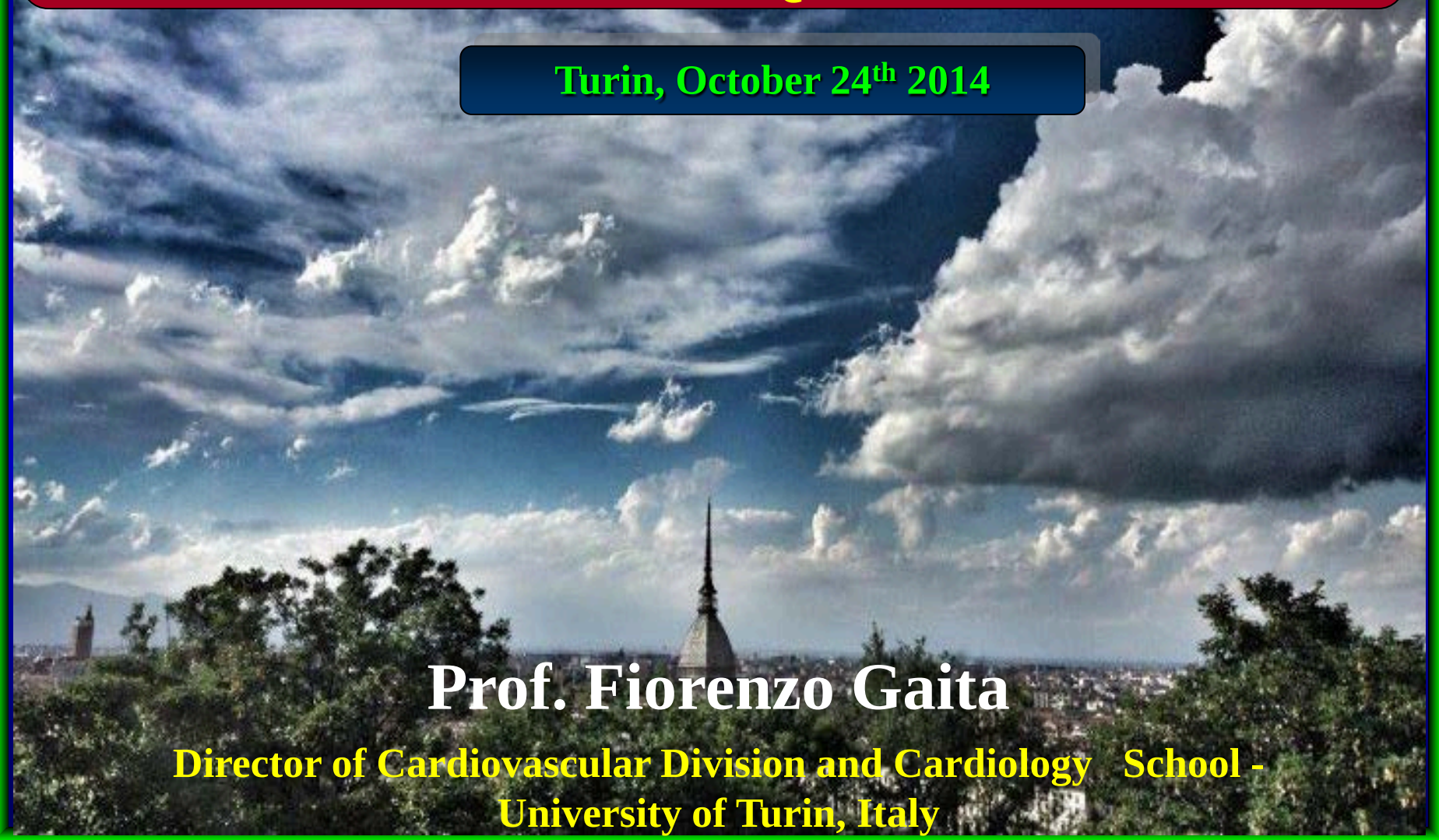
Sudden cardiac death in the setting of cardiac channellopaties

How to manage patients with asymptomatic Short QT

Turin, October 24th 2014



Prof. Fiorenzo Gaita

Director of Cardiovascular Division and Cardiology School - University of Turin, Italy

NO CONFLICT OF INTEREST TO DECLARE CONCERNING THIS TOPIC

Asymptomatic SQTS management: what guidelines say

Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013

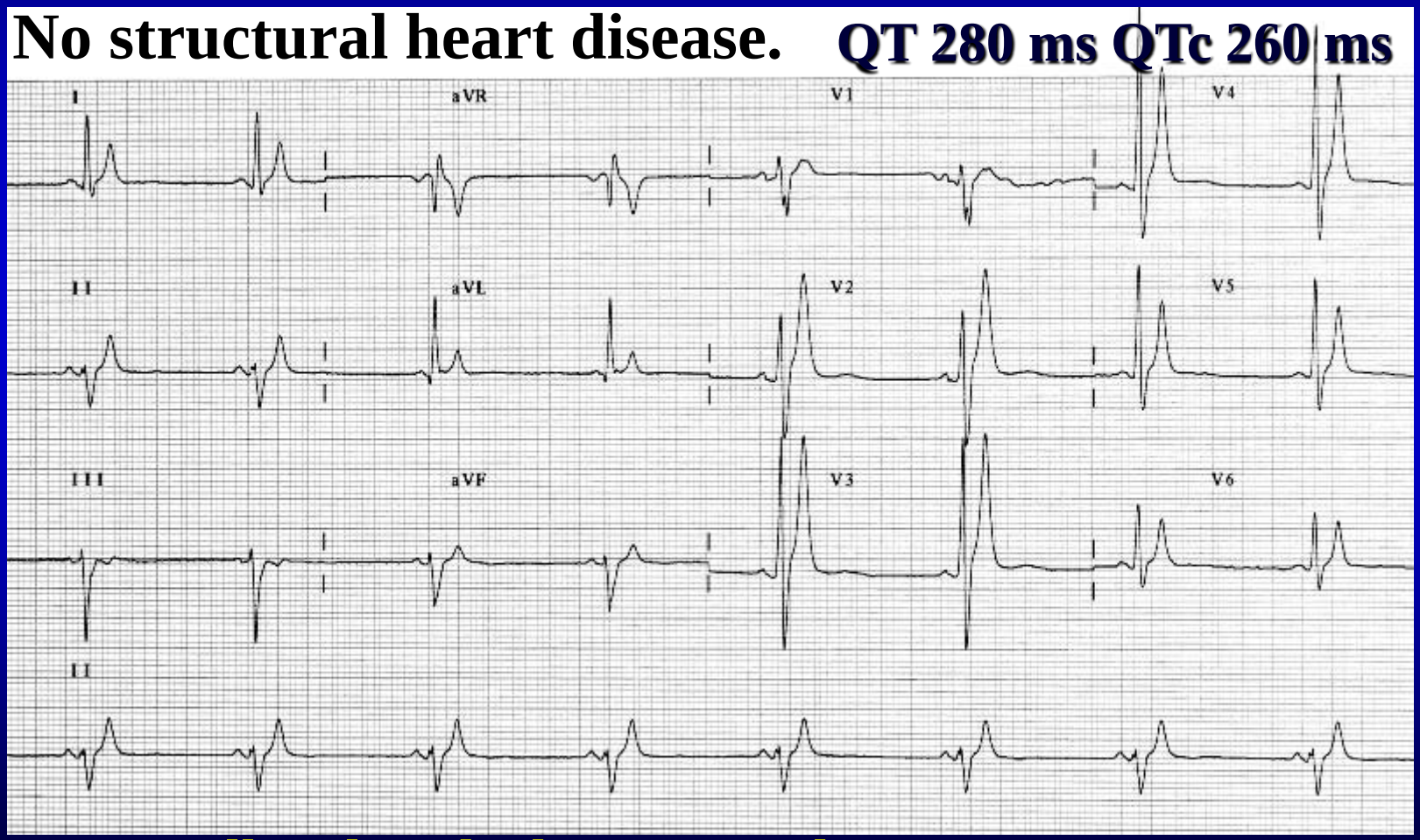
So…what to do?

1984

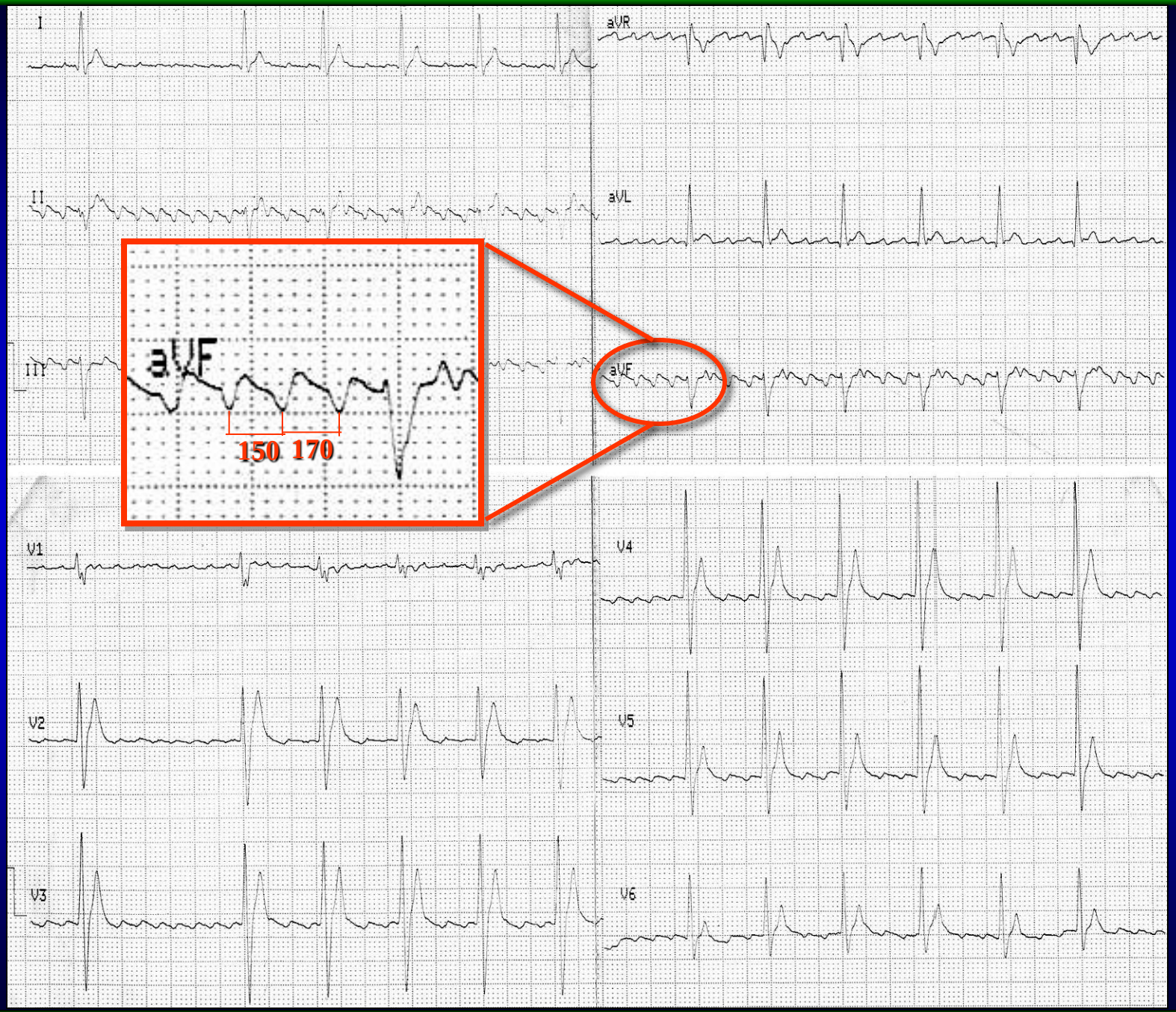
20 year old man, professional runner.

Symptomatic for palpitations, one syncopal episode (18 y).

No structural heart disease. **QT 280 ms QTc 260 ms**



Narrow, tall and peaked T waves; absent ST segment (short J-Tpeak)


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

AF with coarse and regular f waves

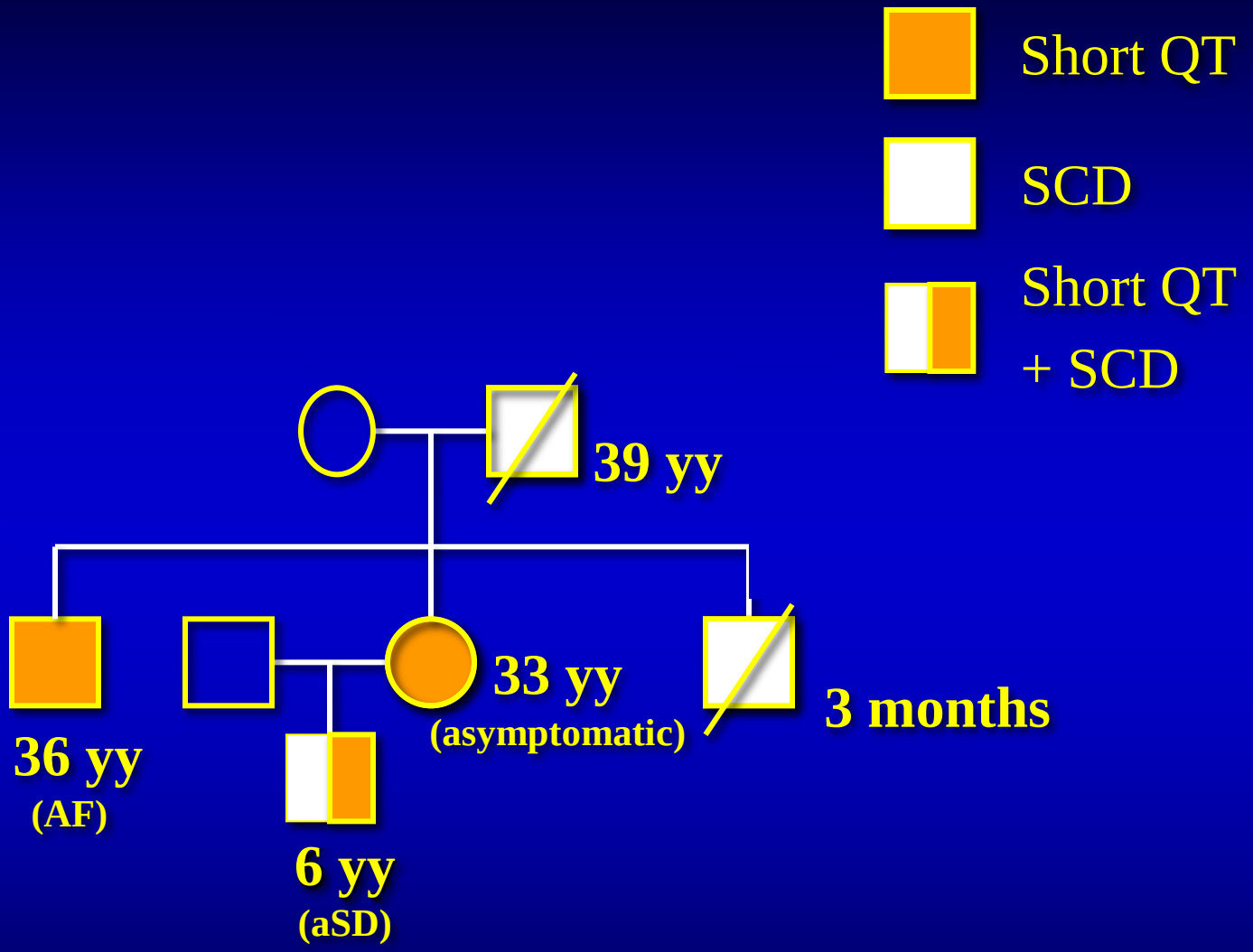
Our diagnosis was:

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

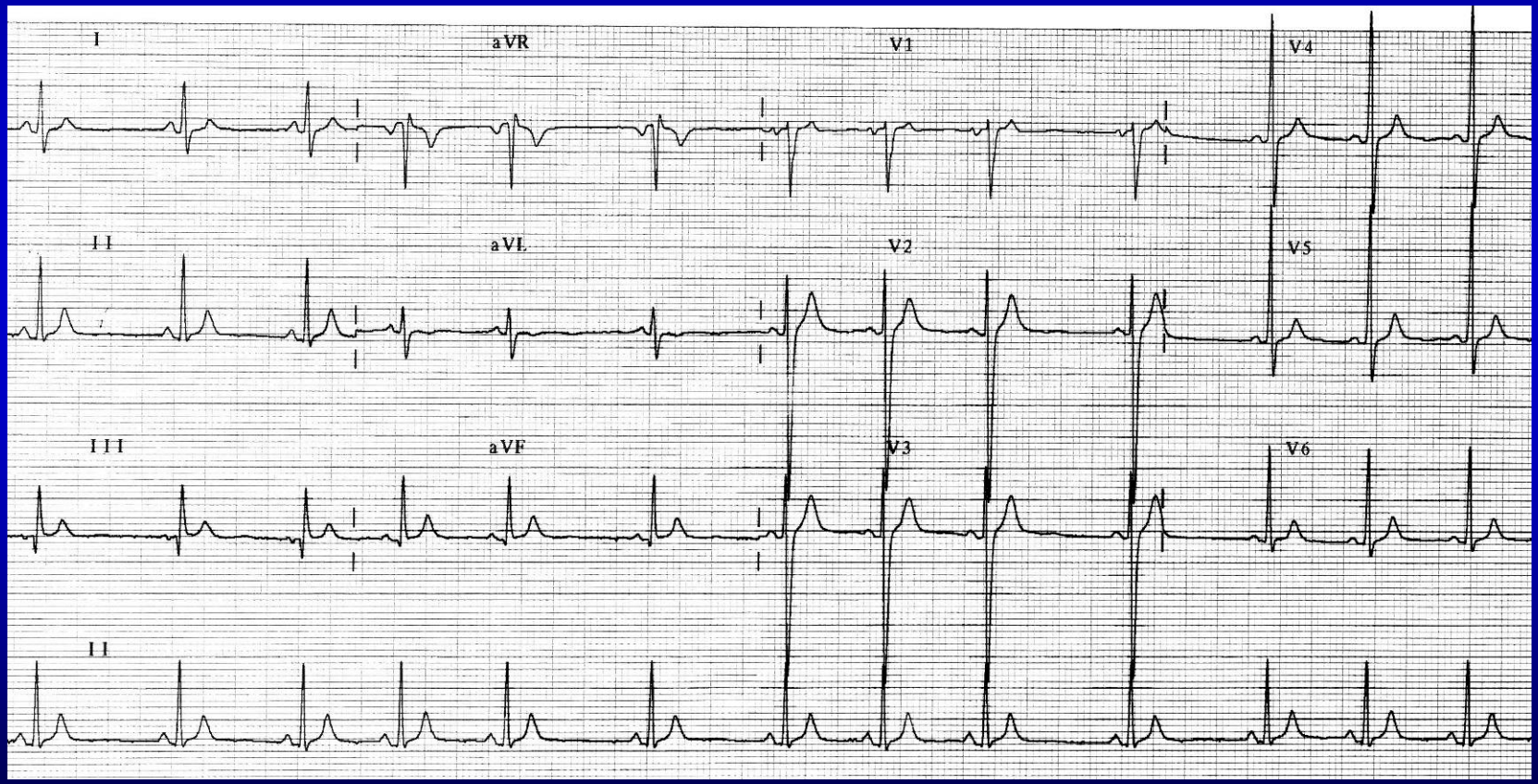
and yearly follow-up were suggested

…16 years later….


Short QT
SCD
Short QT
+ SCD
39 yy
33 yy
(asymptomatic)
3 months
36 yy
(AF)
6 yy
(aSD)

6-year-old patient with cardiac arrest, as first symptom, successfully resuscitated at 8 months with severe neurological sequelae.

No structural heart disease **QT 260 ms QTc 290 ms**

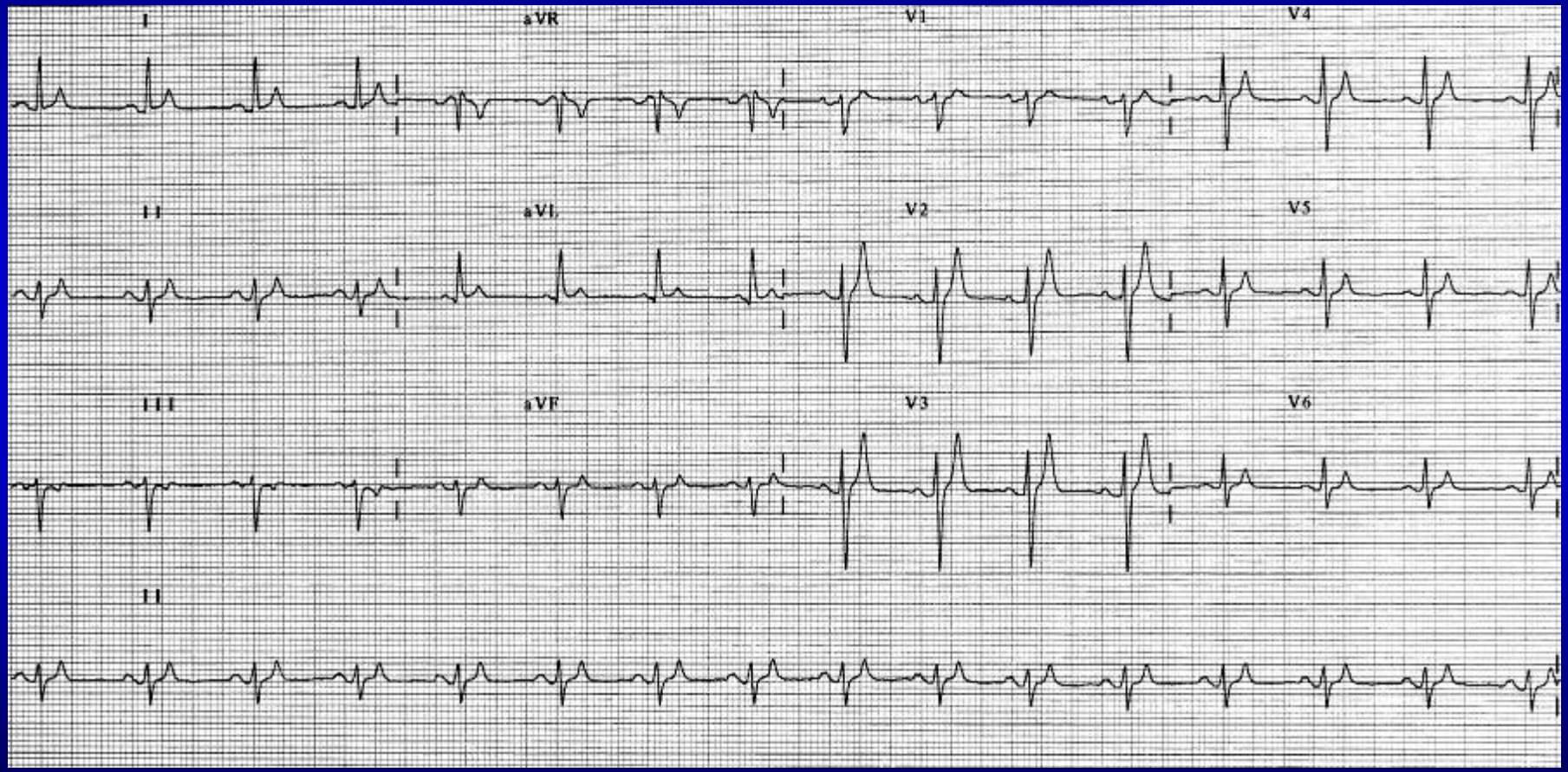


normal T waves, short J-Tpeak

31 year old woman, asymptomatic

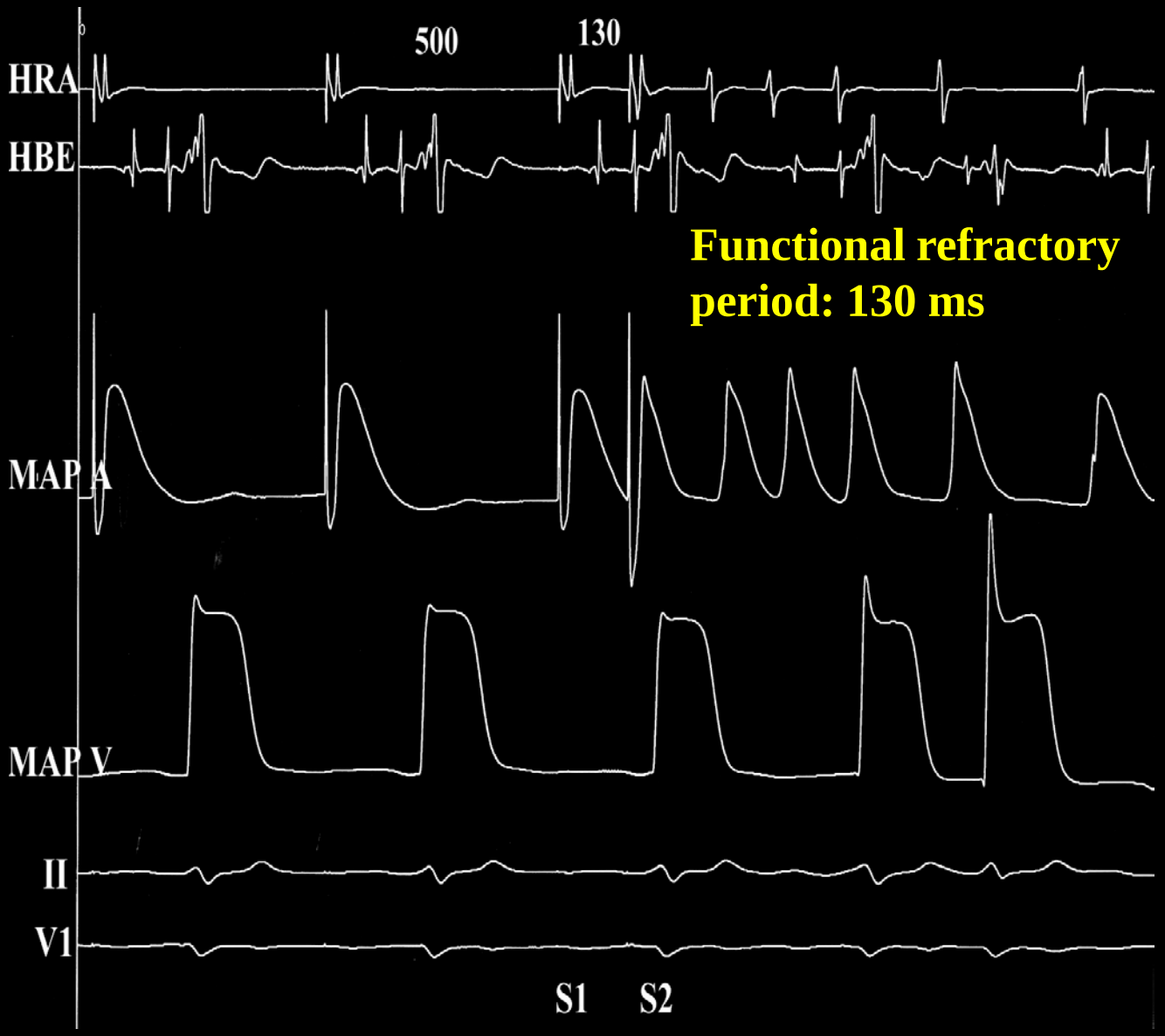
No structural heart disease.

QT 220 ms QTc 270 ms



Narrow, peaked T waves, short J-Tpeak

Atrial programmed stimulation: easy inducibility of AF



Functional refractory period: 130 ms

Ventricular programmed stimulation: easy inducibility of VF

The New England

Journal of Medicine

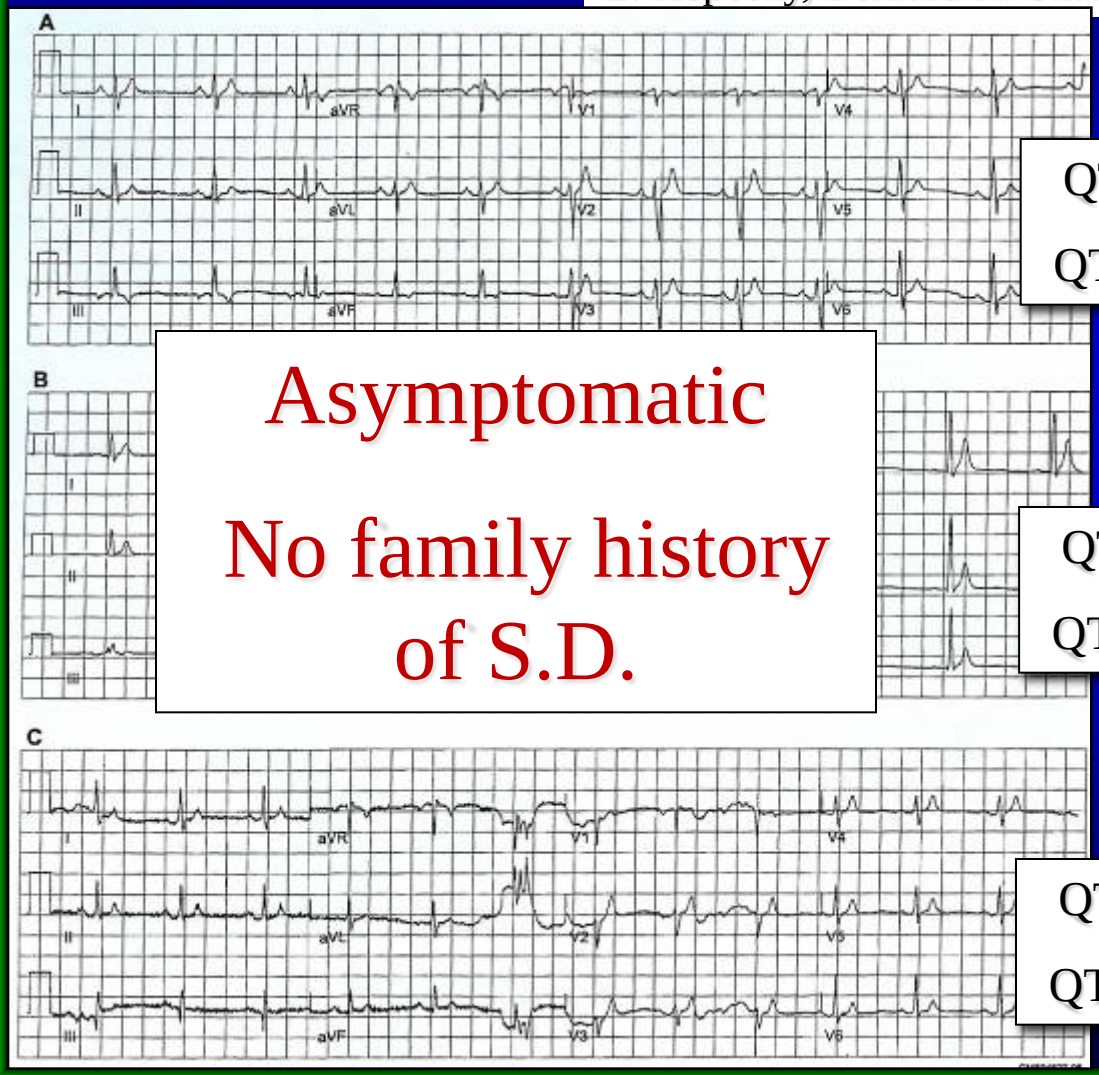
VOLUME NUMBER

REJECTED

Idiopathic Short QT Interval: A new clinical Syndrome?

Ihor Gussak, Pedro Brugada, Josep Brugada, R. Scott Wright, Stephen L. Kopecky, Bernard R. Chaitman, Preben Bjerregaard

Cardiology 2000



QT 280 ms

QTc 300 ms

Asymptomatic

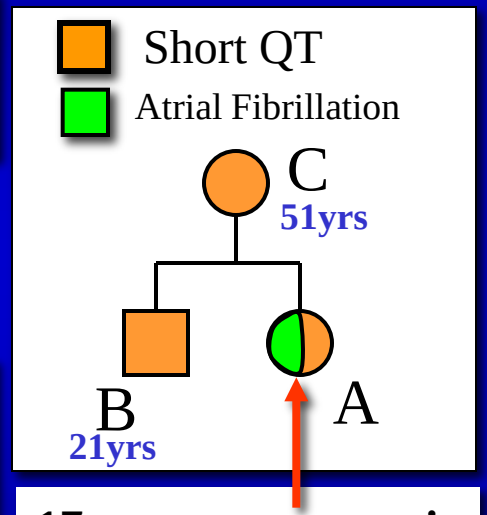
No family history of S.D.

QT 272 ms

QTc 267 ms

QT 260 ms

QTc 289 ms

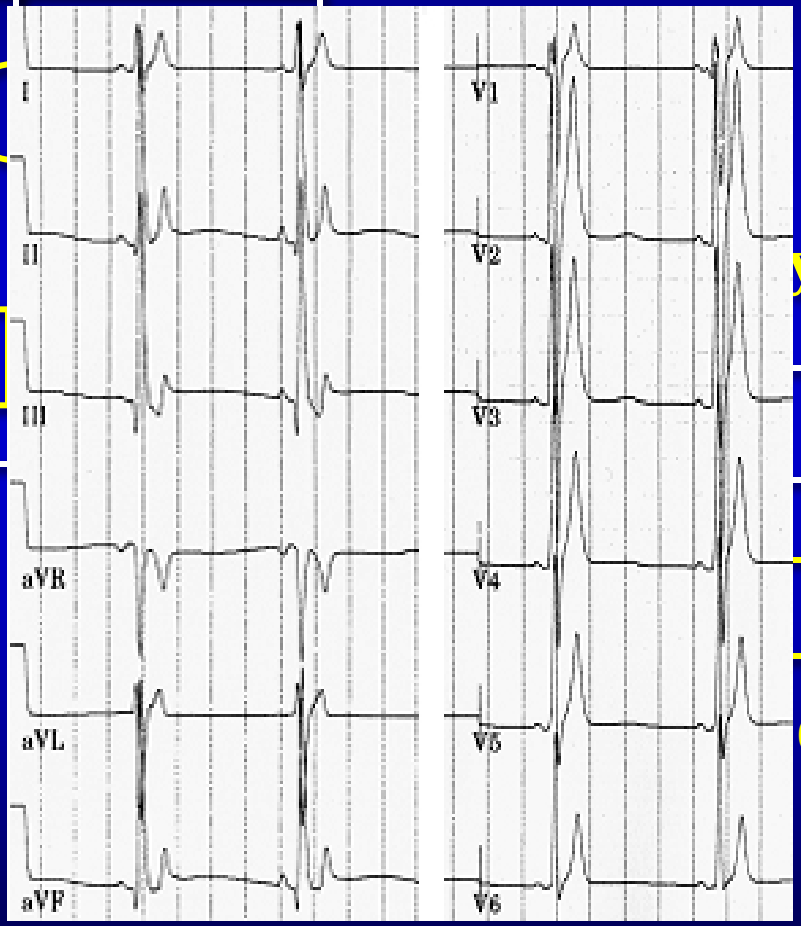


17 yrs asymptomatic with occasional finding of AF before surgery

Short QT

SCD

Short QT + SCD



y (AF)

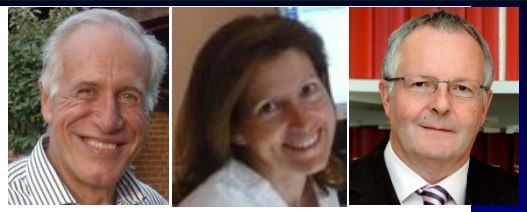
26yy

15yy
(syncope)

40yy
(asymptomatic)

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.)

- **QT ≤ 280 ms and QTc ≤ 300 ms**

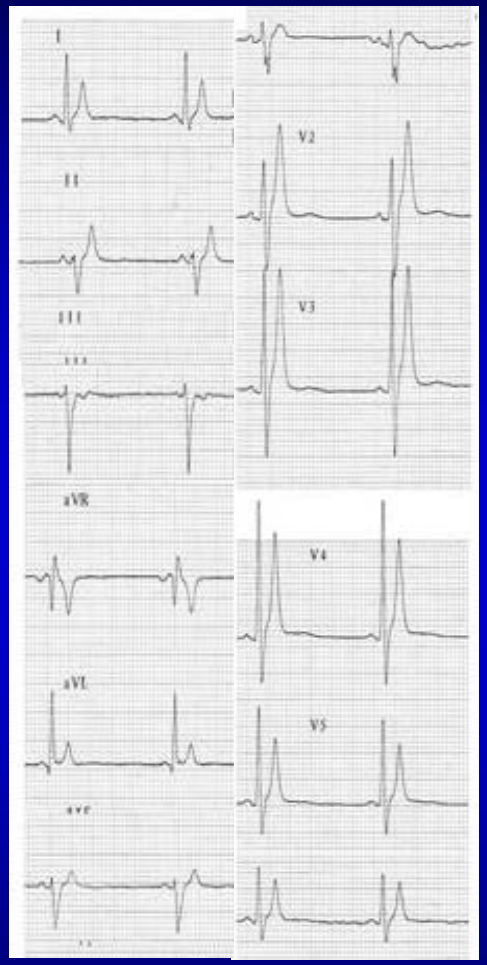
Family history of S.D.

Structural normal heart

Symptomatic for aSD , syncope (43%)

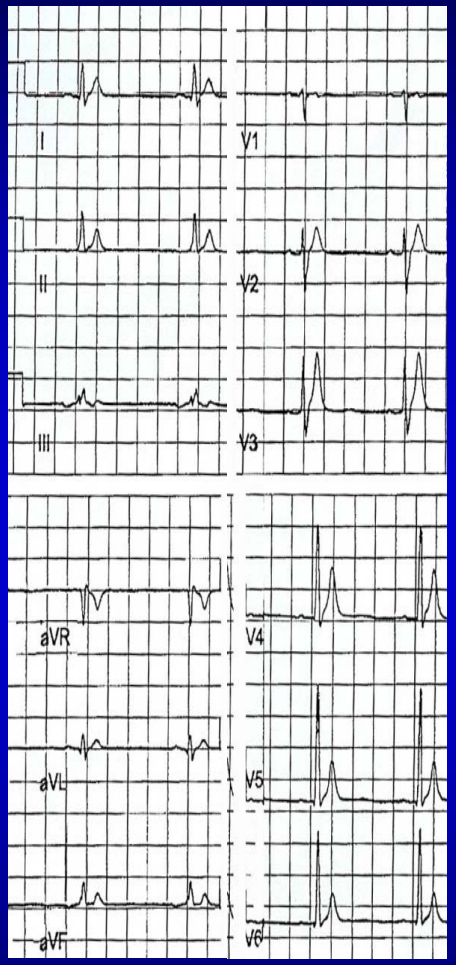
AF/Flutter at young age (57%)

Similar ECG but completely different clinical presentation



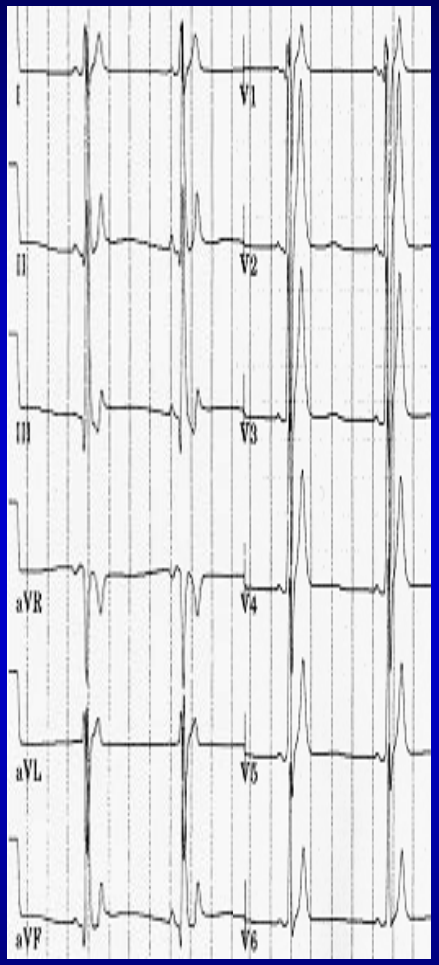
aborted SD

QTc=260ms



Atrial Fibrillation

QTc 267 ms



Asymptomatic

QTc=252ms

Short QT syndrome: clinical findings and diagnostic–therapeutic implications

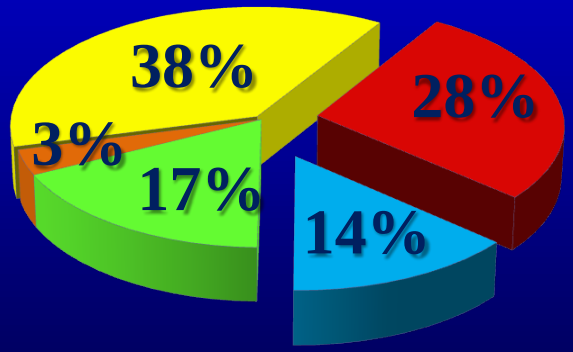
Carla Giustetto[1*], Fernando Di Monte[1], Christian Wolpert[2], Martin Borggrefe[2], Rainer Schimpf[2], Pascal Sbragia[3], Gianpiero Leone[4], Philippe Maury[5], Olli Anttonen[6], Michel Haissaguerre[7], and Fiorenzo Gaita[1]

29 patients

72%

28%

First clinical manifestation



SD/aSD

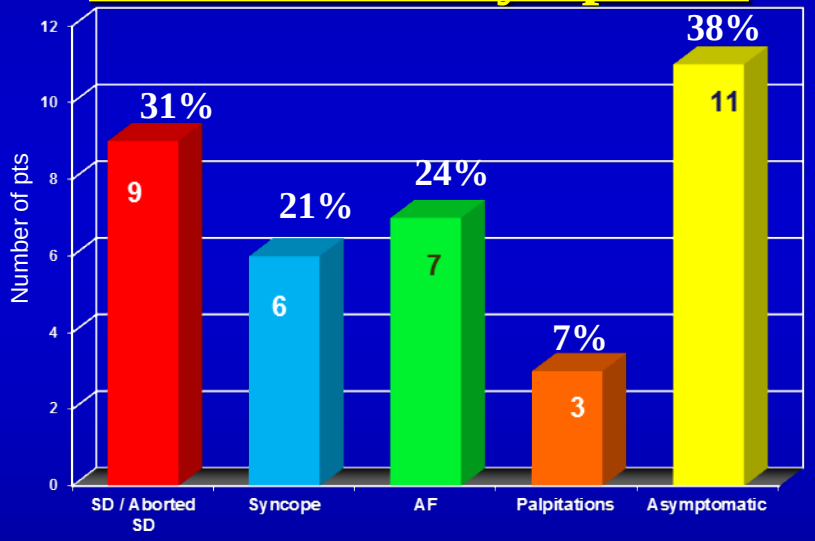
AF

Palpitations

Syncope

Asymptomatic

Prevalence of symptoms



European Heart Journal (2006) 27, 2440–2447

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]

Main findings

- SD is the first symptom in almost 1/3 of patients
- SD can occur from birth to old age
- QTc interval is NOT significantly related to SD

European Heart Journal (2006) 27, 2440–2447

ICD to everyone?

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

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

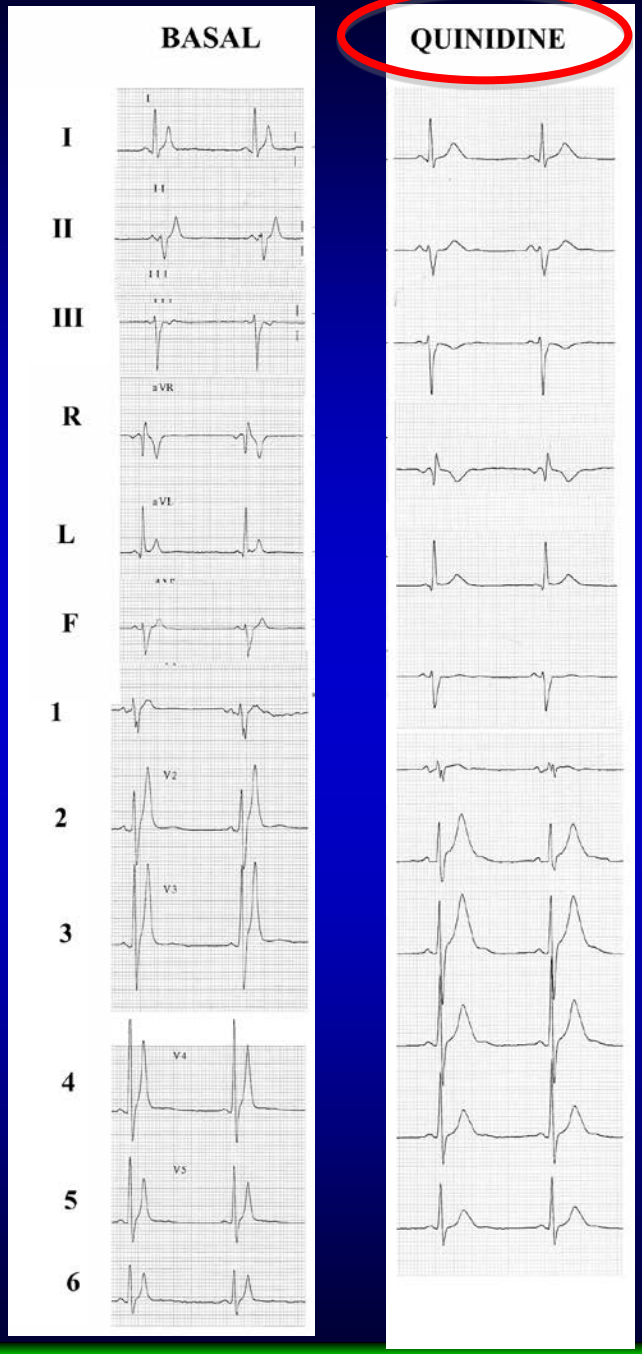
blocks I_{Kr}

blocks I_{Kr}

β-adrenergic receptors

QT 290 ms
QTc 290 ms

Gaita, JACC 2004



Short QT Syndrome: Pharmacological Treatment

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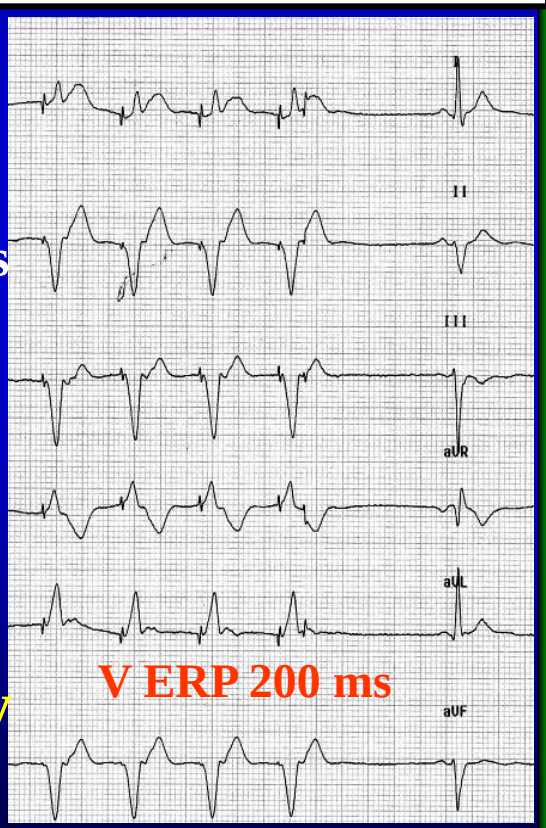
J Am Coll Cardiol 2004; 43: 1494-99

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

QT 440 ms
QTc 390 ms

no more inducibility of VF



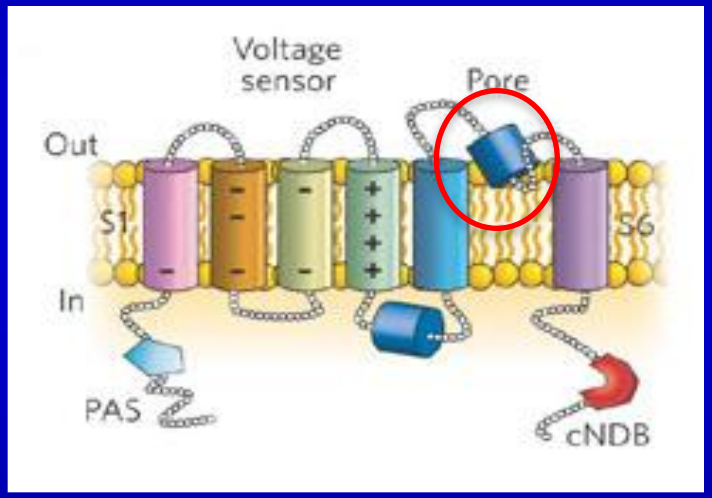
QUINIDINE

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

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

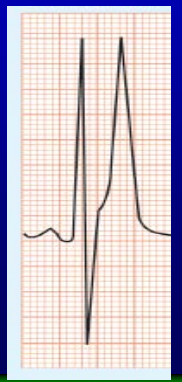
Ramon Brugada, Kui Hong, Robert Dumaine, Jonathan Cordeiro, Fiorenzo Gaita, Martin Borggrefe, Teresa M. Menendez, Josep Brugada, Guido D. Pollevick, Christian Wolpert, Elena Burashnikov, Kiyotaka Matsuo, Yue Sheng Wu, Alejandra Guerchicoff, Francesca Bianchi, Carla Giustetto, Rainer Schimpf, Pedro Brugada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

Two different mutations resulting in the same amino change (N588K) in the S5-P loop region of the cardiac IKr channel HERG



Gain of function of I_{Kr}

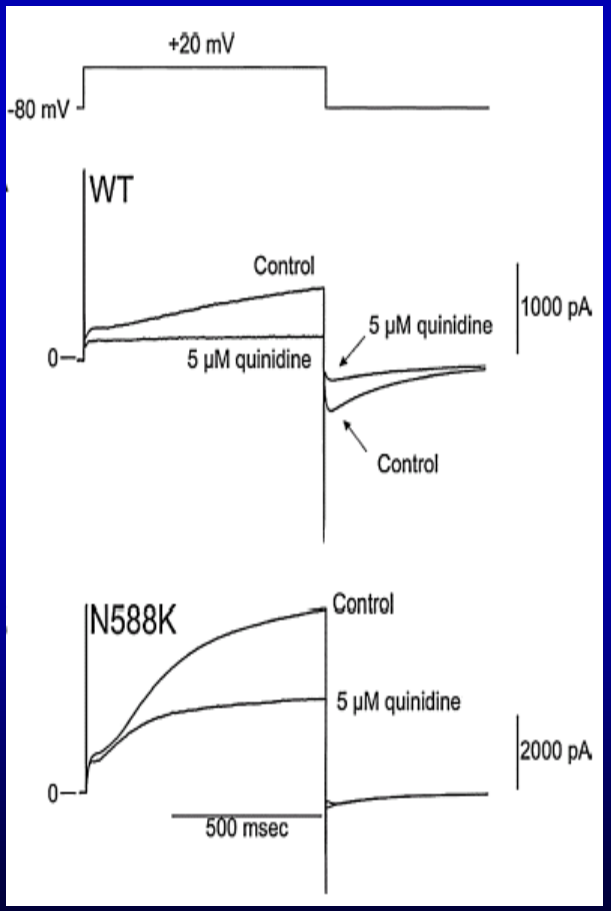
abbreviation of action potential duration and refractoriness



Further Insights into the Effect of Quinidine in Short QT Syndrome Caused by a Mutation in HERG

CHRISTIAN WOLPERT, M.D., RAINER SCHIMPF, M.D., CARLA GIUSTETTO, M.D.,* CHARLES ANTZELEVITCH, PH.D.,† JONATHAN CORDEIRO, PH.D.,† ROBERT DUMAINE, PH.D.,† RAMON BRUGADA, M.D.,† KUI HONG, M.D.,† URS BAUERSFELD, M.D.,‡ FIORENZO GAITA, M.D.,* and MARTIN BORGGREFE, M.D.

J Cardiovasc Electrophysiol 2005; 16: 1-5



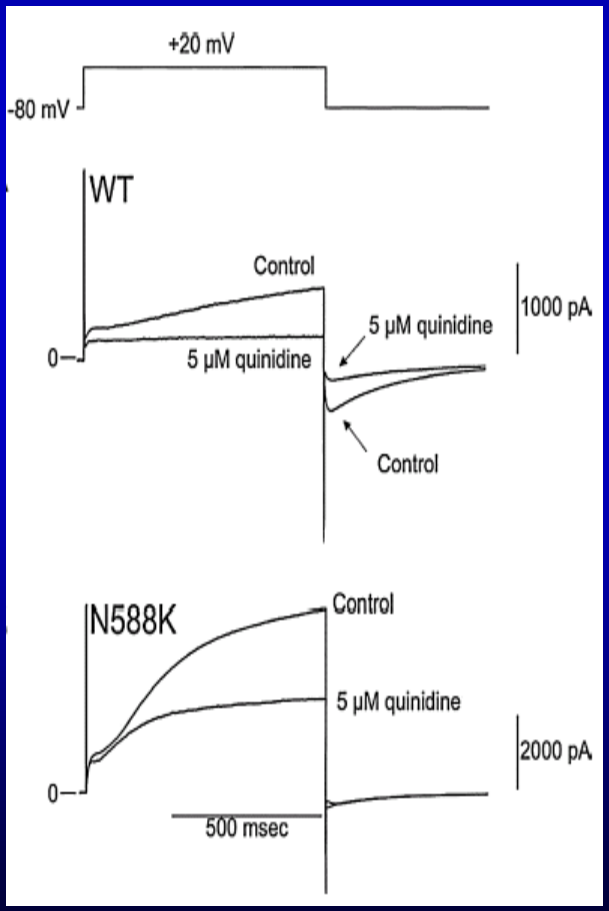
N588K mutation in HERG reduces the affinity of the I_{Kr} channel to sotalol by

20-fold

Further Insights into the Effect of Quinidine in Short QT Syndrome Caused by a Mutation in HERG

CHRISTIAN WOLPERT, M.D., RAINER SCHIMPF, M.D., CARLA GIUSTETTO, M.D.,* CHARLES ANTZELEVITCH, PH.D.,† JONATHAN CORDEIRO, PH.D.,† ROBERT DUMAINE, PH.D.,† RAMON BRUGADA, M.D.,† KUI HONG, M.D.,† URS BAUERSFELD, M.D.,‡ FIORENZO GAITA, M.D.,* and MARTIN BORGGREFE, M.D.

J Cardiovasc Electrophysiol 2005; 16: 1-5



N588K mutation in HERG reduces the affinity of the I_{Kr} channel to quinidine by

5.8-fold

Quinidine also blocks I_{Ks}, I_{to}, I_{K1}

Asymptomatic SQTS management: what guidelines say

Class IIb	2. ICD implantation ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
	3. Quinidine ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
	4. ~~Sotalol ***may be considered*** in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.~~

Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013

Differences in twelve-lead electrocardiogram between symptomatic and asymptomatic subjects with short QT interval

Olli Anttonen, MD,* M. Juhani Junttila, MD,† Philippe Maury, MD,§ Rainer Schimpf, MD,‡ Christian Wolpert, MD,‡ Martin Borggrefe, MD,‡ Carla Giustetto, MD,¶ Fiorenzo Gaita, MD,¶ Frederic Sacher, MD,** Michel Haïssaguerre, MD,** Pascal Sbragia, MD,‖ Ramon Brugada, MD,†† Heikki V. Huikuri, MD†

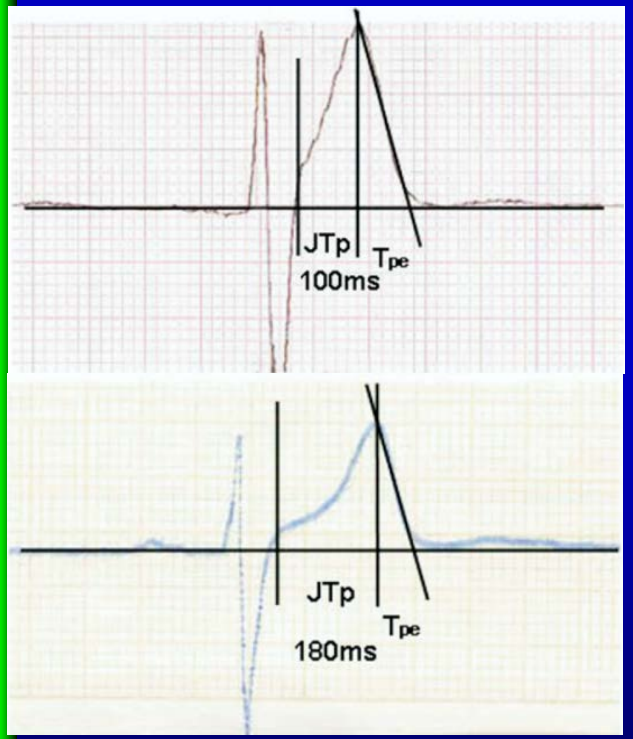


Table 1 ECG measurements in the study populations

	SQTS patients (n = 10)	Subjects with short QTc (n = 12)	Subjects with normal QTc (n = 20)	*P* value (analysis of variance)
Jpoint-Tpeak (ms)				
Mean ± SD	101 ± 18*†	184 ± 27	203 ± 33	<.001
Median	100	180	200	
Range	80–120	150–240	160–280	
Jpoint-Tpeak c (ms)				
Mean ± SD	112 ± 19*†	168 ± 17‡	211 ± 28	<.001
Median	108	170	210	
Range	87–140	136–191	157–268	
Tpeak-Tend/QT ratio corrected				
Mean ± SD	0.30 ± 0.04**††	0.24 ± 0.05	0.24 ± 0.04	.001
Median	0.31	0.24	0.24	
Range	0.25–0.36	0.16–0.34	0.18–0.35	

Heart Rhythm 2009;6:267-271

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

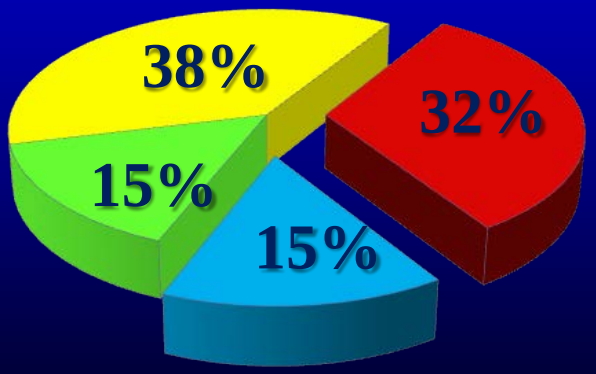
Carla Giustetto, MD,* Rainer Schimpf, MD,† Andrea Mazzanti, MD,* Chiara Scrocco, MD,* Philippe Maury, MD,‡ Olli Anttonen, MD,§ Vincent Probst, MD, PHD,‖ Jean-Jacques Blanc, MD,# Pascal Sbragia, MD,** Paola Dalmasso, MS,†† Martin Borggrefe, MD,† Fiorenzo Gaita, MD*

53 patients

75%

25%

First clinical manifestation



- SD/aSD
- Palpitations/AF/VEBs
- Syncope
- Asymptomatic

J Am Coll Cardiol 2011;58:587–95

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

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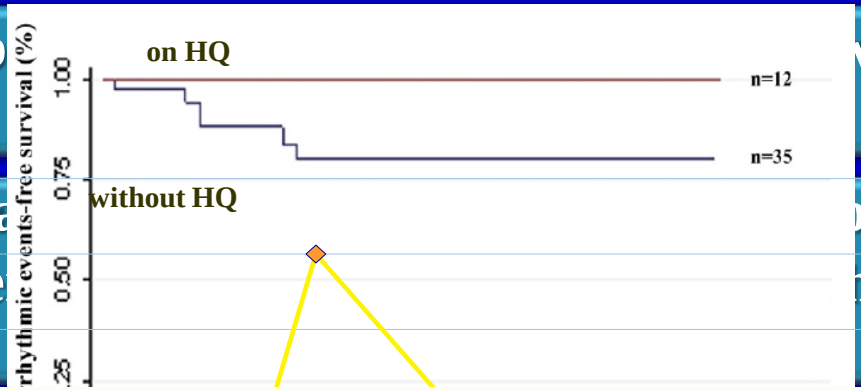
Main findings

aSD occurs esp … veen 15 and 40

QTc interval a… ot statistically differ betwee… n ventricular



	Cardiac Arrest (n = 18)	No Cardiac Arrest or Syncope (n = 27)
HR (beats/min)	79 ± 20	79 ± 23
QRS (ms)	84 ± 5	80 ± 11
QT (ms)	278 ± 44	283 ± 38
QTc (ms)	311 ± 25	315 ± 22
…	…	…
Tp–Te/QT(%)	28 ± 5	26 ± 5

No events in patients on hydroquinidine

J Am Coll Cardiol 2011;58:587–95

Long-Term Follow-Up of a Pediatric Cohort With Short QT Syndrome

Juan Villafañe, MD,* Joseph Atallah, MD, CM, SM,† Michael H. Gollob, MD,‡ Philippe Maury, MD,§ Christian Wolpert, MD,‖ Roman Gebauer, MD,¶ Hiroshi Watanabe, MD, PHD,# Minoru Horie, MD,** Olli Anttonen, MD, PHD,†† Prince Kannankeril, MD,‡‡ Brett Faulknier, DO,§§ Jorge Bleiz, MD,‖‖ Takeru Makiyama, MD, PHD,¶¶ Wataru Shimizu, MD, PHD,## Robert M. Hamilton, MD,*** Ming-Lon Young, MD, MPH†††

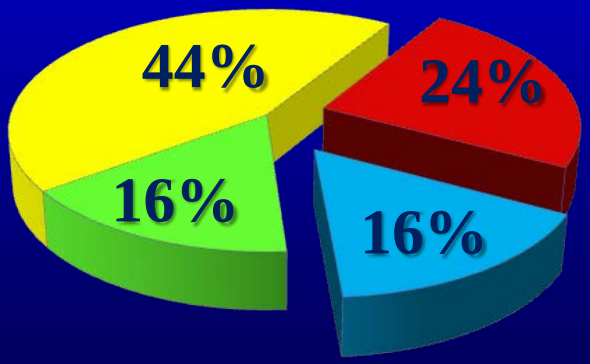
25 patients

median age 15 y [IQR 9-18]

84%

16%

First clinical manifestation



- SD/aSD
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- Syncope
- Asymptomatic

J Am Coll Cardiol 2013;61:1183-91

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Main findings

Table 2 SQTS Diagnostic Criteria: Modified Gollob Score

	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

ntly related to aSD

Asymptomatic patients with a Gollob score <5 remained event free

J Am Coll Cardiol 2013;61:1183-91

Novel Insight Into the Natural History of Short QT Syndrome

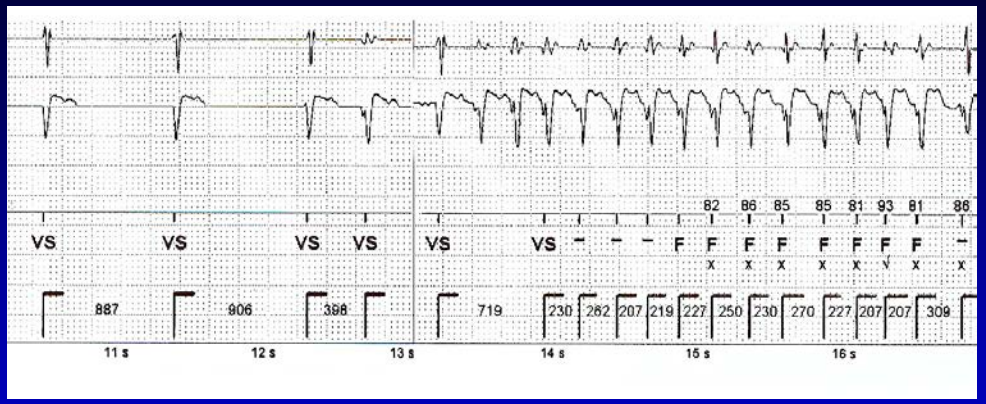
73 pts

Main findings

- aSD/SD can occur from birth to 41 years
- QTc interval is NOT significantly related to aSD/SD
- Previous aSD is the only predictor of arrhythmic events at f-up
- No value of prognostic score in predicting events

Mazzanti et al J Am Coll Cardiol 2013;61:1183-91

…and what about the first SQT family, 15 years later?



Short QT

SCD

Short QT + SCD

39 yy

47 yy

44 yy

3 months

9 yy

18 yy

HQ not tolerated:
ICD recorded NSVTs

on HQ: no ICD interventions

on HQ: no events

on HQ: no events

Asymptomatic SQT

Almost 1/3 rd of SQTS patients experience cardiac arrest as first symptom; this may occur throughout life, however more frequently in the first year or in young adults

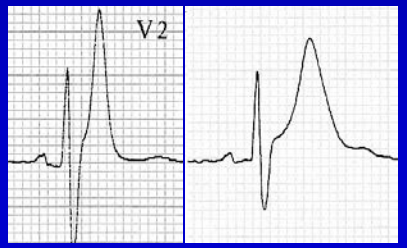
To date no ECG or clinical parameter can predict which asymptomatic short QT will develope symptoms and especially, in this case, which symptom (AF/syncope/SD)

Therapeutic options in ASYMPTOMATIC SQTS

Hydroquinidine

effective in prolonging QT interval?

YES



NO

or not tolerated/refused

> 16 y

class IC

< 16 y

Life-threatning arrhythmias?


Special thanks to:
Andrea Mazzanti
ged QT interval: is QT hysteresis analysis a
nguish healthy athletes from LQTS patients?
Carla Giustetto
Elena Gribaudo
Natascia Cerrato
Chiara Scrocco