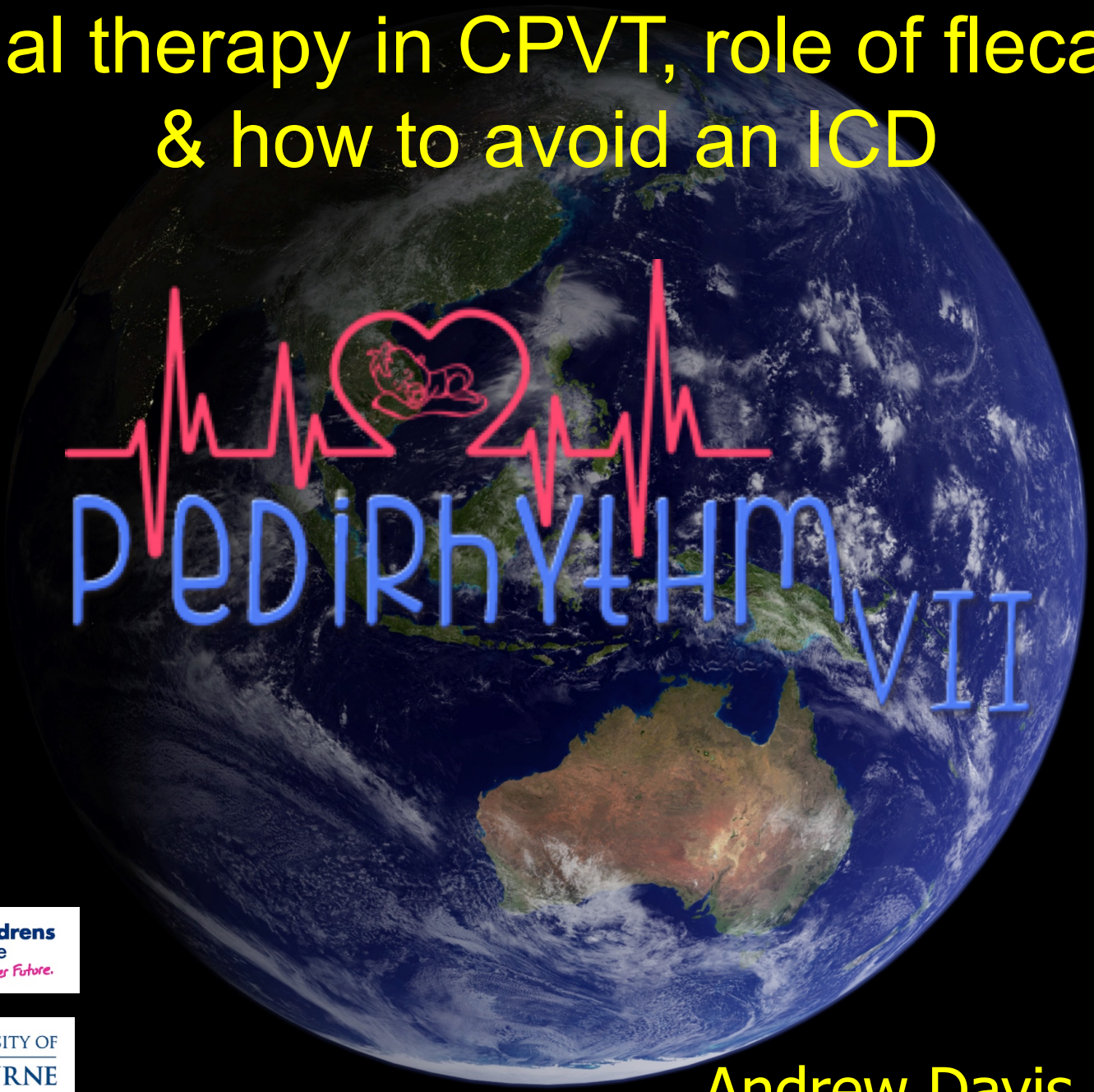
Optimal therapy in CPVT, role of flecainide, & how to avoid an ICD



Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

THE UNIVERSITY OF MELBOURNE

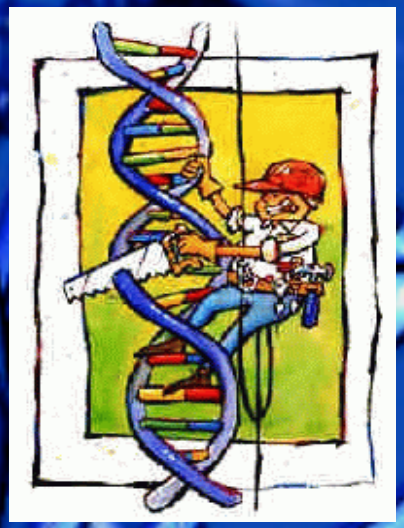
Andrew Davis

The Royal Children's Hospital Melbourne


01:02:56
A 688 N 328 A 352 A 872 N 409 N 367 A 688 A 344 A 344 N 367 A 313 N 219 A 707 N 394 A 375 A 320 A 188 A 383 A
A 344 N 750 A 688 A 375 A 320 A 367 A 305 A 367 A 320 A 320 A 336 A 680 A 930 A 188 A

Single Delivery of an Adeno-Associated Viral Construct to Transfer the *CASQ2* Gene to Knock-In Mice Affected by Catecholaminergic Polymorphic Ventricular Tachycardia Is Able to Cure the Disease From Birth to Advanced Age

Marco Denegri, PhD*; Rossana Bongianino, MSc*; Francesco Lodola, PhD*;
Simona Boncompagni, PhD; Verónica C. De Giusti, MD, PhD; José E. Avelino-Cruz, PhD;
Nian Liu, MD; Simone Persampieri, MS; Antonio Curcio, MD, PhD; Francesca Esposito, MD;
Laura Pietrangelo, MSc; Isabelle Marty, PhD; Laura Villani, MD; Alejandro Moyaho, PhD;
Paola Baiardi, PhD; Alberto Auricchio, MD; Feliciano Protasi, PhD;
Carlo Napolitano, MD, PhD; Silvia G. Priori, MD, PhD




Rx


ADRENALINE
JUNKIE


T2
T3
T4

Clinical and Molecular Characterization of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD; Mirella Memmi, PhD; Barbara Colombi, BS; Fabrizio Drago, MD; Maurizio Gasparini, MD; Luciano DeSimone, MD; Fernando Coltorti, MD; Raffaella Bloise, MD; Roberto Keegan, MD; Fernando E.S. Cruz Filho, MD; Gabriele Vignati, MD; Abraham Benatar, MD; Angelica DeLogu, MD

Circ 106 2002

a follow-up of ≈2 years, 50% of patients with the ICD received an appropriate shock to terminate ventricular tachyarrhythmias (Table 3).

Midterm experience with implantable cardioverter-defibrillators in children and young adults†

Europace 12 2010

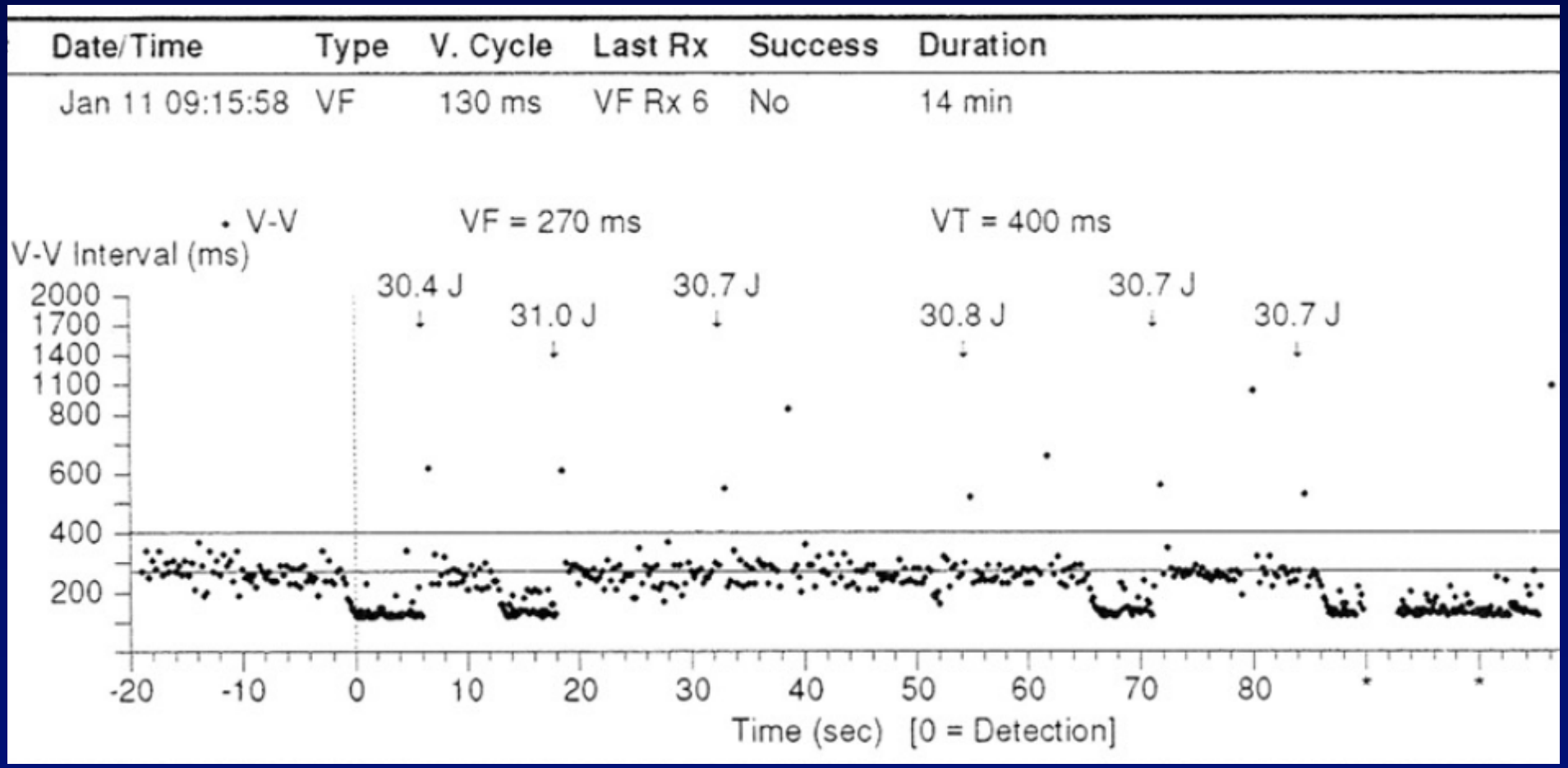
Alpay Çeliker[1], Haşim Olgun[2]*, Tevfik Karagoz[3], Sema Özer[3], Süheyla Özkutlu[3], and Dursun Alehan[3]

treatment can result in SCD.[21] In the present series, we also found a relatively large number of appropriate shocks in CPVT patients (five of seven).

Sudden cardiac death despite an implantable cardioverter-defibrillator in a young female with catecholaminergic ventricular tachycardia

Heart Rhythm 2006

Uwais Mohamed, MBBS,* Michael H. Gollob, MD,† Robert M. Gow, MB, BS,‡ Andrew D. Krahn, MD*



Electrical Storm in Children

PACE 2013

HENNING CLAUSEN, M.D.,* ANDREAS PFLAUMER, M.D.,*,† SULEMAN KAMBERI, B.Sc.,* and ANDREW DAVIS, M.B.B.S., M.D.*,†,‡

From the *Department of Cardiology, Royal Children's Hospital, Parkville, Australia; †Department of Paediatrics, University of Melbourne, Parkville, Australia; and ‡Murdoch Children's Research Institute, Parkville, Australia

Patient Characteristics and Management of Electrical Storm in Children

Patient	Gender	Age at Presentation (Years)	ES Presentation	Clinical/ Genetic Diagnosis	Follow-Up Period (Years)	Appropriate ICD Shocks (n)	Inappropriate ICD Shocks (n)	Medication
1	Female	6.5	Cardiac arrest	CPVT	4.8	0	0	β-blocker
2	Female	4.8	Cardiac arrest	CPVT	3.3	0	0	β-blocker
3	Female	3.3	Cardiac arrest	LQT/CPVT	4.8	1	0	β-blocker
4	Male	9.6	Syncope	IVF	9.8	25	2	Quinidine

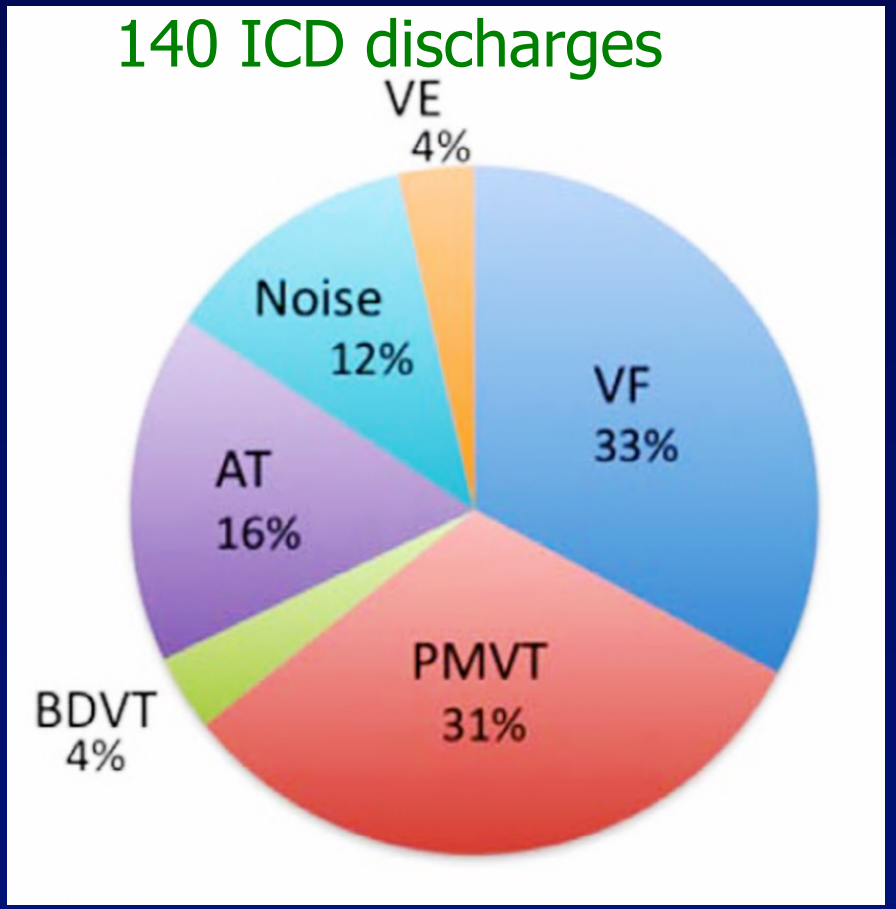
Efficacy of Implantable Cardioverter Defibrillators in Young Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

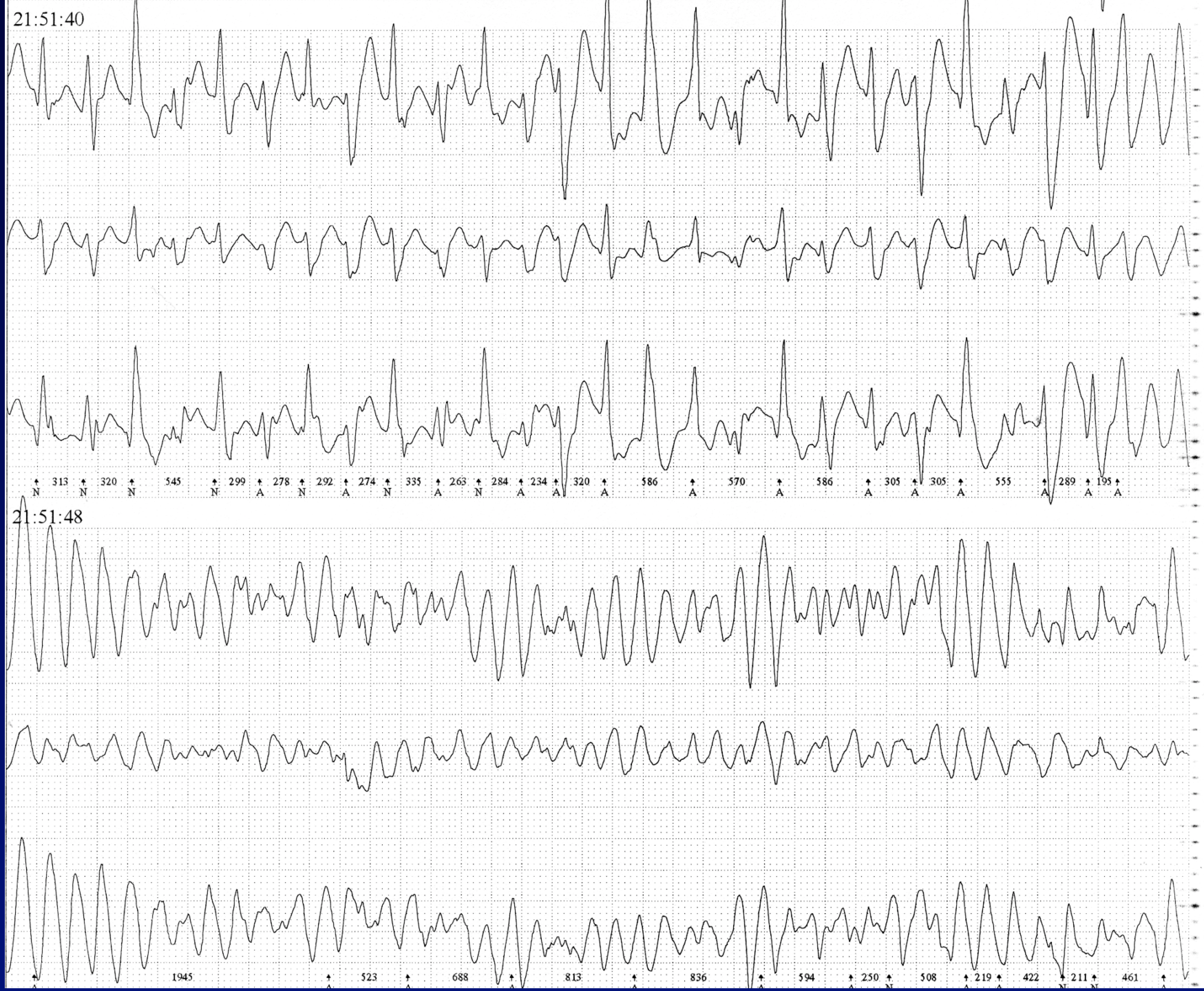
Success Depends on Substrate

Circ Arr EP 2013

Christina Y. Miyake, MD; Gregory Webster, MD; Richard J. Czosek, MD; Michal J. Kantoch, MD; Anne M. Dubin, MD; Kishor Avasarala, MD; Joseph Atallah, MD, CM, SM

- Inappropriate shocks, ES & ICD complications common
- ICD efficacy in CPVT depends on arrhythmia mechanism
- VF was uniformly successfully treated
- PMVT and bidirectional VT did not demonstrate successful primary termination.

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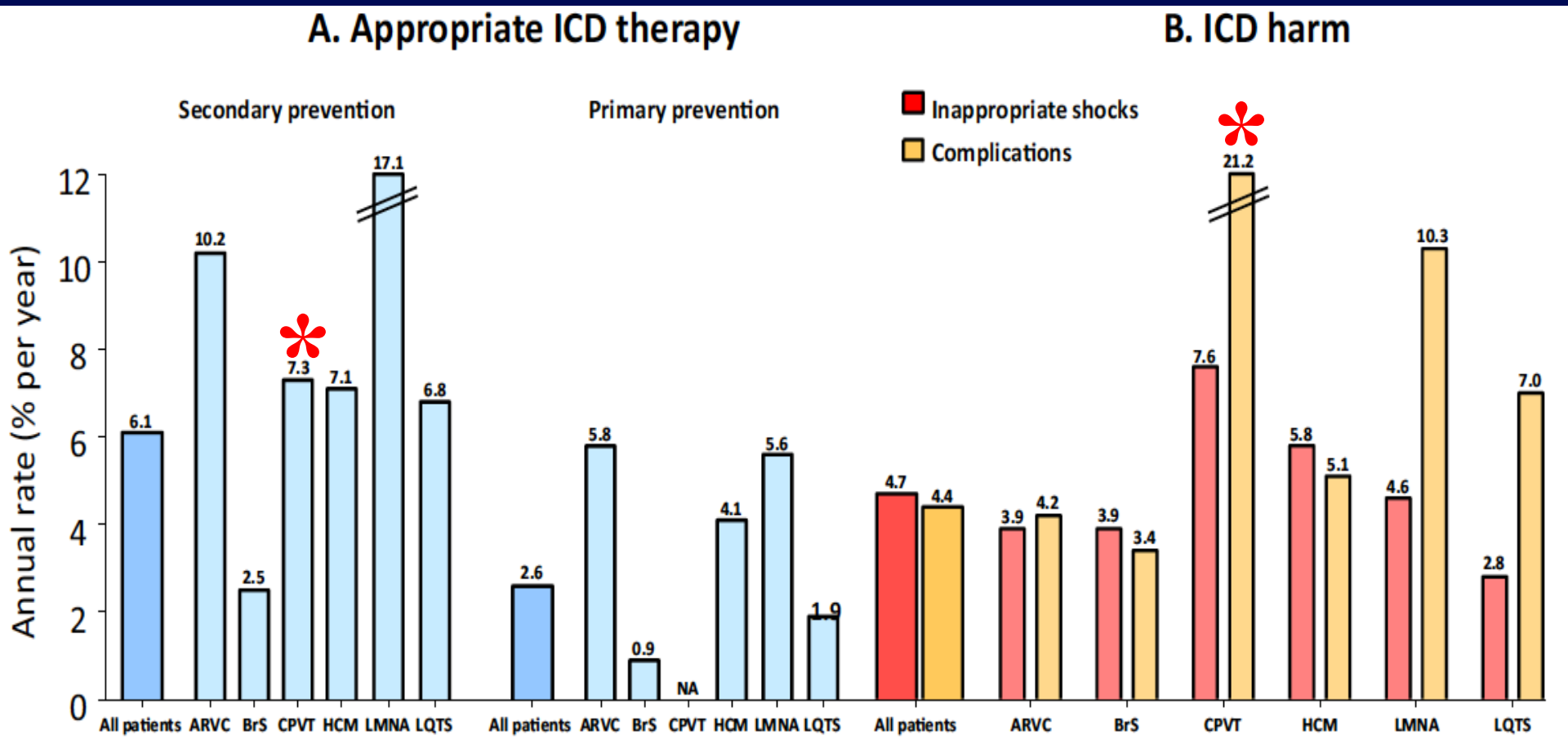
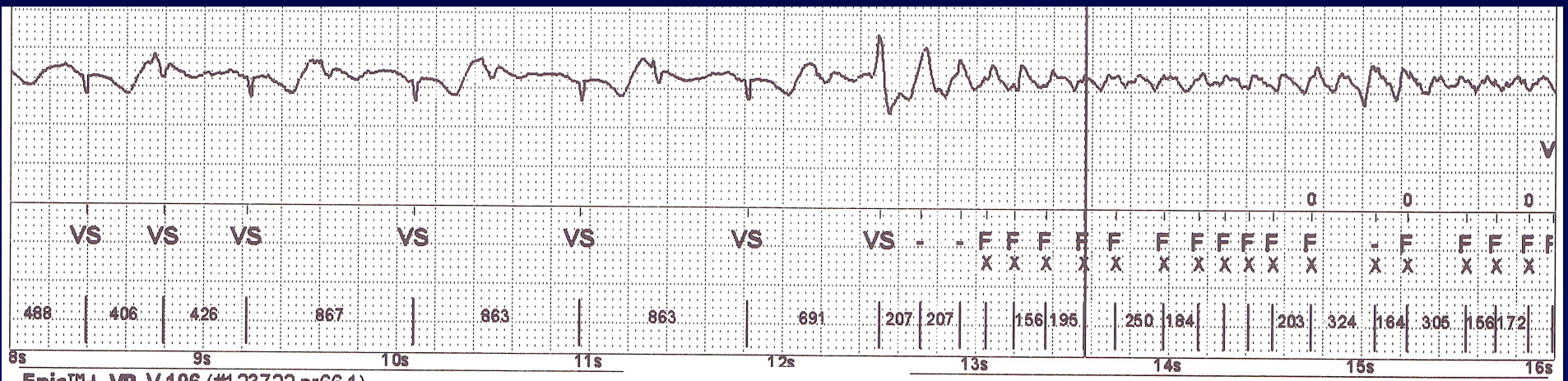
313 320 545 299 278 292 274 335 263 284 234 320 586 570 586 305 305 555 289 195
N N N N A N A N A N A A A A A A A A A A
21:51:48
1945 523 688 813 836 594 250 508 219 422 211 461

Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications

Louise R.A. Olde Nordkamp, MD, PhD,* Pieter G. Postema, MD, PhD,* Reinoud E. Knops, MD,* Nynke van Dijk, MD, PhD,† Jacqueline Limpens, PhD,‡ Arthur A.M. Wilde, MD, PhD,*§ Joris R. de Groot, MD, PhD*

Heart Rhythm 2016





Epic™+ VR V-196 (#123722 pr66.1)

Merlin™ PCS (#12281, 3330 v6.6.2.1)

Tachy Episode page 1 of 2

14 Nov 2008 13:08

Epic™+ VR V-196 (#123722 pr66.1)

ROYAL CHILDRENS HOSPITAL

Tachy Episode

Page 2 of 2

14 Nov 2008 13:08

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

Meiso Hayashi, MD; Isabelle Denjoy, MD; Fabrice Extramiana, MD, PhD; Alice Maltret, MD; Nathalie Roux Buisson, MD; Jean-Marc Lupoglazoff, MD, PhD; Didier Klug, MD; Miyuki Hayashi, MD; Seiji Takatsuki, MD; Elisabeth Villain, MD; Joël Kamblock, MD; Anne Messali, MD; Pascale Guicheney, PhD; Joël Lunardi, MD, PhD; Antoine Leenhardt, MD

Circulation 119 2009

- 8-year event rate: 32%
  - absence of β-blockers & Dx younger age independent predictors
- fatal/near-fatal events 8-year event rate: 13%
  - absence of β-blockers & history of aborted cardiac arrest independent predictors
- no difference in cardiac and fatal or near-fatal event rates between probands and family members

Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments

Europace 14 2012

Christian van der Werf[1], Aeilko H. Zwinderman[2], and Arthur A.M. Wilde[1*]

β-blocker efficacy

Meta analysis (complicated to do) of 11 studies (403 patients), of whom 88% had β-blocker prescribed. Mean follow-up: 20 months to 8 yrs.

Estimated 8-year:

Arrhythmic:	37.2%	(CI: 16.6–57.7)
Near-fatal events:	15.3%	(CI: 7.4–23.3)
Fatal events:	6.4%	(CI: 3.2–9.6)

Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent?

Michael J. Ackerman, MD, PhD,[*] Silvia G. Priori, MD, PhD,[†] Anne M. Dubin, MD, FHRS,[‡] Peter Kowey, MD,[§] Nicholas J. Linker, MD, FHRS,[¶] David Slotwiner, MD, FHRS,[#] John Triedman, MD, FHRS, CCDS, CEPS,[**] George F. Van Hare, MD, FHRS, CCDS, CEPS,[††] Michael R. Gold, MD, PhD, FHRS (Chair)[‡‡]

2009
nature medicine

Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans

Hiroshi Watanabe[1,5,6], Nagesh Chopra[1,6], Derek Laver[2,6], Hyun Seok Hwang[1], Sean S Davies[1], Daniel E Roach[3], Henry J Duff[3], Dan M Roden[1], Arthur A M Wilde[4] & Björn C Knollmann[1]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal inherited arrhythmia syndrome in which drug therapy is often ineffective. We discovered that flecainide prevents arrhythmias in a mouse model of CPVT by inhibiting cardiac ryanodine receptor–mediated Ca^{2+} release and thereby directly targeting the underlying molecular defect. Flecainide completely prevented CPVT in two human subjects who had remained highly symptomatic on conventional drug therapy, indicating that this currently available drug is a promising mechanism-based therapy for CPVT.

Flecainide Suppresses Defibrillator-Induced Storming in Catecholaminergic Polymorphic Ventricular Tachycardia

ROBERT A. HONG, M.D.*, KAHEALANI K. RIVERA, M.D.*, ARKSARAPUK JITTIRAT, M.D.,† and JOON J. CHOI, M.D., PH.D.*

From the *The Queen's Medical Center, John A. Burns School of Medicine, Department of Internal Medicine, Division of Cardiology; and †John A. Burns School of Medicine, Department of Internal Medicine, Honolulu, Hawaii

PACE 2012

Date/Time	Type	Therapy
06 Mar 2010 20:24	VT	41J, 41J, 41Jx4
06 Mar 2010 19:50	VT	41J, 41J, 41Jx6
06 Mar 2010 18:57	VT	41J, 41J, 41Jx6
06 Mar 2010 18:26	VT	41J, 41J, 41Jx6
06 Mar 2010 17:31	VT	41J, 41J, 41Jx6
06 Mar 2010 15:25	VT	41J, 41J, 41Jx6
06 Mar 2010 13:42	VT	41J, 41J, 41Jx4
05 Mar 2010 19:09	VT	41J, 41J, 41Jx4
05 Mar 2010 14:07	VT	41J, 41J, 41Jx4
23 Feb 2010 18:02	VT	41J, 41J, 41Jx6
19 Feb 2010 18:27	VT	41J, 41J, 41Jx6
31 Jan 2010 11:34	VT	41J, 41J, 41Jx5
24 Jan 2010 19:55	VT	No Therapy

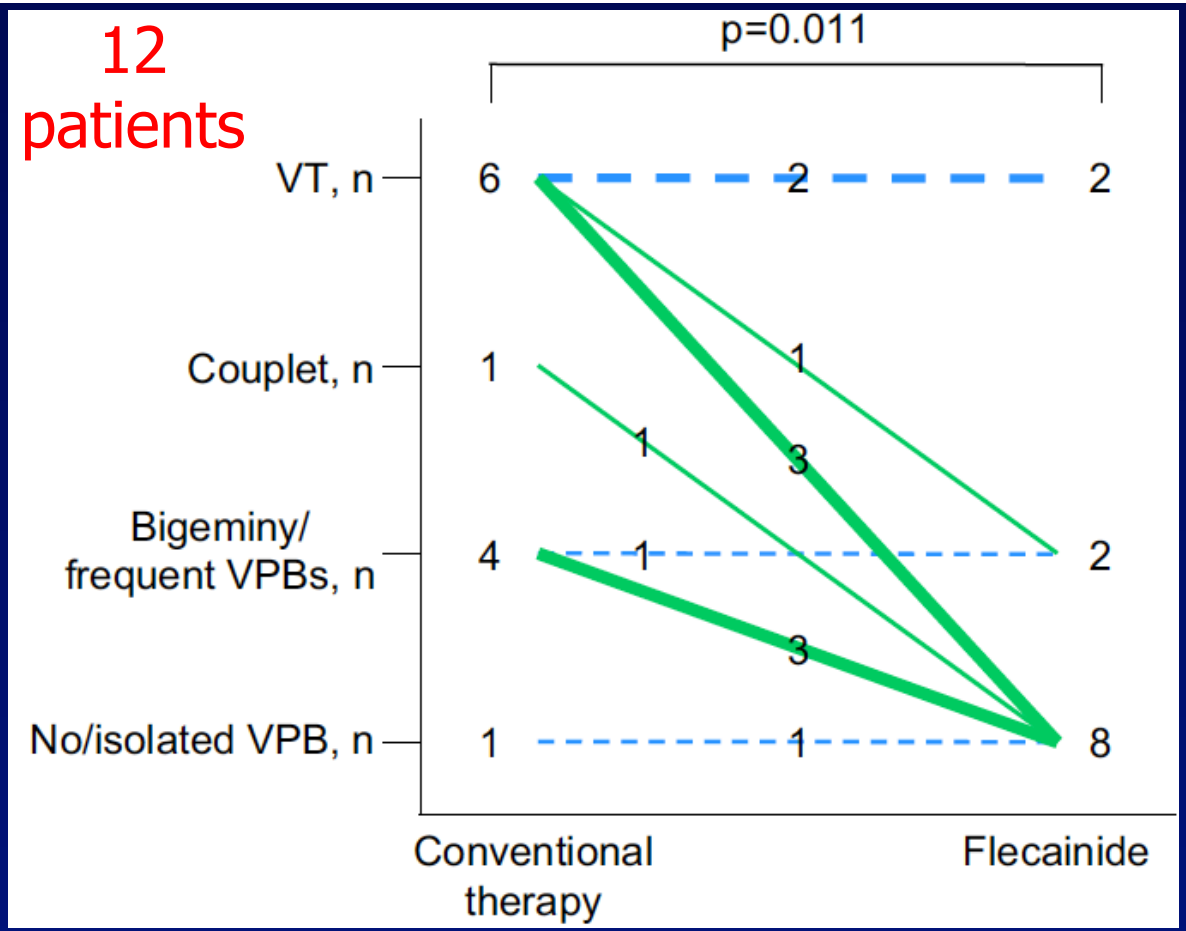
- 14yo with CPVT (CASQ) & ICD induced storming refractory to β-blockers, calcium-channel blockers, amiodarone, and dronedarone.
- Flecainide & β-blocker use suppressed incessant VT and ICD induced storming

Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia

Hiroshi Watanabe, MD, PhD, FESC,[*] Christian van der Werf, MD,[†] Ferran Roses-Noguer, MD,[‡] Arnon Adler, MD,[§] Naokata Sumitomo, MD,[‖] Christian Veltmann, MD,[¶] Raphael Rosso, MD,[§] Zahurul A. Bhuiyan, MD, PhD,[#] Hennie Bikker, PhD,[**] Prince J. Kannankeril, MD, MSCI,[††] Minoru Horie, MD, PhD,[‡‡] Tohru Minamino, MD, PhD,[*] Sami Viskin, MD,[§] Björn C. Knollmann, MD, PhD,[§§] Jan Till, MD,[‡] Arthur A.M. Wilde, MD, PhD[†]

Heart Rhythm 2013

12 patients

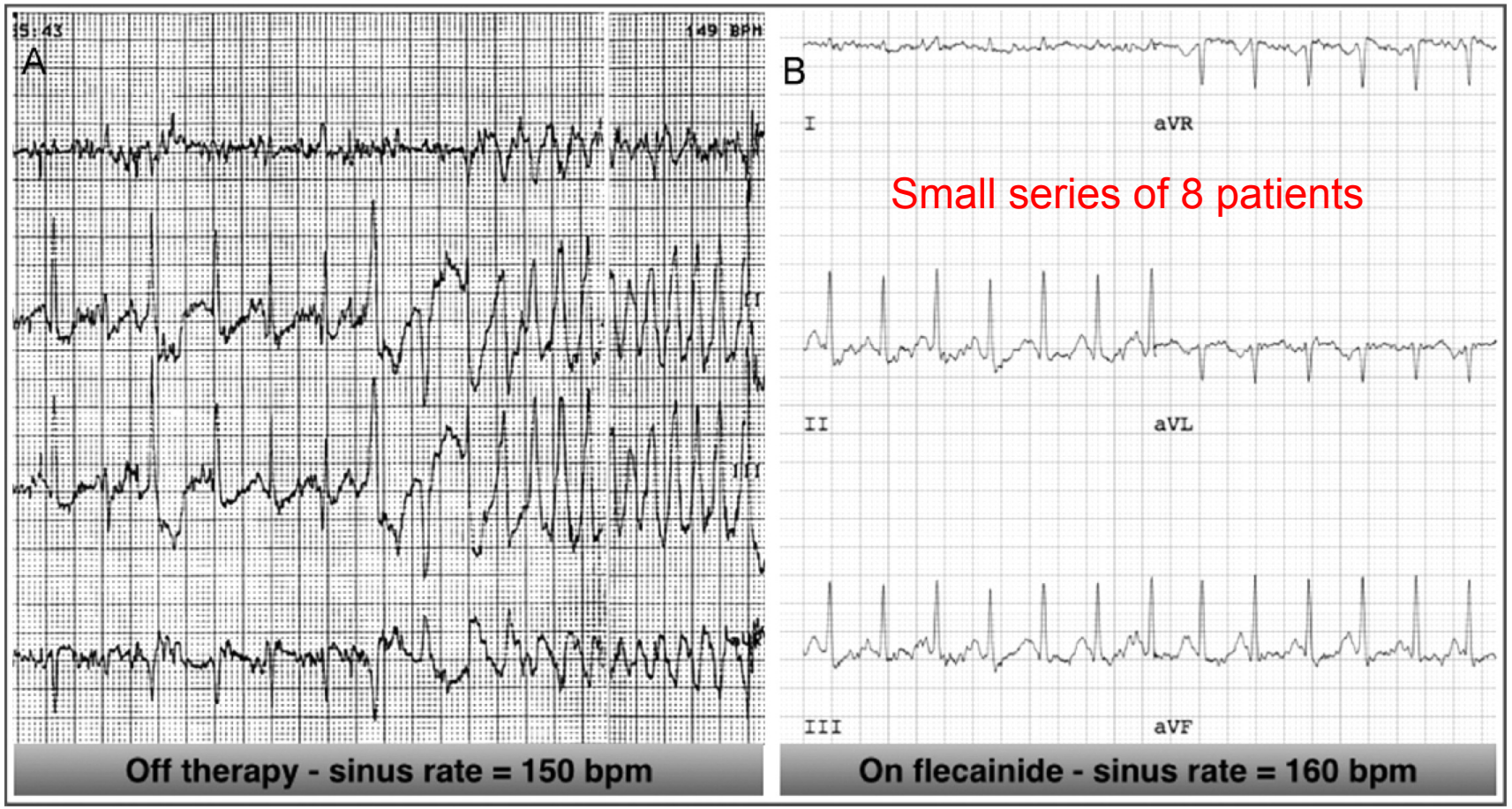


During follow-up: 48 ± 94 months, arrhythmia events (SCD, aborted cardiac arrest) associated with non-compliance occurred in 2 patients.

Flecainide monotherapy is an option for selected patients with catecholaminergic polymorphic ventricular tachycardia intolerant of β-blockade

Gareth J. Padfield, MBChB, PhD,[*] Leenah AlAhmari,[*] Krystien V.V. Lieve, MD,[†] Tasneem AlAhmari,[*] Thomas M. Roston, MD,[*] Arthur A. Wilde, MD, PhD, FHRS,[†‡] Andrew D. Krahn, MD, FHRS,[*] Shubhayan Sanatani, MD, FHRS[*]

Heart Rhythm 2016



The Role of Flecainide in the Management of Catecholaminergic Polymorphic Ventricular Tachycardia

Arrhythmia & Electrophysiology Review 2016

Krystien VV Lieve,[1] Arthur A Wilde,[1,2] Christian van der Werf[1]

1. Heart Centre, Academic Medical Centre, Amsterdam, The Netherlands;

2. Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Kingdom of Saudi Arabia

Conclusion

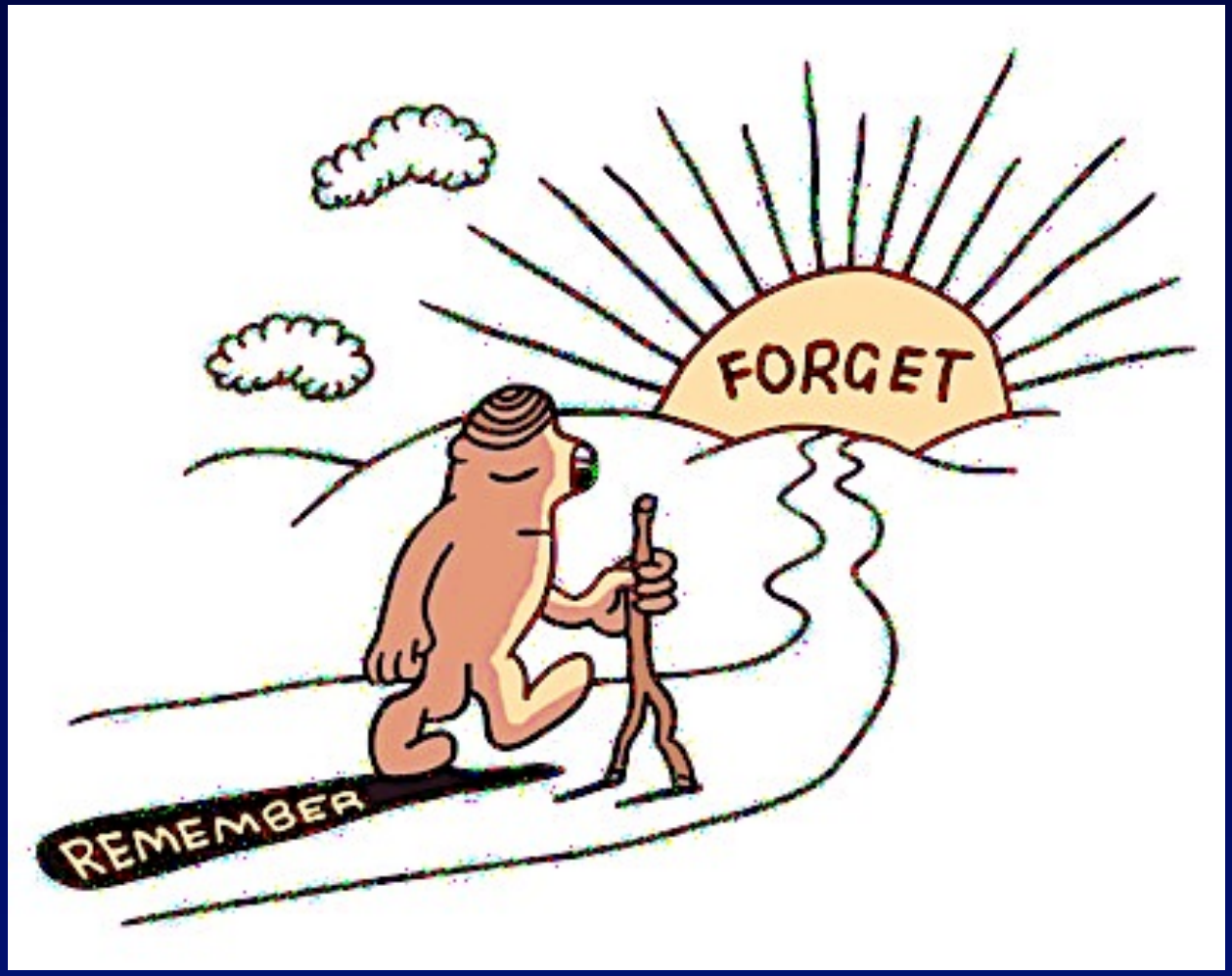
Preliminary results with flecainide in patients with CPVT are encouraging. However, a larger study with long-term follow-up is needed to fully elucidate the efficacy of flecainide, in particular its ability to prevent cardiac events in the long term. ■

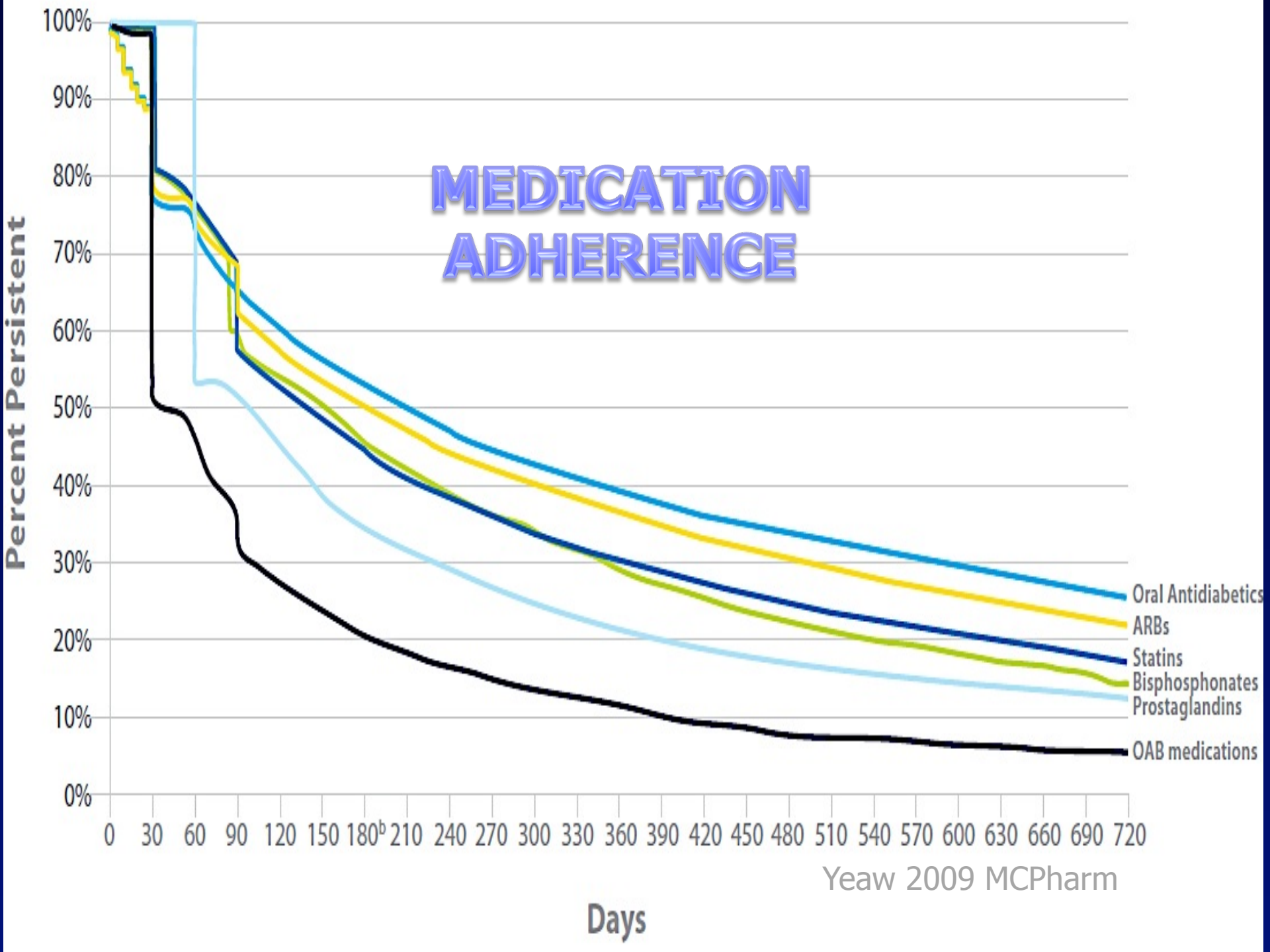
Carvedilol and its new analogs suppress arrhythmogenic store overload–induced Ca^{2+} release

Qiang Zhou[1,2,8], Jianmin Xiao[1,8], Dawei Jiang[1], Ruiwu Wang[1], Kannan Vembaiyan[3], Aixia Wang[3], Chris D Smith[3], Cuihong Xie[1,2,8], Wenqian Chen[1], Jingqun Zhang[2], Xixi Tian[1], Peter P Jones[1,8], Xiaowei Zhong[1], Ang Guo[4], Haiyan Chen[2], Lin Zhang[1], Weizhong Zhu[5], Dongmei Yang[6], Xiaodong Li[7], Ju Chen[7], Anne M Gillis[1], Henry J Duff[1], Heping Cheng[6,8], Arthur M Feldman[5], Long-Sheng Song[4], Michael Fill[2], Thomas G Back[3] & S R Wayne Chen[1,2]

Nature Medicine 17 2011

- Carvedilol is one of the most effective β-blockers preventing VT/VF in CCF.
- Spontaneous Ca waves (SOICR) evoke VT/VF in CCF.
- Carvedilol only β-blocker that suppressed SOICR by directly reducing RyR2 open duration.
- New SOICR-inhibiting, minimally β-blocking carvedilol analog, VK-II-86 which prevented VT/VF in RyR2-mutant mice and did so more effectively when combined with either of the selective beta blockers metoprolol or bisoprolol.


FORGET
REMEMBER


MEDICATION ADHERENCE
Percent Persistent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
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Days
Oral Antidiabetics
ARBs
Statins
Bisphosphonates
Prostaglandins
OAB medications
Yeaw 2009 MCPharm

Self-reported non-adherence to immune-suppressant therapy in liver transplant recipients: demographic, interpersonal, and intrapersonal factors

Clinical Transplant
26 2012

Using a liberal definition, half of our surveyed adult liver recipients report non-adherence to their immune suppressants, which may be a bigger problem than often recognized. Missed physician office appointments may serve as important "tip-off" in identifying non-adherence to immune

50%

DANGER

TEENAGER IN REBELLION MODE

Successful treatment of catecholaminergic polymorphic ventricular tachycardia with bilateral thoracoscopic sympathectomy HR 5 2008

Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery HR 6 2009

EDITORIAL COMMENTARY

Cutting nerves and saving lives Peter J. Schwartz, MD, FHRS HR 6 2009

Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long-term follow-up Bilateral > LCSD HR 11 2014

Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy HR 11 2014

EDITORIAL COMMENTARY

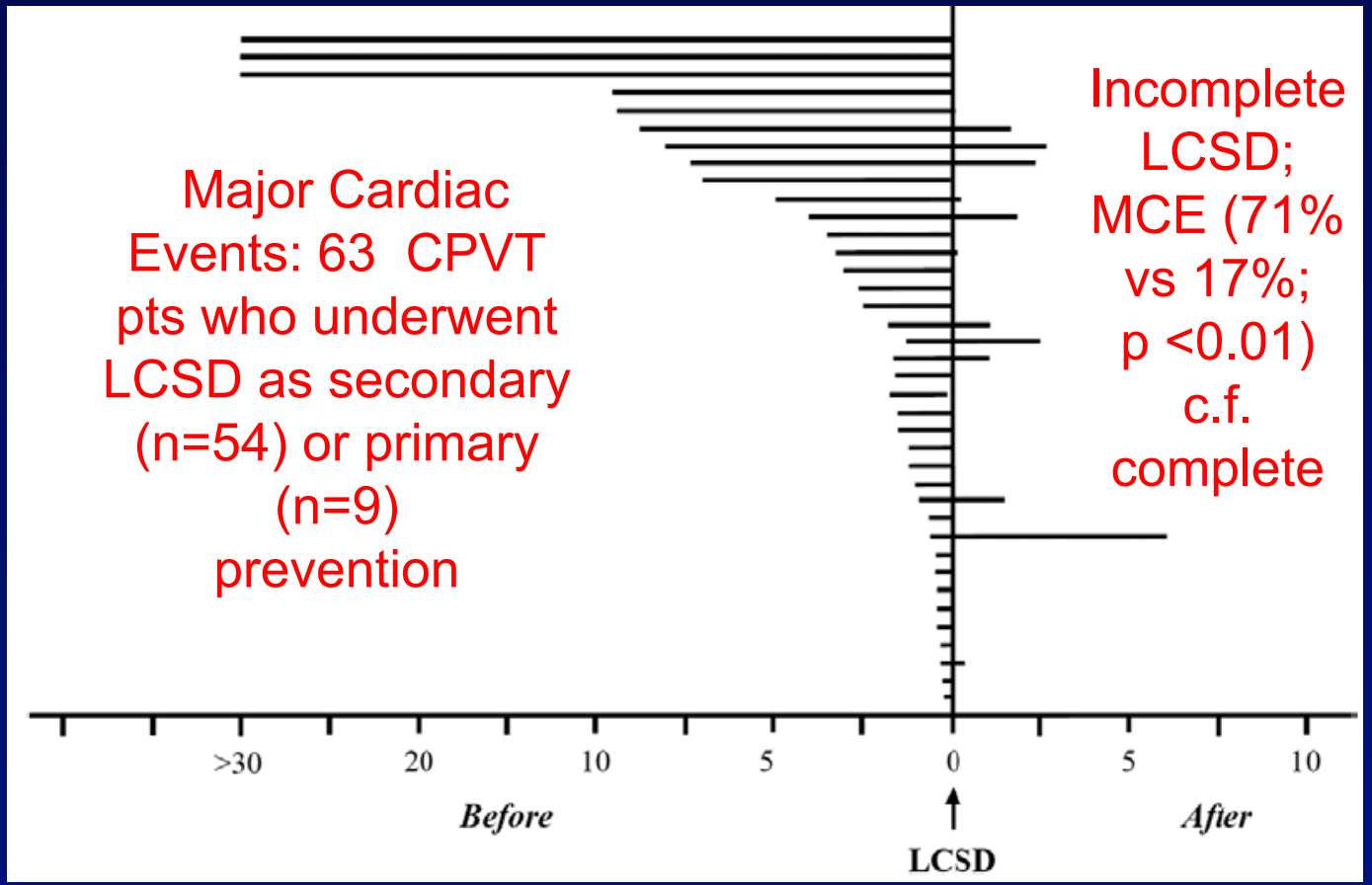
Interventional treatment of ventricular tachycardia and electrical storm: From ablation of substrate and triggers to autonomic modulation by renal denervation HR 11 2014

Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia

Circulation 2015

The Role of Left Cardiac Sympathetic Denervation

Gaetano M. De Ferrari, MD*; Veronica Dusi, MD*; Carla Spazzolini, DVM, MS*; J. Martijn Bos, MD, PhD*; Dominic J. Abrams, MD, MRCP; Charles I. Berul, MD; Lia Crotti, MD, PhD; Andrew M. Davis, MB, BS, MD; Michael Eldar, MD; Maria Kharlap, MD; Asaad Khoury, MD; Andrew D. Krahn, MD; Antoine Leenhardt, MD; Christopher R. Moir, MD; Attilio Odero, MD; Louise Olde Nordkamp, MD; Thomas Paul, MD; Ferran Rosés i Noguer, MD; Maria Shkolnikova, MD; Jan Till, MD; Arthur A.M. Wilde, MD; Michael J. Ackerman, MD, PhD†; Peter J. Schwartz, MD†



HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Heart Rhythm 2013

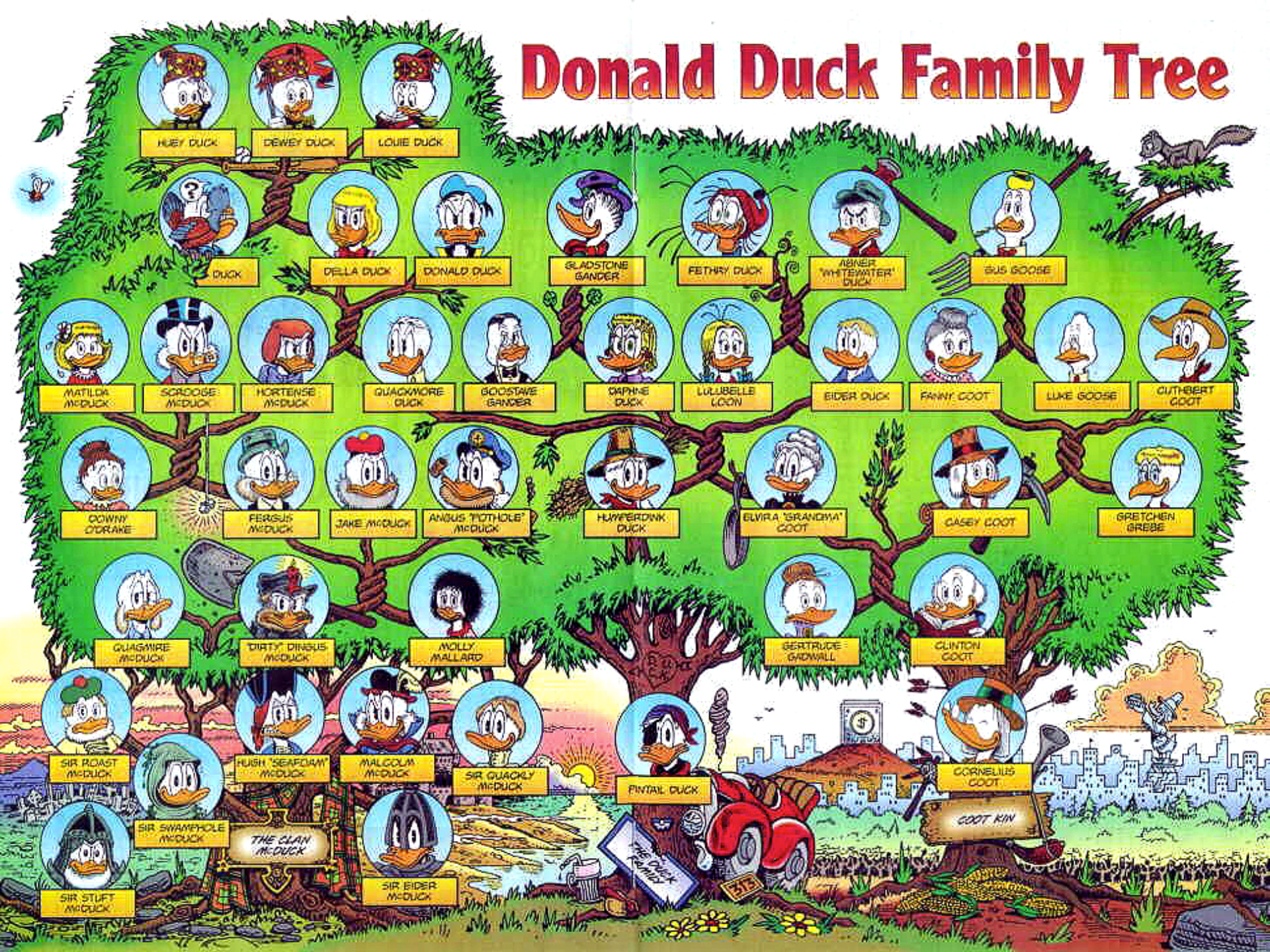
4. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) *Expert Consensus Recommendations on CPVT Diagnosis*

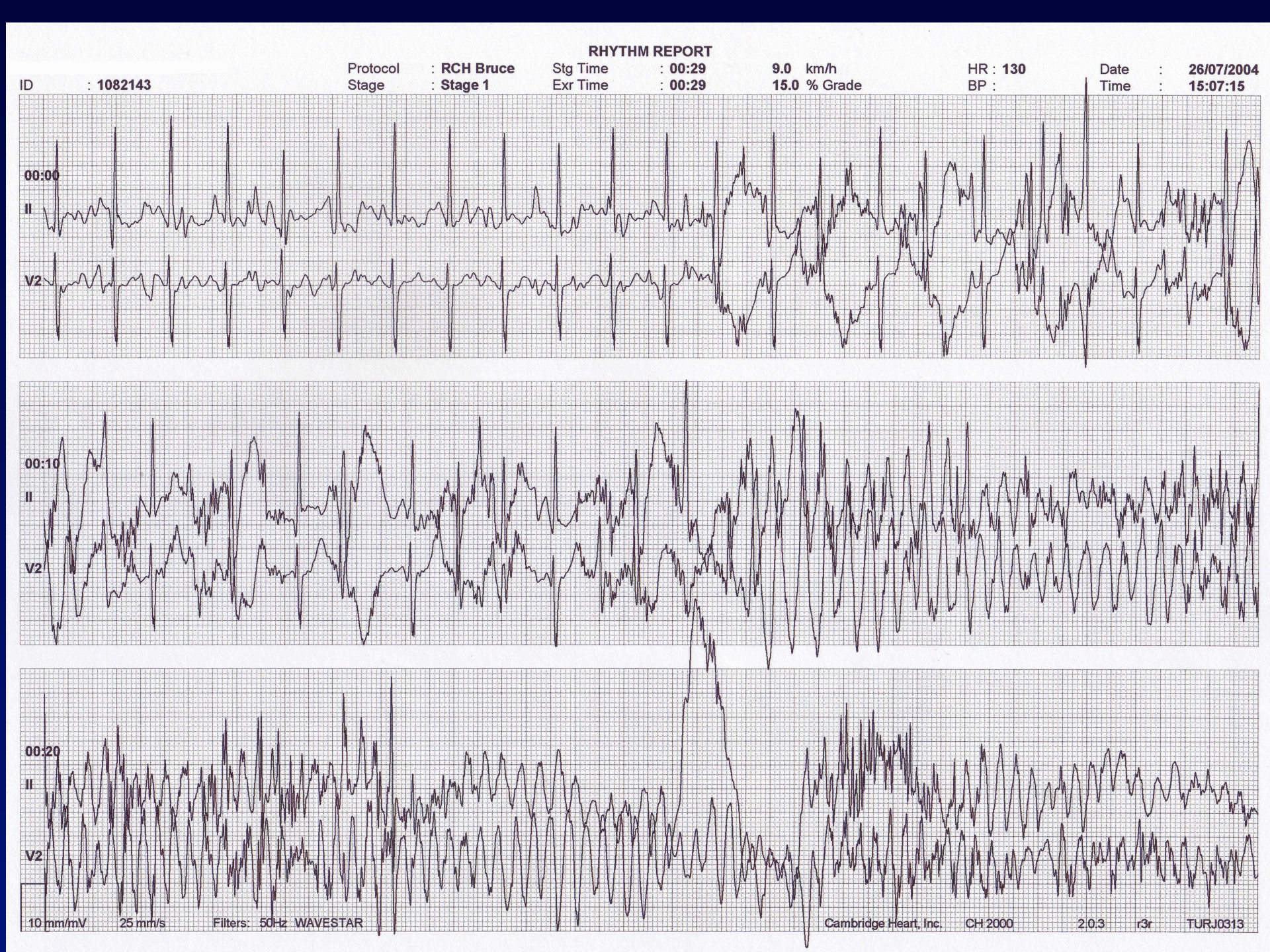
1. CPVT ***is diagnosed*** in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual <40 years of age.
2. CPVT ***is diagnosed*** in patients (index case or family member) who have a pathogenic mutation.
3. CPVT ***is diagnosed*** in family members of a CPVT index case with a normal heart who manifest exercise-induced premature ventricular contractions (PVCs) or bidirectional/polymorphic VT.
4. CPVT ***can be diagnosed*** in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual >40 years of age.

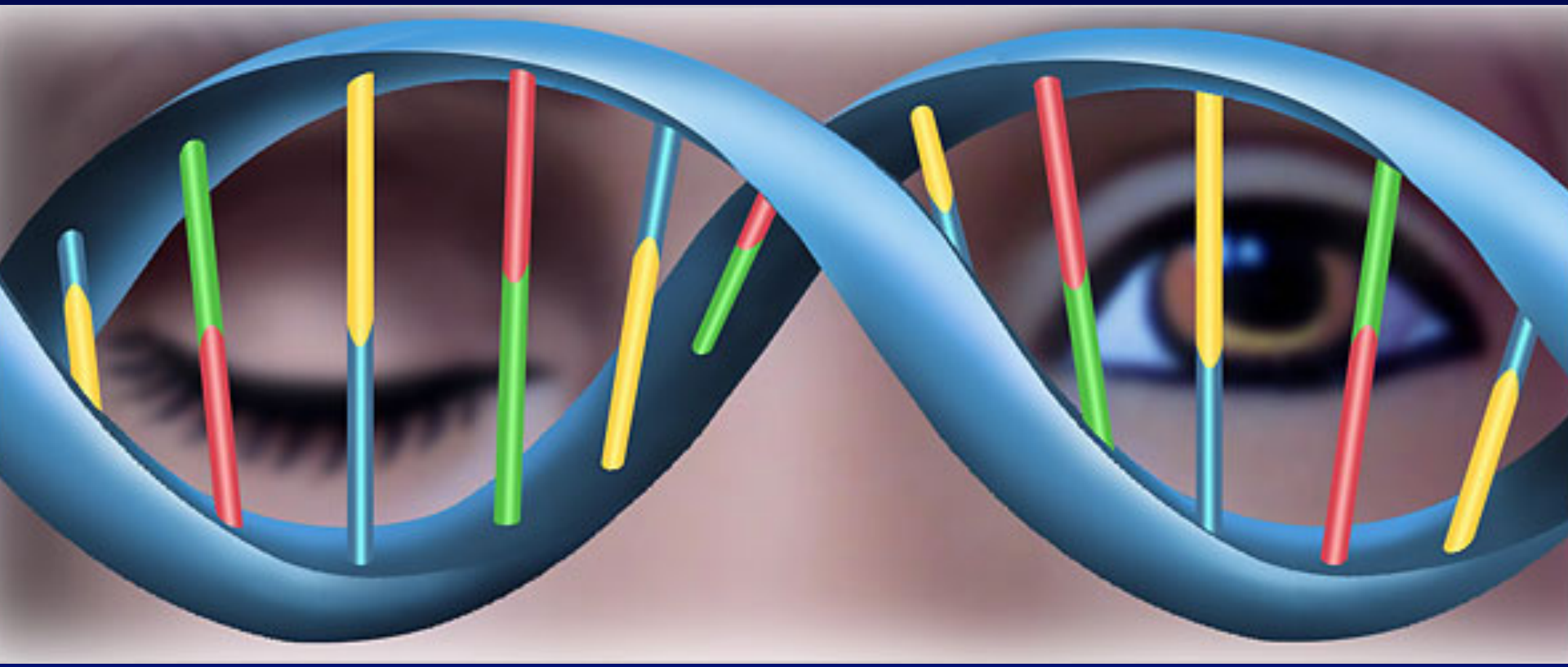
ESC 2015 VA Guidelines European Heart Journal 2015

Risk stratification and management in Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of CPVT: avoidance of competitive sports, strenuous exercise and stressful environments.	I	C	This panel of experts
Beta-blockers are recommended in all patients with a clinical diagnosis of CPVT, based on the presence of documented spontaneous or stress-induced VAs.	I	C	458, 460
ICD implantation in addition to beta-blockers with or without flecainide is recommended in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal therapy.	I	C	458, 461
Therapy with beta-blockers should be considered for genetically positive family members, even after a negative exercise test.	IIa	C	461, 462
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers, when there are risks/ contraindications for an ICD or an ICD is not available or rejected by the patient.	IIa	C	463
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT and carriers of an ICD to reduce appropriate ICD shocks.	IIa	C	463
Left cardiac sympathetic denervation may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT/several appropriate ICD shocks while on beta-blockers or beta-blockers plus flecainide and in patients who are intolerant or have contraindication to beta-blockers.	IIb	C	464, 465
Invasive EPS with PVS is not recommended for stratification of SCD risk.	III	C	14


Donald Duck Family Tree
HUEY DUCK
DEWEY DUCK
LOUIE DUCK
DUCK
DELLA DUCK
DONALD DUCK
GLADSTONE GANDER
FETHRY DUCK
ABNER "WHITEWATER" DUCK
GUS GOOSE
MATILDA McDUCK
SCROOGE McDUCK
HORTENSE McDUCK
QUACKMORE DUCK
GOOSTAVE GANDER
DAPHNE DUCK
LULUBELLE LOON
EIDER DUCK
FANNY COOT
LUKE GOOSE
CUTHBERT COOT
DOWNY O'DRAKE
FERGUS McDUCK
JAKE McDUCK
ANGUS "TOTHOLE" McDUCK
HUFFERDINK DUCK
ELVIRA "GRANDMA" COOT
CASEY COOT
GRETCHEN GREBE
GUAGMIRE McDUCK
"DIRTY" DINGUS McDUCK
MOLLY MALLARD
GERTRUDE GADWALL
CLINTON COOT
SIR ROAST McDUCK
HUGH "SEAFOAM" McDUCK
MALCOLM McDUCK
SIR QUACKLY McDUCK
PINTAIL DUCK
CORNELIUS COOT
SIR SWAMPHOLE McDUCK
THE CLAN McDUCK
COOT KIN
SIR STUFT McDUCK
SIR EIDER McDUCK
THE QUACK RAMBLER


RHYTHM REPORT
Protocol : RCH Bruce
Stage : Stage 1
Stg Time : 00:29
Exr Time : 00:29
9.0 km/h
15.0 % Grade
HR : 130
BP :
Date : 26/07/2004
Time : 15:07:15
ID : 1082143
00:00
II
V2
00:10
II
V2
00:20
II
V2
10 mm/mV
25 mm/s
Filters: 50Hz WAVESTAR
Cambridge Heart, Inc.
CH 2000
2.0.3
r3r
TURJ0313



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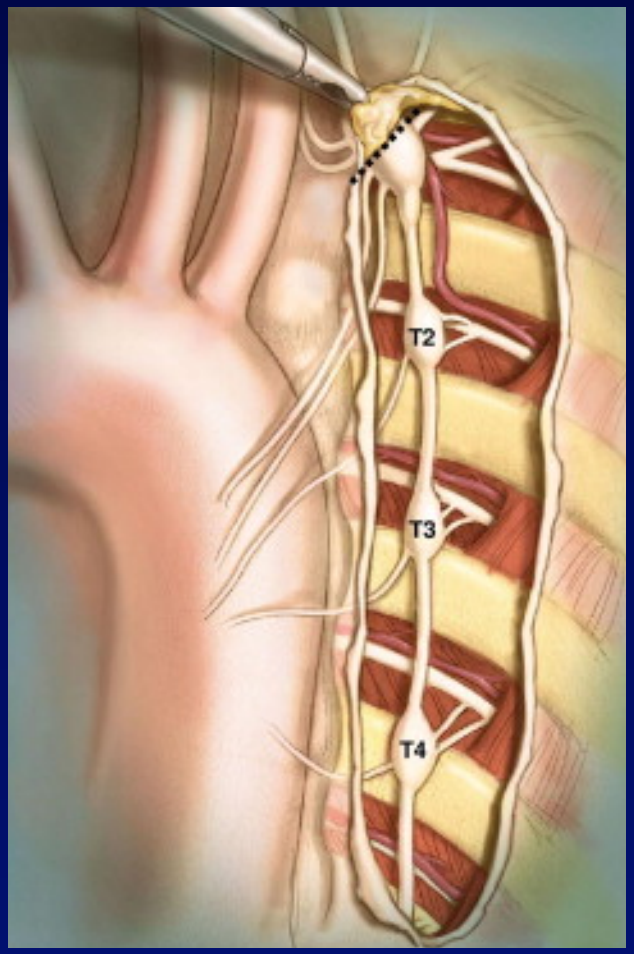
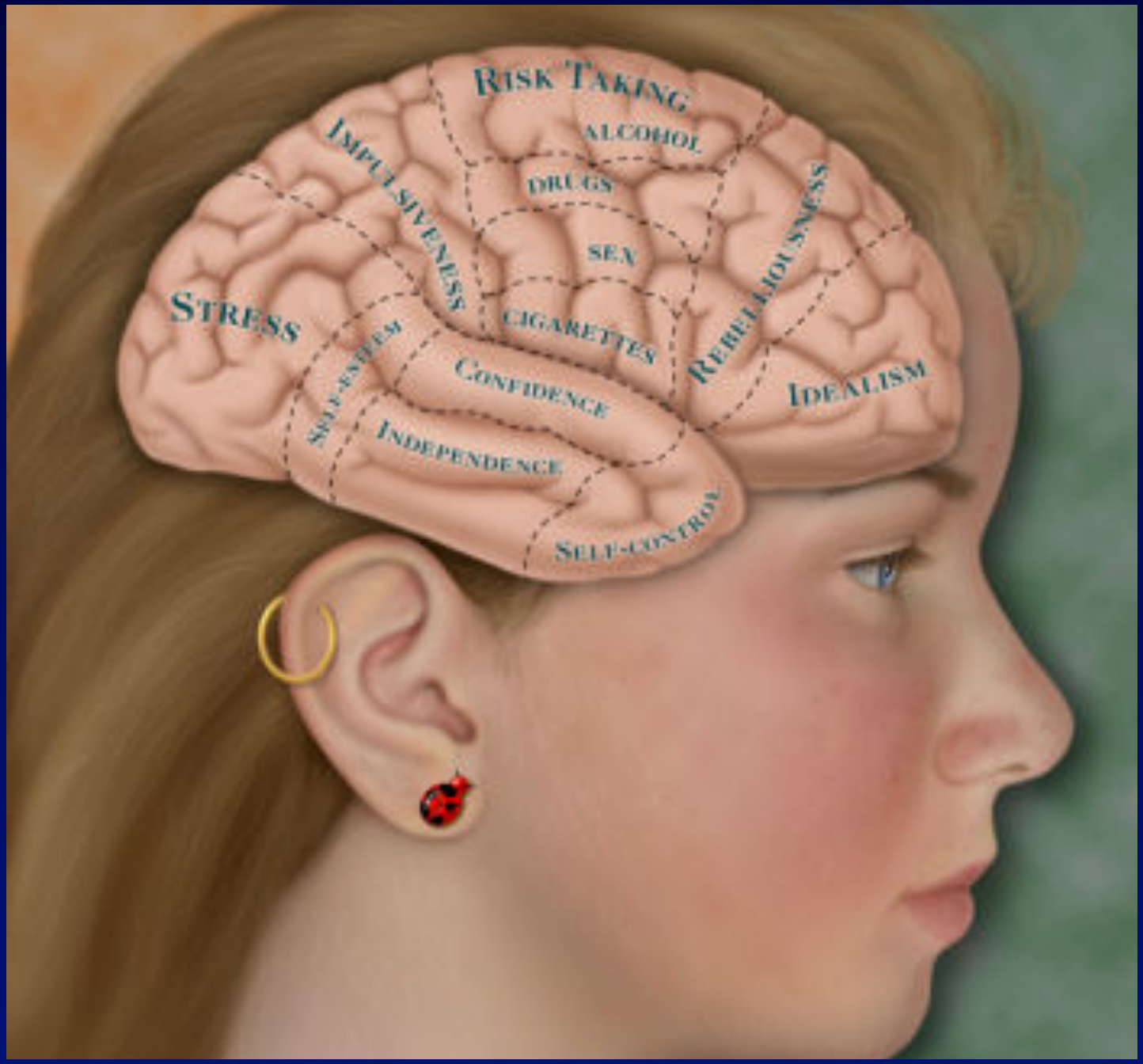
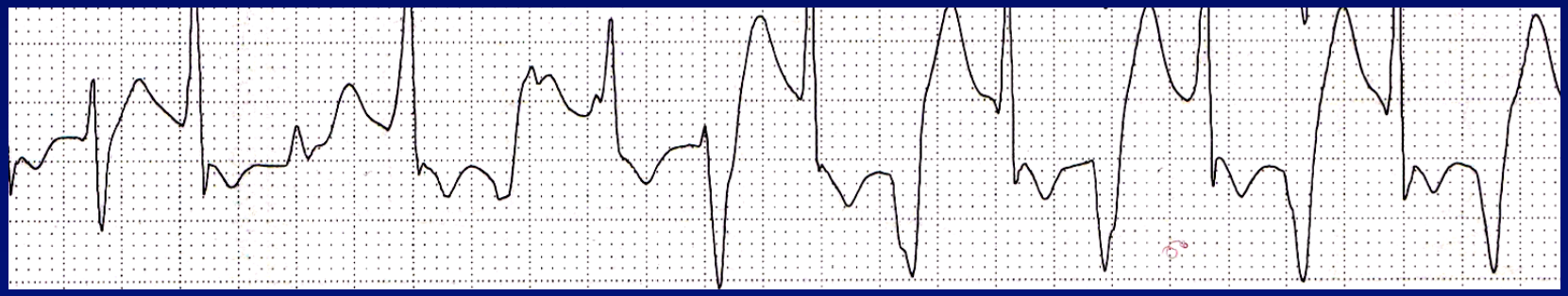


Primary prevention?


RISK TAKING
ALCOHOL
DRUGS
SEX
IMPULSIVENESS
STRESS
CIGARETTES
REBELLIOUSNESS
SELF-ESTEEM
CONFIDENCE
IDEALISM
INDEPENDENCE
SELF-CONTROL

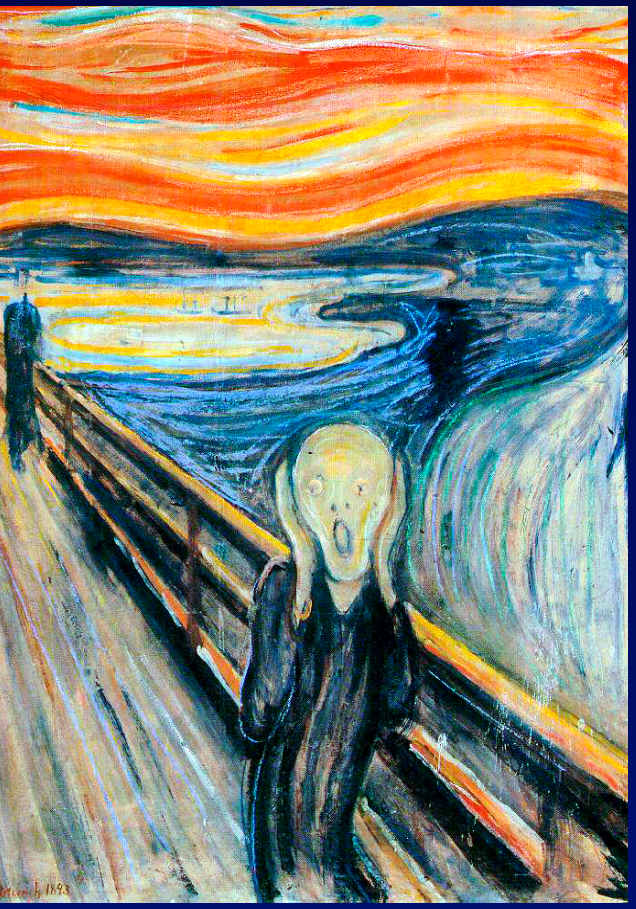
9 year old girl, VF arrest, BiDi VT

- A) Beta-Blocker Rx alone
- B) Beta-Blocker + Flecainide
- C) Beta-Blocker + LCSD
- D) Beta-Blocker + Flecainide + LCSD
- E) Beta-Blocker + ICD
- F) Beta-Blocker + ICD + LCSD
- G) Beta-Blocker + ICD + LCSD + Flecainide



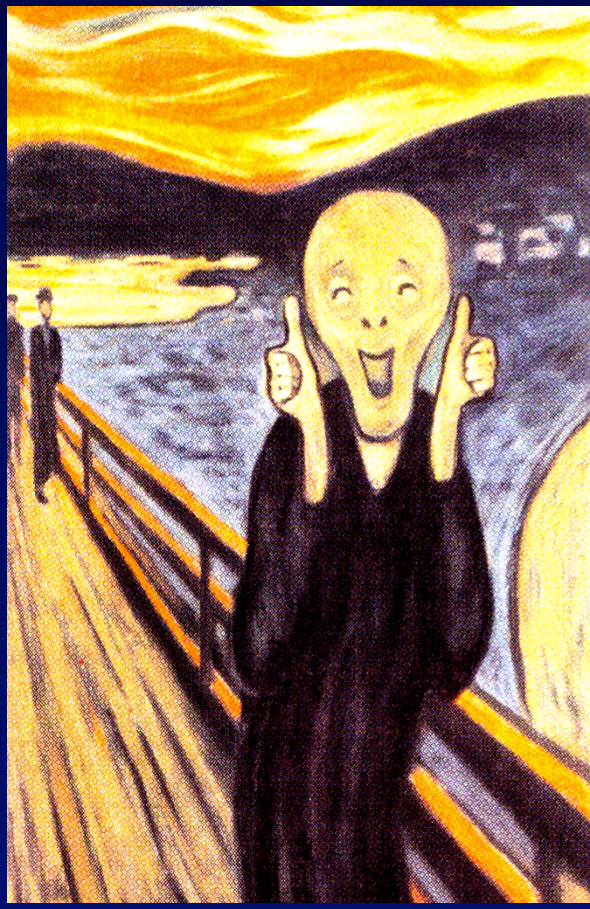
14 year girl, VF arrest & storm 7 yrs ago, proven RyR2, epicardial ICD, BB; LCSD; rare asymptomatic NS AFib; no events

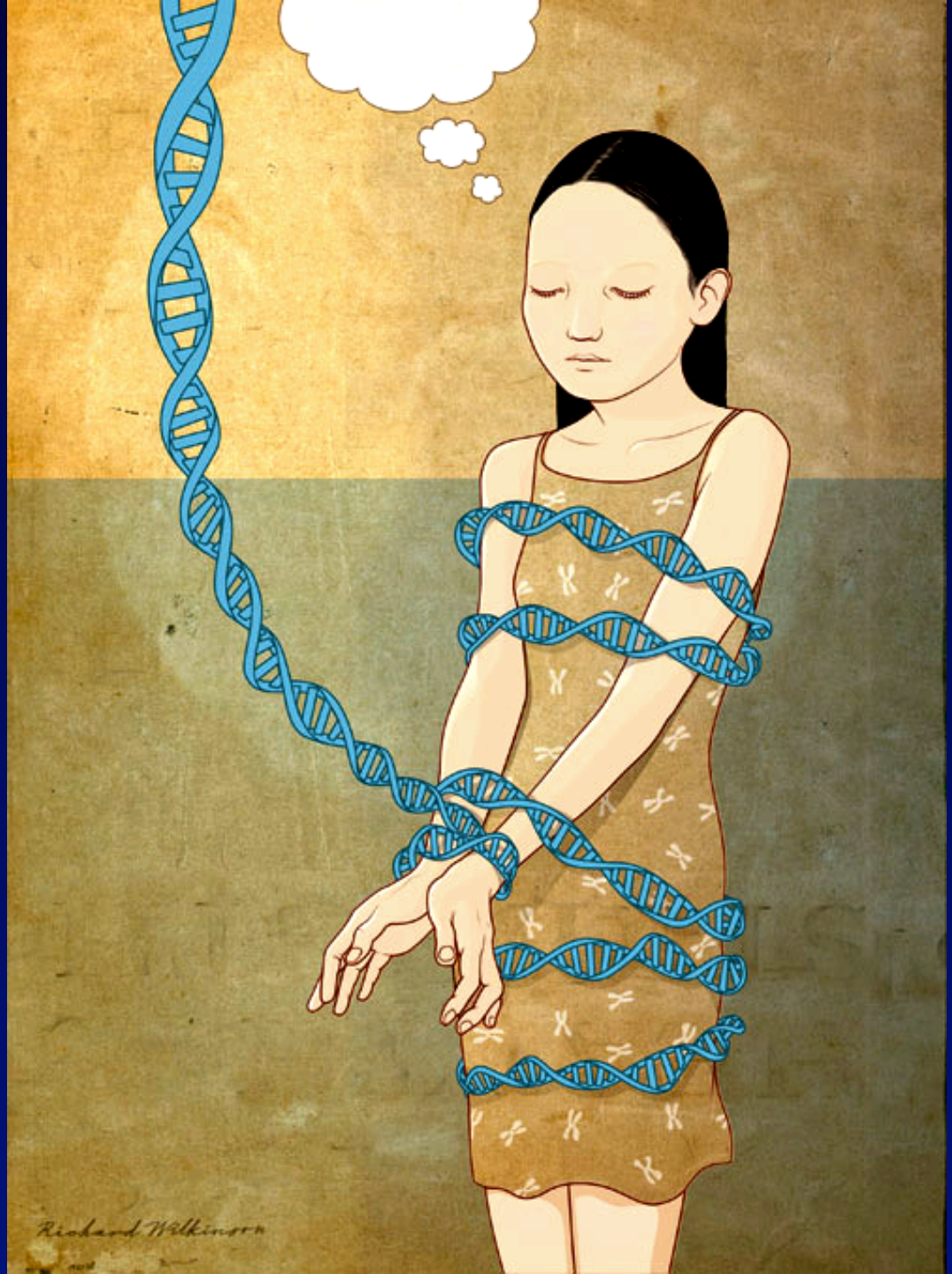
- A) Remove ICD, continue current B-Blocker
- B) Replace ICD
- C) Remove ICD. Beta-Blocker + Flecainide



Comprehensive management of CPVT:

good enough that you made the right decision




Richard Wilkinson