Sudden cardiac death in “healthy” heart

Torino, 27th September 2013

Prof. Fiorenzo Gaita

Director of the Cardiology School - University of Turin, Italy

2010 – M.Garcia, 31 y, ???

2003 – M.V.Foé, 28 y, hypertrophic CMP

2012 – V.Bovolenta, 38 y, ???

2012 - Morosini, 26 y, ARVD/C

Un uomo di nome Anania con la moglie Saffira vendette un suo podere e, tenuta per sé una parte dell`importo d`accordo con la moglie, consegnò l`altra parte deponendola ai piedi degli apostoli. Ma Pietro gli disse: "Ana ... hai ment ... o? Prim ... vato non era sempre a tua disposizione? Perché hai pensato in cuor tuo a quest`azione? Tu non hai mentito agli uomini, ma a Dio". All`udire queste parole, Anania cadde a terra e spirò. E un timore grande prese tutti quelli che ascoltavano. Si alzarono allora i più giovani e, avvoltolo in un lenzuolo, lo portarono fuori e lo seppellirono. Avvenne poi che, circa tre ore più tardi, entrò anche sua moglie, ignara dell`accaduto. Pietro le chiese: "Dimmi: ... via anche te".

Anania cadde a terra e spirò

D`improvviso Saffira cadde ai piedi di Pietro e spirò

D`improvviso Saffira cadde ai piedi di Pietro e spirò. Quando i giovani entrarono, la trovarono morta e, portatala fuori, la seppellirono accanto a suo marito. E un grande timore si diffuse in tutta la Chiesa e in quanti venivano a sapere queste cose.

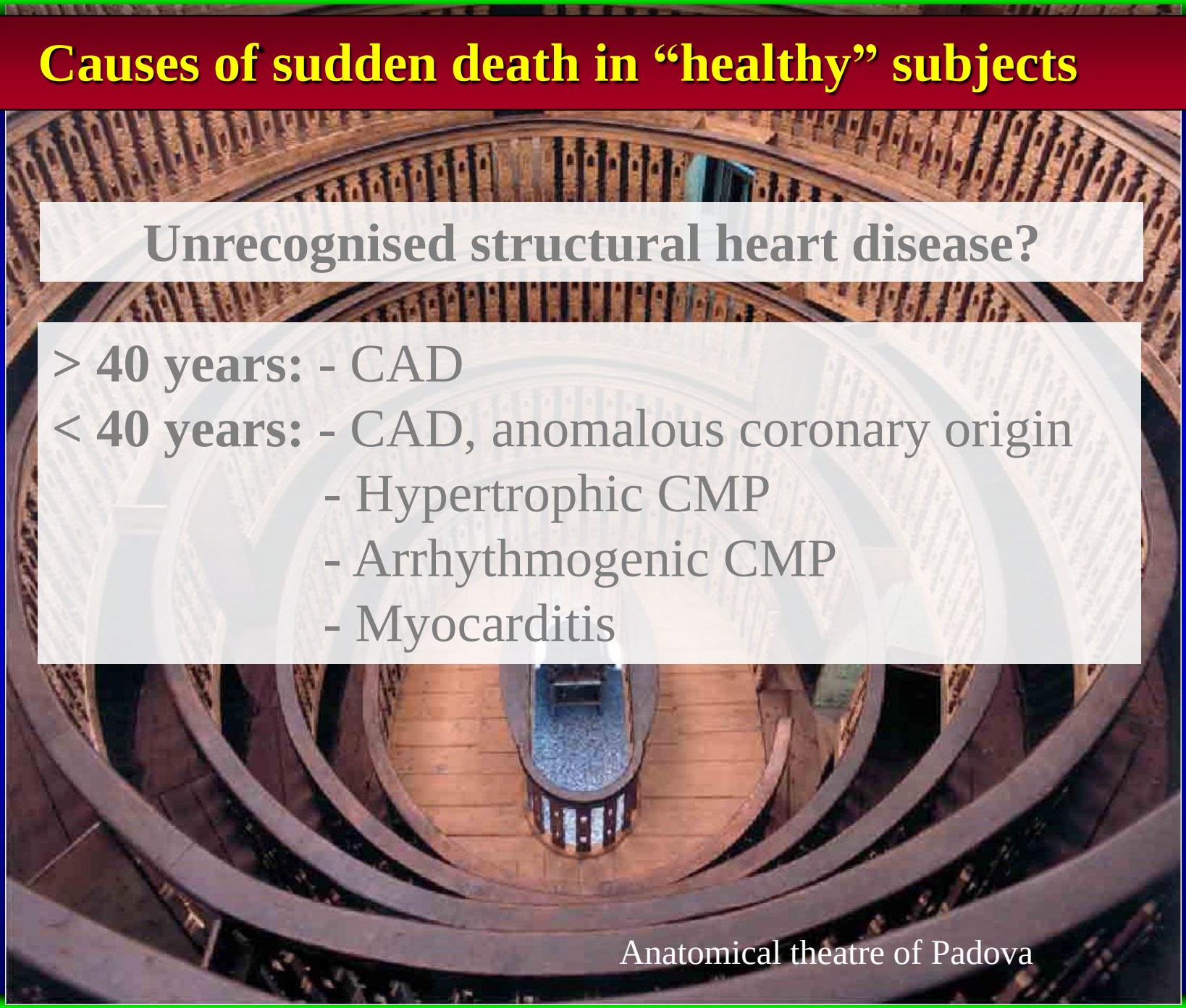
Atti degli Apostoli cap. 5 vers. 1-11

Causes of sudden death in “healthy” subjects

Unrecognised structural heart disease?

> 40 years: - CAD

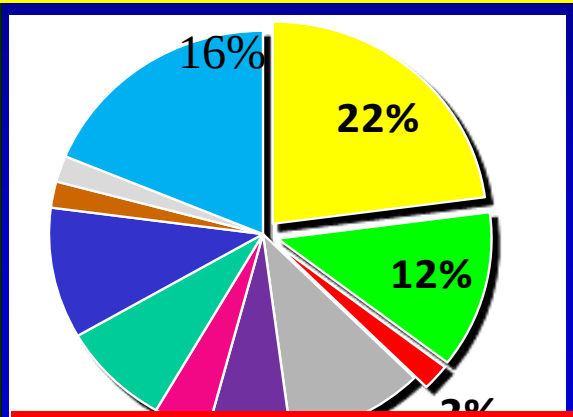
< 40 years: - CAD, anomalous coronary origin
- Hypertrophic CMP
- Arrhythmogenic CMP
- Myocarditis



Anatomical theatre of Padova

Absence of structural heart disease: 6-35% in different series

Sudden death in athlets in Veneto (1979-1996) → 1.6: 100.000 per year
Corrado, N Engl J Med 1998, 339

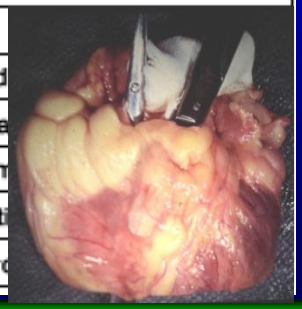


22% Arrhythmogenic Right Ventricular Dysplasia

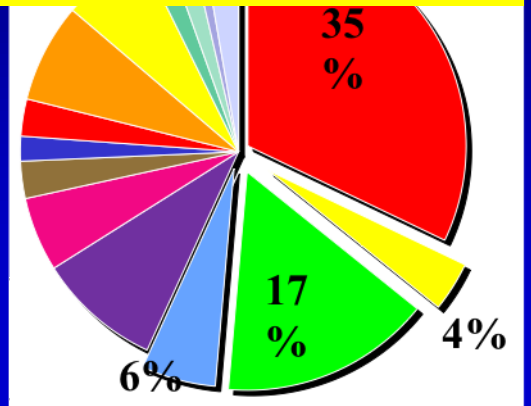
B	18%	Atherosclerotic Coronary Artery Disease
C	12%	Anomalous Origin of Coronary Artery

16% NO structural disease

E	10%	Other
F	8%	Conduction system Disease
G	6%	Myocarditis
H	4%	Myocardial Brid
I	2%	Hypertrophic ca
J	2%	Dilated Cardiom
K	2%	Dissecting Aorti
L	2%	Pulmonary Thro



Minneapolis Heart Institute. Sudden death in athlets → 0.5:100.000
Maron B, Circulation 2007:115



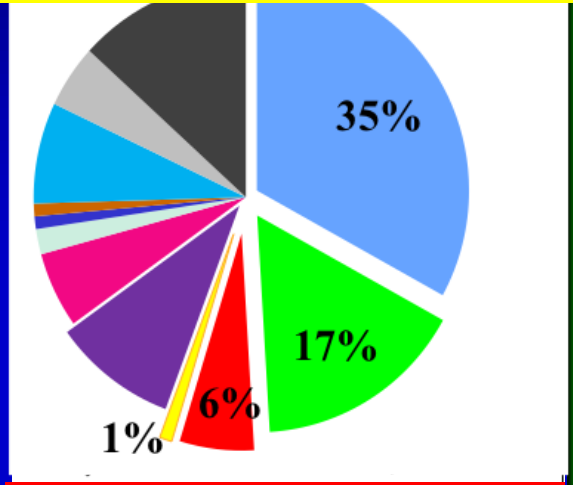
36%Hypertrophic Cardiomyopathy

D	6%	Myocarditis
E	4%	ARVC/D
F	4%	Mitral Valve Prolapse

6% NO structural disease

I	3%	Ion Channelopathies
J	3%	No Structural Cause
K	3%	T
L	3%	C
M	2%	A
N	2%	D
O	2%	C
P	1%	S

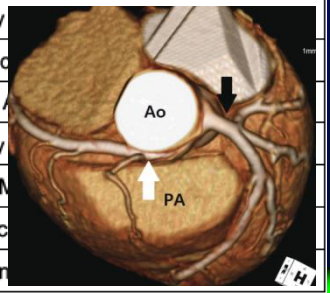
Sudden death in 6.3 million of military recruits → 2:100.000
Eckart R, *Ann Intern Med* 2004;141



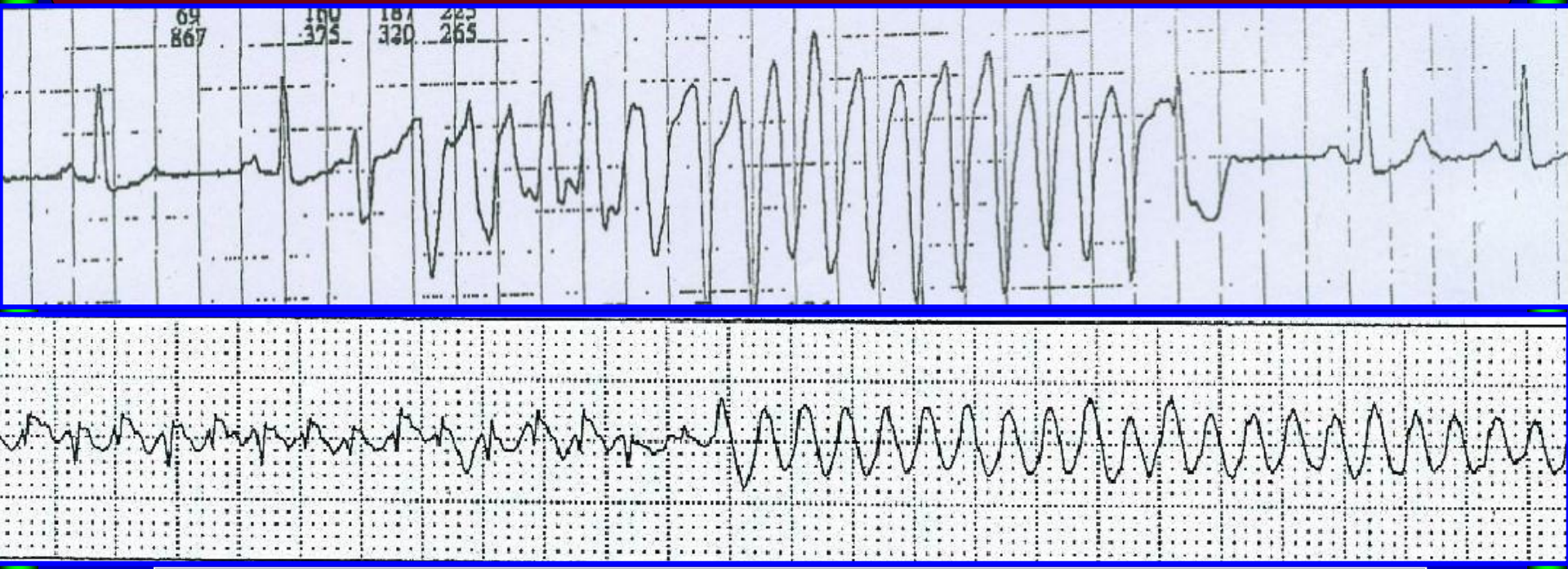
17%Anomalous Coronary Artery

35% NO structural disease

F	6%	Hypertrophic Cardiomyopathy
G	2%	Coronary Aneurysm
H	2%	Coronary
I	2%	Intramyoc
J	1%	Bicuspid A
K	1%	Coronary
L	1%	Embolic M
M	1%	Idiopathic
N	1%	Right Ven



Ion channel diseases:
What do they have in common?



- increased risk of ventricular arrhythmias which cause <u>syncope</u> and/or <u>sudden death, also as first manifestation</u>

- diagnosis based on ECG features

Channelopaties

Long QT
(Romano1963-Ward 1964)

0.2-0.4: 1.000

Polymorphic adrenergic ventricular tachycardia (Coumel 1978)

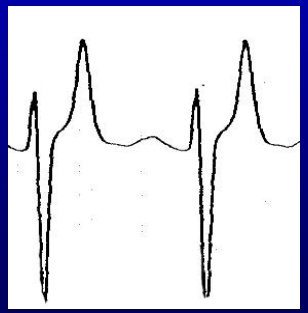
< 0.1 : 1.000

ST elevation V_1-V_3
(Brugada 1991)

0.5-7 : 1.000

Short QT
(Gaita-Giustetto-Borggrefe 2003)

< 0.1 : 1.000



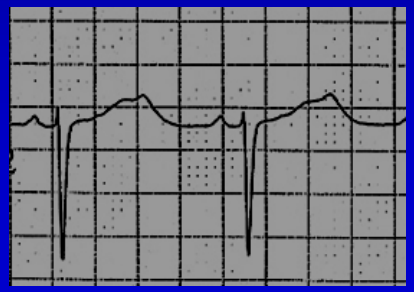
Early repolarization
(Haïssaguerre-Rosso 2008)

10-100 : 1.000

Channelopaties

Long QT
(Romano1963-Ward 1964)

0.2-0.4: 1.000



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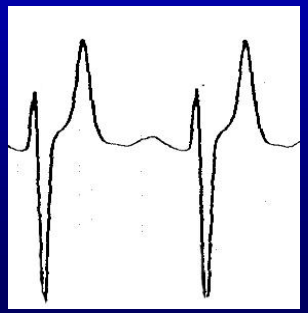

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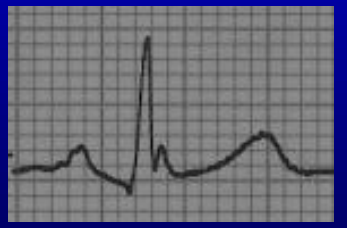

Channelopaties

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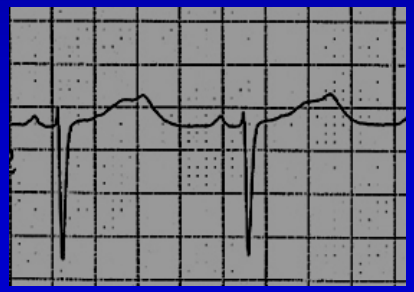

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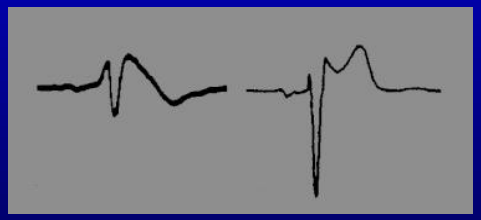

Short QT
(Gaita-Giustetto-Borggrefe 2003)

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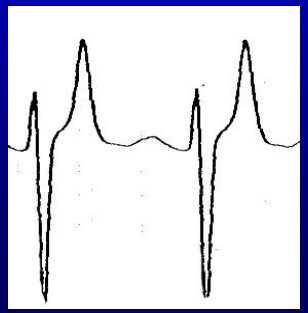

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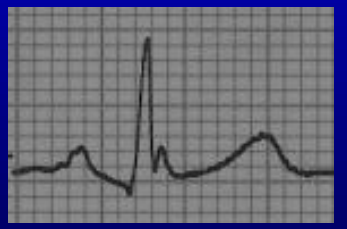
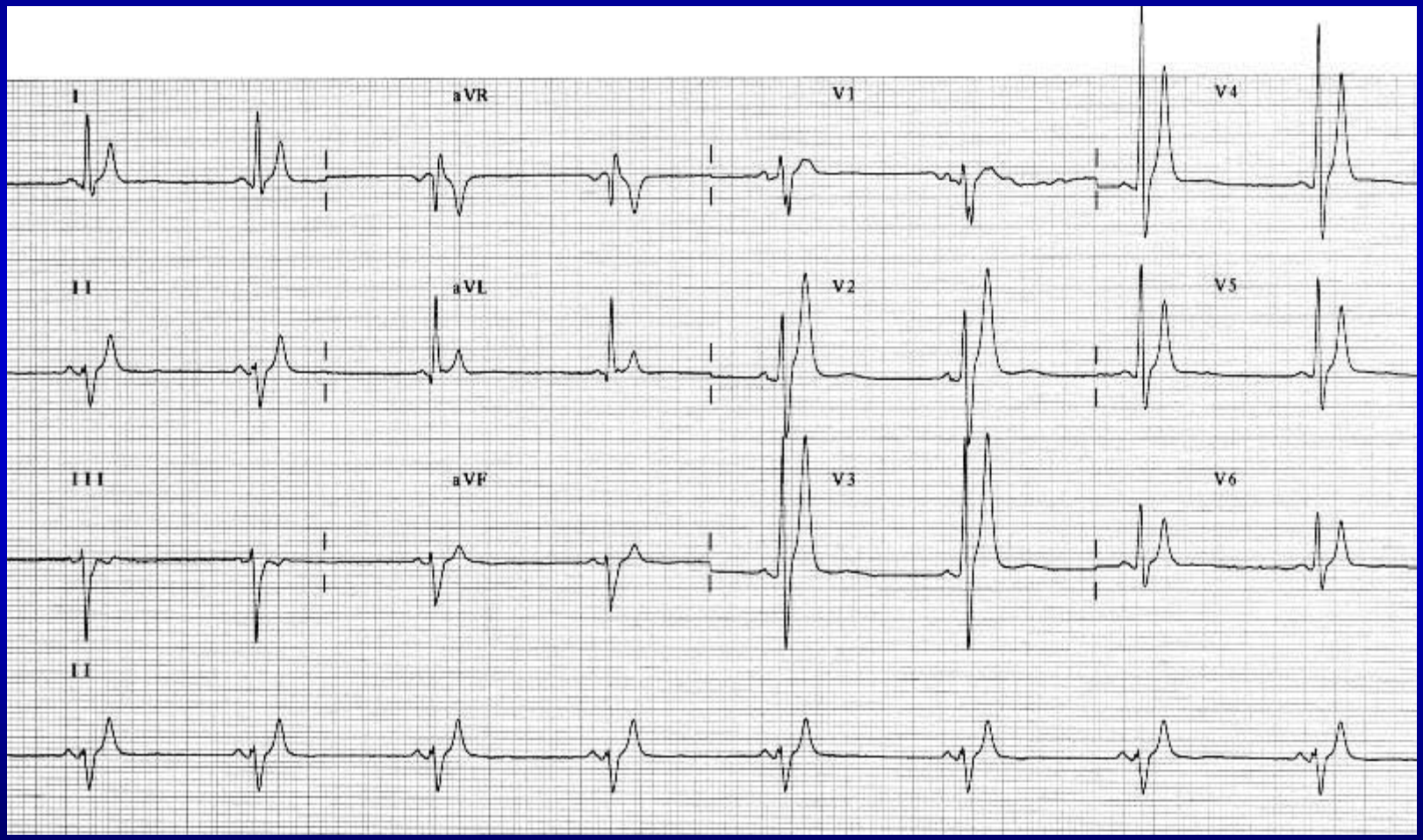
10-100 : 1.000

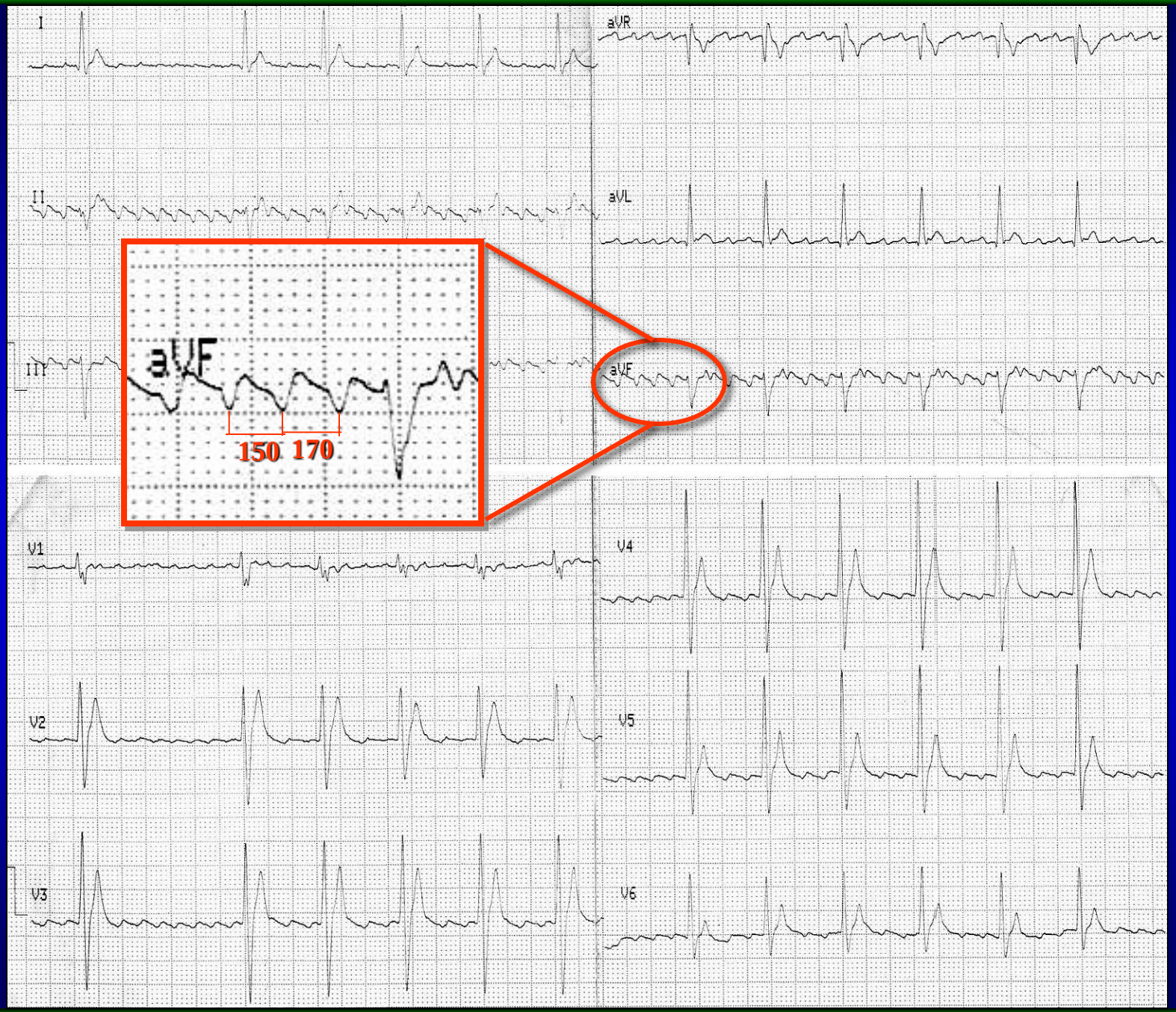


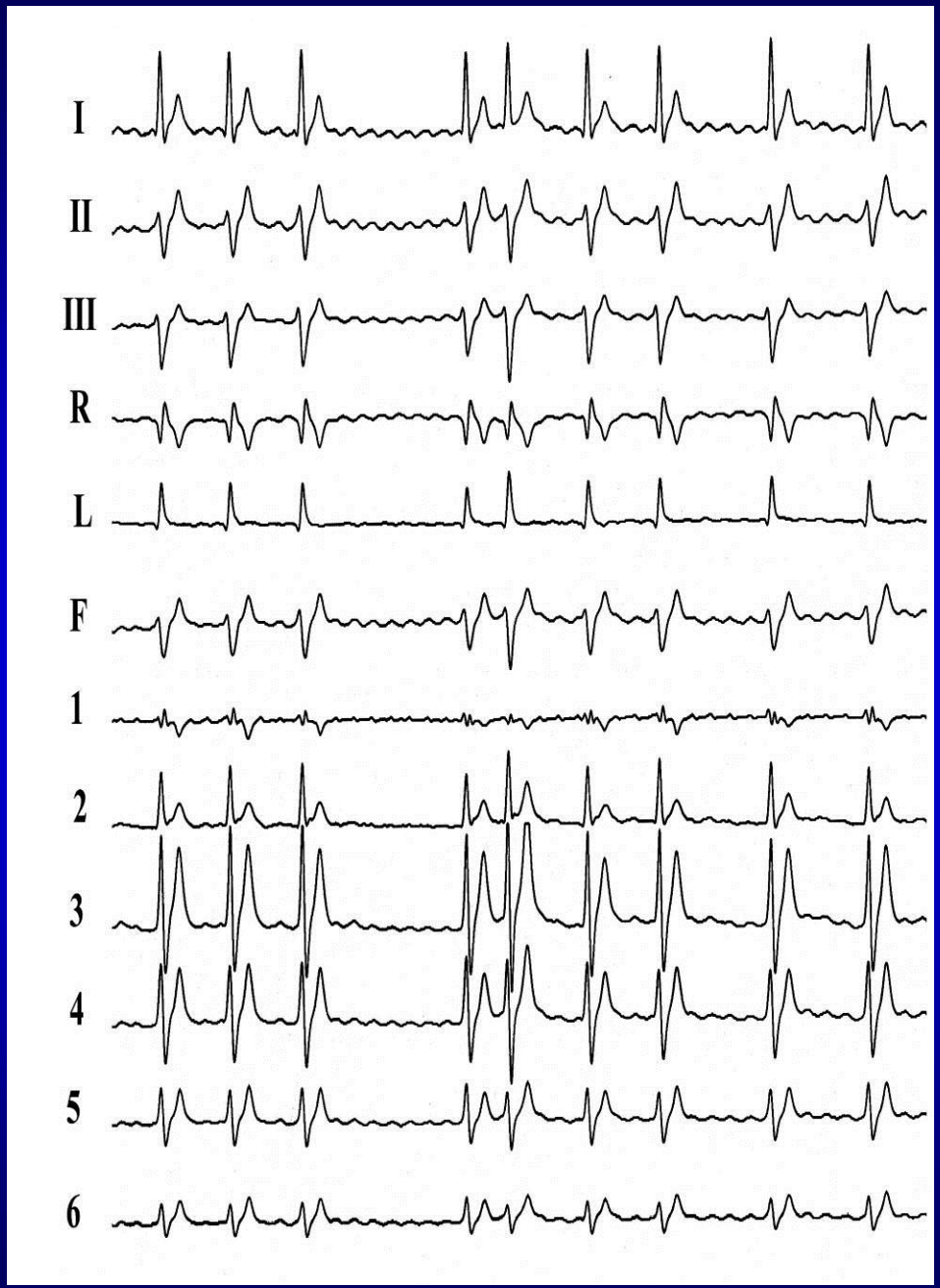
1985: 20 year old man, professional runner.

Symptomatic for palpitations, pre-syncope and one syncopal episode. Father died of S.D.



Narrow, tall and peaked T waves **QT 280 ms QTc 260 ms**


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
aVF
150
170



AF with coarse and regular f waves

Our diagnosis was:

"Episodes of vagal atrial fibrillation and flutter due to short atrial refractory periods (150ms) in a patient with syncope, short QT and family history of S.D."

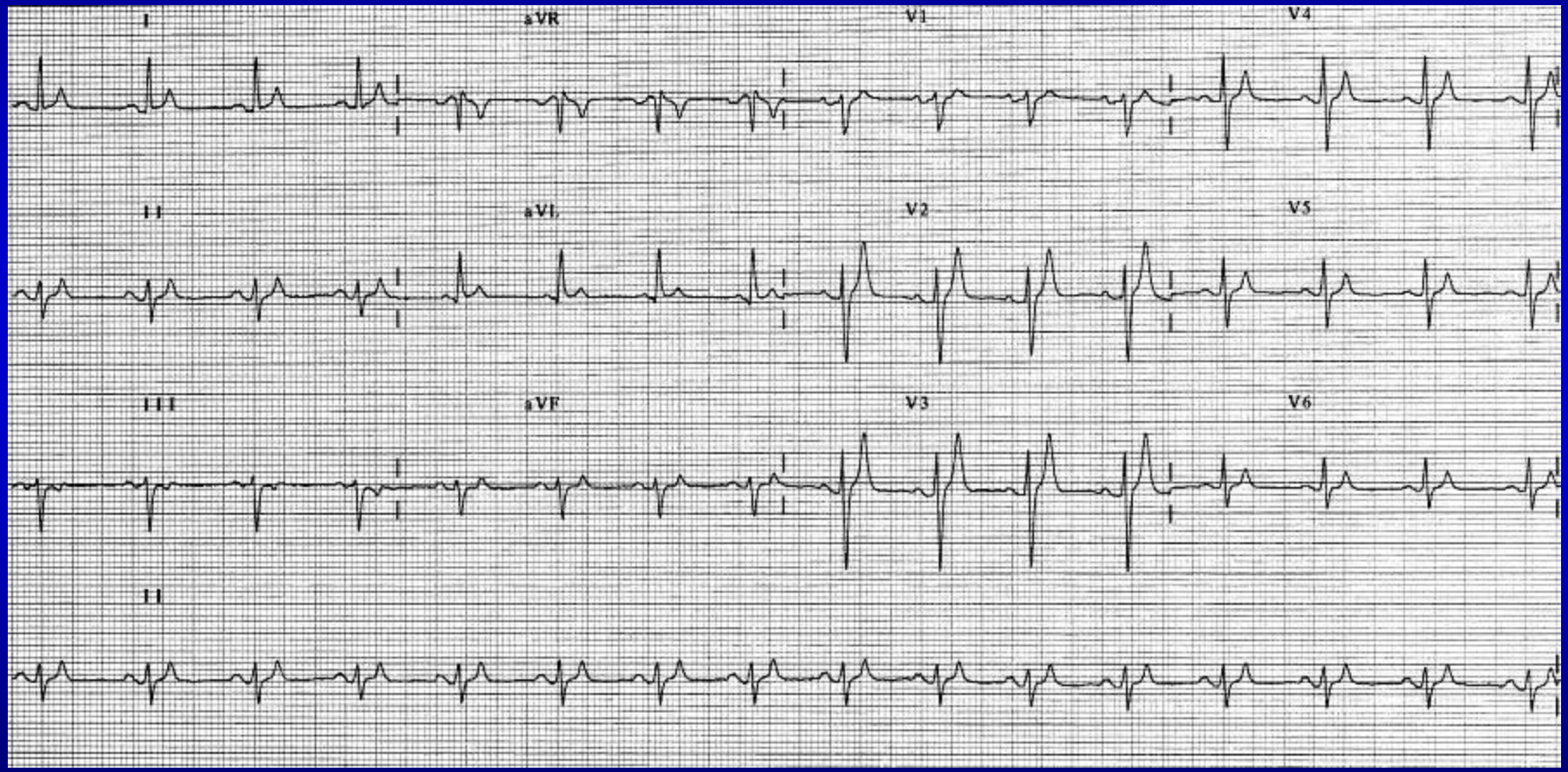
Therapy: Flecainide

and yearly follow-up were suggested

…16 years later….

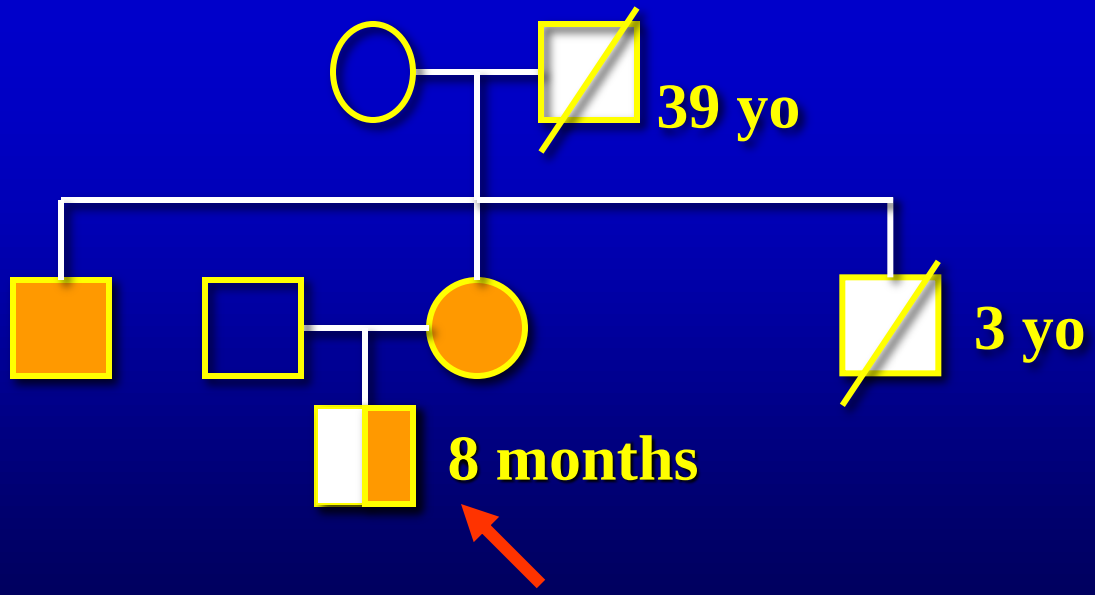
2001: 31 year old woman, symptomatic for palpitations and pre-syncope.

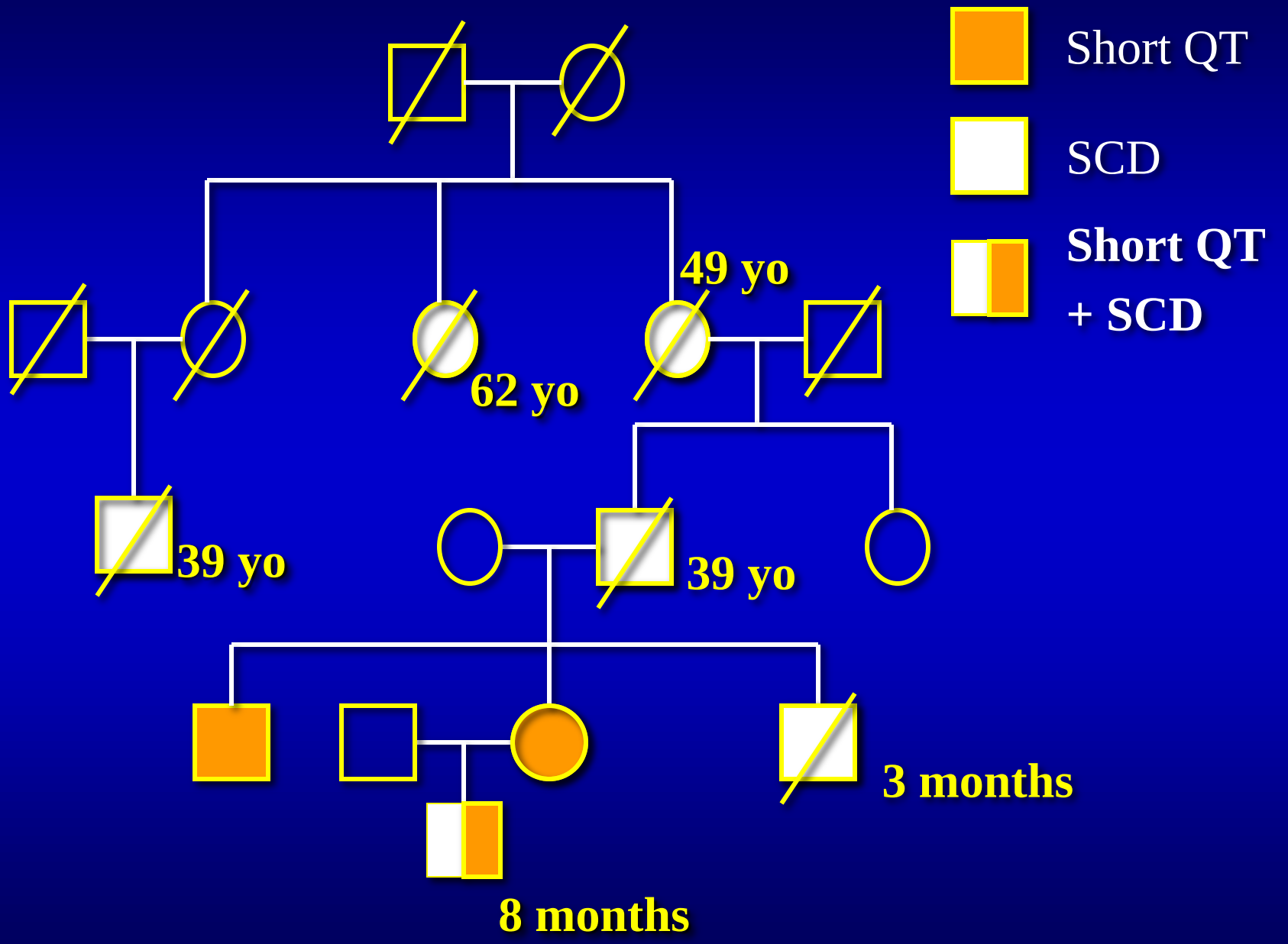
No structural heart disease. Father died of S.D.

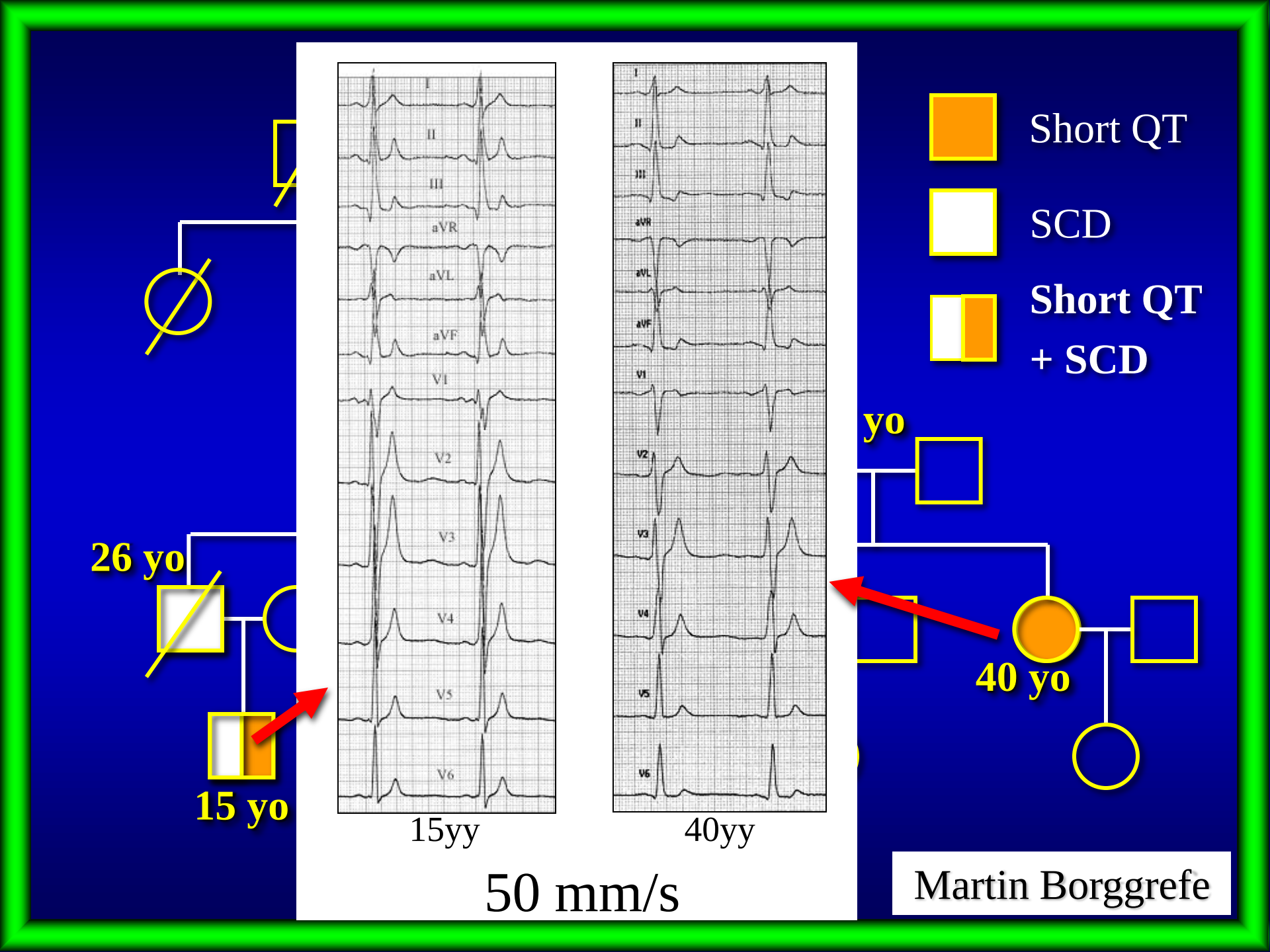


Narrow, tall and peaked T waves

QT 220 ms QTc 270 ms

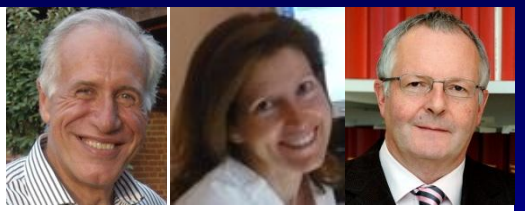

Short QT
SCD
Short QT
+ SCD
39 yo
3 yo
8 months


Short QT
SCD
Short QT
+ SCD
49 yo
62 yo
39 yo
39 yo
3 months
8 months


Short QT
SCD
Short QT
+ SCD
26 yo
15 yo
yo
40 yo
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
15yy
40yy
50 mm/s
Martin Borggrefe

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



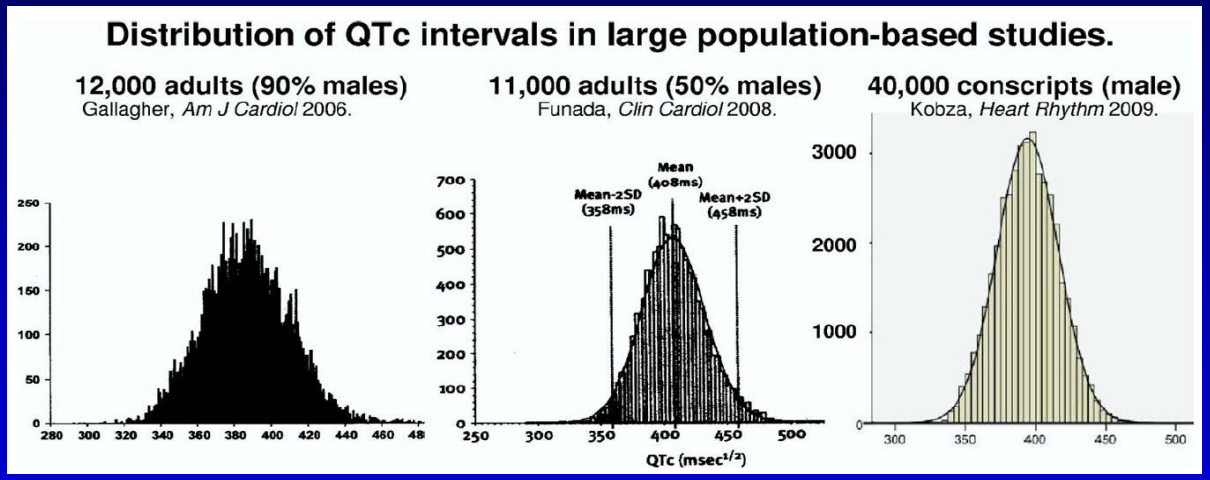
Short QT Syndrome : A Familial Cause of Sudden Death

Fiorenzo Gaita, Carla Giustetto, Francesca Bianchi, Christian Wolpert, Rainer Schimpf, Riccardo Riccardi, Stefano Grossi, Elena Richiardi and Martin Borggrefe

(*Circulation*. 2003;108:965-970.)

- Structural normal heart
- QT < 280 ms QTc ≤ 300 ms
- Narrow, peaked and tall T waves
- Palpitations, syncope and cardiac arrest
- FA/Flutter at young age
- family history of sudden death

Which is the “longest QTc” still compatible with SQTS ?



QTc ≤ 360 ms

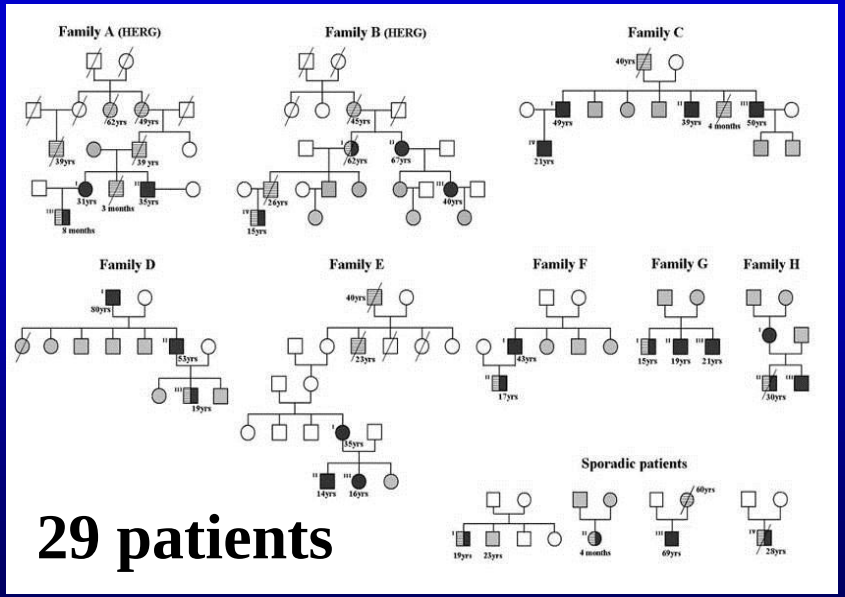
Viskin, *Heart Rhythm* 2009

Short QT syndrome: clinical findings and diagnostic–therapeutic implications

Carla Giustetto[1]*, Fernando Di Monte[1], Christian Wolpert[2], Martin Borggrefe[2], Rainer Schimpf[2], Pascal Sbragia[3], Gianpiero Leone[4], Philippe Maury[5], Olli Anttonen[6], Michel Haissaguerre[7], and Fiorenzo Gaita[1]

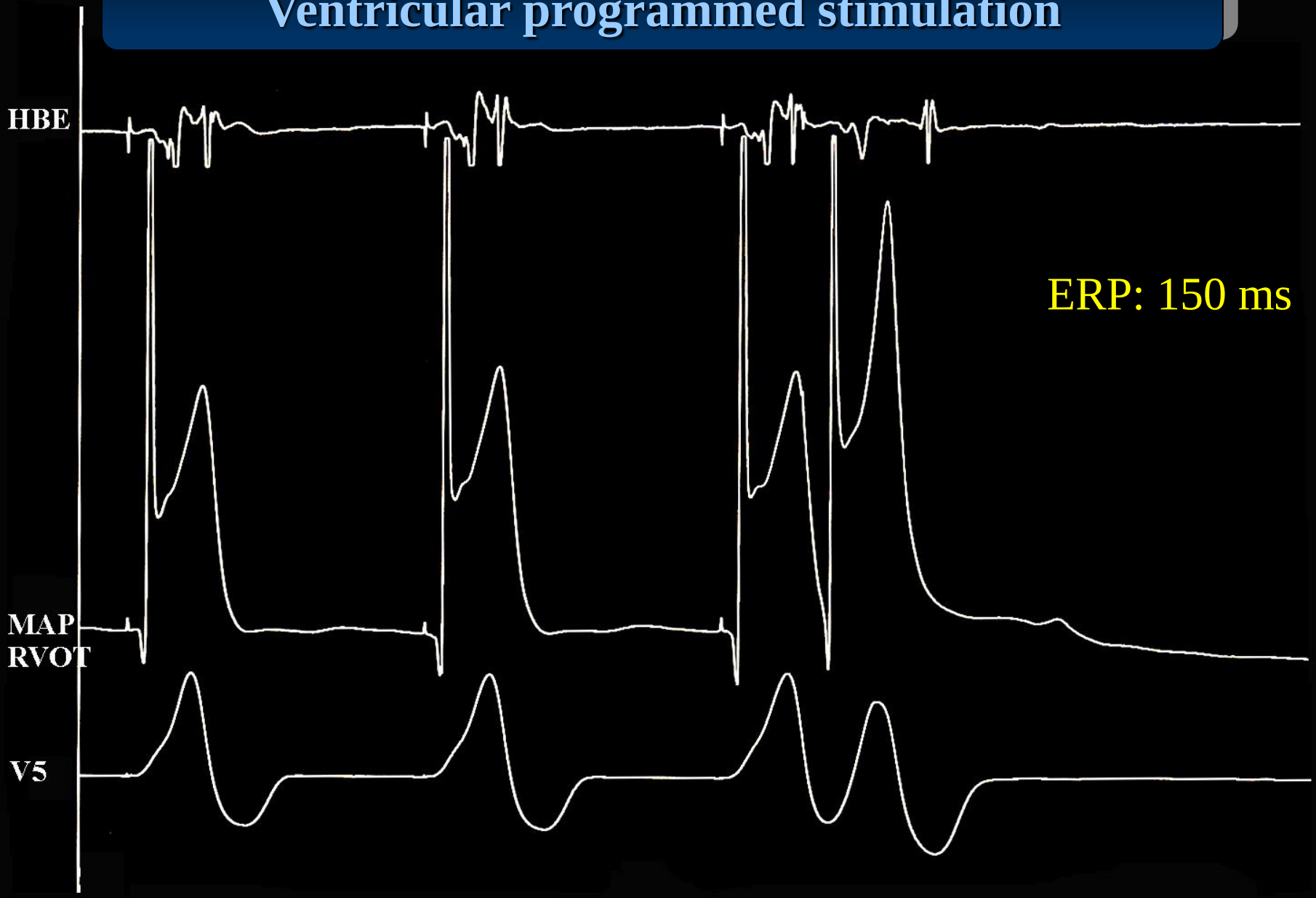
Eur Heart J. 2006

QTc ≤ 340 ms



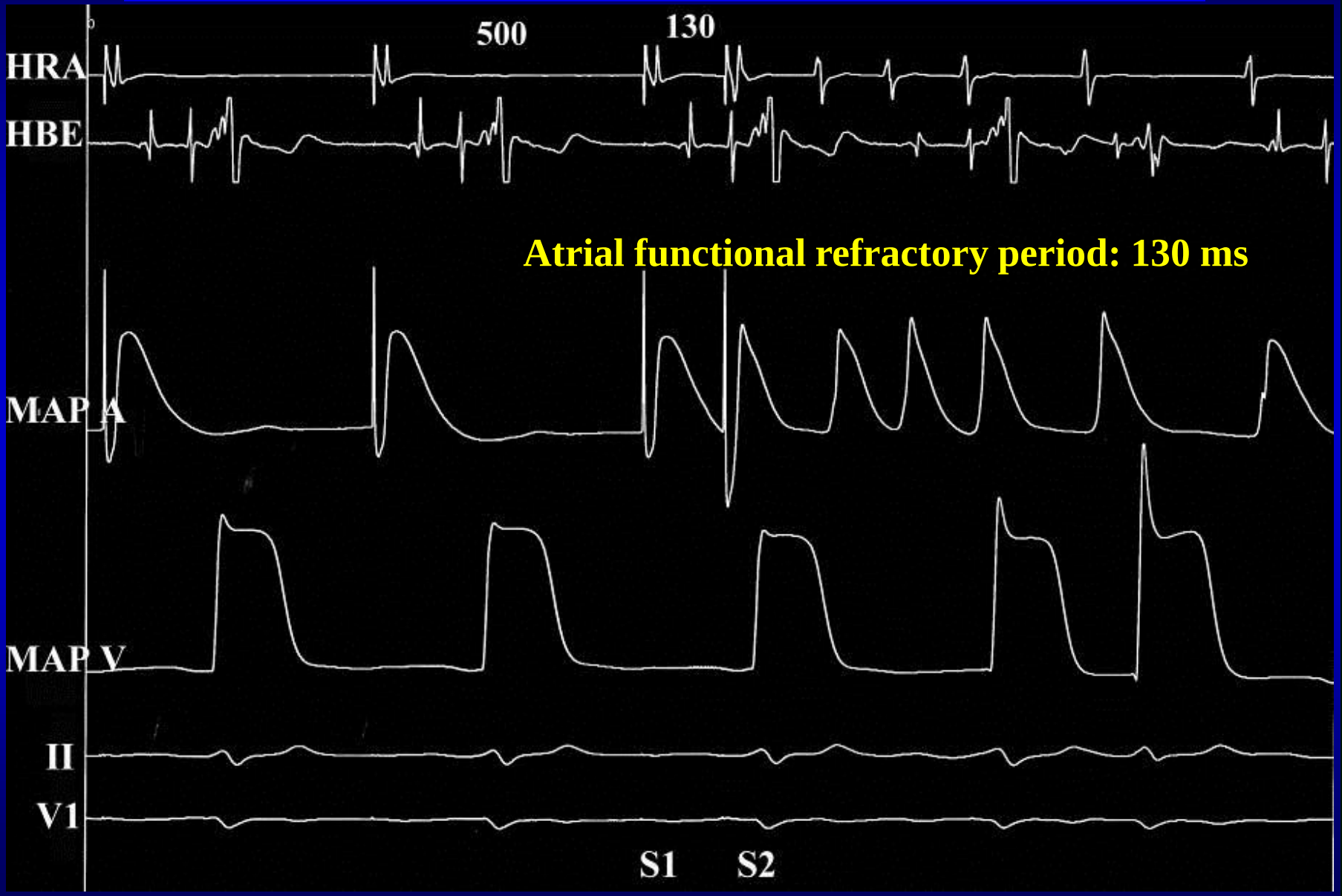
29 patients

Ventricular programmed stimulation

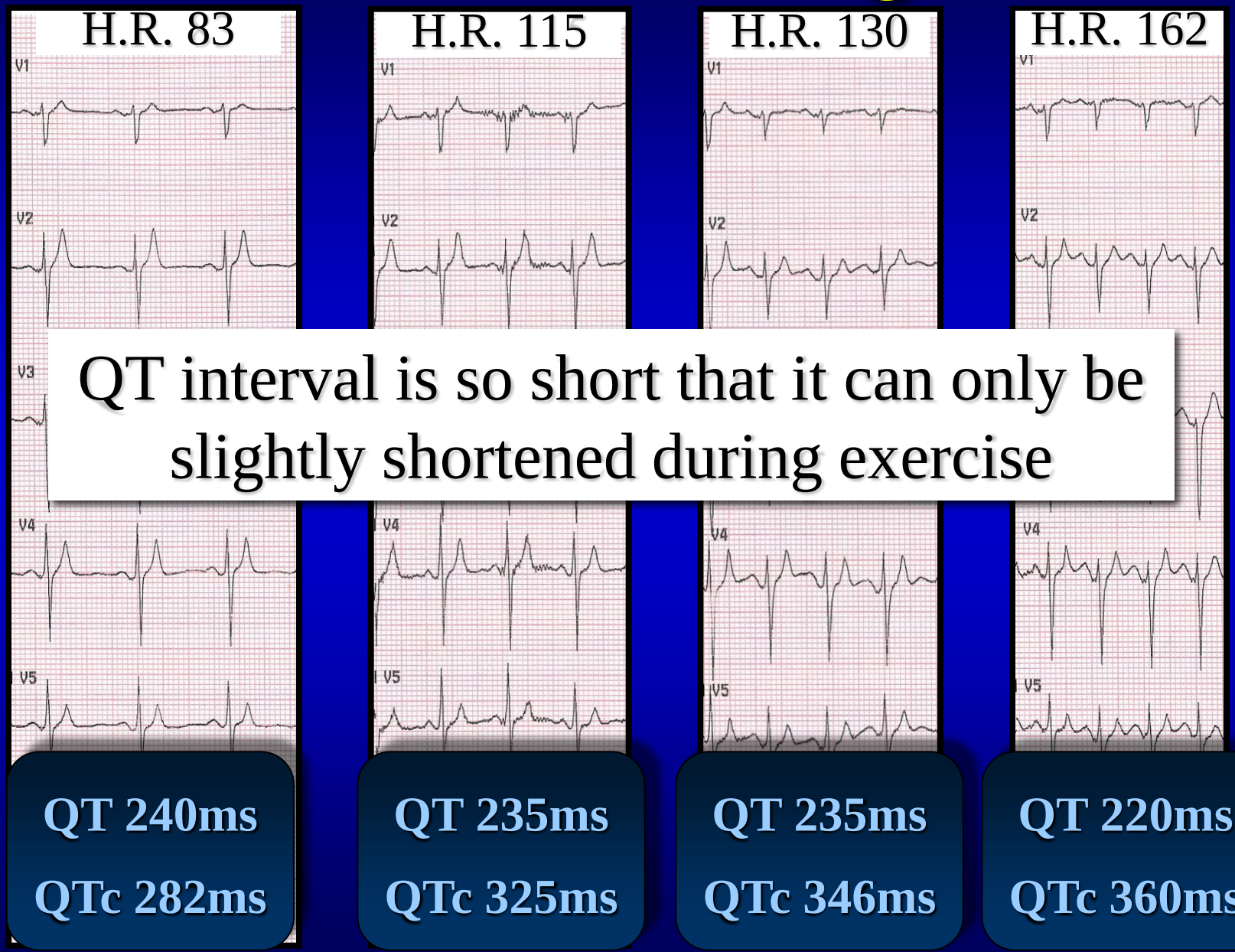


VF induced during catheter positioning

Atrial programmed stimulation



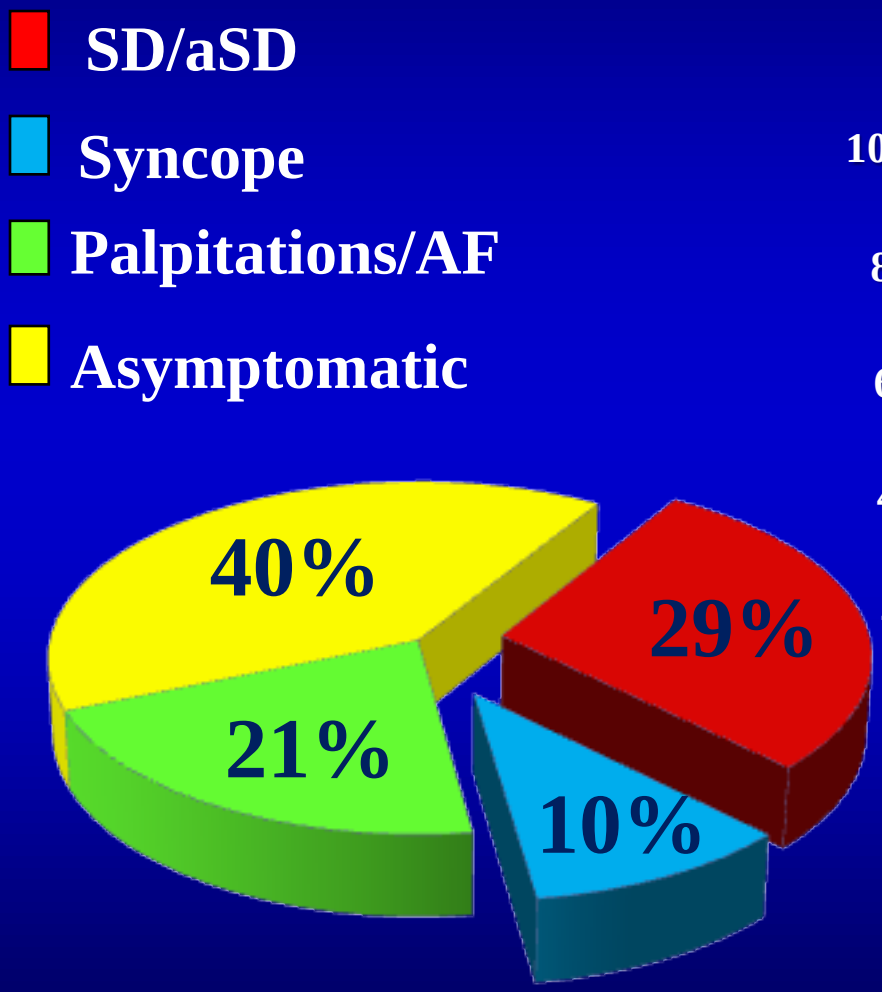
Stress test: 31 yrs

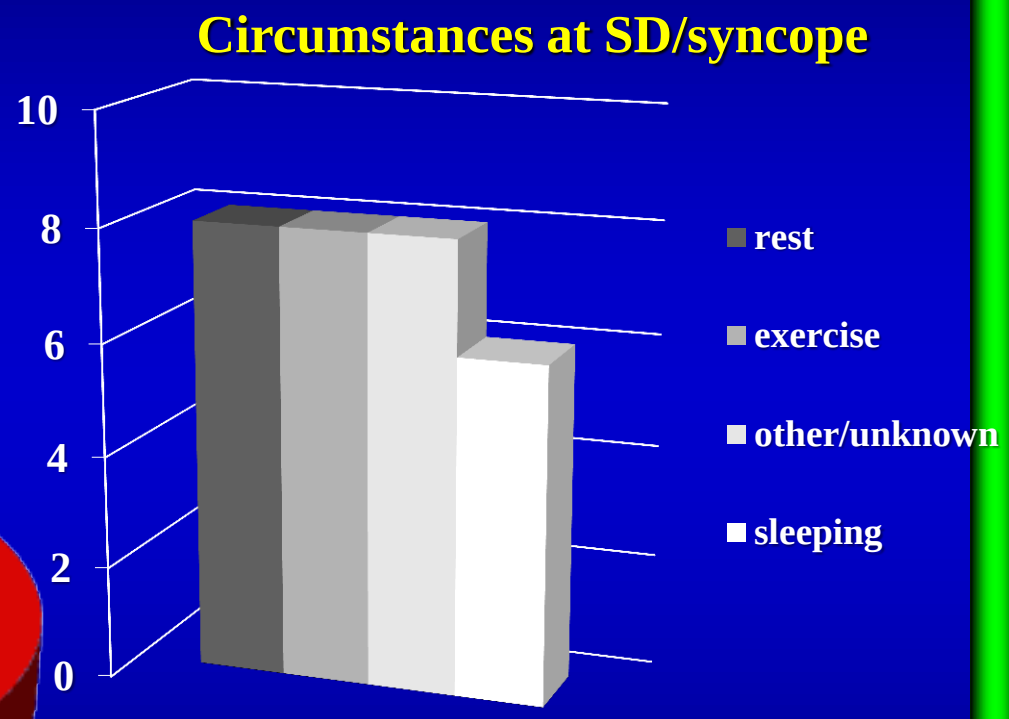


QT interval is so short that it can only be slightly shortened during exercise

QT 240ms	QT 235ms	QT 235ms	QT 220ms
QTc 282ms	QTc 325ms	QTc 346ms	QTc 360ms

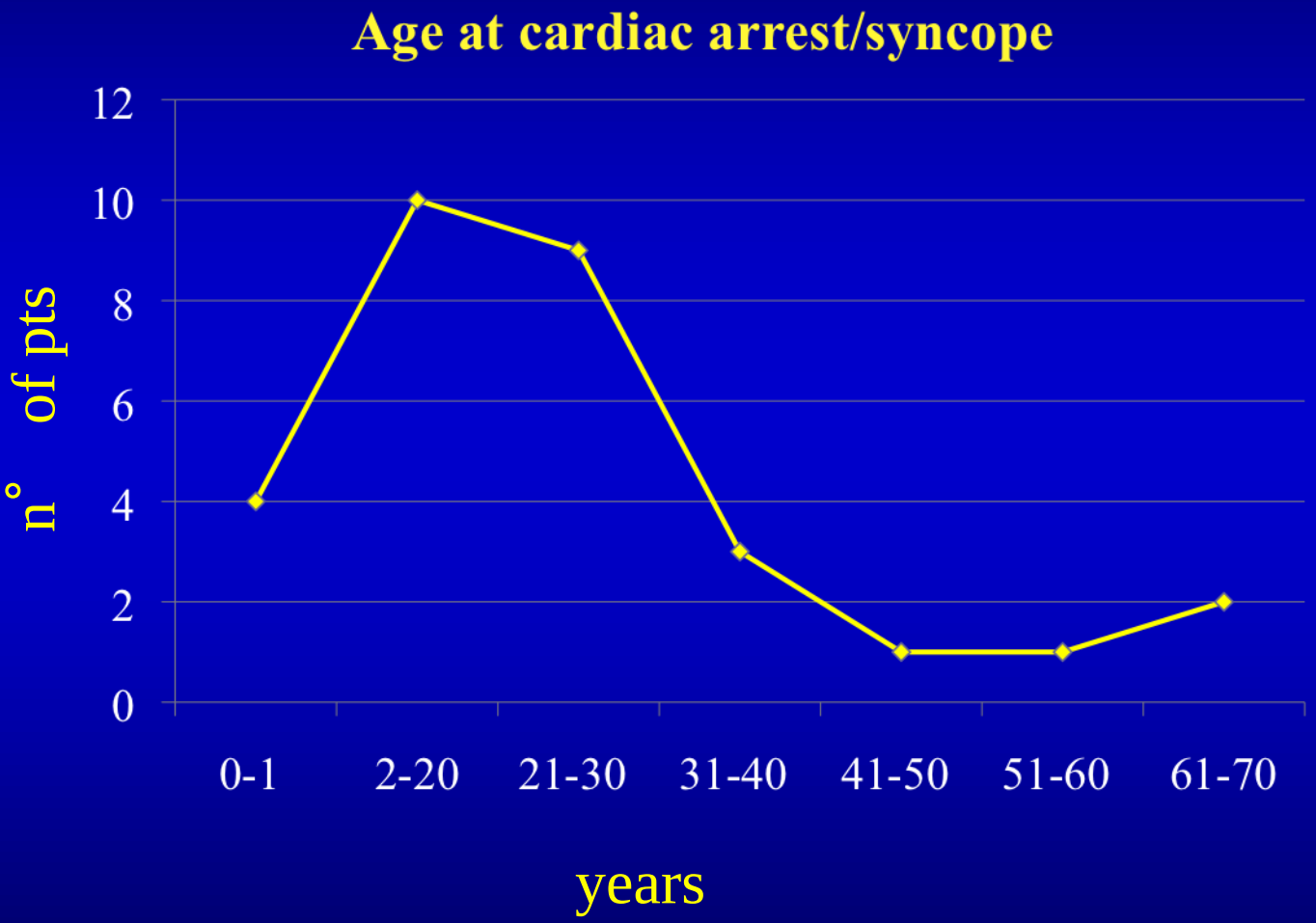
Short QT: first clinical manifestation





Data from SQT Registry, Prof Gaita and Giustetto

Short QT : major arrhythmic events distribution by age and gender

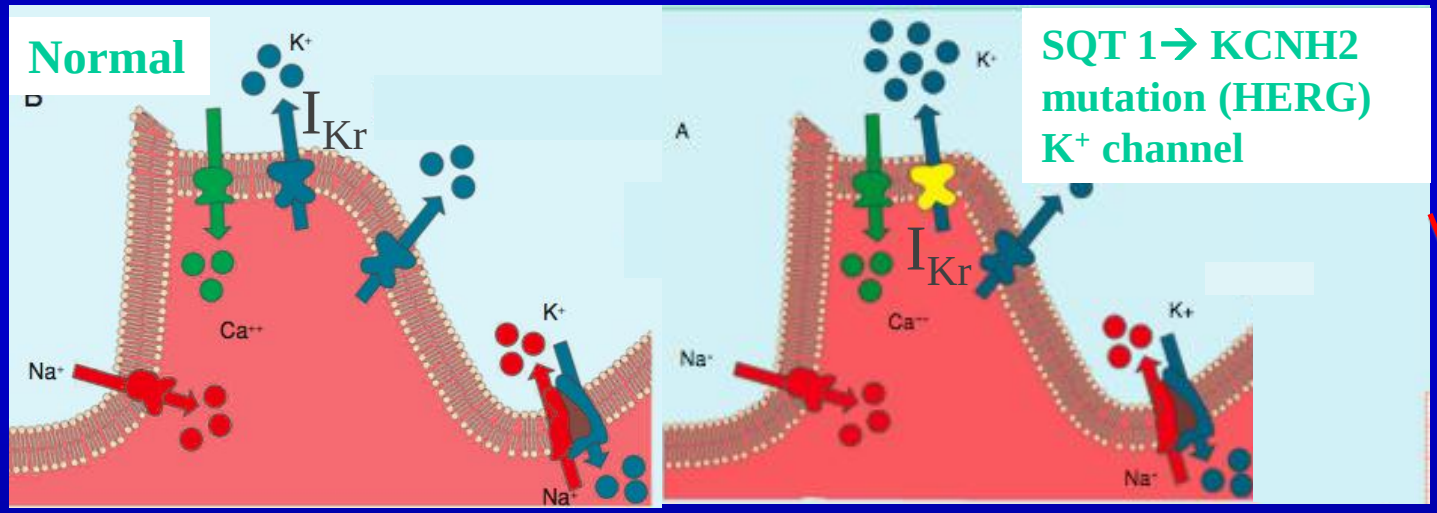


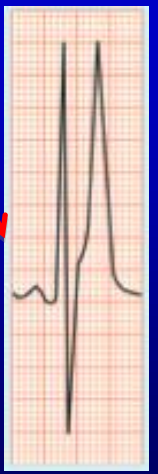
Data from SQT Registry, Prof Gaita and Giustetto

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
(*Circulation*. 2004;109:30-35.)

Sudden Death Associated With Short-QT Syndrome Linked to Mutations in HERG

Ramon Brugada, Kui Hong, Robert Dumaine, Jonathan Cordeiro, Fiorenzo Gaita, Martin Borggrefe, Teresa M. Menendez, Josep Brugada, Guido D. Pollevick, Christian Wolpert, Elena Burashnikov, Kiyotaka Matsuo, Yue Sheng Wu, Alejandra Guerchicoff, Francesca Bianchi, Carla Giustetto, Rainer Schimpf, Pedro Brugada and Charles Antzelevitch

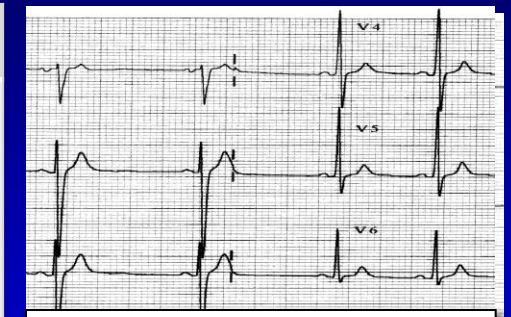




I_{Kr} gain of function → Reduction of action potential duration and refractoriness

Short QT : diagnosis

	Points
QTc, ms	
<300	4
300-320 + peaked and symmetric T wave without ST segment	4
300-320	3
320-339	2
340-360	1
Clinical history	
polymorphic VT/VF triggered by short coupled PVC	3
history of cardiac arrest	3
syncope	1
atrial fibrillation (<40 years old)	1
Family history	
first degree relative with QTc <360 ms	1
family history of sudden death	1
sudden infant death syndrome	2
Genotype	
Genotype positive	2
Exercise test	
poor adaptation of QT interval at heart rate	1



QT 300 ms QTc 330 ms

- **syncope**
- **family history of SCD**
- **poor adaptation of QT to HR**

Probability Score:

≤ 2 points : low

3 points: intermediate

≥ 4 points: high

Prof Gaita, Giustetto and Borggrefe

Short QT : which therapy?

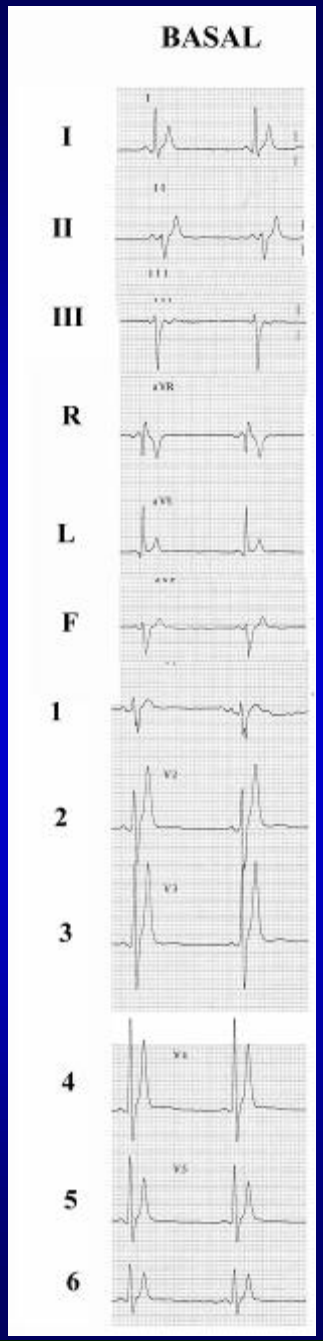
ICD affects the quality of life

- inappropriate shocks
- psychological disorders
- infections
- need of battery replacement every 5-6 years
- need of lead replacement (30-40% after 8 years)*, not negligible mortality in case of necessity of lead removal

Not available in some countries

Still more problems in children

* Maisel et al, Circulation 2008; 117:2721-23



Short QT Syndrome: Pharmacological Treatment

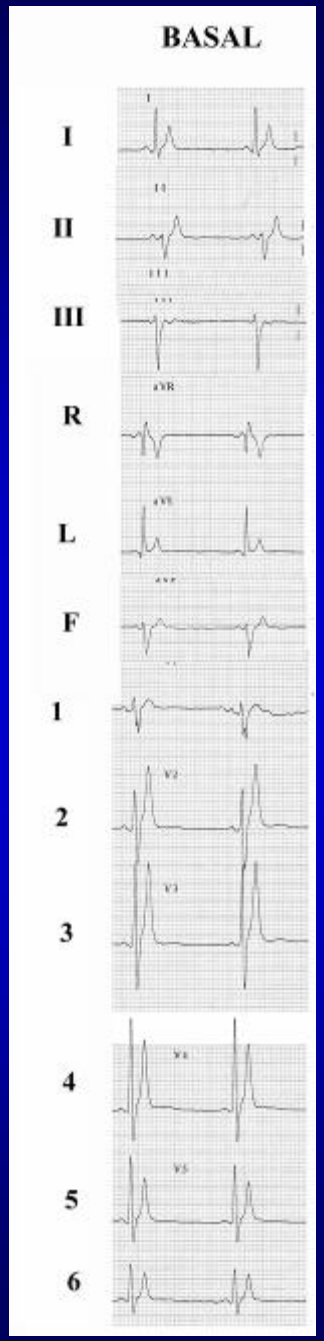
F. Gaita, MD; C. Giustetto, MD; F. Bianchi, MD; R. Schimpf, MD; M. Haissaguerre; MD, L. Calò, MD; R. Brugada, MD; C. Antzelevitch, PhD; M. Borggrefe, MD; C. Wolpert, MD.

J Am Coll Cardiol 2004; 43: 1494-99

blocks I_{Na}^{+}-type, Ca^{++} I_{to}, I_{Kr}, I_{K1}, RYR2 channel

QT 280 ms
QTc 260 ms

Gaita, JACC 2004



Short QT Syndrome: Pharmacological Treatment

F. Gaita, MD; C. Giustetto, MD; F. Bianchi, MD; R. Schimpf, MD; M. Haissaguerre; MD, L. Calò, MD; R. Brugada, MD; C. Antzelevitch, PhD; M. Borggrefe, MD; C. Wolpert, MD.

J Am Coll Cardiol 2004; 43: 1494-99

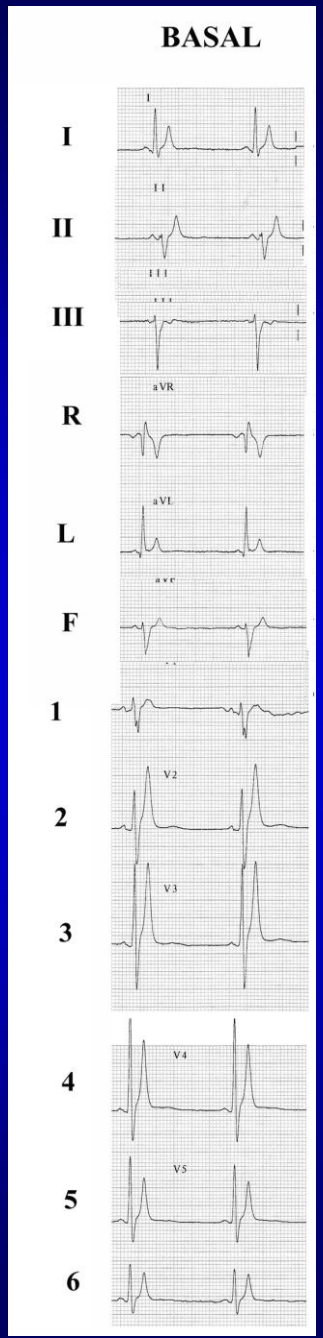
blocks I_{Kr}

blocks I_{Kr}

β-adrenergic receptors

QT 290 ms
QTc 290 ms

Gaita, JACC 2004



Short QT Syndrome: Pharmacological Treatment

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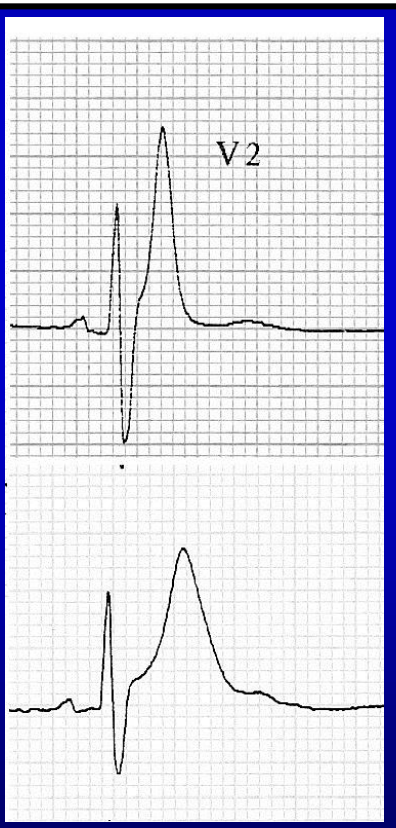
J Am Coll Cardiol 2004; 43: 1494-99

blocks I_{Na+}, I_{Kr}, I_{K1}, I_{to}, I_{K-ATP}, I_{Ks}

QT 440 ms
QTc 390 ms

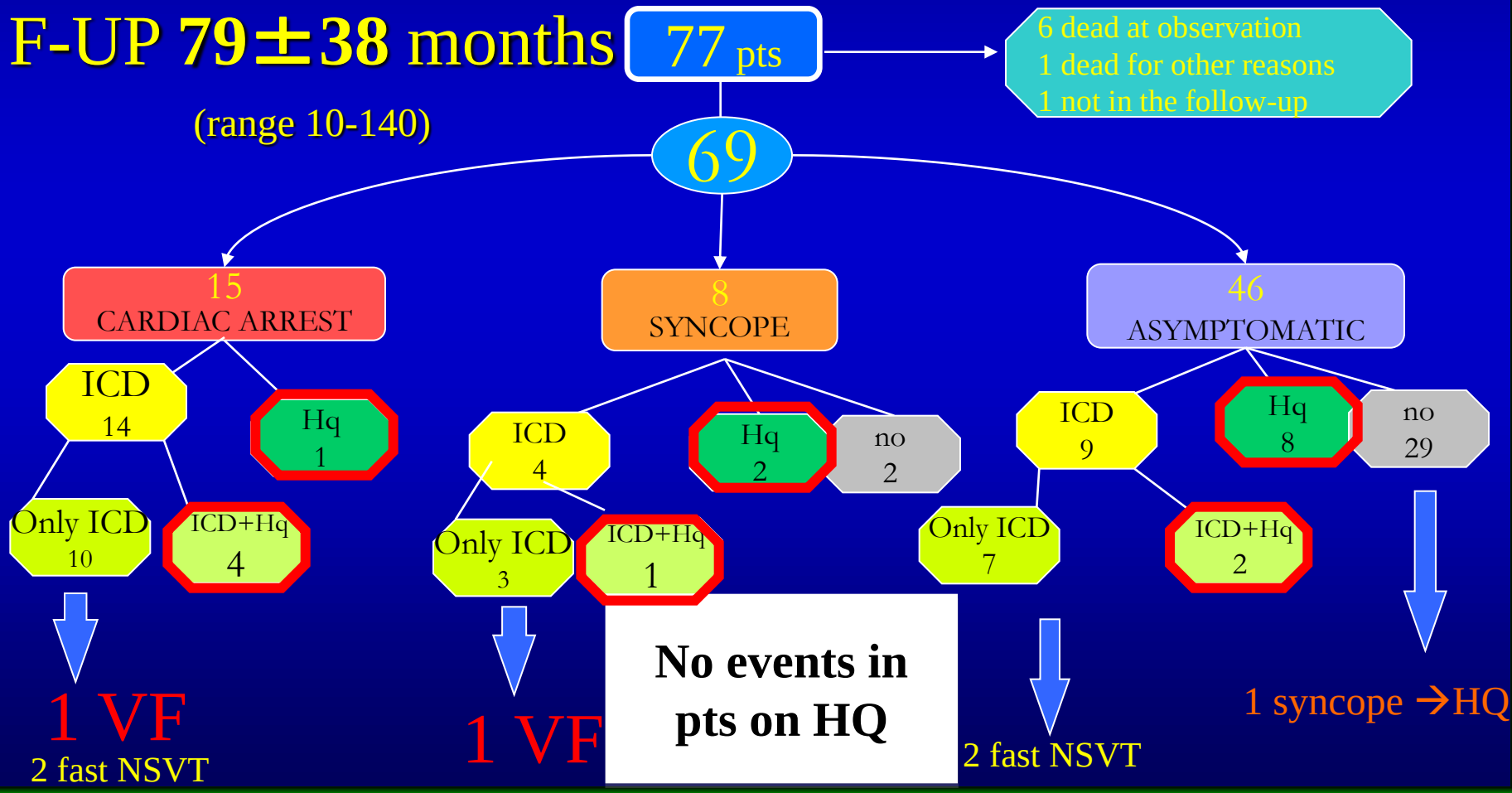


QUINIDINE

Long-Term Follow-Up of Patients With Short QT Syndrome

(J Am Coll Cardiol 2011;58:587–95)

Carla Giustetto, MD,* Rainer Schimpf, MD,† Andrea Mazzanti, MD,* Chiara Scrocco, MD,* Philippe Maury, MD,‡ Olli Anttonen, MD,§ Vincent Probst, MD, PHD,‖ Jean-Jacques Blanc, MD,# Pascal Sbragia, MD,** Paola Dalmasso, MS,†† Martin Borggrefe, MD,† Fiorenzo Gaita, MD*



Short QT : therapy

How to manage symptomatic patients (ACA or syncope)?

In pts with aborted cardiac arrest or syncope, ICD is presently the first-choice therapy

Hydroquinidine must be proposed:

- **those who refuse ICD**
- **those who experience frequent ICD shocks**
- **where ICD is not available**
- **very young patients (bridge to ICD)**

Short QT : therapy

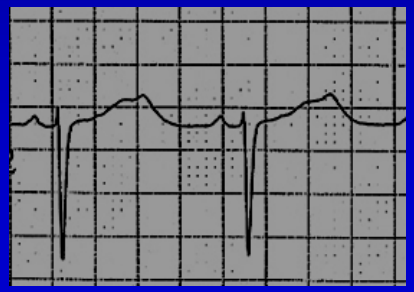
How to manage asymptomatic patients?

As we have not yet definitive data on predictors of SD, prophylactic treatment with **Hydroquinidine** should be proposed in adult patients from highly symptomatic families, and in newborn or children

Channelopaties

Long QT
(Romano1963-Ward 1964)

0.2-0.4: 1.000



Polymorphic adrenergic ventricular tachycardia (Coumel 1978)

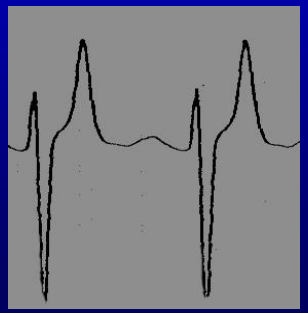
< 0.1 : 1.000

ST elevation V_1-V_3
(Brugada 1991)

0.5-7 : 1.000

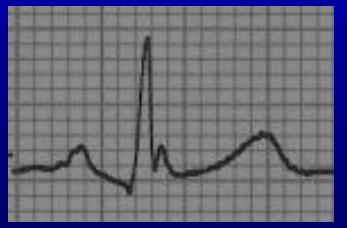
Short QT
(Gaita-Giustetto-Borggrefe 2003)

< 0.1 : 1.000



Early repolarization
(Haïssaguerre-Rosso 2008)

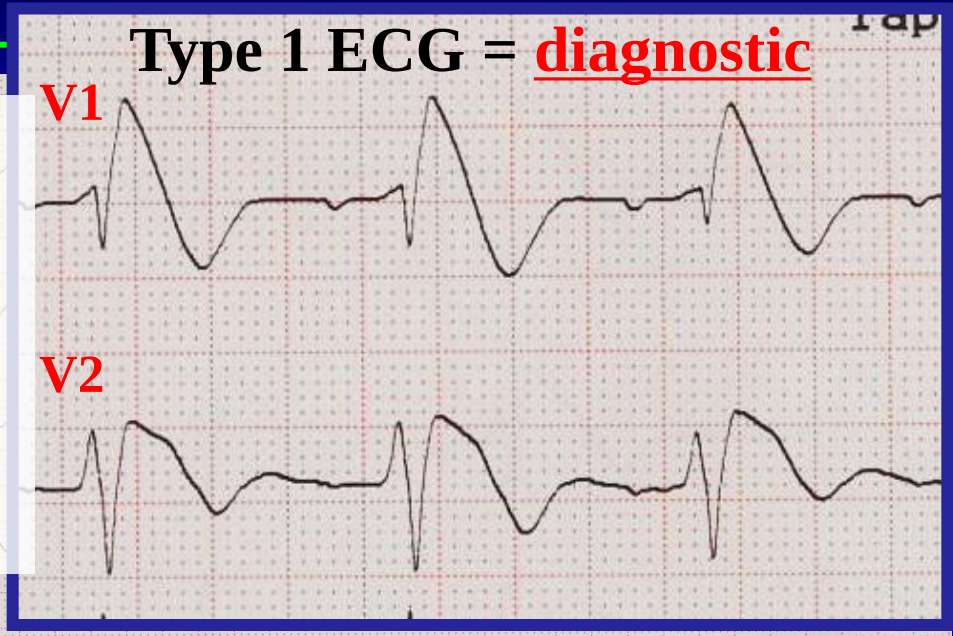
10-100 : 1.000

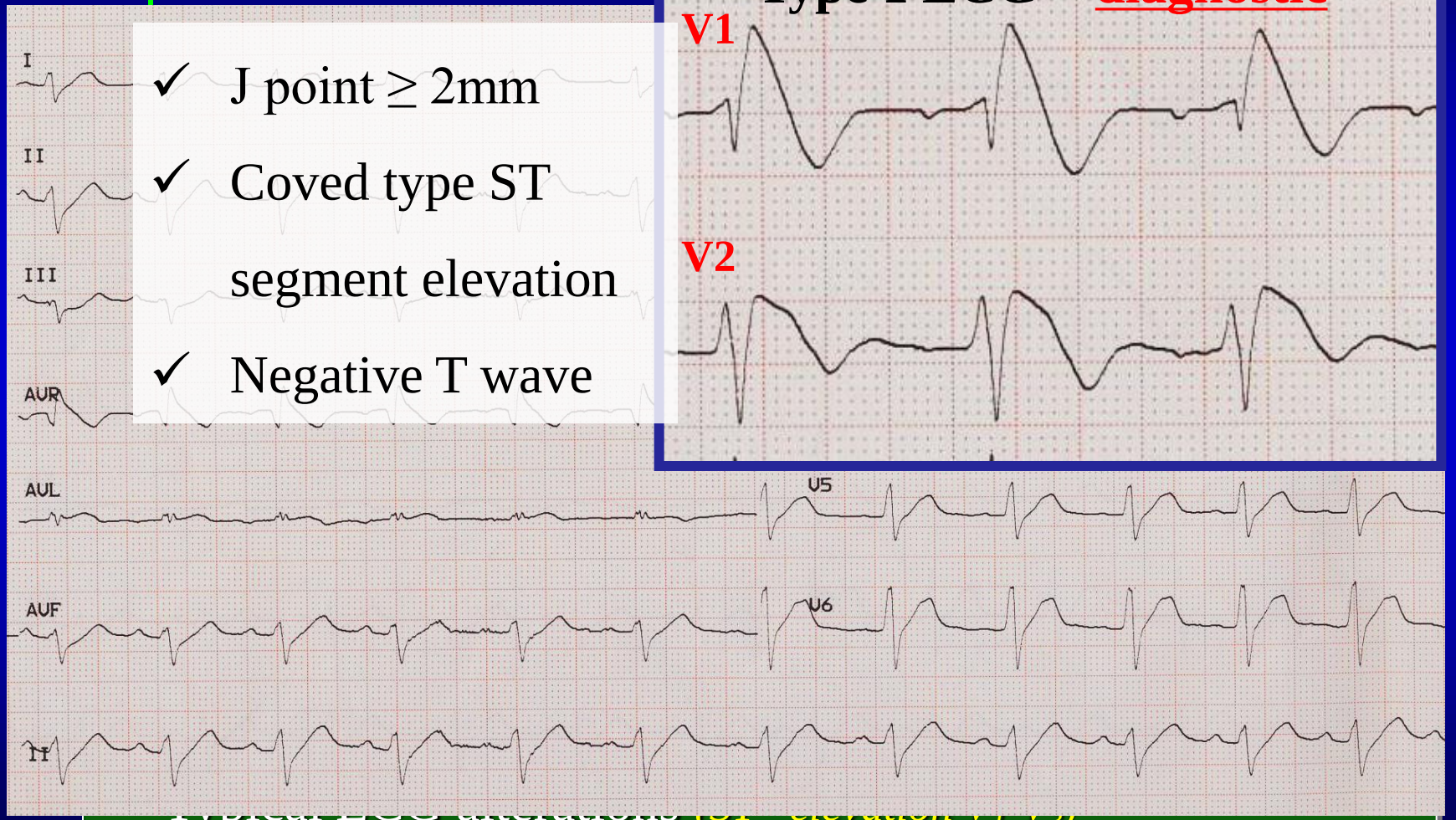


ST segment elevation in right precordial leads (Brugada)

- ✓ J point ≥ 2mm
- ✓ Coved type ST segment elevation
- ✓ Negative T wave

Type 1 ECG = diagnostic





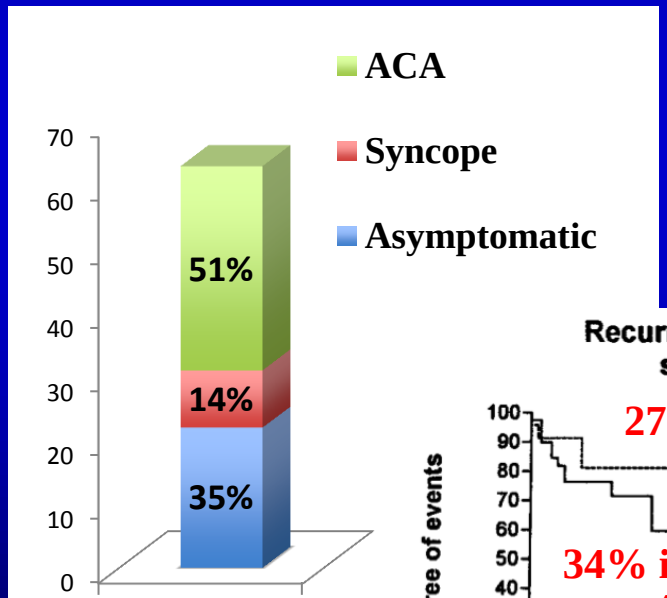
Typical ECG alterations (ST elevation V1-V3)

Circulation. 1998;97:457-460.

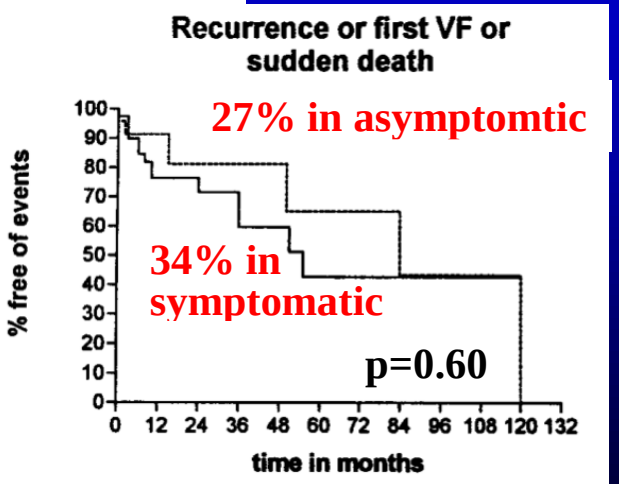
Right Bundle-Branch Block and ST-Segment Elevation in Leads V_1 Through V_3

A Marker for Sudden Death in Patients Without Demonstrable Structural Heart Disease

Josep Brugada, MD; Ramon Brugada, MD; Pedro Brugada, MD

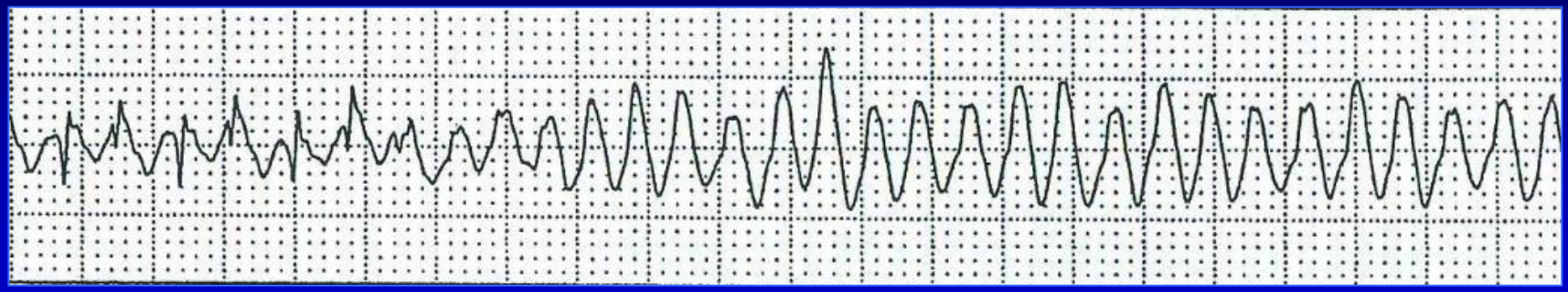


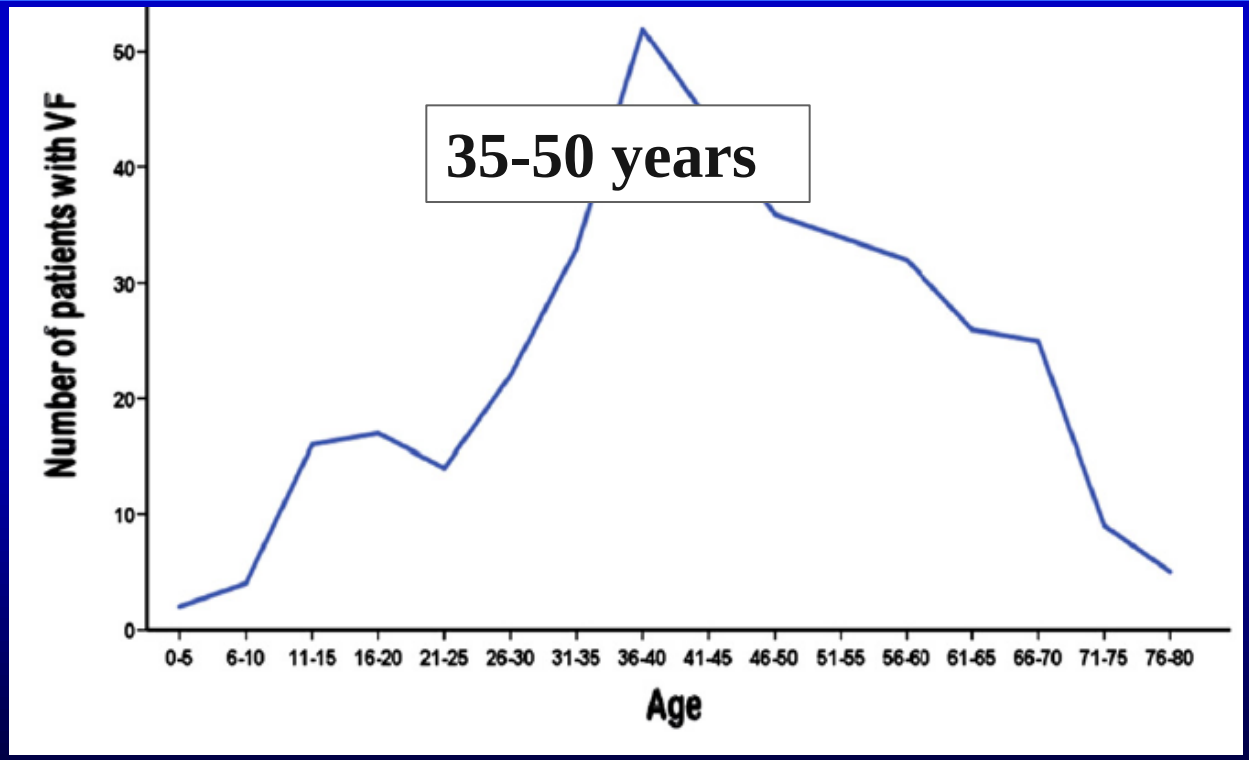
Brugada 1998



ICD for all the pts?

Incidence of arrhythmic events in Brugada pts according to age





Benito *et al*, Progress in Cardiovascular Diseases 2008, 51

Brugada Piedmont Registry 2001-2013

596 pts (mean age 45 ±14 years; 78% males)

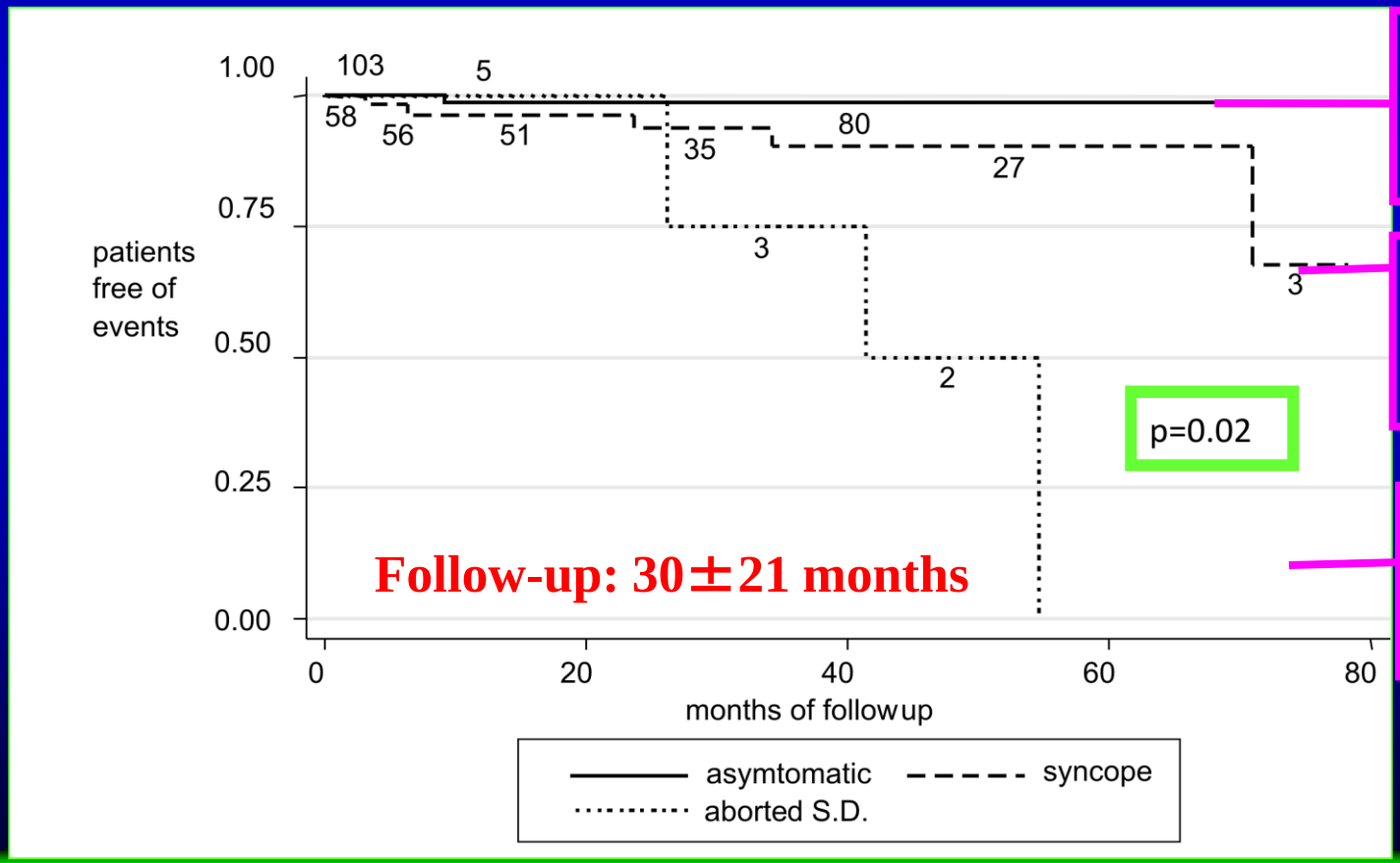
Prospective registry, including consecutive patients with Brugada ECG, from the the main Cardiology Division of the Piedmont region with the aim of evaluating:

- ✓ clinical history
- ✓ previous symptoms (sudden death, syncope)
- ✓ family history
- ✓ presence of spontaneous type 1 ECG pattern
- ✓ age and circumstances of arrhythmic events
- ✓ role of electrophysiological study
- ✓ **prognostic factors**

Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study

Europace 2009; 11 (4): 507-13

Carla Giustetto[1]*, Stefano Drago[1], Pier Giuseppe Demarchi[2], Paola Dalmasso[3], Francesca Bianchi[4], Andrea Sibona Masi[5], Paula Carvalho[6], Eraldo Occhetta[7], Guido Rossetti[8], Riccardo Riccardi[4], Roberta Bertona[9], Fiorenzo Gaita[1], and On behalf of the Italian Association of Arrhythmology and Cardiostimulation (AIAC)—Piedmont Section



1/103 (1%) asymptomatic 0.4% per year

5/58 (8.6%) syncope 3% per year

3/5 (60%) cardiac arrest 17% per year

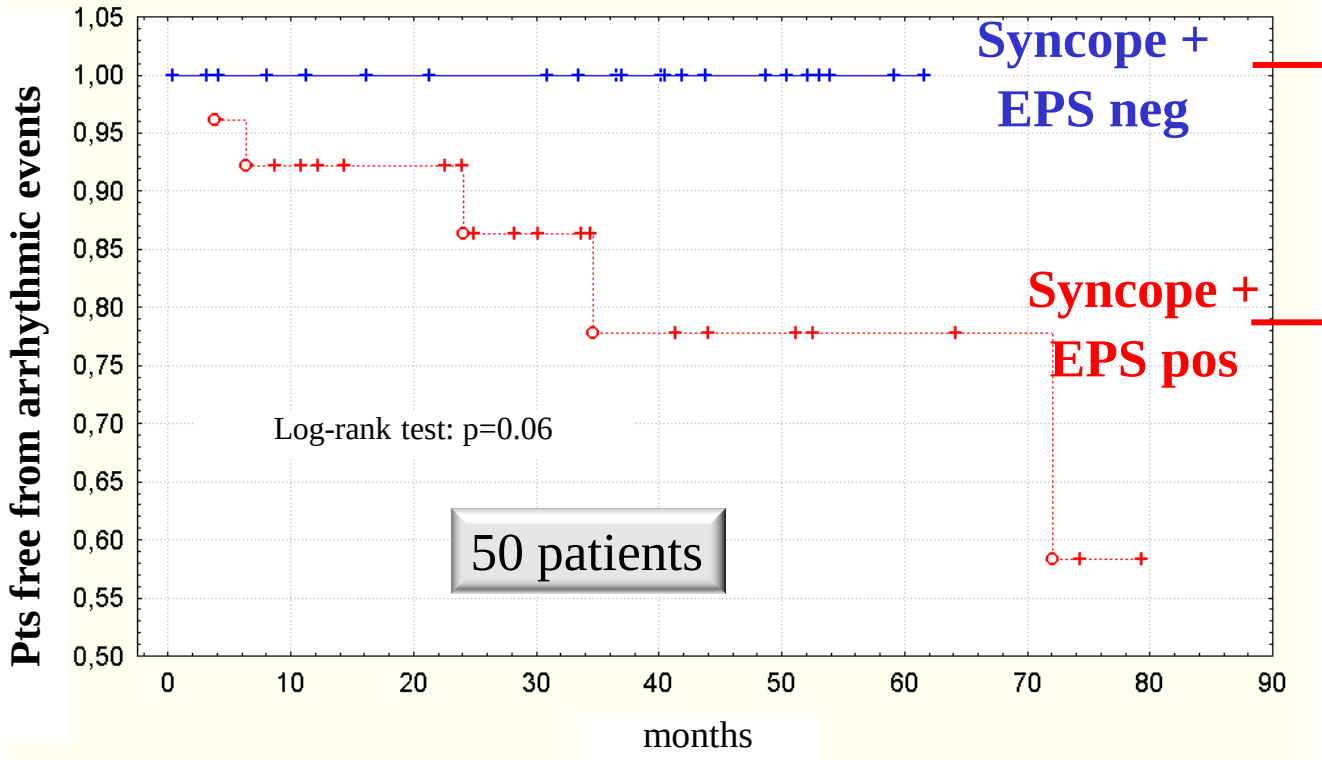
Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study

Carla Giustetto[1]*, Stefano Drago[1], Pier Giuseppe Demarchi[2], Paola Dalmasso[3], Francesca Bianchi[4], Andrea Sibona Masi[5], Paula Carvalho[6], Eraldo Occhetta[7], Guido Rossetti[8], Riccardo Riccardi[4], Roberta Bertona[9], Fiorenzo Gaita[1], and On behalf of the Italian Association of Arrhythmology and Cardiostimulation (AIAC)—Piedmont Section

Europace 2009; 11 (4): 507-13

EP-study in pts with syncope

Mean follow-up 30 ±21 months



0/24 events

5/26 (19%)
2 with spontaneous type 1 ECG

7.6% per year

Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study

Carla Giustetto[1]*, Stefano Drago[1], Pier Giuseppe Demarchi[2], Paola Dalmasso[3], Francesca Bianchi[4], Andrea Sibona Masi[5], Paula Carvalho[6], Eraldo Occhetta[7], Guido Rossetti[8], Riccardo Riccardi[4], Roberta Bertona[9], Fiorenzo Gaita[1], and On behalf of the Italian Association of Arrhythmology and Cardiostimulation (AIAC)—Piedmont Section

Europace 2009; 11 (4): 507-13

Aims Risk stratification of patients with Brugada electrocardiogram (ECG) is being strongly debated. Conflicting results have been suggested from international registries, which enrolled non-consecutive cases, studied with different programmed electrical stimulation (PES) protocols. The aim of this study was to prospectively evaluate the incidence of arrhythmic events and the prognostic role of clinical presentation, ECG, and of a standardized PES protocol in consecutive cases from a community-based population.

Methods and results A total of 166 consecutive patients (45 ± 14 years) with Brugada ECG were enrolled. Type 1 ECG was observed spontaneously in 72 (43%) and after pharmacological testing in 94 (57%). One hundred and three (62%) were asymptomatic, 58 (35%) had syncope, and five (3%) had a prior cardiac arrest. One hundred and thirty-five (81%) underwent PES with two extra stimuli up to ventricular refractoriness and 34% had ventricular fibrillation (VF) induced. Arrhythmic events occurred in nine patients at a mean follow-up of 30 ± 21 months (2.2 events per 100 person-year): in three (60%) patients with aborted sudden death (aSD), five (8.6%) of those with syncope, and one (1%) of the asymptomatic. The only predictors of events were a history of syncope or aSD ($P = 0.02$) and induction at PES ($P = 0.004$).

Conclusion Clinical presentation is the most important parameter in the risk stratification of patients with Brugada ECG. Programmed electrical stimulation seems valuable, particularly in patients with previous syncope.

Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome

Results From the FINGER Brugada Syndrome Registry

V. Probst, MD, PhD*; C. Veltmann, MD*; L. Eckardt, MD*; P.G. Meregalli, MD*; F. Gaita, MD; H.L. Tan, MD, PhD; D. Babuty, MD, PhD; F. Sacher, MD; C. Giustetto, MD; E. Schulze-Bahr, MD, PhD; M. Borggrefe, MD, PhD; M. Haissaguerre, MD; P. Mabo, MD, PhD; H. Le Marec, MD, PhD; C. Wolpert, MD, PhD; A.A.M. Wilde, MD, PhD

Circulation 2010;121:635-643

FINGER registry
(France, Italy, Netherland, Germany)

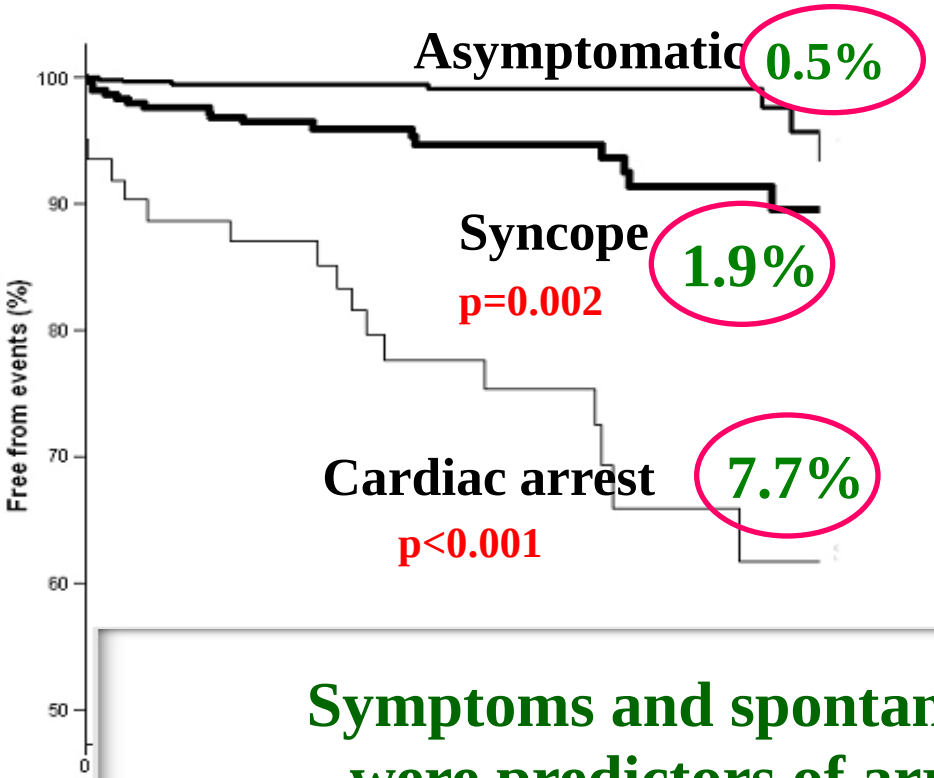
1029 pts

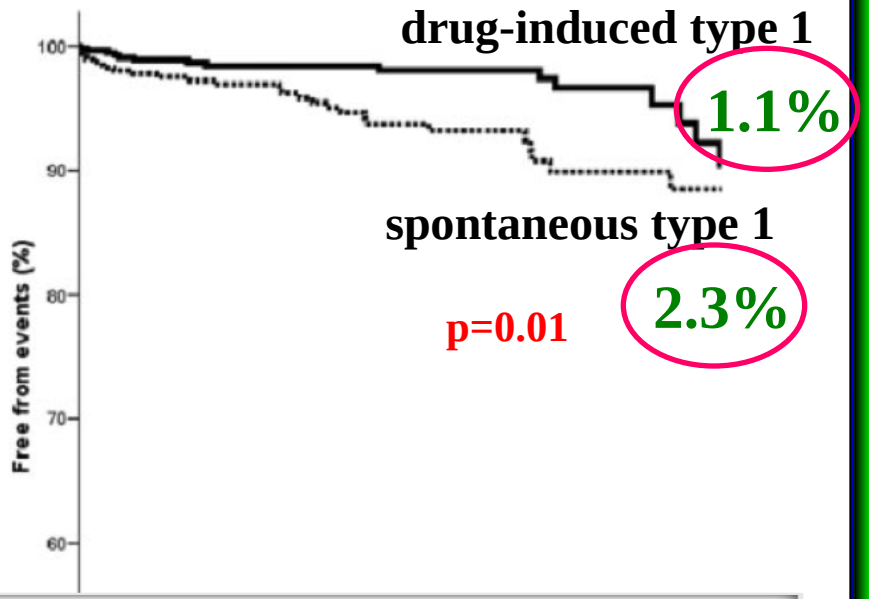
aSD 6% | **syncope 30%** | **asyntomptomatic 64%**

median f-up 32 months

FINGER study: predictors of cardiac events

Event rate per year during 32 months of median f-up





Symptoms and spontaneous type 1 ECG were predictors of arrhythmic events

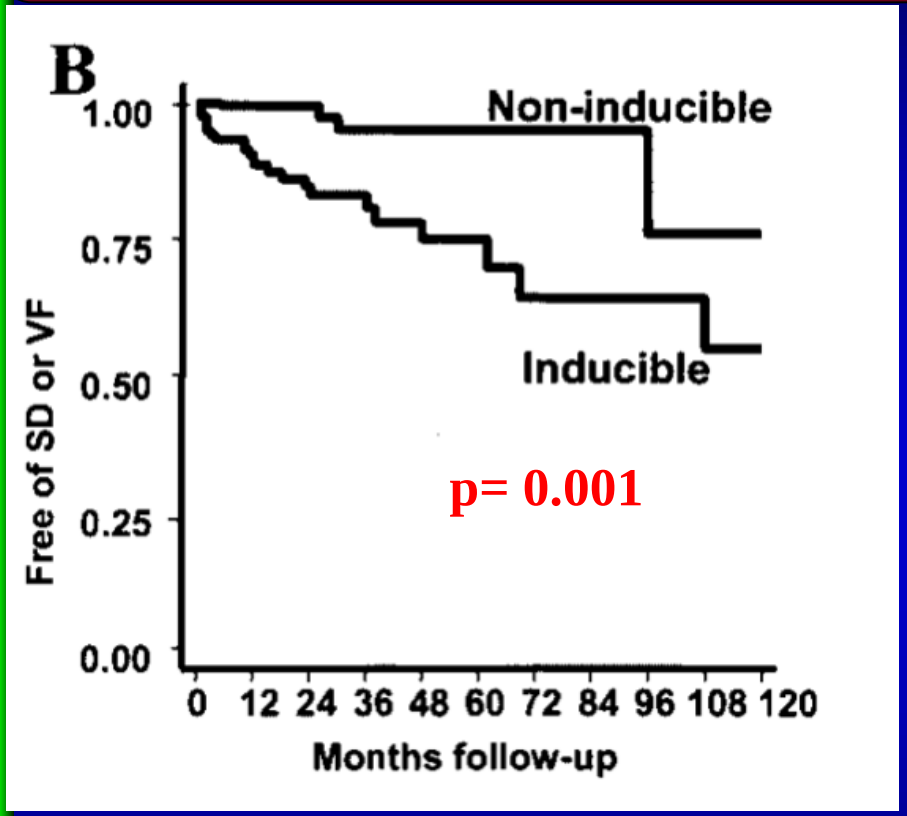
Probst et al, Circulation 2010; 121: 635-643

FINGER study: predictors of cardiac events

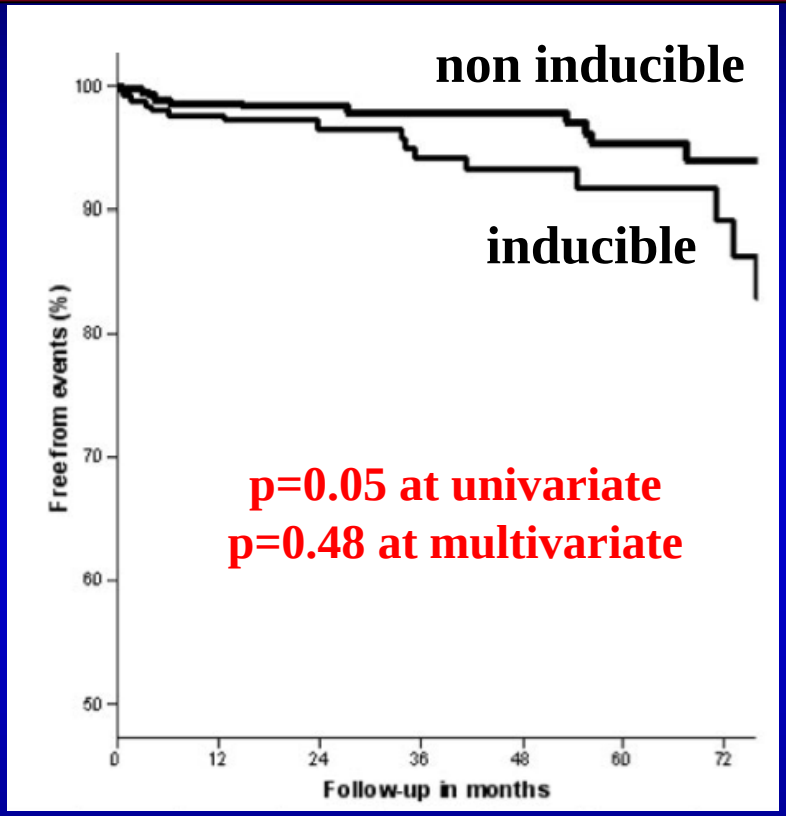
NO predictive factors in asymptomatic patients

- Spontaneous *vs* drug induced type 1 ECG (p=0.26)
- Male *vs* female gender (p=0.35)
- EP study result (p=0.83)

Role of electrophysiological study (EPS) in Brugada patients is debated



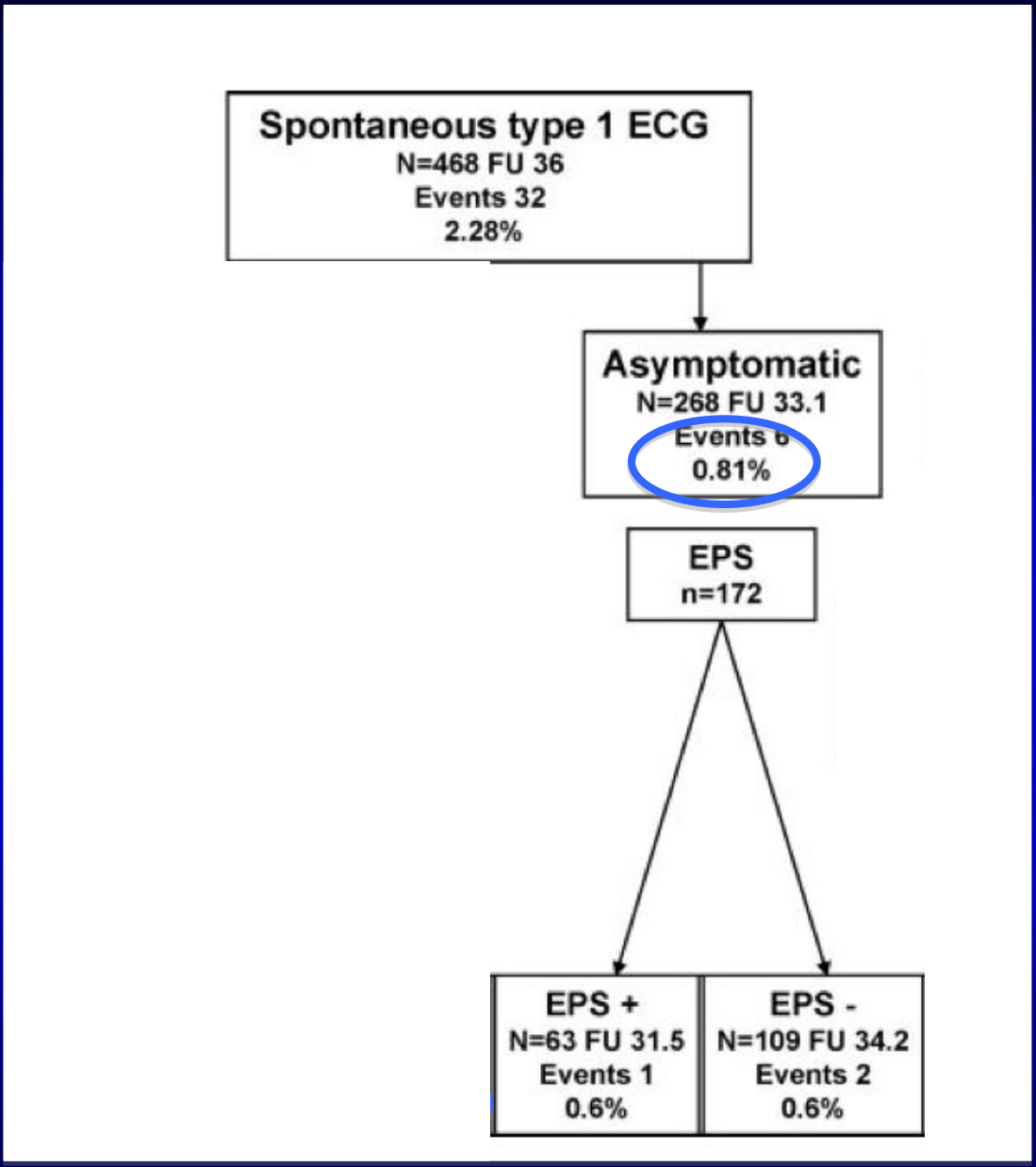
547 pts
- **23% syncope**
- 70% spontaneous type 1 ECG



1029 pts
- **30% syncope**
- 45% spontaneous type 1 ECG

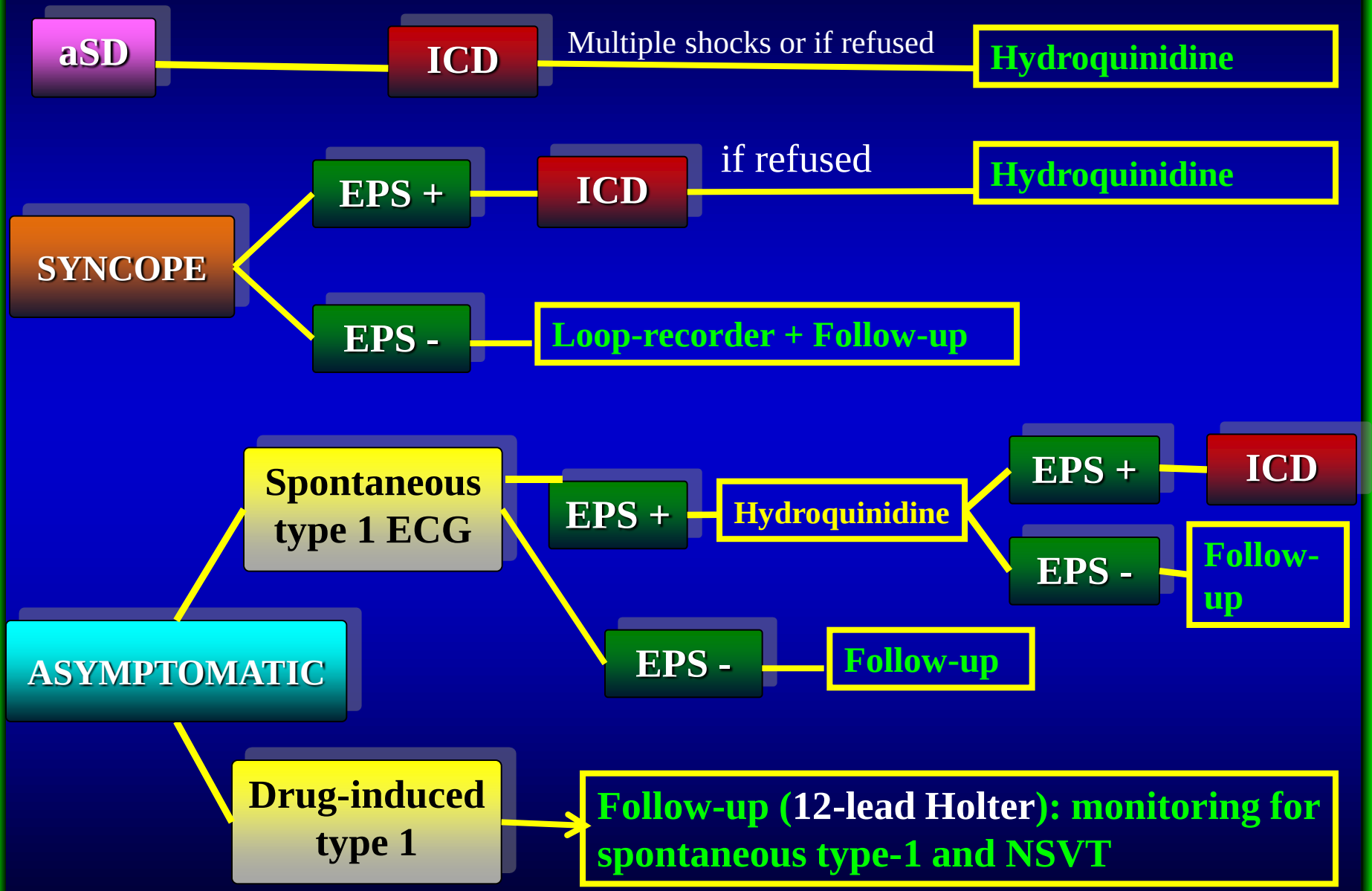
Brugada et al, *Circulation* 2003;108:3092-3096

Probst et al, *Circulation* 2010;121: 635

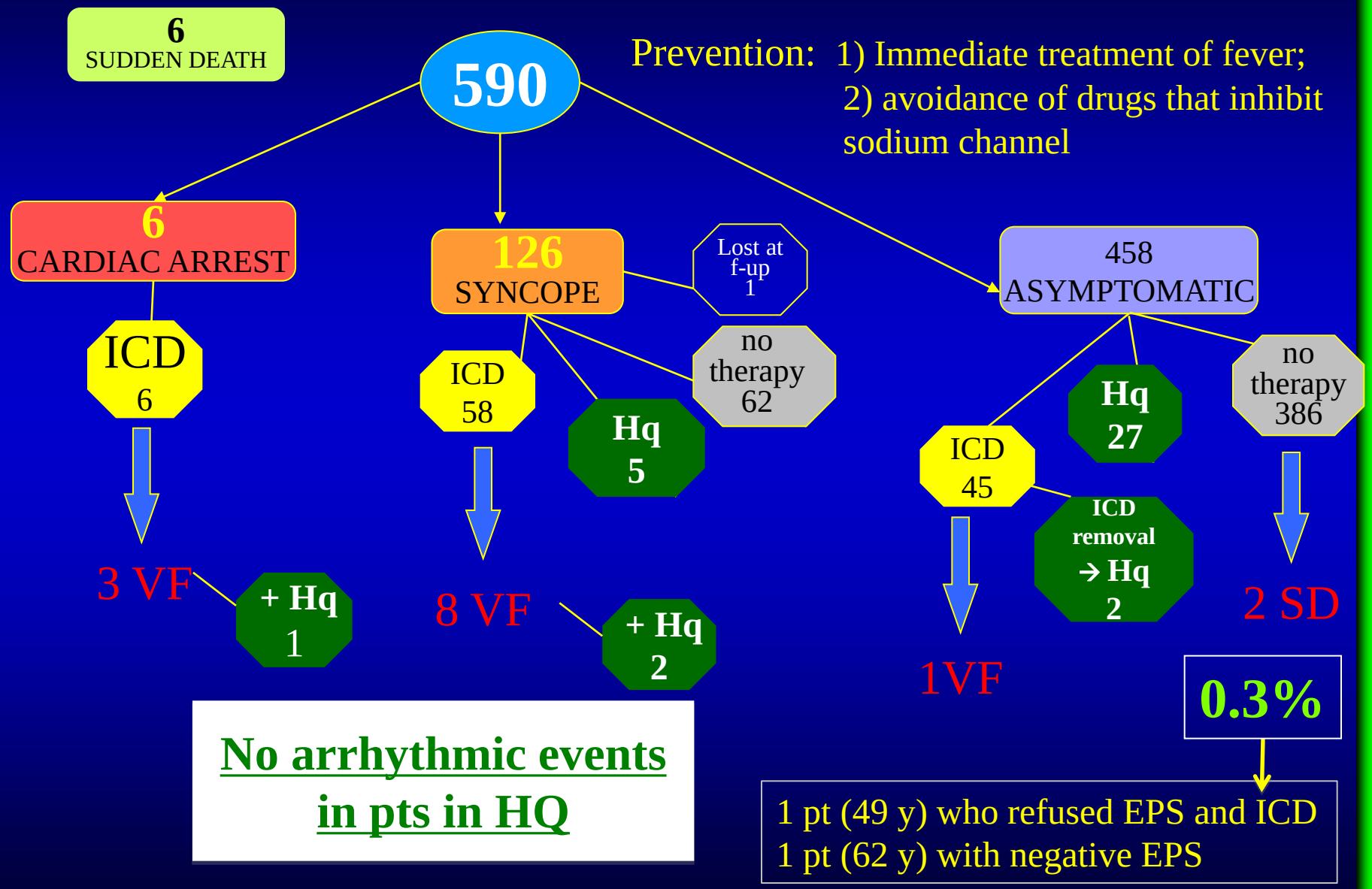


Probst et al, FINGER Registry, Circulation 2010;121: 635

Management of Brugada pts



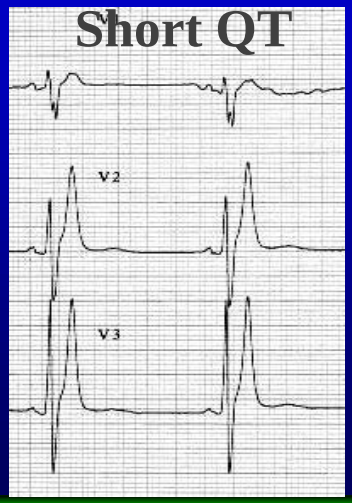
596 pts in the Brugada Piedmont Registry (2001-2013)

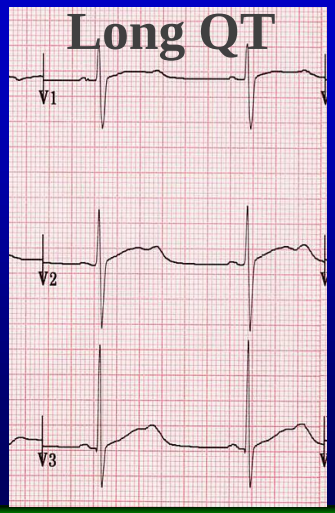


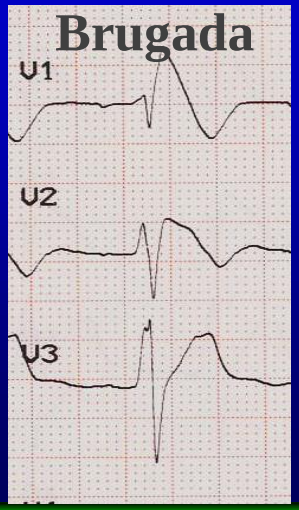
How to identify subjects at risk for sudden death?

Rule out structural heart disease:

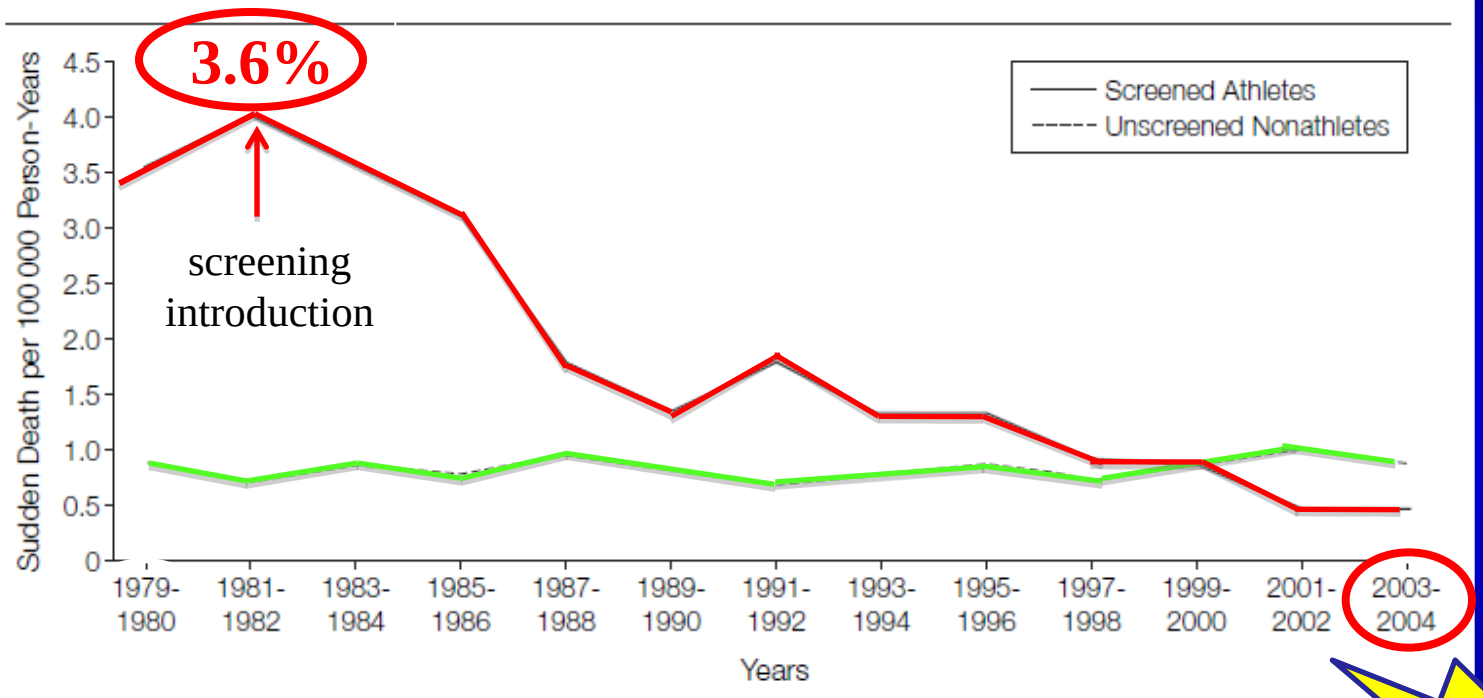
- Cardiological examination
- ECG analysis







Impact of cardiovascular screening in competitive athletes



Reduction of sudden deaths in young athletes= **89%**

Corrado et al, JAMA 2006

Thanks to…

C. Giustetto

R. Riccardi

N. Cerrato

C. Scrocco

M. Borggrefe

E. Richiardi

E. Gribaudo

A. Mazzanti

A. Battaglia

C. Wolpert

P.Carvalho

G. Picciotto

R. Schimpf

PG. Demarchi

Y. Cristoforetti

M. Scaglione

A. Sibona Masi

F. Bianchi

L.Biasco

M. Bortnik

R. Bertona

S. Grossi

C. Budano

E. Occhetta

D. Giachino

GP. Varalda

S. Drago

A. Ferraro

L. Barbonaglia

G. Rossetti