How to manage a patient with short QT syndrome?

Torino, 27 ottobre2012

Carla Giustetto

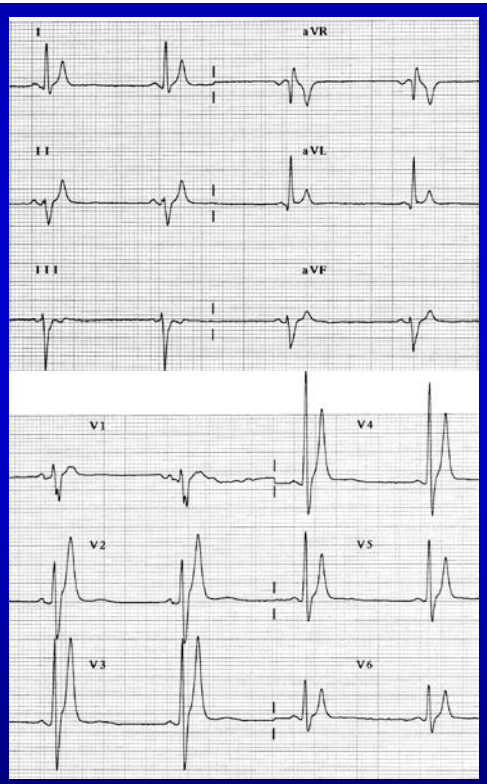
Division of Cardiology
University of Torino

Short QT Syndrome

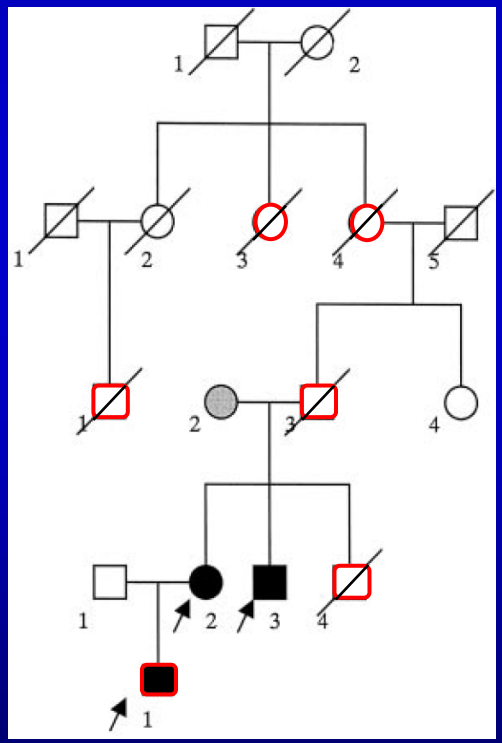
A Familial Cause of Sudden Death

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

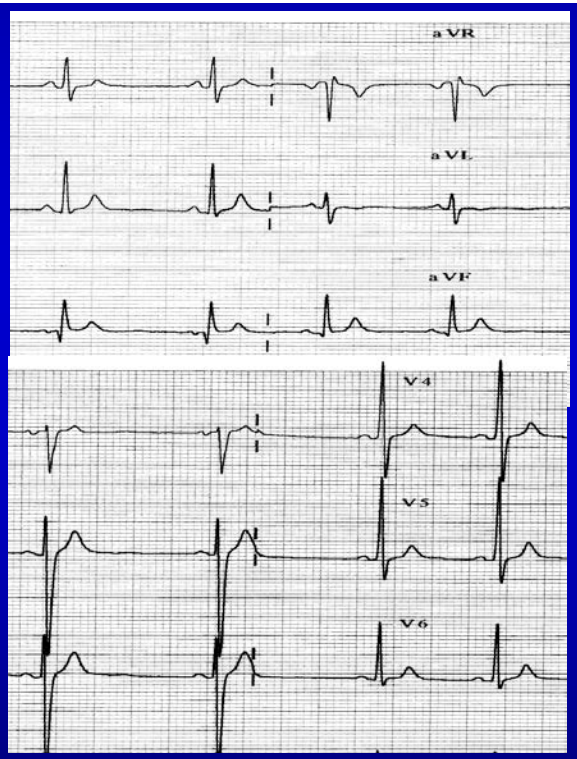
(*Circulation*. 2003;108:965-970.)



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



High incidence of SD



QT 260 ms QTc 290 ms
Normal T waves

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

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

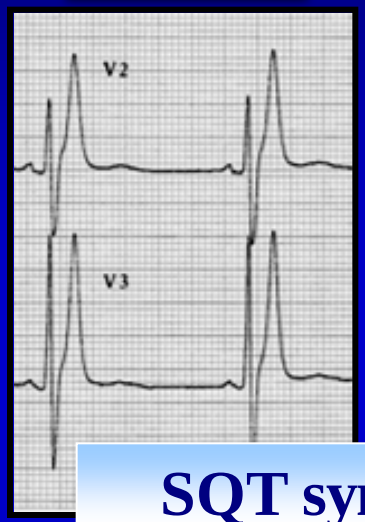
Circulation 2004, 109:30-35

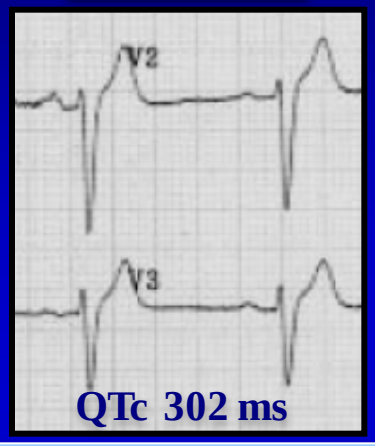
Two different mutations in KCNH2 (HERG) resulting in the same aminoacid change (N588K) in the S5-P loop region of the cardiac IKr channel

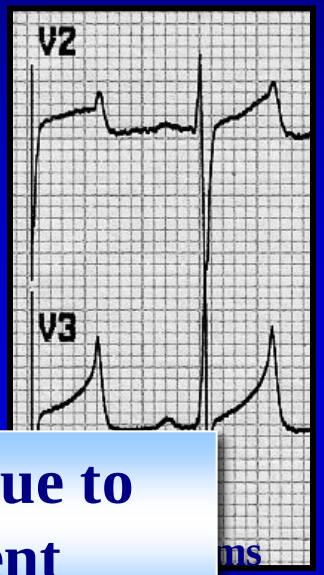
Gain of function of I_{Kr} → abbreviation of action potential duration and refractoriness → **SQT1**

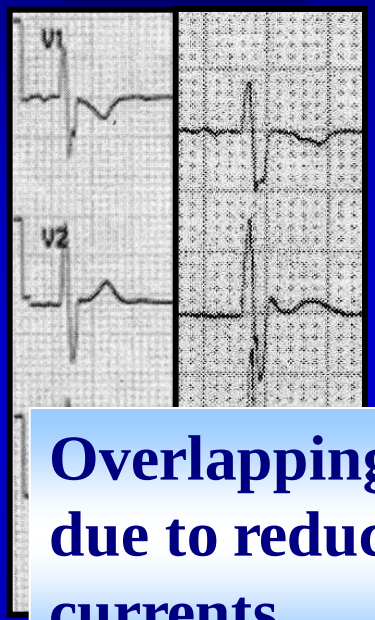
Genetic Background

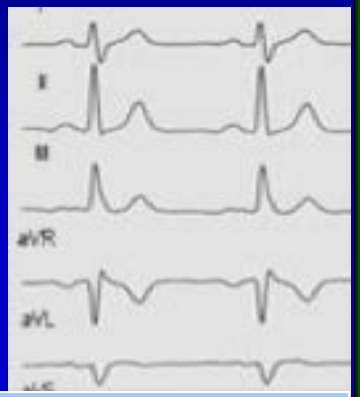
SQT1 | **SQT2** | **SQT3** | **SQT4/5** | **SQT6**





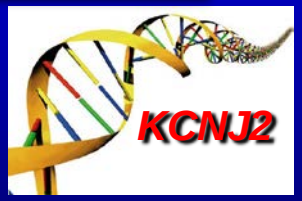


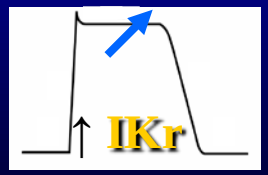


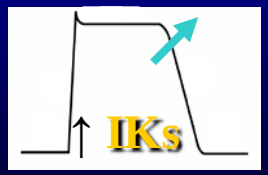


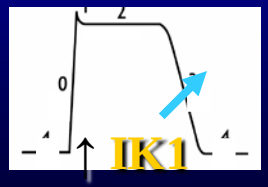
SQT syndromes are due to enhanced K+ current

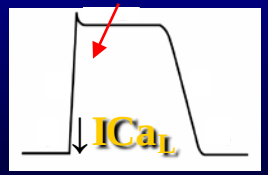
Overlapping syndromes due to reduced Ca+ currents

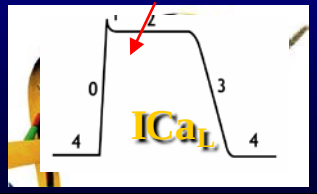






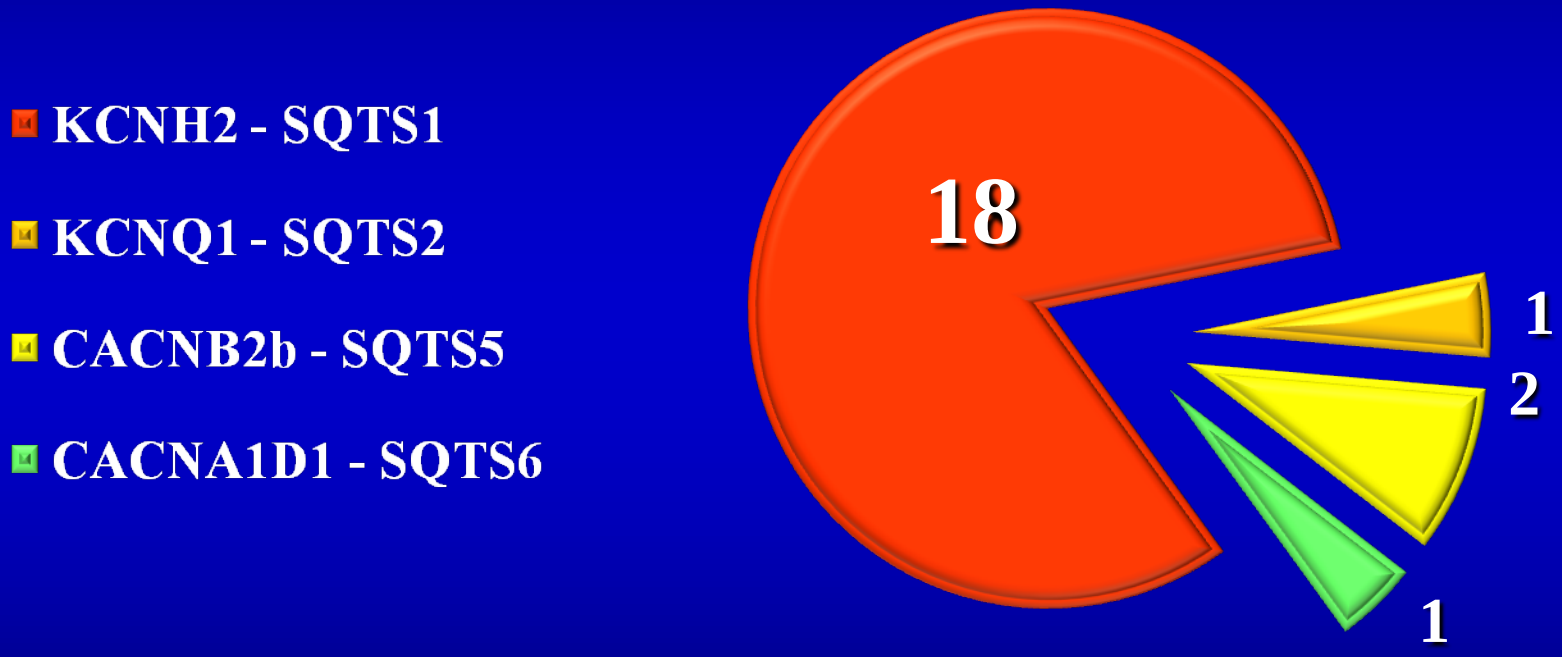






Genotyped SQTS cases in the EuroShort registry

22 out of 72 patients



In the EuroShort Registry genetic mutations were identified in 11 out of 28 (39%) probands who performed the analysis

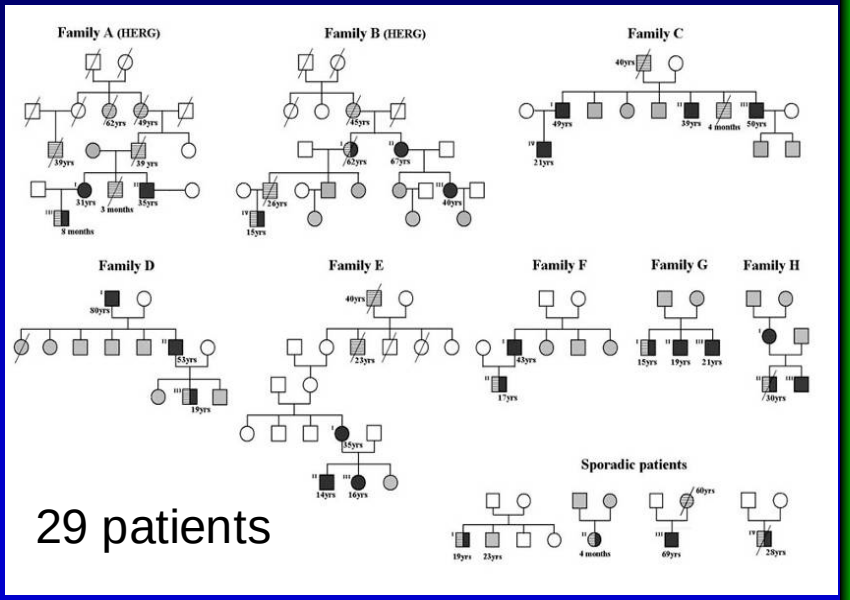
Which is the upper limit of short QT ?

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]

European Heart Journal (2006) 27, 2440–2447

QTc ≤ 340 ms



29 patients

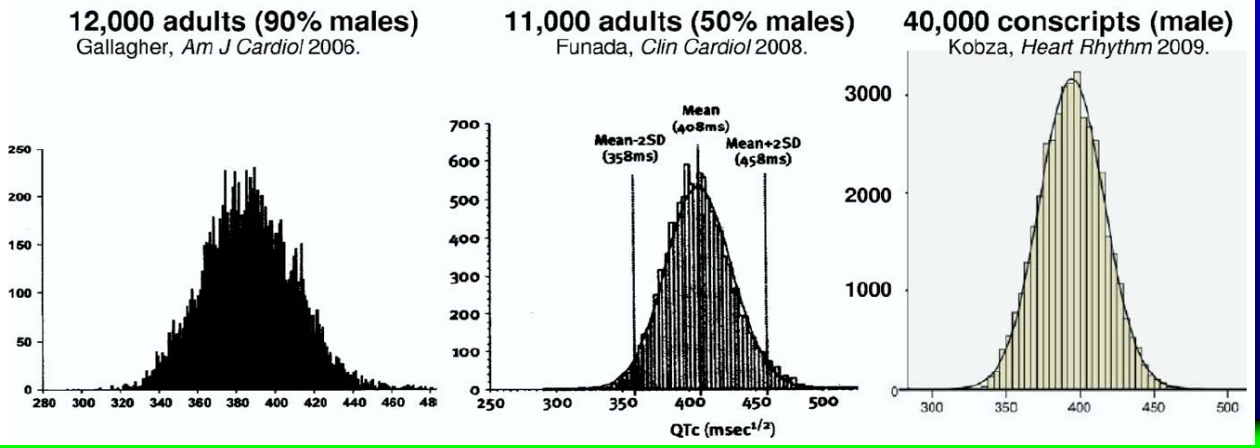
CONTEMPORARY REVIEW

The QT interval: Too long, too short or just right

Sami Viskin, MD

Heart Rhythm 2009;6:711–715

Distribution of QTc intervals in large population-based studies.



QTc ≤ 360 ms

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

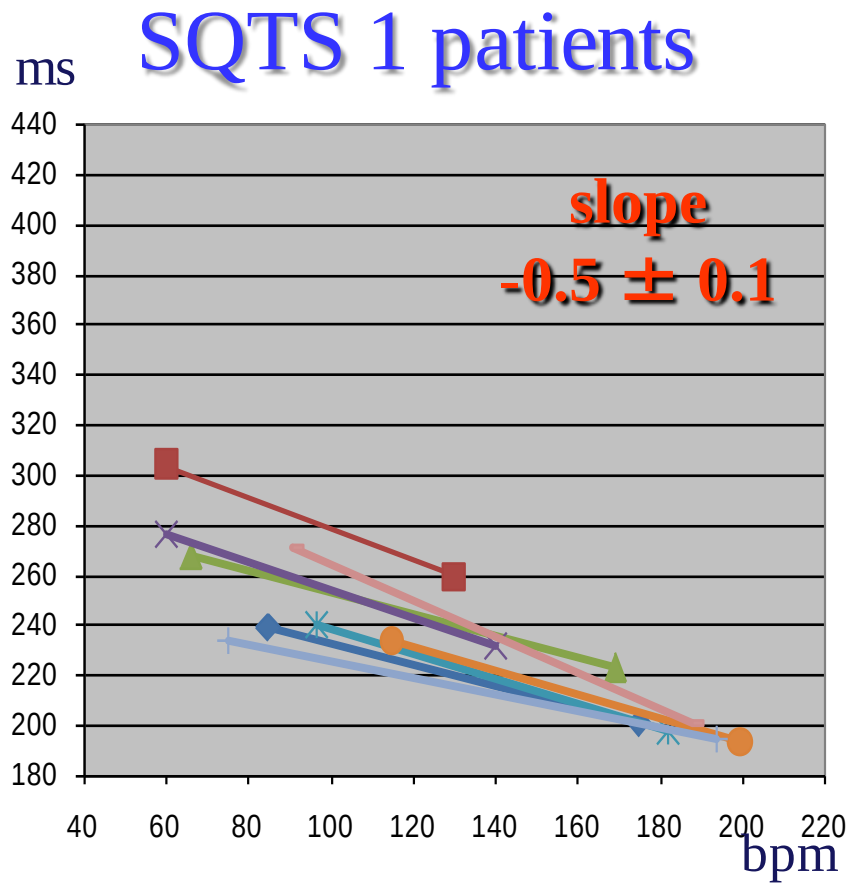
Carla Giustetto, MD,* Rainer Schimpf, MD,† Andrea Mazzanti, MD,* Chiara Scrocco, MD,* Philippe Maury, MD,‡ Olli Anttonen, MD,§ Vincent Probst, MD, PHD,‖ Jean-Jacques Blanc, MD,# Pascal Sbragia, MD,** Paola Dalmasso, MS,†† Martin Borggrefe, MD,† Fiorenzo Gaita, MD*

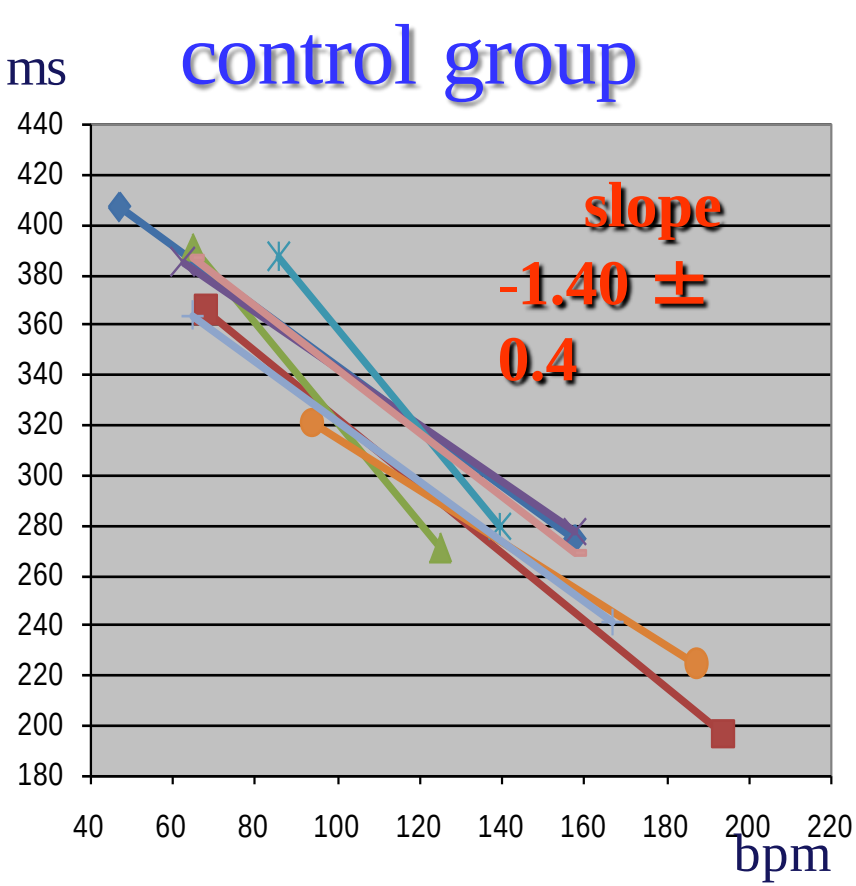
J. Am. Coll. Cardiol. 2011;58;587-595

QTc ≤ 340 ms,
even ASYMPTOMATIC

QTc ≤ 360 ms +
cardiac arrest or syncope
or belonging to families with SQTS

STRESS TEST - QT/HR relation





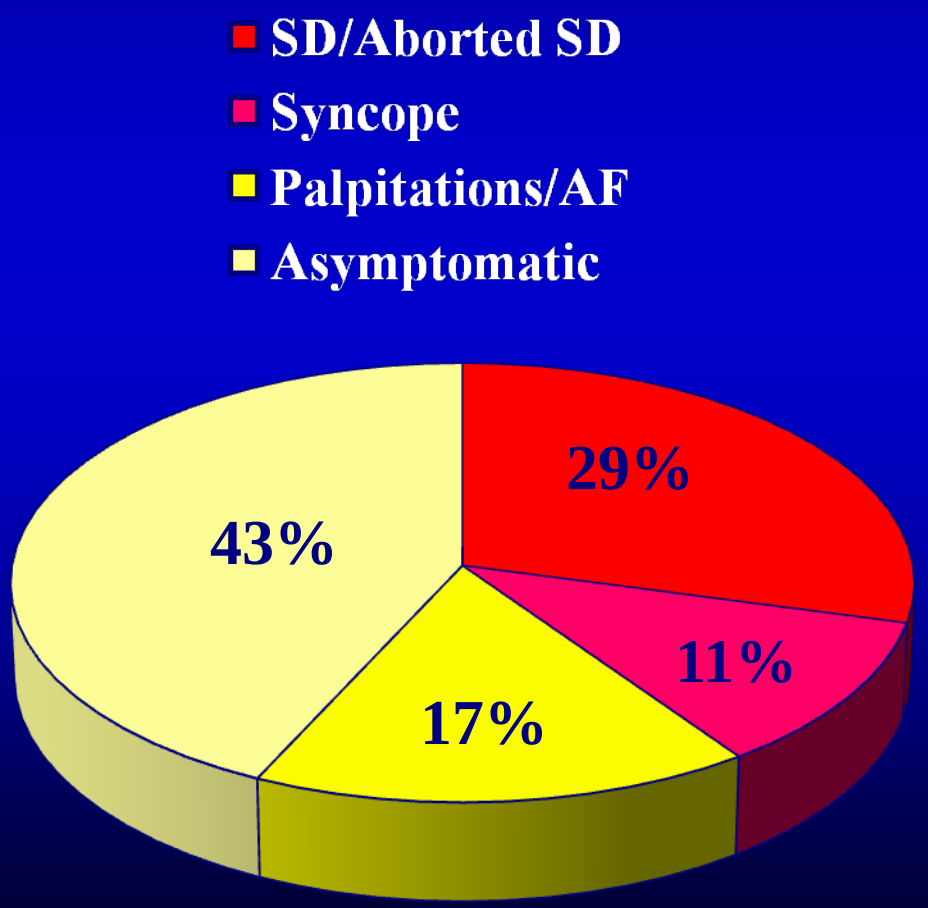
rest QT - peak QT	**48.3±14.2 ms**	**106.7±20.8 ms**	p<0.0001

European Short QT Registry
(Euro-Short)

72 pts

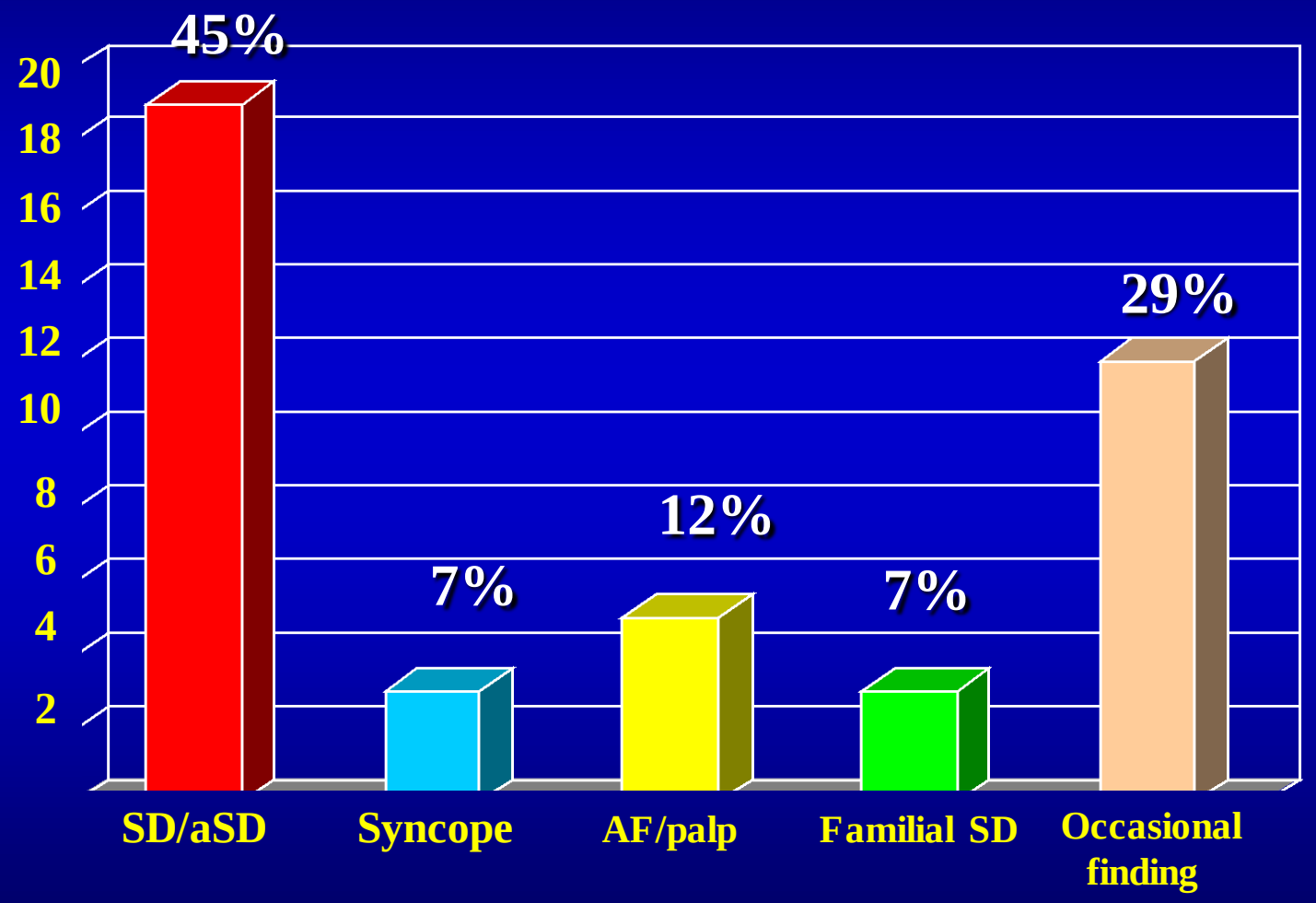
	(n = 72)
Males	49 (74%)
Age at observation (y)	34 ± 17
Familial SD	47 (65%)
QT (ms)	285 ± 36
QTc (ms) [mean HR 76 ± 19]	315 ± 23

FIRST CLINICAL MANIFESTATION

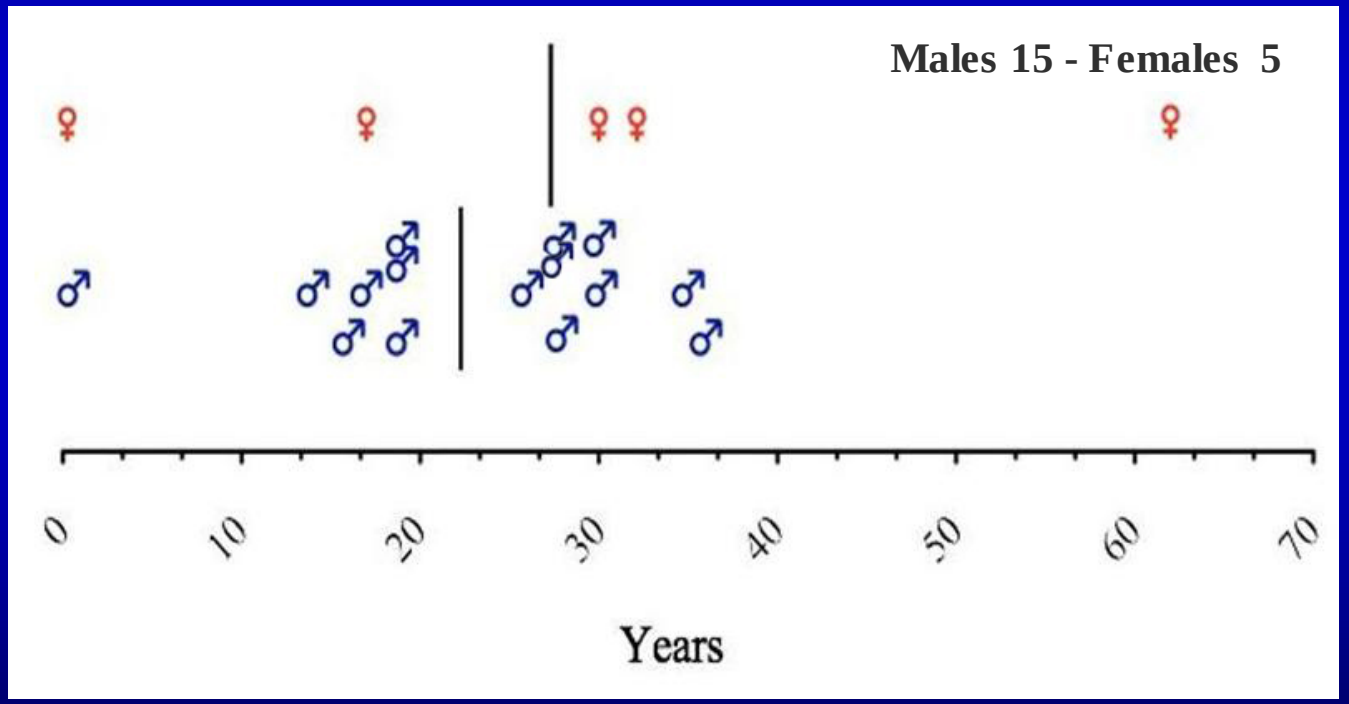


Reason of first clinical observation

42 index patients from European SQT Registry

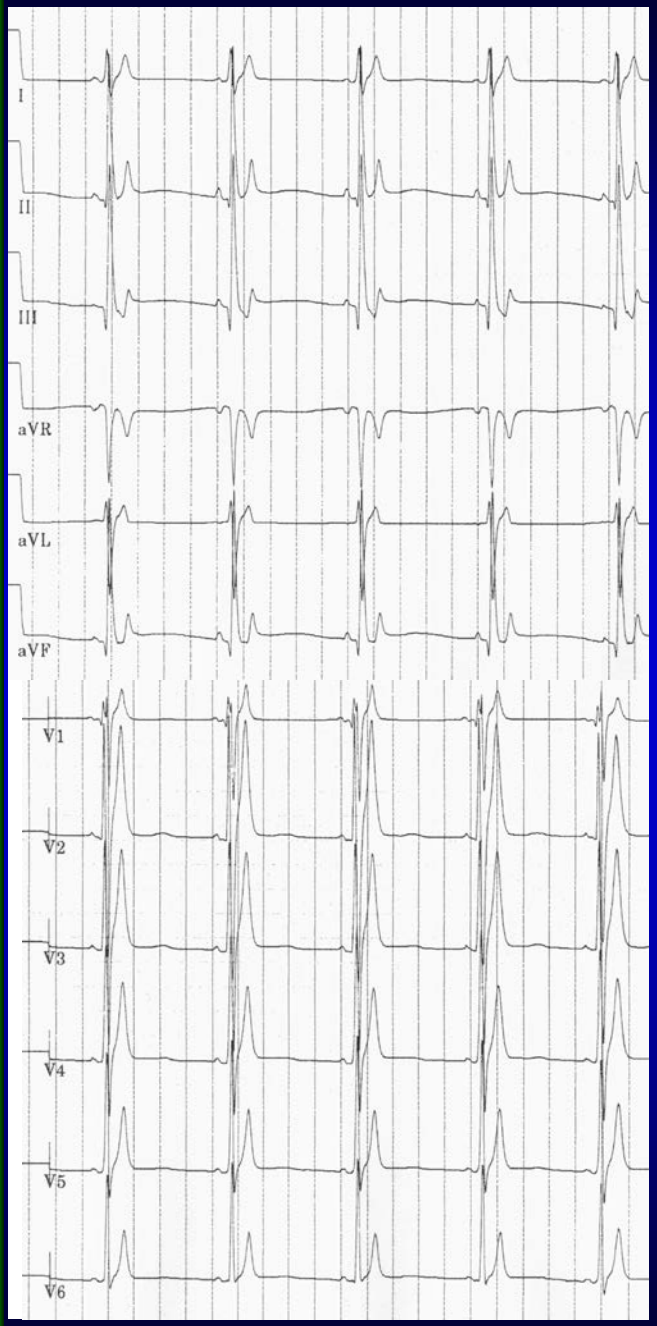


Age distribution of Cardiac Events in Males and Females



Giustetto et al. JACC 2011; 58: 587-95

THERAPY



16 year- old boy with very short QT interval: QT 248 ms/ QTc 252ms

Syncope at 6 months, then completely asymptomatic

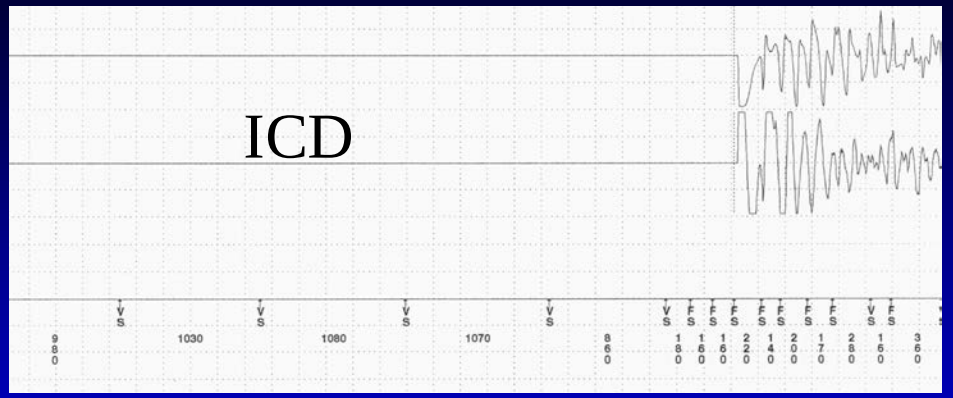
High incidence of sudden death in the family

VF not induced during EPS

The dilemma was:

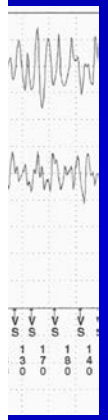
what to do with this patient?

An ICD was implanted:
17 months thereafter the ICD discharged appropriately during sleep

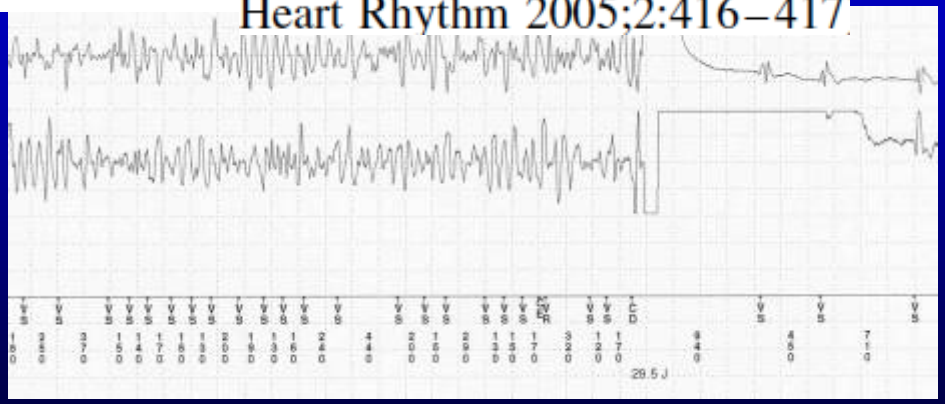


Short QT syndrome: Successful prevention of sudden cardiac death in an adolescent by implantable cardioverter-defibrillator treatment for primary prophylaxis

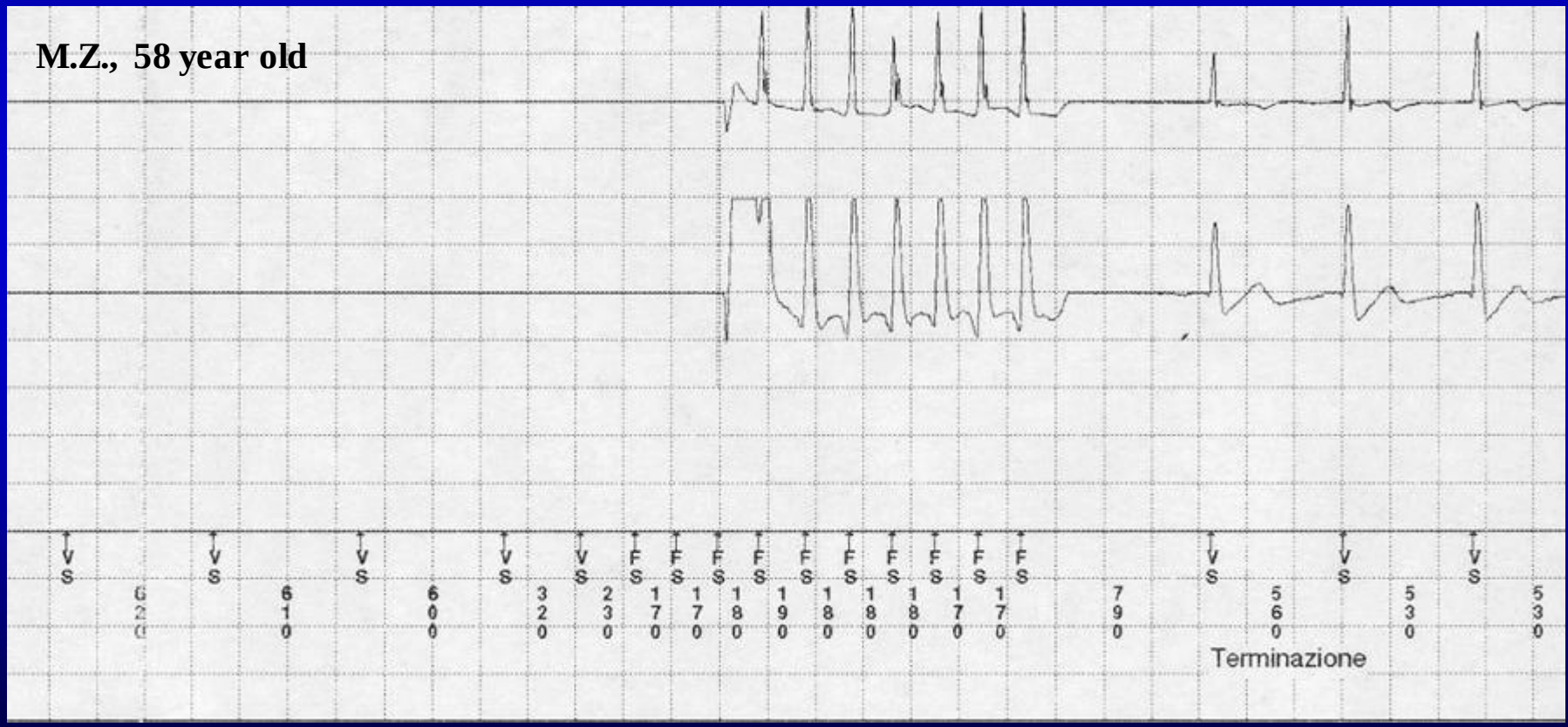
Rainer Schimpf, MD,[a] Urs Bauersfeld, MD,[b] Fiorenzo Gaita, MD,[c] Christian Wolpert, MD[a]



Heart Rhythm 2005;2:416–417



ICD interrogation may show episodes of rapid nsVT in asymptomatic subjects



ICD to everyone?

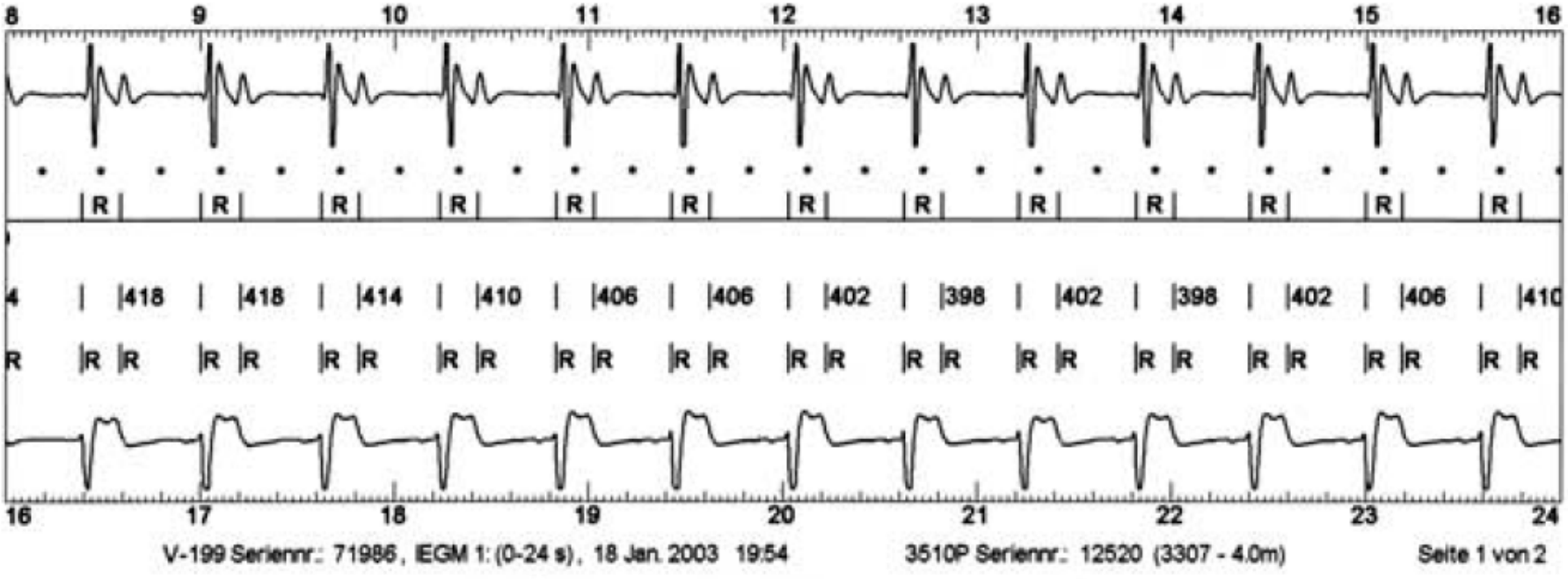
Early/Late complications

Children

Congenital Short QT Syndrome and Implantable Cardioverter Defibrillator Treatment: Inherent Risk for Inappropriate Shock Delivery

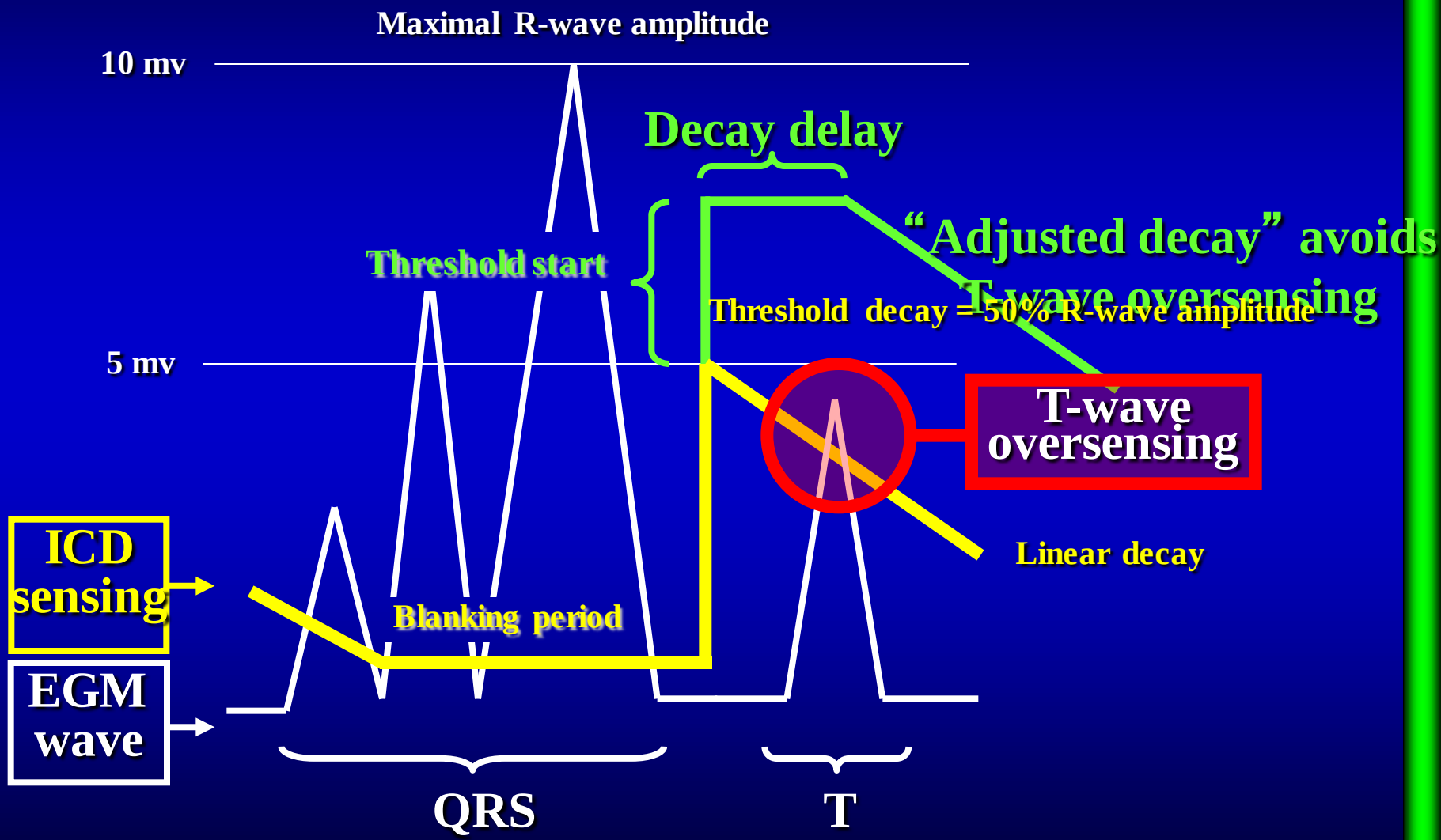
RAINER SCHIMPF, M.D., CHRISTIAN WOLPERT, M.D., FRANCESCA BIANCHI, M.D.,*
CARLA GIUSTETTO, M.D.,* FIORENZO GAITA, M.D.,* URS BAUERSFELD, M.D.,†
and MARTIN BORGGREFE, M.D.

J Cardiovasc Electrophysiol, Vol. 14, pp. 1273-1277, December 2003



T wave oversensing = double counting → Causing inappropriate shocks

Technical solutions to reduce T wave oversensing



Schimpf et al. JCE 2003

Late complications of ICD in pts with channelopathies

	Pts with Brugada Syndrome		
	Sacher et al. Circ. 2006	**Sarkozy et al. EHJ 2007**	**Rosso et al. IMAJ 2008**
	220 pts f-up 38±27m	47 pts f-up 47.5m	59 pts f-up 45±35m
Lead failure requiring extraction and reimplantation of lead/device	**19 (8%)**	**6 (13%)**	**9 (15%)**
Pocket and/or lead infection requiring lead/device replacement	**3 (1.3%)**		**1 (2%)**
Pericardial effusion	**1 (0.5%)**		**1 (2%)**
Pocket revision	**2 (1%)**	**1 (2%)**	
Inappropriate shocks (due to: lead failure/dislodgement, T wave oversensing, sinus tachycardia, supraventricular arrhythmias)	**45 (20%)**	**19 (40%)**	**14 (24%)**
Severe psychological difficulties	**2 (1%)**		**8 (13%)**
Total device related Complication	**62 pts (28%)**	**18 pts (38%)**	**19 pts (32%)**

ICD for everyone?

Early/Late complications

Children

ICD implant in childhood
Issues

High technical complexity due to:

- small body and heart size
- difficult vascular access
- modifications of the implant owing to growth

Psychosocial distress linked to device discharges (**especially if inappropriate**)

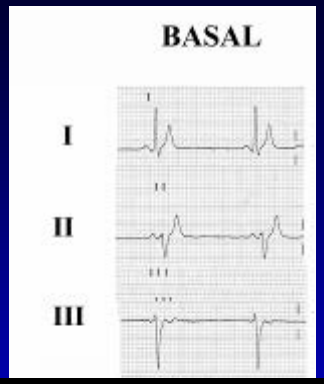
High rates of **leads complications**

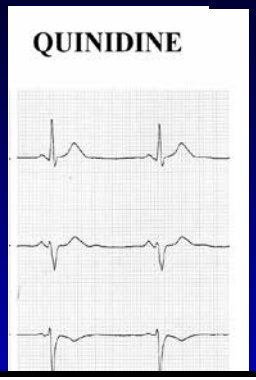
Late complications of ICD in children with LQTS

	Pts with LQTS
	Etheridge et al. JACC 2007
	23 pts, mean age 9.4±5.4 y f-up 4.4 ±3.5
Lead failure requiring extraction and reimplantation of lead/device	**2 (10%)**
Pocket and/or lead infection requiring lead/device replacement	**1 (4%)**
Pericardial effusion	
Pocket revision	
Inappropriate shocks (due to: lead failure/dislodgement, T wave oversensing, sinus tachycardia, supraventricular arrhythmias)	**4 (17%)**
Severe psychological difficulties	
Total device related Complication	**13 pts (48%)**

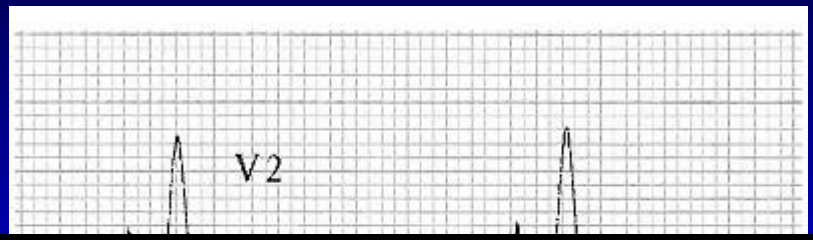
THERAPY

Drug therapy: may it play a role in the treatment of Short QT patients?





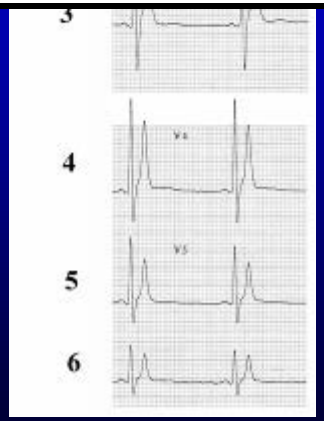
BASAL

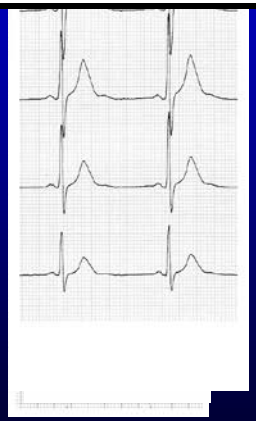


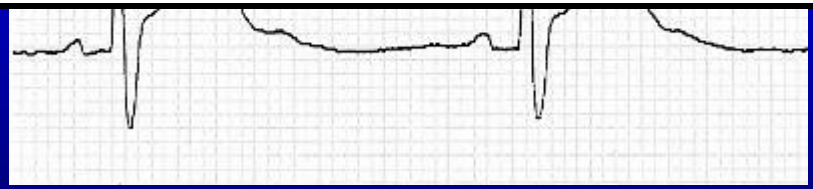
Short QT Syndrome: Pharmacological Treatment

Fiorenzo Gaita, MD; Carla Giustetto, MD; Francesca Bianchi, MD; Rainer Schimpf, MD; Michel Haissaguerre; MD, Leonardo Calò, MD; Ramon Brugada, MD; Charles Antzelevitch, PhD; Martin Borggrefe, MD; Christian Wolpert, MD.

J Am Coll Cardiol 2004; 43: 1494-99







QUINIDINE

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

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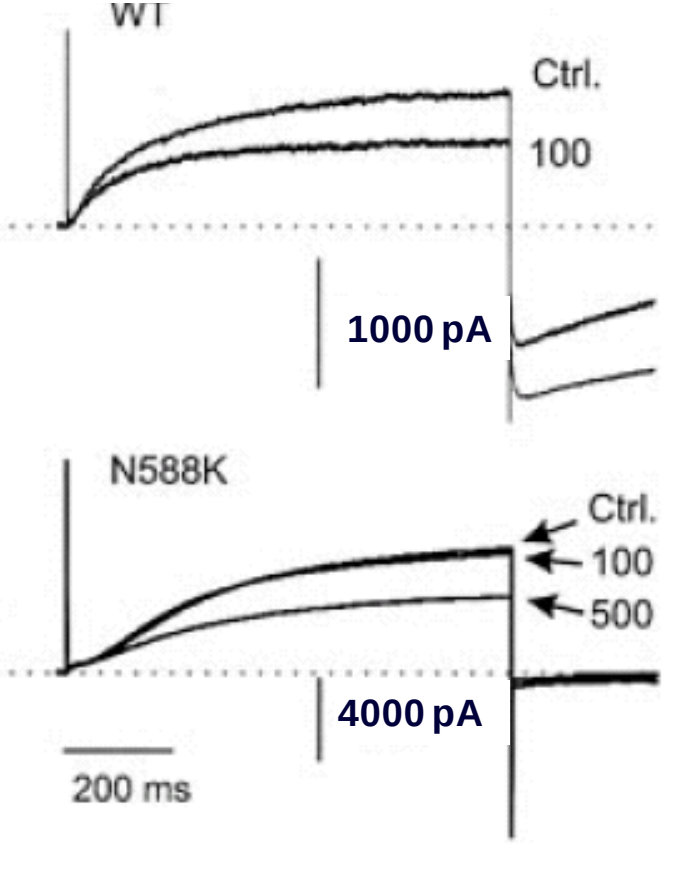
Circulation 2004, 109:30-35

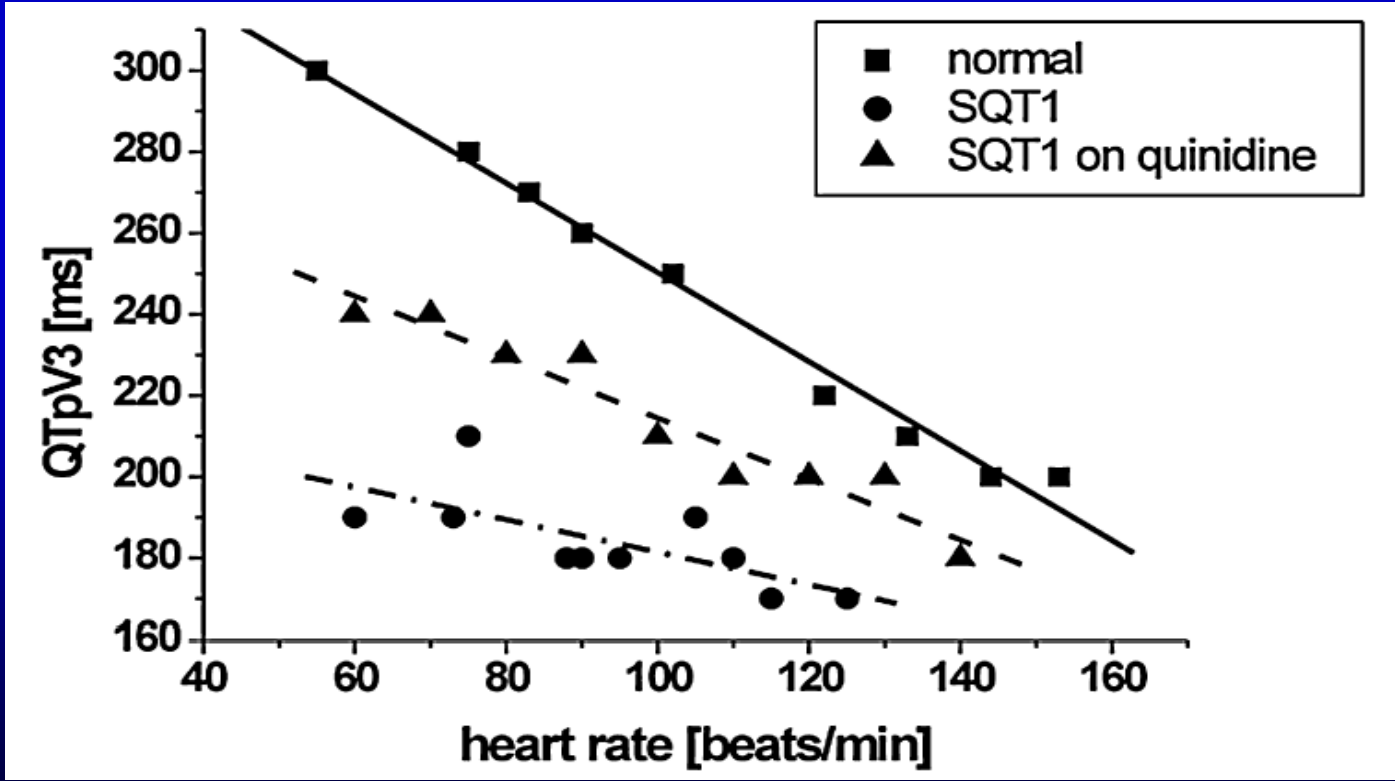


N588K mutation in HERG reduces the affinity of the I_{Kr} channel to sotalol by 20-fold

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, Vol. 16, pp. 1-5, January 2005



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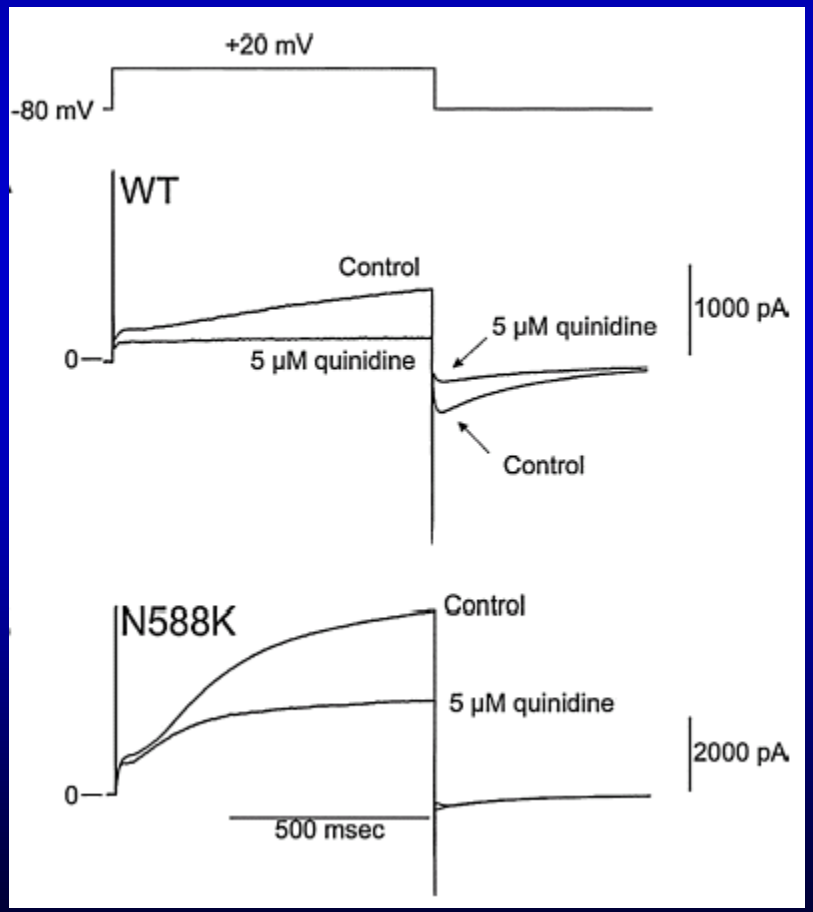


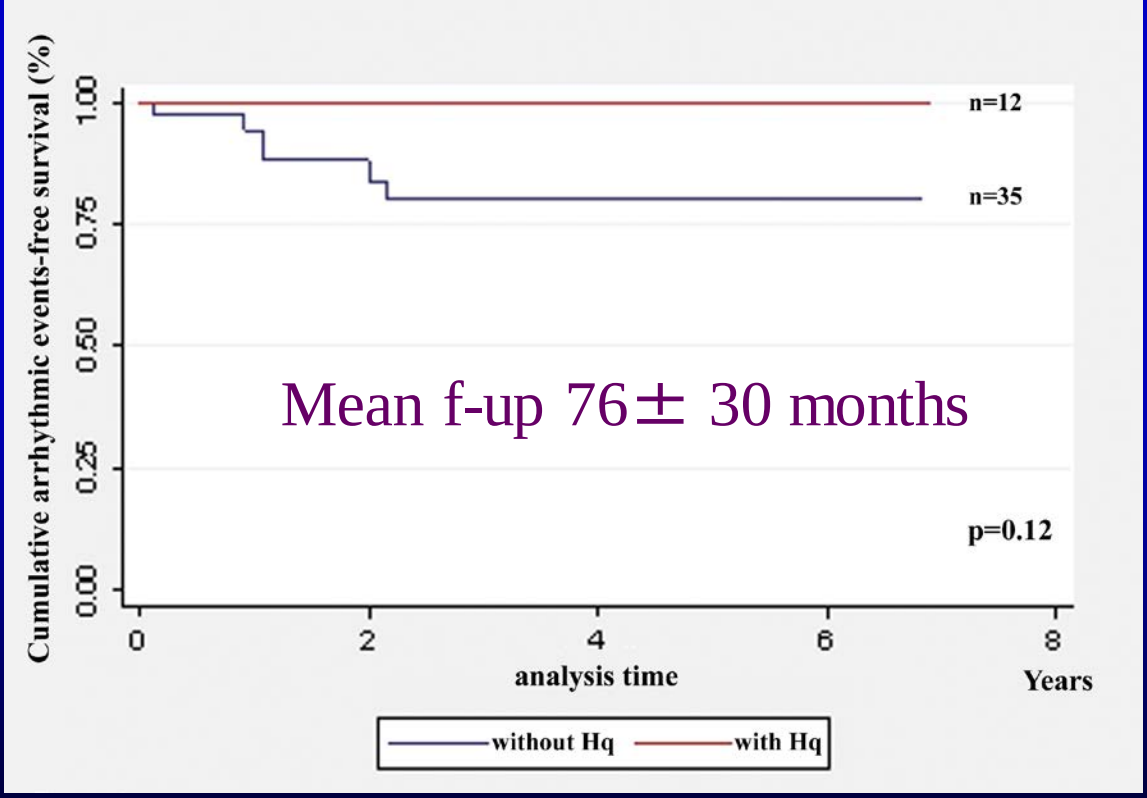
N588K mutation in HERG reduces the affinity of the I_{Kr} channel to quinidine by 5.8-fold

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

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*

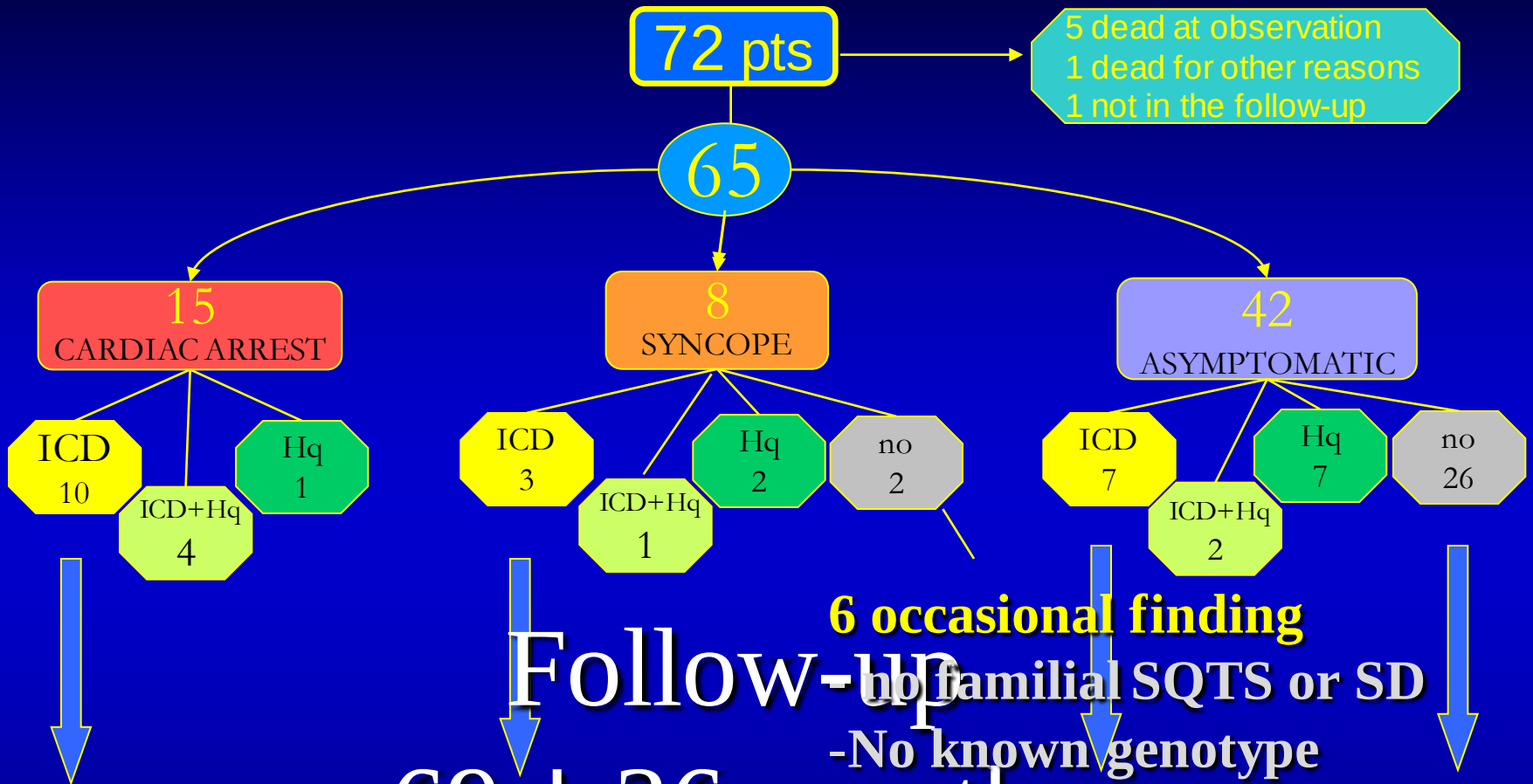
J. Am. Coll. Cardiol. 2011;58;587-595



12 pts with HQ
event Rate 0%/ year

35 pts without HQ
event Rate 4.9%/ year

72 patients from EuroShort Registry



6 occasional finding

-no familial SQTS or SD

-No known genotype

Follow-up

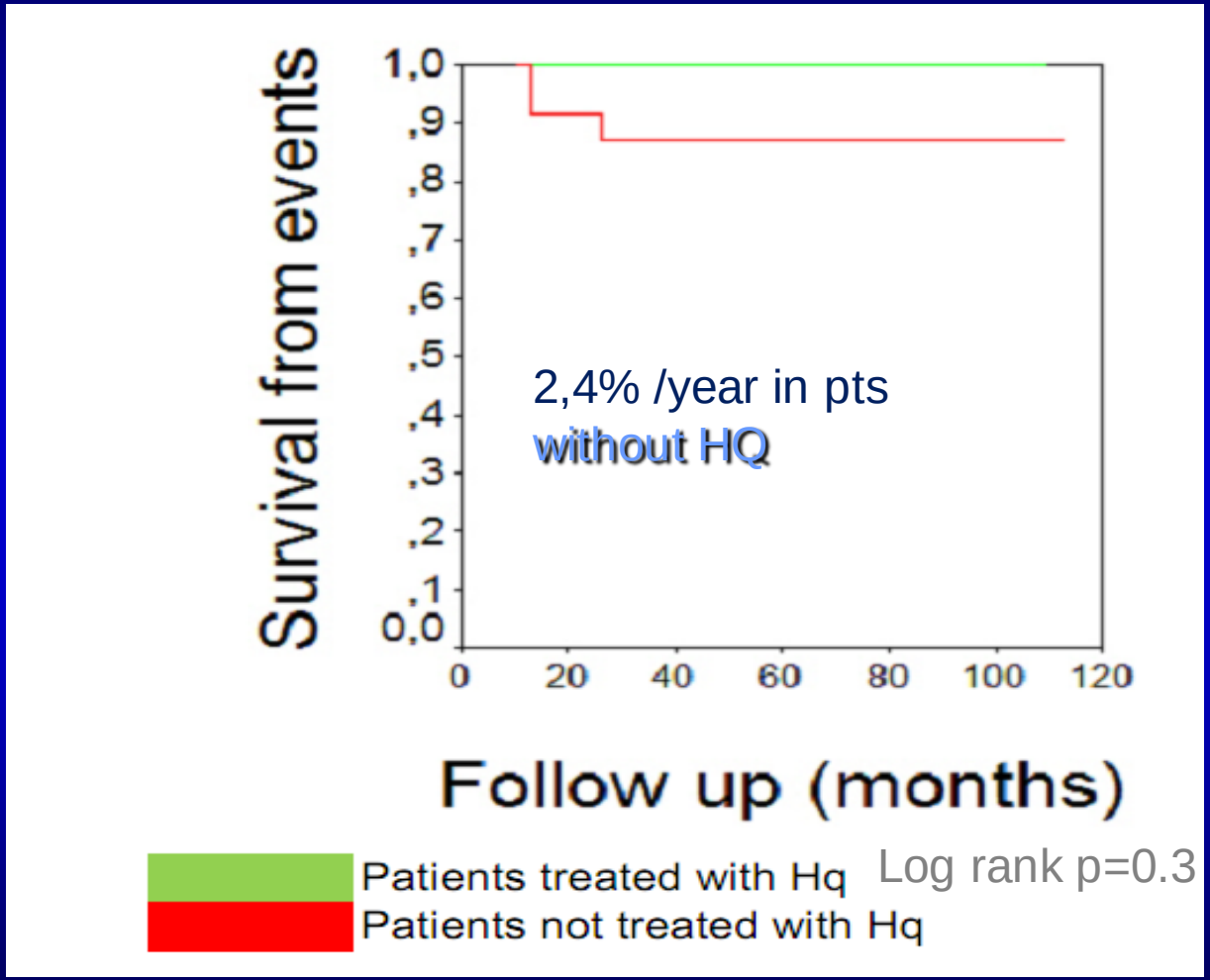
69±36 months

(range 4-129)

Rate event: previously symptomatic **3.5%**/year,

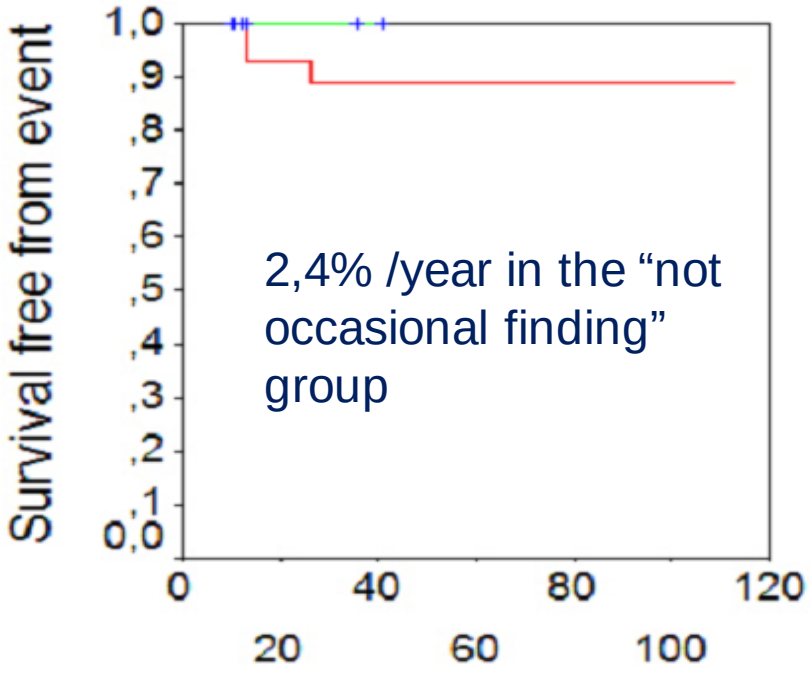
asymptomatic **1.9%**/year p=0.3

42 ASYMPTOMATIC pts



42 ASYMPTOMATIC pts:

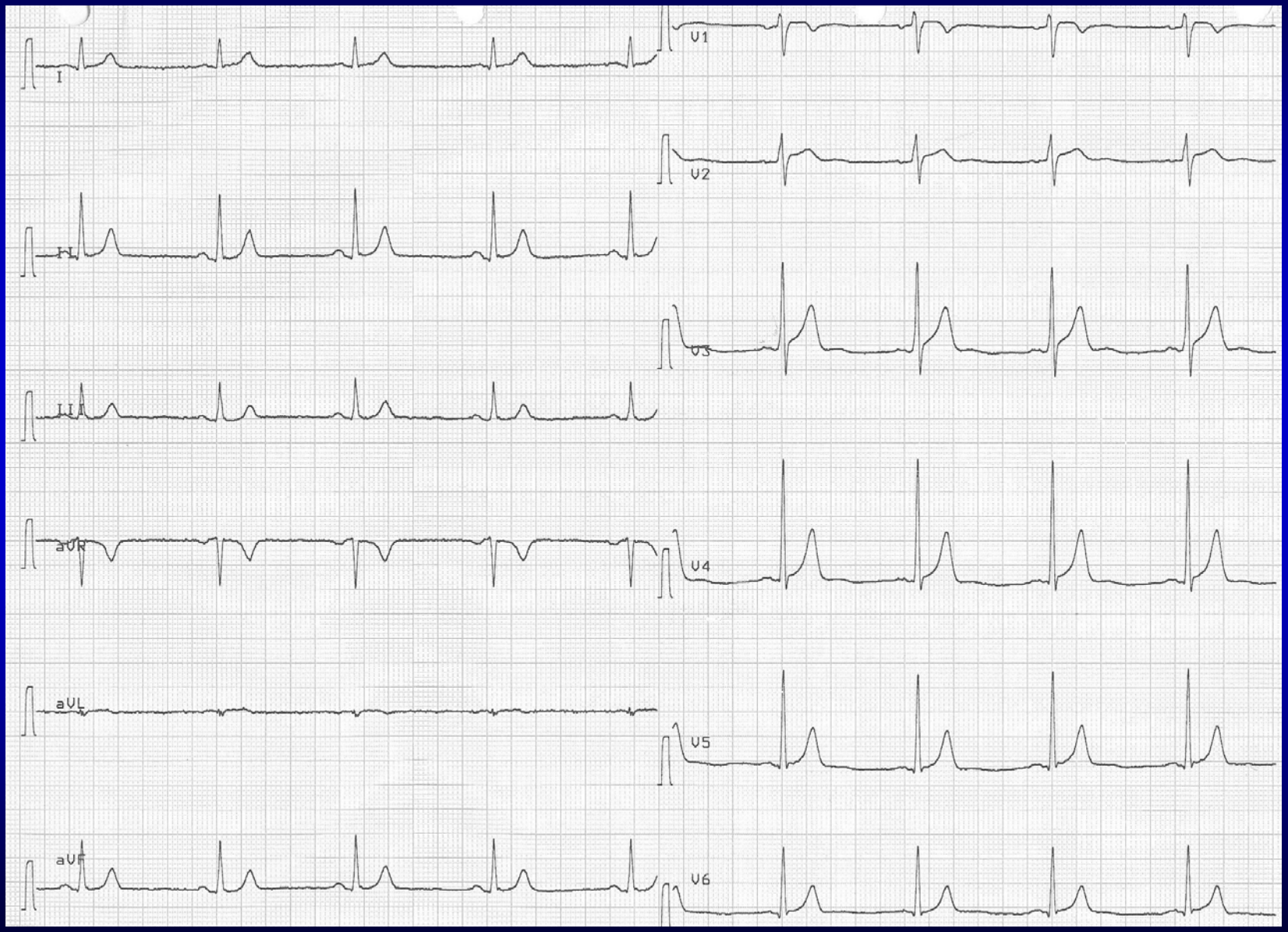
6 occasional finding



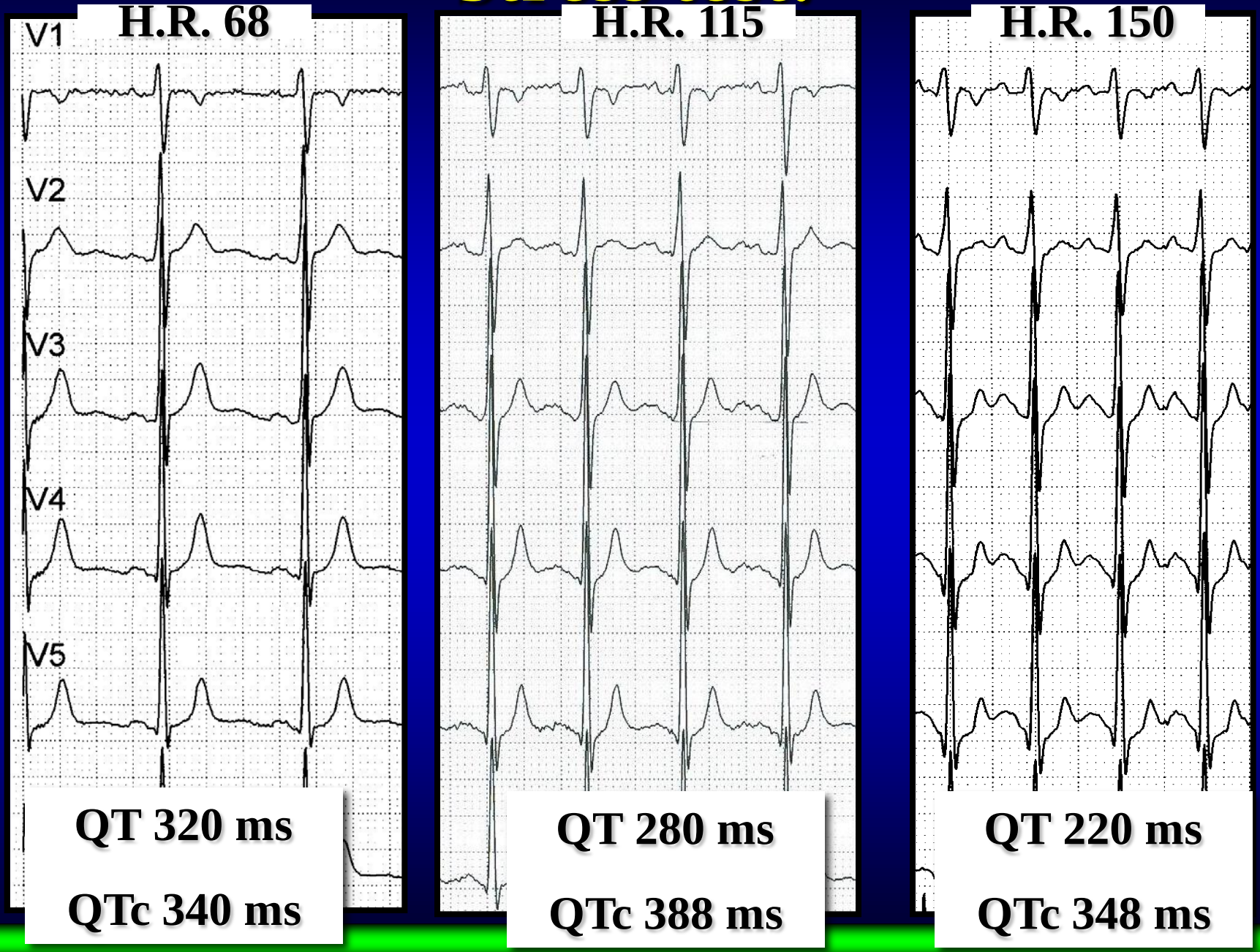
Log rank p=0.5

36 yrs, cyclist. No symptoms

QT 350 ms
QTc 335 ms

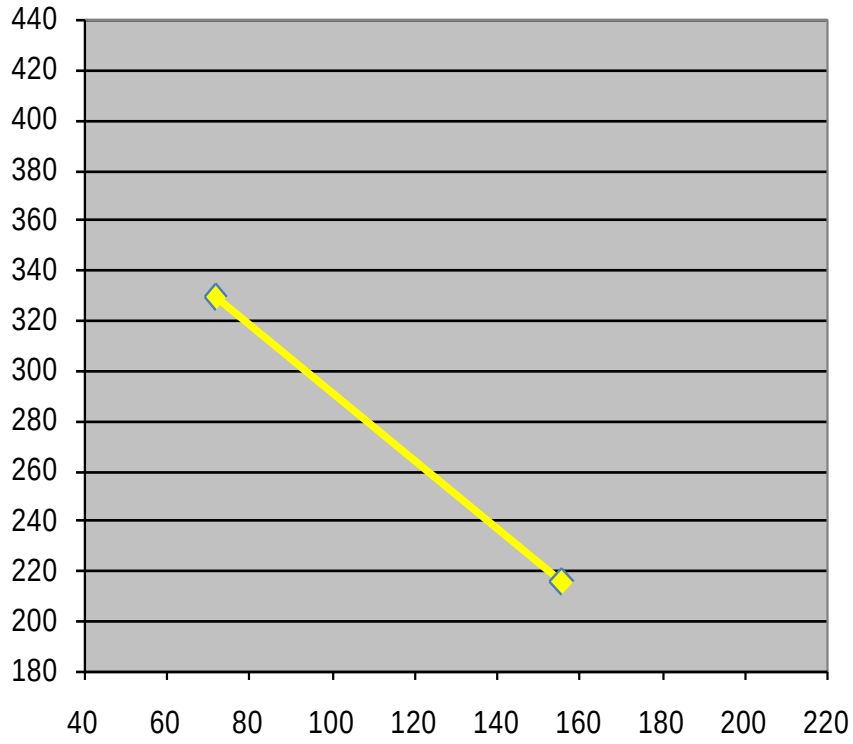


Stress test:


H.R. 68
V1
V2
V3
V4
V5
QT 320 ms
QTc 340 ms
H.R. 115
QT 280 ms
QTc 388 ms
H.R. 150
QT 220 ms
QTc 348 ms

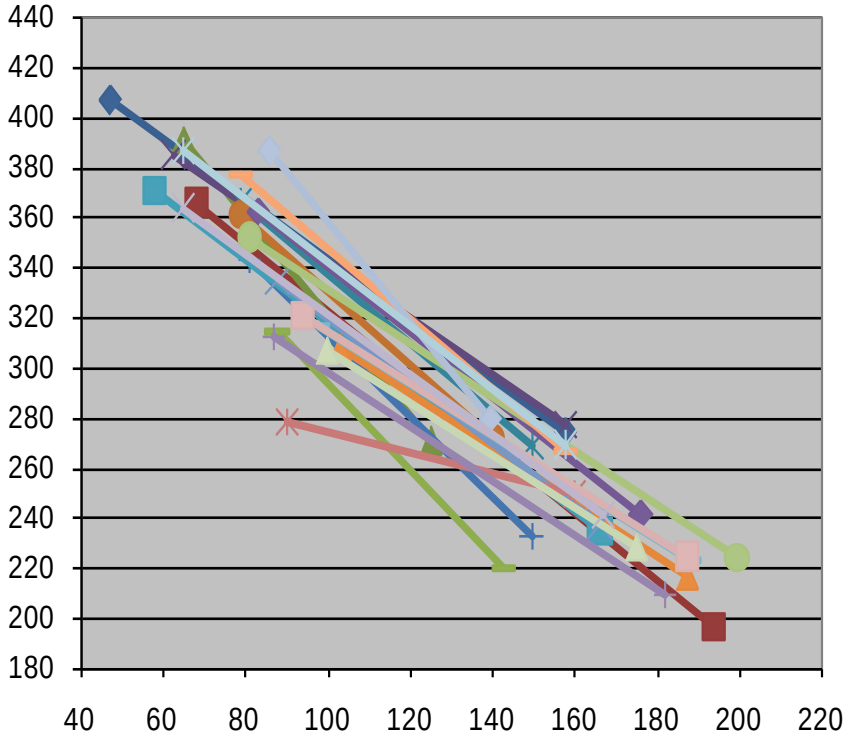
SQTS 2

slope
-1.35



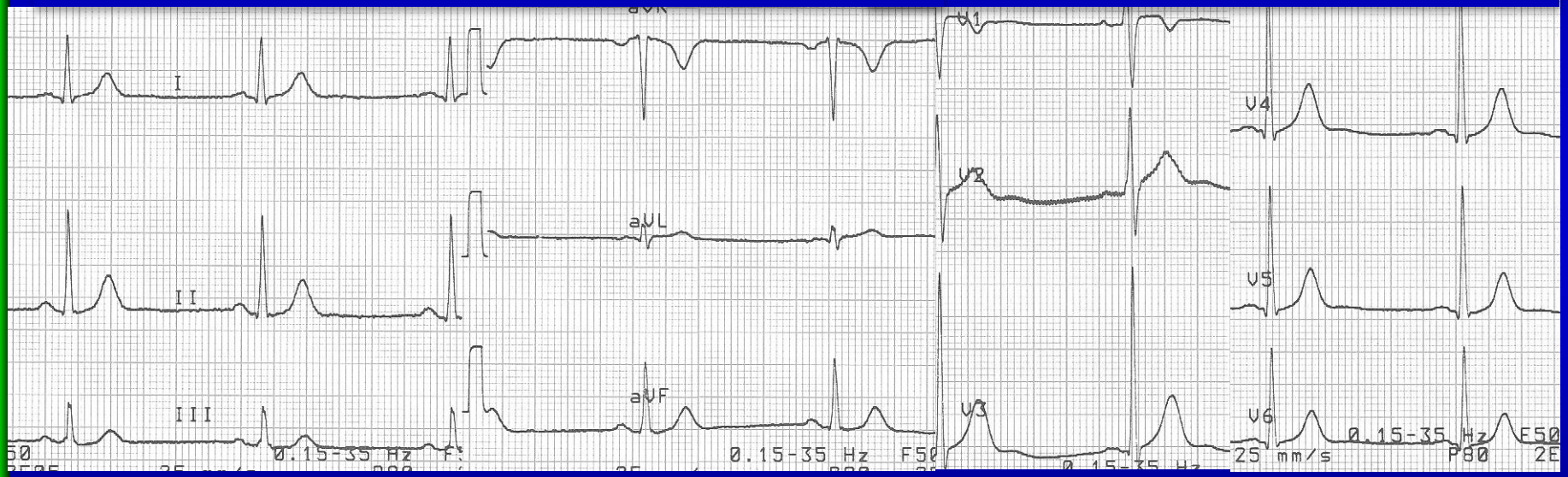
control group

slope
-1.30±0.3

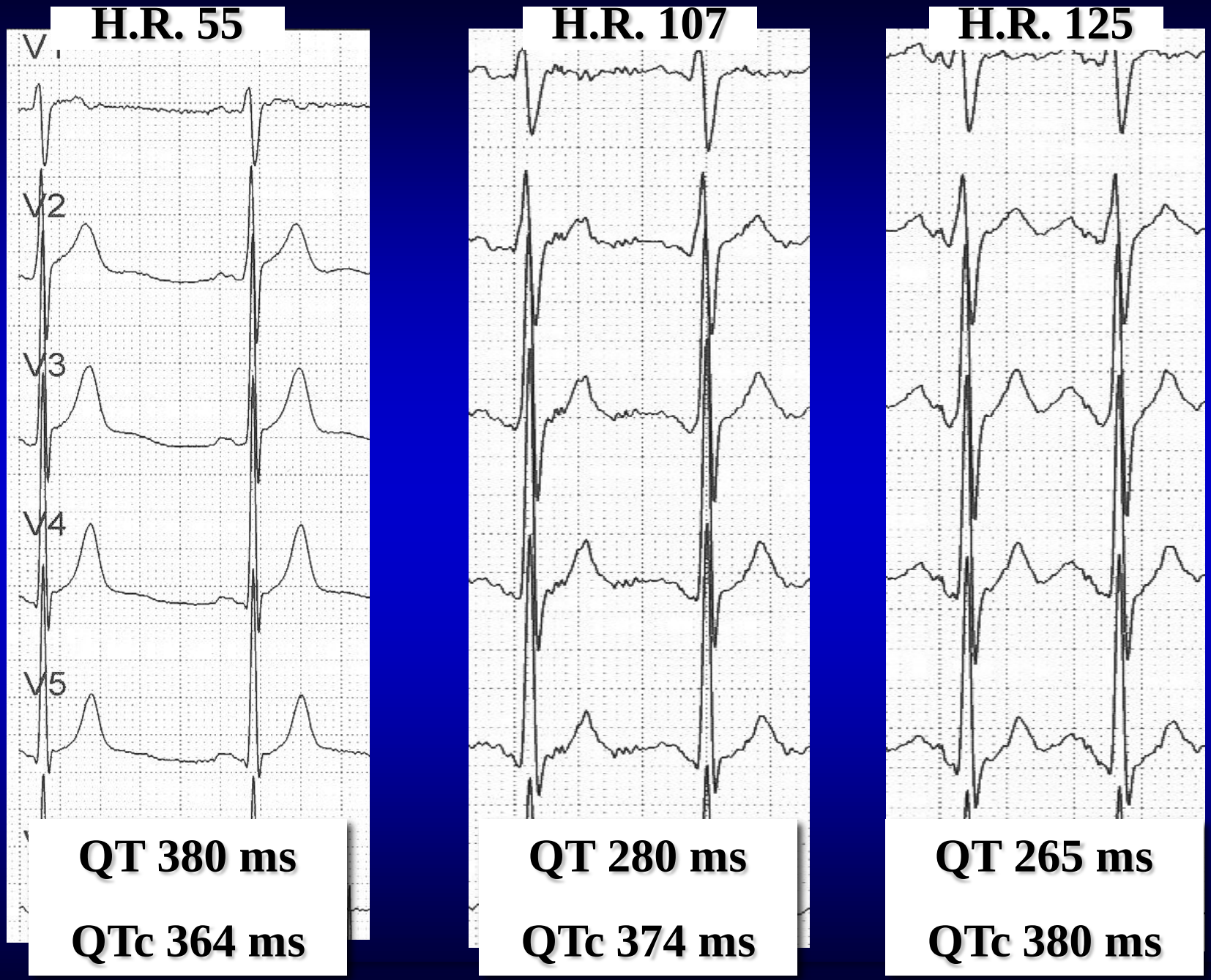


- no arrhythmias induced at EP study
- KCNQ1 V307L mutation (IKs)

QT 370 ms
QTc 350 ms



- discharged on Hydroquinidine 250 mg BID


H.R. 55
V1
V2
V3
V4
V5
QT 380 ms
QTc 364 ms
H.R. 107
QT 280 ms
QTc 374 ms
H.R. 125
QT 265 ms
QTc 380 ms

Short QT Syndrome: How to manage a symptomatic patient with SQTS?

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

Short QT Syndrome: How to menage an asymptomatic patient with SQTS?

Patients with occasional short QT finding should undergo stress test and 24-hour Holter monitoring to study the QT behavior at different heart rates and genetic testing to better define the diagnosis and, maybe, to guide therapy

Short QT Syndrome: How to manage asymptomatic pts?

- As we have not definitive data on predictors of SD yet, ICD should be proposed to adult patients from highly symptomatic families

- Prophylactic treatment with Hydroquinidine should be considered for newborn and children and also for adult patients who refuse ICD implantation

EUROPEAN REGISTRY ON SHORT QT SYNDROME

"EURO-SHORT"

Supported by the European Heart Rhythm Association (EHRA)

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