KHRS 2023
June 23(Fri.) - 24(Sat.), 2023
Grand Walkerhill Seoul, Korea
The 15th Annual Scientific Session of the Korean Heart Rhythm Society

Pediatric 2: CPVT, June 24 (Sat) 13:30-15:00

Medical Management in CPVT: Beta Blocker? Flecainide? Both?

Hwa Jin Cho

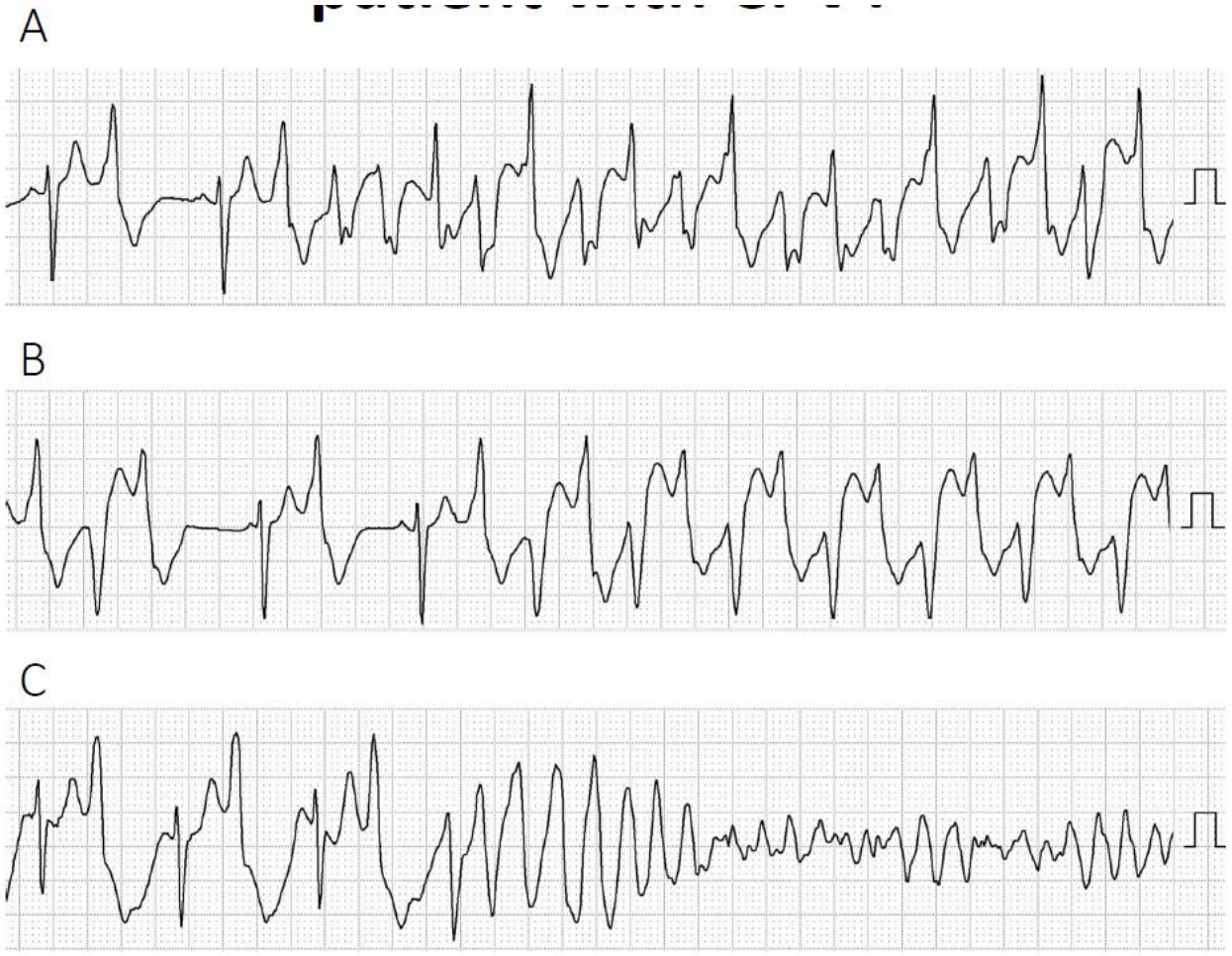
Department of Pediatrics, Chonnam National University Children's Hospital and Medical School, Gwangju, Korea

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

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

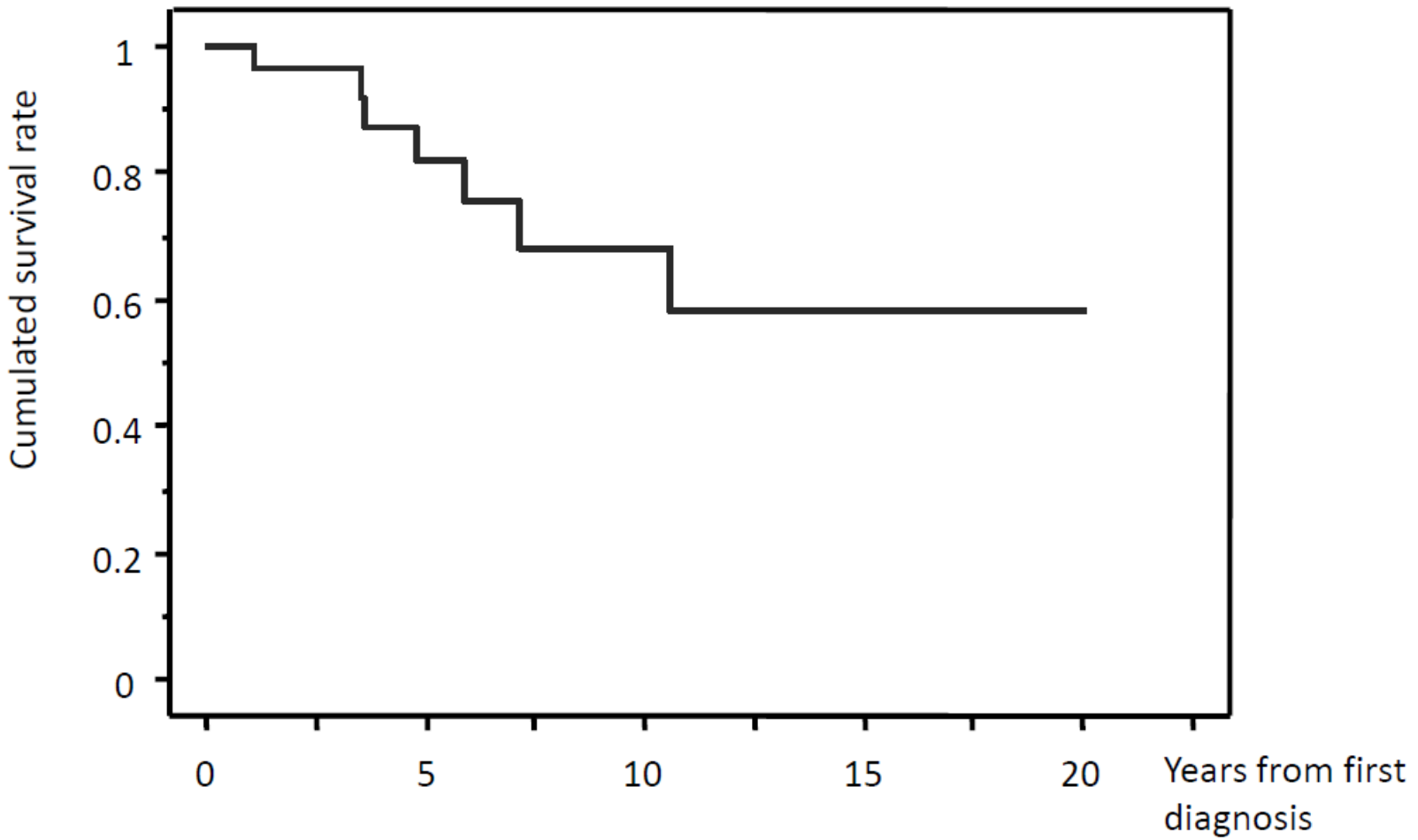
Priori SG, et al. Euopace. 2015;17:1601–1687

Typical features of ventricular tachycardia in a patient with CPVT

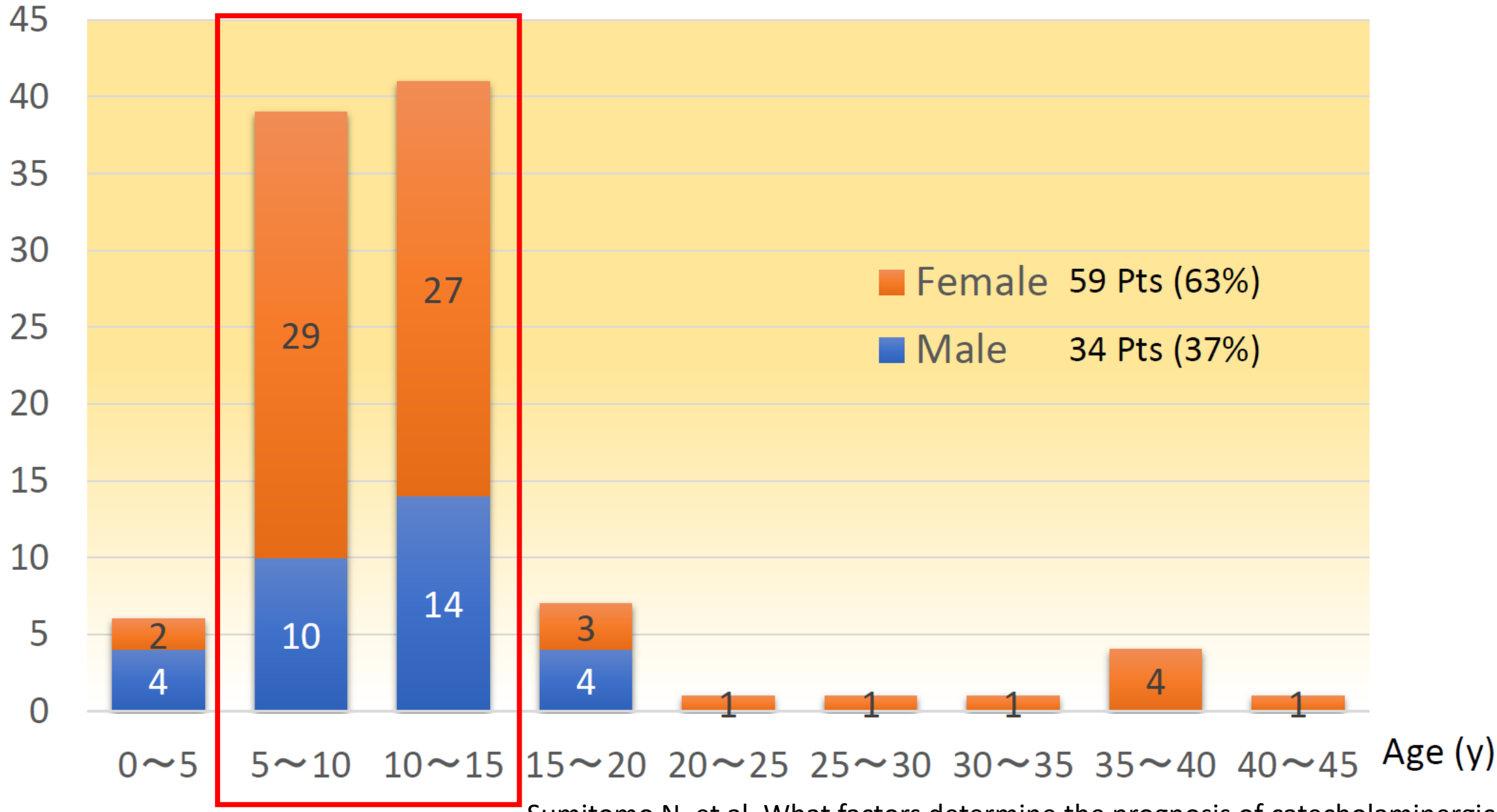


Sumitomo N. J Arrhythm2016;32:344-351

Kaplan-Mayer Survival Curve



Sumitomo N, et al. Heart. 2003;89:66-70



Sumitomo N, et al. What factors determine the prognosis of catecholaminergic polymorphic ventricular tachycardia? AHA 2017

	CPVT1	CPVT2	CPVT3	CPVT4	CPVT5	CPVT related diseases	
						ATS	LQT4
Incidence (%)	50 - 60	1	<<1	<<1	<<1	<<1	<<1
inheritance	AD	AR	AR	AD	sporadic	AD	AD
Onset of symptoms (yrs)	10	7	22, 18, 4	4	2, 26	14, 9, 17	?
Sex (M:F)	1:1	1:1	1:1	1:1	M=3	F>M?	?
Chromosome locus	1q43	1p13.1	4p13.1	14q32.11	6q22.31	17q24.3	4q25-26
Gene	*RyR2*	*CASQ2*	*TECRL*	*CALM1*	*TRD*	*KCNJ2*	*ANK2*
Protein	Ryanodine receptor	Carsequestrin 2	trans-2,3-enoyl-CoA reductase like protein	CaM	Triadin	$K_{ir}2.1\alpha$	Ankyrin-B
Sudden death (%)	≈10	≈42	≈57	≈18	≈25	?	?

Modified from Guidelines for Diagnosis and Management of Inherited Arrhythmias (JCS 2017);
http://www.j-circ.or.jp/guideline/pdf/JCS2017_aonuma_h.pdf

Acute Medical Management during catecholamine surge

- Acute initial management focuses on rapid termination of polymorphic VT.
- Treatment decisions are often made in the absence of a detailed knowledge of underlying cardiac disease, thus our recommendations do not make clear distinctions based upon the presence of coronary heart disease or primary electrical disease.

- Patients with polymorphic VT who are hemodynamically unstable or become pulseless require prompt treatment with electrical cardioversion/defibrillation.

- use propranolol (40 mg oral doses [or appropriate weight-based dosing in children] every six hours for the first 48 hours, with additional **intravenous doses** as needed for recurrent breakthrough ventricular arrhythmias) for acute suppression of recurrent polymorphic VT.

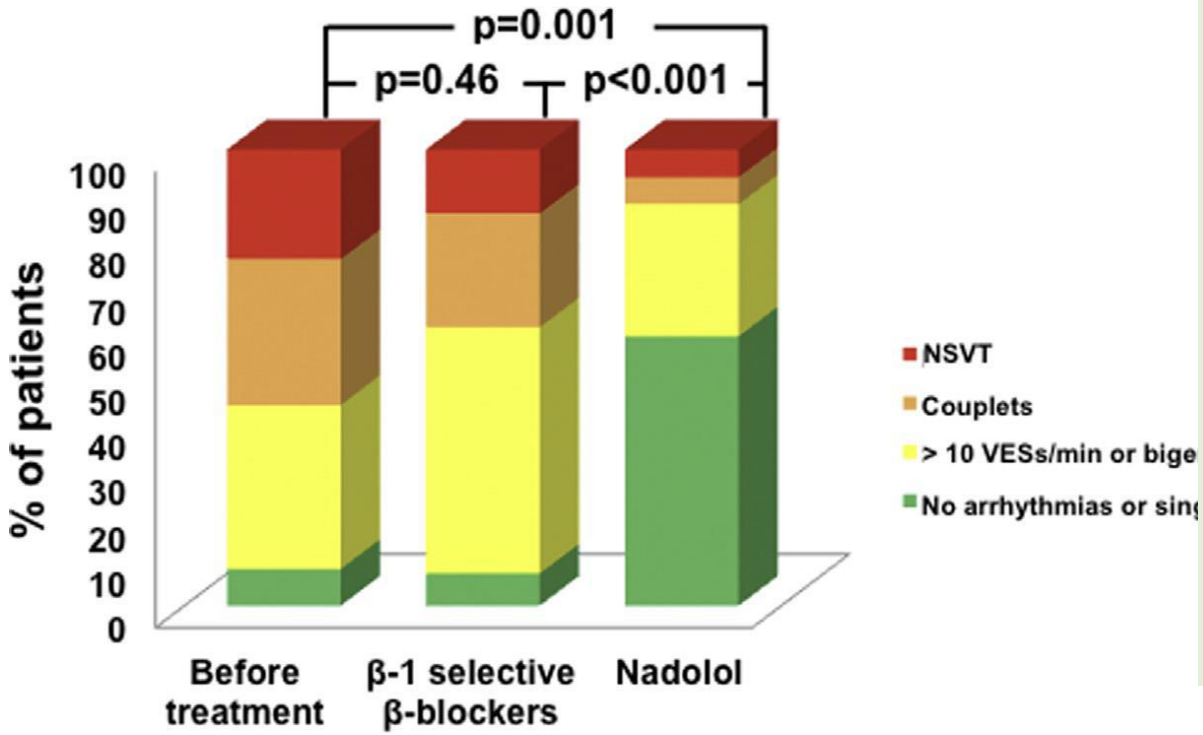
- For long-term preventive therapy, nadolol (1 to 2 mg/kg) is preferred (because of its long duration of action).

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

Beta blockers

- recommend beta blocker treatment for all patients with spontaneous or documented stress-induced ventricular arrhythmias.
- suggest the following treatment approaches:
  - Use of long-acting, nonselective beta blockers
    - **Nadolol 1 to 2 mg/kg).**
    - The long duration of action aides with compliance.
- Some studies suggest that nonselective beta blockers (eg, nadolol, propranolol) are more effective than beta-1 selective beta blockers at preventing exercise-induced arrhythmias.

Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with β1-selective β-blockers in patients with CPVT



The incidence and severity of ventricular arrhythmias decreased during treatment with nadolol compared with during treatment with β1-selective β-blockers.

β1-Selective β-blockers did not change the occurrence or severity of arrhythmias compared with no medication.

(3) 46 weeks after nadolol

LerenIS, et al. Heart Rhythm 2016;13:433–440

β-blockers

- Effective pharmacological approach.
- Unfortunately, ≈30% of patients have recurrences, and an ICD may be required.
- The long acting β-blocker, **nadolol** is preferred for prophylactic treatment of CPVT.
- **Propranolol** is also an effective medication.
- Among various β-blockers, **carvedilol** inhibits RyR2 activity (Zhou et al., 2011).

Pérez-RieraAR, et al. Ann Noninvasive Electrocardiol. 2017;e12512.

High-risk patients

- High-risk patients are survivors of cardiac arrest (SCA), syncope, sustained VT or ventricular fibrillation (VF), as well as those who have recurrent arrhythmia despite treatment with beta blockers.

- **Implantable cardioverter-defibrillators** — For patients with CPVT who have survived sudden cardiac arrest (SCA) or who experience syncope due to sustained VT or VF despite therapy with beta blockers, we recommend **ICD implantation in addition to beta blocker therapy.**

Verapamil

- Beneficial effects in some CPVT patients (Rosso et al., 2007).
- The long-term efficacy of verapamil is controversial.

Pérez-RieraAR, et al. Ann Noninvasive Electrocardiol. 2017;e12512.

Second-line therapy : Preferably Flecainide

- For patients with an ICD who continue to have stress-induced ventricular arrhythmias despite beta blocker therapy, we suggest the addition of flecainide for further arrhythmia suppression.
- For patients who cannot tolerate beta blockers, flecainide may be used as monotherapy.
- If a patient has a contraindication to flecainide such as coronary disease or a medication intolerance, then verapamil can also be used in its place.

Flecainide

- Very effective medication to decrease incidence and severity.
- It is recommended with the use of ß-blocker.
- Flecainide blocks cardiac sodium channels and inhibits the cardiac ryanodine receptor (*RyR2*).
- These combined effects make it an attractive potential therapy for CPVT.
- Flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy.

Pérez-RieraAR, et al. Ann Noninvasive Electrocardiol. 2017;e12512.

- Flecainide can be added for primary prevention of an SCA when β-blockers alone cannot control the onset of arrhythmias during TST

- CPVT is predominantly associated with genetic abnormalities involving the cardiac ryanodine receptor type 2 sarcoplasmic reticular (SR) Ca2+ release channel (RyR2) and the SR binding protein calsequestrin type 2 (CASQ2), respectively.

Pérez-RieraAR, et al. Ann Noninvasive Electrocardiol. 2017;e12512.

- Initial findings that flecainide prevented ventricular arrhythmia in two patients with respective CASQ2 and RyR2 mutations in TSTs suggested a mechanism involving reduced triggering activity.

- Recently, in a randomized multicenter, single-blind, placebo-controlled crossover clinical trial of patients with CPVT was published.

Pérez-RieraAR, et al. Ann Noninvasive Electrocardiol. 2017;e12512.

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

IMPORTANCE Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal genetic arrhythmia syndrome characterized by polymorphic ventricular tachycardia with physical or emotional stress, for which current therapy with β-blockers is incompletely effective. Flecainide acetate directly suppresses sarcoplasmic reticulum calcium release—the cellular mechanism responsible for triggering ventricular arrhythmias in CPVT—but has never been assessed prospectively.

OBJECTIVE To determine whether flecainide dosed to therapeutic levels and added to β-blocker therapy is superior to β-blocker therapy alone for the prevention of exercise-induced arrhythmias in CPVT.

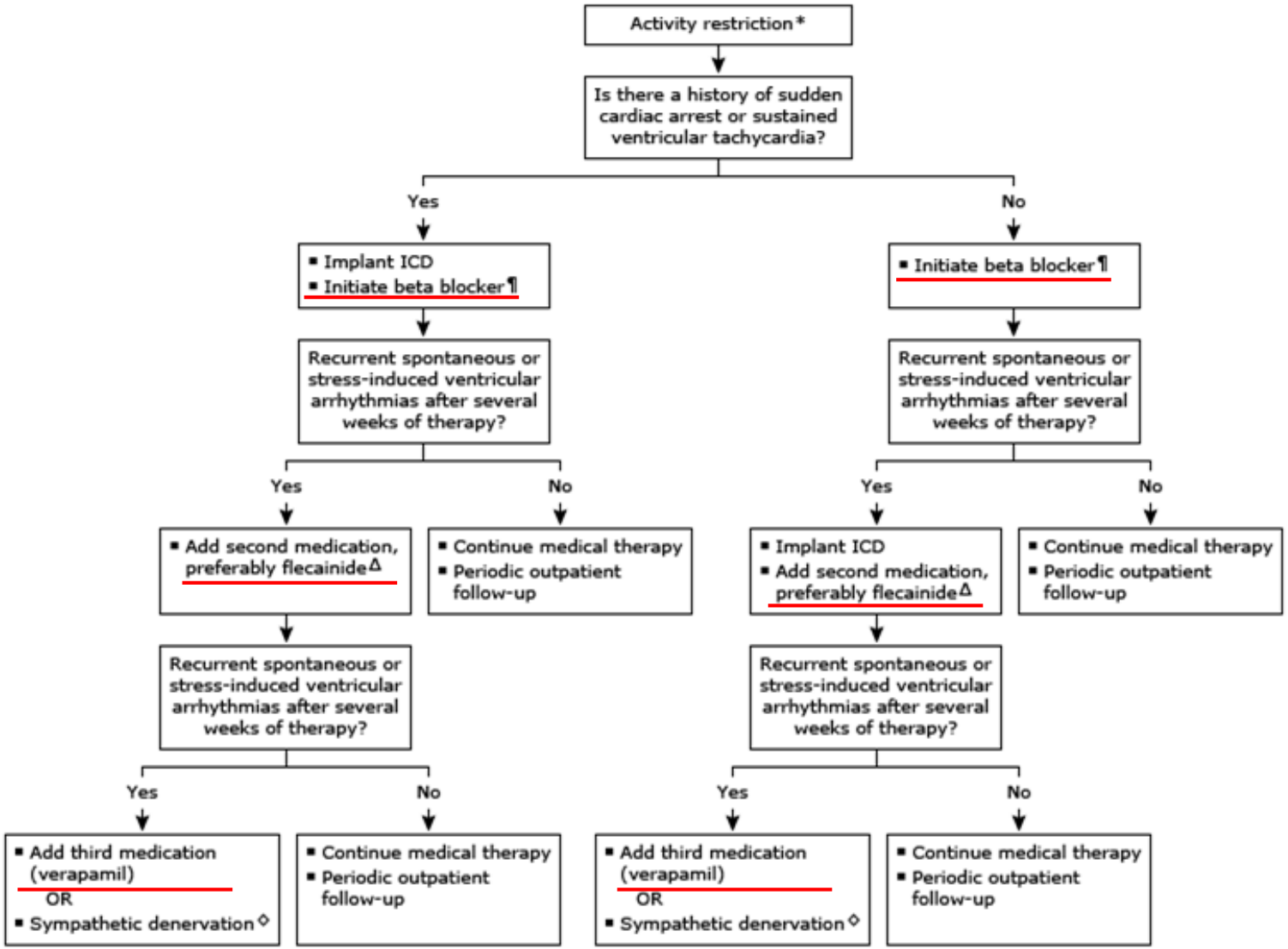
Supplemental content

JAMA Cardiol. 2017;2(7):759-766.
doi:10.1001/jamacardio.2017.1320

- Patients with a clinical diagnosis of CPVT and an ICD underwent a baseline TST while receiving maximally tolerated β-blocker therapy that was continued throughout the trial.
- Patients were then randomized to treatment A (flecainide or placebo) for 3 months, followed by exercise testing. After a 1-week washout period, patients crossed over to treatment B (placebo or flecainide) for 3 months, followed by exercise testing.
- **Flecainide plus β-blocker significantly reduced PVCs during exercise compared with placebo plus β-blocker and β-blocker alone**

Kannankeril et al., 2017

Algorithm for the long-term management of catecholaminergic polymorphic ventricular tachycardia



Conclusion

- **β-blocker is recommend for all patients with spontaneous or documented stress-induced ventricular arrhythmias.**
- **Nadolol is the most effective β-blocker.**
  - **The incidence and severity of ventricular arrhythmias decreased during treatment with nadolol compared with during treatment with β1-selective β-blockers.**
- **Flecainide plus β-blocker significantly reduced PVCs during exercise compared with placebo plus β-blocker and β-blocker alone**
- **ICD is effective in some patients but association with optimal medical treatment is mandatory**

Thank you for listening.