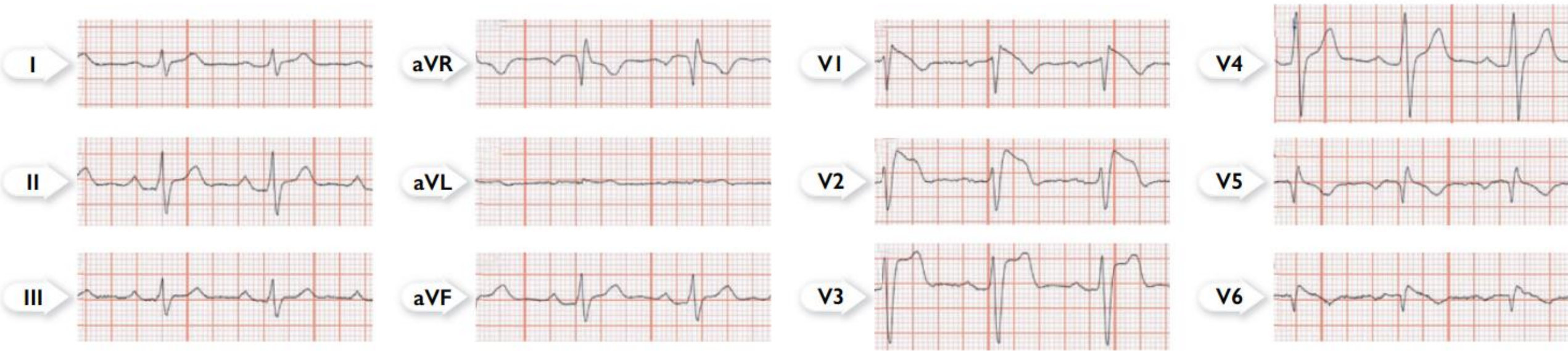


Treatment of Brugada Syndrome without Quinidine

Min Kim
Clinical assistant professor
Division of Cardiology, Department of Internal Medicine
Chungbuk National University Hospital



Diagnosis of BrS based on expert consensus recommendation

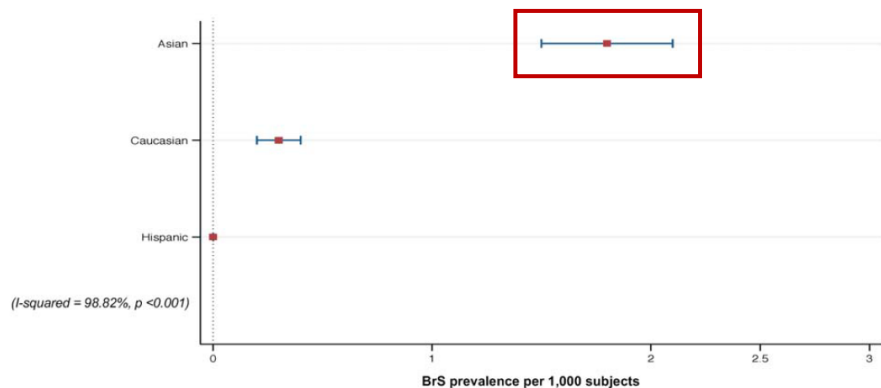
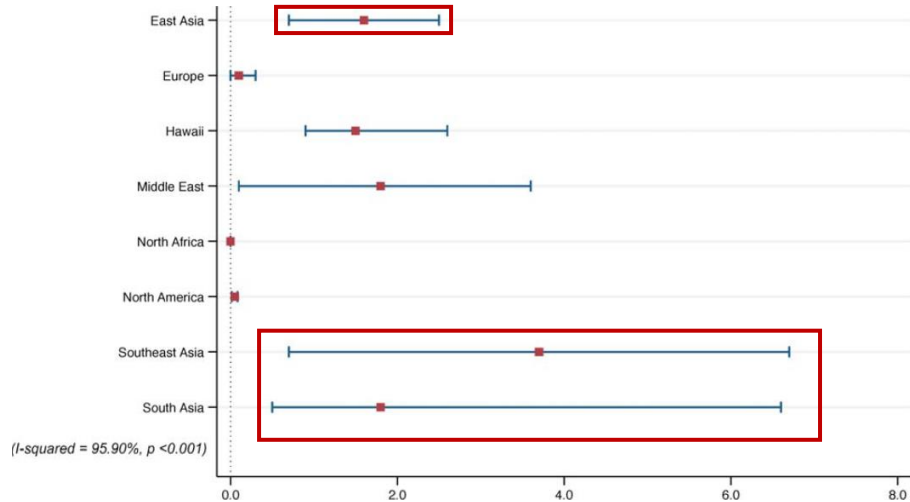


Expert Consensus Recommendation

1. BrS is diagnosed in patients with ST-segment elevation with **type 1 morphology** ≥ 2 mm in ≥ 1 lead among the right precordial leads V₁, V₂, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.
2. BrS is diagnosed in patients with type 2 or type 3 ST-segment elevation in ≥ 1 lead among the right precordial leads V₁, V₂, positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs **induces a type 1 ECG morphology**.

Prevalence of BrS

- ✓ Its prevalence is much higher in Asian and Southeast Asian countries



Prevalence of Electrocardiographic Findings Suggestive of Sudden Cardiac Death Risk in 10,867 Apparently Healthy Young Korean Men

Review

Epidemiology of Brugada syndrome in Japan and rest of the world

- ✓ Overall, the prevalence of BrS in adults

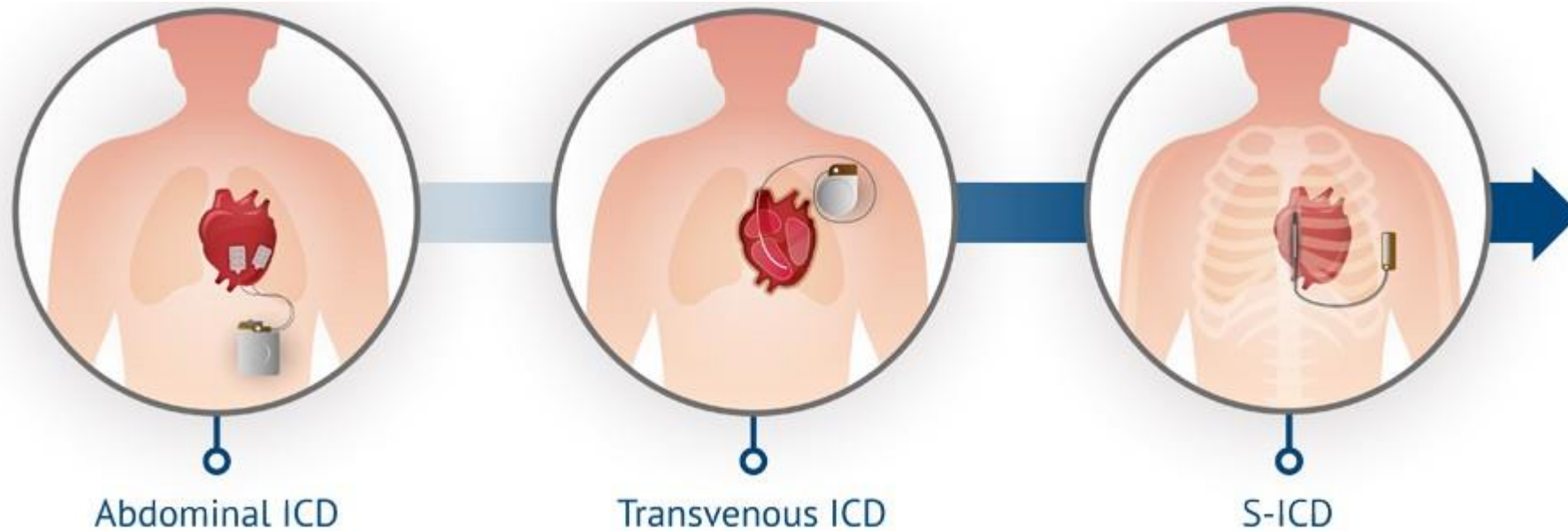
- ✓ ~0.15% in Asian
- ✓ 0.02~0.1% in Middle Eastern
- ✓ <0.02% in Western

Kamakura S, et al. *J of Arrhythmia*. 2013;29:52-55

Uhm JS, et al. *PACE*. 2011;34:717-723.

Vutthikraivit W, et al. *Acta Cardiol Sin*. 2018;34:267-277.

Implantable cardioverter defibrillator



- ✓ ICD is recommended in BrS patients who have survived a cardiac arrest.
- ✓ However, some concerns due to device-related complications
 - ✓ **Inappropriate shock**
 - ✓ **Lead failure**
- ✓ *** Device therapy can not prevent the arrhythmias**

Drug therapy in BrS

- ✓ **Acute management of arrhythmic storm**
- ✓ **Prevention of arrhythmic events**
 - ✓ **in patients with implanted ICD who require many shocks**
- ✓ **As an alternative to ICD**
 - ✓ **when the latter is contraindicated or not feasible**

Quinidine: The most extensively used drug

Recommendations	Class
3. ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.	IIa
4. Quinidine can be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24hours.	IIa
5. Quinidine can be useful in patients with a diagnosis of BrS: a) Who qualify for an ICD but present a contraindication to the ICD or refuse it and/or b) Have a history of documented supraventricular arrhythmia that require treatment.	IIa
6. Isoproterenol infusion can be useful in suppressing arrhythmic storms in BrS patients.	IIa
7. ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients).	IIb
8. Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type I ECG .	IIb
9. Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.	IIb
10. <u>ICD implantation is not indicated in asymptomatic BrS patients with a drug-induced type I ECG and on the basis of a family history of SCD alone.</u>	III

Antzelevitch C, et al. Circulation. 1999;15:1660-1666.

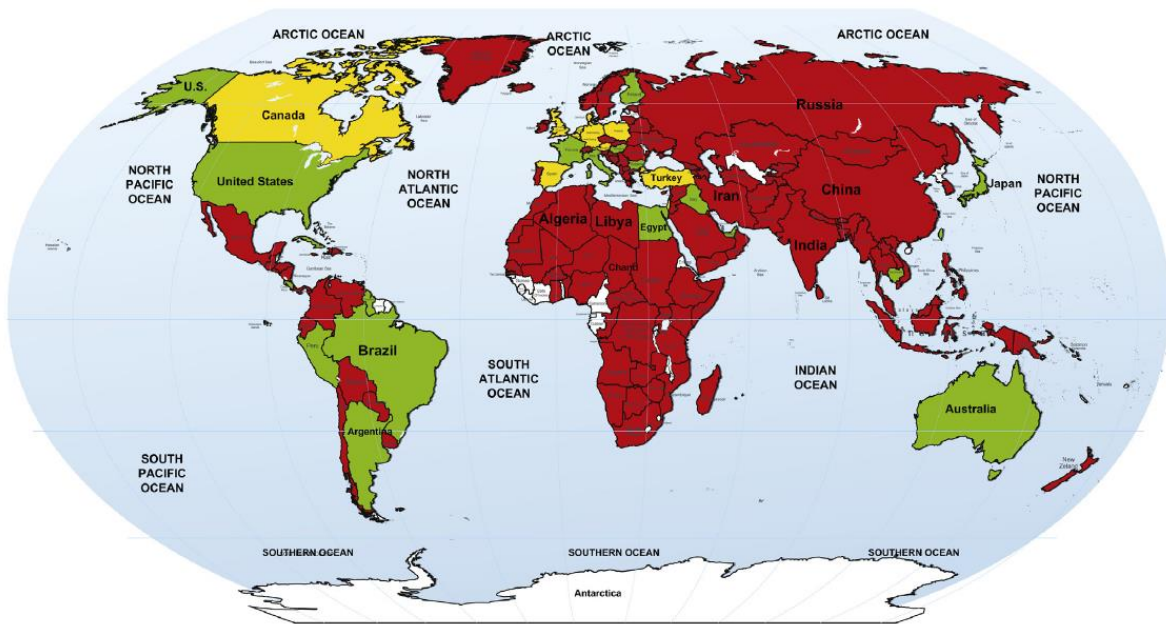
Antzelevitch C, et al. Curr Opin Cardiol. 1999;14:274.

Belhassen B, et al. Pacing Clin Electrophysiol. 2002;25:1634-1640.

Quinidine: Lack of accessibility in the World

Heart Rhythm Disorders

Quinidine, A Life-Saving Medication for Brugada Syndrome, Is Inaccessible in Many Countries



제약바이오 > 국내사

75배 가격 급등한 심부전약 퀴니딘, 사태 일단락되나



최선 기자 | 발행날짜: 2023-06-01 13:21:57



한국희귀필수의약품센터, 수입선 다변화
병당 5만원대 → 3만 5천원으로 부담 경감

[메디칼타임즈=최선 기자] 생산 중단으로 가격이 급등했던 심부전약 퀴니딘 사태가 일단락될 전망이다.

작년 말 대한부정맥학회가 5만원대의 퀴니딘이 380만원대로 급등하며 대란 가능성을 경고했지만 수입선 다변화로 우려하던 사태는 빗겨간 것으로 풀이된다.

1일 한국희귀필수의약품센터에 따르면 환자들의 약값 부담 완화 및 희귀·필수의약품의 접근성을 제고하기 위한 관세청과 협업으로 퀴니딘 대체재를 확보했다.



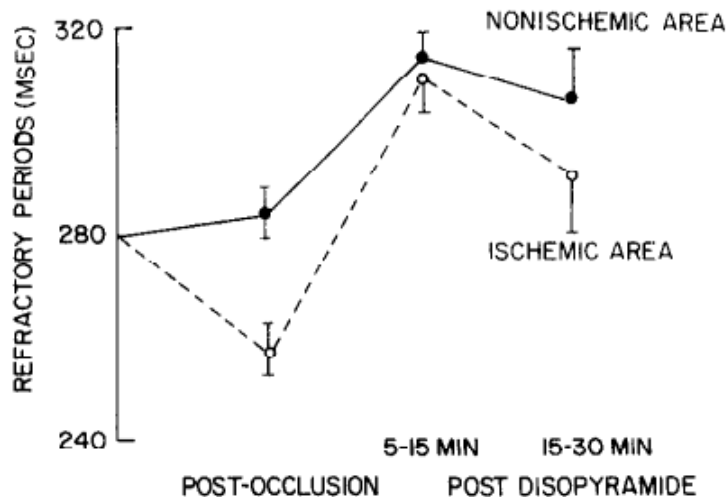
퀴니딘은 조기 재분극 증후군(early repolarization syndrome), 브루가다 증후군 등 희귀성 질환 환자의 심실성 부정맥 치료에 투약되는데 대체 불가능한 약제이기 때문에 약제를 복용하지 못할 경우 심실세동이나 심정지로 인한 사망 가능성이 매우 높아진다.

*Reports in Medical Times by Choi. 2023.06.01.
Viskin S, et al. J Am Coll Cardiol. 2013;61:2383-2387.*

Drug therapy without Quinidine in BrS: Disopyramide

Electrophysiological effects of disopyramide phosphate during experimental myocardial ischemia*

Rafael Levites, M.D., F.A.C.C.
Gary J. Anderson, M.D., F.A.C.C.
Philadelphia, Pa.



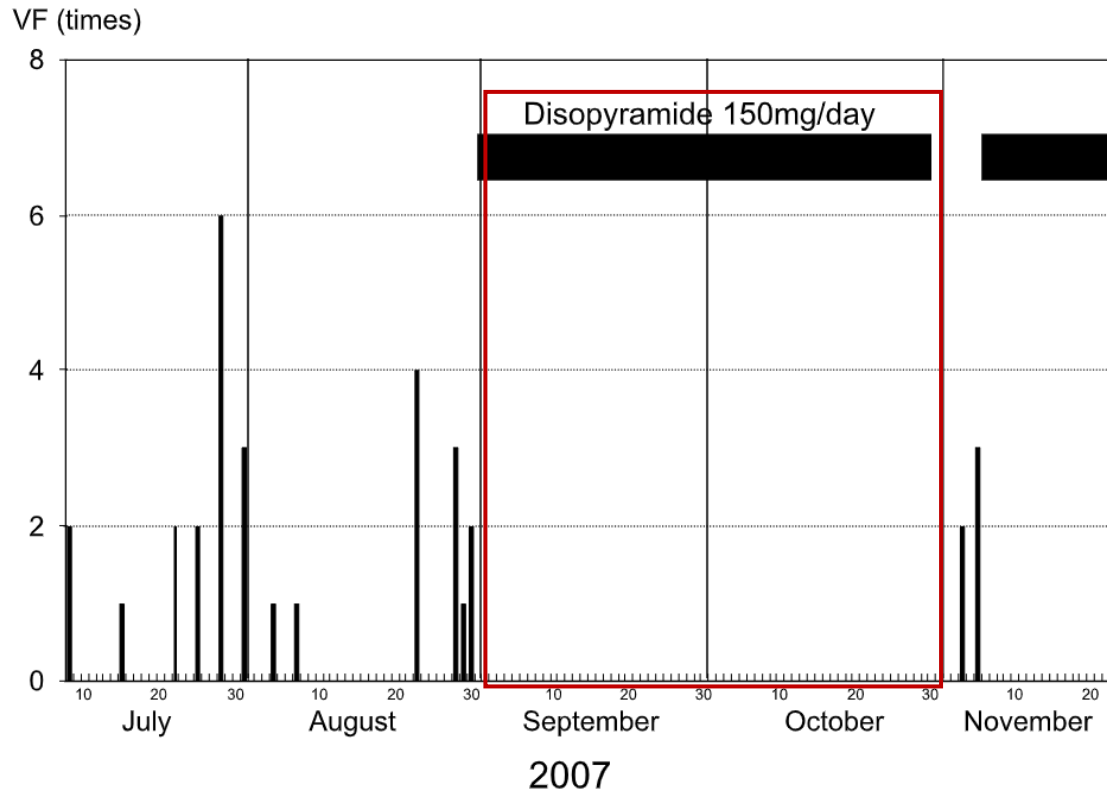
- ✓ Class IA antiarrhythmic drugs
 - ✓ Moderate block of I_{Na}
 - ✓ Moderate block of I_{to}
- ✓ Decreasing the inhomogeneity between
 - ✓ Infarcted area and normal myocardium refractory period
- ✓ Lengthening the ventricular refractory period

→ Decreasing change for phase two re-entry

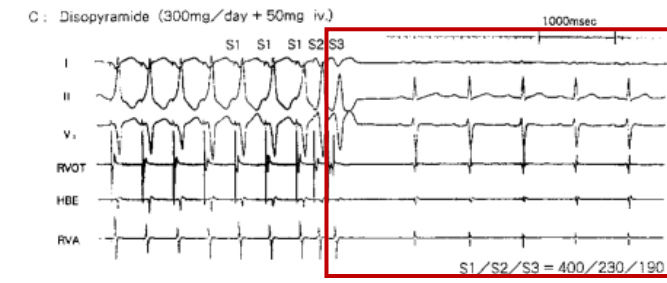
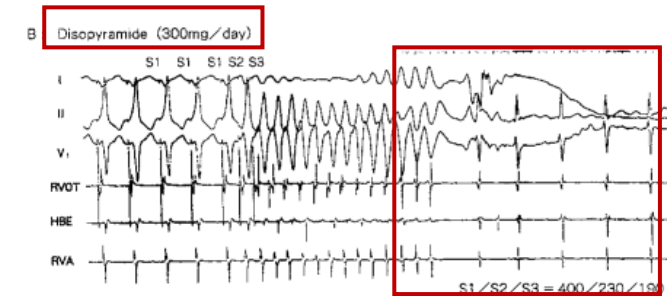
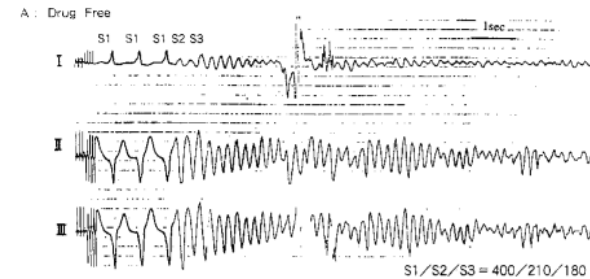
Drug therapy without Quinidine in BrS: Dysopyramide

CASE REPORTS

High Efficacy of Disopyramide in the Management of Ventricular Fibrillation Storms in a Patient with Brugada Syndrome



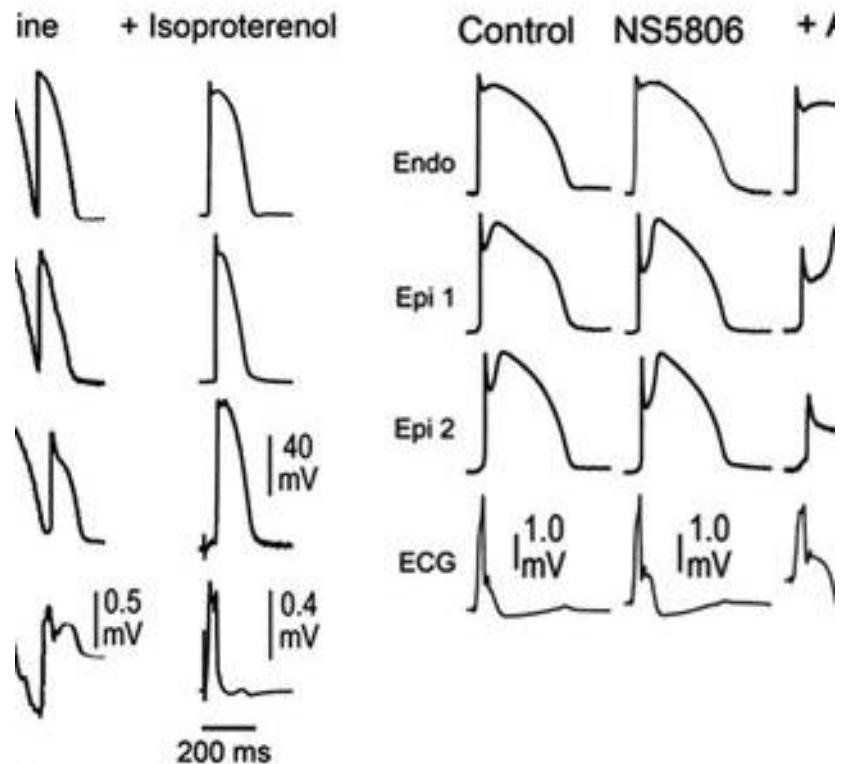
Discrepant Drug Action of Disopyramide on ECG Abnormalities and Induction of Ventricular Arrhythmias in a Patient With Brugada Syndrome



*Chinushi M, et al. J Eletrocardiol. 1997;30:133-136.
Sumi S, et al. PACE. 2010;33:e53-e56.*

Drug therapy without Quinidine in BrS: Beta agonists

Novel Therapeutic Strategies for the Management of Ventricular Arrhythmias Associated with the Brugada Syndrome

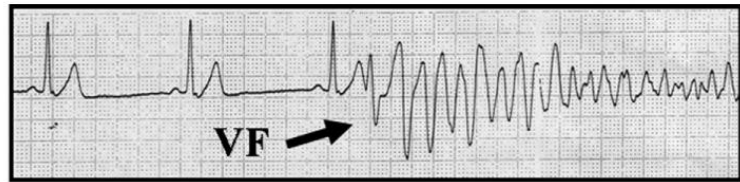


- ✓ Beta adrenergic agonists
- ✓ Phase 1 repolarization
 - ✓ L-type Ca^{2+} channels activate
- ✓ Isoproterenol, denopamine, orciprenaline

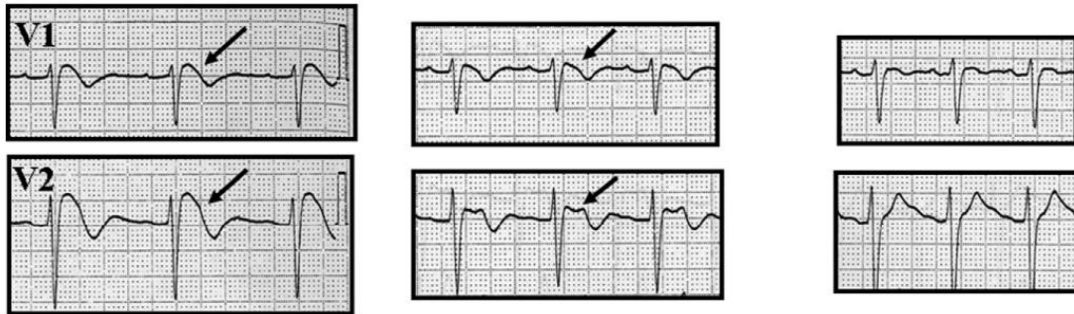
→ Loss of the action potential dome

Drug therapy without Quinidine in BrS: Isoproterenol

Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation



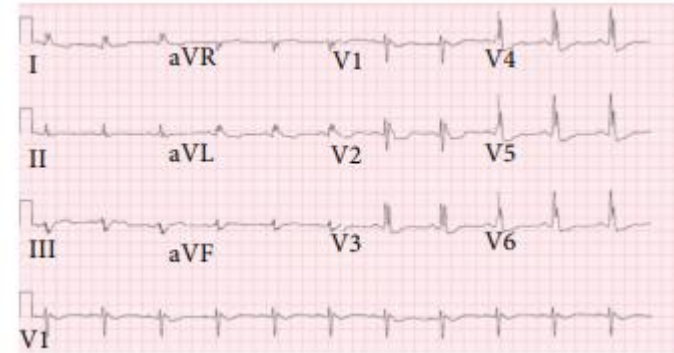
ST elevation \Rightarrow ISP (0.002 μ g/kg/min) \Rightarrow ISP (0.004 μ g/kg/min)



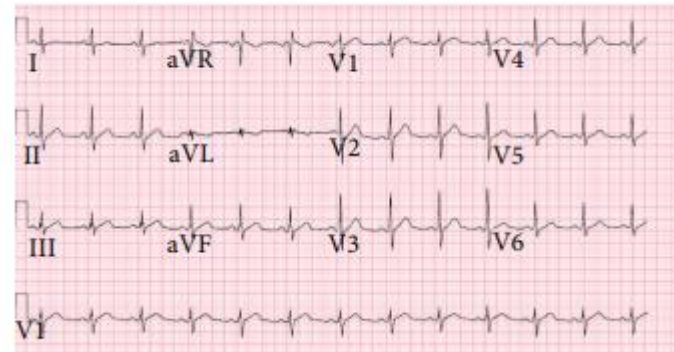
✓ N=67, average FU: 5 years

Case Report

Beneficial Effects of Isoproterenol and Quinidine in the Treatment of Ventricular Fibrillation in Brugada Syndrome



↓ Isoproterenol infusion



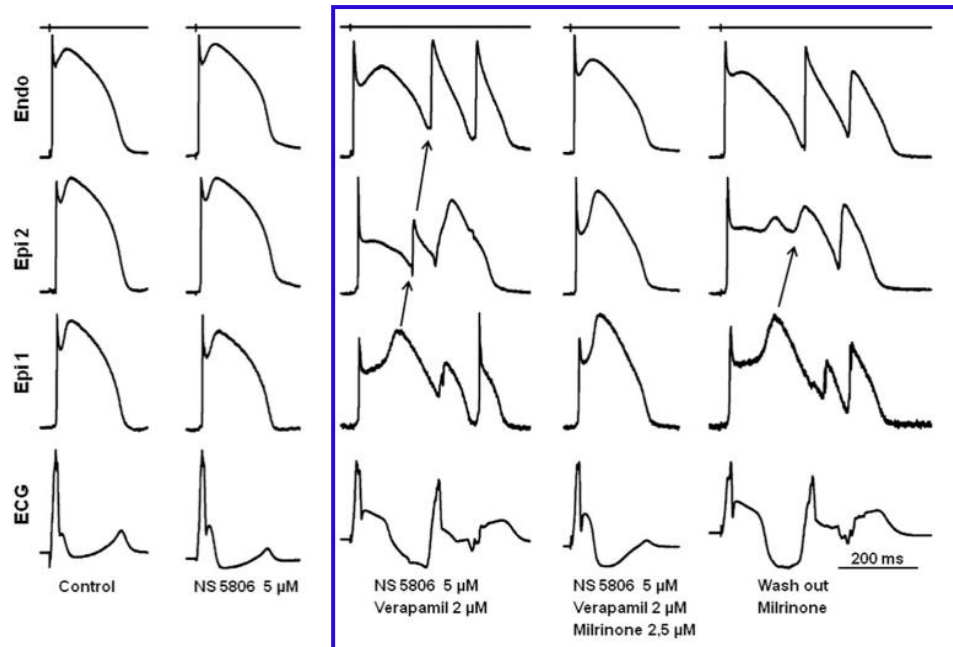
*Dakkak M, et al. Case Rep Cardiol. 2015;2015:753537.
Ohgo T, et al. Heart rhythm. 2007;4:695-700.*

Drug therapy without Quinidine in BrS: PDE III inhibitors

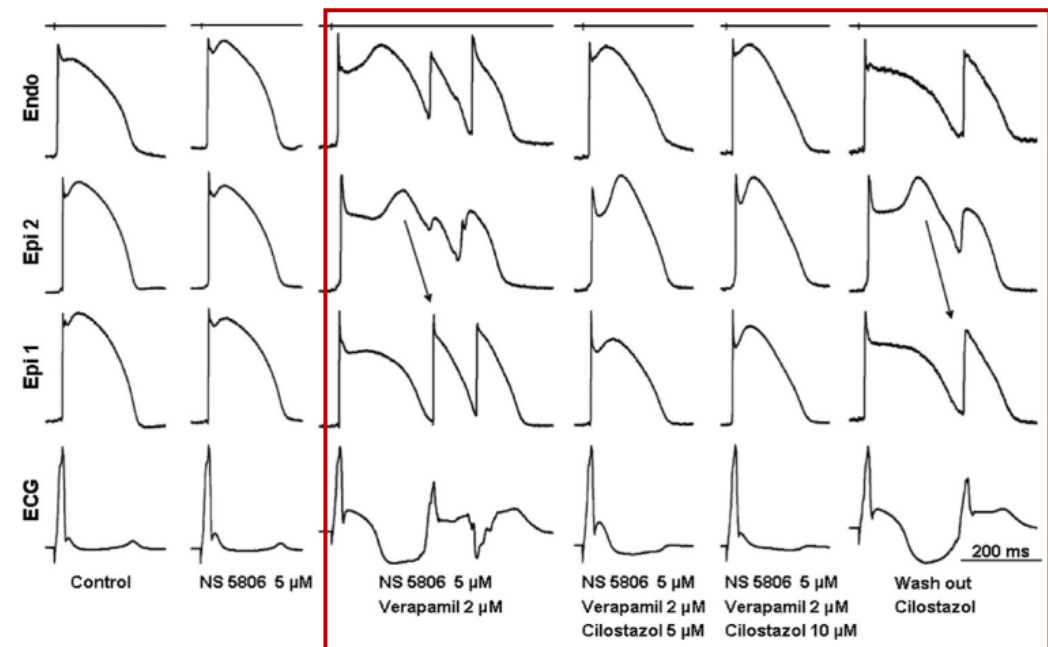
Cellular mechanisms underlying the effects of milrinone and cilostazol to suppress arrhythmogenesis associated with Brugada syndrome

- ✓ Increasing cellular cAMP and L-type calcium currents
- ✓ Counteracts I_{to} → reduction electrical inhomogeneity
 - ✓ Prevent phase two re-entry

✓ Milrinone



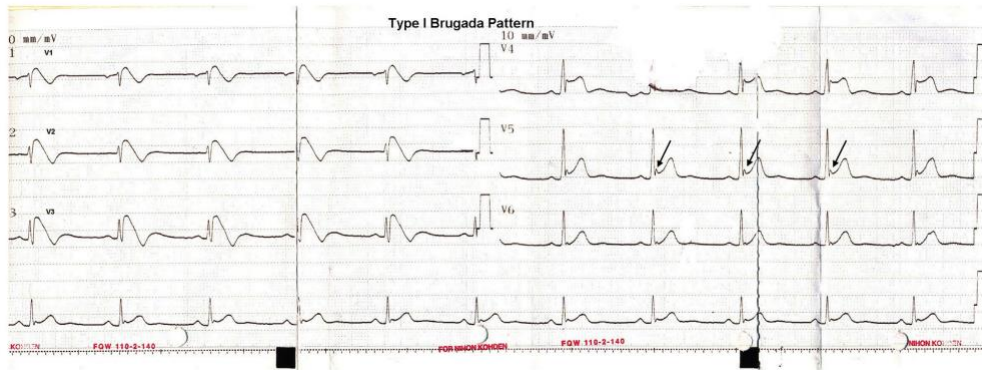
✓ Cilostazol



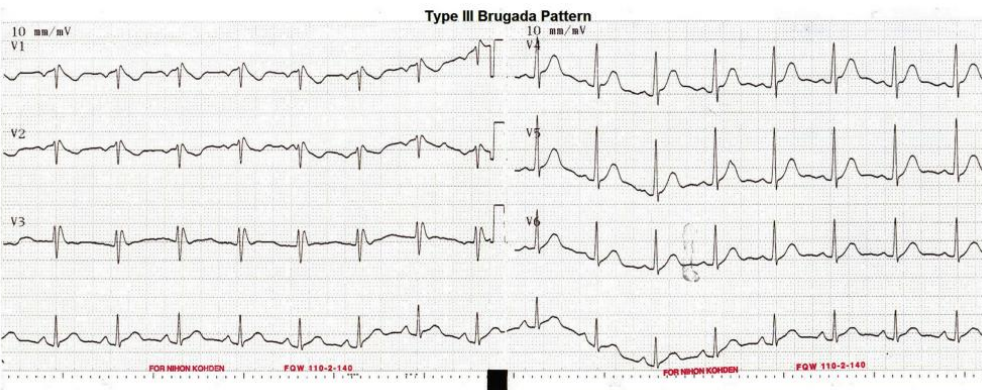
→ Milrinone and Cilostazol reverse repolarization effects, restoring AP duration, normalizing the ECG, and abolishing all arrhythmic activity.

Drug therapy without Quinidine in BrS: PDE III inhibitors

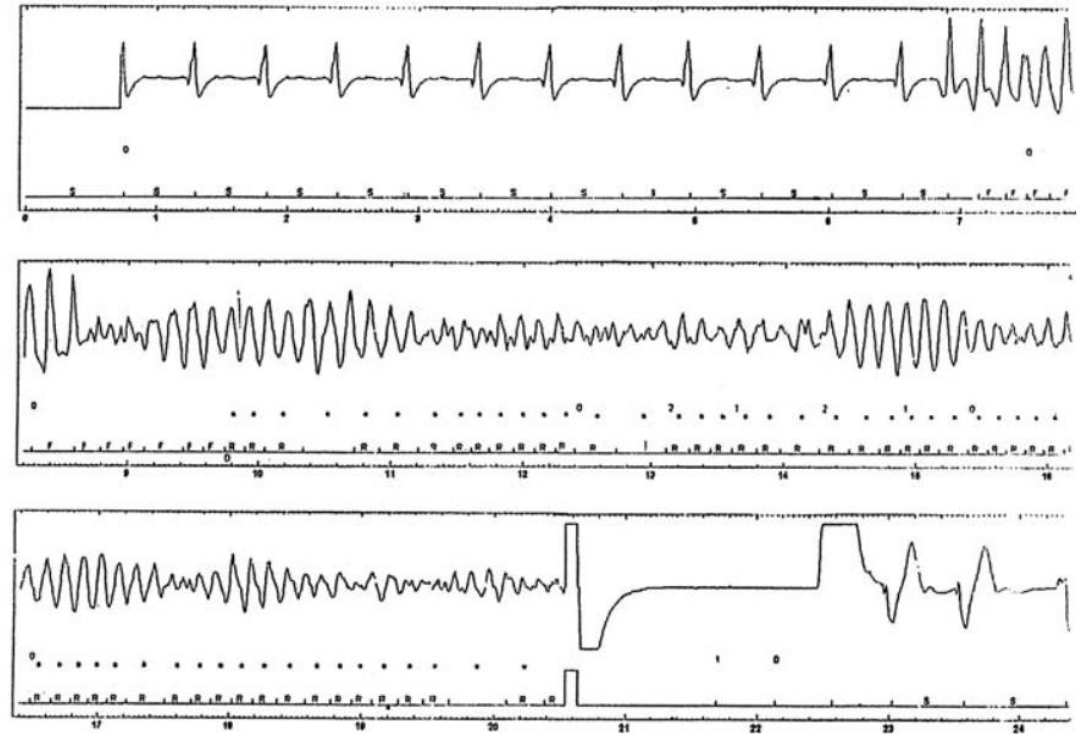
Conversion of Brugada type I to type III and successful control of recurrent ventricular arrhythmia with cilostazol



↓ Cilostazol



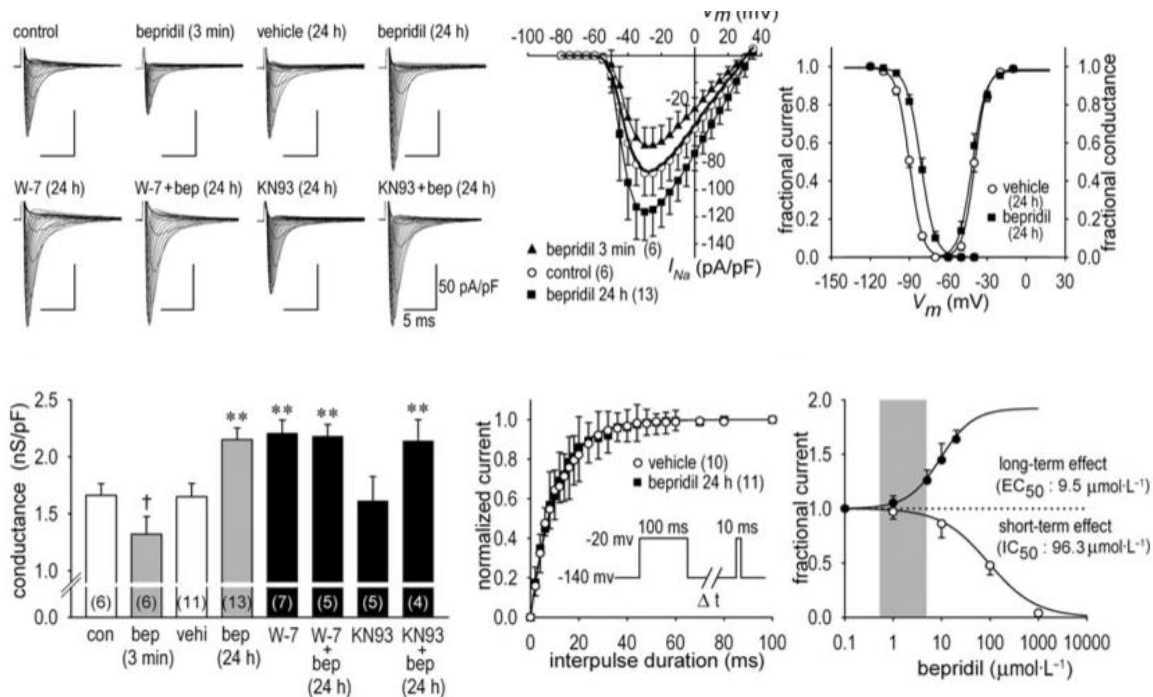
Failure of Cilostazol in the Prevention of Ventricular Fibrillation in a Patient with Brugada Syndrome



Abud A, et al. *J Cardiovasc Electrophysiol.* 2006;17:210-212.
Agac MT, et al. *Arch Cardiovasc Dis.* 2014;107:476-478.

Drug therapy without Quinidine in BrS: Bepridil

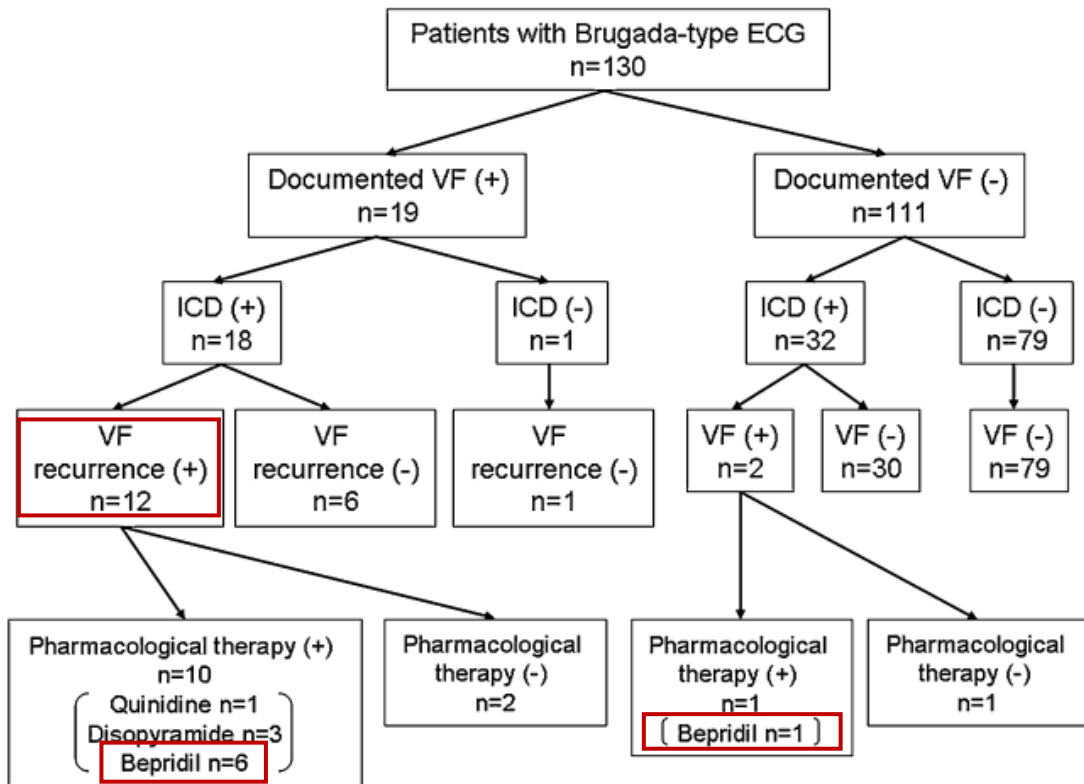
Bepridil up-regulates cardiac Na⁺ channels as a long-term effect by blunting proteasome signals through inhibition of calmodulin activity



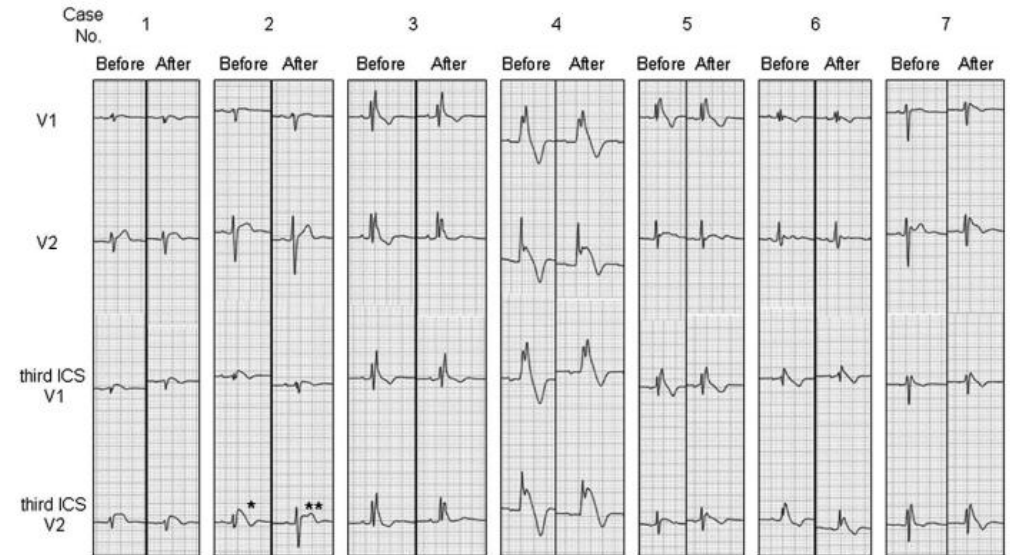
- ✓ Long acting, non-selective, amine calcium channel blocker
- ✓ Antiarrhythmic effect have not been fully characterized
 - ✓ Ito block
 - ✓ Augmentation of I_{na}
 - ✓ Prolongation of QT at slow rates

Drug therapy without Quinidine in BrS: Bepridil

Efficacy of Low-Dose Bepridil for Prevention of Ventricular Fibrillation in Patients With Brugada Syndrome With and Without *SCN5A* Mutation



- ✓ Bepridil treatment=7
 - ✓ *SCN5A* mut (+): 4
 - ✓ *SCN5A* mut (-): 3



- ✓ *SCN5A* mut (+): 1,2,3
- ✓ *SCN5A* mut (-): 4,5,6,7

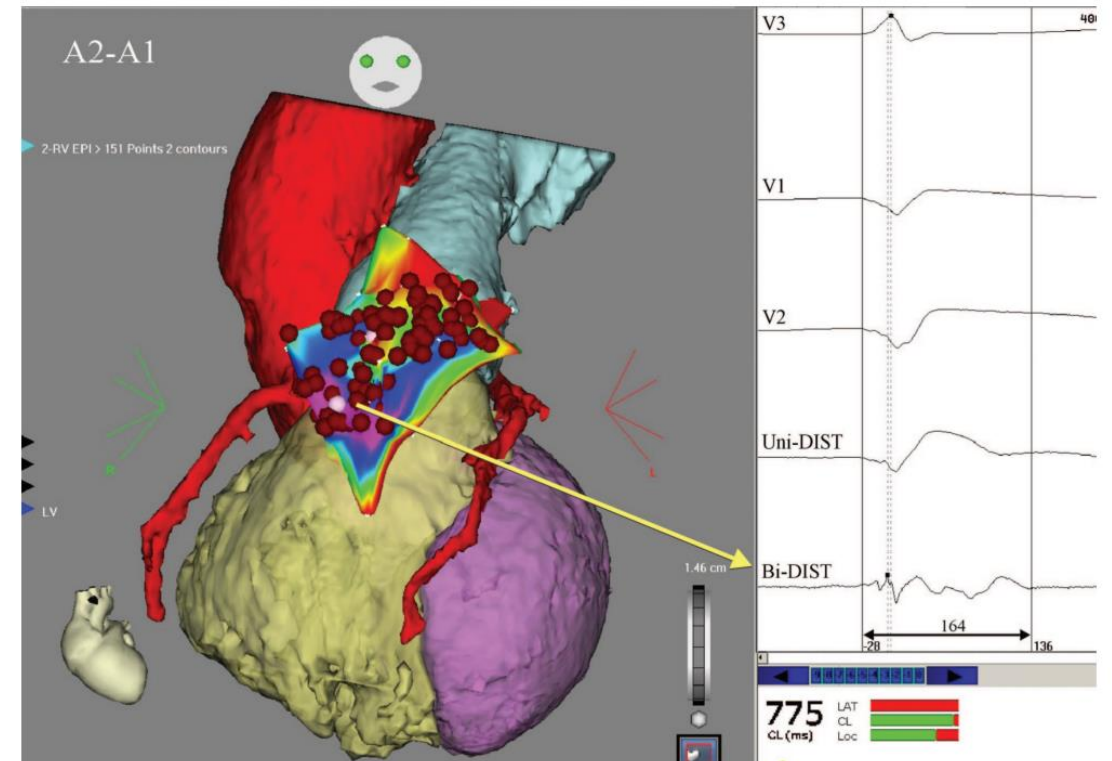
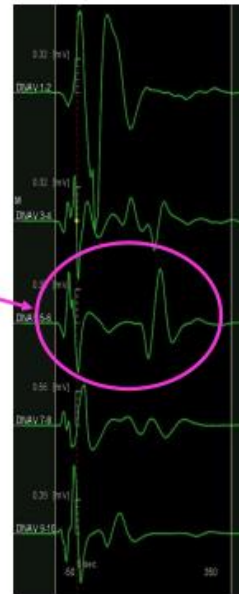
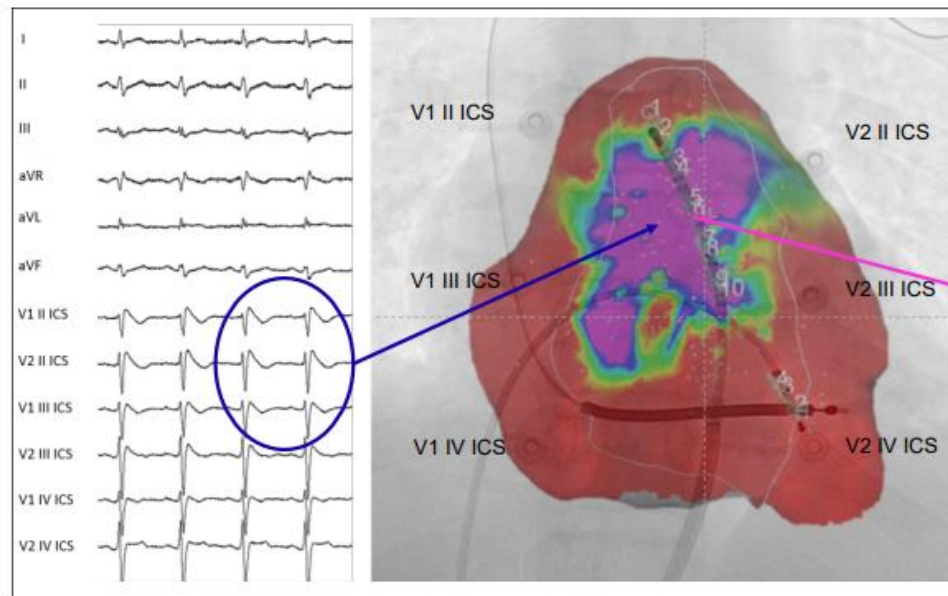
Drug therapy without Quinidine in BrS: Summary

Drugs	Dosing	Storm	VF prophylaxis	Asymptomatic BrS
Quinidine	HQ 600-900 mg/d, BSQ 1-2.25 g/d	*** ***	*** ***	**
Disopyramide	300-600 mg/d		*	
Isoproterenol	0.003 ± 0.003 ug/kg/min	***		
Denopamine	30 mg/d		*	
Orciprenaline	IV bolus 0.5 mg, followed by IV drip 3.3 ug/min	*		
Cilostazol	200 mg/d		*	
Bepridil	100-200 mg/d		*	

* = evidence from case reports, ** = evidence from small cohort studies, *** = evidence from several large cohort studies

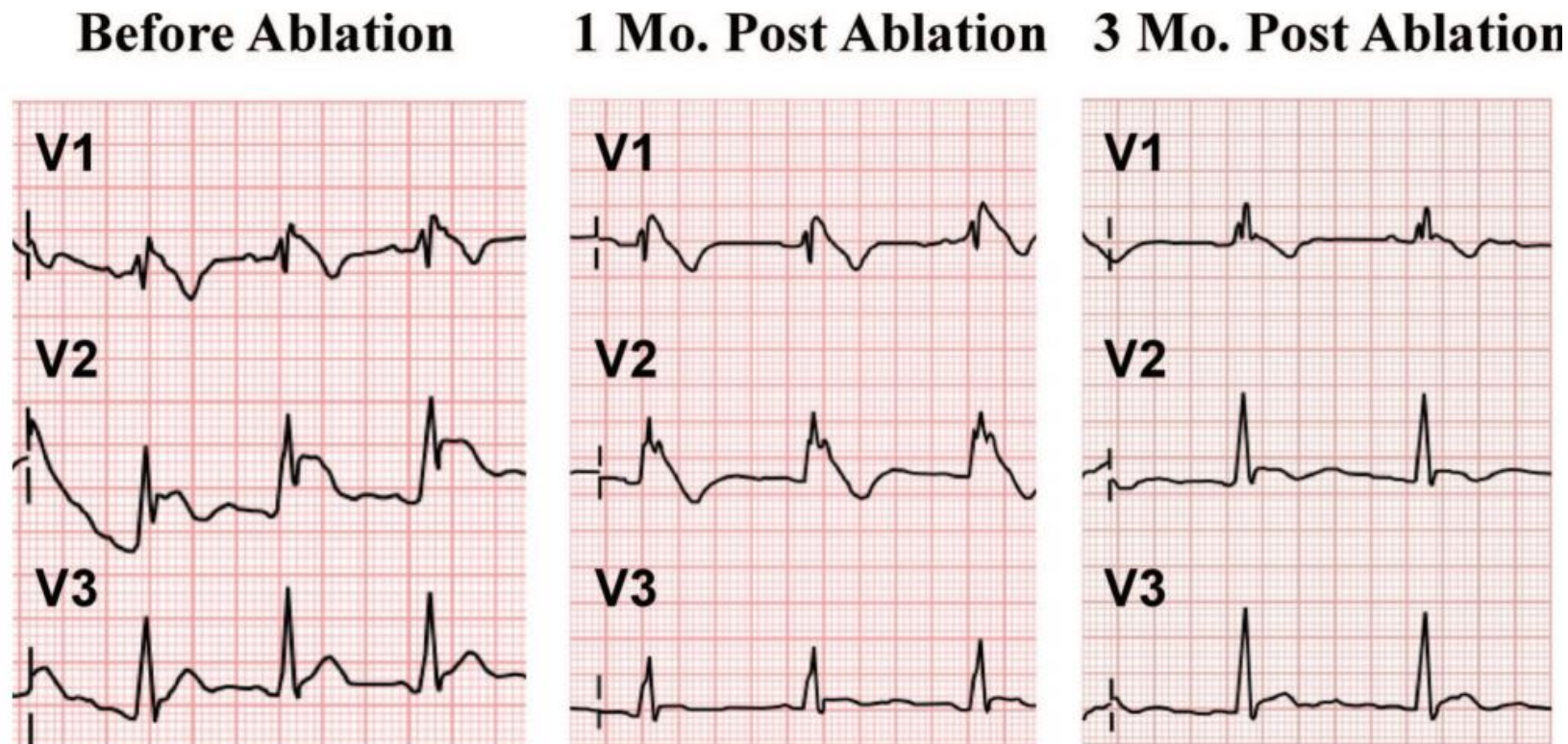
Radiofrequency catheter ablation in BrS

Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium



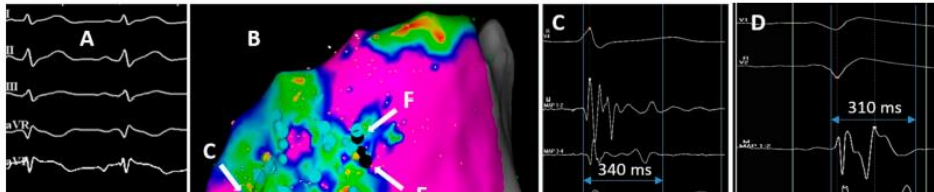
Radiofrequency catheter ablation in BrS

Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

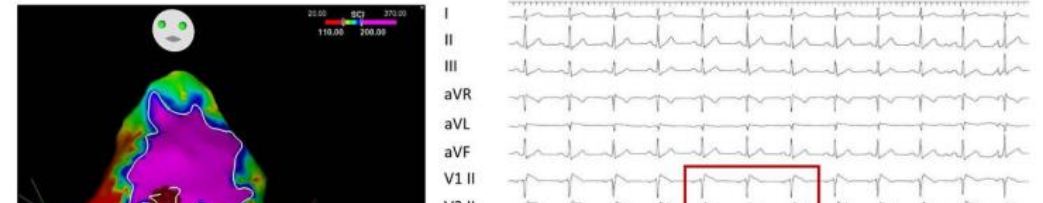


Radiofrequency catheter ablation in BrS

Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation



Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome



Recommendations

Catheter ablation of triggering PVCs and/or RVOT epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy.

Class

Level

IIa

C



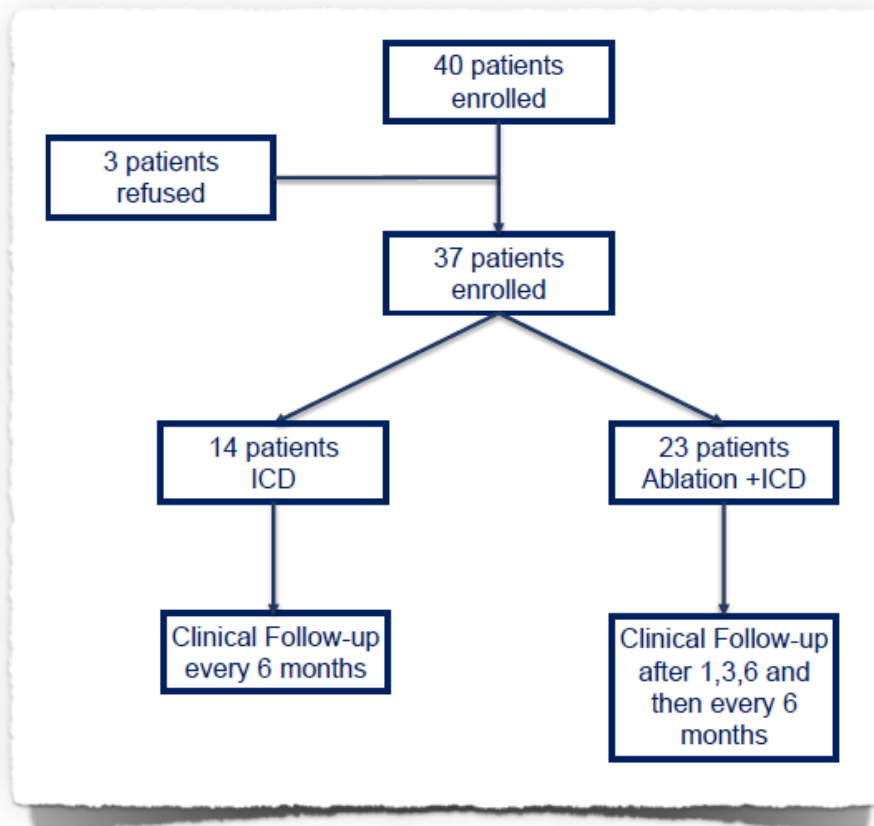
- ✓ **Brugada ECG pattern disappeared after RFCA**

Pappone C, et al. *Circ Arrhythm Electrophysiol.* 2017;10:e005053.
Brugada J, et al. *Circ Arrhythm Electrophysiol.* 2015;8:1373-1381.

Radiofrequency catheter ablation in BrS

✓ Prospective RCT

STUDY DESIGN



- Prospective, single-centered study since September 2017.
- A projected 150 patients enrolled and randomized to receive ablation or not in a 2:1 fashion (Ablation+ICD 105 patients vs ICD only arm 45 patients).
- All patients were then clinically followed up every 6 months for the ICD only group and after 1, 3 and 6 months then every 6 months for the ablation and ICD group.

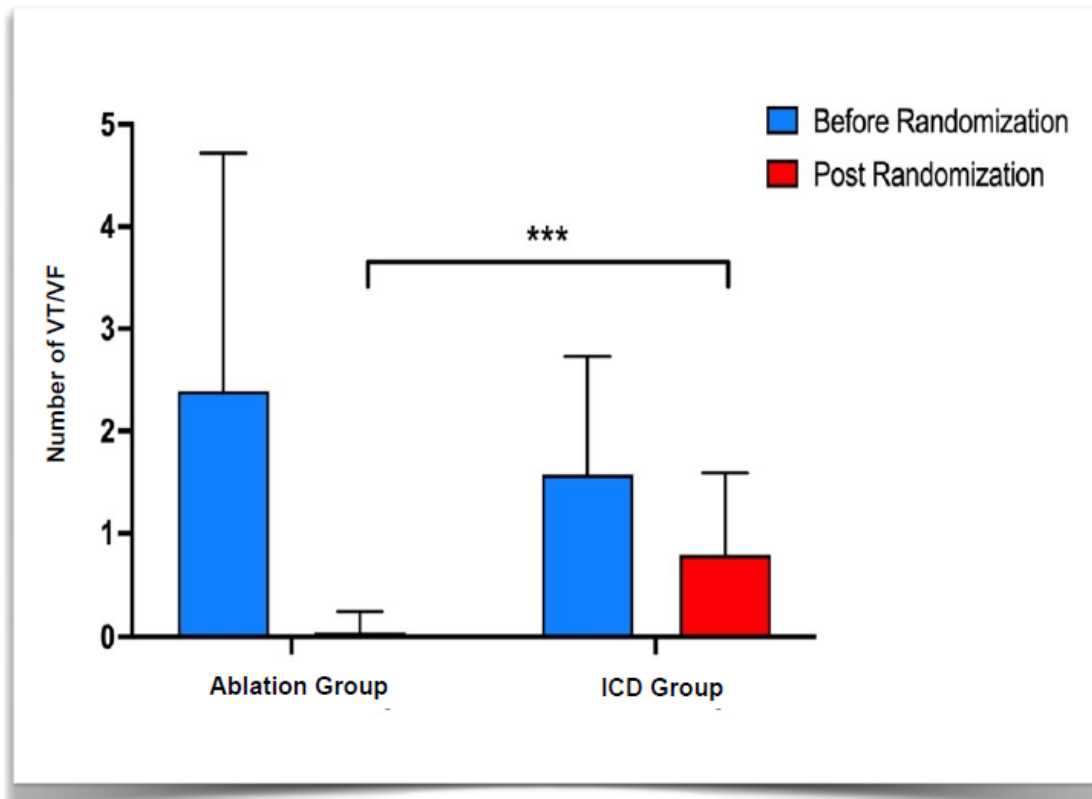
Radiofrequency catheter ablation in BrS

✓ Prospective RCT

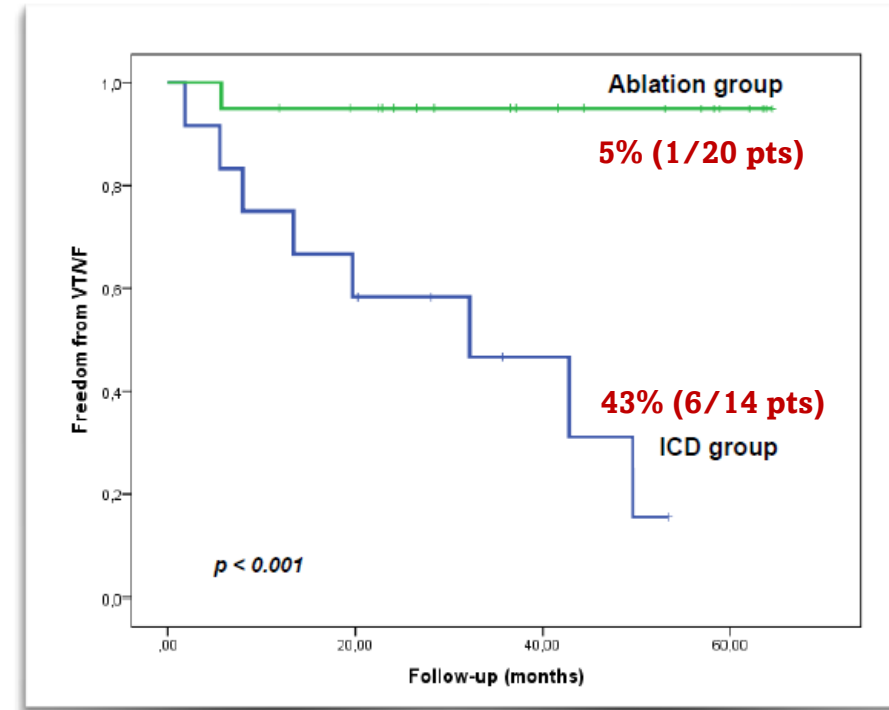
	Overall (n=37)	Ablation (n=23)	ICD (n=14)	p-value
Age, <u>years</u> ± SD	43.3±12.5	43.5±13.7	41.4±10.7	0.65
Male gender, n (%)	27 (72.9)	16 (69.6)	11 (71.4)	0.62
Spontaneous type 1 ECG, n (%)	19 (51.4)	13 (56.5)	6 (42.8)	0.51
Family history of SD, n (%)	27 (72.9)	16 (69.6)	11 (71.4)	0.71
Previous atrial arrhythmias, n (%)	12 (32.4)	7 (30.4)	5 (35.7)	1.00
Inducible at EPS, n (%)	26 (70.2)	16 (69.5)	10 (71.4)	1.00
SCN5A mutations, n (%)	13 (35.1)	8 (34.8)	5 (35.7)	1.00
Previous Aborted SD (%)	20 (54.0)	12 (52.2)	8 (57.1)	0.71
Appropriate shocks pre RFA, mean ± SD (range)	2.1 ± 1.9 (1-10)	2.5 ± 2.4 (1-10)	1.6 ± 1.3 (1-4)	0.15

Radiofrequency catheter ablation in BrS

✓ VT/VF burden before and after randomization



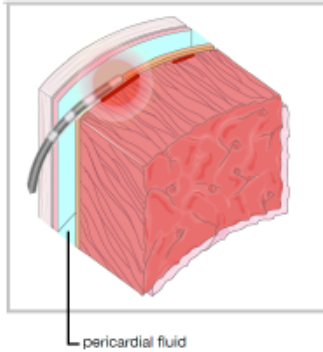
✓ VT/VF recurrences



✓ Follow-up: mean 31 months

Radiofrequency catheter ablation in BrS

✓ Complications



- After the procedure **2 patients** had pericarditis with pericardial effusion:
 - ➔ 1 solved with colchicine and NSAIDs
 - ➔ 1 required pericardiocentesis



- **7 patients (19%)** had major complication due to ICD

➤ 2 (29%) Inappropriate shocks due to SVT

ICD reprogramming

➤ 4 (57%) ICD Lead malfunction

ICD extraction

➤ 1 (14%) Device infection

Radiofrequency catheter ablation in BrS

✓ Limitations

Experienced EP team



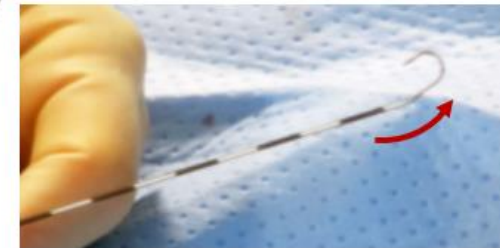
3x 8Fr
1x 6Fr A



VF Induction during EPS in RVOT

HD mapping & ablation catheter

Steerable sheath



Tuohy needle floppy wire



BrS type I ECG during Ajmaline stimulation

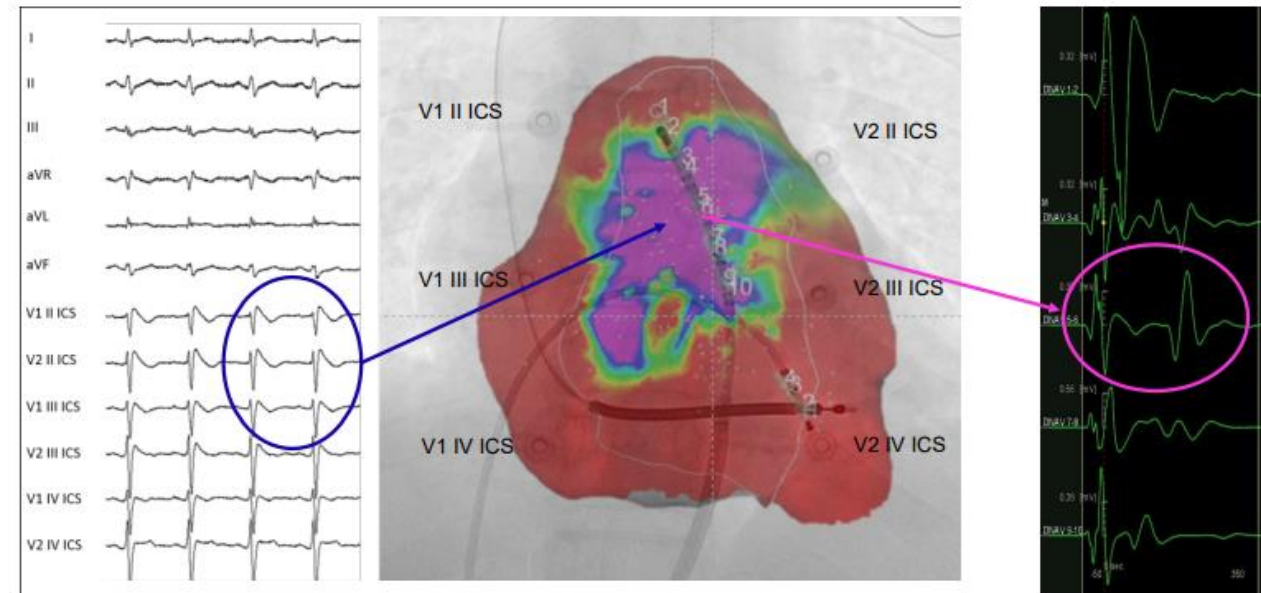
Conclusion

✓ Drug therapy without quinine

Drugs	Dosing	Storm	VF prophylaxis	Asymptomatic BrS
Quinidine	HQ 600-900 mg/d, BSQ 1-2.25 g/d	*** ***	*** ***	**
Disopyramide	300-600 mg/d		*	
Isoproterenol	0.003 ± 0.003 ug/kg/min	***		
Denopamine	30 mg/d		*	
Orciprenaline	IV bolus 0.5 mg, followed by IV drip 3.3 ug/min	*		
Cilostazol	200 mg/d		*	
Bepidil	100-200 mg/d		*	

* = evidence from case reports, ** = evidence from small cohort studies, *** = evidence from several large cohort studies

✓ RFCA for BrS



Thank you for your attention.



인류 건강과 의학발전을 선도하는 미래 의료의 새로운 중심