Genetik Aritmik Sendromlarda Gelişmeler

BRUGADA SENDROMU

Dr. Sabri Demircan
İstanbul Bilim Üniversitesi
Kardiyoloji Anabilim Dalı

AFD atriyal fibrilasyon derneği
7. Atriyal Fibrilasyon Zirvesi 2018
9 - 10 Şubat 2018
Kempinski Hotel The Dome
Belek, Antalya

Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome

A Multicenter Report

İlk bulgu 1986'da

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD*†

Aalst, Belgium and Barcelona, Spain

Objectives. The objectives of this study were to present data on eight patients with recurrent episodes of aborted sudden death unexplainable by currently known diseases whose common clinical and electrocardiographic (ECG) features define them as having a distinct syndrome different from idiopathic ventricular fibrillation.

Background. Among patients with ventricular arrhythmias who have no structural heart disease, several subgroups have been defined. The present patients constitute an additional subgroup with these findings.

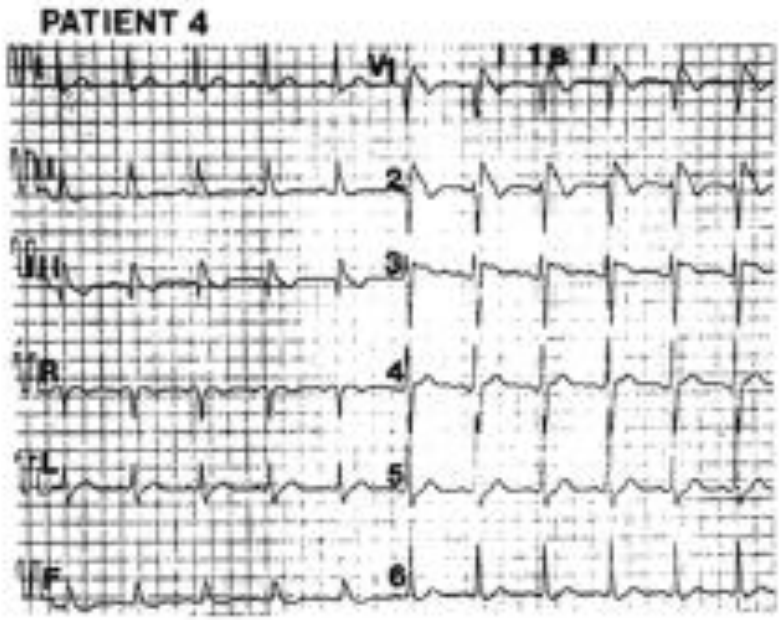
Methods. The study group consisted of eight patients, six male and two female, with recurrent episodes of aborted sudden death. Clinical and laboratory data and results of electrocardiography, electrophysiology, echocardiography, angiography, histologic study and exercise testing were available in most cases.

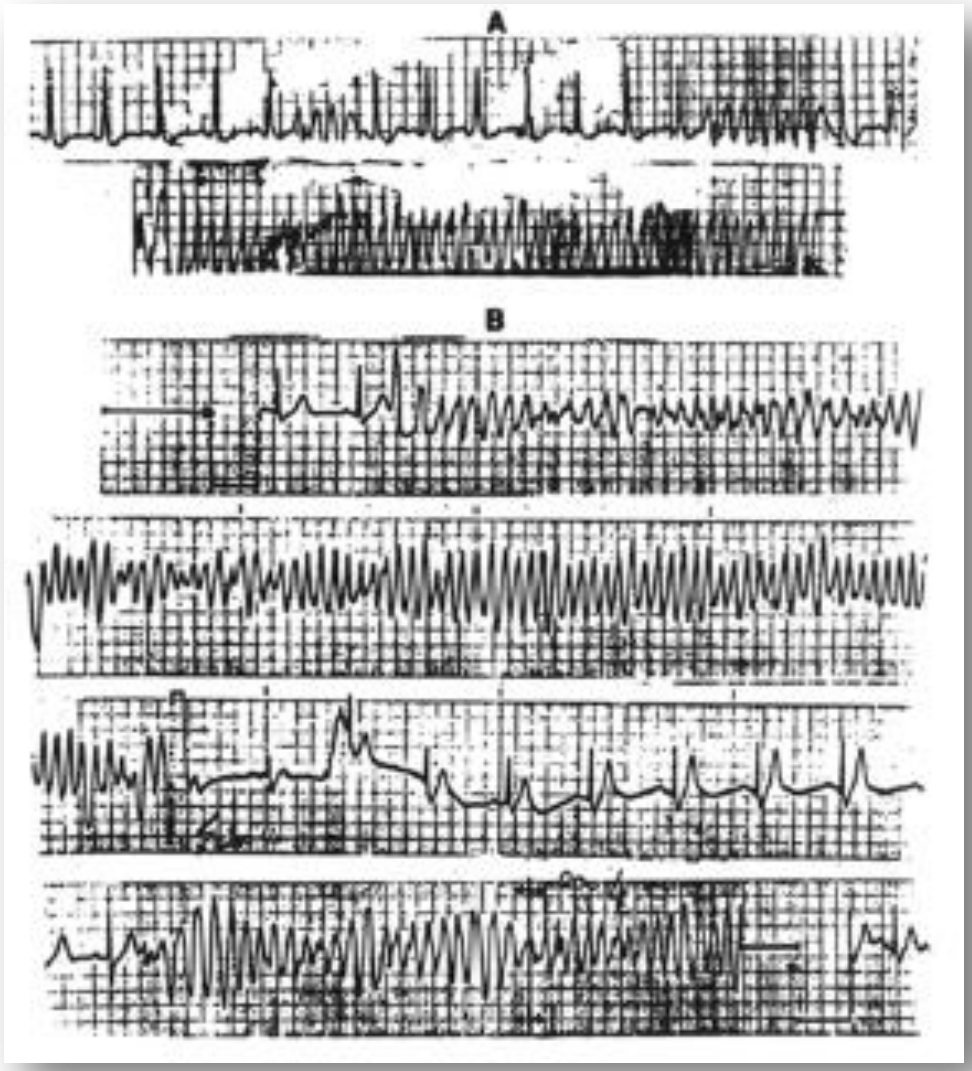
Results. The ECG during sinus rhythm showed right bundle branch block, normal QT interval and persistent ST segment elevation in precordial leads V_1 to V_2–V_3 not explainable by electrolyte disturbances, ischemia or structural heart disease. No histologic abnormalities were found in the four patients in whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic ventricular tachycardia initiating after a short coupled ventricular extrasystole. A similar arrhythmia was initiated by two to three ventricular extrastimuli in four of the seven patients studied by programmed electrical stimulation. Four patients had a prolonged HV interval during sinus rhythm. One patient receiving amiodarone died suddenly during implantation of a demand ventricular pacemaker. The arrhythmia of two patients was controlled with a beta-adrenergic blocking agent. Four patients received an implantable defibrillator that was subsequently used by one of them, and all four are alive. The remaining patient received a demand ventricular pacemaker and his arrhythmia is controlled with amiodarone and diphenylhydantoin.

Conclusions. Common clinical and ECG features define a distinct syndrome in this group of patients. Its causes remain unknown.

(J Am Coll Cardiol 1992;20:1391–6)

1 ve 4. hastanın telemetri kayıtları





Brugada P, Brugada J. J Am Coll Cardiol 1992;20:1391-6.

Brugada Sendromu

- Yapısal olarak normal kalp
- Genç bireyler
- Sağ prekordiyal leadlerde ST yüksekliği
- Ani ölüm riskinde artış
- Genel populasyonda: 1 – 5 / 10,000
- Tüm ani ölümlerin %4'ünden sorumlu
- Yapısal kalp hastalığı olmayanlarda ani ölümlerin %20'sinden sorumlu

Klinik Özellikler

- Açıklanamayan ani ölüm
- Senkop, bilinç kaybı
- Agonal noktürnal respirasyonlar
- Olguların çoğu erkek (8:1)
- Genellikle semptomlar 3 – 4. dekatta
- Ortalama tanı veya ani ölüm yaşı 40±20
- Bildirilen olgu yaşları; 2 gün – 84 yaş.

Antzelevitch C et al. Circulation. 2005;111:659-670.
Chen and Priori. JACC 2008;51:1176–80

Kalıtım

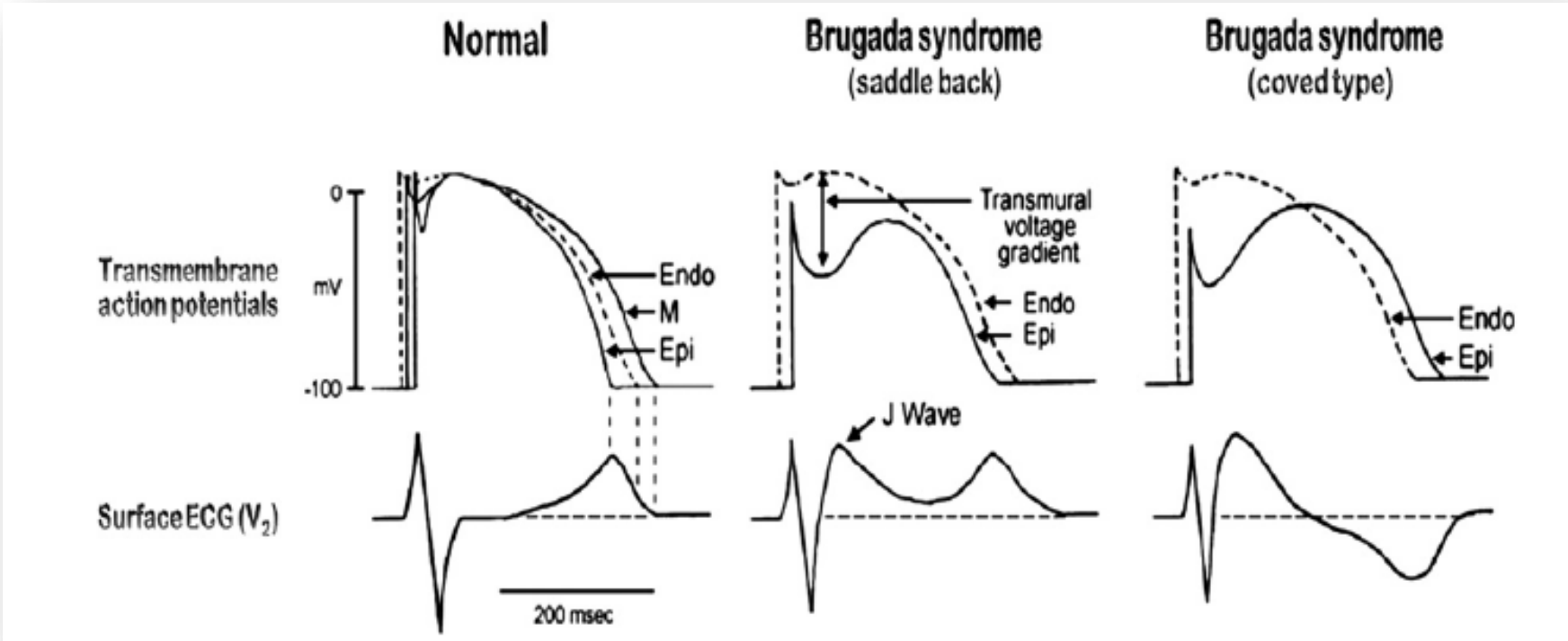
- Sendromla ilişkili gen olan SCN5A'da (kromozom 3) 60 farklı mutasyon
- Otozomal dominant

Table 1. Identified Genes Linked to BS

Variant	Gene	Ionic current	Functional effect	Inheritance	% of carriers among BS patients
BS1	SCN5A	I_{Na}	Loss of function	Autosomal dominant	11–18%
BS2	GPD1-L	I_{Na}	Loss of function	Autosomal dominant	<1%
BS3	CACNA1c	I_{Ca}	Loss of function	Autosomal dominant	<1%
BS4	CACNB2	I_{Ca}	Loss of function	Autosomal dominant	<1%
BS5	SCN1B	I_{Na}	Loss of function	Autosomal dominant	<1%
BS6	KCNE3	I_{to}	Gain of function	Autosomal dominant	<1%
BS7	SCN3B	I_{Na}	Loss of function	Autosomal dominant	<1%
BS8	MOG1	I_{Na}	Loss of function	Autosomal dominant	<1%
BS9	KCNE5	I_{to}	Gain of function	Autosomal dominant	<1%
BS10	KCND3	I_{to}	Gain of function	Autosomal dominant	<1%

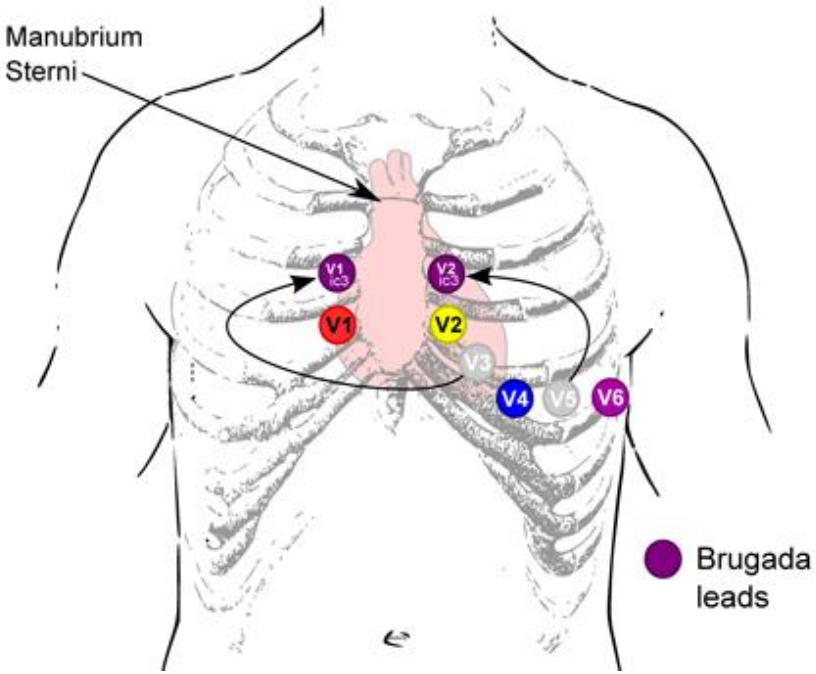
BS, Brugada syndrome.

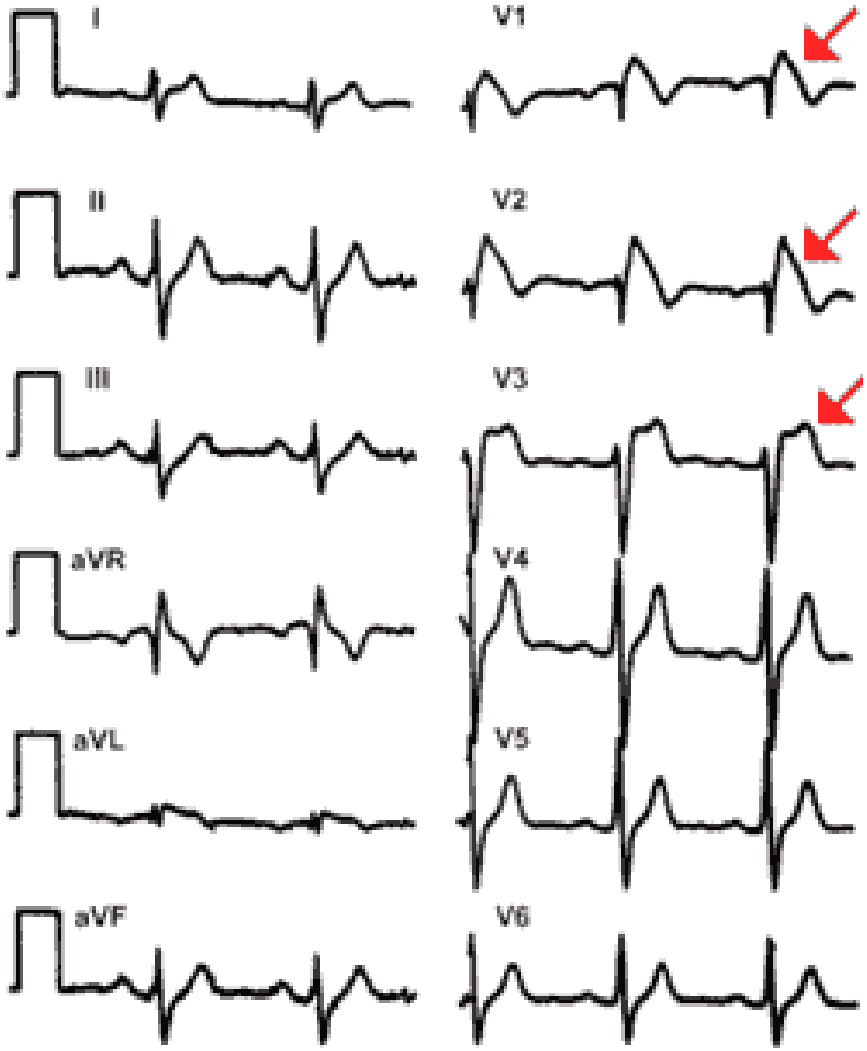
Berne P, Brugada J. Circ J 2012; 76: 1563 – 1571


Normal
Brugada syndrome
(saddle back)
Brugada syndrome
(coved type)
Transmembrane
action potentials
0
mV
-100
Endo
M
Epi
Transmural
voltage
gradient
Endo
Epi
Endo
Epi
J Wave
Surface ECG (V2)
200 msec

Brugada Sendromu

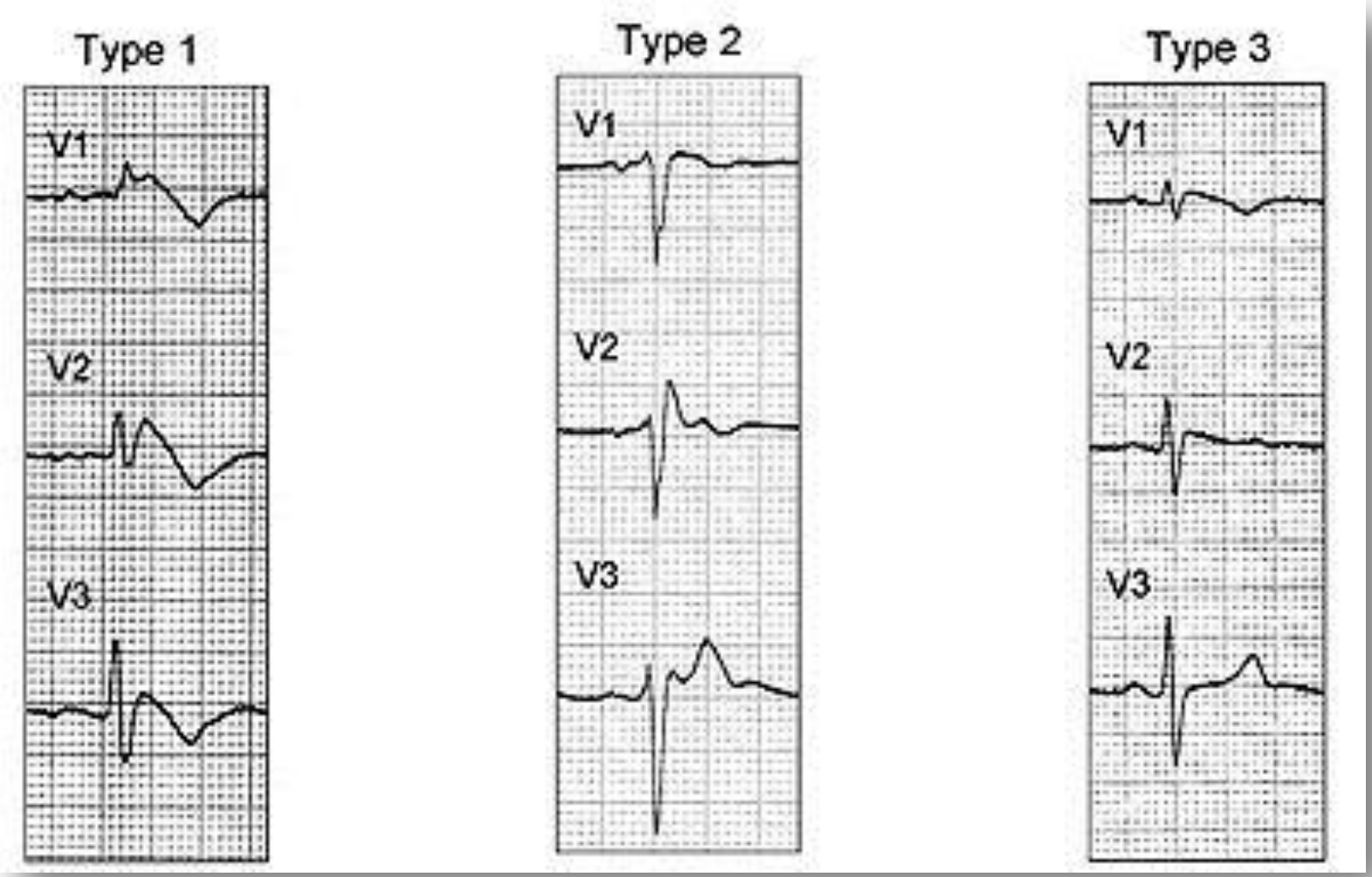
EKG





Brugada Sendromu

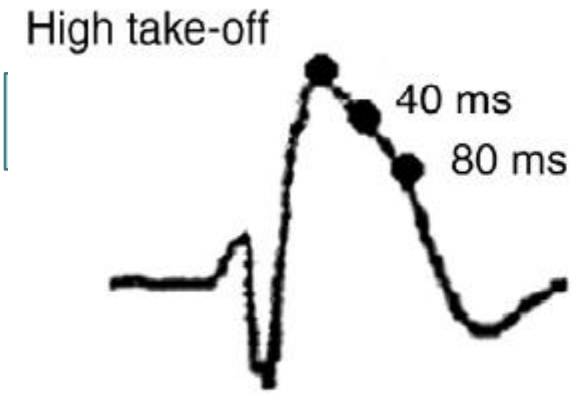
EKG



Brugada Sendromu

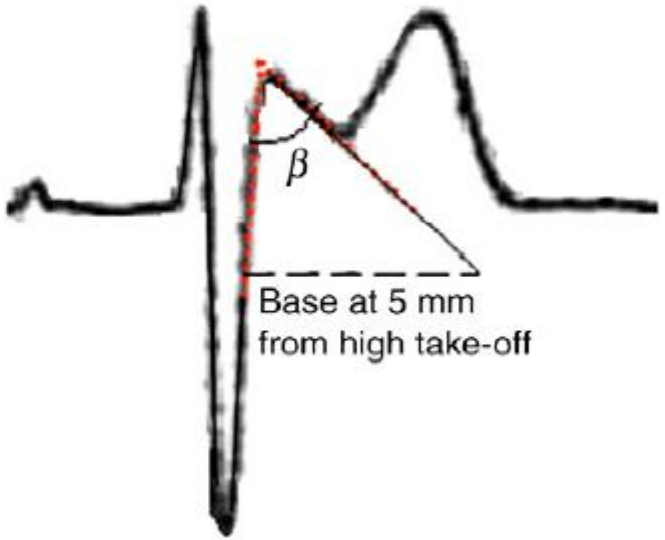
EKG

Type 1: coved pattern



- QRS son kısmı ≥2 mm, ve downslope, açıklılığı aşağı bakan ST
- r' yok
- Yüksek pik J noktasının karşılığı değil
- ST pik noktasından 40 ms sonrasına kadarki azalma ≤4 mV
- ST pik > ST 40 msn> ST 80 msn
- ST den sonra simetrik – T dalgası
- QRS süresi RBBB'den daha uzun, V1 – V6 uyumsuz

Type 2: saddle-back pattern

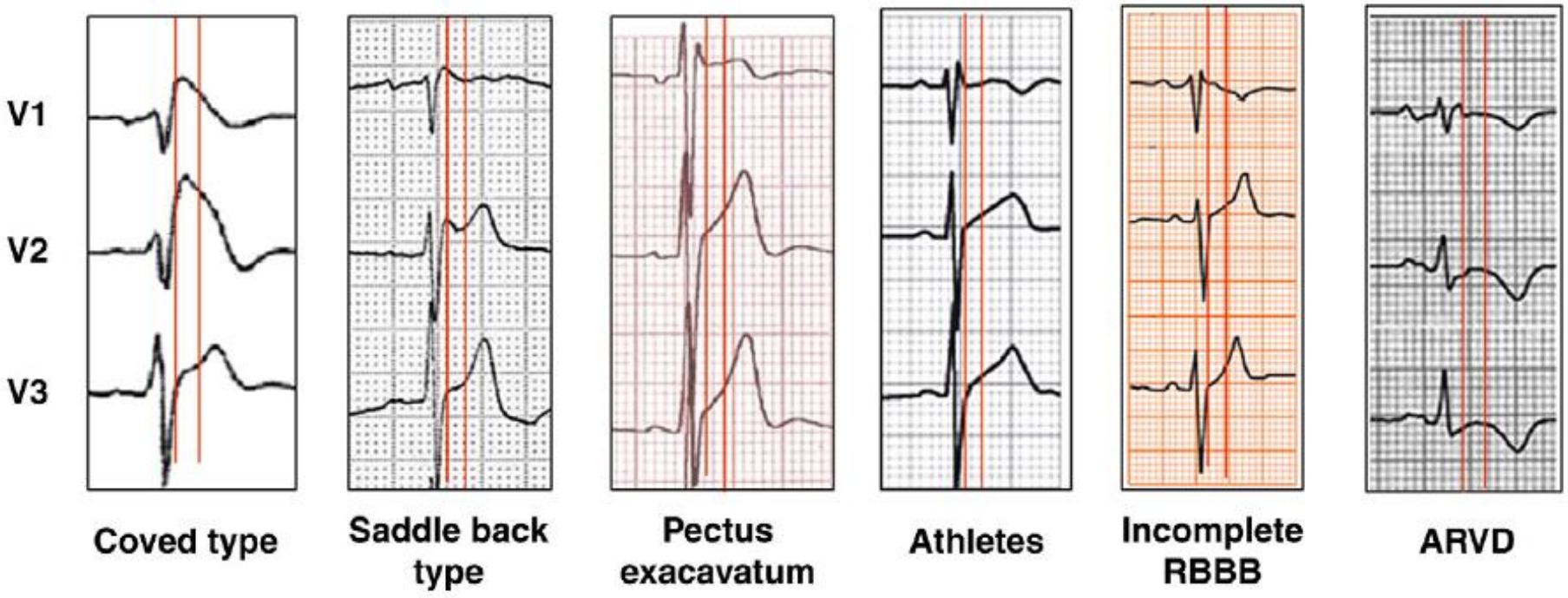


- QRS sonunda r'≥2 mm
- r' inen bacağı ST başına denk gelir
- Minimum ST yükselmesi ≥0.5mm
- ST sonrası + T dalgası
- r' nün beta açısı var ve üçgen süresi >3,5mm
- r'-nin süresi diğer r' yapan durumlardan uzundur ve V1-v6 uyumsuzdur

Journal of Electrocardiology 2012;45:433 - 42

Brugada Sendromu

EKG



Journal of Electrocardiology 2012;45:433 - 42

Brugada tipi EKG bulgusuna yol açan durumlar

- Ateş
- Antiaritmik ilaçlar
  - Na kanal blokerleri
    - Sınıf 1c: flekainid, pilsicianid, propafenon
    - Sınıf 1a: Ajmaline, procainamide, disopiramid, cibenzoline
  - Ca kanal blokerleri: Verapamil
  - Beta-blokerler
- Antianjinal ilaçlar
  - Ca kanal blokerleri: nifedipin, diltiazem
  - Nitratlar: İsosorbit dinitrat, nitrogliserin
  - K kanal açıcılar: Nicorandil
- Psikotropik ilaçlar
  - Trisiklik antidepresanlar: Amitriptin, nortriplin, desipramin, klomipramin
  - Tetrasiklik antidepresanlar: maprotilin
  - Fenotiazin: perfenazin, cyamemazine
  - SSRI:fluoksetin
- Diğer ilaçlar
  - Dimenhidrinat
- Kokain, alkol intoksikasyonu
- Ciddi iskemi
- Elektriksel kardiyoversiyon
- Elektrolit bozuklukları
  - Hiperkalemi
  - Hiperkalsemi

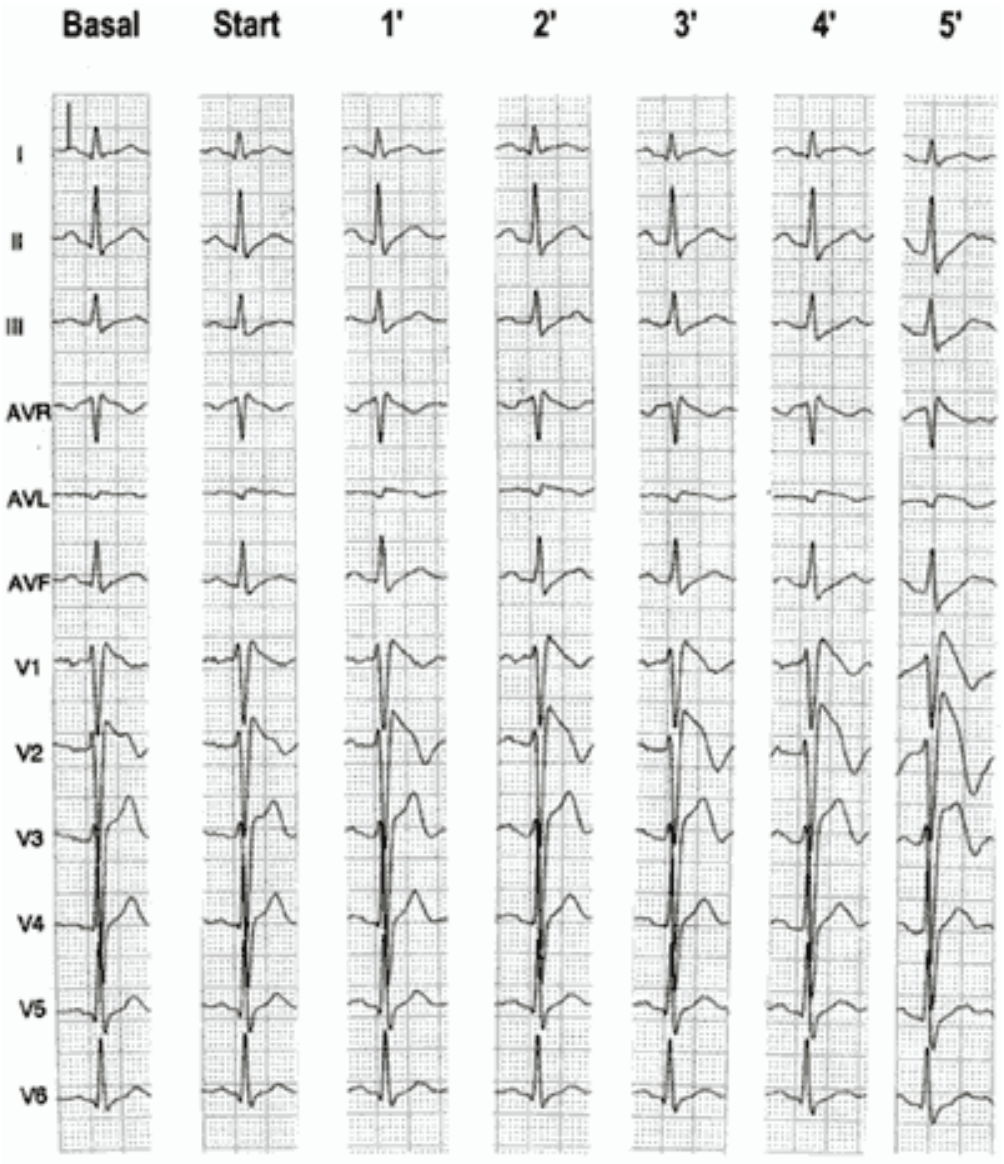
Antzelevitch C et al. Circulation 2005;111:659-670

Tipik EKG bulgusuna ulaşma yolları

- Farklı zamanlardaki EKG
- Egzersiz sonrası dinlenme anında EKG
- Ağır yemek sonrası EKG “Tam dolu mide testi”
- V1-V3 derivasyonlarının 3. veya 2. interkostal aralığa taşınması
- Sodyum kanal blokerleri ile ilaç testi

Miyazaki T et al. J Am Coll Cardiol 1996;27:1061–70
Antzelevitch C. Pacing Clin lectrophysiol 2006; 29: 1130 – 59.
HRS/EHRA/APHRS Expert Consensus Statementon the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. Heart Rhythm. 2013;10:1932-63

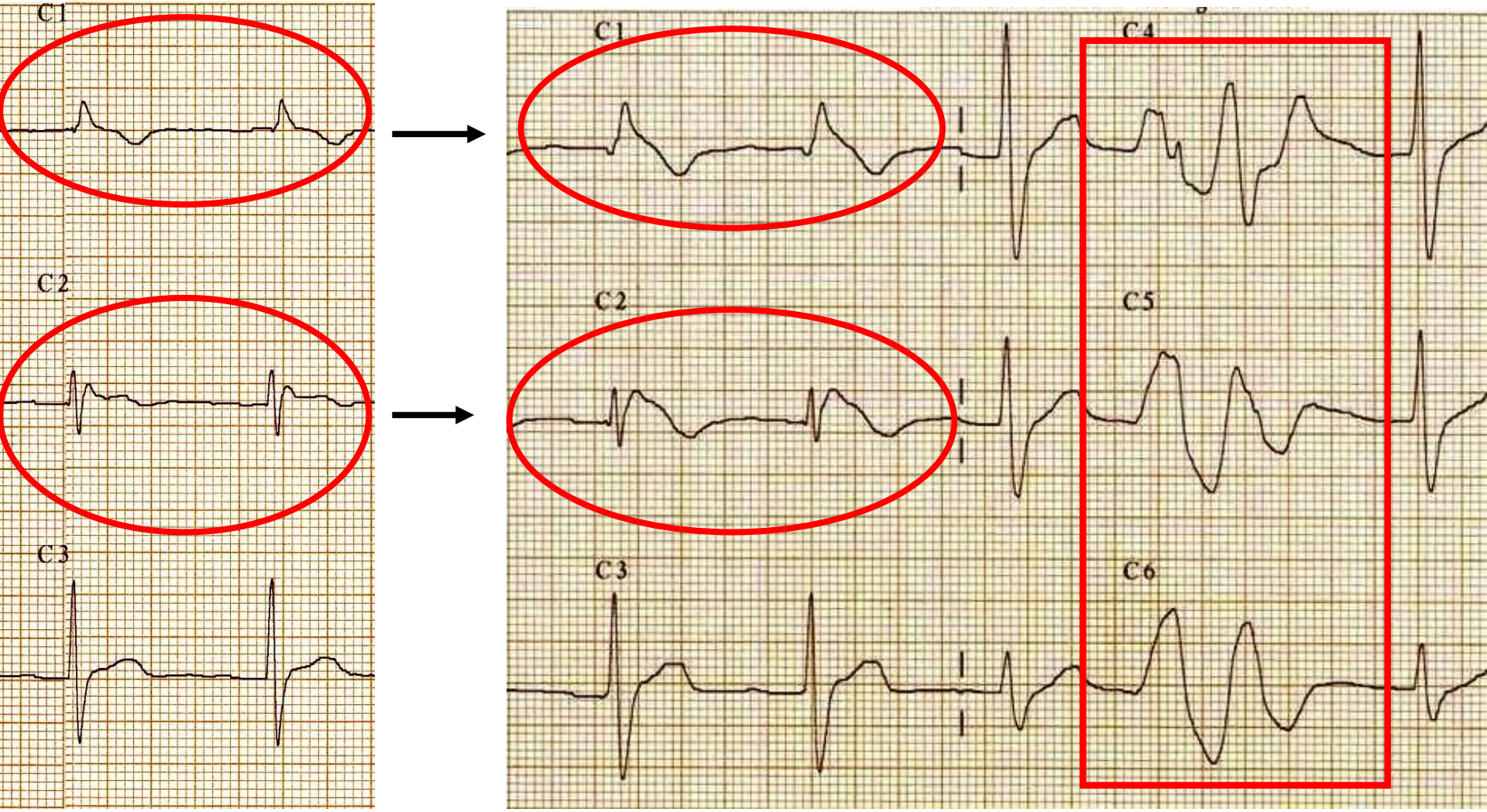
Ajmalin Testi



Ajmalin Testi

Bazal

IV Ajmalin



Brugada Sendromu

Klinik Özellikler

- Semptomlar: Asemptomatik, senkop, AKÖ (genellikle uykuda)
- FM: Normal
- Soygeçmiş: AKÖ için güçlü öykü
- EKG: Brugada hastaları için en önemli test
  - Tipik bulguları oluşturmak için provokasyon gerekebilir
  - ST elevasyonu, RBBB
- Görüntüleme: Genellikle yapısal hastalık yok
- Stres testleri: Genellikle egzersizle oluşmayan semptoma ve EKG

Brugada Sendromu

Klinik Özellikler

- Semptomlar:
  - Senkop
  - Ani kardiyak ölüm
  - PVT/VF
  - Nöbet
  - Çarpıntı
  - Agonal solunum
  - Göğüste rahatsızlık hissi
- Semptom zamanlaması:
  - Uyku, istirahat, ağır yemek sonrası, vagal uyarı

HRS/EHRA/APHRS Expert Consensus Statementon the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. Heart Rhythm. 2013;10:1932-63

Brugada Sendromu

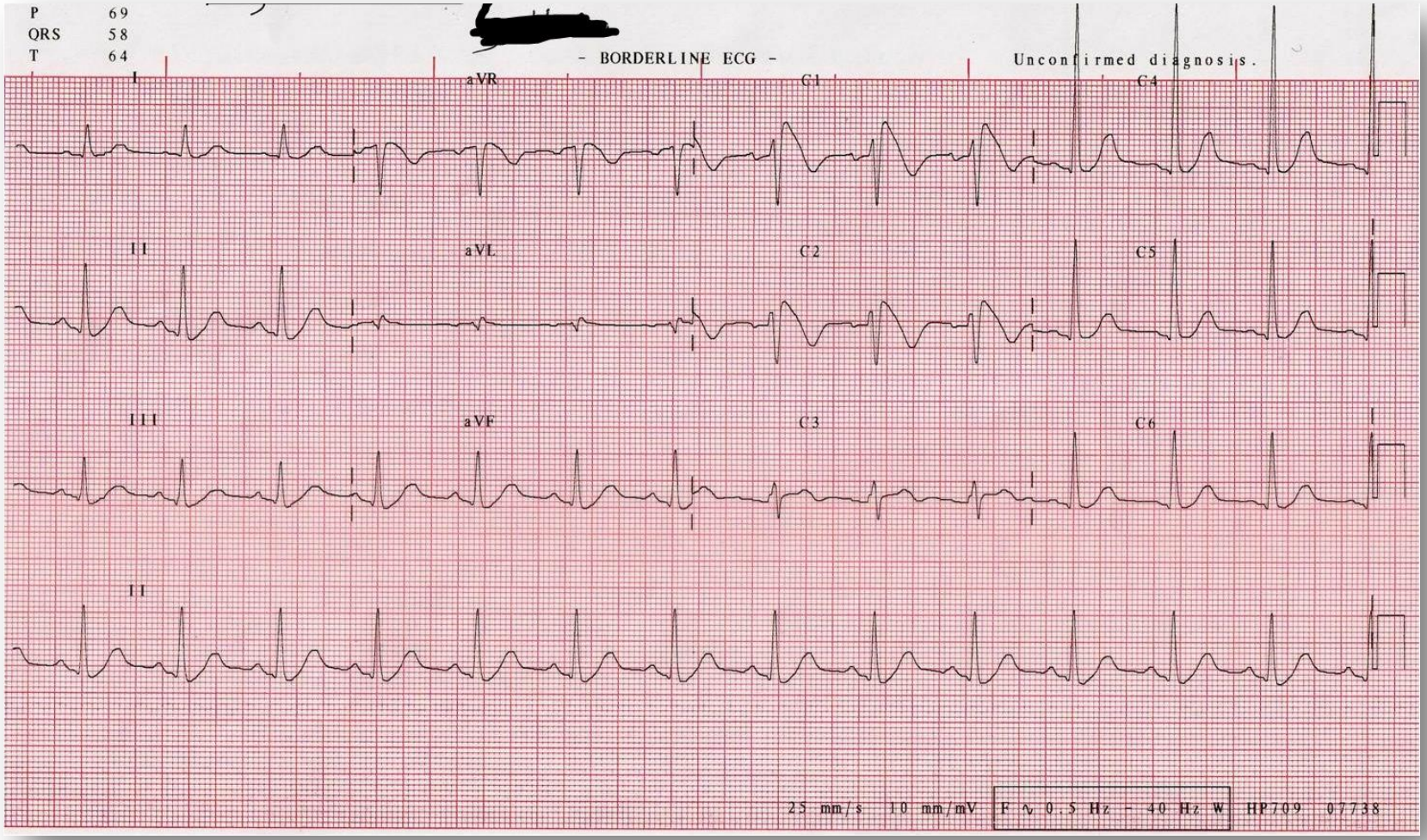
Riskin belirlenmesi

- Ailede AKÖ öyküsü
- Spontan Tip 1 EKG
- EPS: Ventriküler aritmi indüklenmesi
- Genç yaş
- Belirli gen mutasyonları

Antzelevitch C et al. Circulation. 2005;111:659-670.
Chen and Priori. JACC 2008;51:1176–80
Antzelevitch C. Pacing Clin Electrophysiol. 2006;29:1130–59.

Brugada Sendromu

Riskin belirlenmesi



Brugada Sendromu

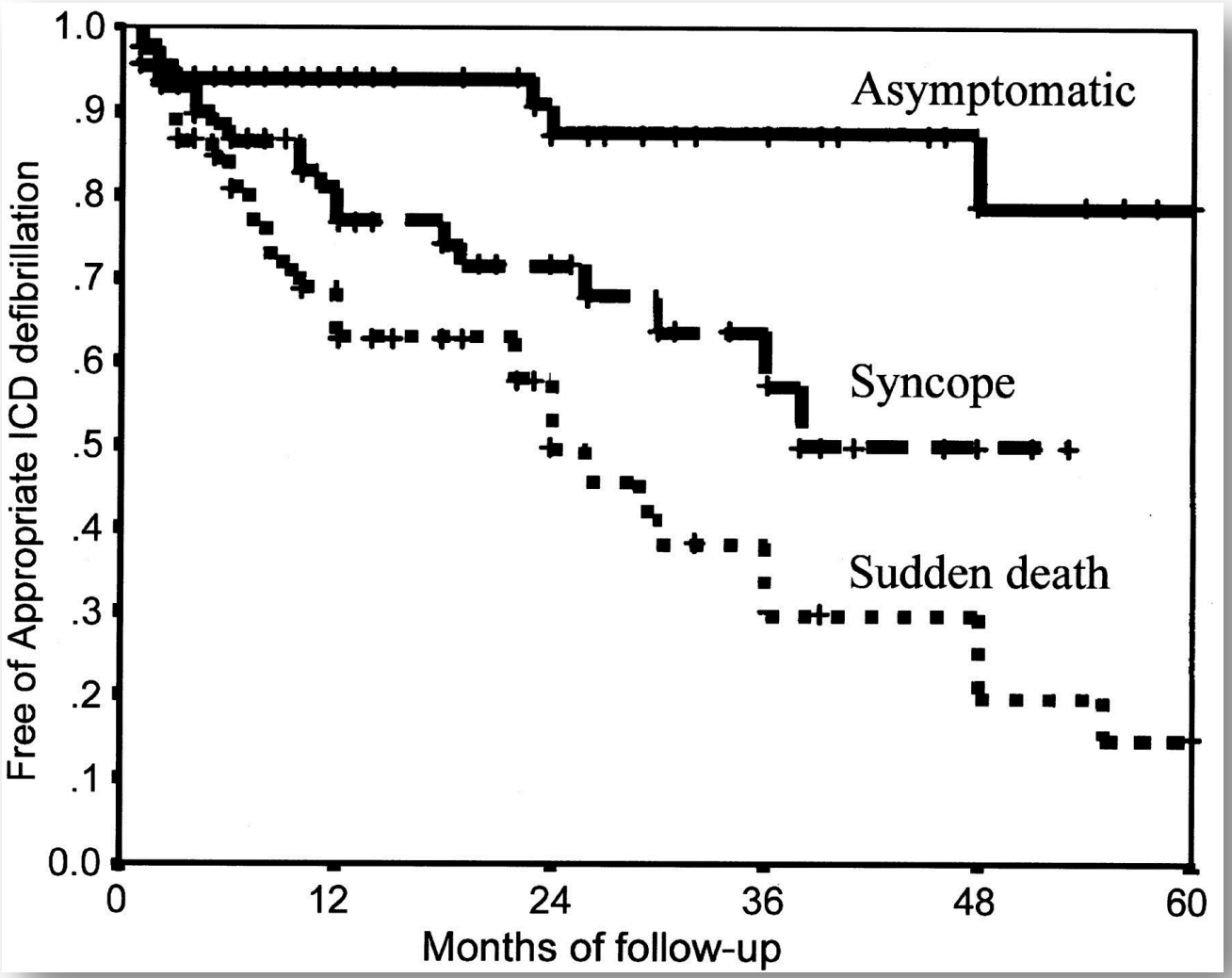
Riskin belirlenmesi

- Resüsite edilmiş ani kardiyak ölüm / Ventriküler taşikardi
  - 48-84 ay izlemde ventriküler aritmi tekrarı %17-62
- Senkop
  - 24-36 ay izlemde ventriküler aritmi tekrarı % 6-19

Antzelevitch C et al. Circulation. 2005;111:659-670.
Chen and Priori. JACC 2008;51:1176–80
Antzelevitch C. Pacing Clin Electrophysiol. 2006;29:1130–59.
Berne P, Brugada J. Circ J 2012; 76: 1563 – 1571

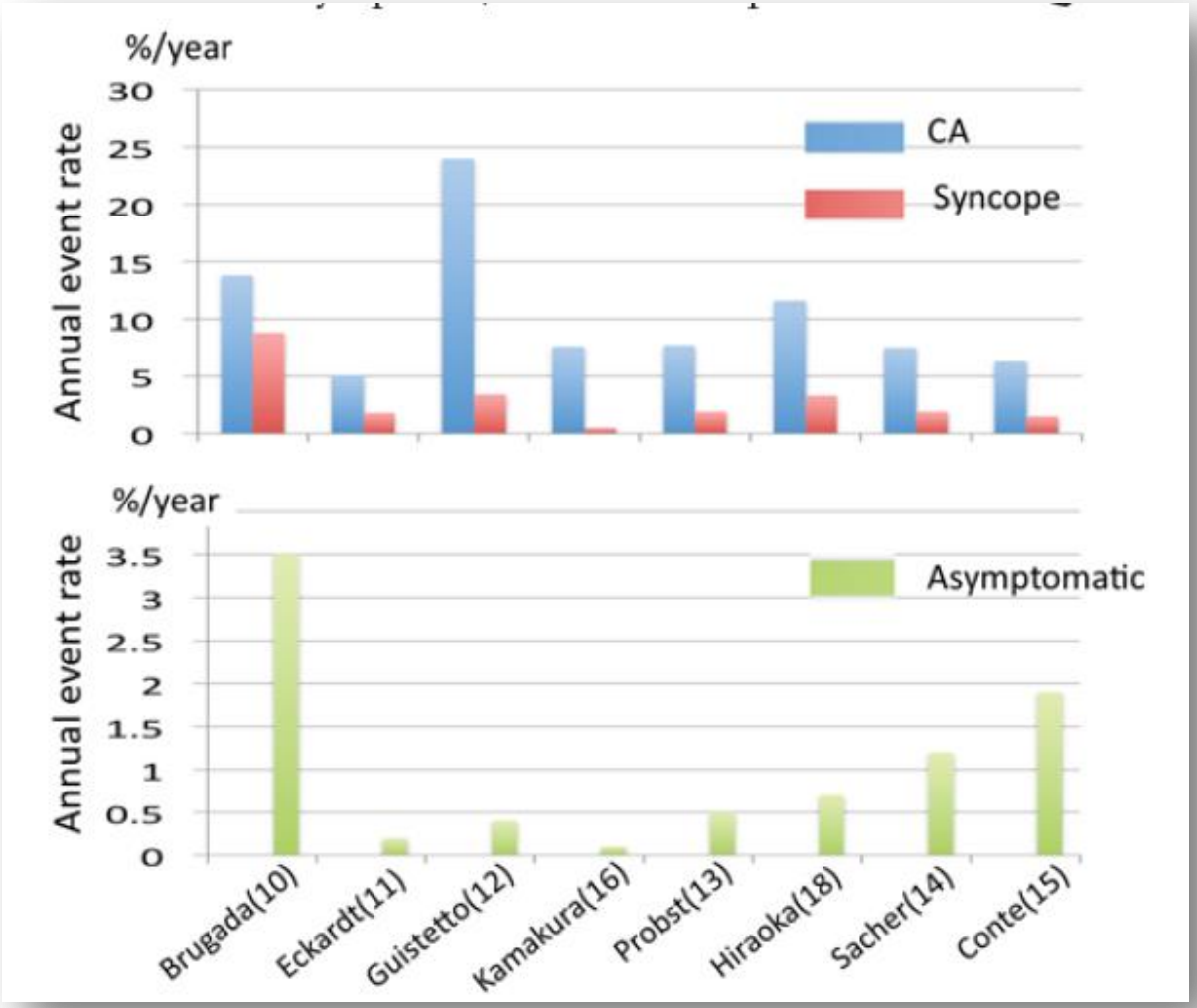
Brugada Sendromu

Riskin belirlenmesi



Brugada Sendromu

Riskin belirlenmesi



Aizawa Y. Journal of Atrial Fibrillation 2016

Brugada Sendromu

Riskin belirlenmesi

- Aile öyküsü?
- Brugada serisi
  - 267 hasta 33 ± 31 ay izlem
  - 16 (%6) VF veya AKÖ
  - Spontan EKG bulgusu (+): 136 hastada 15 olay % 11
  - Spontan EKG bulgusu (-): 131 hastada 1 olay % 0.7
- Brugada dışı literatür
  - Ciddi ek bir risk yaratmıyor

Antzelevitch C et al. Circulation. 2005;111:659-670.
Chen and Priori. JACC 2008;51:1176–80
Antzelevitch C. Pacing Clin Electrophysiol. 2006;29:1130–59.
Berne P, Brugada J. Circ J 2012; 76: 1563 – 1571

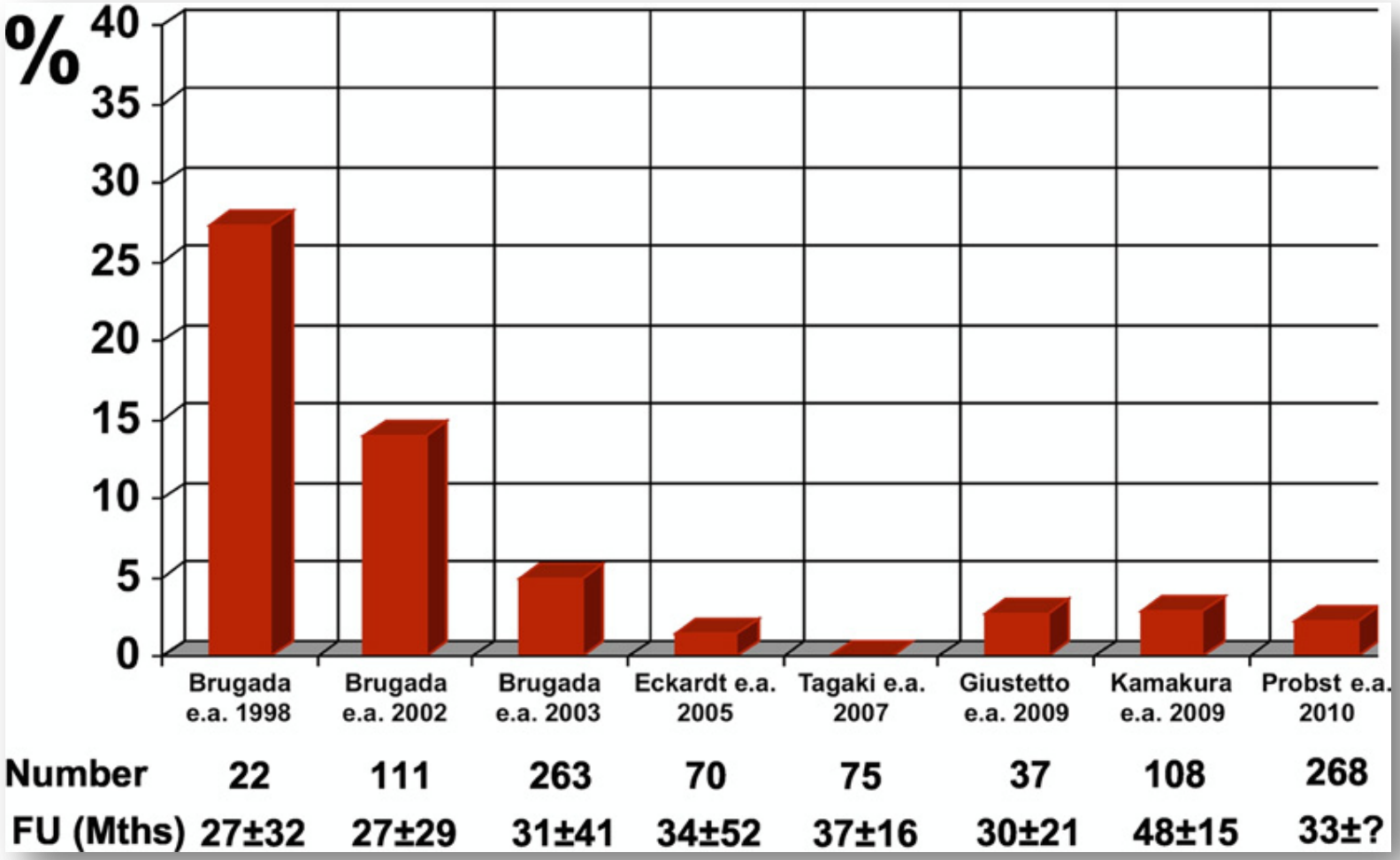
Brugada Sendromu

Riskin belirlenmesi

- Elektrofizyolojik çalışma
  - Pozitif prediktif değeri düşük: % 23
  - Negatif prediktif değeri yüksek: 3 yıllık izlemde % 93
  - Stimülasyon protokolü
  - Hasta gruplarının farklılığı
- Brugada'ların görüşü: Risk belirlemede önemli
- Diğerleri: Risk belirlemede yeri tartışmalı??

Antzelevitch C et al. Circulation. 2005;111:659-670.
Chen and Priori. JACC 2008;51:1176–80
Antzelevitch C. Pacing Clin Electrophysiol. 2006;29:1130–59.

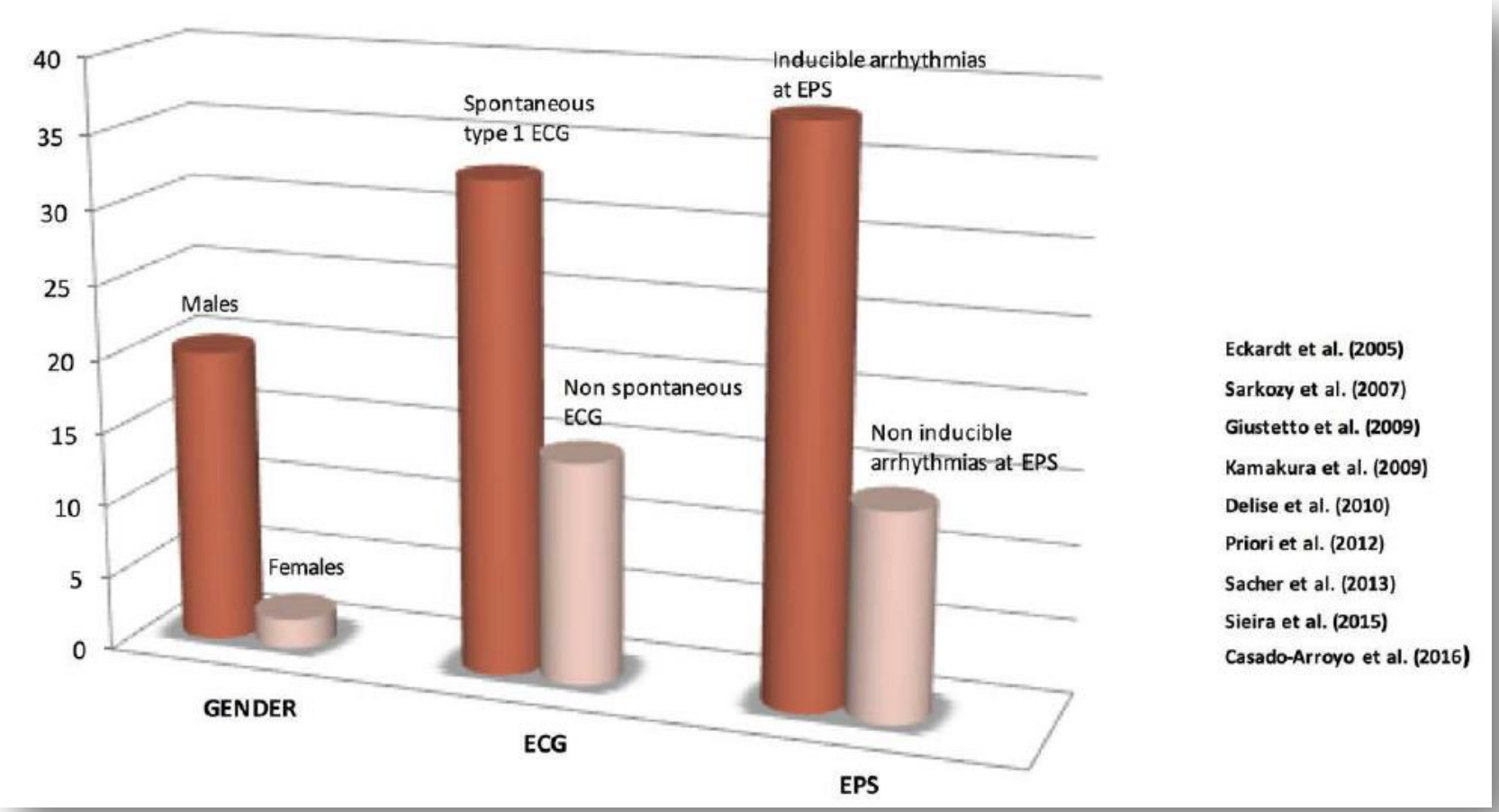
Spontan tip 1 hastada Elektrofizyolojik çalışma



Wilde and Viskin. Heart Rhythm 2011;8:1598 –1600

Brugada Sendromu

Ani Ölüm Yaşayanı



Letsas KP, et al. Pacing Clin Electrophysiol. 2017;40(12):1332-45.

Table 1 Variables identified as being associated with sudden cardiac death in Brugada syndrome.

Variables	Definition	Effect on SCD
Aborted SCD	–	Increased risk[a]
Syncope	Cause by arrhythmia	Increased risk[a]
Spontaneous ECG pattern	Type 1 ECG	Increased risk
Old age	Aged > 60 years	Decreased risk, but needs to be confirmed[b]
Sex	Female sex	Decreases risk[b]
EPS	VF occurrence	Increased risk, with conflicting data, particularly with three extra stimuli[b]
Sinus dysfunction	In females	Increased risk, but needs to be confirmed[b]
S wave in D1	S wave > 0.1 mV and/or > 40 ms	Increased risk, but needs to be confirmed[b]
QRS fragmentation	At least four spikes in one or at least eight spikes in all of the precordial leads	Increased risk, but needs to be confirmed[b]
Inferior type 1	Type 1 ECG in inferior or lateral leads	Increased risk, but needs to be confirmed[b]
Tpeak–Tend interval	Maximum Tpeak–Tend interval > 100 ms in precordial lead	Increased risk, but needs to be confirmed[b]
Early repolarization	J wave > 0.1 mV in two inferolateral leads	Increased risk, with conflicting data[b]
Post-exercise ST-segment elevation	≥0.05 mV in V1–V3 post exercise	Increased risk, but needs to be confirmed[b]
Type 1 ECG burden	24-h Holter monitoring	Increased risk, but needs to be confirmed[b]
Young age	Aged < 18 years	Conflicting data[c]
Family history of SCD	SCD in first-degree relatives	Conflicting data[c]
Genetic	*SCN5A* mutations	Conflicting data[c]
Atrial fibrillation	–	Conflicting data[c]
PR duration	PR > 200 ms	Conflicting data[c]
QRS duration	QRS > 120 ms	Conflicting data[c]
Late potentials	Two of three positive criteria	Conflicting data[c]
aVr sign	R wave ≥ 0.3 mV or R/q ≥ 0.75 in aVr	Conflicting data[c]

Gourraud JB, et al. Archives of Cardiovascular Disease 2017;110:188—195

Brugada Sendromu

Tedavi

Tedavi seçenekleri

- Yaşam biçim değişimleri
- ICD
- Kinidin
- RF ablasyon ??

Elektriksel fırtına tedavisi

- İsoproteronol
- Kinidin

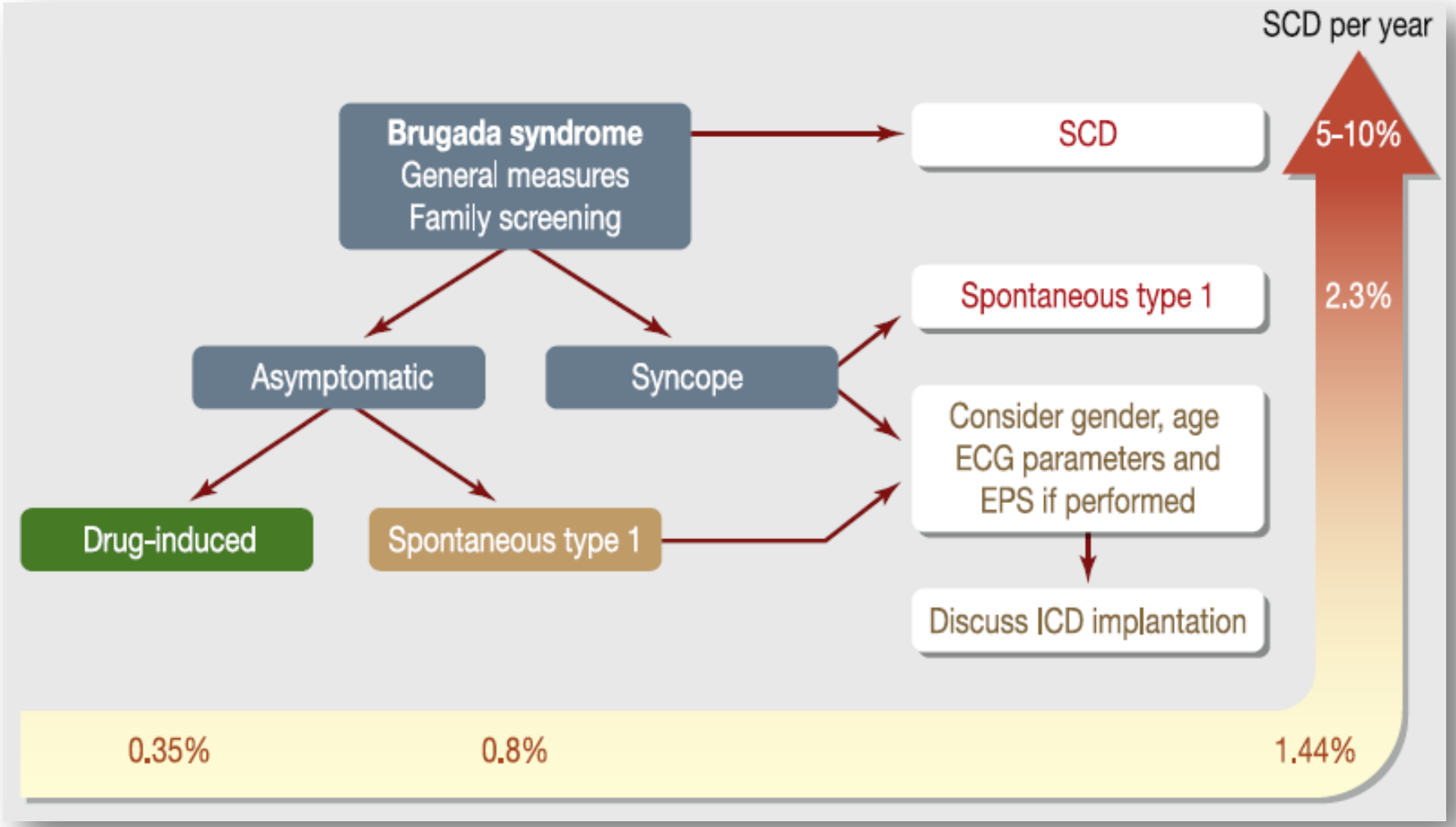
Brugada Sendromu

Tedavi

- **Yaşam biçim değişimleri**
  - ST yüksekliği yapan ilaçların kullanımından kaçınılmalı
  - Aşırı alkol alımından kaçınılmalı
  - Ateş çok hızlı tedavi edilmeli

Brugada Sendromu

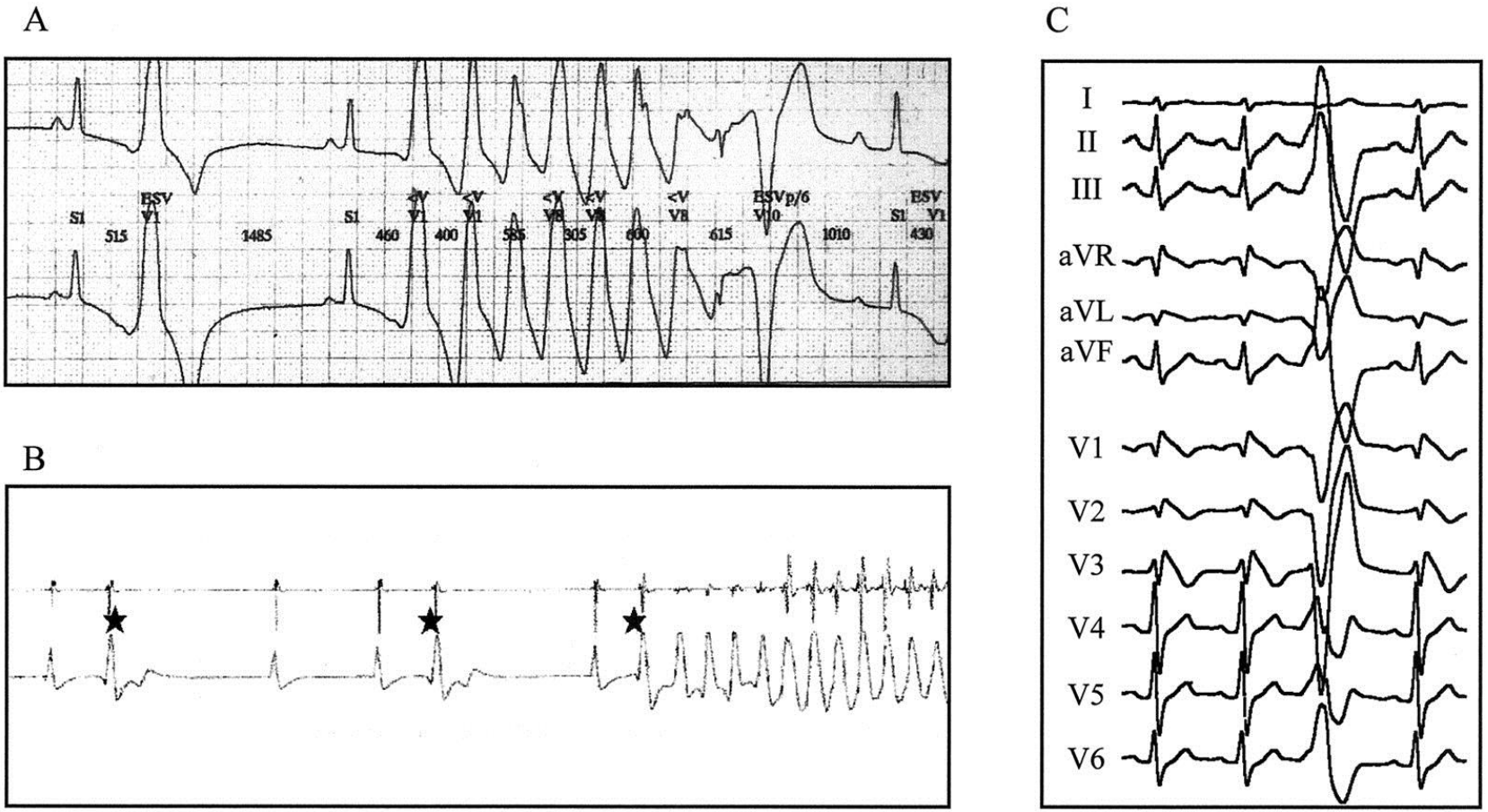
ICD



Gourraud JB, et al. Archives of Cardiovascular Disease 2017;110:188—195

Brugada Sendromu

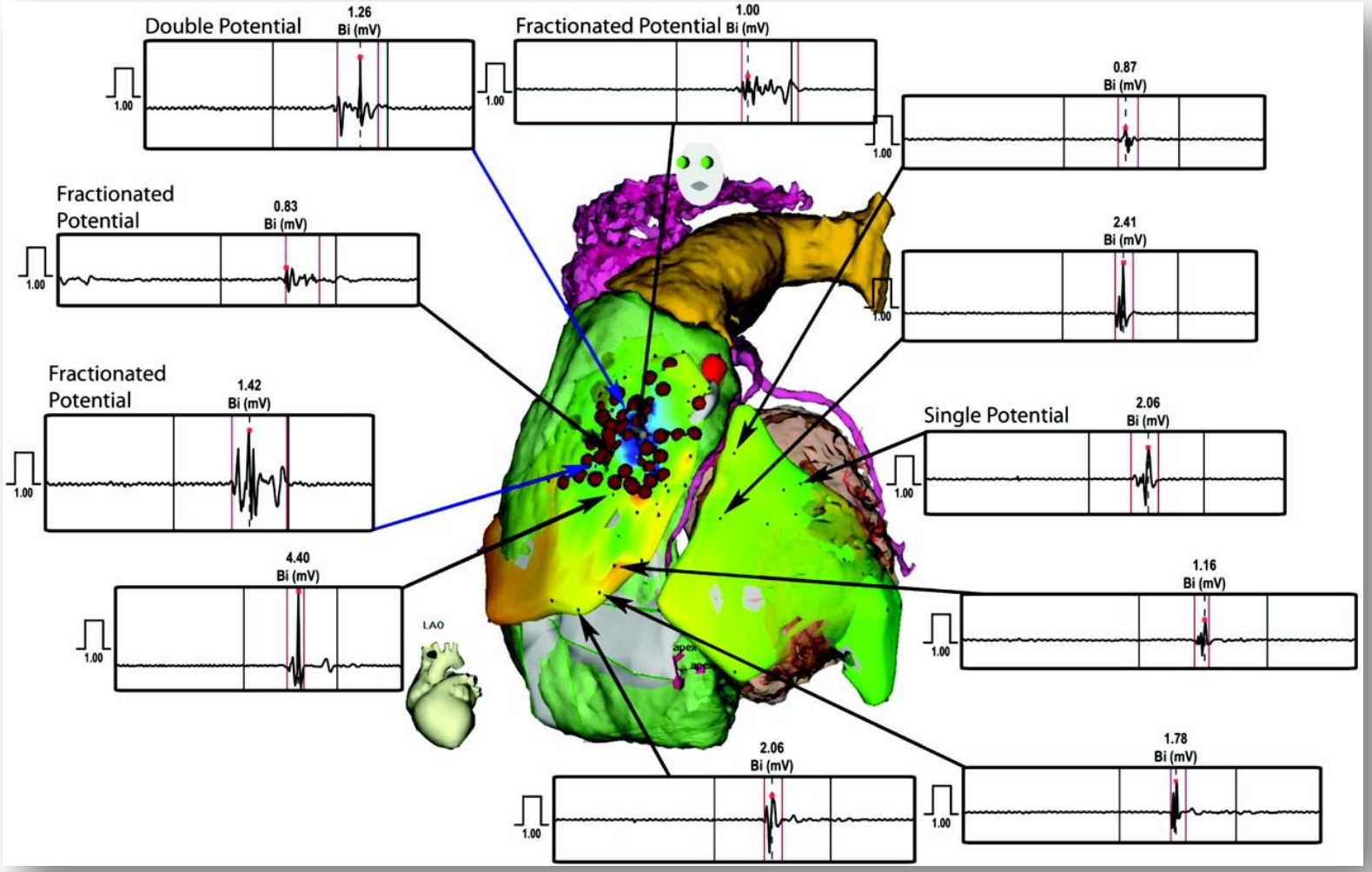
Kateter Ablasyonu



Haissaguerre M, et al. Circulation 2003;108:925–8

Brugada Sendromu

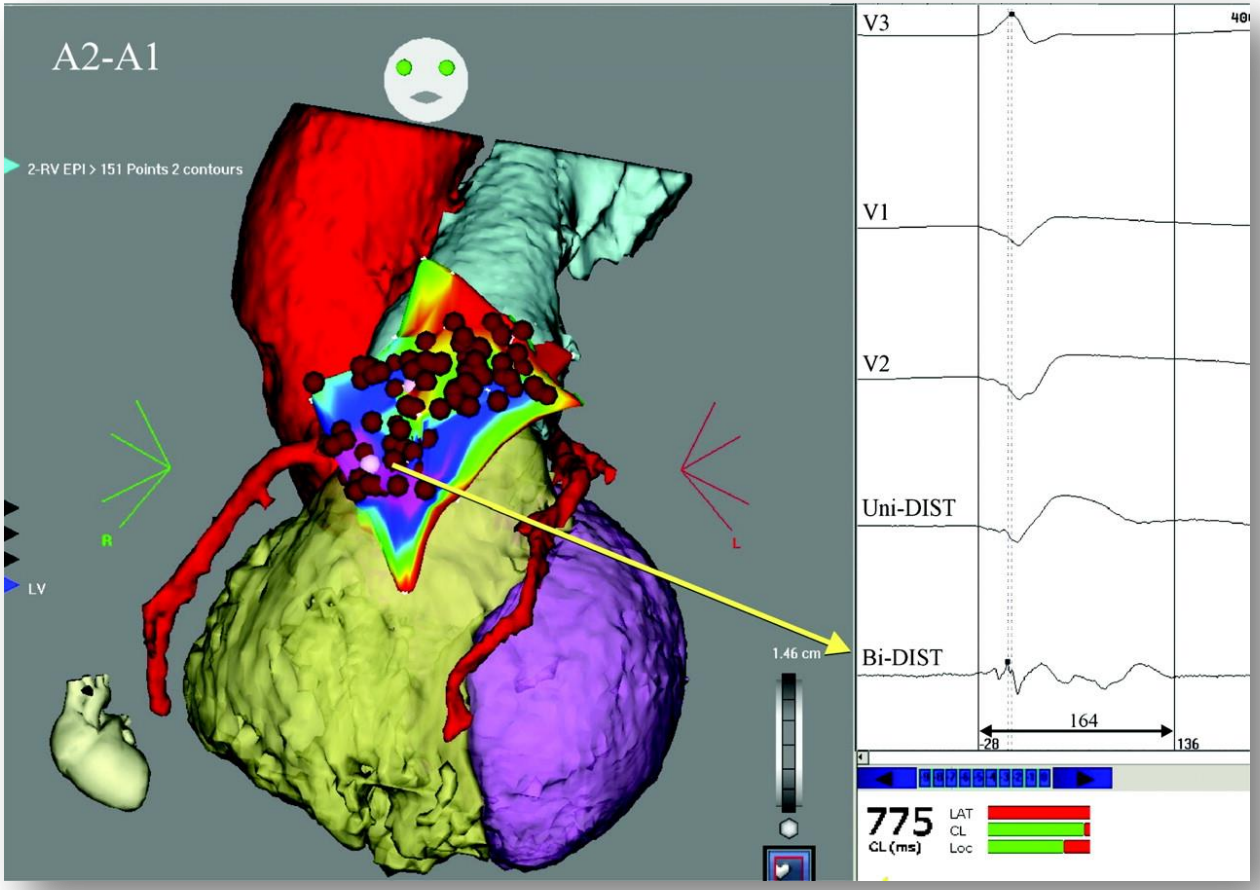
Kateter Ablasyonu



Nademanee K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011;123:1270–9.

Brugada Sendromu

Kateter Ablasyonu



Nademanee K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011;123:1270–9.

Brugada Sendromu

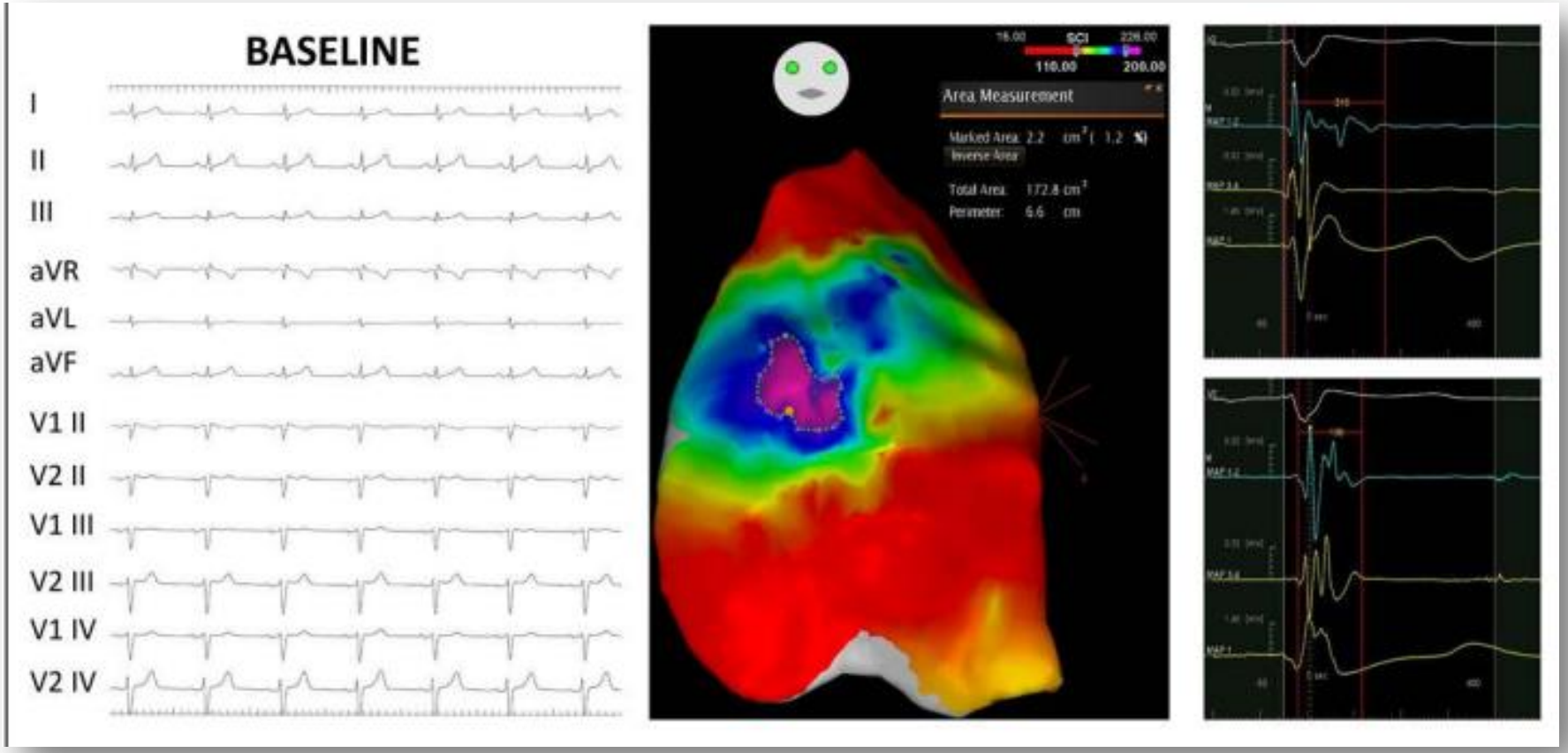
Kateter Ablasyonu

- Ablasyon sonrası 9 hastanın 7'si (%78) non-inducible
- 8 hastada (% 89)EKG'de normalleşme
- 20±6 aylık takipte 8 hastada (% 89) VF rekürrensi ve ICD şoku yok
- 1 hastada ablasyon sonrası VF rekürrensi ve 100 mg Amiodarone (33 ayda olay yok)

Nademanee K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011;123:1270–9.

Brugada Sendromu

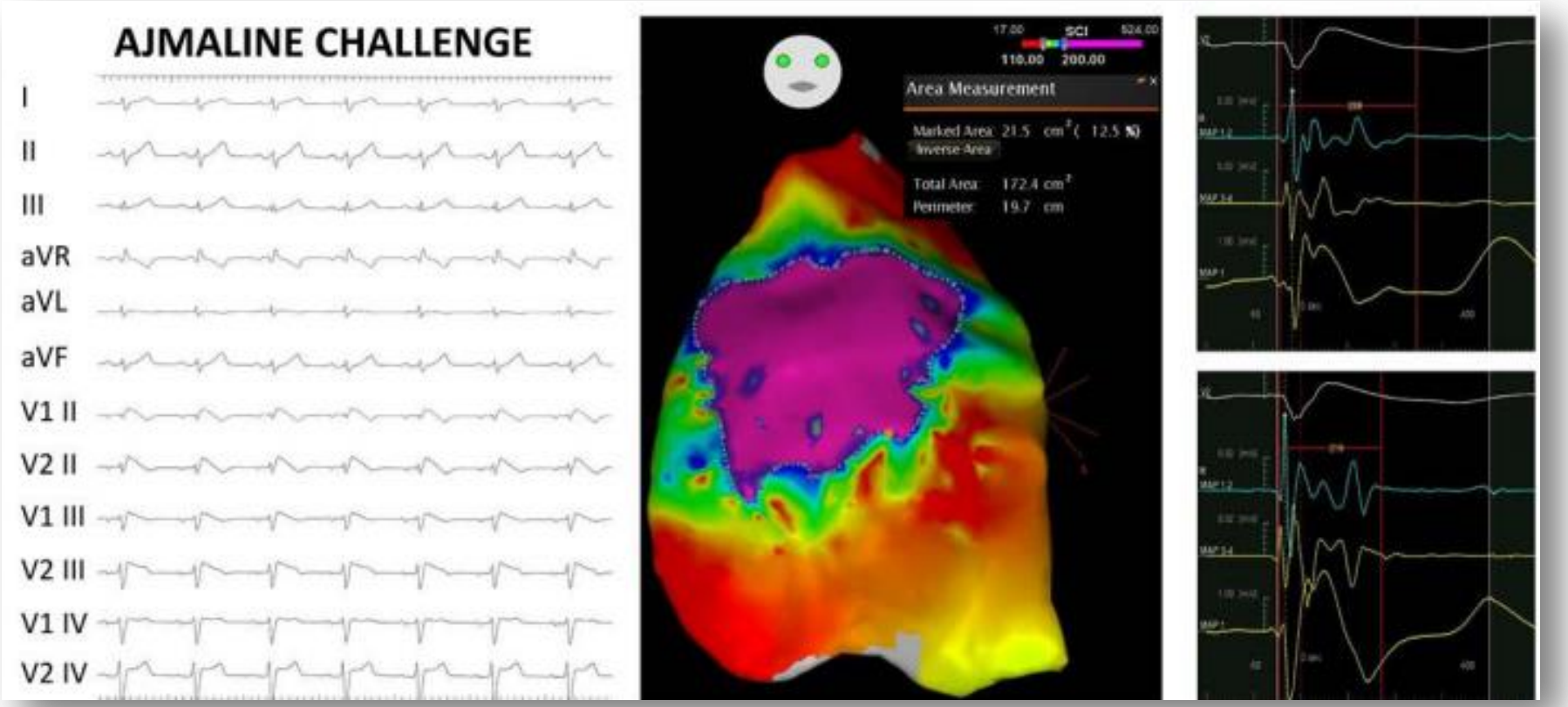
Kateter Ablasyonu



Pappone C, et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017;10(5):e005053.

Brugada Sendromu

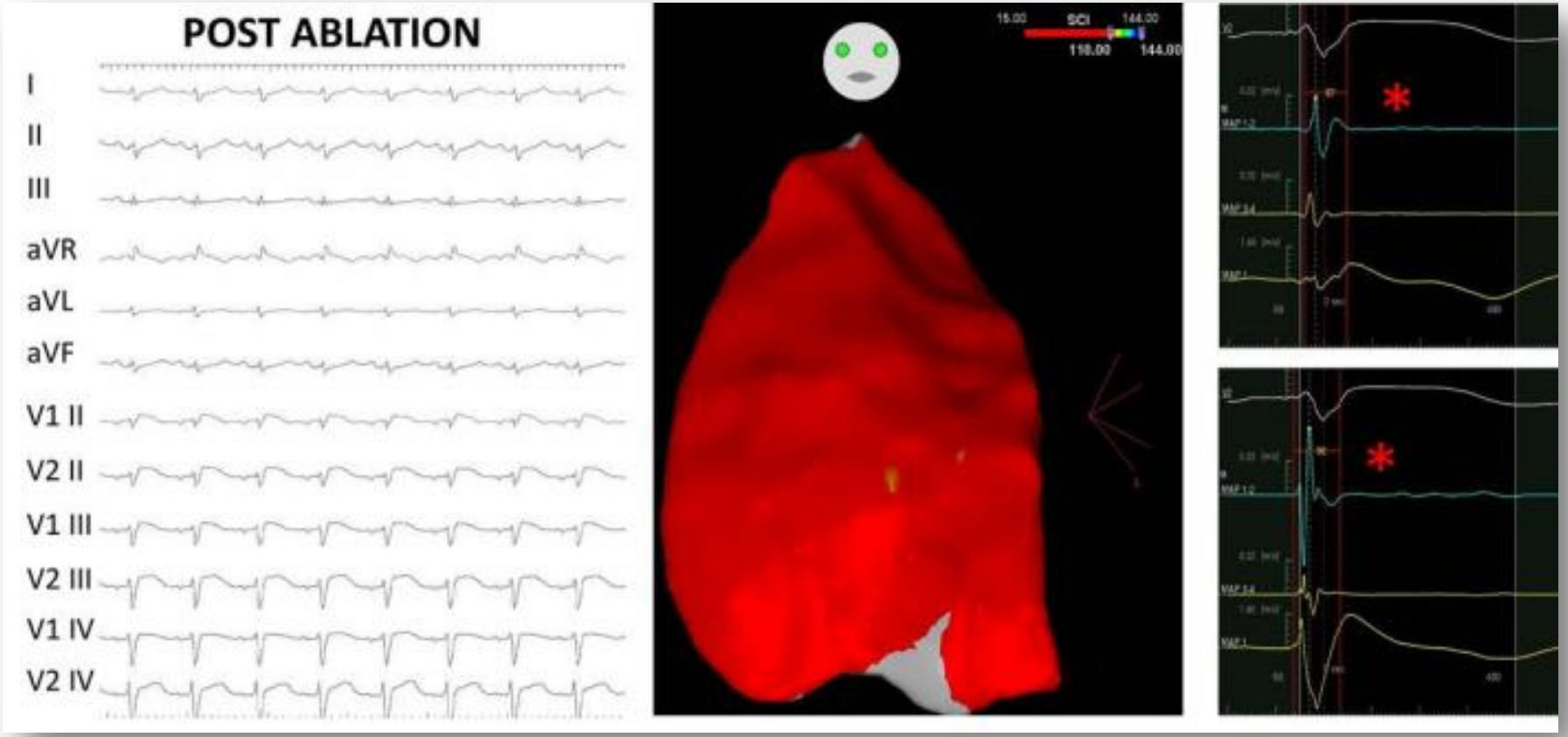
Kateter Ablasyonu



Pappone C, et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017;10(5):e005053.

Brugada Sendromu

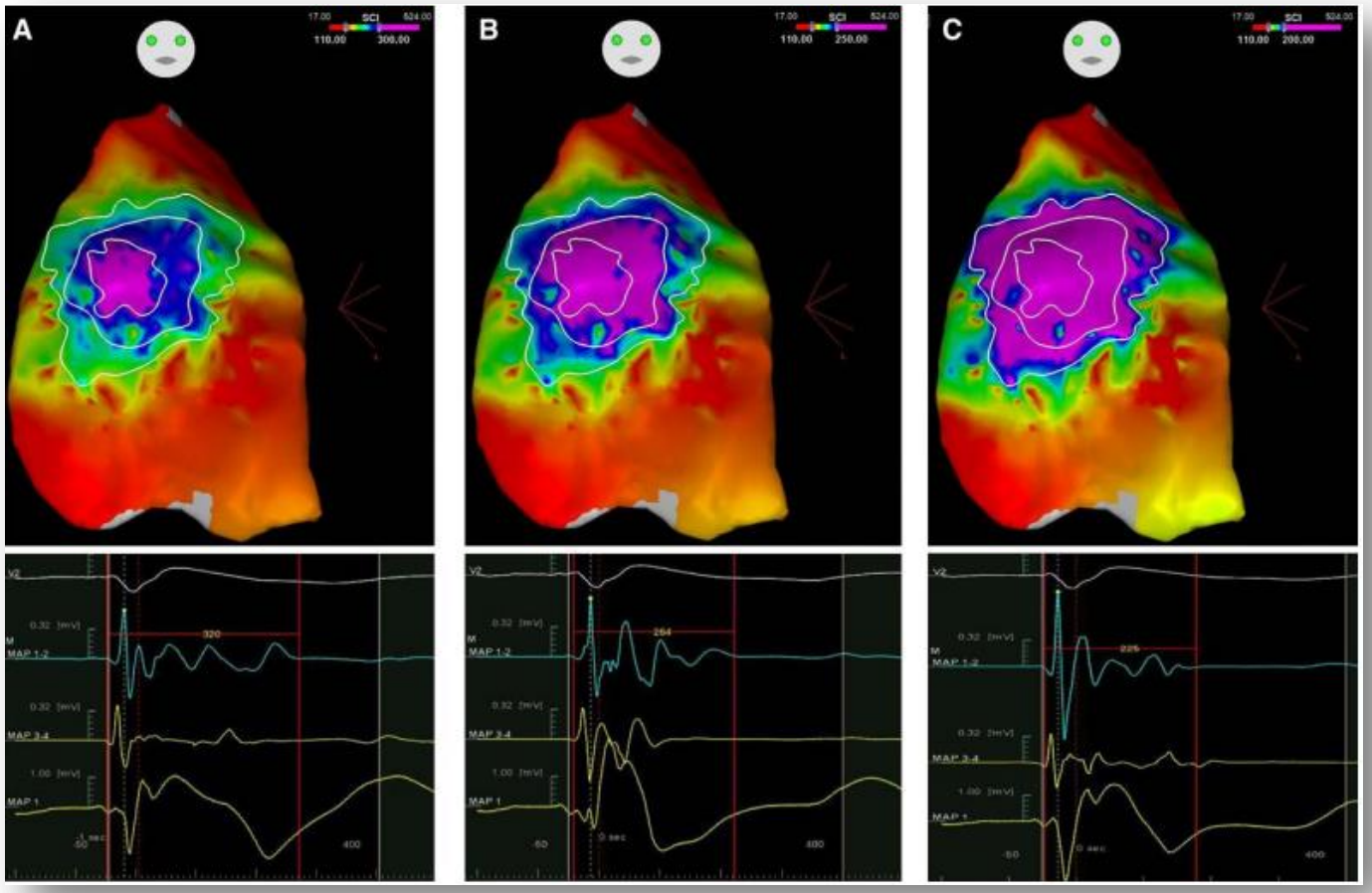
Kateter Ablasyonu



Pappone C, et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017;10(5):e005053.

Brugada Sendromu

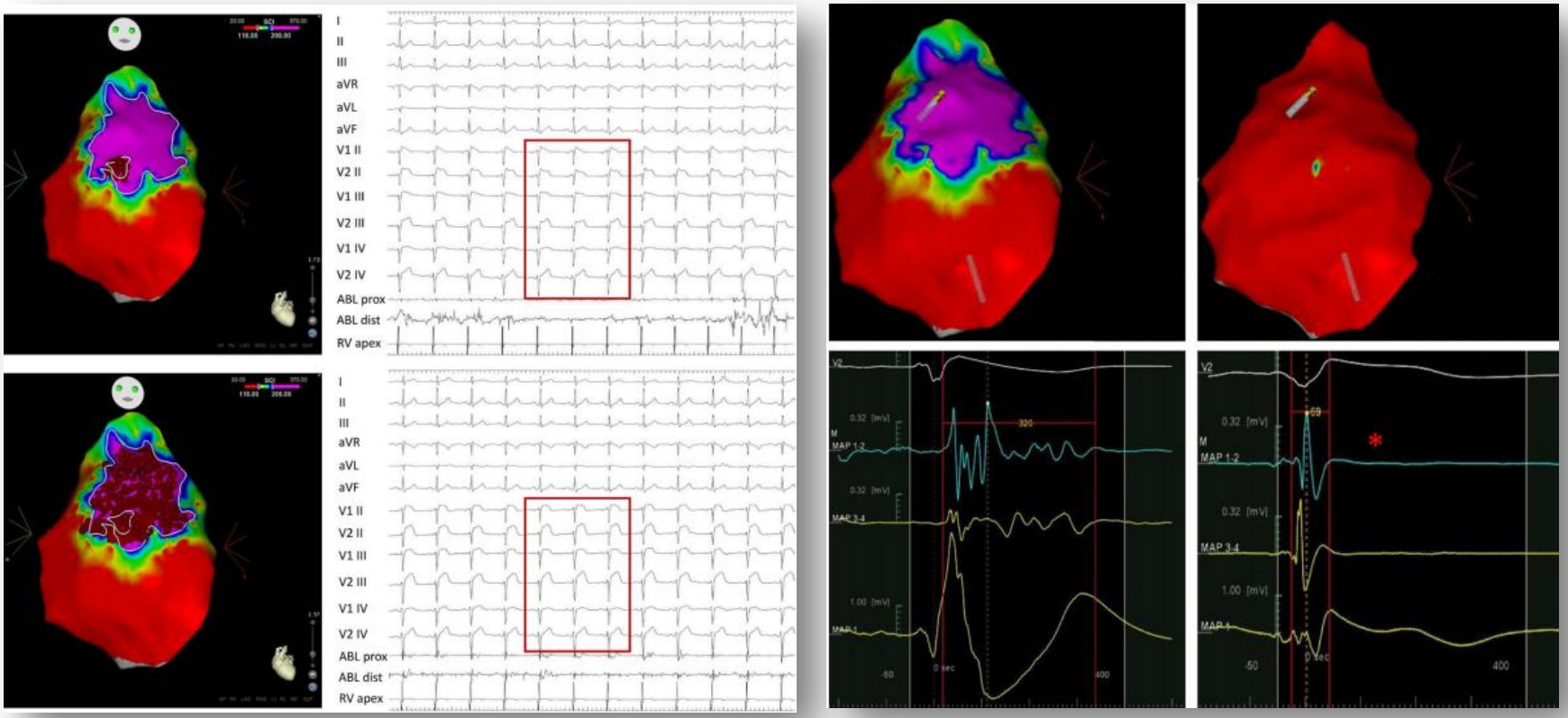
Kateter Ablasyonu



Pappone C, et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017;10(5):e005053.

Brugada Sendromu

Kateter Ablasyonu



Pappone C, et al. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017;10(5):e005053.

World Journal of Cardiology

Submit a Manuscript: http://www.f6publishing.com

World J Cardiol 2017 September 26; 9(9): 737-741

DOI: 10.4330/wjc.v9.i9.737

ISSN 1949-8462 (online)

MINIREVIEWS

Brugada type 1 electrocardiogram: Should we treat the electrocardiogram or the patient?

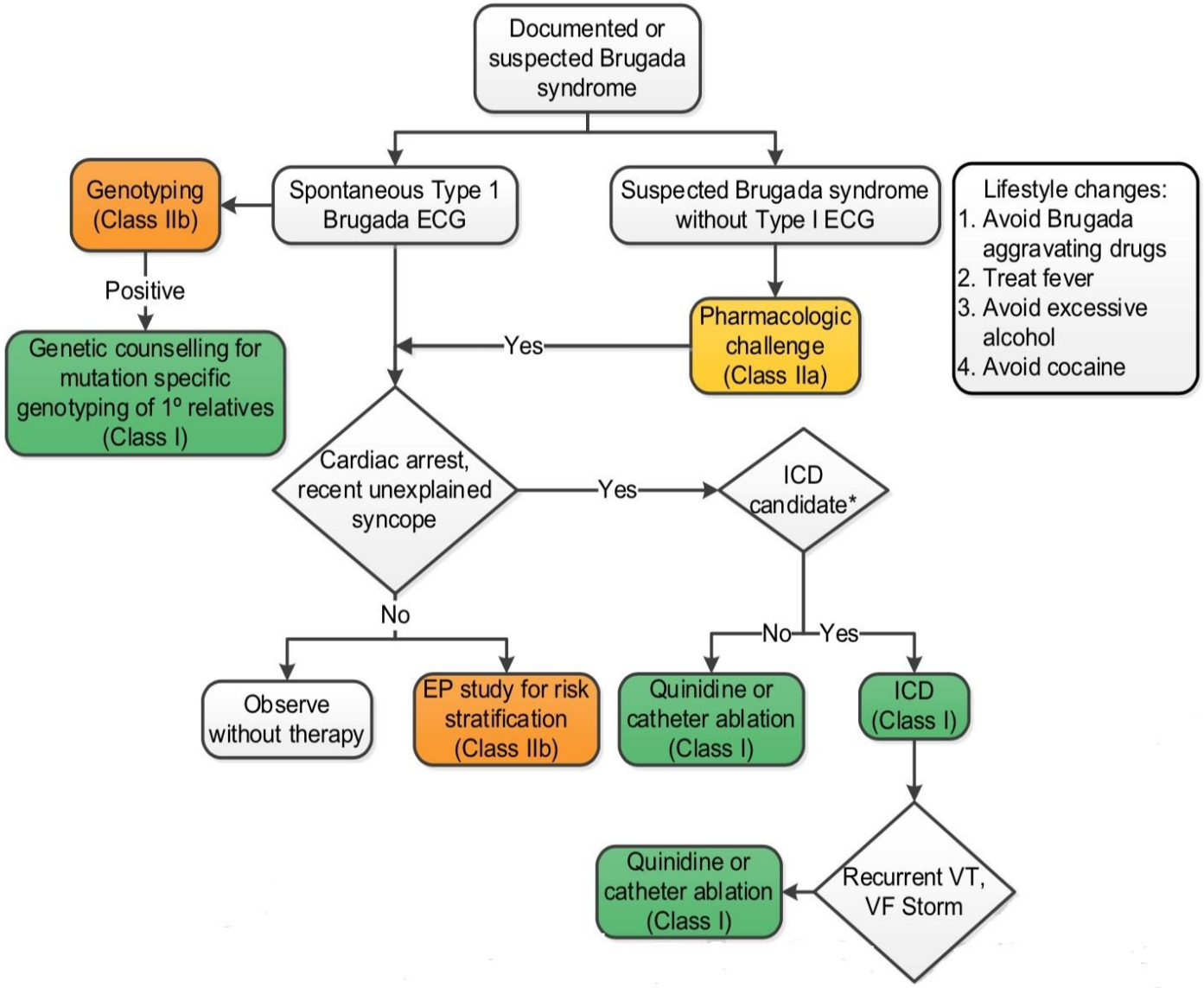
Pietro Delise, Giuseppe Allocca, Nadir Sitta

Brugada Sendromu

Tedavi

COR	LOE	Recommendations
I	B-NR	1. In asymptomatic patients with only inducible type 1 Brugada electrocardiographic pattern, observation without therapy is recommended (1-5).
I	B-NR	2. In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA, an ICD is recommended if a meaningful survival of greater than 1 year is expected (4, 6).
I	B-NR	3. In patients with Brugada syndrome experiencing recurrent ICD shocks for polymorphic VT, intensification of therapy with quinidine or catheter ablation is recommended (7-11).
I	B-NR	4. In patients with spontaneous type 1 Brugada electrocardiographic pattern and symptomatic VA who either are not candidates for or decline an ICD, quinidine or catheter ablation is recommended (7, 9-11).
IIa	B-NR	5. In patients with suspected Brugada syndrome in the absence of a spontaneous type 1 Brugada electrocardiographic pattern, a pharmacological challenge using a sodium channel blocker can be useful for diagnosis (12-14).
IIb	B-NR^{SR}	6. In patients with asymptomatic Brugada syndrome and a spontaneous type 1 Brugada electrocardiographic pattern, an electrophysiological study with programmed ventricular stimulation using single and double extrastimuli may be considered for further risk stratification (1, 6, 13, 15-17).
IIb	C-EO	7. In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives (18-20).

Al-Khatip SM, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2017



Al-Khatip SM, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2017

Brugada Sendromu

Sonuç

- Tanı ve ani ölüm riskinin belirlenmesi
- EKG özelliklerinin iyi yorumlanması
- Ailenin değerlendirmesi ve genetik çalışma
- ICD endikasyonu iyi değerlendirilmeli
- Aritmi epizodunun tedavisi
- Uygun hastada ablasyon (risk / fayda)
- Ablasyonun uzun dönemdeki etkileri

Teşekkürler...