4	3 (23)

Abbreviations: *CASQ2*, cardiac calsequestrin gene; IQR, interquartile range; *RYR2*, ryanodine receptor 2 calcium release channel gene.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] β-Blocker use was unchanged throughout the trial. For nadolol, median daily dose was 80 mg; for atenolol, median daily dose was 112 mg; for metoprolol succinate, daily dose was 50 mg; and for propranolol hydrochloride, daily dose was 240 mg.

[c] Scores are for β-blocker treatment alone, with 0 indicating no ectopy; 1, isolated premature ventricular contractions; 2, bigeminy; 3, couplets; and 4, nonsustained ventricular tachycardia.

JAMA Cardiol. 2017;2(7):759-766.

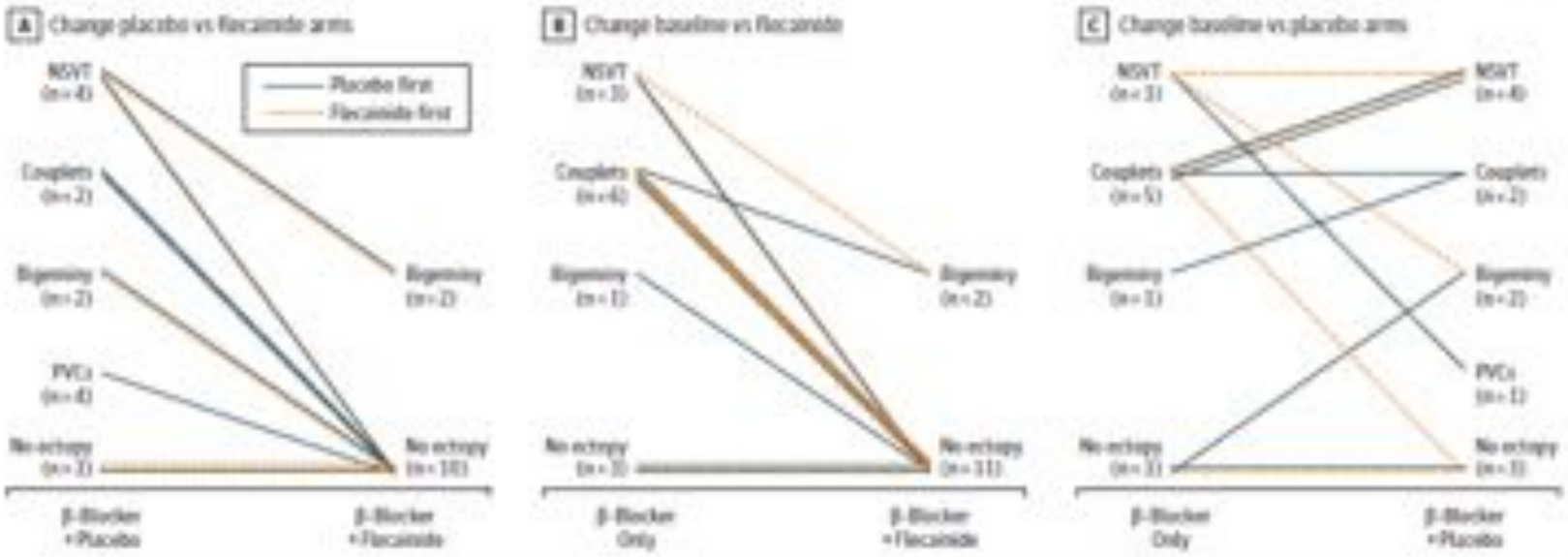
Table 2. Proportions of Patients With Each Ventricular Arrhythmia Score

Ventricular Arrhythmia	No. (%) of Patients[a]		
	β-Blocker Alone	β-Blocker + Flecainide Acetate	β-Blocker + Placebo
NSVT	3 (23)	0	4 (33)
Couplets	6 (46)	0	2 (17)
Bigeminy	1 (8)	2 (17)	2 (17)
PVCs	0	0	1 (8)
No ectopy	3 (23)	10 (83)	3 (25)

Abbreviations: NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contractions.

[a] $P = .005$, baseline compared with flecainide arm; $P = .008$, flecainide vs placebo arms; and $P = .70$, baseline compared with placebo arms.

Figure 2. Efficacy of Flecainide in Reducing Ventricular Arrhythmias During Exercise in Catecholaminergic Polymorphic Ventricular Tachycardia



A, Change in arrhythmia score for each patient between the placebo and flecainide acetate arms for the 12 patients with available data ($P = .008$). B, Change in arrhythmia score for each patient between baseline (β-blocker only) vs flecainide arm for the 13 patients with available data ($P = .005$). C, Change in arrhythmia score for each patient between baseline (β-blocker only) vs placebo arm for the 12 patients with available data ($P = .70$). NSVT indicates nonsustained ventricular tachycardia; PVC, premature ventricular contractions.

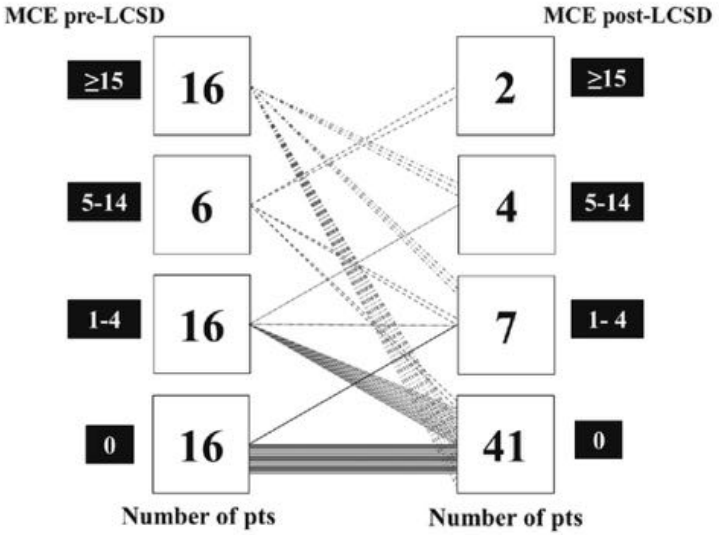
Expert Consensus Recommendations on CPVT
Therapeutic Interventions

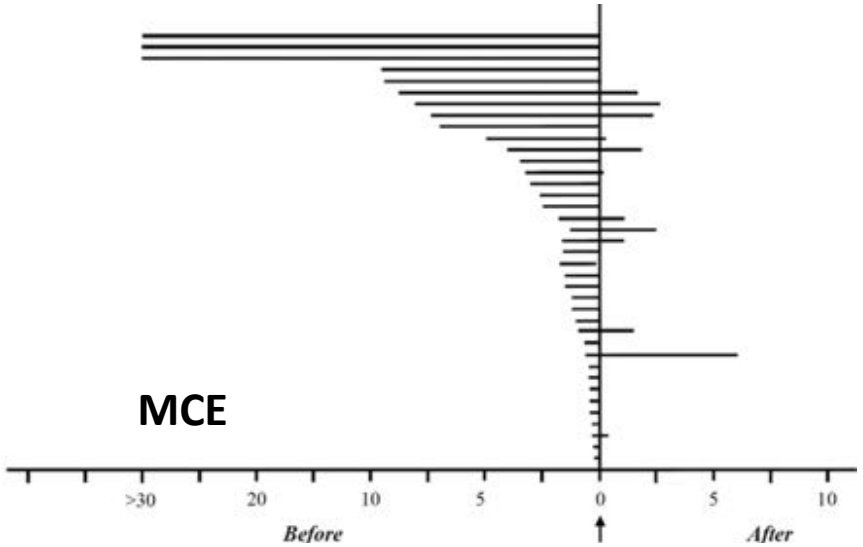
Class	LCSD Recommendations
Class IIb	LCSD ***may be considered*** in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT/ several appropriate ICD shocks while on beta-blockers and in patients who are intolerant or with contraindication to beta-blockers.

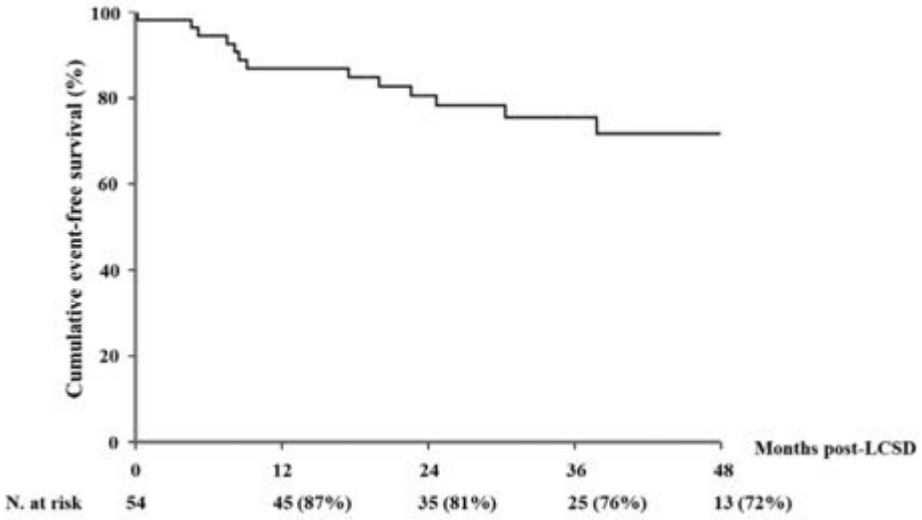
Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia

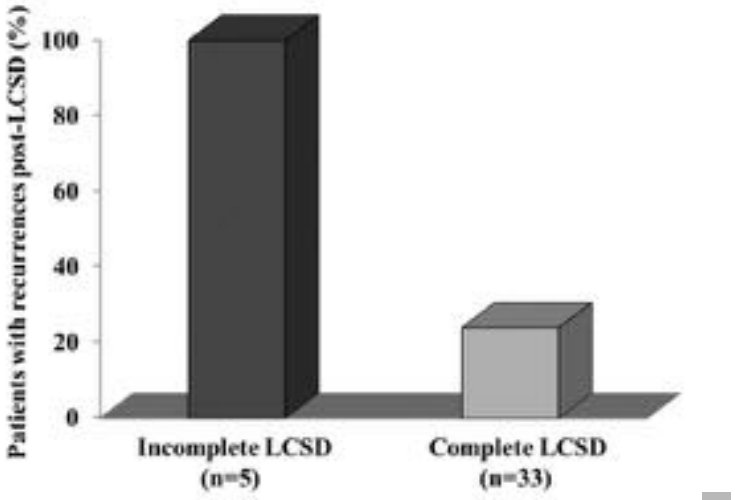
The Role of Left Cardiac Sympathetic Denervation

Nadolol 35%









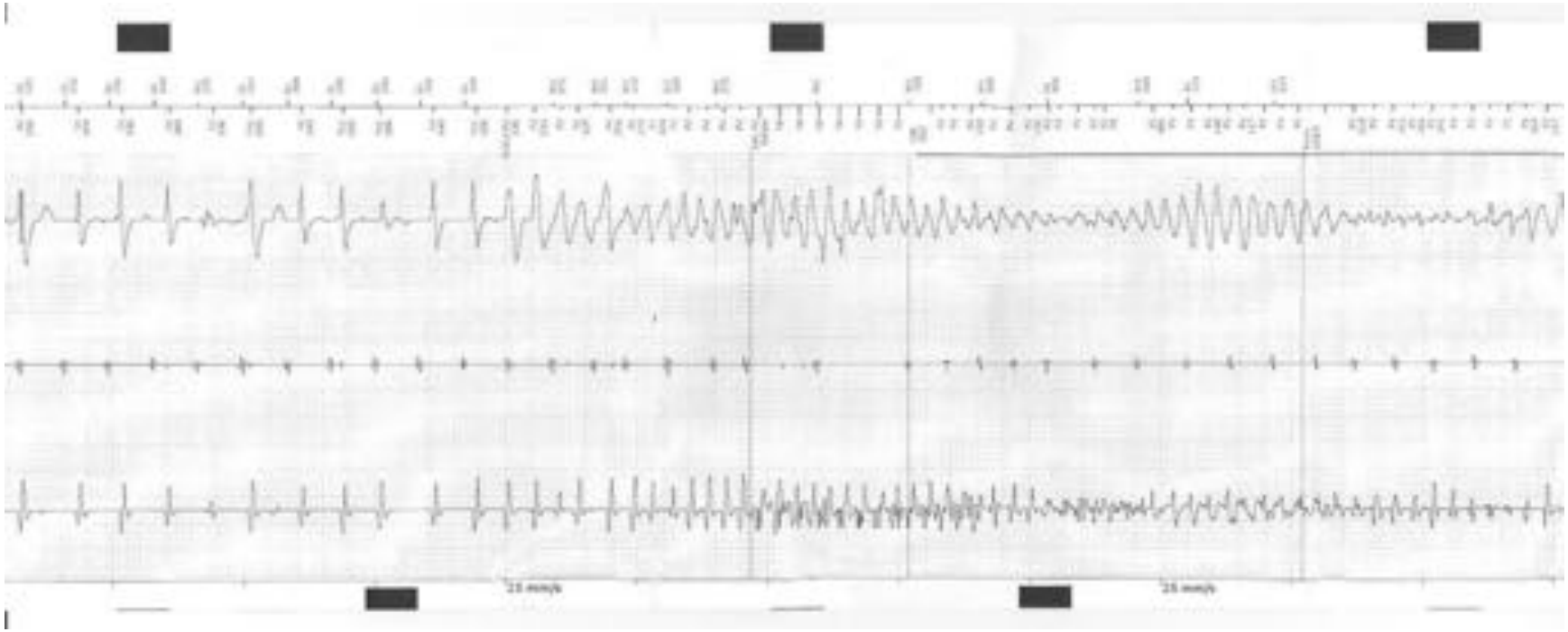
Circulation 2015;131:2185-93

Expert Consensus Recommendations on CPVT
Therapeutic Interventions

Class	ICD Recommendations
Class I	ICD implantation ***is recommended*** in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/ bidirectional VT despite optimal medical management, and/or LCSD.
Class III	ICD as a standalone therapy ***is not indicated*** in an asymptomatic patient with a diagnosis of CPVT.

EUROPEAN Heart Rhythm ASSOCIATION
APHRS
Heart Rhythm Society

Syncopes + convulsions à l'émotion ou l'effort depuis l'âge de 10 ans
Traitement anti épileptique : sans effet
MS en courant, récupérée à l'âge de 16 ans
DAI sans diagnostic étiologique
Choc approprié 1 mois après implantation en courant…



Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications.

- Systematic review and meta-analysis inherited arrhythmia syndromes (ARVC/D, BS, CPVT, HCM, lamin DCM, LQTS, SQTS)
- 63 studies including 4916 patients mean FU 54±43 months
- Inappropriate shocks in 20% of patients (4.7% per year)

  CPVT 36%, p=0.04
- 22% ICD-related complications (4.4% per year)

  CPVT 85%
- 0.5% ICD-related mortality (0.08% per year)

Olde Nordkamp LR, et al **Heart Rhythm. 2016;13:443-54**

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

STATE OF GENETIC TESTING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Class I (is recommended)

Comprehensive or CPVT1 and CVPT2 (RYR2 and CASQ2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion.

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.

Positif 70%

KEYWORDS Genetics; Cardiomyopathies; Channelopathies (Heart Rhythm 2011; 8:1308–1339)

CPVT Management

Expert Consensus Recommendations on CPVT Therapeutic Interventions

Class I	1. The following lifestyle changes ***are recommended*** in all patients with diagnosis of CPVT: a) Limit/ avoid competitive sports; b) Limit/avoid strenuous exercise; c) Limit exposure to stressful environments. 2. Beta-blockers ***are recommended*** in all symptomatic patients with a diagnosis of CPVT. 3. ICD implantation ***is recommended*** in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/ bidirectional VT despite optimal medical management, and/or LCSD.
Class IIa	4. Flecainide ***can be a useful*** addition to beta- blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT while on beta-blockers. 5. Beta-blockers ***can be useful*** in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (concealed mutation-positive patients).
Class IIb	6. LCSD ***may be considered*** in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT/ several appropriate ICD shocks while on beta-blockers and in patients who are intolerant or with contraindication to beta-blockers.
Class III	7. ICD as a standalone therapy ***is not indicated*** in an asymptomatic patient with a diagnosis of CPVT. 8. Programmed Electrical Stimulation ***is not indicated*** in CPVT patients.

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes 2013- Recos ESC 2015

Tachycardie ventriculaire catécholergique

- ✓ **N = 226 (170 cas index)**
- ✓ **Symptômes = 78%**

  PC = 112 (64%); ACR = 58 (33%)
- ✓ **Age symptômes = 11 ans**
- ✓ **Age Δic = 12 ans**
- ✓ **Traitement BB - = 97%**
- ✓ **Suivi (3,5 ans) = 25 % PC/ACR/MS**
  - ✓ **Mauvaise compliance/ sous dosage BB-**
  - ✓ **Orage rythmique**
- ✓ **Tous les patients avec Σ↕ sont devenus asymptomatiques (n =15/18)**

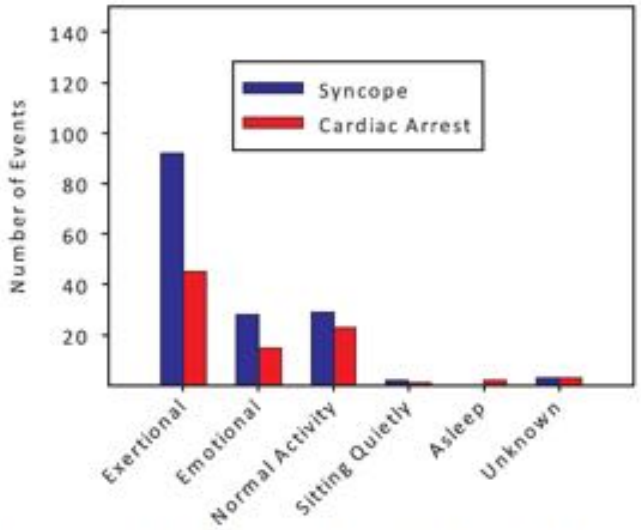


Figure. Circumstances immediately preceding life-threatening cardiac event(s) in the 122 patients reporting syncope and 86 with cardiac arrest.

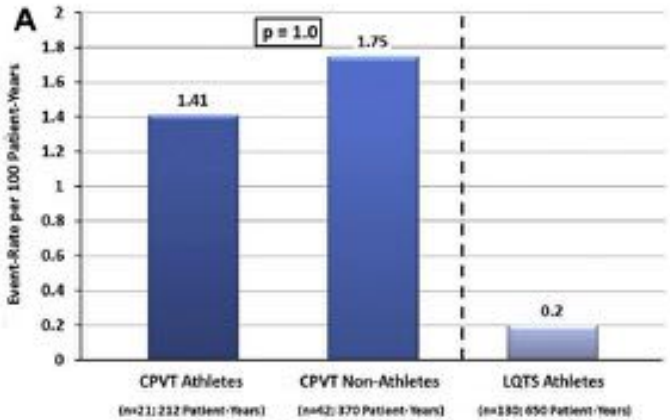
Roston et al. Circ Arrhyth Electrphysiol 2015; 8: 633-642

Tachycardie ventriculaire catécholergique

- **Diagnostic :**
  - Holter + effort : > 2 ans
  - Adrénaline > 2 ans
  - Epreuve d'effort > 8 ans

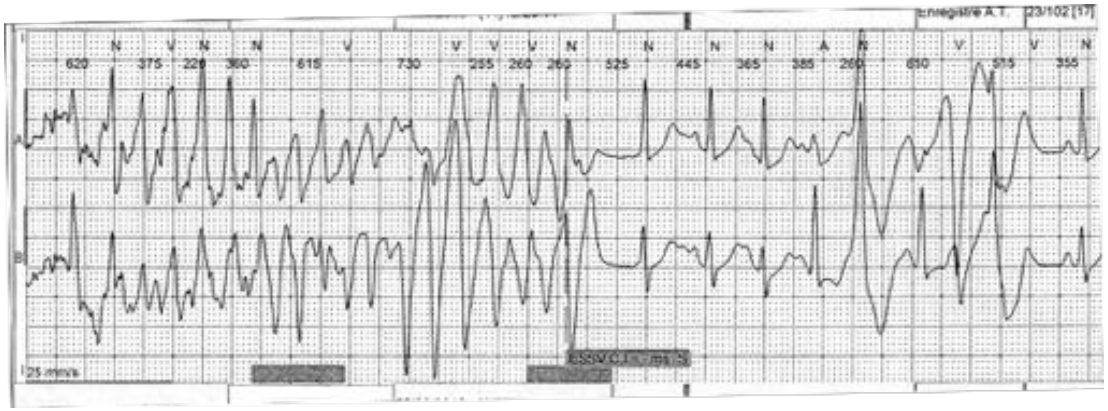
- **Tests génétiques** (RyR2, CASQ2, Triadin) : les apparentés du 1er degré au moment du bilan familial + enfants (> 2 ans)

- **Traitement** :
  - Béta-bloquant (nadolol) : dès le diagnostic
  - ± Flécainide
  - Sympathectomie /DAI
  - **Activité sportive restreinte**

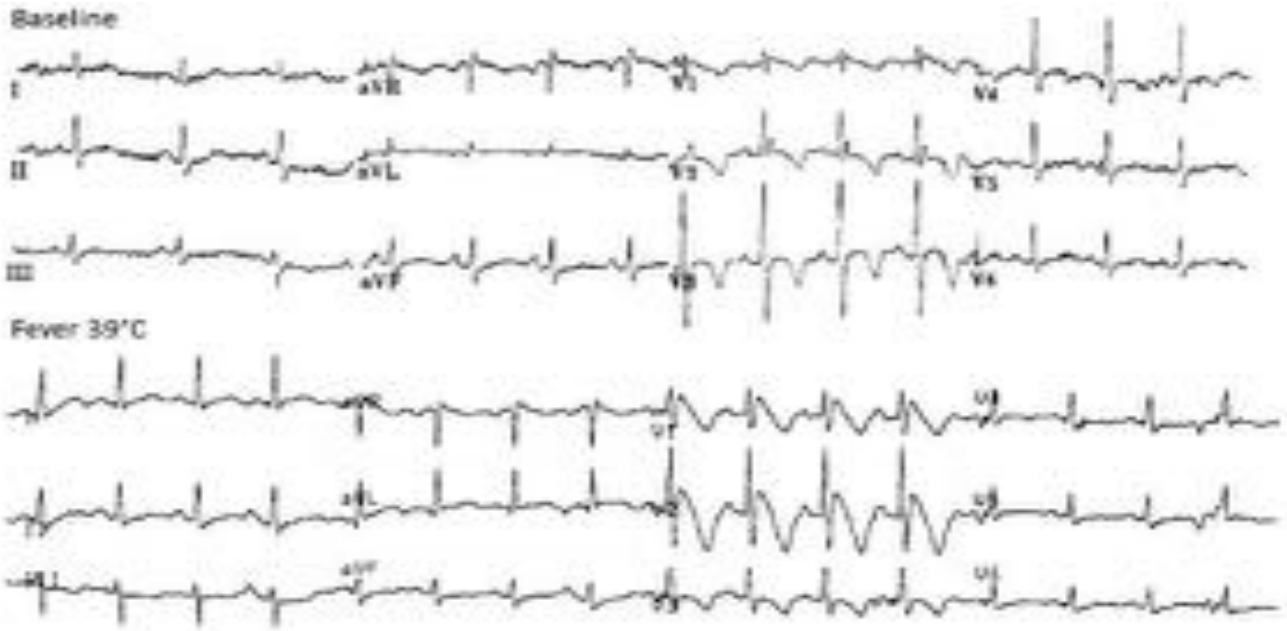


CPVT : conclusions

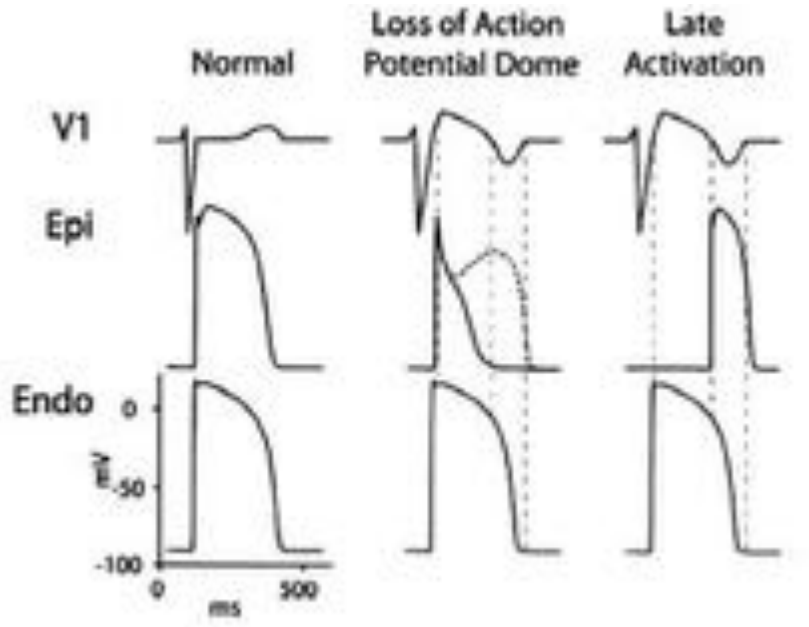
- Diagnosis +++ (Epruve effeort, Holter, Isu)
- Use a“potent” non cardio selective beta blocker – Nadolol 1- 2 mg/kg BID titrated with treadmill testing
- Breakthrough events or ectopy on treadmill: add flecainide 0.5-2 mg/kg BID or long acting
- Sympathectomy very effective in high risk patients
- ICDs are dangerous in CPVT, use sparingly, target at VF
- Future : Ablation ? New drugs ?



Syndrome de Brugada



- Tachycardie ventriculaire polymorphe/FV => syncopes ou mort subite. 4% du total des MS, 20 % des MS sur cœur sain.
- Prévalence 20 / 100 000 *(Orphanet 2011)* Formes familiales
- Génétique : 10 gènes (**SCN5A ++**)
- Pénétrance 30% (variable
- Retard de conduction intra-ventriculaire droite avec sus-décalage segment ST V1/V2/V3 (surélévation J ≥ 0.2 mV)



Name	Gene	Protein	Prevalence
BrS1	*SCN5A*	α-subunit Nav1.5 Sodium channel	20%–25%
BrS2	*GPD1L*	Glycerol-3-phosphate dehydrogenase 1-like	Rare
BrS3	*CACNA1C*	α-subunit α1C Cav1.2 Calcium channel	1%–2%
BrS4	*CACNB2b*	β-subunit Cavβ2b calcium channel	1%–2%
BrS5	*SCN1b*	β-subunit Navβ1 sodium channel	Rare
BrS6	*KCNE3*	β-subunit MiRP2 potassium channel	Rare
BrS7	*SCN3b*	β-subunit Navβ3 sodium channel	Rare
BrS8	*HCN4*	Hyperpolarization-activated cyclic nucleotide-gated channel 4	Rare
BrS9	*KCND3*	α-subunit KV4.3 potassium channel	Rare
BrS10	*KCNJ8*	α-subunit KIR6.1 potassium channel	Rare
BrS11	*CACNA2D1*	δ-subunit Caνα2δ1 calcium channel	Rare
BrS12	*KCNE5*	β-subunit potassium channel	Rare
BrS13	*RANGRF*	RAN guanine nucleotide release factor	Rare
BrS14	*KCND2*	α-subunit KV4.2 potassium channel	Rare
BrS15	*TRPM4*	Calcium-activated nonselective ion channel	Rare
BrS16	*SCN2B*	β-subunit Navβ2 sodium channel	Rare
BrS17	*PKP2*	Plakophilin 2	Rare
BrS18	*ABCC9*	ATP-sensitive potassium channels	Rare
BrS19	*SLMAP*	Sarcolemma-associated protein	Rare
BrS20	*KCNH2*	α-subunit of HERG potassium channel	Rare
BrS21	*SCN10A*	α-subunit Nav1.8 sodium channel	1%–16%
BrS22	*FGF12*	Fibroblast growth factor 12	Rare
BrS23	*SEMA3A*	Semaphorin family protein	Rare

Syndrome de Brugada et mort subite de l'enfant

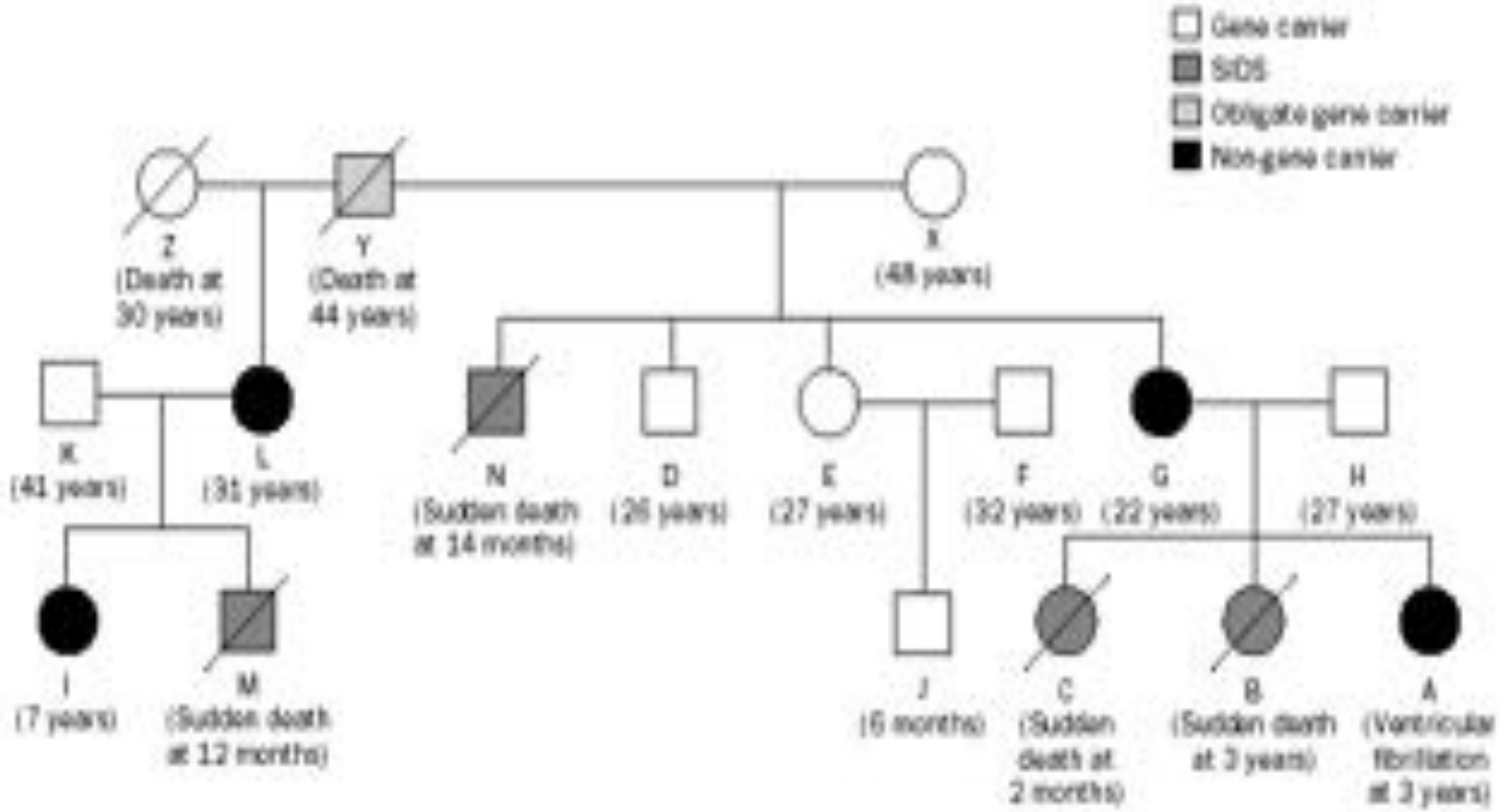
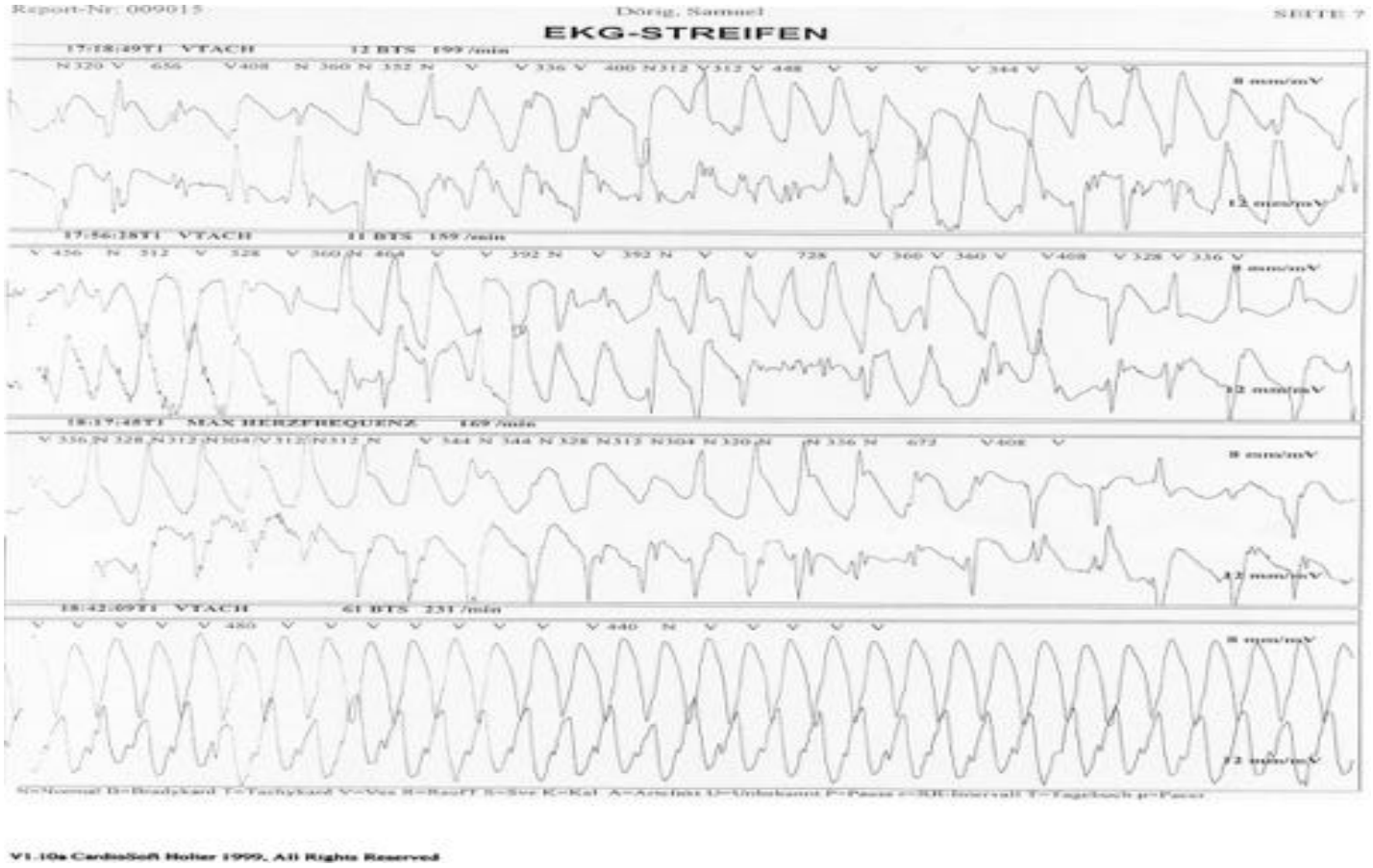


Figure 1: Family pedigree
Squares indicate males, circles indicate females. Ages and age at death/event in brackets.

Priori S et al, Lancet 2000; 555 : 808- 809

FV Brugada



Enfant de 3 ans adressé pour malaise avec PC dans un contexte fébrile

Evènements cardiaques (âge)

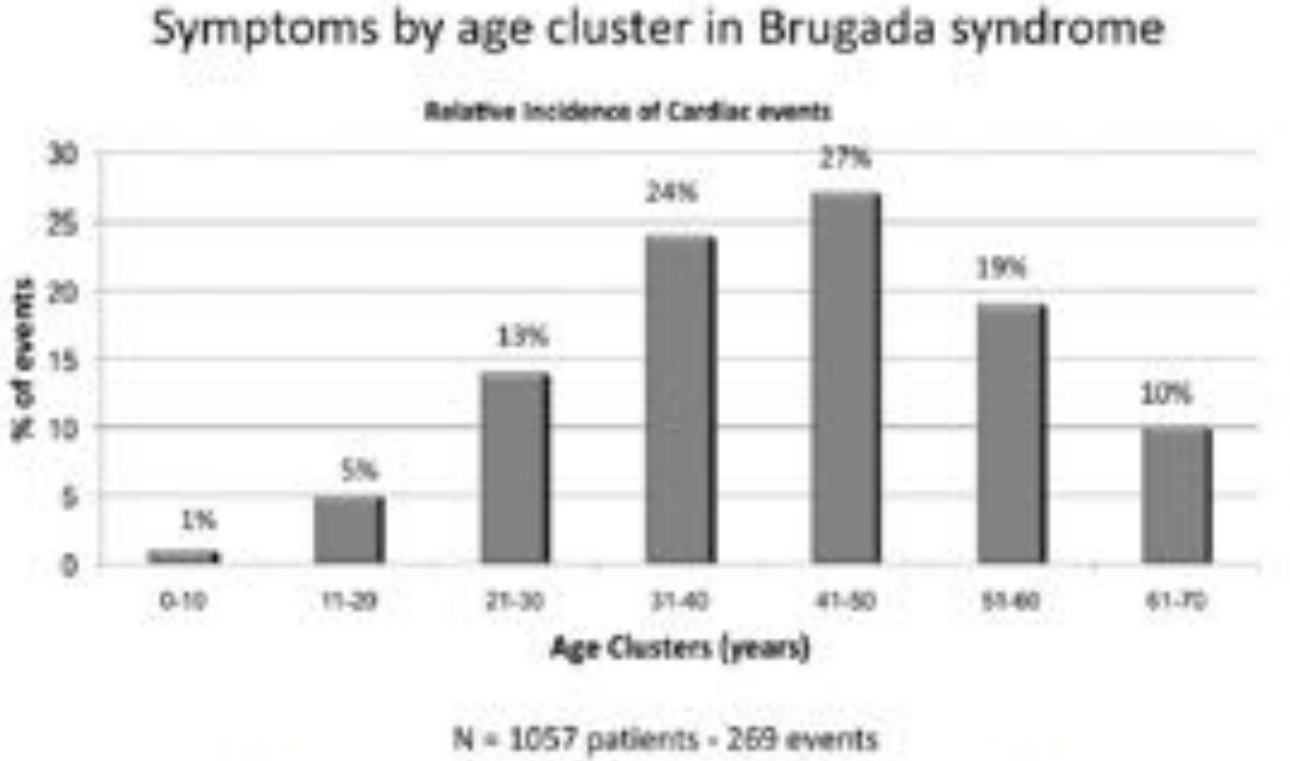
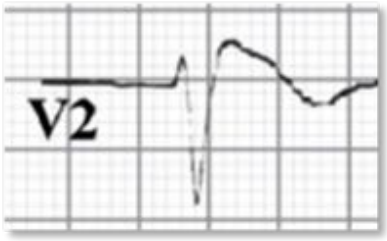


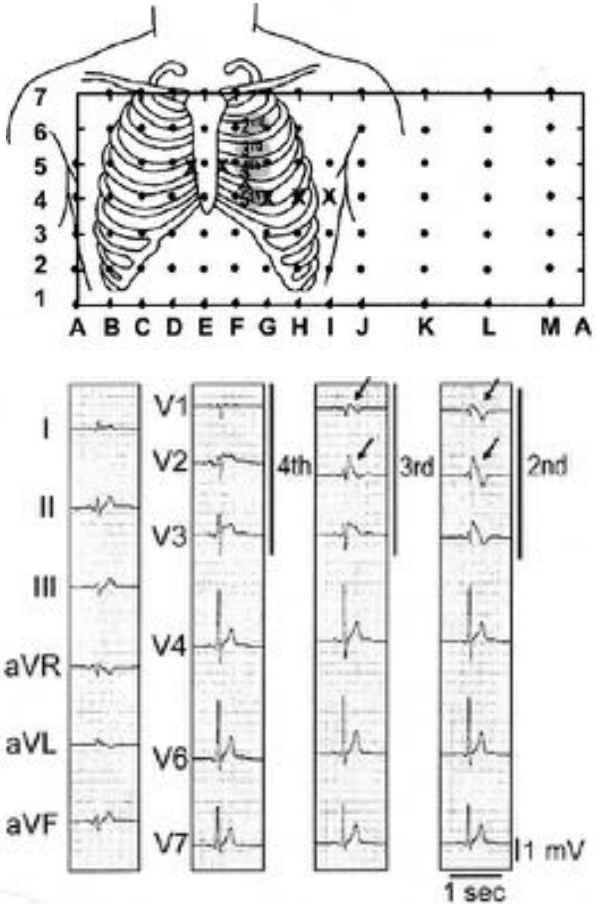
Figure 4. Relative percentage of symptomatic Brugada syndrome patients by age clusters showing a peak of incidence in the third and fourth decades of life (data from the Pavia Brugada syndrome registry).

Brugada Syndrome : diagnosis



Diagnosis of Brugada Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
Brugada syndrome is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium channel blockers (such as ajmaline, flecainide, procainamide or pilsicainide).	I	C	This panel of experts



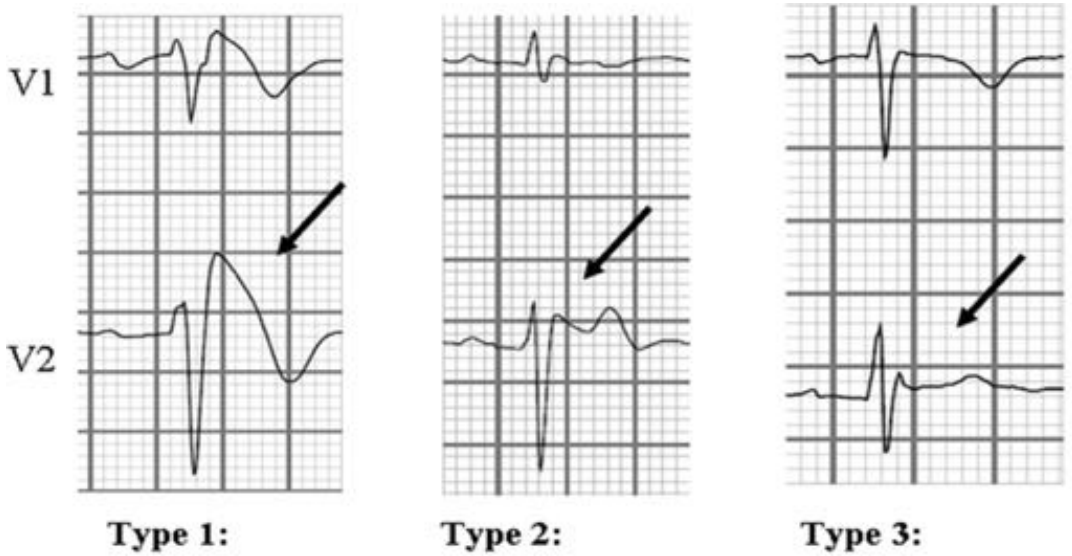
ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

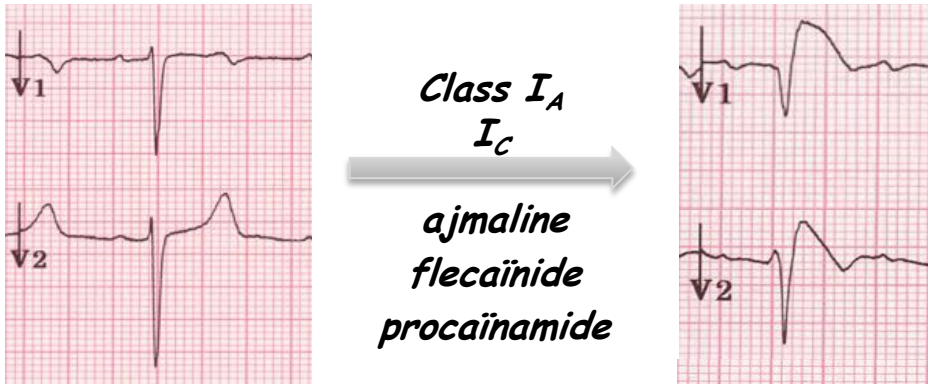
Brugada Syndrome

- **ECG pattern of Brugada Syndrome**

- **Diagnosis**
  - Type 1 ECG pattern
  - At least in one right precordial lead
  - Spontaneous or drug-induced

- **Clinical data**
  - Low prevalence : 0.02 %
  - Venticular arrhythmia and SCD
  - Lack of data





Brugada Syndrome, Mizusawa & Wilde, Circ EP, 2012
Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes, Priori S., HR, 2013

Sodium blocker challenge

- 106 Brugada pts age 11.1 ± 5.7 yrs
- Drug induced 76% :
  - **Ajmaline** : n=42 ; 14.3 ± 3.7 yrs
  - **Flecaïnide** : n=27 ; 13.4 ± 4.5 yrs
- 33 challenges were performed < 15 yrs
- 2 non-sustained ventricular tachycardia during drug challenge (SCN5A+)

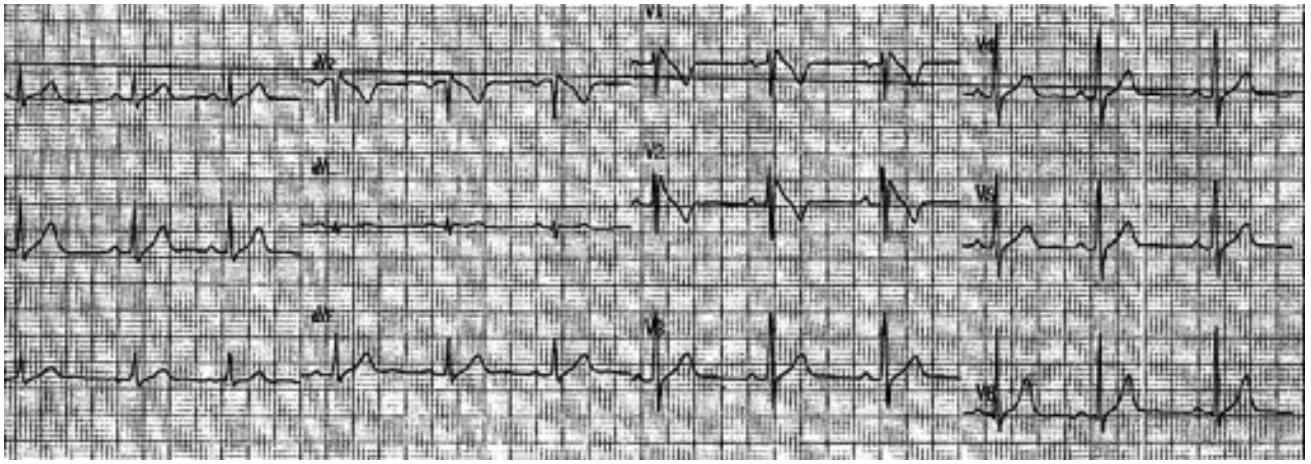
Andorin, Heart rhythm, 2016

Table 1. Clinical Characteristics and Electrocardiogram Parameters of Study Population

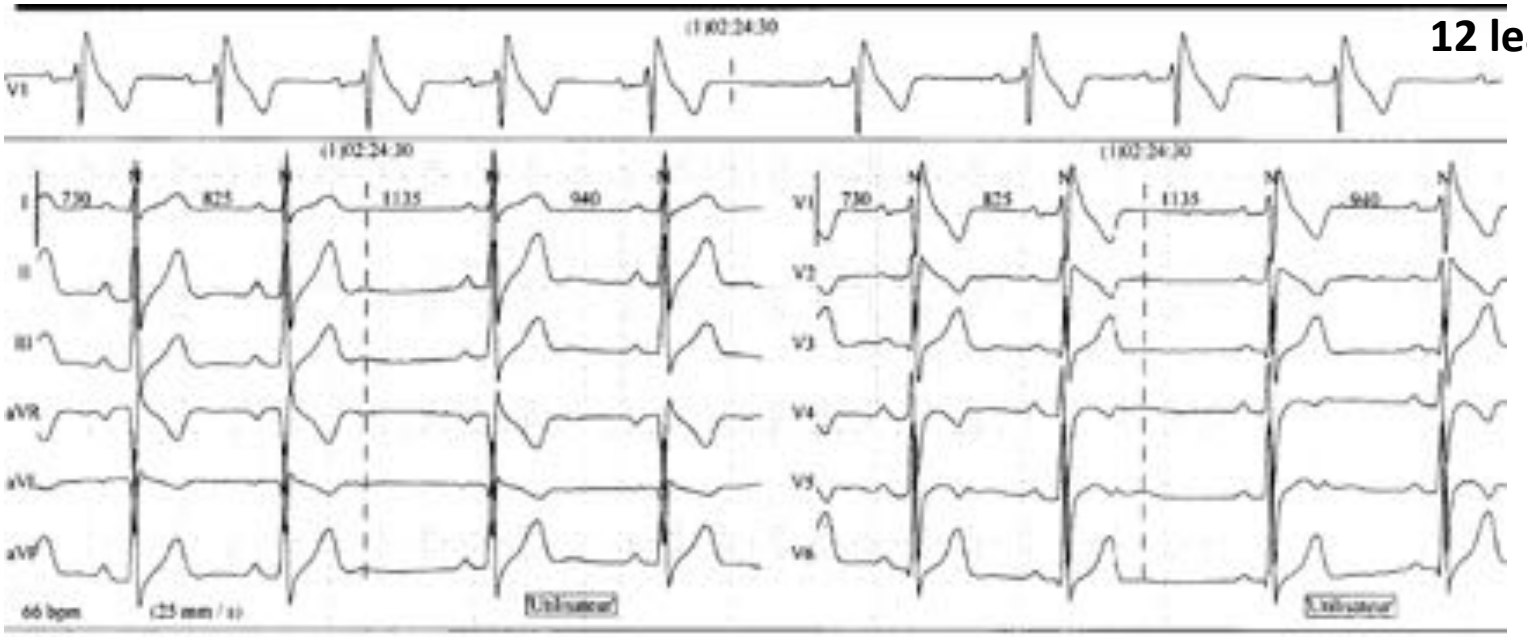
	Study Population (N = 43)
Male sex, No. (%)	21 (49)
Age, mean (SD) [range], y	
First ajmaline challenge	11 (1) [2-15]
Repeat ajmaline challenge	19 (3) [16-30]
Family history of sudden death, No. (%)	23 (53)
Development of symptoms before repeat ajmaline challenge, No. (%)	4 (9)
Ajmaline-induced sustained ventricular arrhythmias, No. (%)	
First ajmaline challenge	0
Repeat ajmaline challenge	1 (2)
Positive repeat ajmaline challenge, No. (%)	10 (23)
Electrocardiogram baseline parameters	
PR interval, mean (SD), ms	148 (24)
QRS duration, mean (SD), ms	91 (14)
QTc interval, mean (SD), ms	401 (33)
Maximal ST elevation, mean (SD), mm	0.52 (0.25)
Type 2 electrocardiogram pattern, No. (%)	5 (12)
Incomplete right bundle branch block, No. (%)	2 (5)
First-degree atrioventricular block, No. (%)	3 (7)

Follow-up From Childhood to Adulthood of Individuals With Family History of Brugada Syndrome and Normal Electrocardiograms

Conte G, et al. JAMA 2014. 312(19): 2039-41

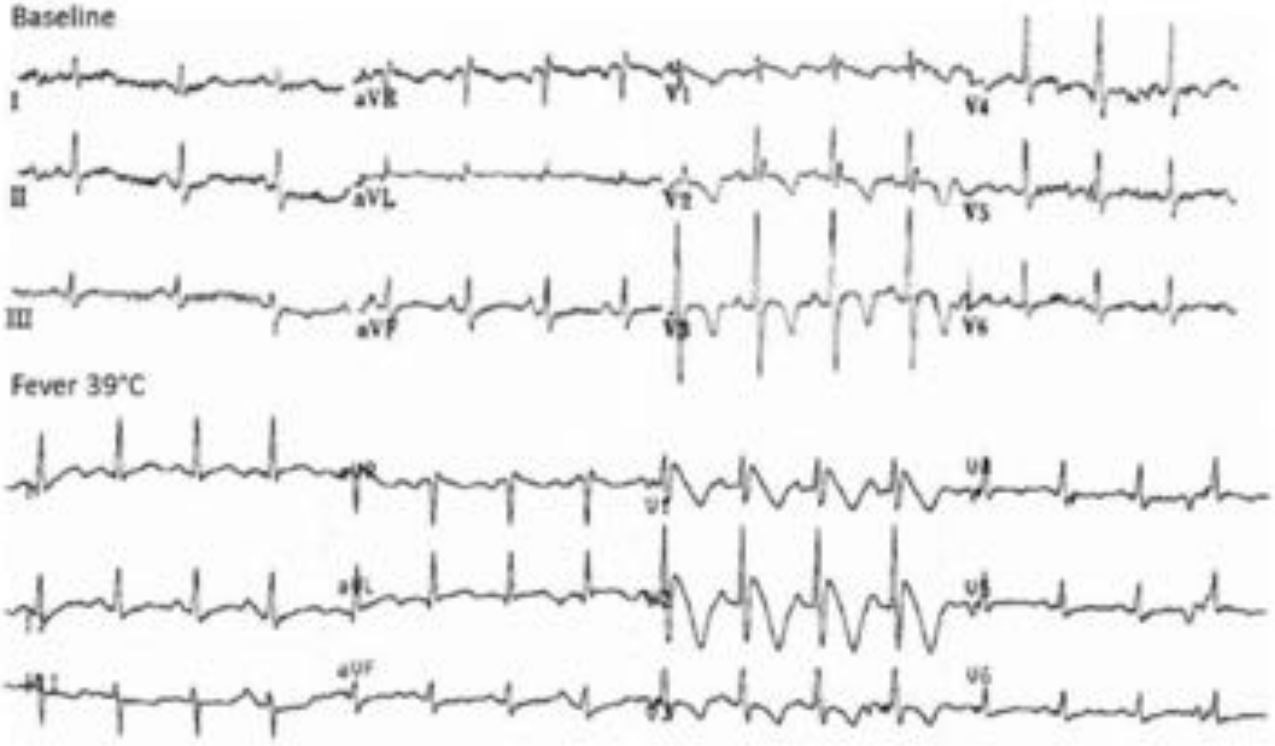


ECG



12 lead Holter

5 year old Brugada Syndrome


Baseline
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
Fever 39°C

Presentation at diagnosis

Total	106
Male, n (%)	58 (55)
Age at diagnosis, y	11.1 ± 5.7
Follow-up, mo	54 [15-99]
Spont. Type 1 ECG Pattern, n	36 (34)
SCN5A mutation, n (*n=75*)	58 (77)
Familial history of SCD, n (%)	46 (43)

- Symptoms : n = 21
  - 15 syncopes
  - 4 aSCD and 2 VT
- No symptoms : n = 80
  - 63 familial screening
  - 13 incidental ECG

Andorin, Heart rhythm, 2016

Most Common Initial Presentation of Patients with Brugada

Incidental ECG finding	25%
Syncope	14%
Family history	47%
Arrhythmia	13.0%
Aborted sudden cardiac death	1.0%

ECG = electrocardiogram.

USA PACES Survey PACE 2014

Follow-up

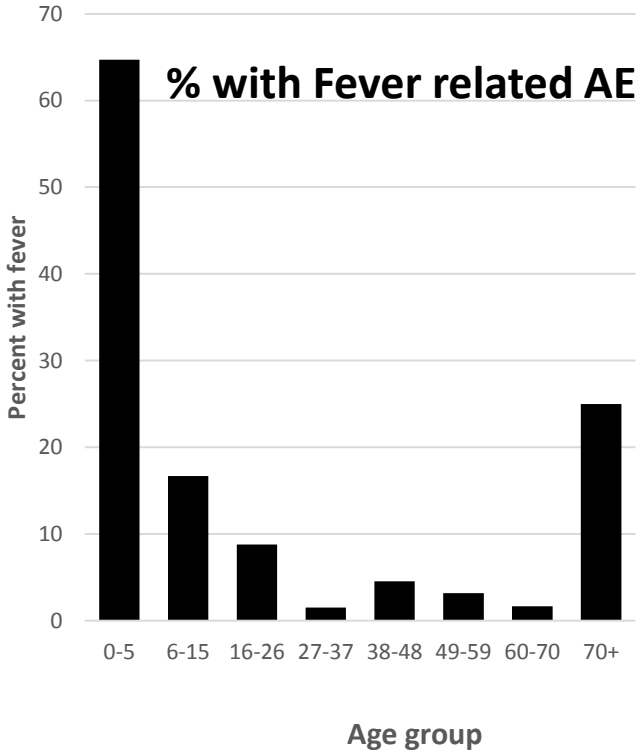
- Treatment
  - 11 child have been treated with hydroquinidine
  - 22 were implanted with an ICD

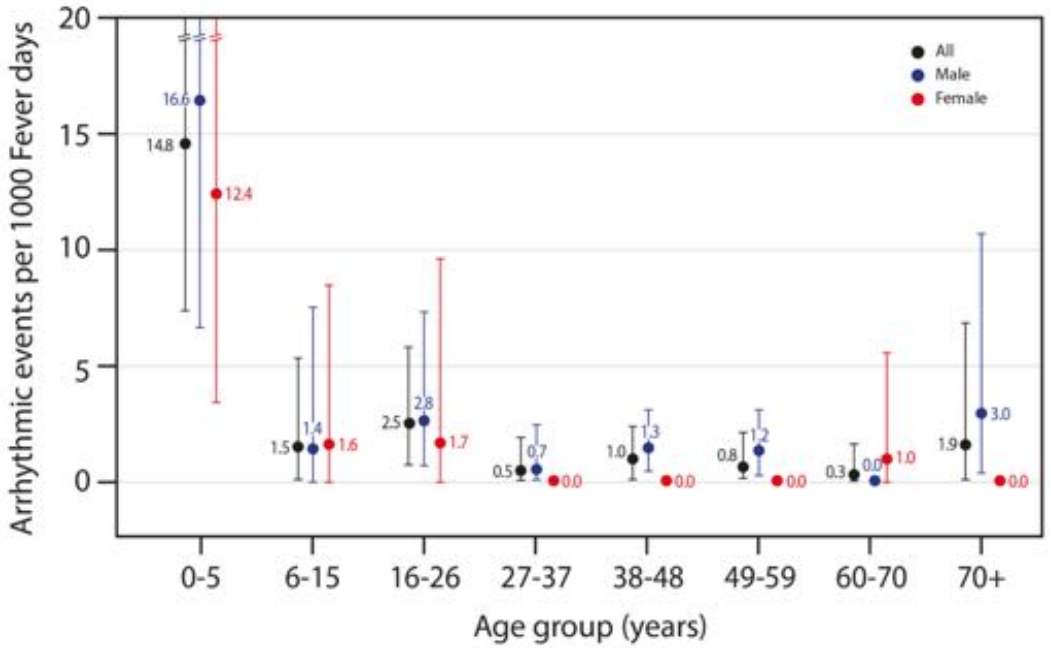
- 15 life threatening events among 10 patients
  - 3 deaths
  - 2 ventricular fibrillation and tachycardia
  - 5 ventricular tachycardia only
  - 6 syncope without documented arrhythmia
  - 4 supra ventricular tachycardia

⟹ **25% triggered by fever**

- 8 of 11 free of events on hydroquinidine
- 9 (41%) of the 22 ICD implanted experienced serious ICD-related complications
- No event in the 17 *SCN5A* negative

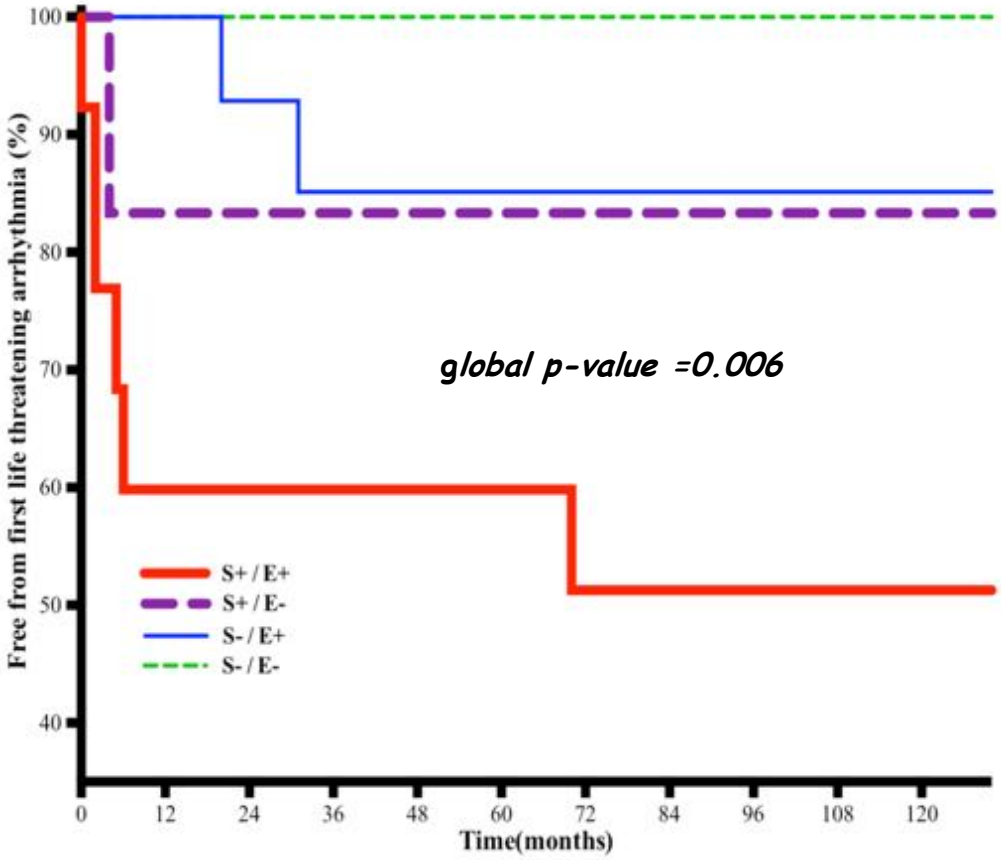
Andorin, Heart rhythm, 2016





Michowitz Y, et al. SABRUS cohort; Heart Rhythm 2018

Risk stratification



n=106 months	0	12	24	60	96	120
S+/E+ = Sympto. & Spont. Type 1	14	6	6	6	3	2
S+/E- = Sympto. & Drug induced	7	5	5	4	3	2
S-/E+ = Asympto. & Spont. Type 1	22	22	13	11	6	3
S-/E- = Asympto. & Drug induced	63	63	63	63	63	63

Asymptomatic AND drug-induced type 1 ECG pattern ➔ LOW RISK

Others clinical situations

➔ Intermediate risk ?

Symptoms AND Spontaneous type 1 ECG pattern ➔ HIGH RISK

Andorin, Heart Rhythm, 2016

Drug induced type 1

Age = 8 ± 3 yrs	Group I (n = 40)
Clinical characteristics	
Male	24 (60)
Family history of SCD	24 (60)
Clinical presentation	
Asymptomatic	30 (75)
Syncope	8 (20)
Aborted SCD	2 (5)
History of atrial arrhythmias	3 (7.5)
Documented SND	3 (7.5)
ECG baseline parameters	
PR interval, ms	140 ± 28
QRS duration, ms	92 ± 15
QTc interval, ms	404 ± 37
Maximal ST-segment elevation, mm	0.52 ± 0.25
Brugada type II ECG	3 (7.5)
Incomplete RBBB	1 (2.5)
First-degree AV block	1 (2.5)

Table 3 Long-Term Follow-Up of Children With Brugada Syndrome

FU = 83 ± 51 months

SCD	0
Syncope	2 (5%)
Documented life-threatening arrhythmias	1 (2%)*
Newly diagnosed AF	1 (2%)
Appropriate ICD interventions	1 (8%)*
Inappropriate ICD interventions	4 (33%)
Device-related complications	4 (33%)
Pulmonary vein isolation	1 (8%)

Values are n or n (%). *Same patient.
ICD = implantable cardioverter defibrillator; other abbreviations as in Table 1.

Conte et al, JACC 2014

Brugada group experience

Table 1
Demographic data of the young population cohort (n = 95). Patients divided into pediatric and adolescent age groups

Group	Ages < 13 years	13–19 years	Entire Cohort	p value
Patients	n = 48	n = 47	n = 95	
Male	27 (56%)	26 (55%)	53 (55%)	>0.99
Age at diagnosis (years)	9.0 ± 4.7	17.3 ± 3.1	12.9 ± 8.3	
Family history SCD	24 (50%)	19 (40%)	43 (45%)	0.41
Age familiar SCD (years)	34.0 ± 26.7	22.5 ± 20.7	30.0 ± 21.0	0.47
SCD < 20 years old	6 (12%)	5 (11%)	11 (11%)	>0.99
SCD < 12 years old	2 (4%)	1 (2%)	3 (3%)	>0.99
Clinical presentation				
Asymptomatic	33 (69%)	35 (75%)	68 (72%)	0.65
Symptomatic	15 (31%)	12 (25%)	27 (28%)	0.65
SCD	4 (8%)	3 (6%)	7 (7%)	>0.99
Syncope	11 (23%)	9 (19%)	20 (21%)	0.80
Electrical Characteristics				
Spontaneous ECG type I	6 (12%)	5 (10%)	11 (12%)	>0.99
Sinus Node dysfunction	6 (12%)	3 (6%)	9 (9%)	0.48
Maximal PR (ms)	156.7 ± 38.5	169.2 ± 38.2	162.9 ± 38.6	0.13
First degree AV block	7 (15%)	9 (19%)	16 (17%)	0.59
Maximal QRS (ms)	104.6 ± 24.9	107.9 ± 24.2	106.2 ± 24.6	0.53
QRS fragmentation	5 (10%)	2 (4%)	7 (7%)	0.43
R ≥ 3 mV aVR	10 (21%)	6 (5%)	16 (17%)	0.41
QTc DII (ms)	410.1 ± 34.4	398.8 ± 33.5	402.8 ± 30.0	0.12
Atrial arrhythmias	4 (8%)	4 (8%)	8 (8%)	>0.99
Conduction abnormalities	18 (37%)	17 (36%)	35 (36%)	>0.99
EPS n	32 (67%)	40 (85%)	72 (75%)	0.05
EPS_HV	41.3 ± 9.1	44.7 ± 10.4	43.1 ± 9.8	0.20
Induction V arrhythmias	0 (0%)	3 (6%)	3 (3%)	0.11
Genetic test				
Performed	20 (42%)	16 (34%)	36 (38%)	0.52
SCN5A mutation	13 (27%)	11 (23%)	24 (25%)	0.81
ICD implantation	13 (27%)	11 (23%)	24 (25%)	0.81
Events at follow-up	4 (8%)	5 (10%)	9 (9%)	0.74

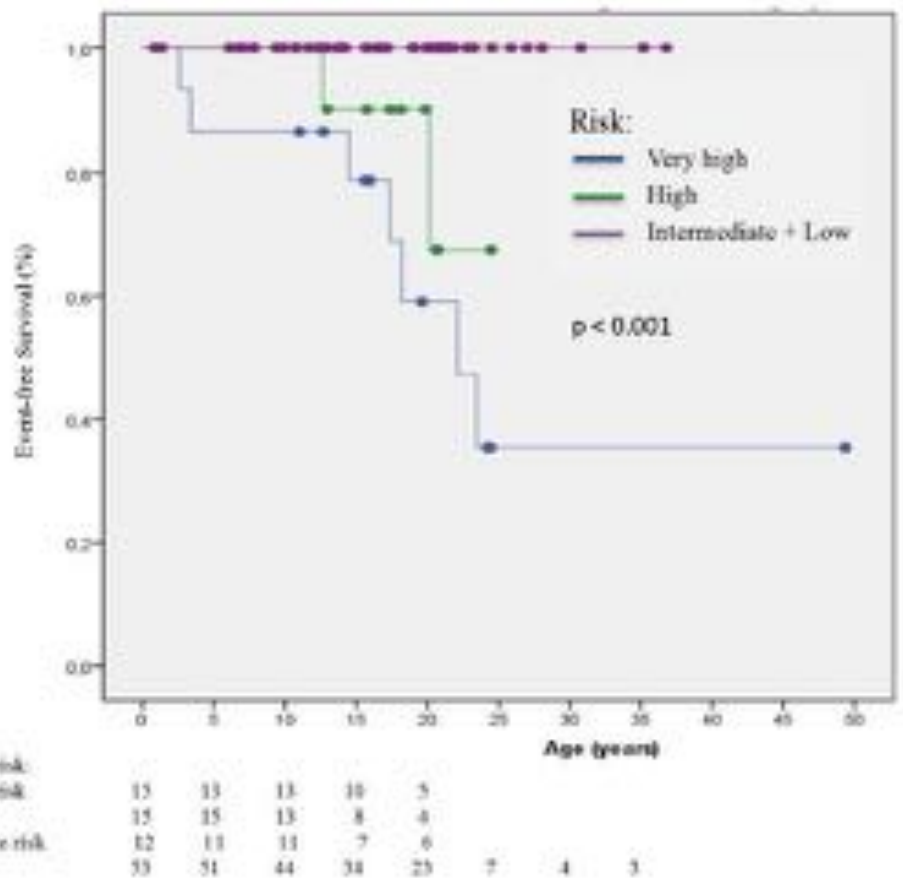
Gonzales, Am J of Cardiol, 2017

Patient characteristics according to risk score

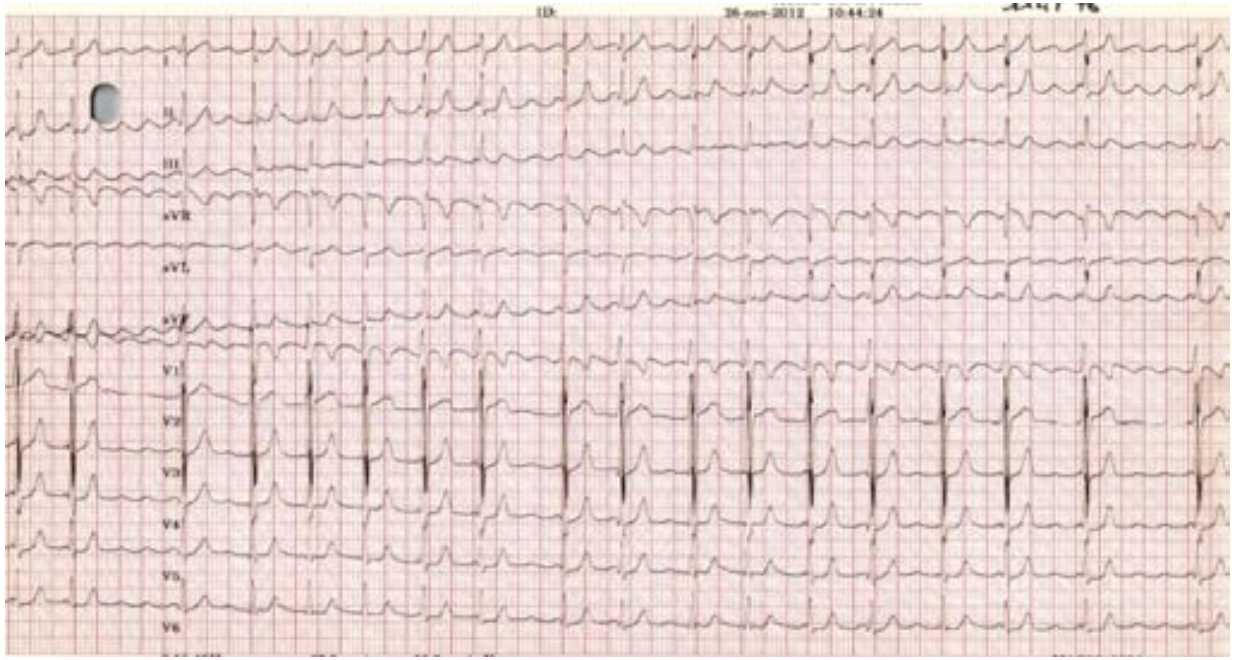
Risk Category	Score	N	Clinical presentation	ICD (%)	Events (%)
Low Risk	0	53	Asymptomatic with no electrical abnormality	0	0
Intermediate Risk	1–3	12	Asymptomatic with electrical abnormality	0	0
High Risk	4–5	15	Syncope with or without single electrical abnormality	11 (73%)	2 (13%)
Very High Risk	≥6	15	aSCD or syncope with multiple electrical abnormalities	14 (93%)	7 (47%)

Score

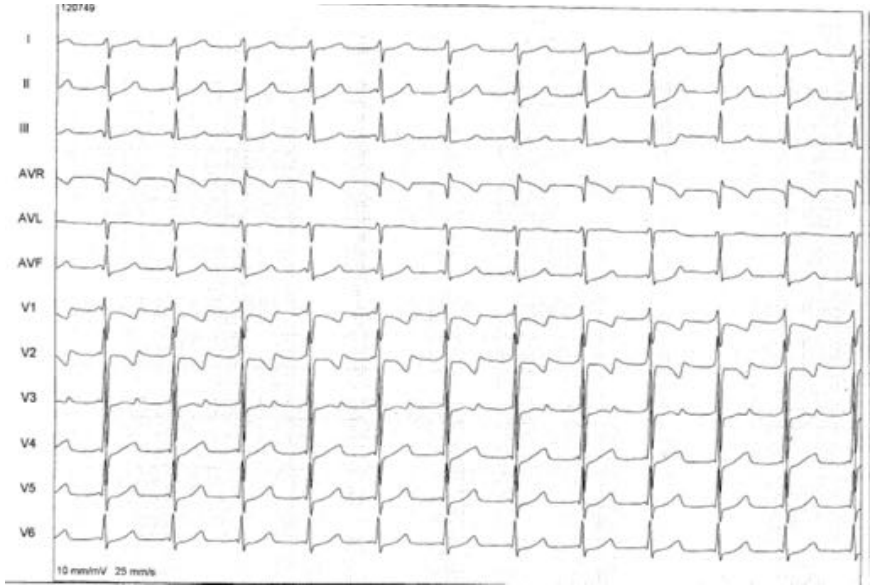
- **CE = 4 pts**
- **sType 1= 3pts**
- **SND ± SVT = 2 pts**
- **Conduction = 1 pt**

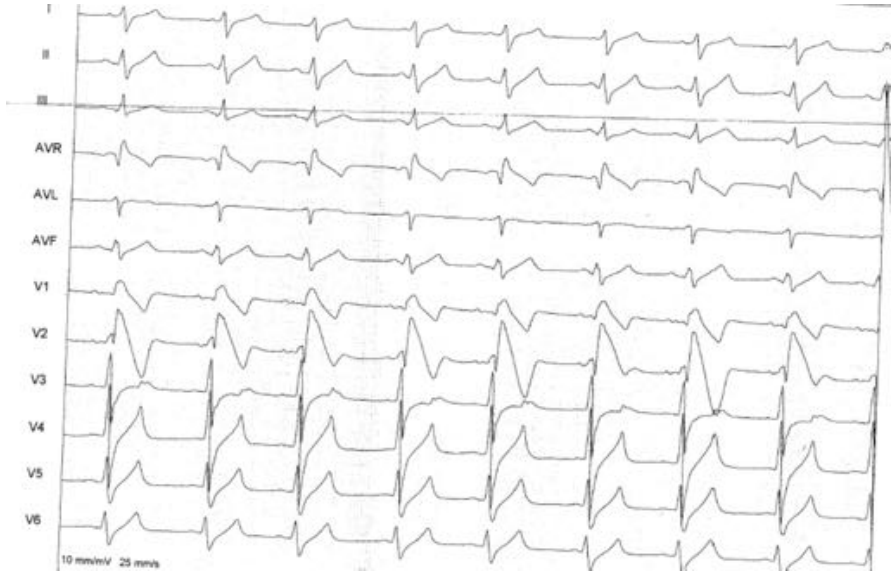


Gonzales, Am J of Cardiol, 2017



2 year old boy
Atrial flutter
Ajmaline +
SCN5A+



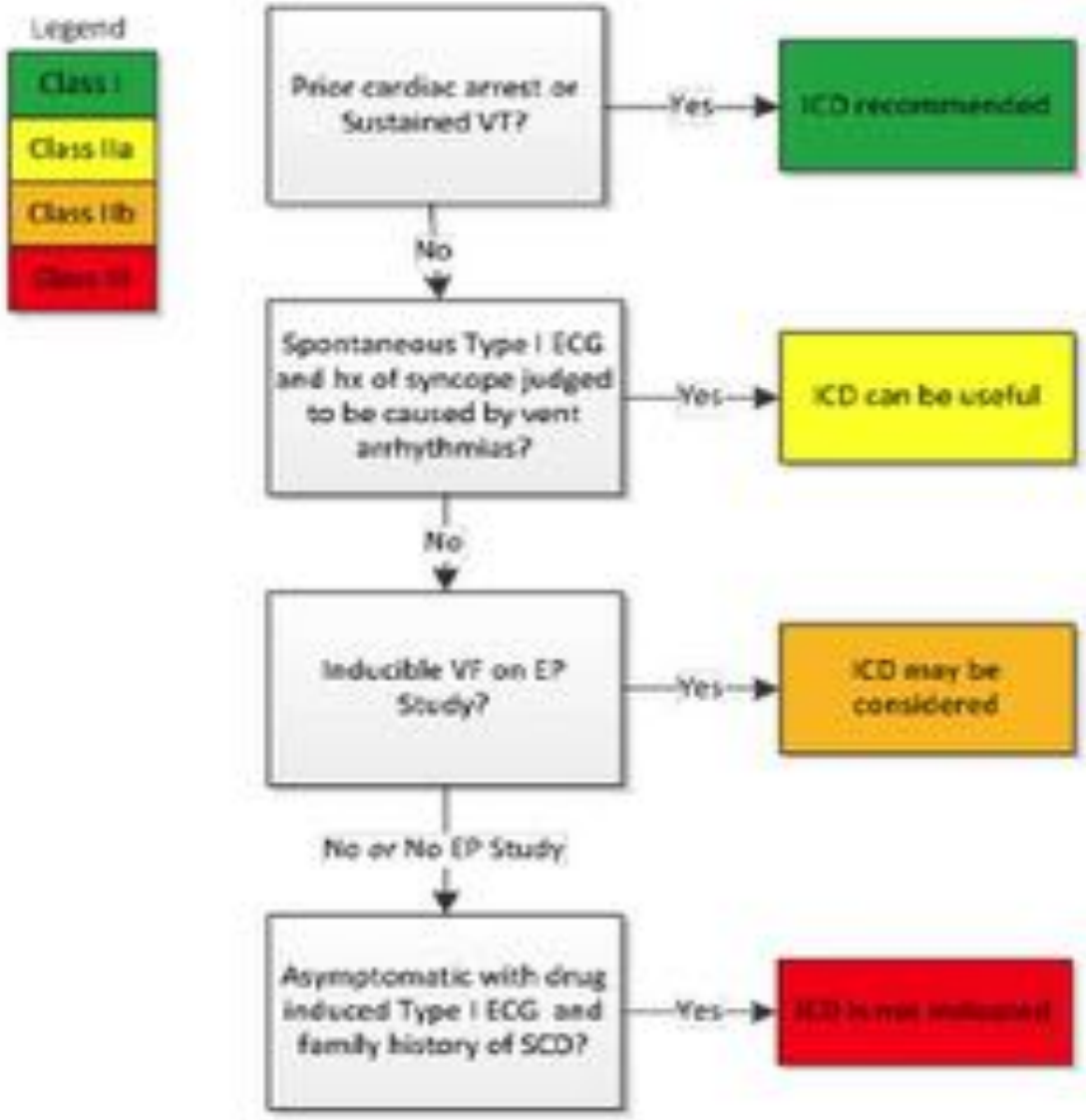


Brugada management : ESC 2015

Recommendations	Class[a]	Level[b]
The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome: (a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org) (b) Avoidance of excessive alcohol intake and large meals (c) Prompt treatment of any fever with antipyretic drugs.	I	C

Expert Consensus Recommendations on Brugada

ICD Recommendations



ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who (a) Are survivors of an aborted cardiac arrest and/or (b) Have documented spontaneous sustained VT.	I	C
ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa	C
ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during PVS with two or three extrastimuli at two sites.	IIb	C

ICD in Brugada children

- N= 35
- Age ICD = 13.9 ±6.2 yrs
- Symptoms at implantation = 92%
  - aSCD = 29%
  - Syncope = 63%
- FU = 88 months
  - Death (electrical storm) = 9 %
  - Appropriate shocks = 26%; ATP = 3%
  - Inappropriate shocks = 20%
  - Device related complications = 14%

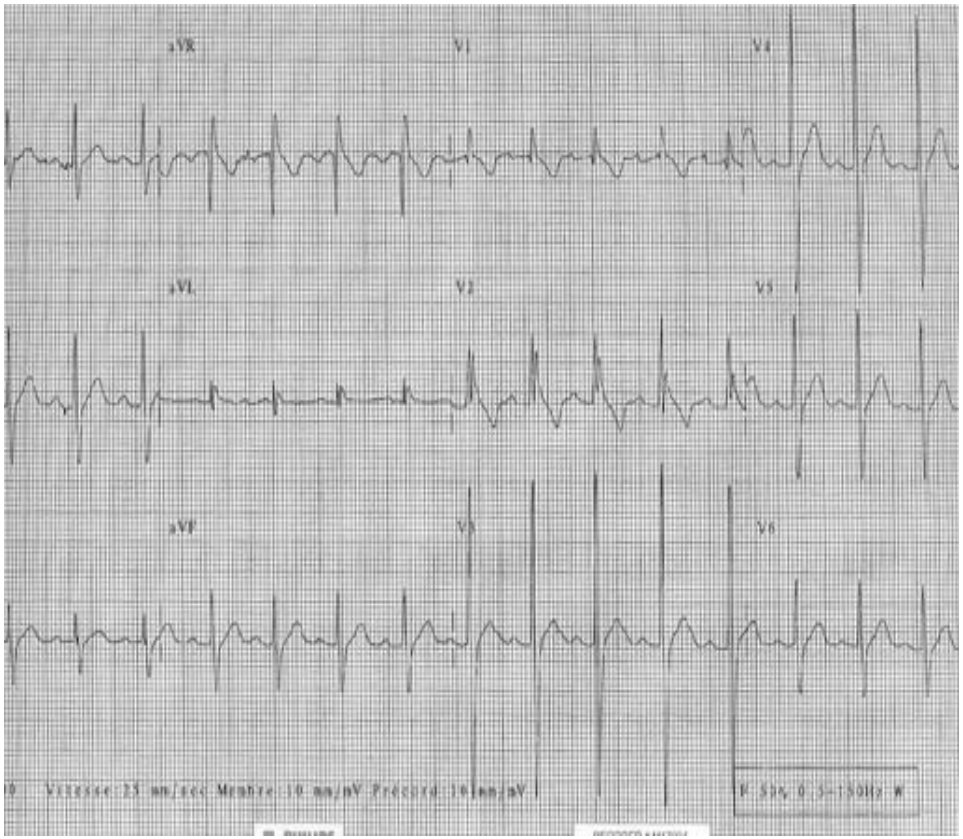
Gonzales Corcia et al, JACC 2018

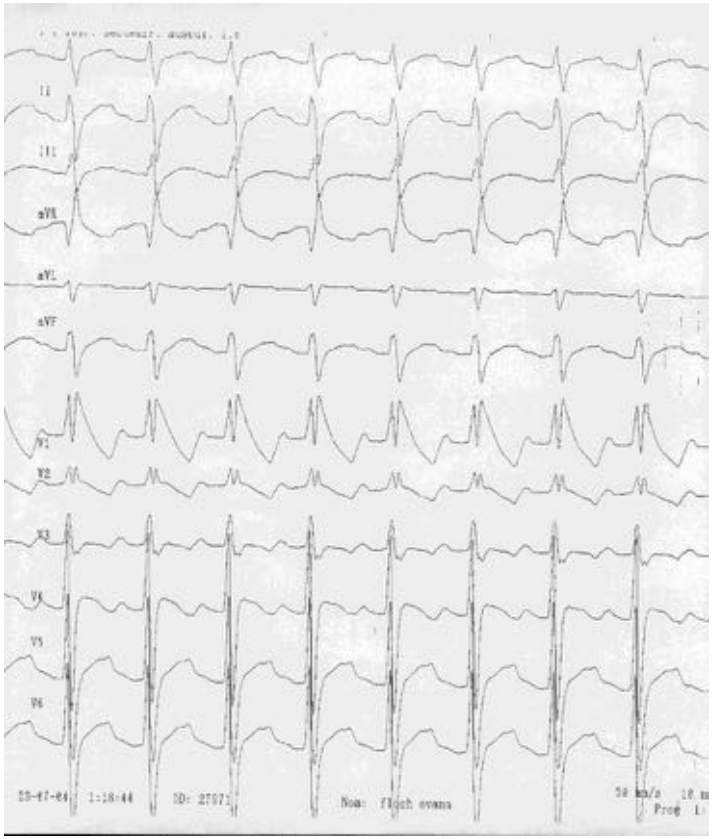
Brugada Syndrome : management

Quinidine or isoproterenol should be considered in patients with Brugada syndrome to treat electrical storms.	IIa	C
Quinidine should be considered in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias.	IIa	C

- Father : Brugada type 1 ECG. Asymptomatic. EPS negative. SCN5A +. No TTT
- 1st son:
  - SD at one month (fever and urinary infection);
  - Negative autopsy; molecular autopsy SCN5A +

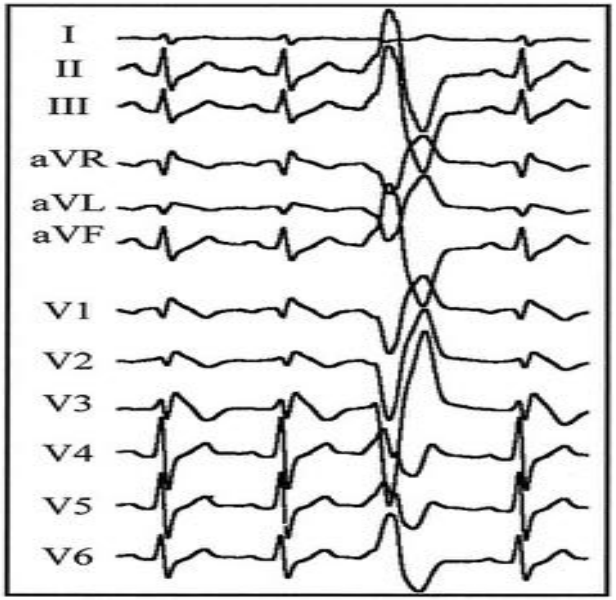
•EF, 1 month. Flecainide +. SCN5A +. HQ. FU : 10 yrs CE = 0

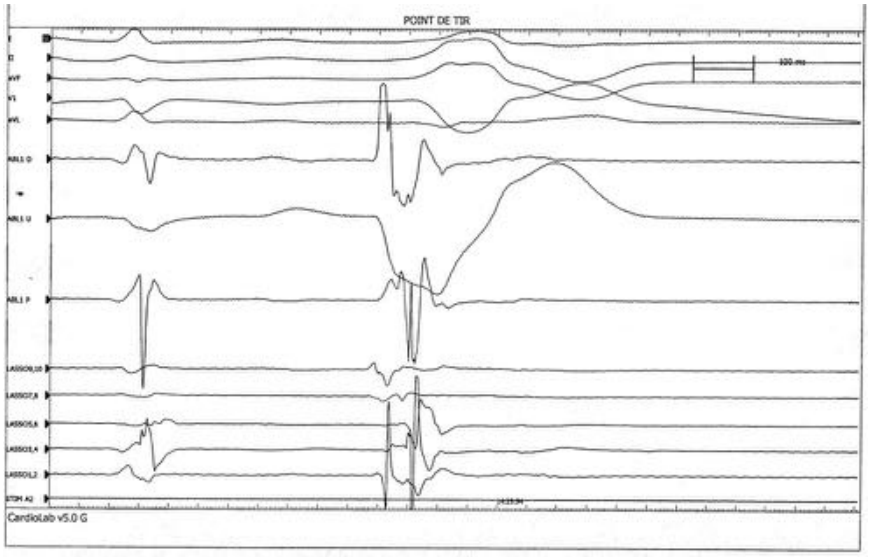




Brugada Syndrome : management

Catheter ablation may be considered in patients with a history of electrical storms or repeated appropriate ICD shocks.	IIb	C





Haissaguerre M et al. Circulation. 2003

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)

Class I (is recommended)

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

Class IIa (can be useful)

Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

Class III (is not indicated/recommended)

Genetic testing **is not indicated** in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

Positif 20%

KEYWORDS Genetics; Cardiomyopathies; Channelopathies (Heart Rhythm 2011; 8:1308–1339)

Particularités pédiatriques

- Syncope/Arrêt Cardiaque/Mort Subite **fébrile**
- **2 périodes à risque : 0-3 ans et > 15 ans**
- FDR : ECG type 1 spontané + PC
- Traitement : Hydroquinidine / DAI
- Liste de médicaments contre indiqués (brugada.org)
- Génétique
- Famille : ECG ; Test Ajamaline ?

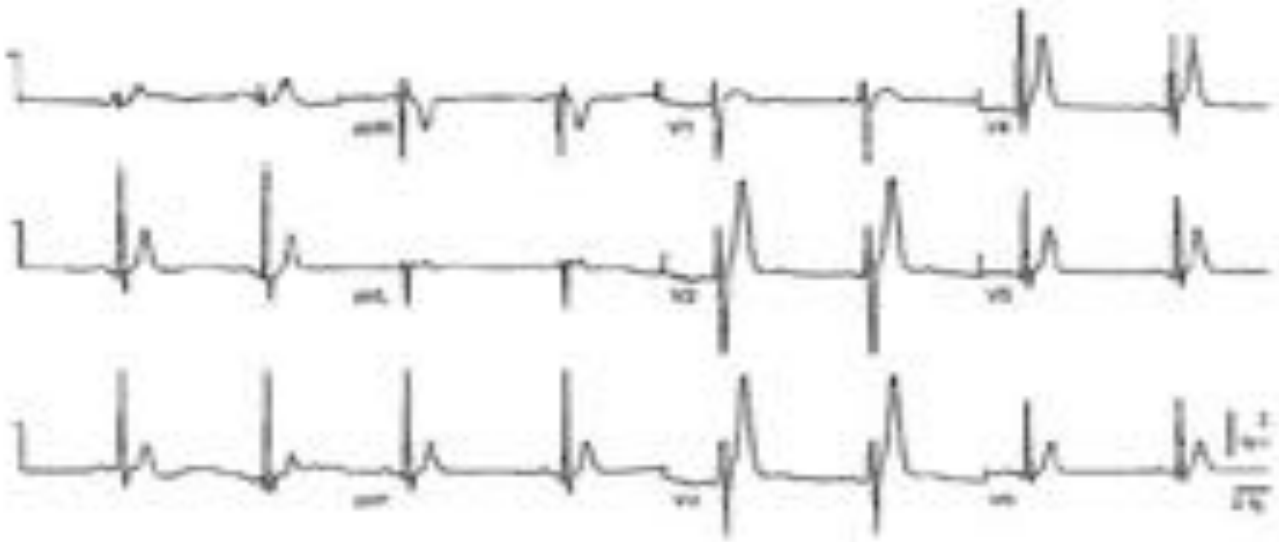
Conclusions

- Syndrome de Brugada chez l'enfant :
  - cause exceptionnelle de PC/AC/MS (fièvre +++)
  - peu d'évènements :
  - Test Ajmaline : à partir de 15 ans ou contexte familial MS enfants
- Test génétique :
  - Oui chez le proband
  - Recherche directe de mutation : > 15 ans

Conclusions

- **Brugada syndrome in children is unfrequent**
- **Spontaneous type 1 ECG pattern and symptoms at diagnosis are predictive of a shorter time to first arrhythmic event. Arrhythmic risk is high in patients with both symptoms and spontaneous type 1 and they need to be considered for ICD**
- **Regular clinical follow-up seems to be sufficient for patients with drug-induced type 1 without any symptom.**
- **Consider hydroquinidine in other situations (asymptomatic type 1) ?**
- **Conduction ± SND ± SVT frequent specially in the very young (atrial ablation + βb)**
- **High prevalence of SCN5A mutations in index patients (47%)**
- **Fever remains the most important trigger and needs to be taken care of.**

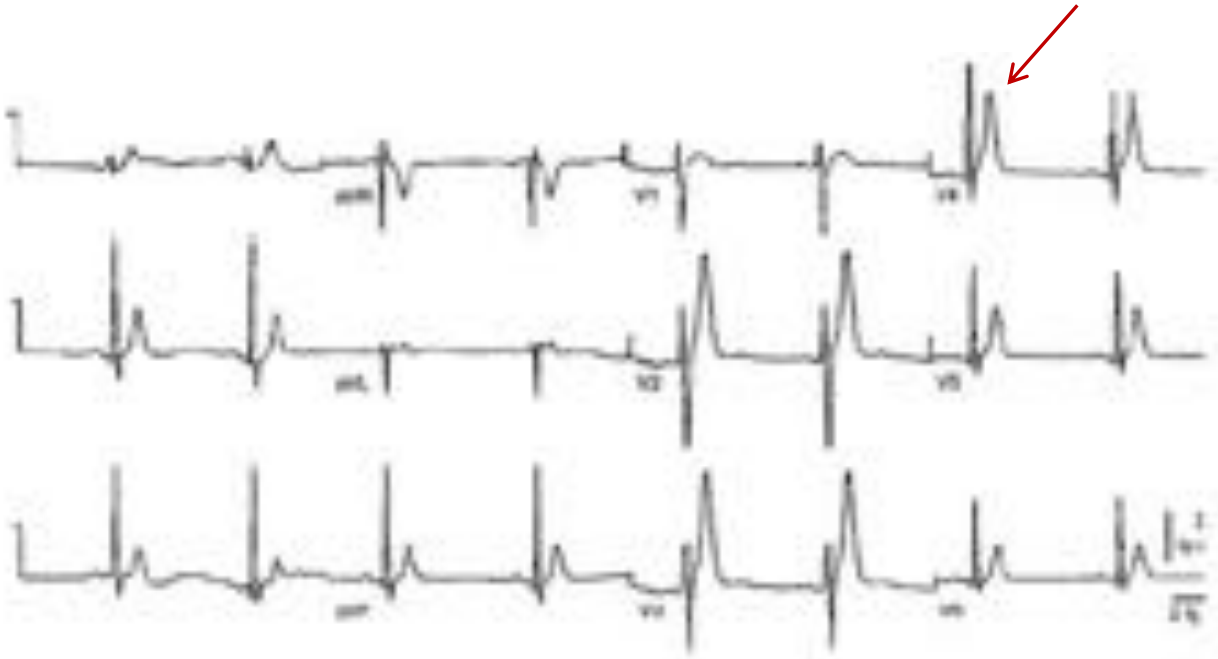
Syndrome du QT court



FAMILY 30-339: PATIENT II:2
QTc 293 msec

QTc < 330ms sur tous les ECG
Fibrillation Auriculaire Paroxystique
Fibrillation Ventriculaire (inductible)
Gènes : HERG, KCNQ1,KCNJ2

Syndrome du QT court



FAMILY 30-339: PATIENT II:2
QTc 293 msec

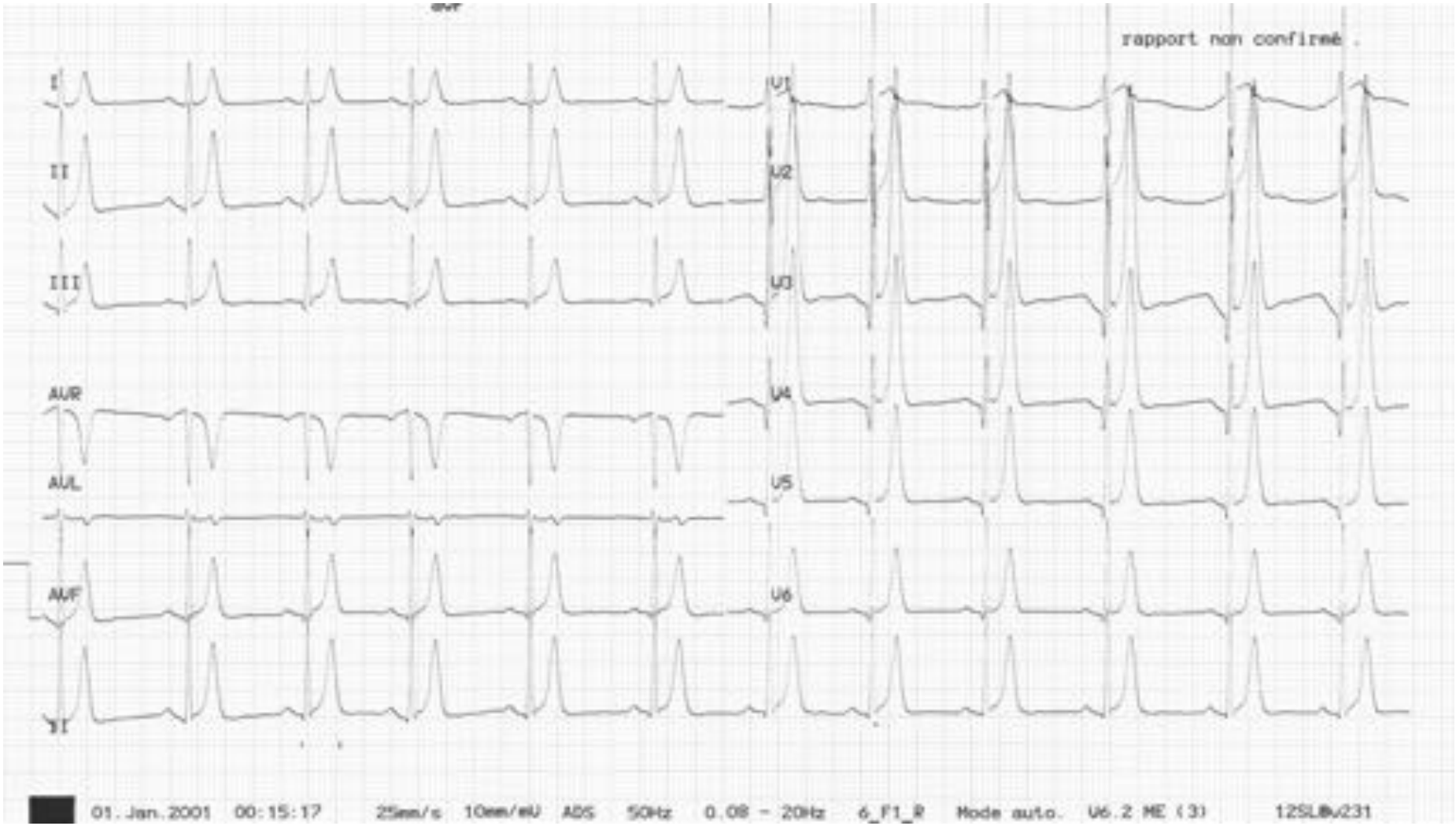
FA Paroxystique
VF inductible

Gènes :

-HERG
-KCNQ1
-KCNJ2
-CACNA1C
-CACNB2

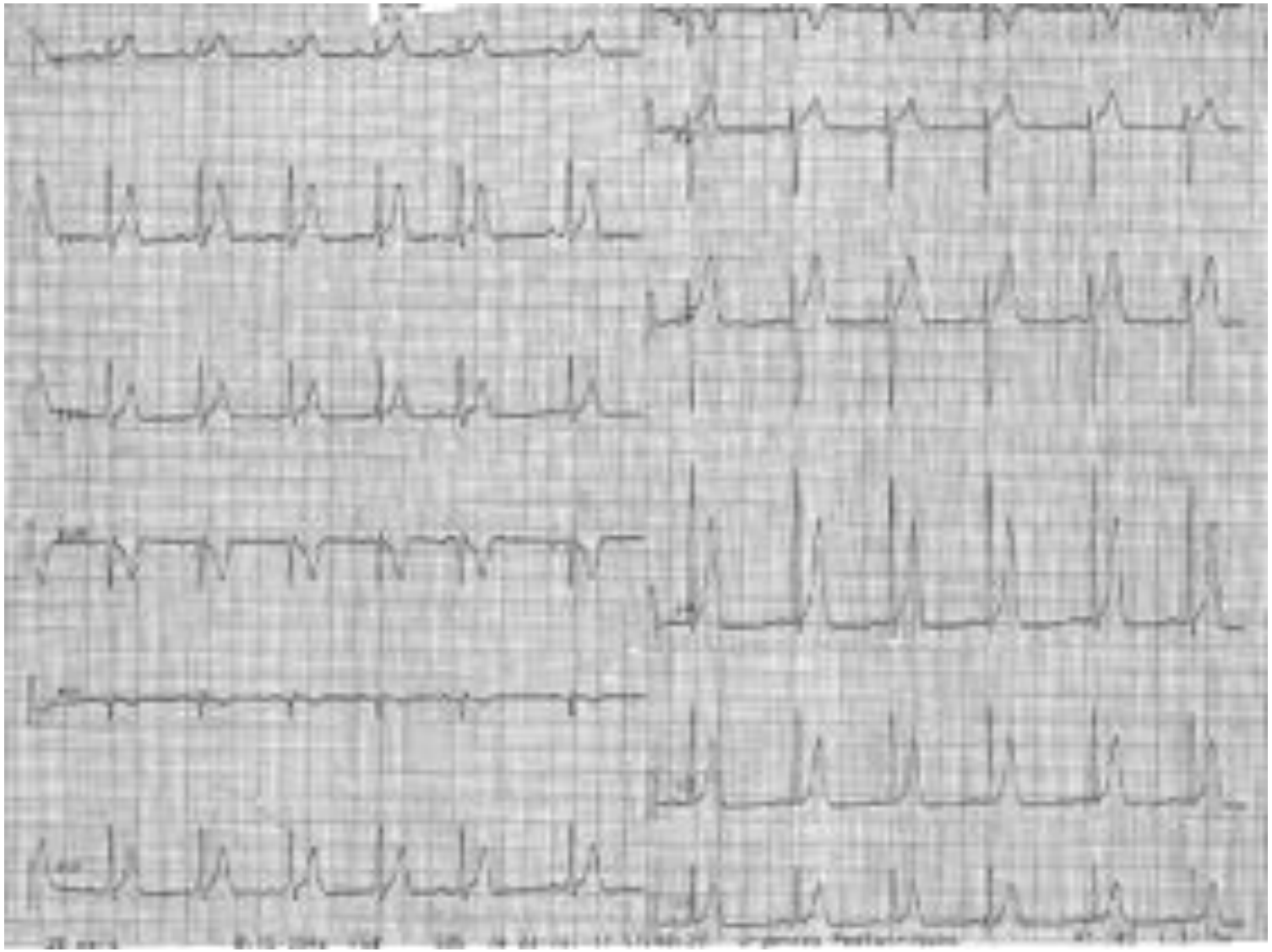
QTc court dans toutes les dérivations

Fille de 4 ans, ECG pour bradycardie



QTc = 320 ms; morphologie anormale T

Fille de 10 ans, ECG pour le sport



QTc = 330 ms

Causes de QT court

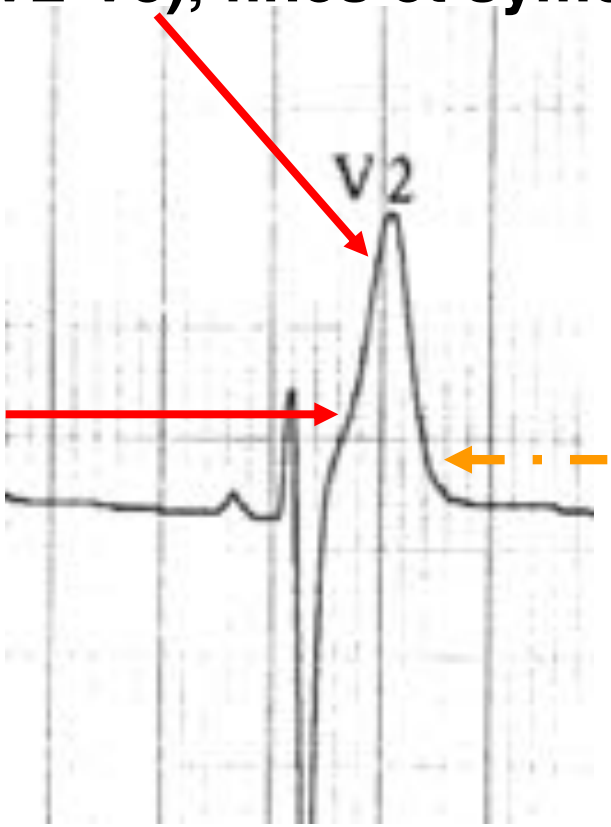
- **l'hypercalcémie, l'hyperkaliémie**
- **la tachycardie, l' acidose**
- **les catécholamines**
- **l'acétylcholine**

- **le syndrome du QT court**

Éliminer causes secondaires : acidose, hyper K, hyper Ca, fièvre, tachycardie, dysautonomie, catécholamines, acétylcholine, imprégnation ou surtout surdosage en digitaliques

Mesure QT court

ondes T amples (V2-V5), fines et symétriques



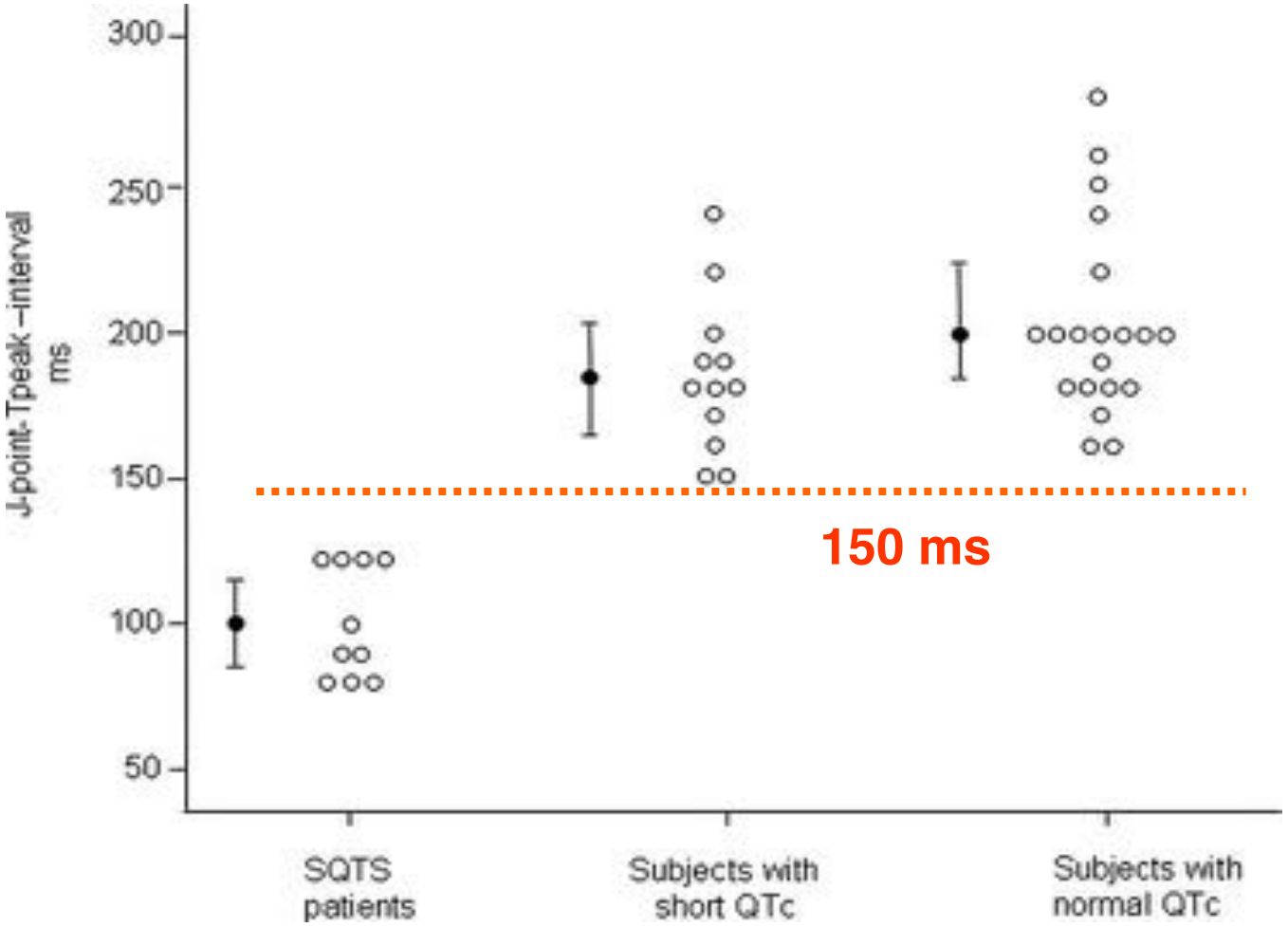
segment ST absent

segment T-P long

Durée et morphologie

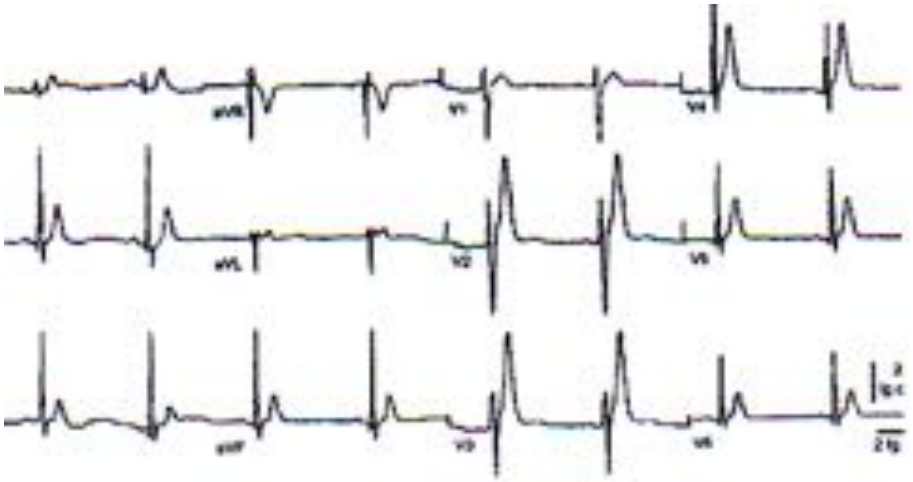
	10 SQT avec MS	12 QT<320 ms asymptomatiques suivis 30 ans		20 témoins
QTc	317 ± 27ms	314 ± 14ms (biais?)	NS	405 ± 28 ms
T amplitude	1.2 ± 0.5 mV	1.1 ± 0,5 mV	NS	0.6 ± 0,3 mV
T peak-T end/QT	0.30 ± 0.04	0.24 ± 0.05	p=0,001	0.24 ± 0.04
		ns		
J-T peak	101 ± 18ms	184 ± 27ms	p< 0,001	203 ± 33ms
		ns		

Anttonen O et al., Heart Rhythm 2009;6:267-271

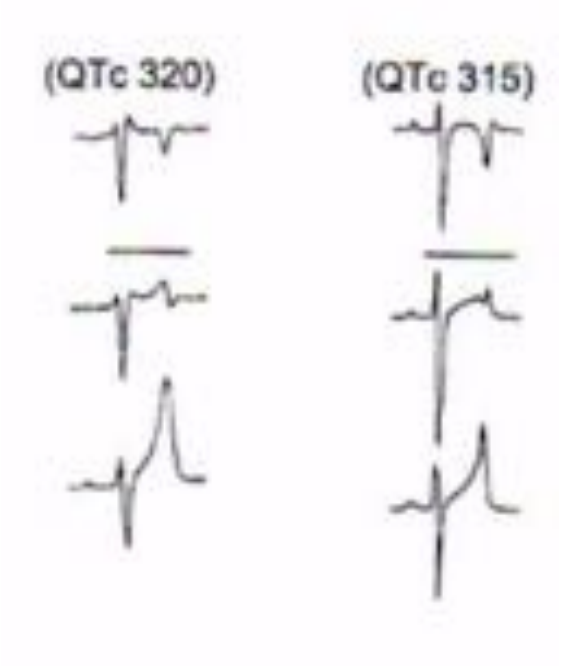


pas d'overlap

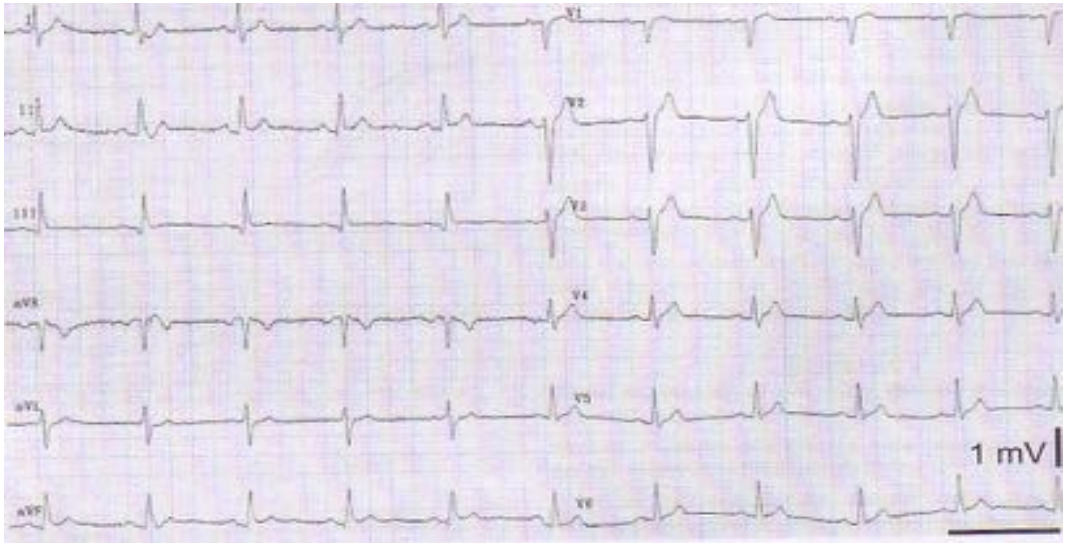
Anomalies morphologiques onde T



SQTS 1



SQTS 3



SQTS 2

Table 1 SQTS Diagnostic Criteria: Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: ≤2 points. Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history events must occur in the absence of an identifiable cause, including structural heart disease. Points can be received only for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history points can only be received once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

QTc = corrected QT interval for heart rate using the Bazett formula; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2 SQTS Diagnostic Criteria: Modified Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T-wave. Family history points can be received only once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points.

SQTS is associated with aborted sudden cardiac death among the pediatric population. Asymptomatic patients with a Gollob score of <5 remained event free, except for an isolated episode of supraventricular tachycardia, over an average 6-year follow-up. A higher modified Gollob score of 5 or more was associated with the likelihood of clinical events. Young SQTS patients have a high rate of inappropriate ICD shocks. (J Am Coll Cardiol 2013;61:1183–91)

Syndrome du QT court

Recommendations	Class[a]	Level[b]	Ref.[c]
SQTS is diagnosed in the presence of a QTc ≤340 ms.	I	C	This panel of experts
SQTS should be considered in the presence of a QTc ≤360 ms and one or more of the following: (a) A confirmed pathogenic mutation (b) A family history of SQTS (c) A family history of sudden death at age <40 years (d) Survival from a VT/VF episode in the absence of heart disease.	IIa	C	This panel of experts

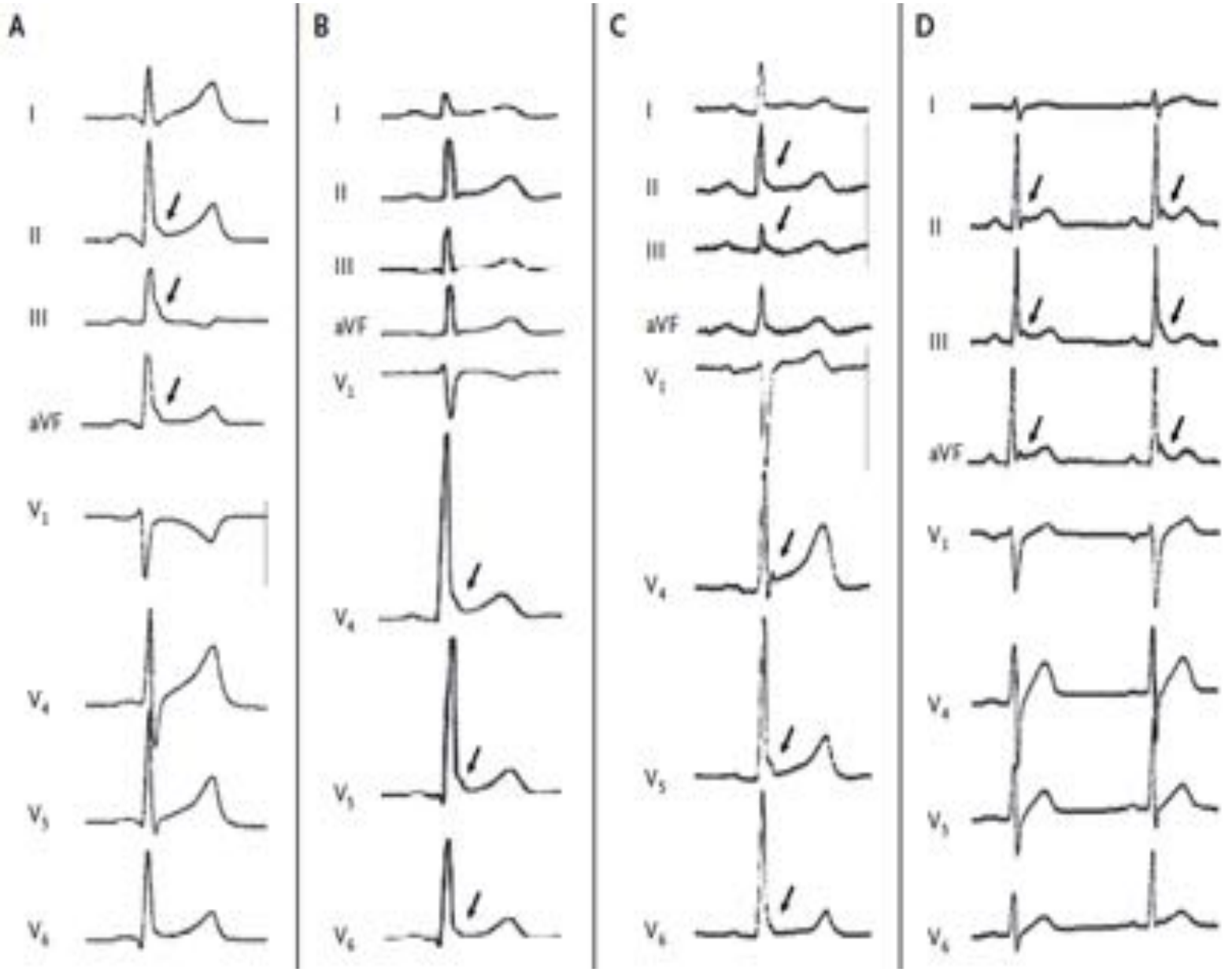
ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

Syndrome du QT court

Short QT Syndrome			
Recommendations	**Class[a]**	**Level[b]**	**Ref.[c]**
ICD implantation is recommended in patients with a diagnosis of SQTS who (a) Are survivors of an aborted cardiac arrest, and/or (b) Have documented spontaneous sustained VT.	I	C	119, 447
Quinidine or sotalol may be considered in patients with a diagnosis of SQTS who qualify for an ICD but present a contra-indication to the ICD or refuse it.	IIb	C	118, 448
Quinidine or sotalol may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.	IIb	C	118, 448
Invasive EPS with PVS is not recommended for SCD risk stratification.	III	C	118, 119

ESC Guidelines 2015 for the management of patients with ventricular arrhythmias and the prevention of sudden death. Eur Heart Journal 2015

Syndrome de repolarisation précoce



M Haïssaguerre et al. N Engl J Med 2008;358:2016-23

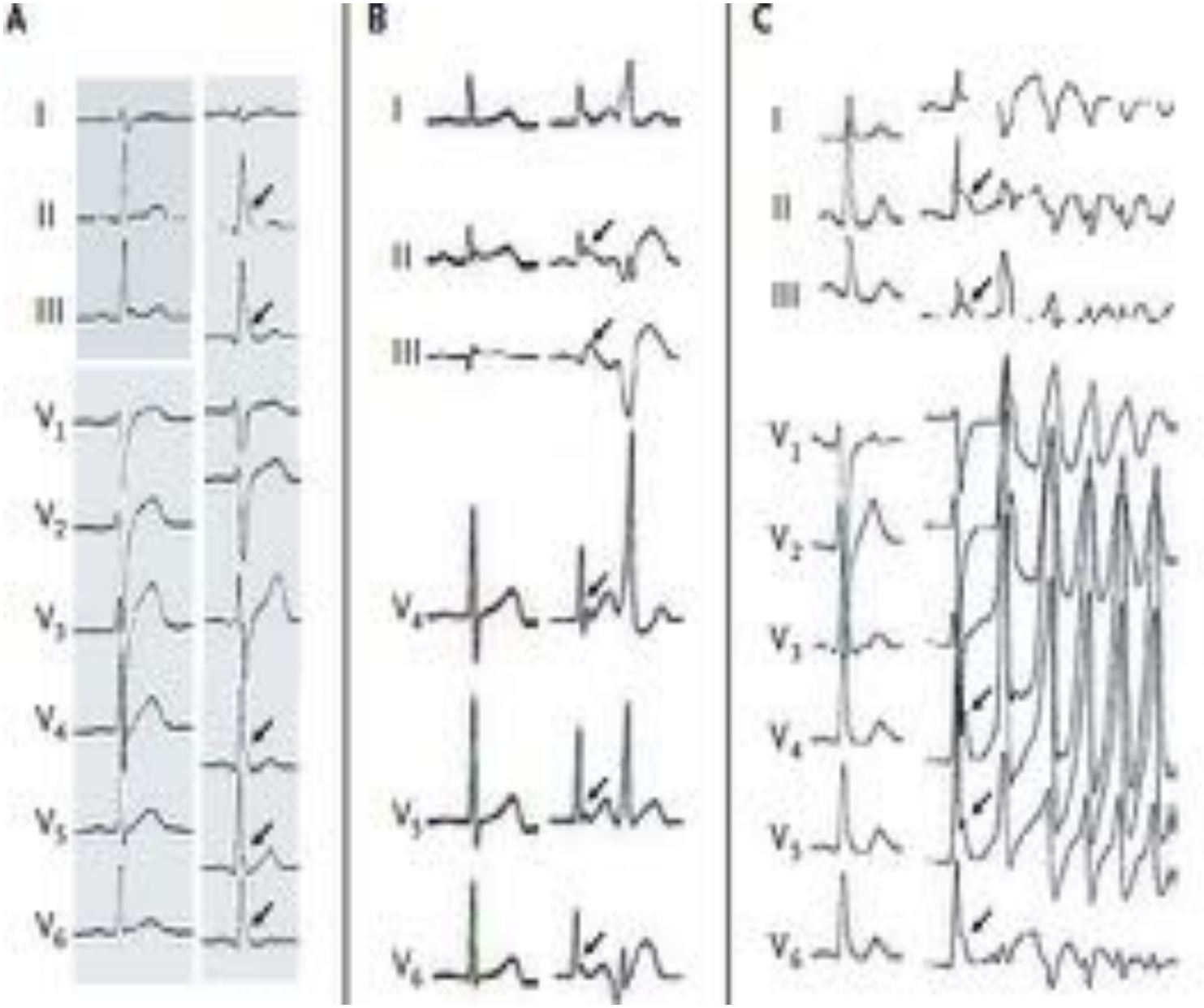
Repolarisation précoce : diagnostic

Expert Consensus Recommendations on Early Repolarization Diagnosis

1. ER ***syndrome is diagnosed*** in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/ Polymorphic VT
2. ER syndrome ***can be diagnosed*** in a SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG 3. ER pattern ***can be diagnosed*** in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes 2013

Syndrome de repolarisation précoce



M Haïssaguerre et al. N Engl J Med 2008;358:2016-23.

ST : ascendant/descendant

ST ascendant

→ **bon pronostic**

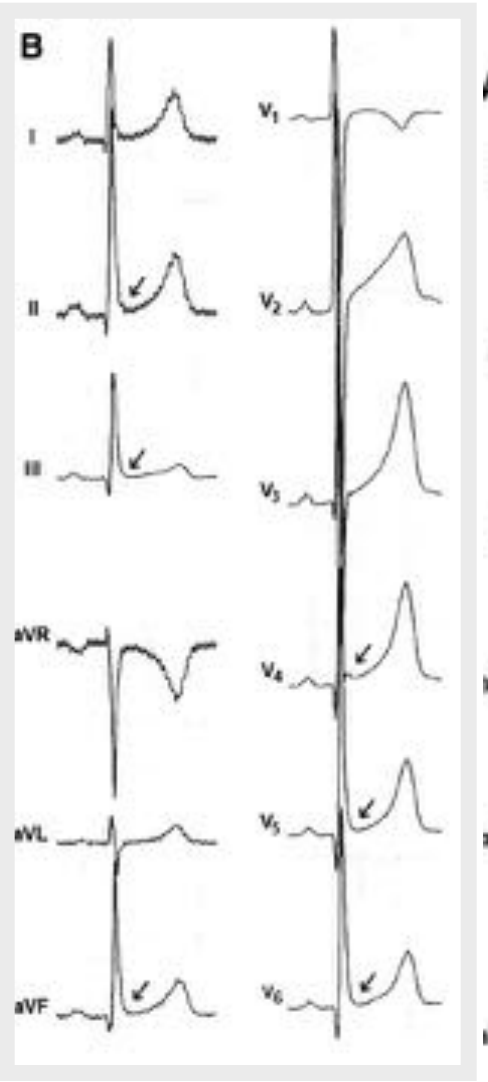
ST descendant

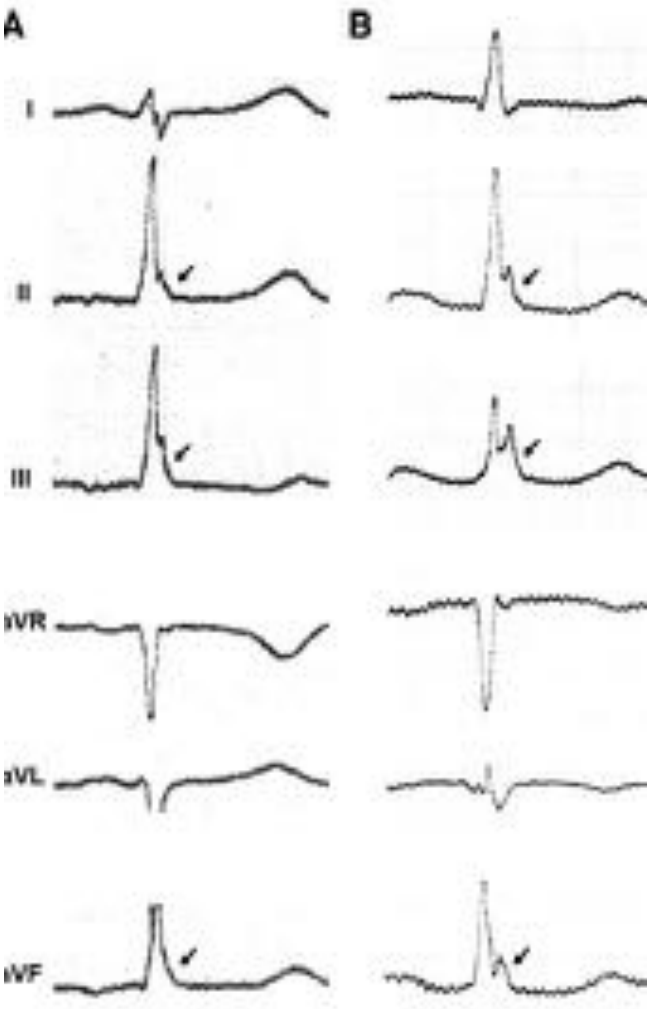
→ **mauvais pronostic**

Mortalité CV :

HR: 8.75 (CI 3.48-22.0, p<0.0001)

Tikkanen J et al. Circulation 2011





Rosso R,Glikson E, Belhassen B,Katz A Halkin A, Steinvil A Viskin S Heart Rhythm 2011

Effets des tests pharmacologiques

- Aucun: ajmaline, flecainide, cibenzoline, verapamil , epinephrine, ATP, Ca
- Légère accentuation : bradycardie, bétabloquants, Valsalva
- Diminution : effort/isoproterenol et quinidine (prévention orage rythmique ++).

Repolarisation précoce

Expert Consensus Recommendations on ***Early Repolarization Therapeutic Interventions***

Class I	1. ICD implantation ***is recommended*** in patients with a diagnosis of ER syndrome who have survived a cardiac arrest
Class IIa	2. Isoproterenol infusion ***can be useful*** in suppressing electrical storms in patients with a diagnosis of ER syndrome 3. Quinidine in addition to an ICD ***can be useful*** for secondary prevention of VF in patients with a diagnosis of ER syndrome
Class IIb	4. ICD implantation ***may be considered*** in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST segment elevation >1mm in 2 or more inferior or lateral leads 5. ICD implantation ***may be considered*** in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/ descending ST-segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation
Class III	6. ICD implantation ***is not recommended*** asymptomatic patients with an isolated ER ECG pattern

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes 2013

Enquête familiale

Décrets, arrêtés, circulaires

TEXTES GÉNÉRAUX

MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ

Arrêté du 20 juin 2013 fixant le modèle de lettre adressée par le médecin aux membres de la famille potentiellement concernés en application de l'article R. 1131-20-2 du code de la santé publique

NOR : *AFSP1311883A*

La ministre des affaires sociales et de la santé,

Vu le code de la santé publique, notamment ses articles L. 1131-1-2 et R. 1131-20-2,

Arrête :

Art. 1er. – Le modèle de lettre mentionné à l'article R. 1131-20-2 du code de la santé publique est annexé au présent arrêté.

Art. 2. – Le directeur général de la santé est chargé de l'exécution du présent arrêté, qui sera publié au *Journal officiel* de la République française.

Fait le 20 juin 2013.

Marisol Touraine

ANNEXE

MODÈLE DE LETTRE

Coordonnées du médecin.
Référence du courrier.

Madame, Monsieur,

En ma qualité de médecin, j'ai été amené(e) à prendre en charge un membre de votre famille.

Les examens effectués sur cette personne ont mis en évidence une anomalie génétique d'origine familiale qui peut faire l'objet de mesures de prévention ou de soins. Appartenant à la même famille, il est possible que vous soyez également concerné(e) par cette anomalie de façon directe ou indirecte. Cela ne signifie, ni que vous êtes vous-même porteur de cette anomalie et, si tel était le cas, que vous êtes ou serez atteint d'une maladie.

Tenu au respect de la loi, je ne peux vous révéler ni l'identité de cette personne ni l'anomalie génétique concernée.

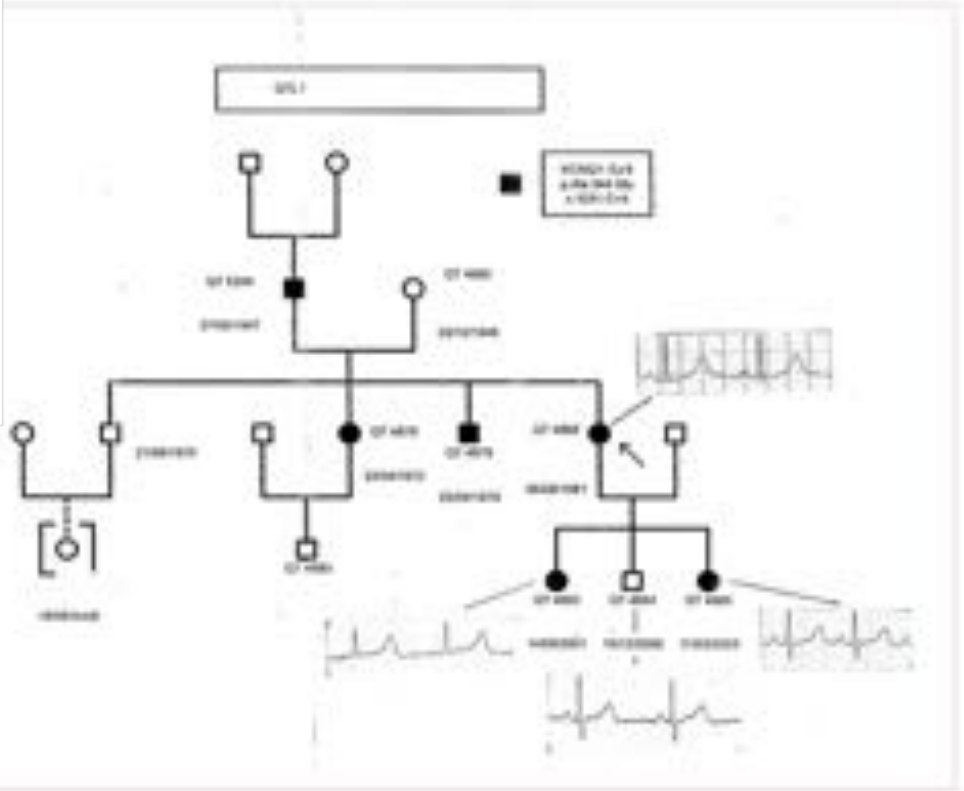
En revanche, il est de mon devoir de vous inviter à consulter un médecin généticien qui sera à même de vous donner plus de précisions et de vous proposer les examens qu'il jugera utiles. Ce médecin pourra prendre contact avec moi pour obtenir plus d'informations (1). A titre indicatif, je vous transmets les coordonnées des consultations de génétique les plus proches de votre domicile. Vous pouvez également consulter un autre médecin de votre choix.

Je comprends que ce courrier puisse vous surprendre. D'autres membres de votre famille ont probablement reçu le même courrier. Certains en parleront et d'autres préféreront se taire. Il est souhaitable de respecter les choix de chacun. Vous pouvez évoquer également ces aspects avec le médecin généticien que vous consulterez.

Bien entendu, vous restez totalement libre de donner suite ou non à ce courrier.

Je vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

(1) En me contactant, ce médecin devra mentionner la référence figurant en en-tête de la présente lettre.



Bilan familial de canalopathies chez les apparentés 1er degré : parents, fratrie, enfants

Examens	QTL	TVC	Brugada
Quand ?	Naissance	> 2 ans	> 15 ans
ECG	QTc ↑ , morpho, debout	QTc normal	Type 1 (< 3 ans)
Holter	QTc ↑, morpho, pente	ESV poly, salves	12 d, charge type1
E Effort	QTc ↑ 4mn	ESV, salves	Type 1↓
Test Pharmaco	Adrénaline	Adrénaline	Ajmaline
SVP	Non	Non	Non ?
Génétique	Oui +++	Oui +++	Recherche directe

Procédure du diagnostic pré-symptomatique

Consultation individuelle

⇓

Etape 1 : Information (trio: cardiologue, généticien, psychologue)

Etape 2: Prélèvement sanguin et biologie moléculaire

⇓

Etape 3 : Annonce du résultat par le clinicien

Etape 4 : Suivi régulier (évaluation de l ’impact psychologique)

et traitement + bilan cardiologique régulier si test positif

Test génétique et conseil génétique

- Identifications des « porteurs sains » chez les apparentés
  - **Test présymptomatique : QTL,TVC**
- Evaluation du risque de transmission
  - **Test prénatal : NON QTL, TVC ? JLN**
- Intérêt diagnostique
  - **Test diagnostique : QTL, TVC**
- Stratification du pronostic chez les patients
  - **Test pronostique :QTL**

Description de la filière nationale de santé CARDIOGEN
Maladies cardiaques héréditaires

cardiogen
filière nationale de santé
maladies cardiaques héréditaires

Les canalopathies

- Syndromes familiaux avec risque de mort subite
- Consultation spécialisée multidisciplinaire (centre de référence/compétence) www.cardiogen.aphp.fr
  - Test génétique
  - Bilan cardiologique spécifique : ECG et Holter, Epreuve d'effort, tests pharmocologiques
- QTL : BB-; sports adaptés; éducation « médicale » ++
- TVC : place de la Σectomie ?
- Brugada : HQ ?