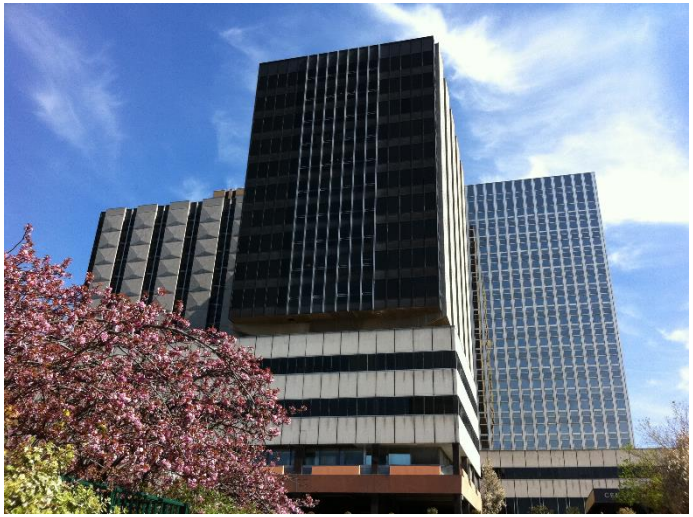
Tachycardie ventriculaire catécholergique

Centre de Référence des Maladies Cardiaques Héréditaires

39e séminaire de cardiologie congénitale et pédiatrique. 23 mars 2018. Necker Paris



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Service de Cardiologie

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Tachycardies ventriculaires catécholergiques

- CPVT is a rare (1:10,000) and one of the most malignant inherited arrhythmogenic disorders
- It is characterized by adrenergic-induced premature ventricular complexes (PVCs), polymorphic or bidirectional VT or sudden death, usually associated with vigorous physical exercise or mental stress.
- Beta-blockers are the standard therapy in CPVT, although evidence of treatment failure has grown recently.

Leenhardt A et al. Catecholaminergic Polymorphic Ventricular Tachycardia in Children Circulation. 1995;91:1512-19.

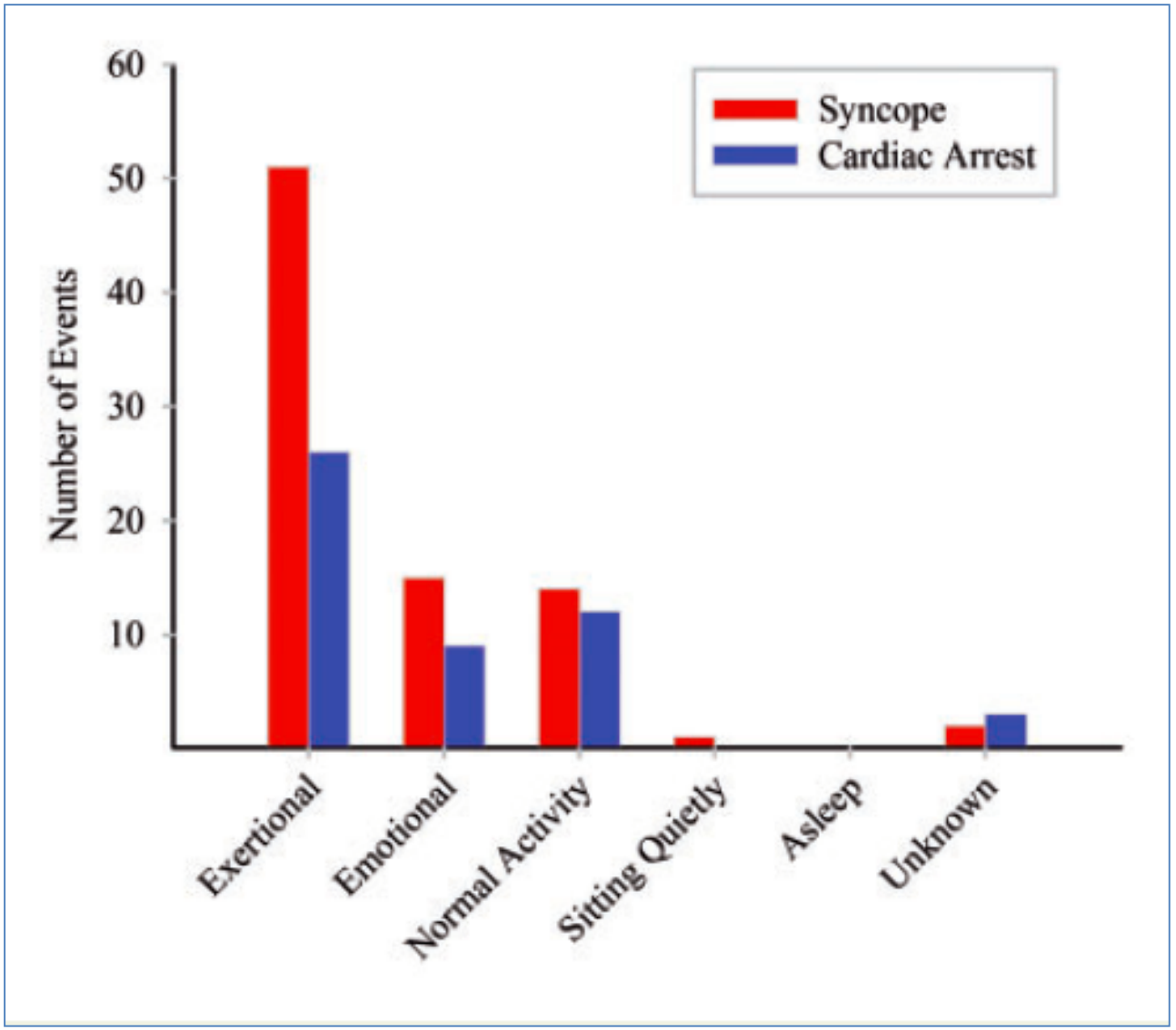
Coumel P et al. Catecholamine-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. Br Heart J. 1978;40:28-37.

Tachycardies ventriculaires catécholergiques

- Children : 2 y. < age < 15 y., experiencing syncope during typical circumstances : emotion, stress, exercice, noyade (1)
- Neurologic symptoms: seizures
- History of familial sudden cardiac death/syncope, same circumstances
- **Normal basal EKG** (QTc), bradycardia
- No morphologic cardiac abnormality

(1) Leenhardt A et al. Circulation.1995;91:1512-9.

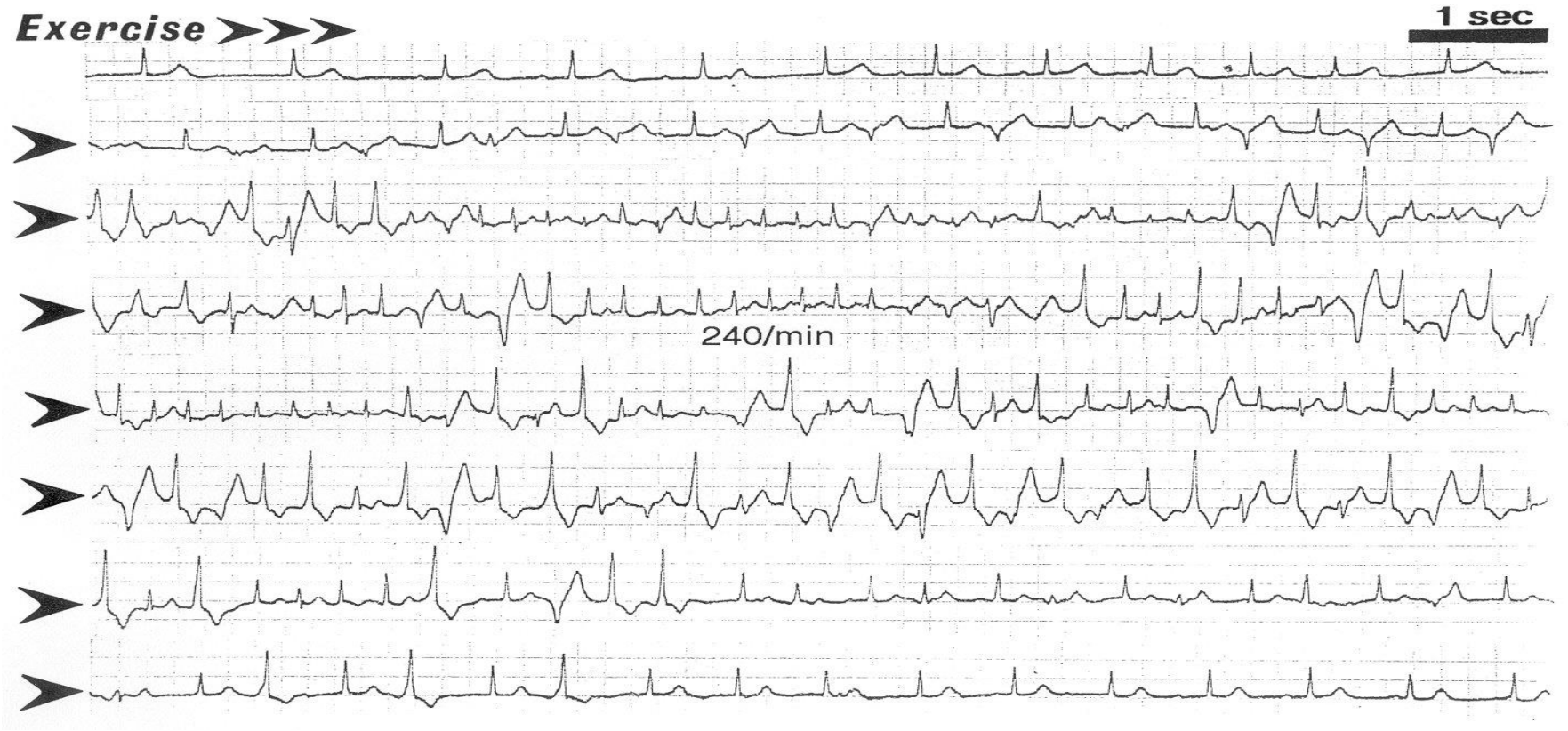
Circumstances immediately preceding syncope or cardiac arrest



From 236 patients, 25% had atypical triggers

Roston T.M. et al. Europace 2018; 20: 541-7.

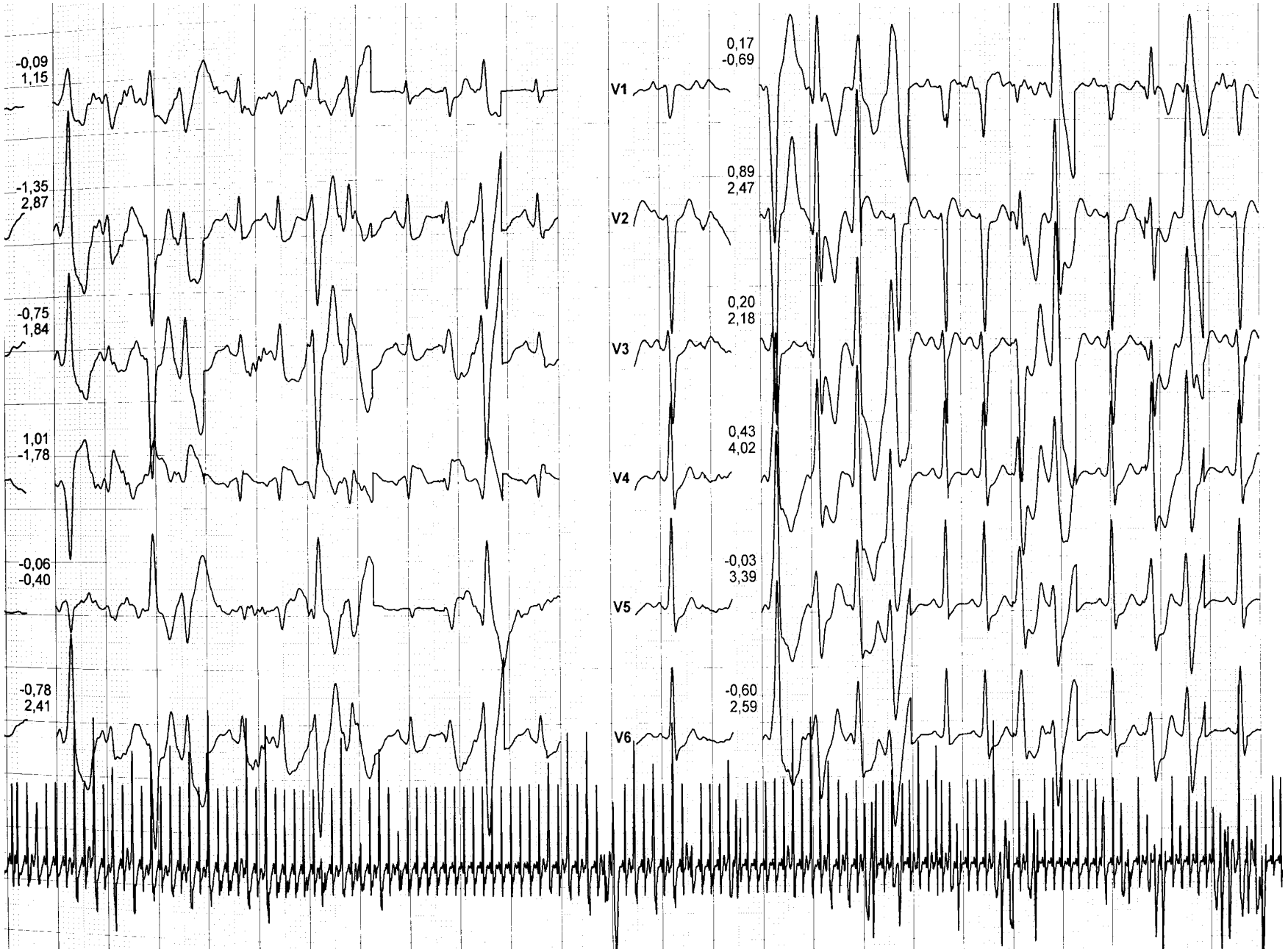
Tachycardies ventriculaires catécholergiques



- **ESV polymorphes à l'effort** :
  - ESV isolées,
  - Bigéminisme
  - Salves polymorphes
  - TV bidirectionnelles et TV polymorphes

- **Reproductibilité :**
  - Effort (Holter/ ECGE) si FC > 110 bpm
  - Sous isoprotérénol
  - Non inductibilité EEP

Leenhardt A et al. Circulation.1995;91:1512-9.


-0,09
1,15
-1,35
2,87
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-1,78
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V1
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V3
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V5
V6
0,17
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2,47
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-0,03
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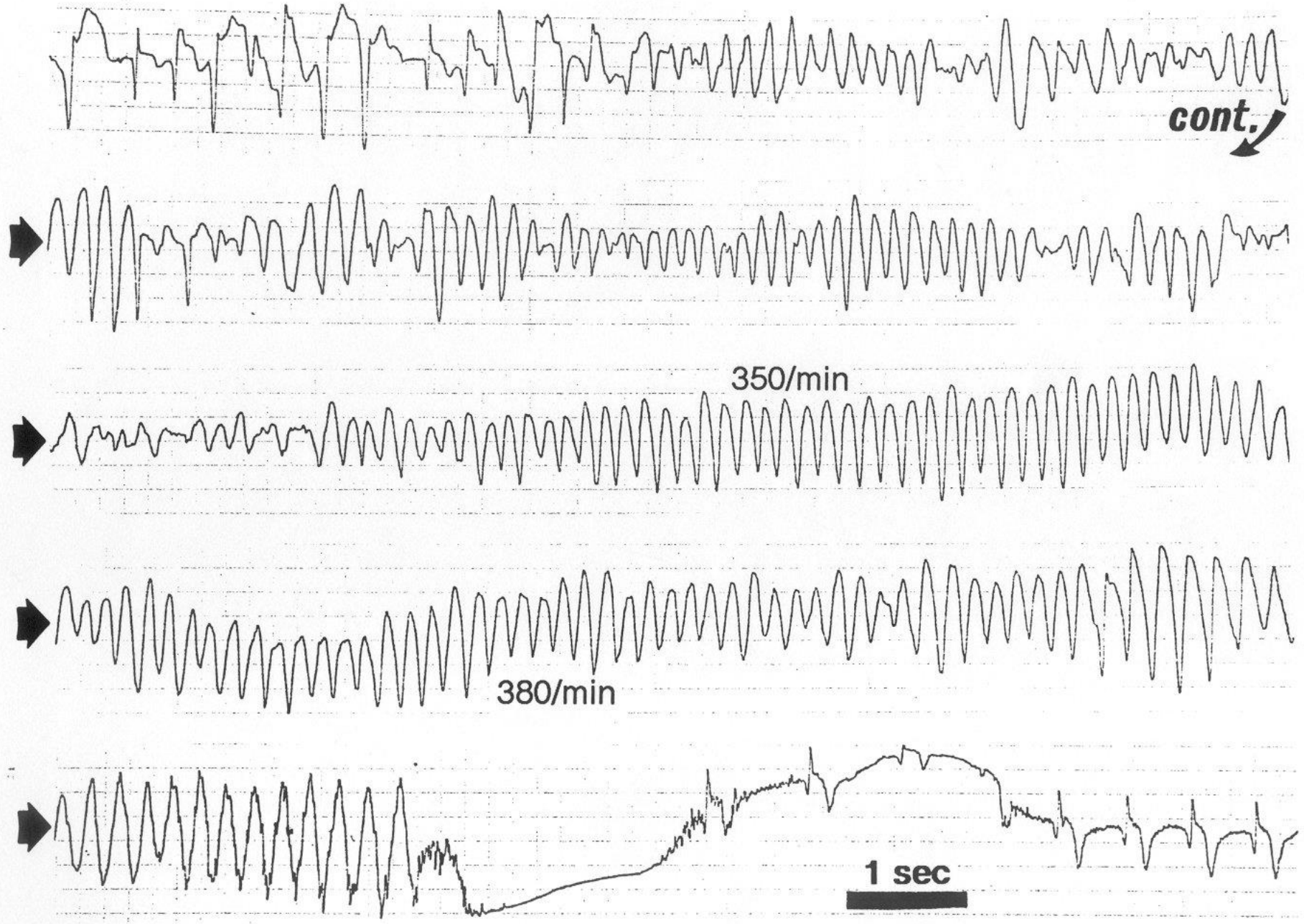
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Tachycardies Ventriculaires Catécholergiques
Diagnostic

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;13:1389-406.

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;17:1601-87.

STATE-OF-THE-ART PAPER

Impact of Genetics on the Clinical Management of Channelopathies

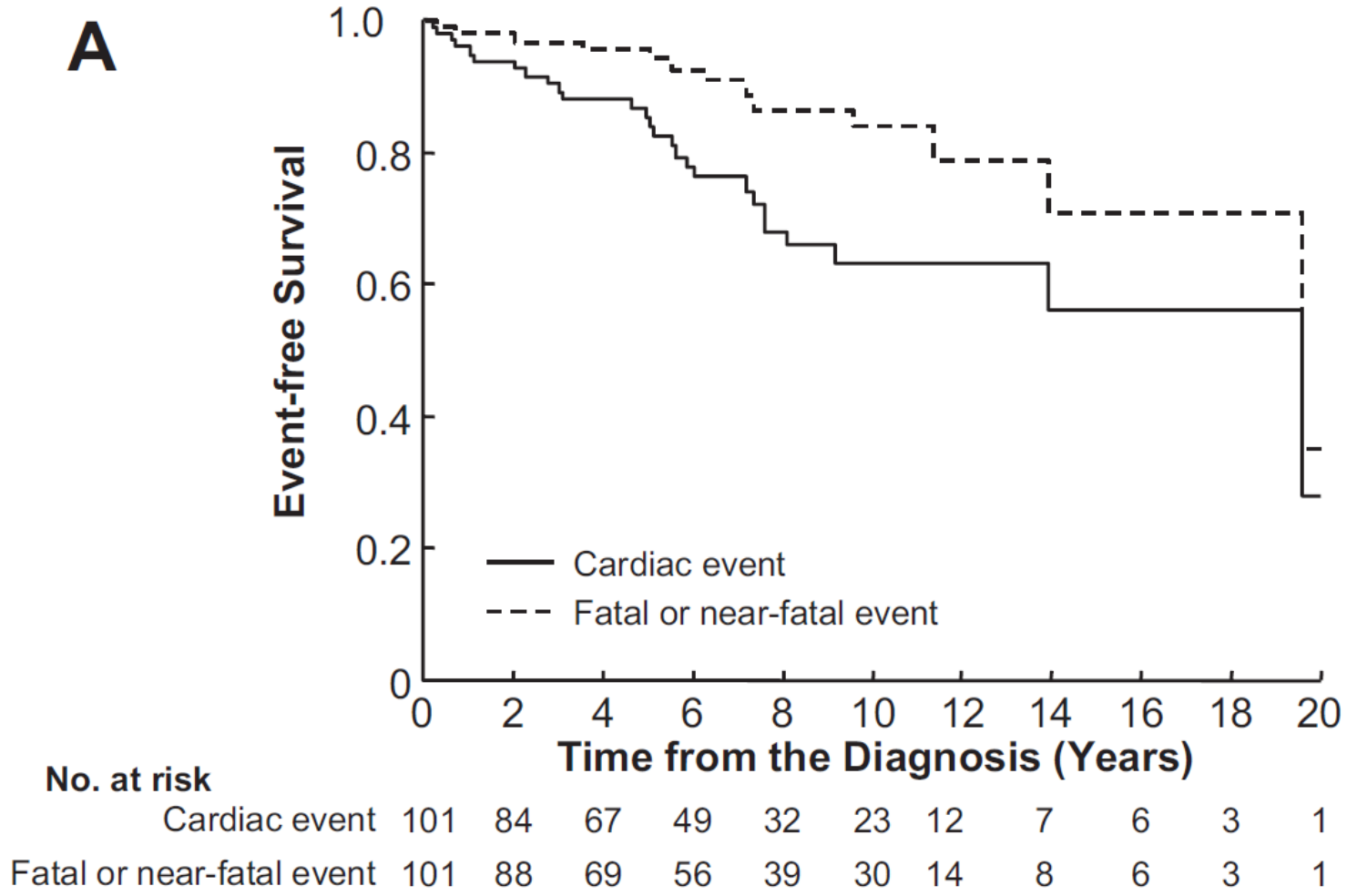
Peter J. Schwartz, MD,*†‡§|| Michael J. Ackerman, MD, PhD,¶#** Alfred L. George, Jr, MD,†††‡‡ Arthur A. M. Wilde, MD, PhD§§||||

JACC 2013;62

- Approximately 50% to 60% of CPVT = heritable or sporadic mutations in the RYR2-encoded cardiac ryanodine receptor/calcium release channel
  - a critical regulator of intracellular calcium
  - RYR2 is one of the largest genes in the human genome, 105 translated exons, encodes for a protein containing 4,967 amino acids
- Rare autosomal recessive subtypes = mutations in CASQ2-encoded calsequestrin 2 (CPVT2) or TRDN encoding the junctional protein triadin (CPVT4).
- Mutations in CALM1 encoding calmodulin were discovered recently in 1 family with autosomal dominant CPVT-like phenotype (CPVT5)
- Mutations in the KCNJ2-encoded Kir2.1 can express a clinical phenotype that mimics autosomal dominant CPVT

Tachycardies ventriculaires catécholergiques

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia



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

Tachycardies ventriculaires catécholergiques

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

- After diagnosis : mean F.up 7.9±4.9 years
- After 8 years:
  - Cardiac events : **27%**
  - Fatal or near fatal events : **11%**

- Index case vs. Family :
  - No difference

- Asymptomatic + mutation vs. Others :
  - No difference

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

Tachycardies ventriculaires catécholergiques

Modification du style de vie

''NO SPORT''

Sir Winston Churchill

NO STRESS

Tachycardies ventriculaires catécholergiques

Modification du style de vie

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

Europace. 2013;13:1389-406.

Class I

1. The following lifestyle changes ***are recommended*** in all patients with a diagnosis of CPVT:
   a. Limit/avoid competitive sports
   b. Limit/avoid strenuous exercise
   c. Limit exposure to stressful environments.

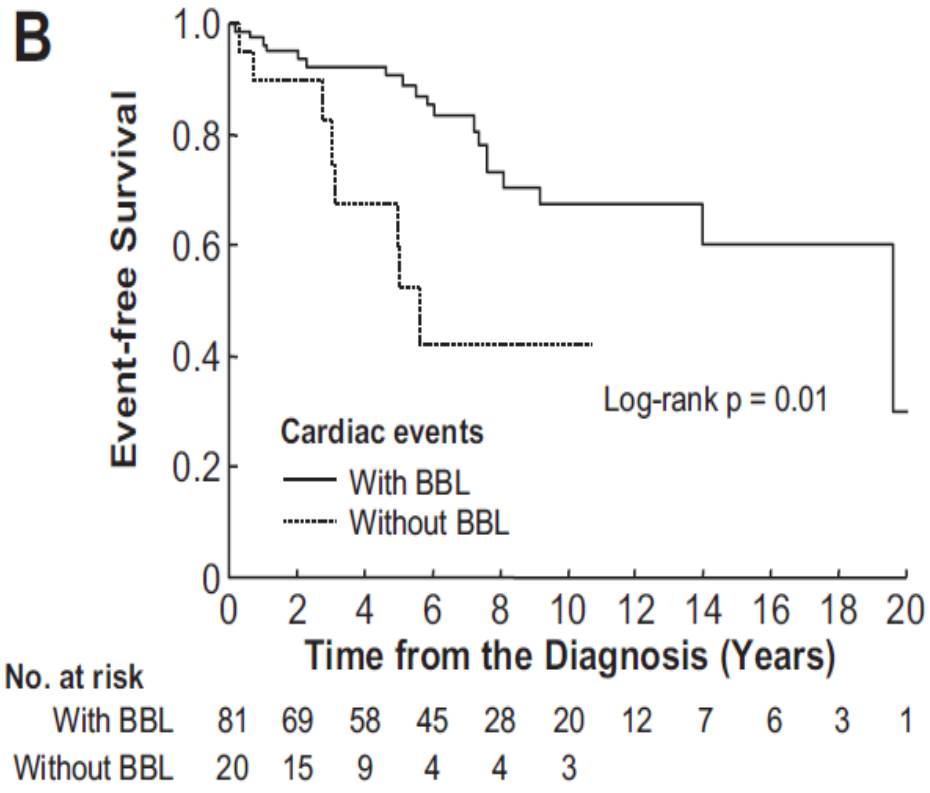
2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Europace. 2015;17:1601-87.

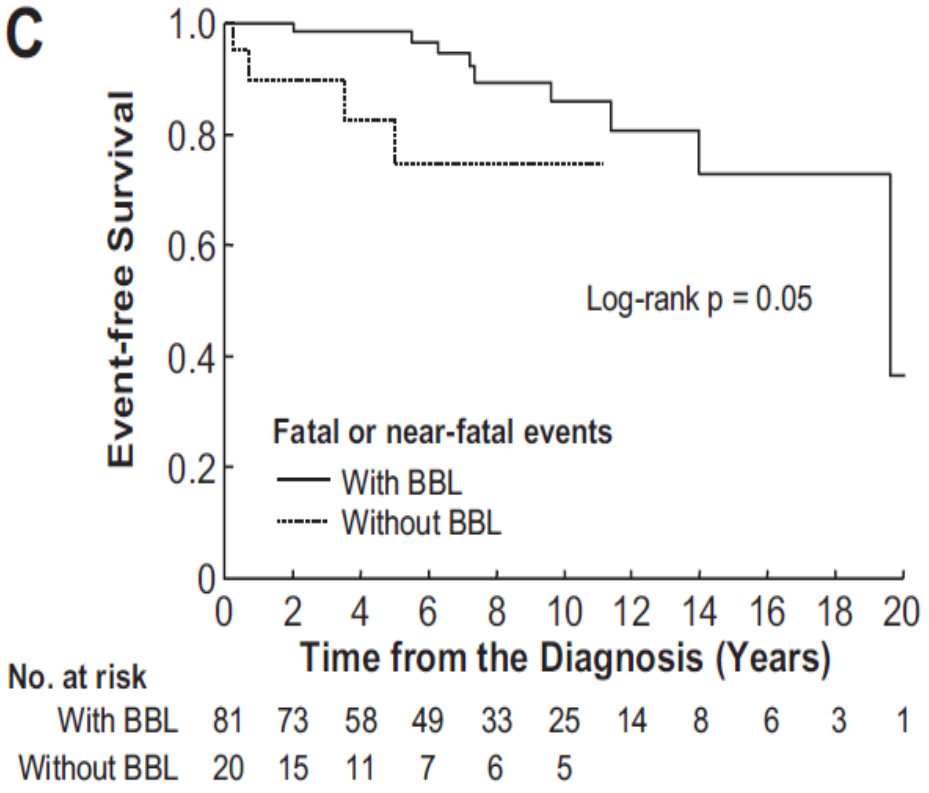
Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of CPVT: avoidance of competitive sports, strenuous exercise and stressful environments.	I	C	This panel of experts

Tachycardies ventriculaires catécholergiques

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia



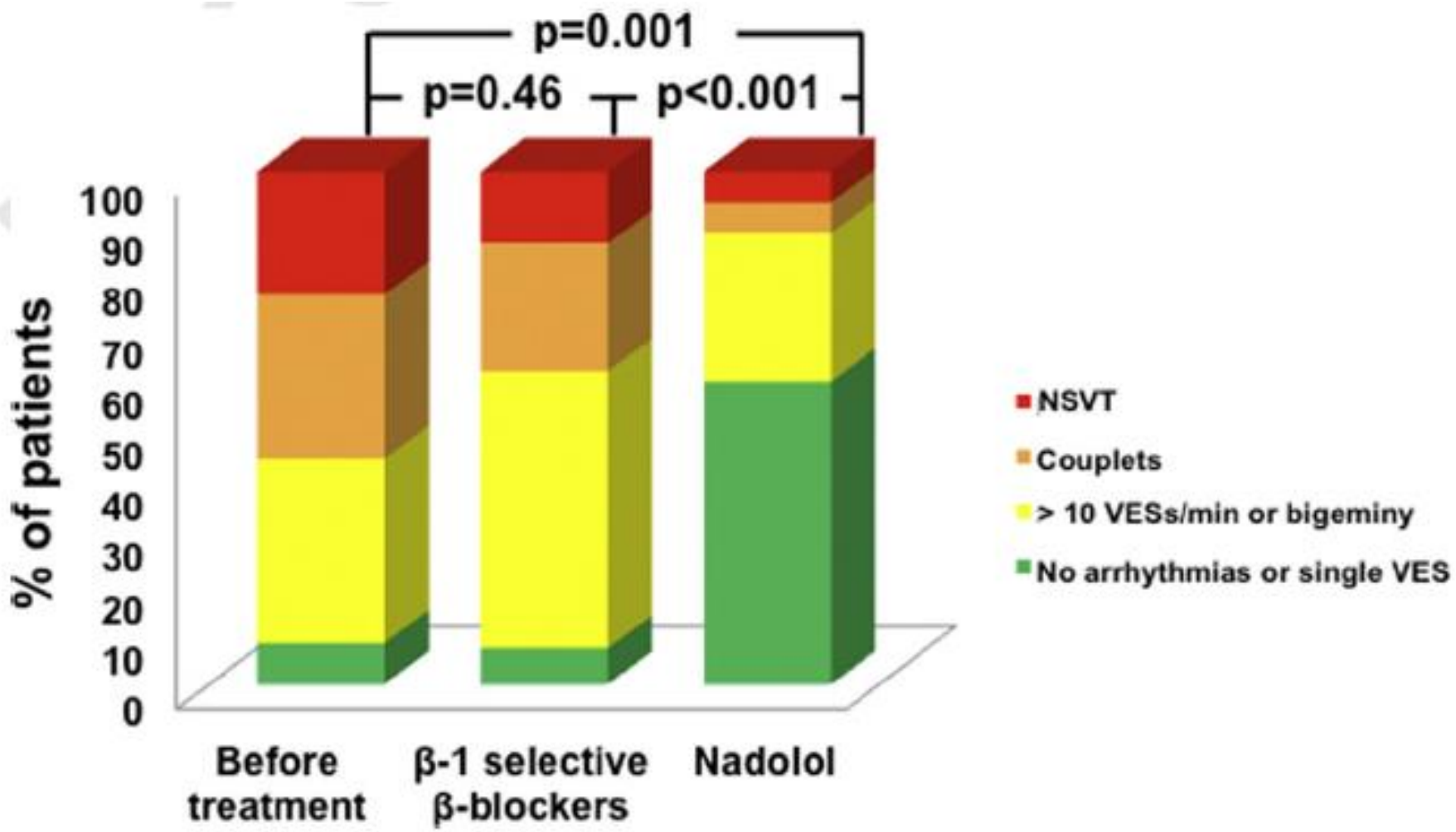
Estimation 8 ans: 27% vs. 58%



Estimation 8 ans: 11% vs. 25%

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

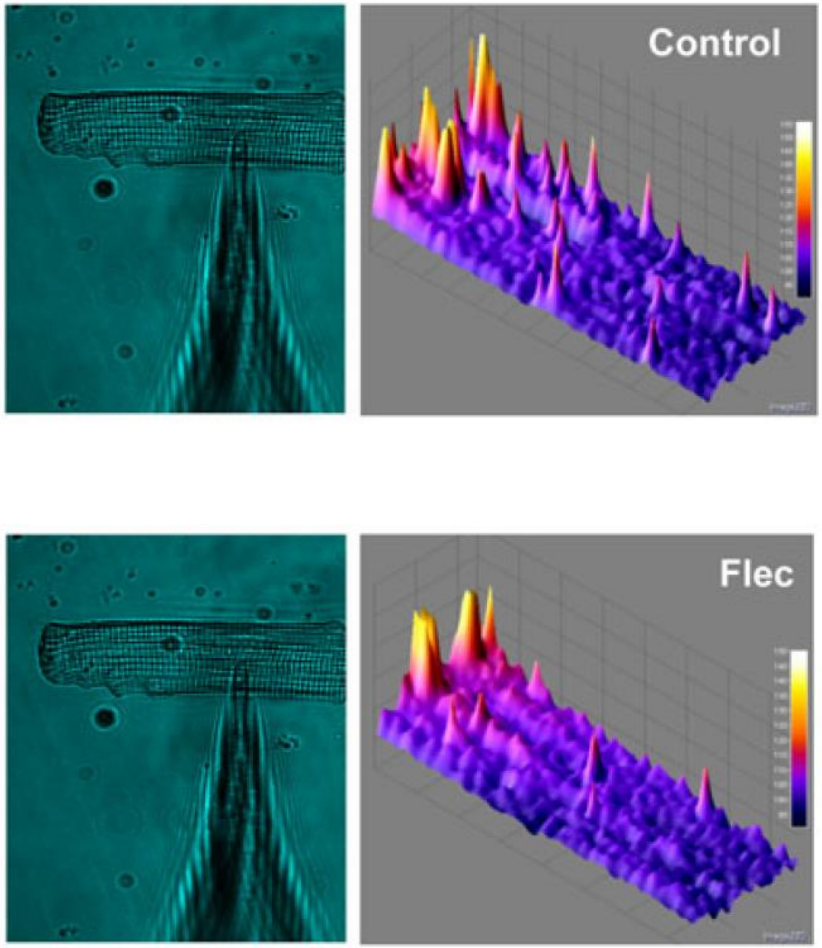
Efficacy of Nadolol in CPVT patients

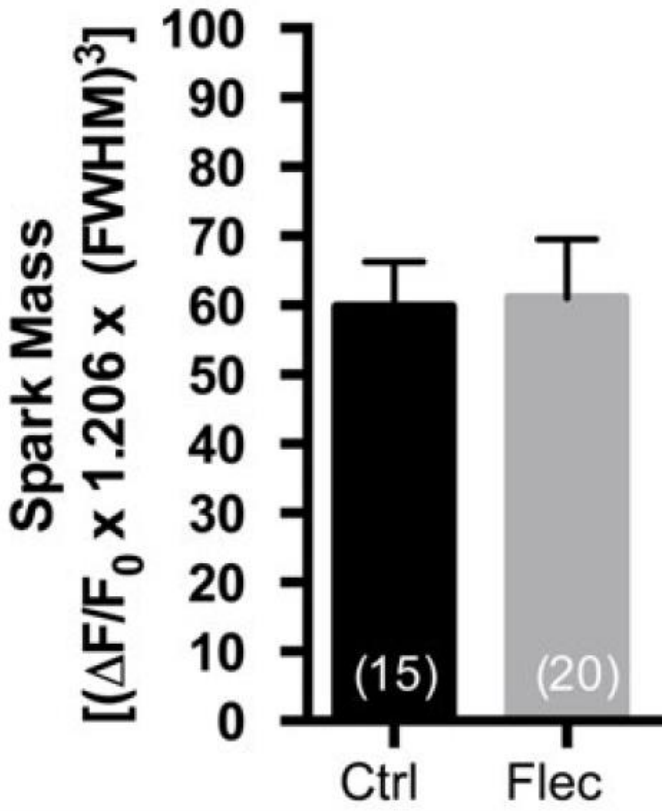


Arrhythmias were less frequent and less severe during nadolol treatment than both before the initiation of β-blocker treatment and during β1-selective β-blocker treatment

I.S. Leren et al. Heart Rhythm 2016; 13:433-40.

Effect of flecainide derivatives on sarcoplasmic reticulum calcium release suggests a lack of direct action on the cardiac ryanodine receptor

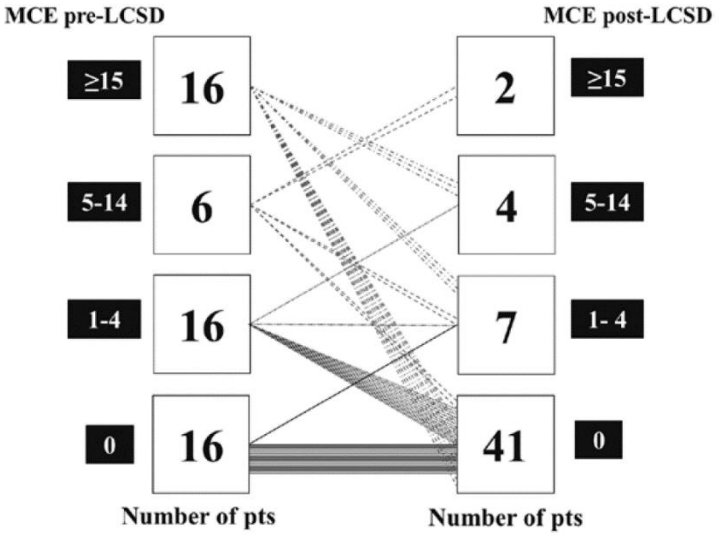


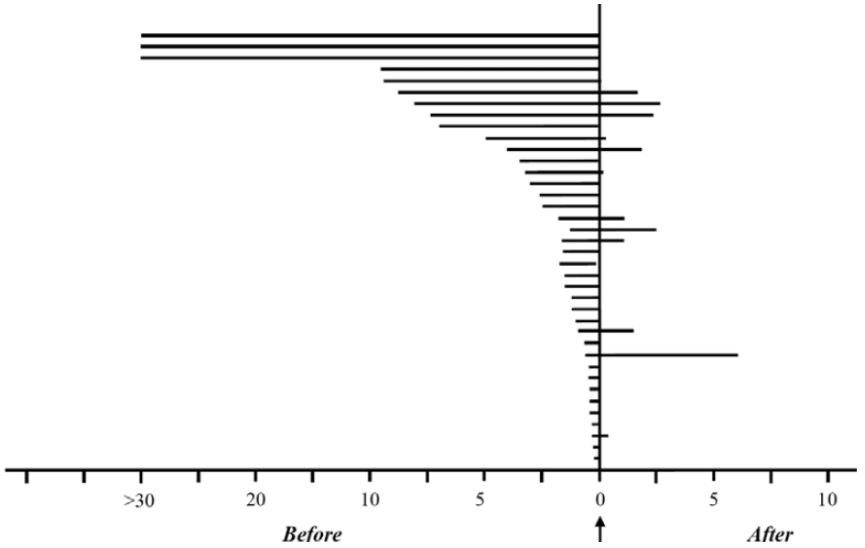


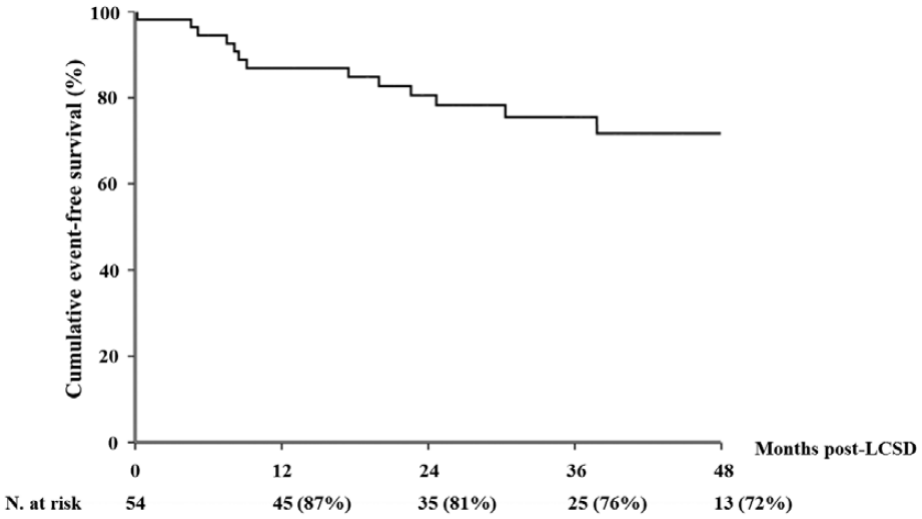
Br J Pharmacol 2016;173:2446-59.

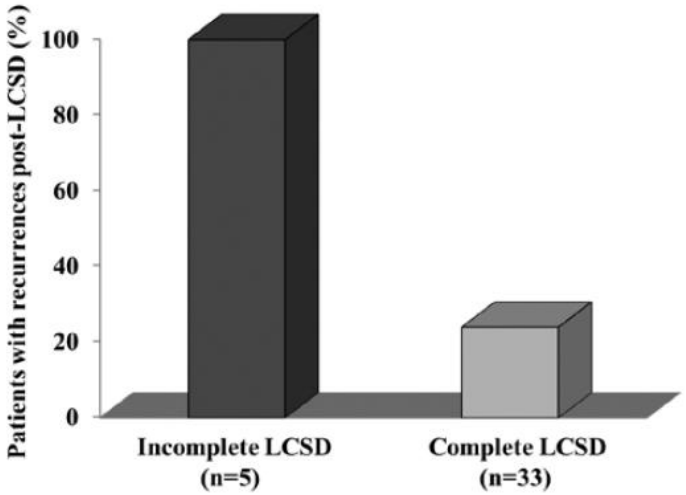
Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia

The Role of Left Cardiac Sympathetic Denervation





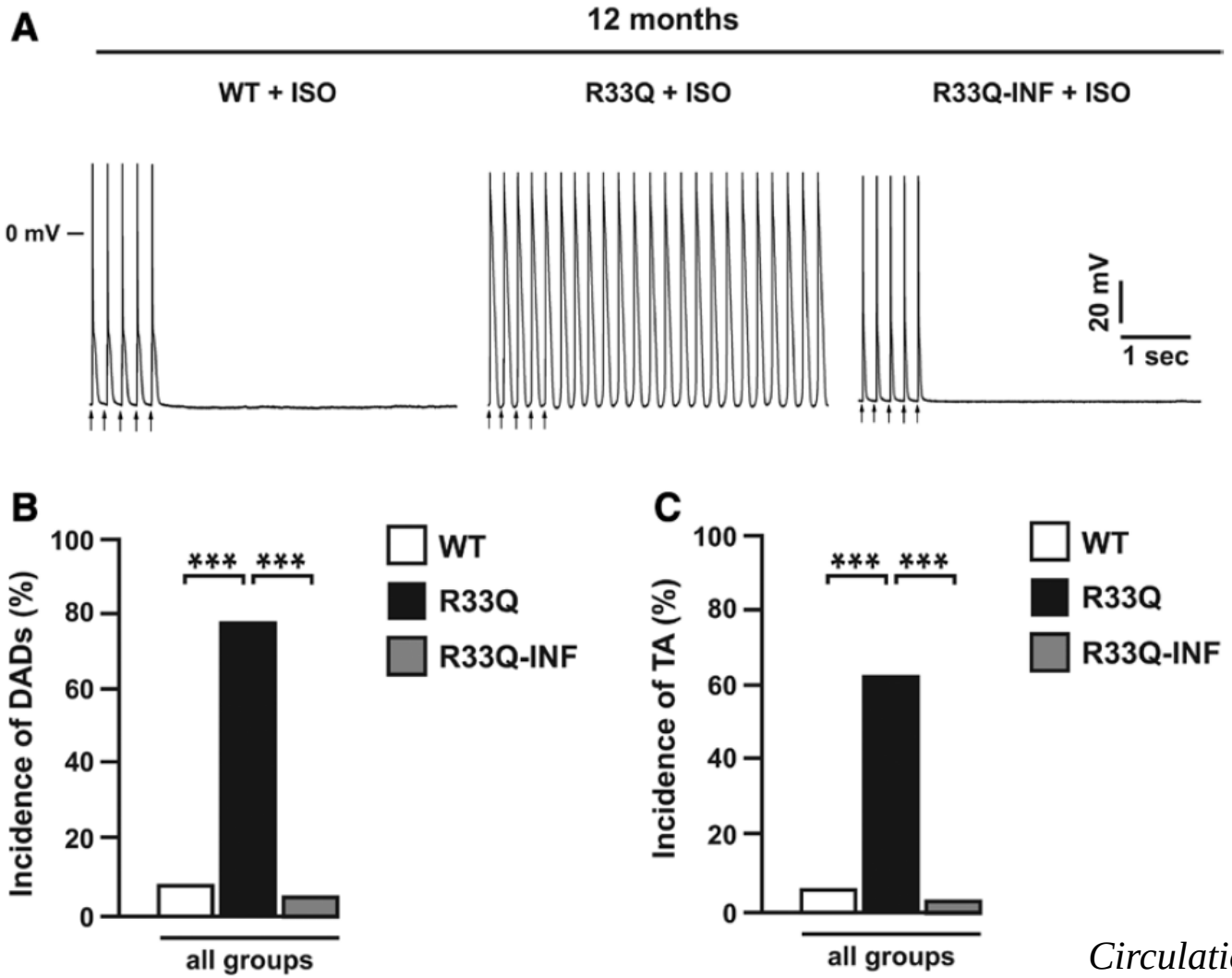




Circulation 2015;131:2185-93.

Single Delivery of an Adeno-Associated Viral Construct to Transfer the *CASQ2* Gene to Knock-In Mice Affected by Catecholaminergic Polymorphic Ventricular Tachycardia Is Able to Cure the Disease From Birth to Advanced Age

Marco Denegri, PhD*; Rossana Bongianino, MSc*; Francesco Lodola, PhD*; Simona Boncompagni, PhD; Verónica C. De Giusti, MD, PhD; José E. Avelino-Cruz, PhD; Nian Liu, MD; Simone Persampieri, MS; Antonio Curcio, MD, PhD; Francesca Esposito, MD; Laura Pietrangelo, MSc; Isabelle Marty, PhD; Laura Villani, MD; Alejandro Moyaho, PhD; Paola Baiardi, PhD; Alberto Auricchio, MD; Feliciano Protasi, PhD;



Circulation 2014;129:2673-81

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 of inherited arrhythmia syndromes (ARVC/D, BS, CPVT, HCM, lamin DCM, LQTS, SQTS)
- 63 studies comprising 4916 patients
- Inappropriate shocks in 20% of patients (crude annual rate of 4.7% per year)

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

  CPVT 85% - mean FU 54±43 months
- 0.5% ICD-related mortality (0.08% per year)

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

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

Silvia G. Priori, (HRS Chairperson)[1], Arthur A. Wilde, (EHRA Chairperson)[2], Minoru Horie, (APHRS Chairperson)[3], Yongkeun Cho, (APHRS Chairperson)[4], Elijah R. Behr[5], Charles Berul[6], Nico Blom[7*], Josep Brugada[8], Chern-En Chiang[9], Heikki Huikuri[10], Prince Kannankeril[11‡], Andrew Krahn[12], Antoine Leenhardt[13], Arthur Moss[14], Peter J. Schwartz[15], Wataru Shimizu[16], Gordon Tomaselli[17†], Cynthia Tracy[%18]

Europace. 2013; 13:1389-406

Verapamil

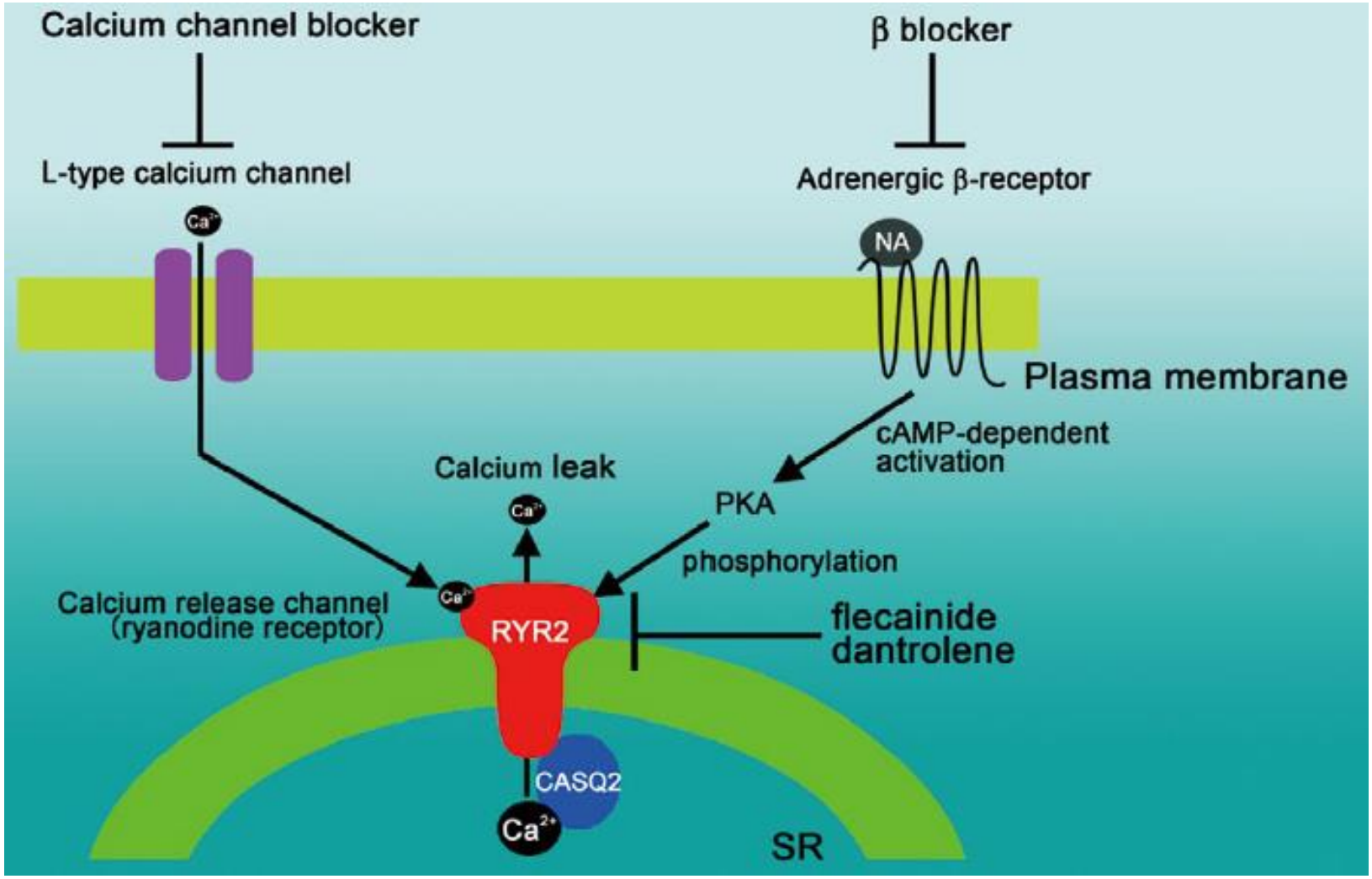
Verapamil has been shown to be beneficial in some CPVT patients by reducing the ventricular arrhythmia burden on top of beta-blocker therapy during a short-term follow- up period,[63,64] though its long-term effect remains controversial.

Catheter ablation

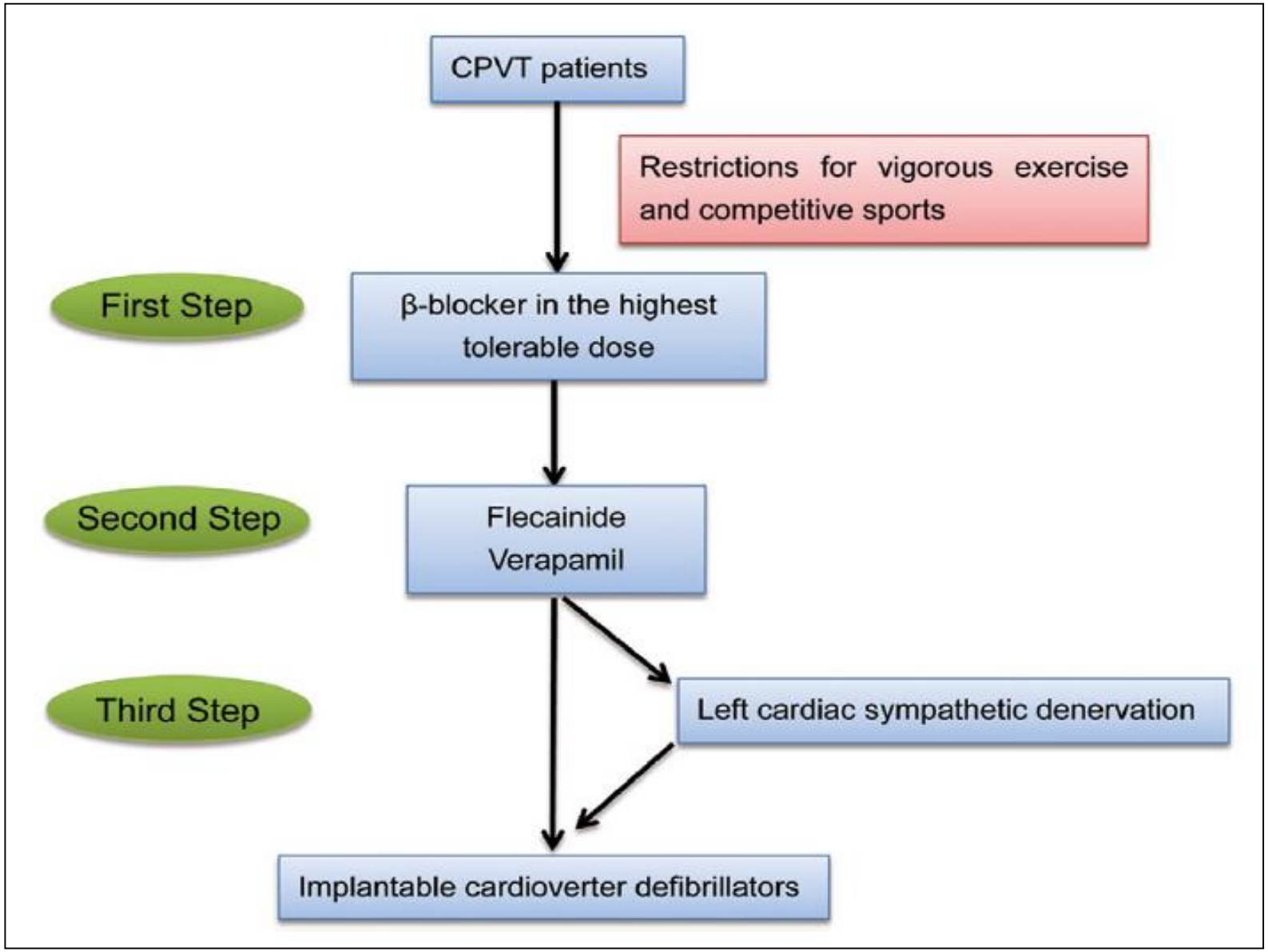
Catheter ablation of the bidirectional VPBs that trigger VF may become an adjunctive therapy in patients with refractory CPVT. However, the published experience is very limited and is therefore not discussed in the recommendation.[74]

Evaluation of family members

Family screening (siblings and parents) by clinical evaluation and genetic testing (when a mutation has been detected) is mandatory to identify undiagnosed patients and asymptomatic carriers who are at risk of arrhythmic events and should be treated. It is suggested that genetically positive family members should receive beta-blockers even after a negative exercise test.[60,75]



Yamazoe M et al. Circ J 2016; 80: 1892-4.



Yamazoe M et al. Circ J 2016; 80: 1892-4.

Tachycardies ventriculaires catécholergiques

- Actually no good markers of prognosis.
- >90% of severe events between 13 and 26 y. of age in our cohort
- Younger age at diagnosis (HR: 0.31 per decade; 95% CI: 0.14–0.69; P = 0.004).
- The presence of couplets or more successive VPBs during exercise testing are significantly associated with future arrhythmic events (sensitivity 0.62; specificity 0.67).
- Treatment with beta-blockers other than nadolol [HR: 3.12; 95% CI: 1.16–8.38; P=0.02] is associated with future arrhythmic events.

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

Tachycardies ventriculaires catécholergiques

- Maladie rare, mais grave
- Y penser, c'est en faire le diagnostic
  - Syncope effort++++
  - Convulsion effort
  - Mort subite effort – piscine
- Importance du bilan familial
- Bêtabloquant (nadolol +++ 1,8 mg/kg). Observance ++, ± flecaïnide ± stellectomie ± DAI
- Centres de référence