SUDDEN CARDIAC DEATH

EPIDEMIOLOGY, PATHOPHYSIOLOGY,
PREVENTION & THERAPY

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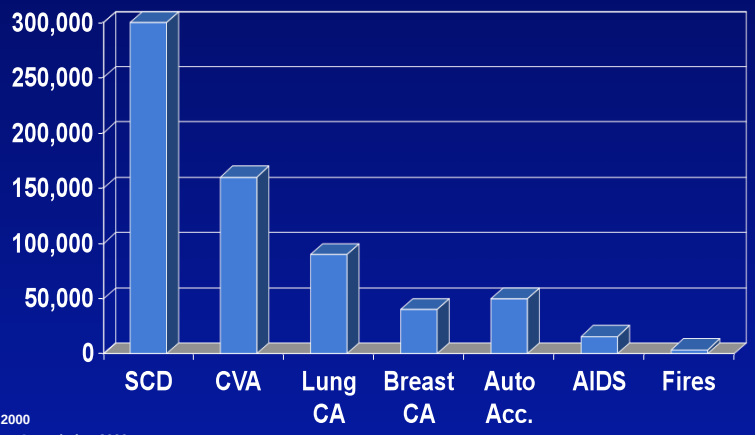
SUDDEN CARDIAC DEATH(SCD): Definition

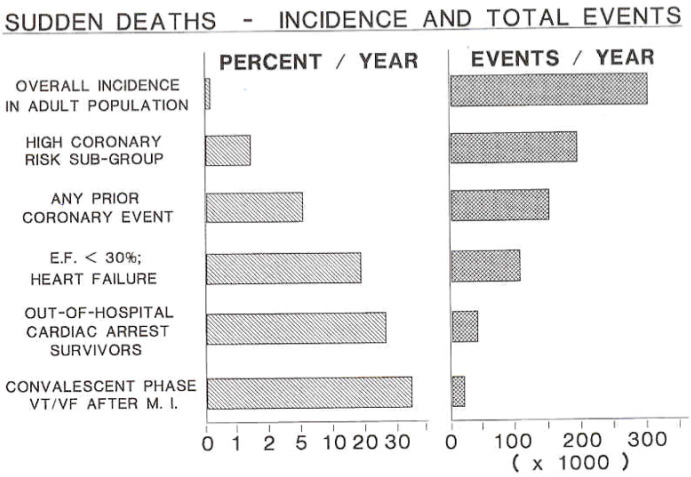
DEATH DUE TO A CARDIAC CAUSE IN A CLINICALLY STABLE PATIENT, WITH OR WITHOUT PRE-EXISTING HEART DISEASE, WITHIN A PERIOD OF UP TO ONE HOUR AFTER AN ABRUPT AND DRASTIC CHANGE IN CLINICAL STATUS

EPIDEMIOLOGIST'S VIEW
ANNUAL DEATHS IN U.S.A



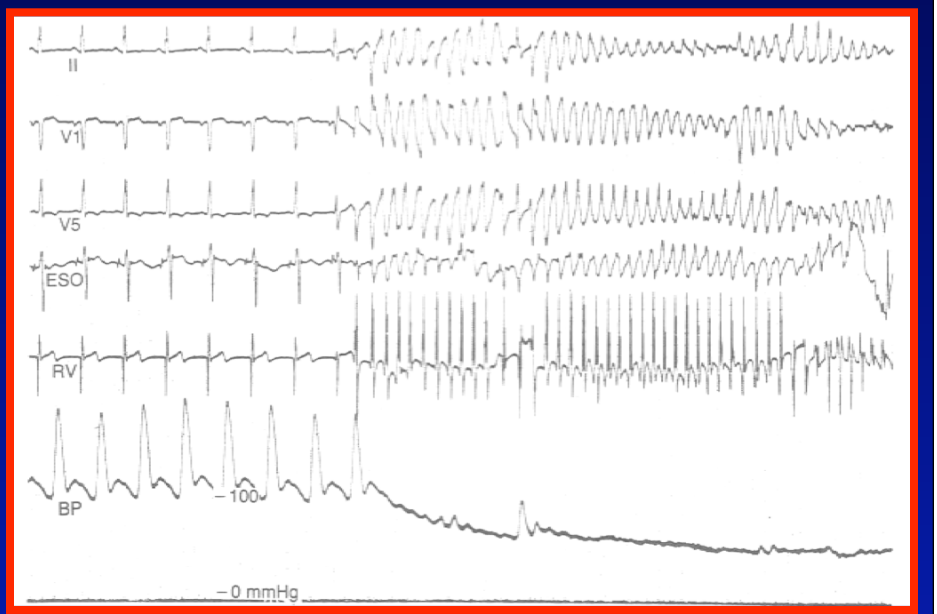
[1]NASPE, May 2000
[2]American Heart Association 2000
[3]National Cancer Institute 2001
[4]National Transportation Safety Board, 2000
[5]Center for Disease Control 2001
[6]NFPA, US Facts & Figures, 2000

EPIDEMIOLOGIST'S VIEW

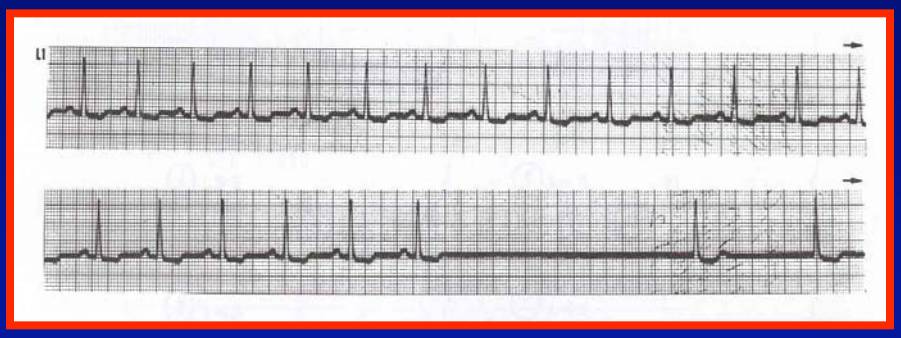


CAUSES OF SCD

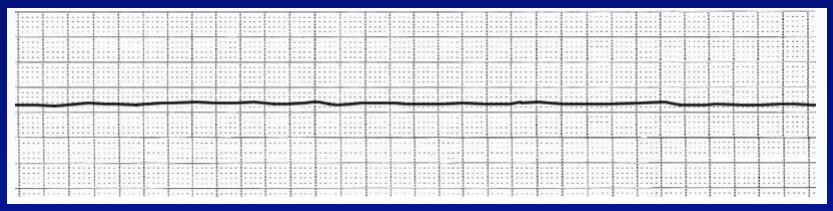
- CARDIAC ARRHYTHMIA
  - Ventricular tachycardia/fibrillation
  - Asystole without an escape rhythm
- PULSELESS ELECTRICAL ACTIVITY
  - Massive myocardial infarction
  - Massive pulmonary embolus
  - Pericardial tamponade
  - Aortic tear/rupture



Sinus Arrest with Junctional Escape



ASYSTOLE



PATHOPHYSIOLOGY OF VT/VF

Myocyte/myocardial tissue

Conduction block,
Slow conduction

↓

Reentry

Abnormal repolarization

↓

Early afterdepolarizations

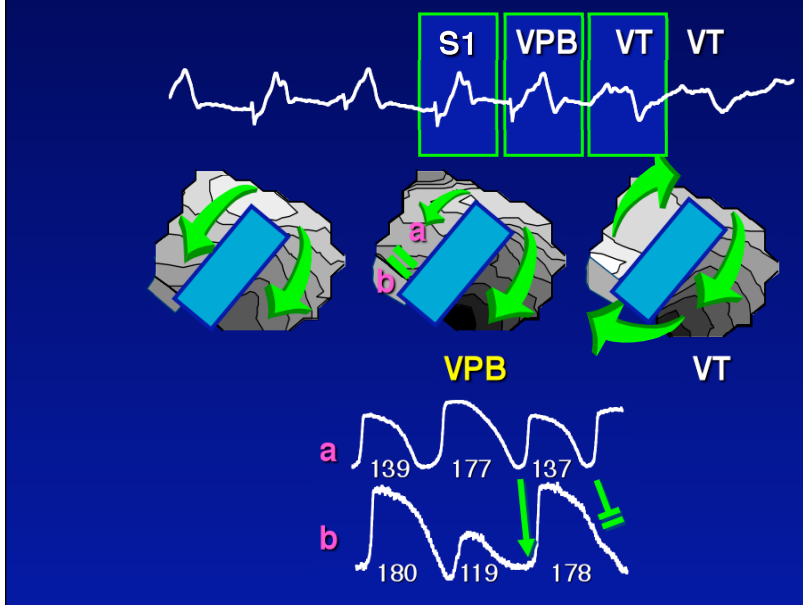
↘ ↙

Ventricular tachycardia

↓

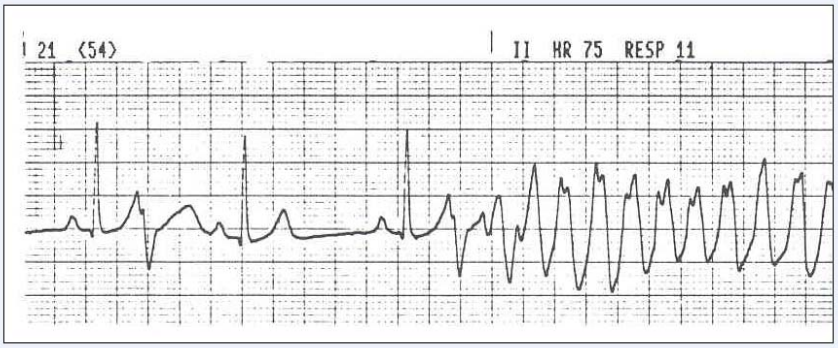
Ventricular fibrillation

Reentry-based VT



Pastore et al. Circ.Res. 2000;87:1157-1163.

REENTRY → VT

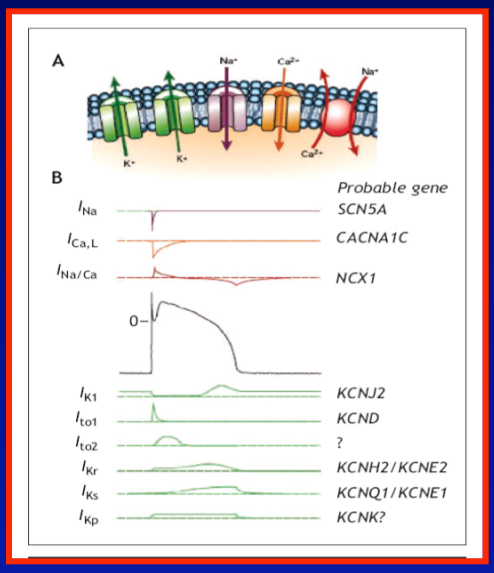


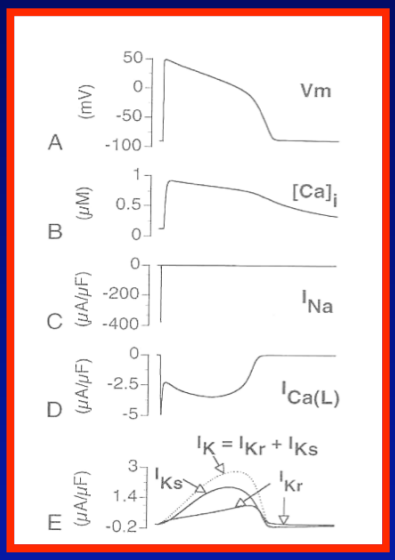
Factors Promoting Re-entrant Arrhythmias

Decreased conduction velocity
- Partially depolarized tissue with inactivated sodium channels; myocardial ischemia
- Scarring, disruption of architecture; chronic MI, cardiomyopathies
- Remodeling/redistribution of connexins; ischemic heart disease, cardiomyopathies, CHF

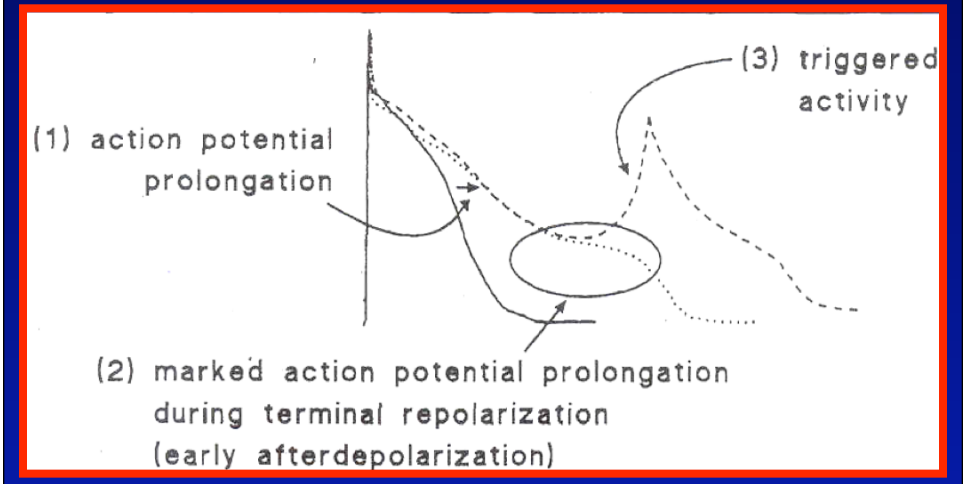
Heterogenous refractoriness
- Myocardial ischemia/infarction
- Inflammation
- Electrolyte abnormalities/drugs

Ionic Currents during the Action Potential

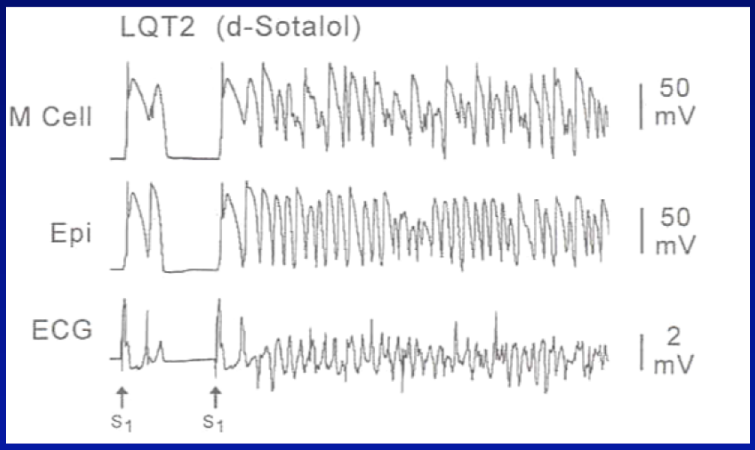




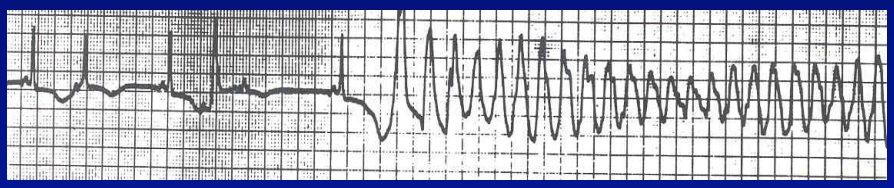
EARLY AFTERDEPOLARIZATIONS



Early Afterdepolarizations Initiating VT



Long QT → EAD → Torsades de Pointes



SCD
CLINICIAN'S VIEW

DISEASES & CONDITIONS PREDISPOSING TO SCD

STRUCTURAL HEART DISEASE:

A) Acute myocardial infarction
B) Chronic ischemic heart disease
C) Hypertensive heart disease
D) Dilated non-ischemic cardiomyopathy
   Congenital, alcoholic, post-inflammatory
E) Mixed dilated and hypertrophic: valve disease
F) Infiltrative cardiomyopathy
   Amyloidosis, hemochromatosis)
G) Cardiac sarcoidosis

DISEASES/CONDITIONS PREDISPOSING TO SCD WITH STRUCTURAL HEART DISEASE WITH OR WITHOUT CHF, BUT WITHOUT LOW LVEF

- Hypertrophic Cardiomyopathy
- Arrhythmogenic Right Ventricular Cardiomyopathy
- Cardiac Sarcoidosis
- Anomalous Coronary Arteries
- Mitral Valve Prolapse
- Adult Congenital Heart Disease
- Severe Restrictive Disease

DISEASES & CONDITIONS PREDISPOSING TO SCD: NO STRUCTURAL HEART DISEASE

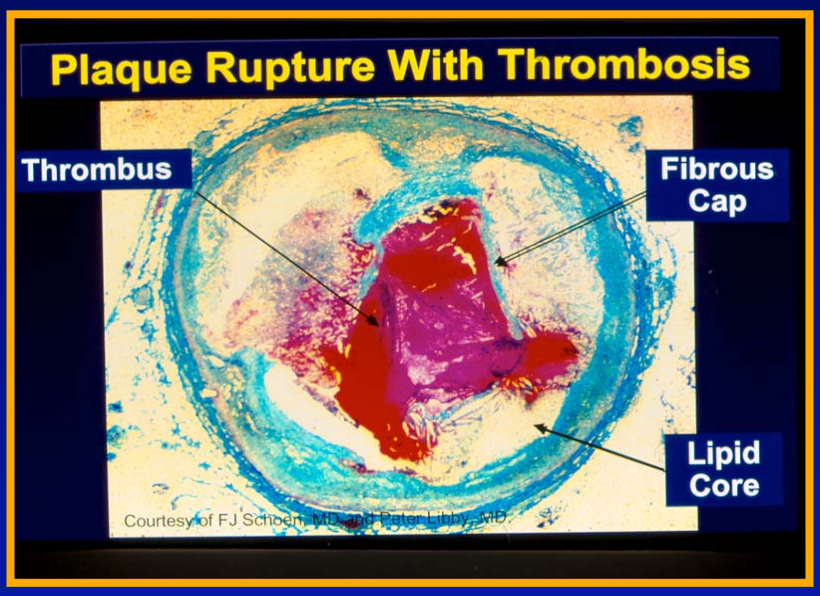
CHANNELOPATHIES/PRIMARY ELECTRICAL DISTURBANCES

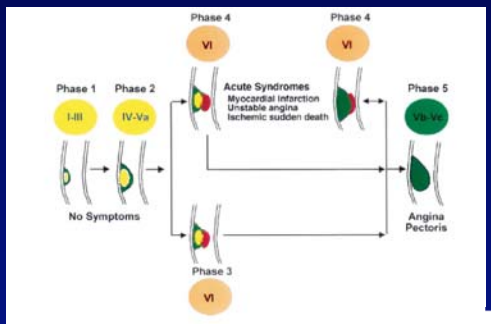
A) Long QT syndromes
B) Brugada syndrome
C) Wolff-Parkinson-White syndrome
D) Familial catecholaminergic polymorphic VT
E) Short QT syndrome
F) Other repolarization abnormalities

DISEASES & CONDITIONS PREDISPOSING TO SCD

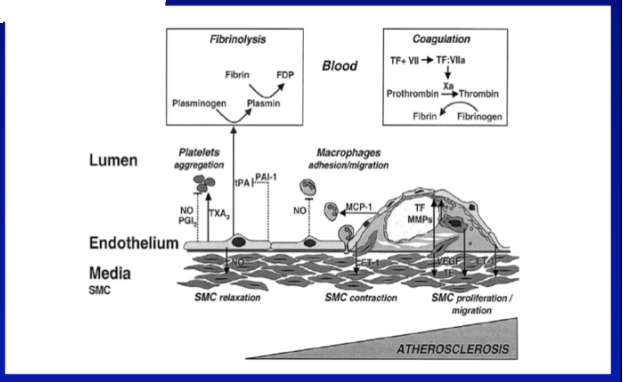
REVERSIBLE CONDITIONS

A) Acute myocardial ischemia
B) Severe electrolyte imbalance
C) Drug-related long QT syndrome
D) Proarrhythmic effects of drugs
E) Interactions with genetic polymorphisms



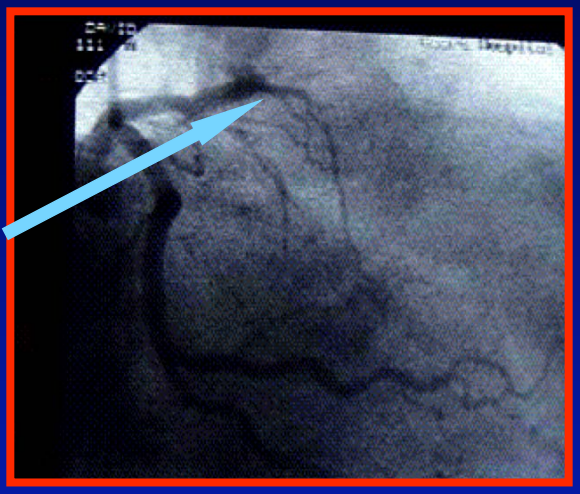


VULNERABLE PLAQUE

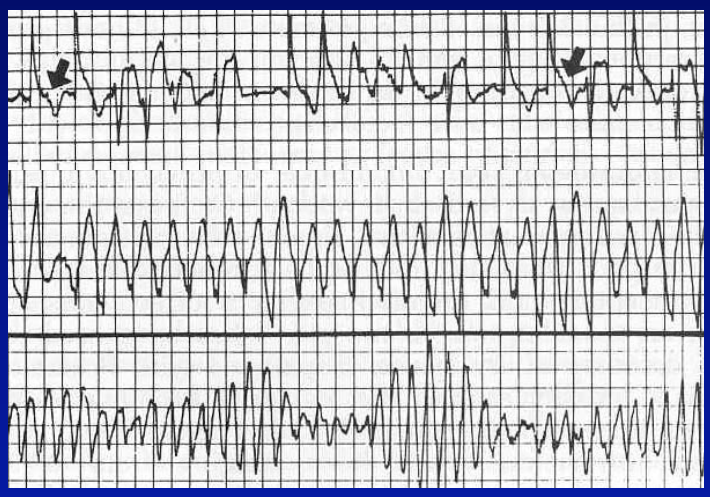


ACUTE CORONARY THROMBOSIS

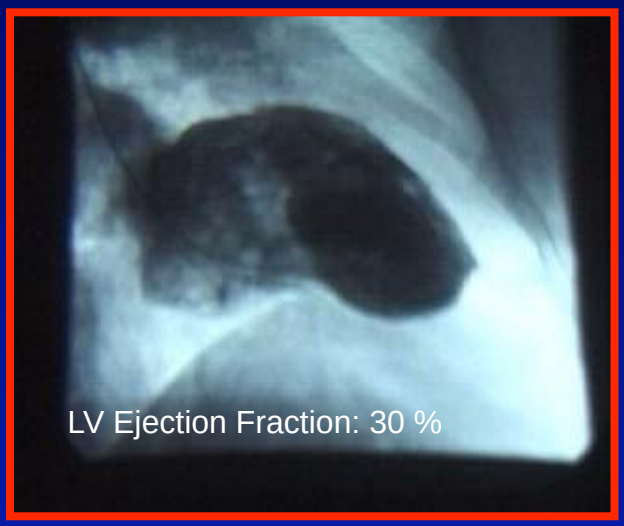
LAD: TOTAL OCCLUSION



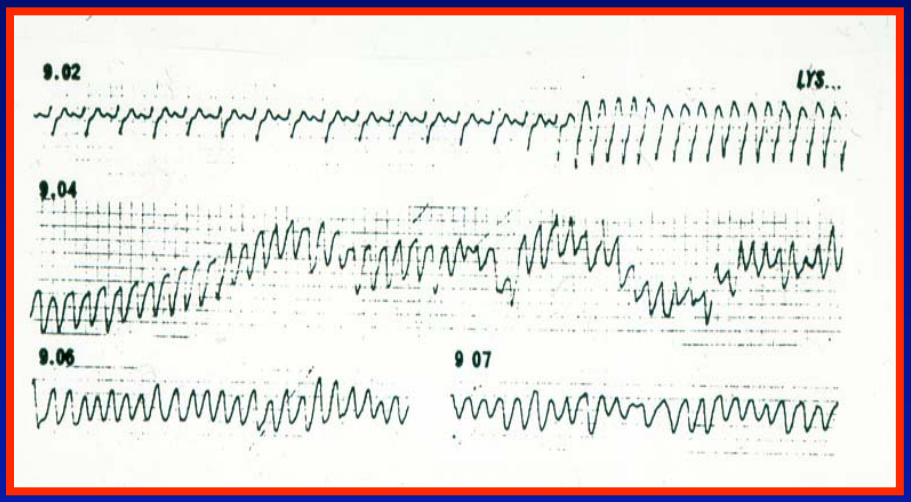
VT ⟶ VF during acute myocardial necrosis (STEMI)



CHRONIC ISCHEMIC HEART DISEASE

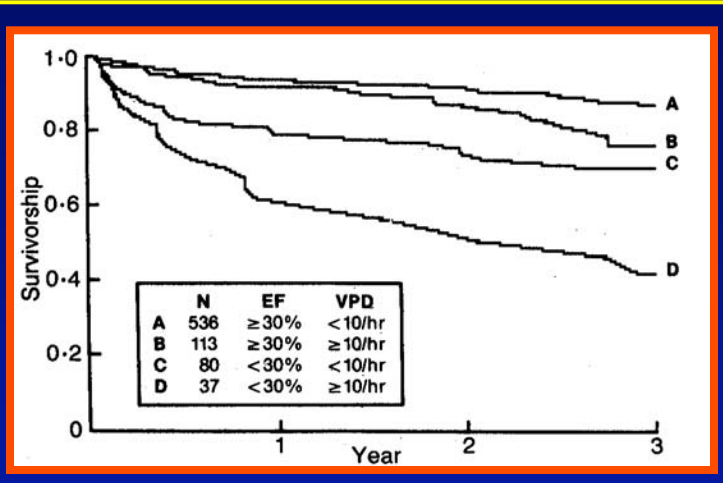


VT → VF IN A PATIENT WITH CHRONIC MI



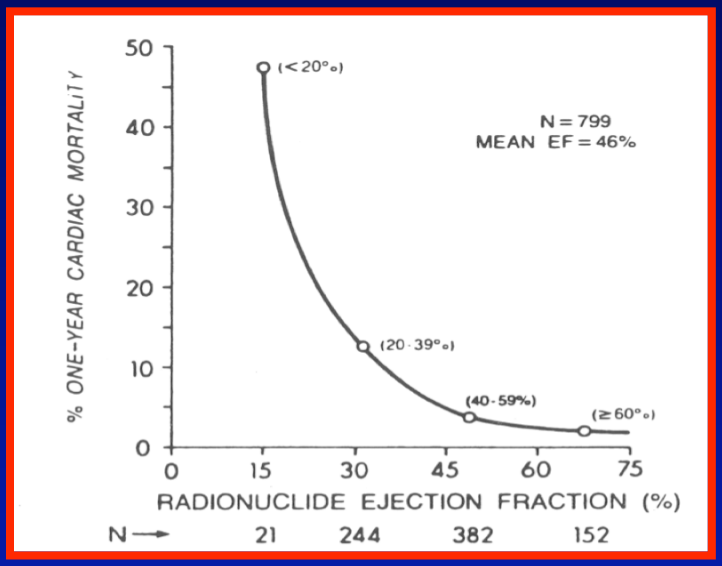
SCD RISK STRATIFICATION

ISCHEMIC HEART DISEASE: SURVIVAL AFTER MI



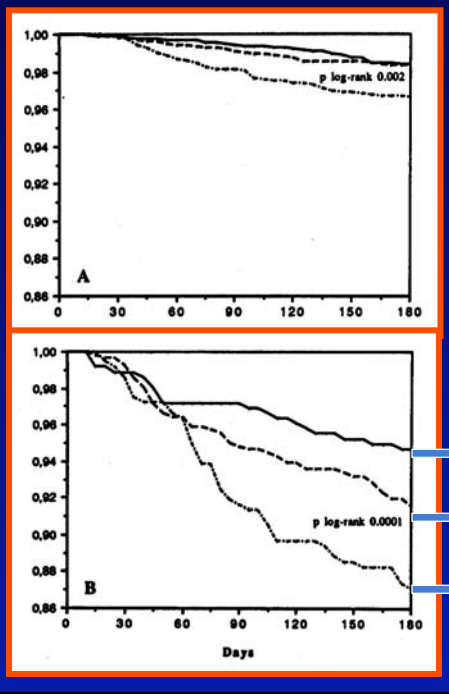
J. Thomas Bigger, Jr. Am J Cardiol 1986;57:8B

LV FUNCTION AS PREDICTOR OF SCD IN ISCHEMIC HEART DISEASE



GISSI-2

SURVIVAL



NO PVCs

1-10 PVCs

> 10 PVCs

Sudden Cardiac Death in the Young

Eckart RE et al. Ann Intern Med 2004;141:829

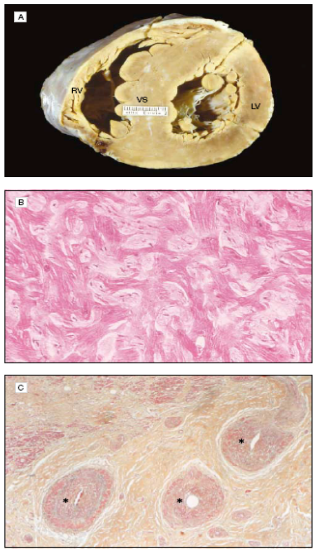
Table 3. **Nontraumatic Sudden Deaths with an Identifiable Cardiac Abnormality during Recruit Training, 1977–2001 ($n = 64$)**

Cardiac Abnormality	Sudden Deaths, *n* (%)*
Cardiomyopathy	23 (36)
Myocarditis	13 (20)
Hypertrophic cardiomyopathy	8 (13)
Idiopathic dilated cardiomyopathy	1 (2)
Right ventricular dysplasia	1 (2)
Coronary artery pathology	39 (61)
Anomalous coronary artery	21 (33)
Atherosclerotic coronary artery disease	10 (16)
Coronary artery hypoplasia	3 (5)
Coronary aneurysm	2 (3)
Intramyocardial coronary bridge	2 (3)
Coronary dissection	1 (2)
Miscellaneous cardiac findings	2 (3)
Bicuspid aortic valvular stenosis	1 (2)
Embolic myocardial infarction	1 (2)

* Some numbers have been rounded.

Cardiac cause identified in 64/126; 44/126 no cause identified

Morphologic Features of the Myocardial Substrate for SCD in HCM



RISK FACTORS FOR SUDDEN CARDIAC DEATH IN HCM

ACC/ESC Clinical Expert Consensus Document on HCM
(European Heart Journal 2003;24:1965)

MAJOR

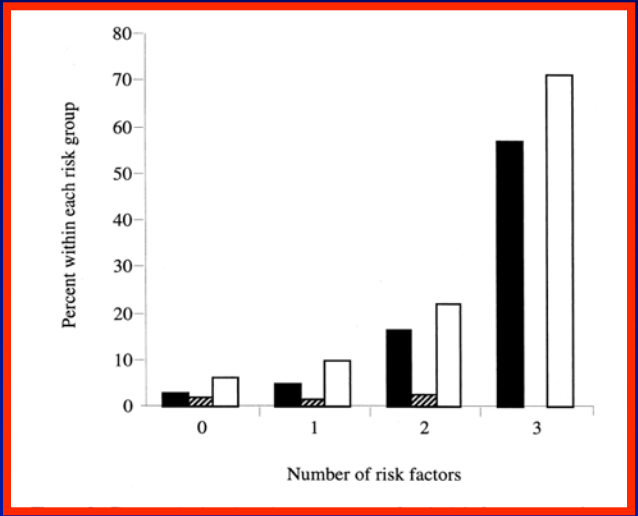
- Cardiac arrest (VT/VF)
- Spontaneous sustained VT
- Unexplained syncope
- Family history of premature SCD
- Maximum LV thickness ≥ 30 mm
- Abnormal BP response to exercise
- Non-sustained VT

POSSIBLE IN INDIVIDUALS

- Atrial fibrillation
- Myocardial ischemia
- LV outflow obstruction
- High-risk mutation
- Intense physical effort

Risk of SCD in HCM

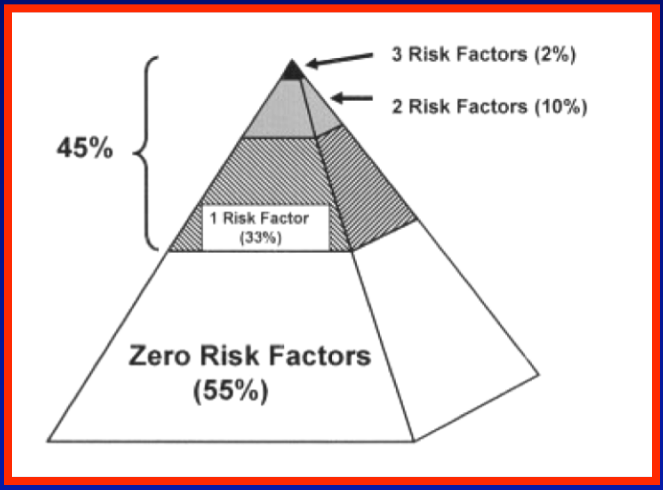
Elliott PM et al. J Am Coll Cardiol 2000; 36:2212



Black bars=SCD, hatched bars=CHF or Tx, white bars=total mortality

RISK FACTORS FOR SUDDEN CARDIAC DEATH IN HCM

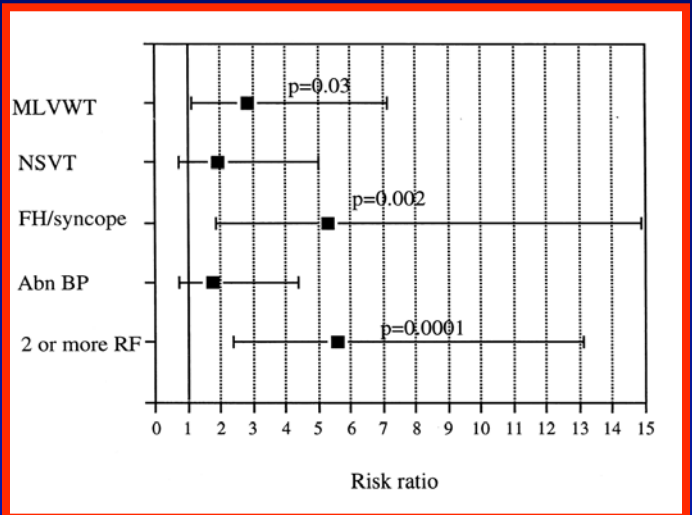
Maron BJ, et al. Circulation 2003;107:2872



Multivariate Risk Ratios for 4 Risk Factors in HCM

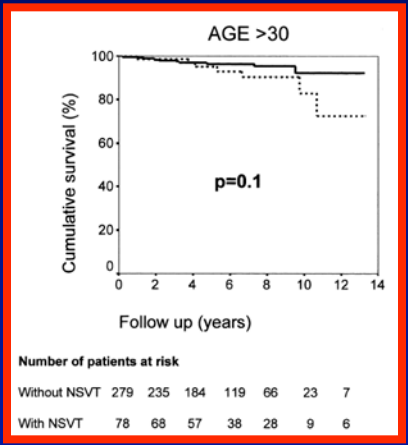
The Bars Represent the Upper and Lower 95% Confidence Intervals

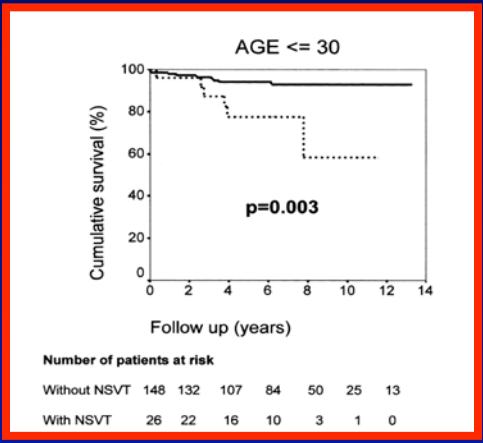
Elliott PM et al. J Am Coll Cardiol 2000; 36:2212



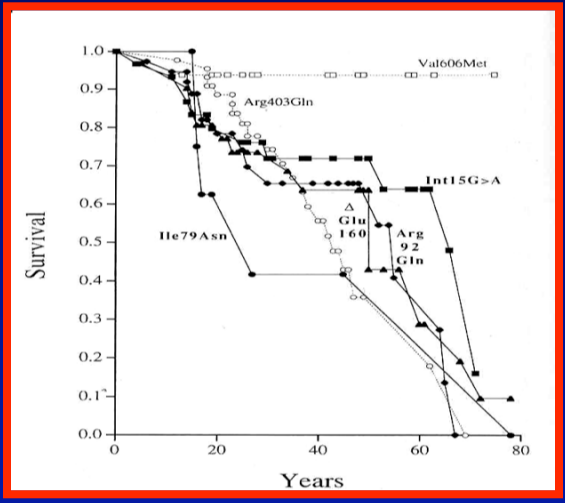
Non-sustained VT in HCM

Monserrat L et al. J Am Coll Cardiol 2003;42:873



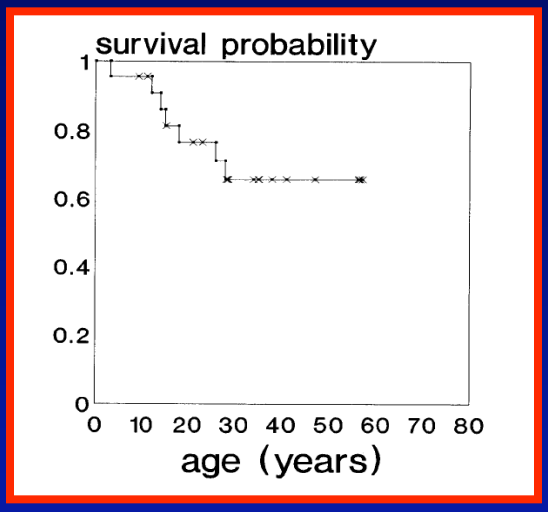


HCM: Specific Mutations & Survival

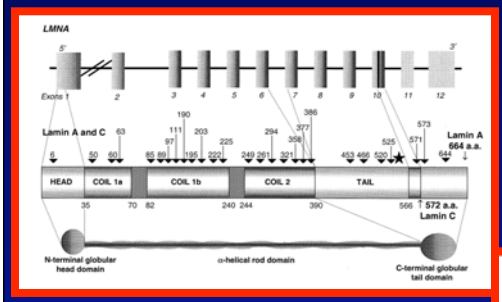


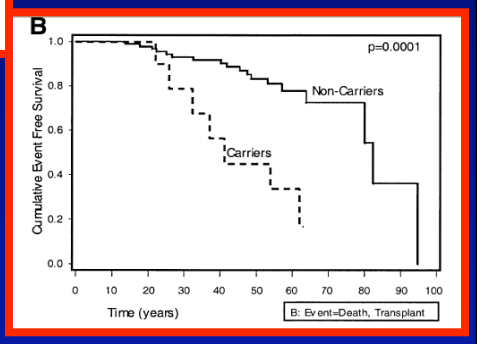
Kaplan-Meier curves for survival in patients in HCM families carrying TNNT2 arginine 92 tryptophan mutation

Moolman JC et al J Am Coll Cardiol 1997;29:549

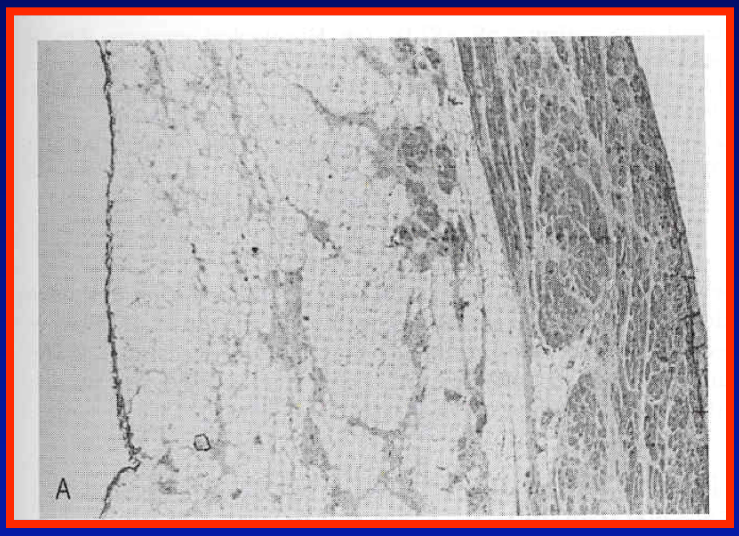


LAMIN A/C (*LMNA*) MUTATIONS AND DCM

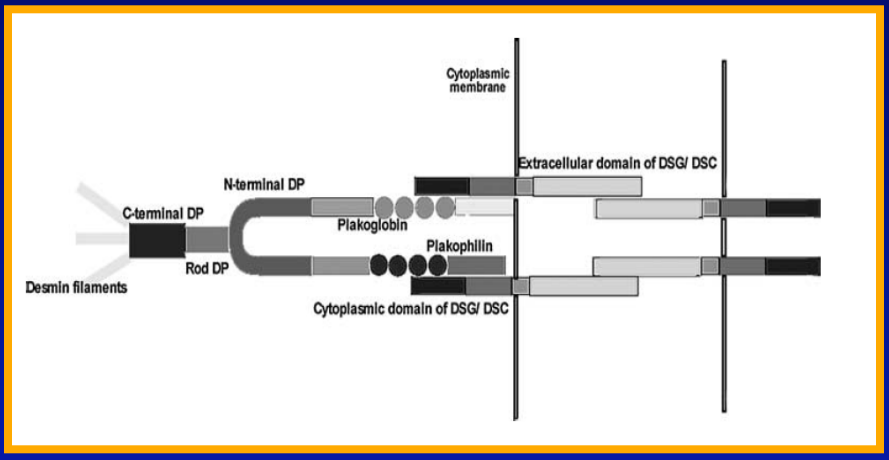




ARRHYTHMOGENIC RV DYSPLASIA

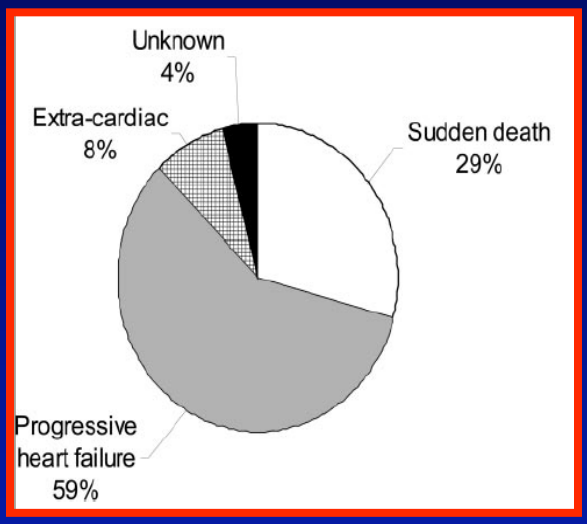


Schematic Picture of Desmoplastic Structure



The Risk of SCD in ARVC/D

Hulot J et al. Circulation 2004;110:1879

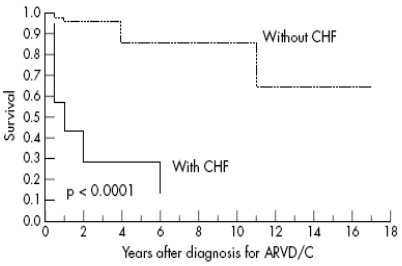


ARRHYTHMOGENIC RV DYSPLASIA:
RISK FACTORS FOR SCD

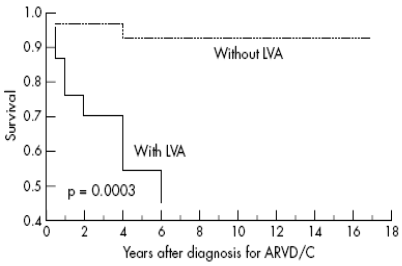
- Premature SCD in family
- Syncope
- Severe RV dysfunction
- LV involvement
- Hemodynamically unstable VT
- Congestive heart failure
- Epsilon waves

The Risk of SCD in ARVD/C

Lemola K et al. Heart 2005;91:1167



FU year	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
No CHF	50	42	36	31	29	24	20	16	10	6	6	4	2	2	2	2	2	1	0
CHF	7	4	3	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0



FU year	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
No LVA	34	30	26	22	22	20	16	13	10	6	6	4	2	2	2	2	2	1	0
LVA	23	16	13	11	9	6	6	4	1	1	1	1	0	0	0	0	0	0	0

SCD after Surgical Correction of CHD

Silka MJ et al. JACC 1998;32:245

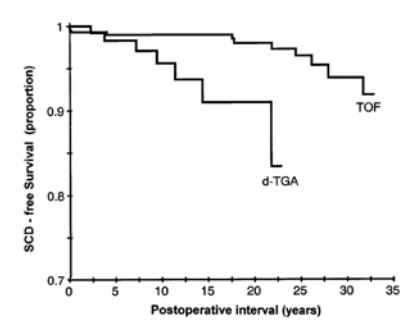
Table 1. Specific Congenital Heart Defects and Incidence of Sudden and Nonsudden Cardiac Death

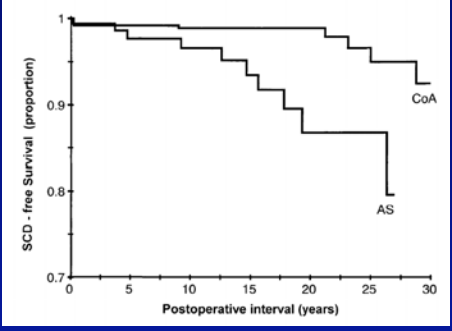
	No. (%) of Pts With Complete Follow-Up	Total Follow-Up (pt-yr)	Sudden Cardiac Death		Nonsudden Cardiac Death	
			No.	Incidence/ 1,000 Pt-yr	No.	Incidence/ 1,000 Pt-yr
ASD	622 (86%)	7,904	0	0	0	0
VSD	527 (87%)	6,354	1	0.2	8	1.2
AVSD	254 (87%)	2,217	2	0.9	15	6.7
PDA	623 (82%)	8,753	0	0	4	0.4
PS	241 (91%)	3,568	1	0.3	2	0.6
AS	169 (94%)	1,860	10	5.4	9	4.8
CoA	536 (92%)	6,706	9	1.3	17	2.5
TOF	445 (91%)	7,082	11	1.5	9	1.3
D-TGA	172 (95%)	1,413	7	4.9	10	6.9
Total	3,589	45,857	41	0.9	74	1.6

AS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; PDA = patent ductus arteriosus; PS = pulmonary stenosis; pt-yr = patient-years; Pts = patients; D-TGA = dextro-transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

SCD after Surgical Correction of CHD

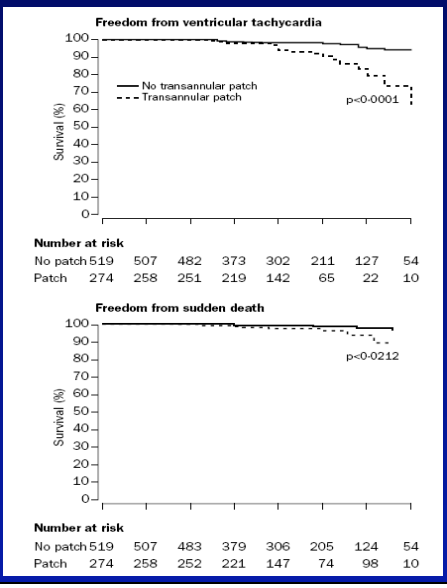
Silka MJ et al. JACC 1998;32:245





VT and SCD Late after Repair of TOF

Gatzoulis MA et al. Lancet 2000;356:975



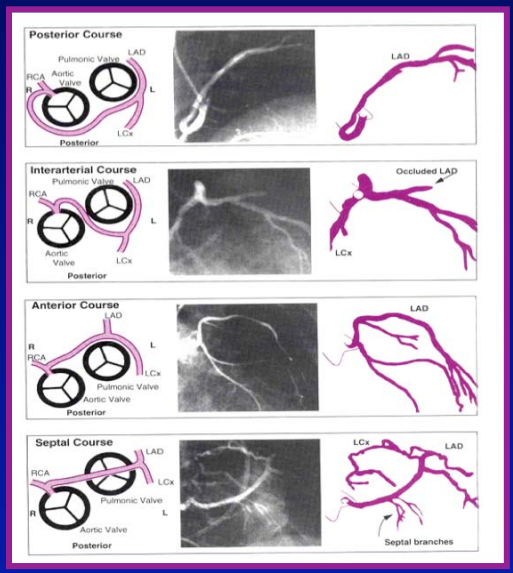
SCD LATE AFTER SURGICAL CORRECTION OF CONGENITAL HEART DISEASE

For defects such as AS and d-TGA, the risk of SCD is much higher than the age-matched general population. This risk increases primarily > 20 years after the operation. Patients with syncope or non-sustained VT, especially in the presence of poor systolic function, dilation and hypertrophy of the systemic ventricle, should be protected with ICD therapy.

Late SCD after TOF repair is rare. Patients with sustained VT, and patients with syncope in the setting of trans-annular patch and QRS>180 ms, probably need protection with ICD. The role of PCS for risk stratification is not well established

ANOMALOUS LEFT CORONARY ARTERY

Surgically treatable cause of SCD



SCD in Coronary Artery Anomalies

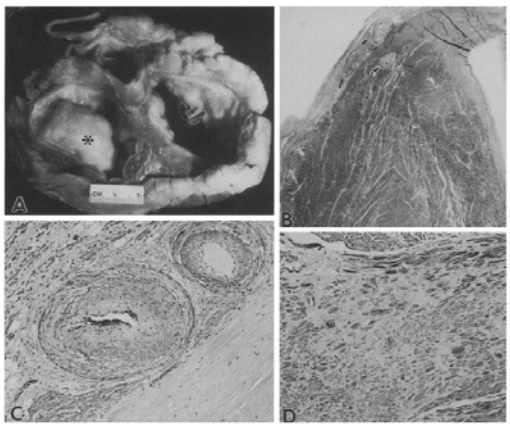
Taylor AJ et al. Am Heart J 1997;133:428

Coronary anomaly–related death			*Non-anomaly-related death*		
Patient age (yr)	*Anomaly*	*Comments*	*Patient age*	*Anomaly*	*Comments*
14	LCA	Soccer	24	RCA	Homicide
14	RCA	Walking	25	LCA	Construction accident
17	LCA	Running	29	RCA	Motor vehicle accident
17	RCA	Nonexertional	29	RCA	Crushed by falling object
18	LCA	Basketball	33	RCA	Alcohol poisoning
18	LCA	Unspecified exertion	33	RCA	Found dead; toxicology positive for morphine
19	RCA	Football	33	RCA	Left main coronary disease
20	LCA	Basketball	34	RCA	Found dead; toxicology positive for morphine
21	LCA	Running	35	RCA	One-vessel coronary artery disease
21	LCA	Unspecified exercise	41	RCA	Three-vessel coronary artery disease
33	LCA	Unspecified exertion	42	RCA	Found dead; toxicology positive for cocaine
57	RCA	Nonexertional	43	RCA	Hypoglycemic event
			45	RCA	Homicide
			46	RCA	Found dead; right ventricular dysplasia
			48	RCA	Found dead; toxicology positive for cocaine
			70	RCA	Three-vessel coronary artery disease
			79	RCA	Cardiac amyloidosis
			82	RCA	Homicide

LCA, Left coronary artery; *RCA*, right coronary artery.

Fibromuscular Dysplasia of Small Coronary Arteries in MVP

Burke AP et al. Am Heart J 1997; 134:282



Mitral valve prolapse (case 10). **A**, Gross heart specimen demonstrating marked prolapse of posterior leaflet of mitral valve *(asterisk)*. **B**, In area of AV node posterior to major portion of central fibrous body there is arterial thickening within AV node *(upper arrowhead)* and ventricular septum *(lower arrowhead)*(magnification ×5). **C**, Higher magnification of artery to AV node in different area demonstrates severe fibrointimal proliferation and disruption of internal elastic lamina *(arrowheads)* (Movat pentachrome) (×30). **D**, Myocardium within ventricular septum distal to AV node demonstrates diffuse interstitial fibrosis (×30).

SCD IN PATIENTS WITH MVP

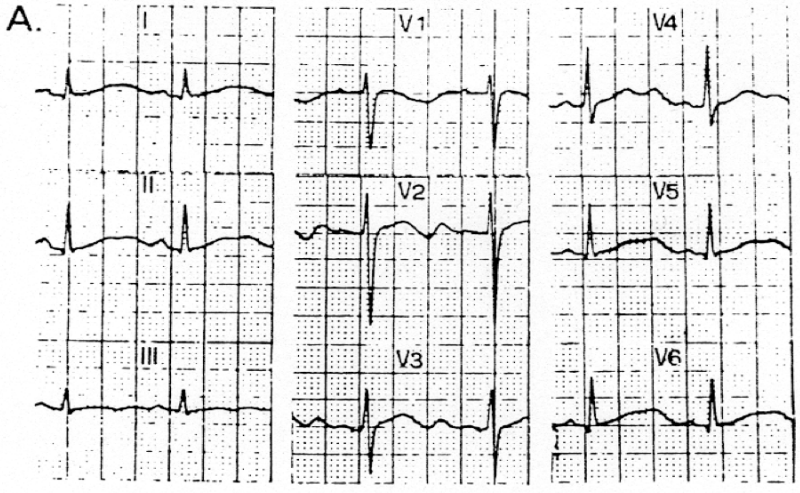
- The risk is very small in minimally symptomatic or asymptomatic, echocardiographically diagnosed patients. This risk, is probably present only in patients with redundant mitral valve leaflets. 237 such patients followed for a mean period of 6.2 years, 2 SCD in patients with redundant leaflets.
- There may be abnormalities of ventricular repolarization in a subgroup of patient with MVP. Their clinical utility is uncertain.
- In patients with syncope and documented spontaneous or PCS-induced sustained ventricular arrhythmia, and no other probable explanation for syncope, ICD should be considered

DISEASES/CONDITIONS PREDISPOSING TO SCD WITHOUT STRUCTURAL HEART DISEASE

CHANNELOPATHIES/PRIMARY ELECTRICAL DISTURBANCES

A) Long QT syndromes
B) Brugada syndrome
C) Familial catecholaminergic polymorphic VT
D) Short QT syndrome
E) Other repolarization abnormalities
F) Wolff-Parkinson-White syndrome

ECG in Long QT Syndrome



GENES IDENTIFIED TO DATE IN LQT SYNDROME

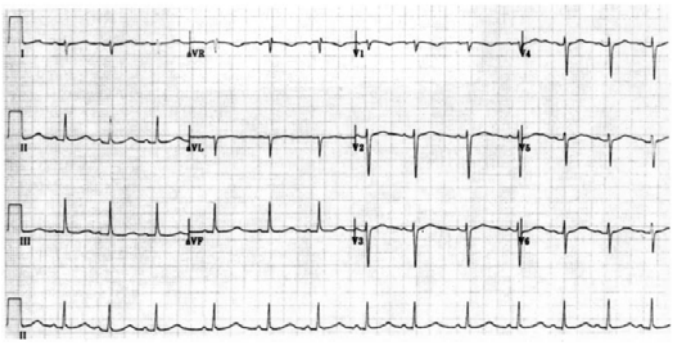
Nomenclature, gene names, and proteins associated with LQTS

Disease	Gene (historical name)	Protein
LQT1	*KCNQ1* (KVLQT1)	I_{Ks} K^+ channel α subunit
LQT2	*KCNH2* (HERG)	I_{Kr} K^+ channel α subunit
LQT3	SCN5A	I_{Na} Na^+ channel α subunit
LQT4	ANKB	Ankyrin-B
LQT5	*KCNE1* (minK)	I_{Ks} K^+ channel β subunit
LQT6	*KCNE2* (MiRP1)	I_{Kr} K^+ channel β subunit
LQT7	KCNJ2	$I_{Kr2.1}$ K^+ channel α subunit
LQT8	*CACNA1*	Cav1.2 Calcium channel α subunit

LQTS 9

Mutant Caveolin-3 Induces Persistent Late Sodium Current and Is Associated With Long-QT Syndrome

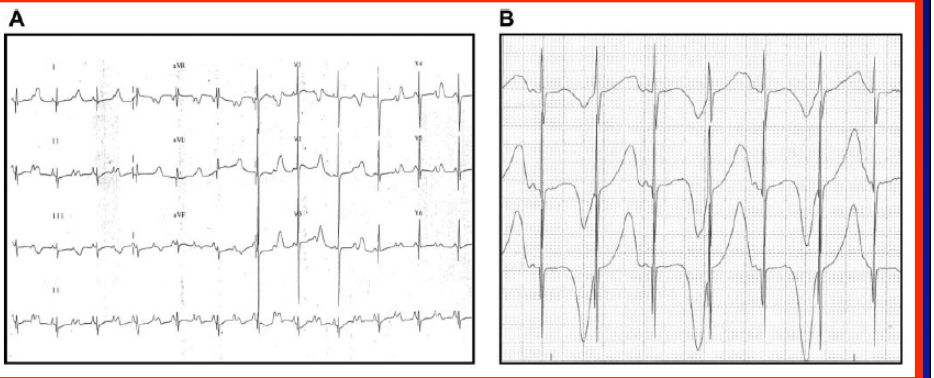
Matteo Vatta, PhD*; Michael J. Ackerman, MD, PhD*; Bin Ye, PhD; Jonathan C. Makielski, MD; Enoh E. Ughanze, MD; Erica W. Taylor, BS; David J. Tester, BS; Ravi C. Balijepalli, PhD; Jason D. Foell, BS; Zhaohui Li, PhD; Timothy J. Kamp, MD, PhD; Jeffrey A. Towbin, MD



LQTS 10

***SCN4B*-Encoded Sodium Channel β4 Subunit in Congenital Long-QT Syndrome**

Argelia Medeiros-Domingo, MD*; Toshihiko Kaku, MD, PhD*; David J. Tester, BS; Pedro Iturralde-Torres, MD; Ajit Itty, MD; Bin Ye, PhD; Carmen Valdivia, MD; Kazuo Ueda, MD, PhD; Samuel Canizales-Quinteros, PhD; Maria Teresa Tusié-Luna, MD, PhD; Jonathan C. Makielski, MD; Michael J. Ackerman, MD, PhD

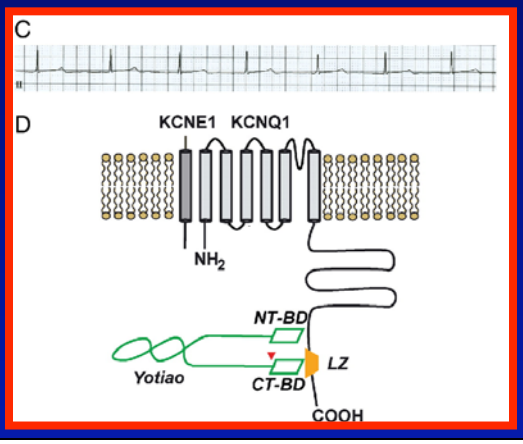


LQTS 11

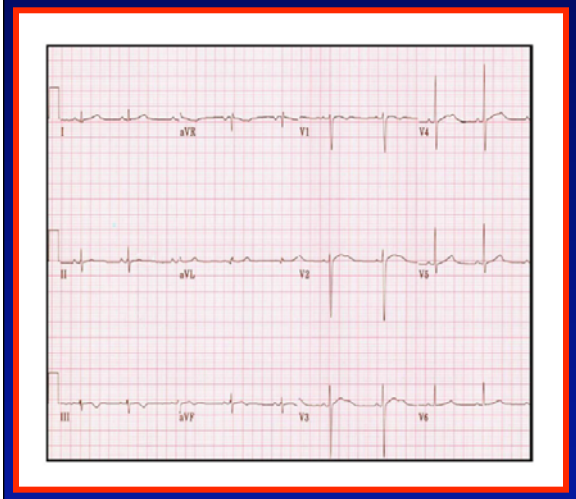
Mutation of an A-kinase-anchoring protein causes long-QT syndrome

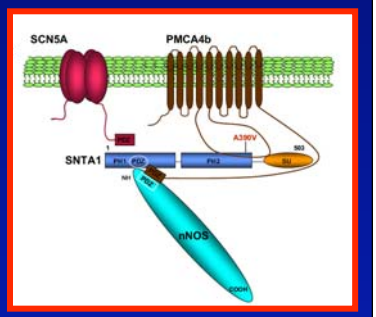
Lei Chen*, Michelle L. Marquardt†, David J. Tester‡, Kevin J. Sampson*, Michael J. Ackerman‡§, and Robert S. Kass*¶

*Department of Pharmacology, College of Physicians and Surgeons of Columbia University, New York, NY 10032; and †Departments of Medicine, Pediatrics, and Molecular Pharmacology and Therapeutics, Divisions of Cardiovascular Diseases and Pediatric Cardiology, Mayo Clinic College of Medicine, Rochester, MN 55905

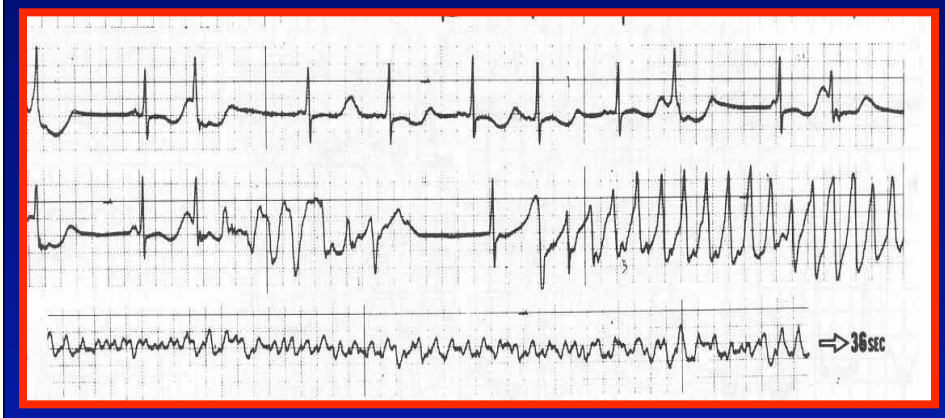


LQTS 12

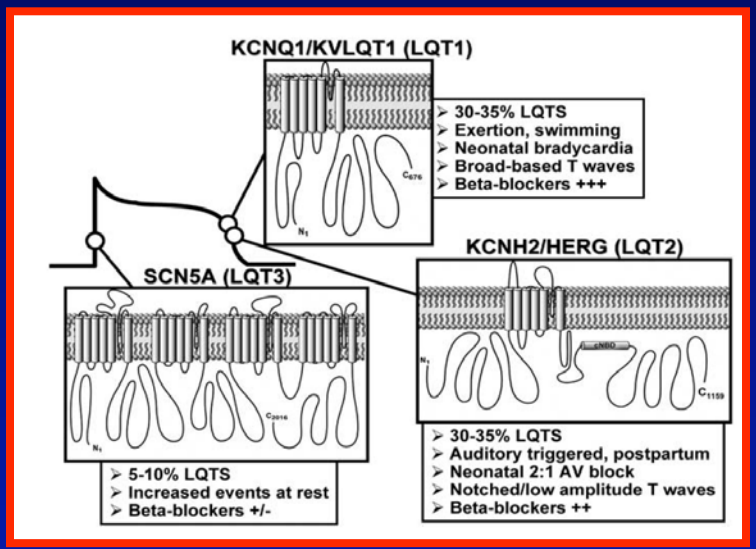




LQTS and Torsades de Pointes



GENOTYPE-PHENOTYPE SUMMARY OF THREE MOST COMMON LQT SYNDROMES



CARDIAC ARREST/SCD IN LQTS:
Gender differences

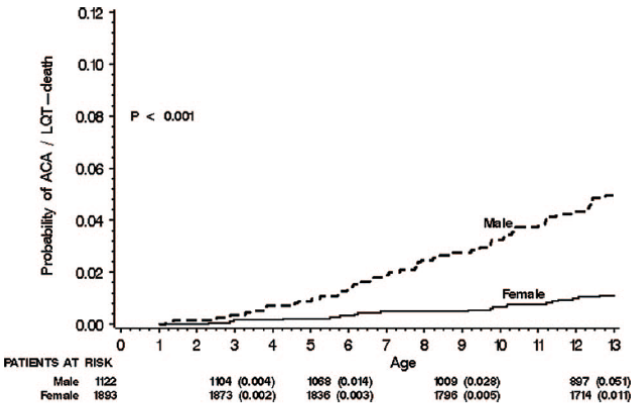
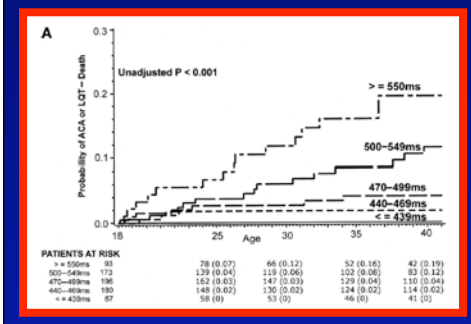
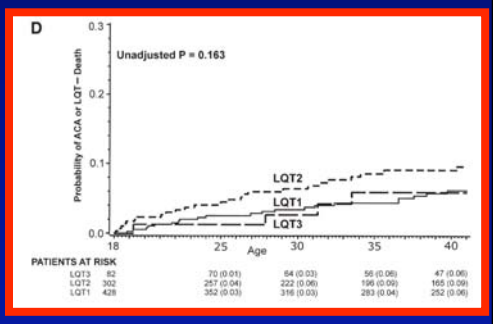


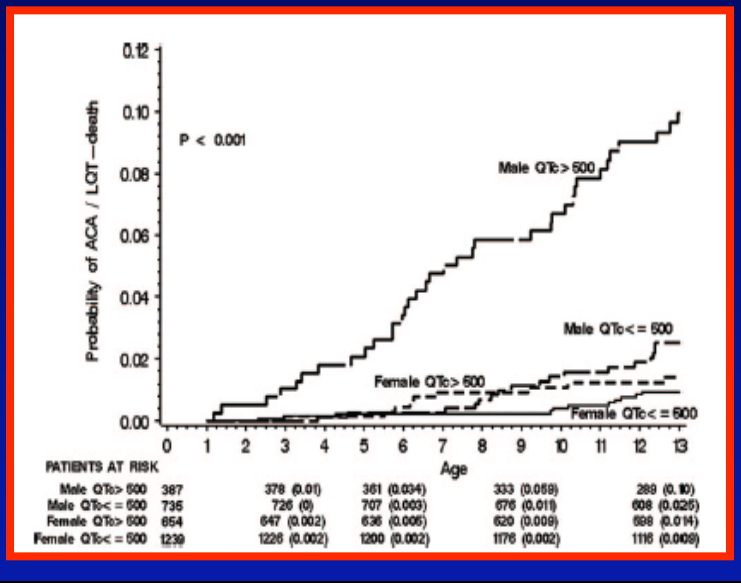
Figure 1. Kaplan–Meier estimates of the probability of ACA or SCD by gender (values in parentheses are event rates).

Risk Stratification in the Long QT Syndrome
Sauer AJ et al. JACC2007;49:329

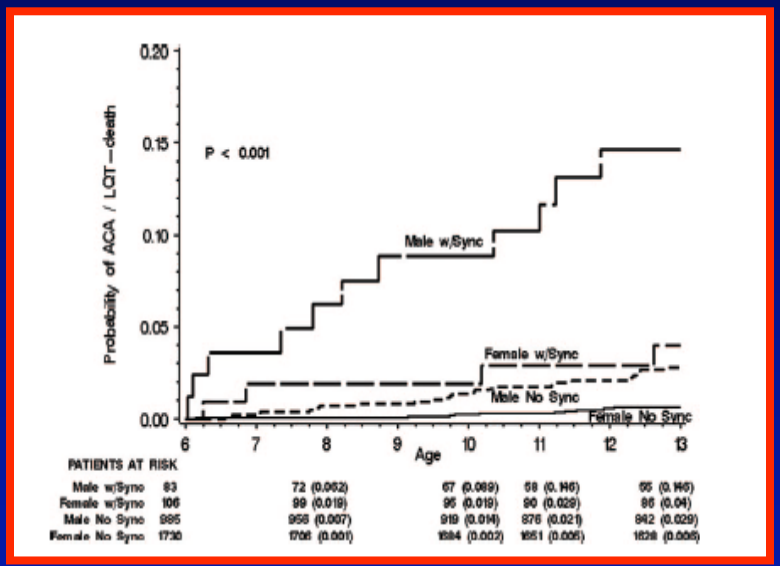




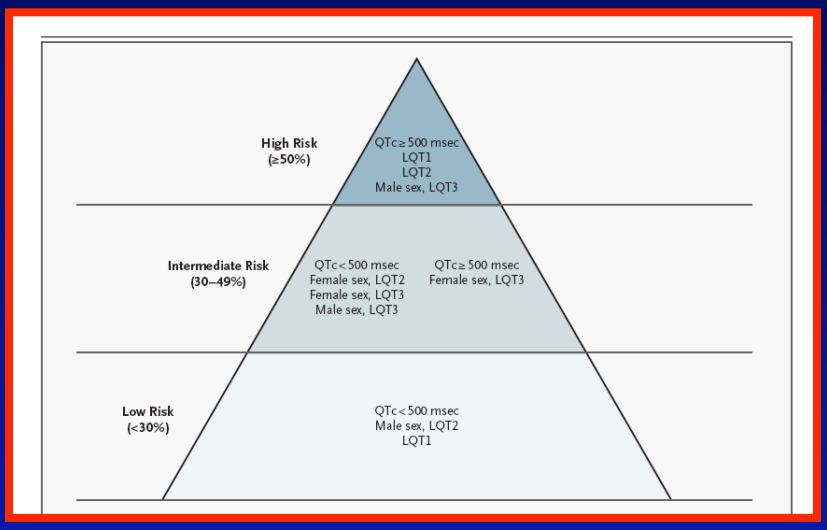
CARDIAC ARREST/SCD IN LQTS:
Gender/QT duration relationship



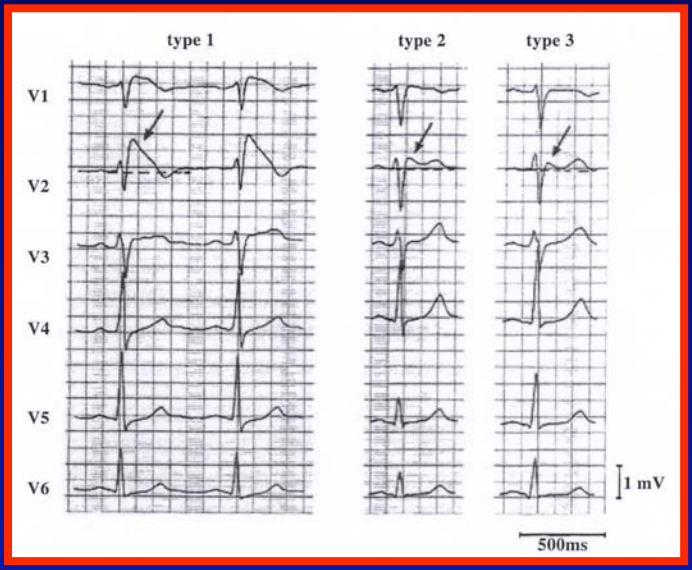
CARDIAC ARREST/SCD IN LQTS:
Gender /Symptom relationship



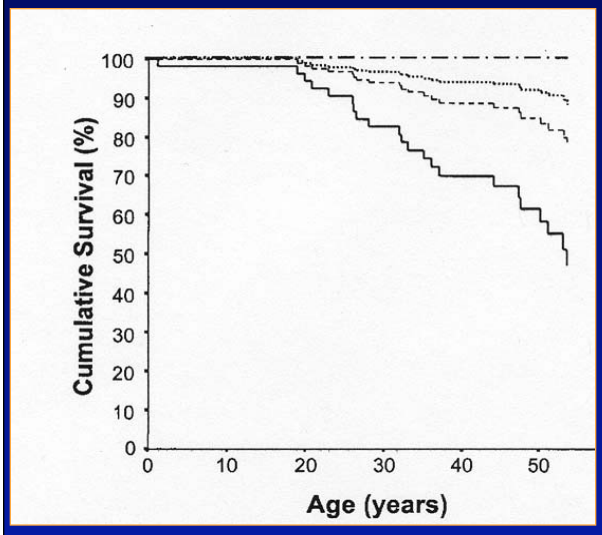
Risk Stratification in Long QT Syndrome: Genotype & Gender



BRUGADA SYNDROME



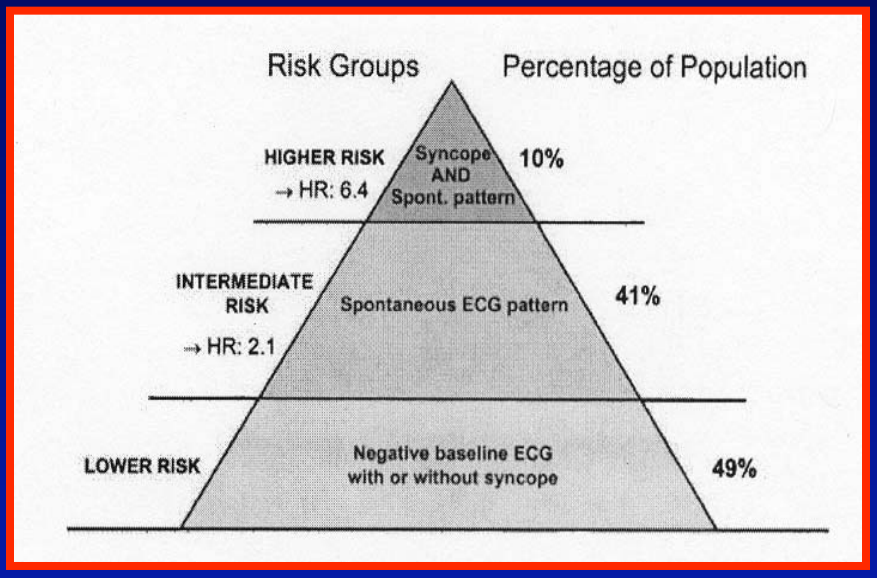
Natural History of Brugada Syndrome



Syncope, - ECG baseline
Syncope, + ECG challenge
+ ECG baseline

Syncope, + ECG baseline

Risk Stratification in Brugada Syndrome



Familial catecholaminergic polymorphic VT

Mutations in the Cardiac Ryanodine Receptor Gene (*hRyR2*) Underlie Catecholaminergic Polymorphic Ventricular Tachycardia

Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD; Natascia Tiso, PhD; Mirella Memmi, PhD; Gabriele Vignati, MD; Raffaella Bloise, MD; Vincenzo Sorrentino, MD; Gian Antonio Danieli, BSc

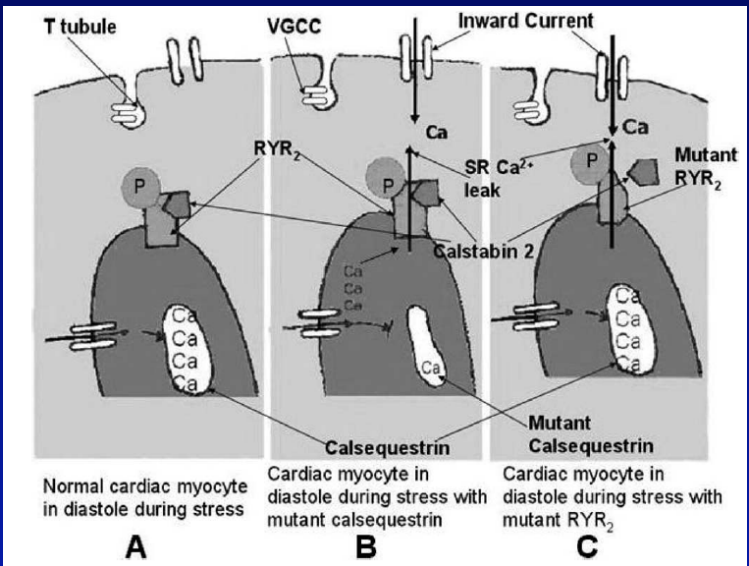
Background—Catecholaminergic polymorphic ventricular tachycardia is a genetic arrhythmogenic disorder characterized by stress-induced, bidirectional ventricular tachycardia that may degenerate into cardiac arrest and cause sudden death. The electrocardiographic pattern of this ventricular tachycardia closely resembles the arrhythmias associated with calcium overload and the delayed afterdepolarizations observed during digitalis toxicity. We speculated that a genetically determined abnormality of intracellular calcium handling might be the substrate of the disease; therefore, we considered the human cardiac ryanodine receptor gene (*hRyR2*) a likely candidate for this genetically transmitted arrhythmic disorder.

Methods and Results—Twelve patients presenting with typical catecholaminergic polymorphic ventricular tachycardia in the absence of structural heart abnormalities were identified. DNA was extracted from peripheral blood lymphocytes, and single-strand conformation polymorphism analysis was performed on polymerase chain reaction–amplified exons of the *hRyR2* gene. Four single nucleotide substitutions leading to missense mutations were identified in 4 probands affected by the disease. Genetic analysis of the asymptomatic parents revealed that 3 probands carried de novo mutations. In 1 case, the identical twin of the proband died suddenly after having suffered syncopal episodes. The fourth mutation was identified in the proband, in 4 clinically affected family members, and in none of 3 nonaffected family members in a kindred with 2 sudden deaths that occurred at 16 and 14 years, respectively, in the sisters of the proband.

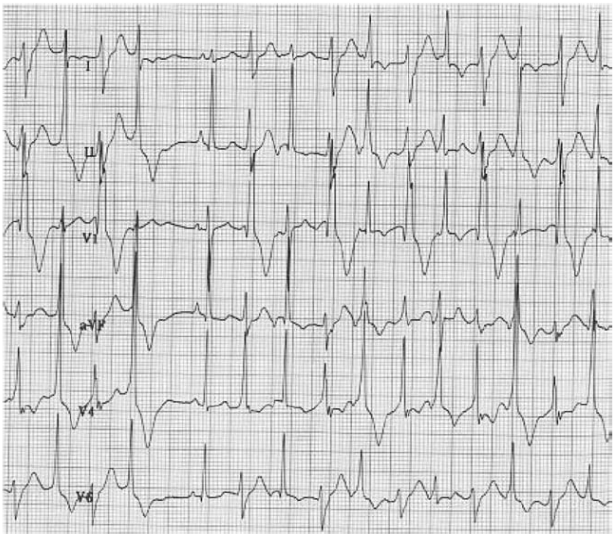
Conclusions—We demonstrated that, in agreement with our hypothesis, *hRyR2* is a gene responsible for catecholaminergic polymorphic ventricular tachycardia. (***Circulation*. 2001;103:196-200.**)

Key Words: arrhythmia ■ genetics ■ tachycardia ■ ryanodine receptor calcium release channel

Familial catecholaminergic polymorphic VT

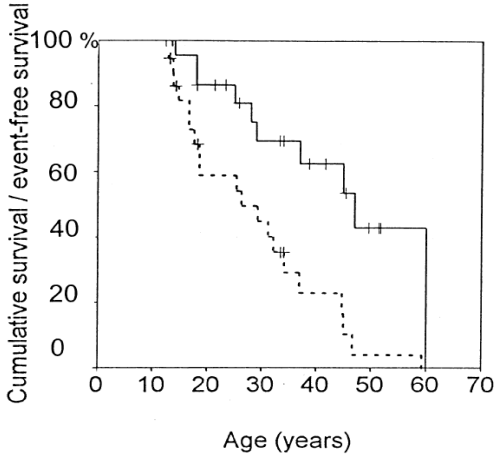


Familial catecholaminergic polymorphic VT:
Bidirectional VT in a Child

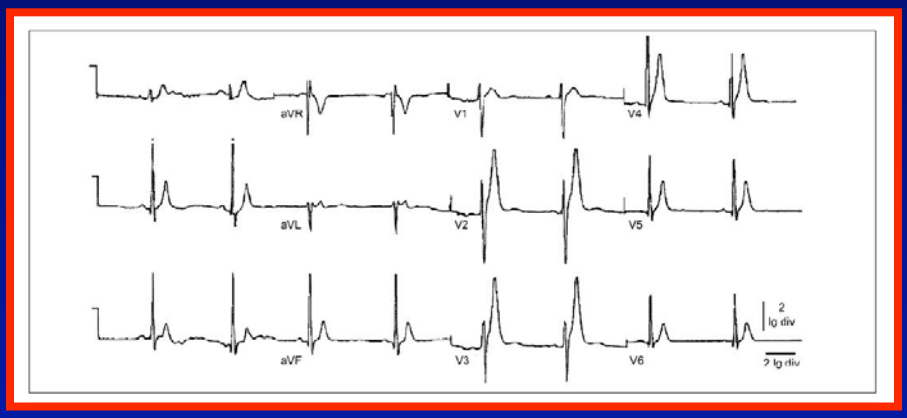


Malignant PVT and SCD in 2 Unrelated Families

Swan H et al. JACC1999;34:2035



SHORT QT SYNDROME



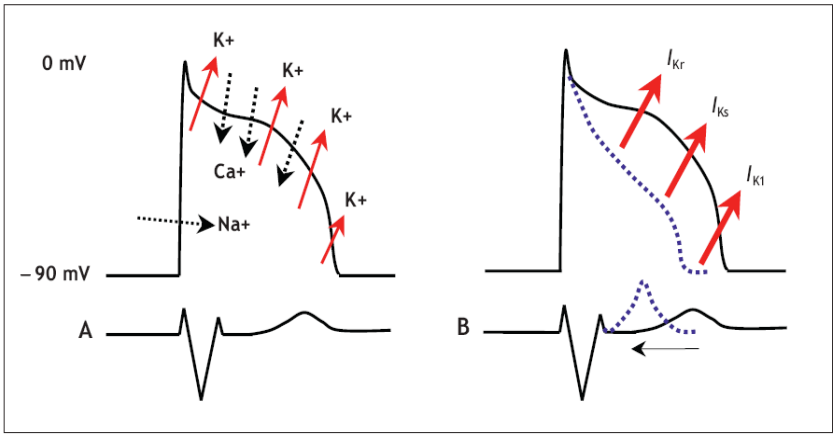
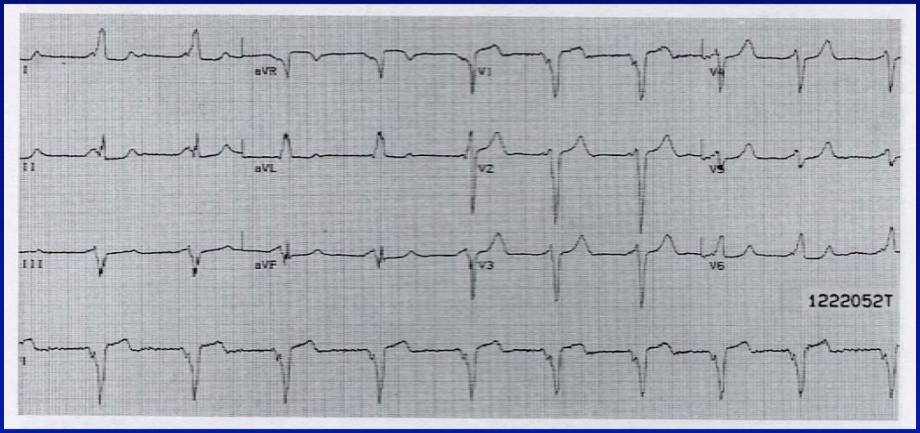
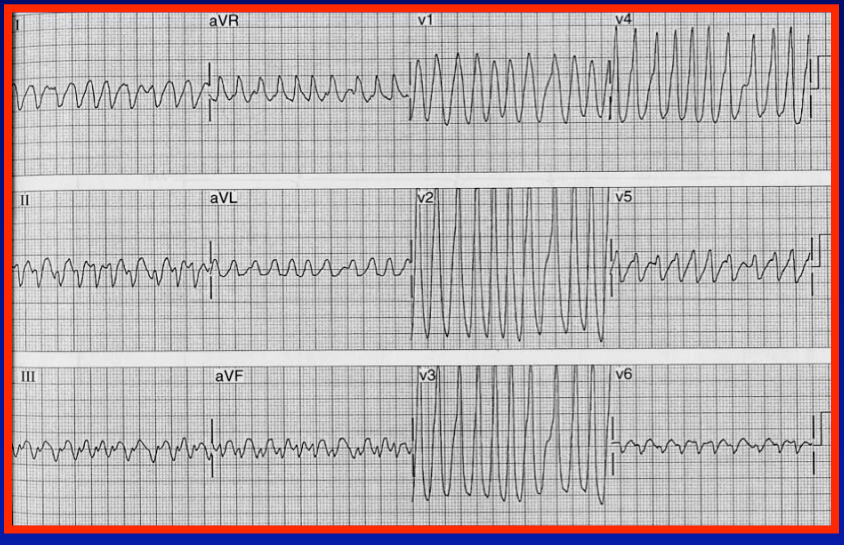


Fig. 2: A. Schematic representation of the normal action potential and the flux of ions. B. With gain-of-function mutations in any of 3 different potassium channels, the cardiac action potential shortens and the QT interval decreases.

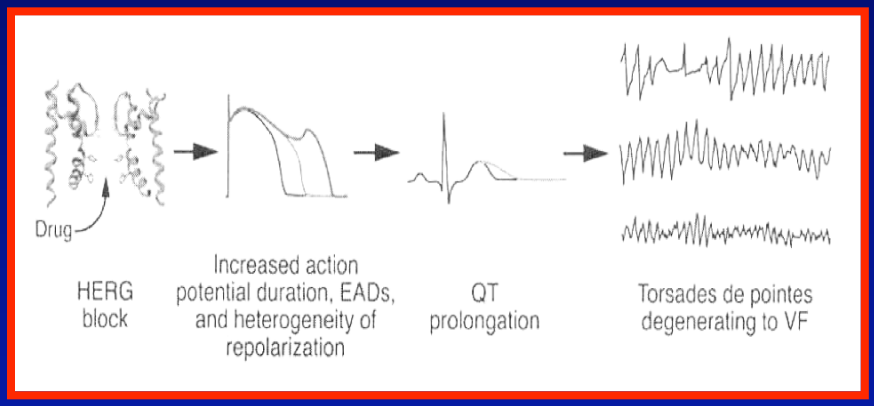
PRE-EXCITED QRS COMPLEXES IN A PATIENT WITH WPW SYNDROME

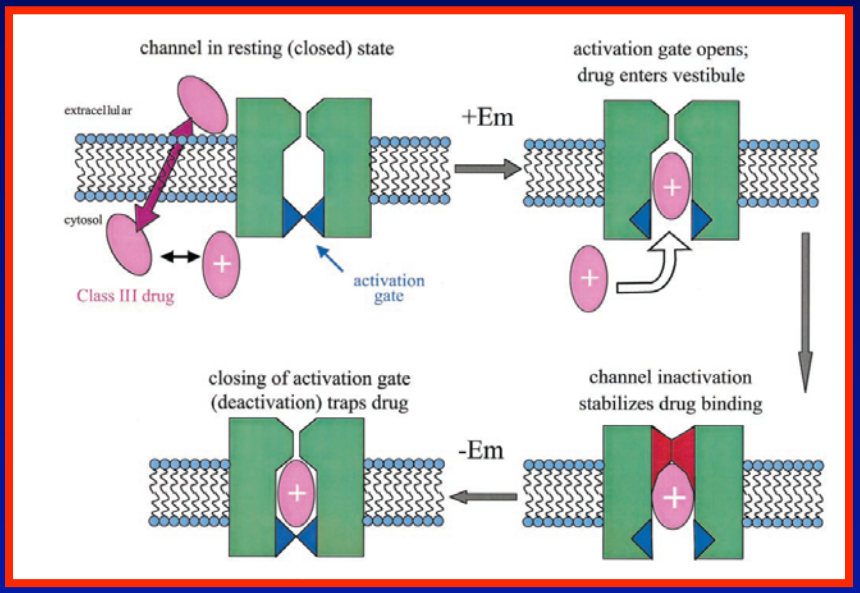


AF with rapid ventricular response in WPW Syndrome



ACQUIRED LONG QT
Drug-related Repolarization Abnormality





CAUSES OF ACQUIRED LONG QT

- Drugs
  - Drugs that frequently cause torsade de pointes
    - Disopyramide
    - Dofetilide
    - Ibutilide
    - Procainamide
    - Quinidine
    - Sotalol
  - Drugs clearly associated with torsade de pointes but with low incidence[A]
    - Amiodarone
    - Arsenic trioxide
    - Erythromycin
    - Droperidol
    - Haloperidol
    - Thioridazine
    - Methadone
- Heart block
- Hypokalemia, hypomagnesemia[B]
- Acute myocardial infarction[B]
- Subarachnoid hemorrhage and other CNS injury[B]
- Liquid protein diets and other forms of starvation[B]

SCD
DETECTION OF RISK

LARGE NUMBERS OF PATIENTS AT RISK

- Need simple, inexpensive, non-invasive diagnostic tests with high clinical accuracy
  - sensitivity: percentage of patients with the disease identified by the test. Need screening tests with high sensitivity not to miss any patients at high risk.
  - positive predictive accuracy (ppa): percentage of patients with a positive test that will go on to have an event. Need screening tests with high ppa to minimize unnecessary treatment with expensive therapies in patients not at high risk

SCD RISK STRATIFICATION

AVAILABLE TESTING METHODS/PREDICTIVE MARKERS

NON-INVASIVE

- Ventricular Systolic Function (Echocardiogram, MUGA Scan, MRI)
- Ambulatory Cardiac Rhythm Monitoring for VEA/NSVT
- T-Wave Alternans
- Exercise Testing
- HR Variability
- Baroreflex Sensitivity
- SAECG
- Genetic Markers

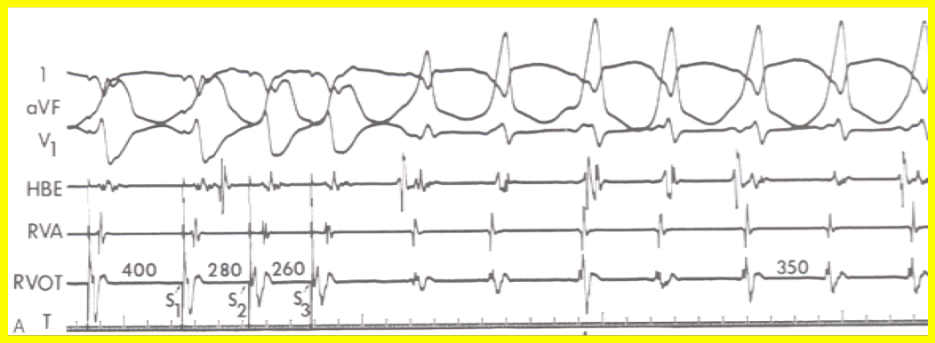
INVASIVE

- Programmed Cardiac Stimulation (PCS)

PROGRAMMED CARDIAC STIMULATION (PCS):

Introducing one or more timed, premature, paced ventricular beats, via electrode-catheters placed percutaneously inside the heart, in an effort to reproduce clinical VT in the Cardiac EP Laboratory

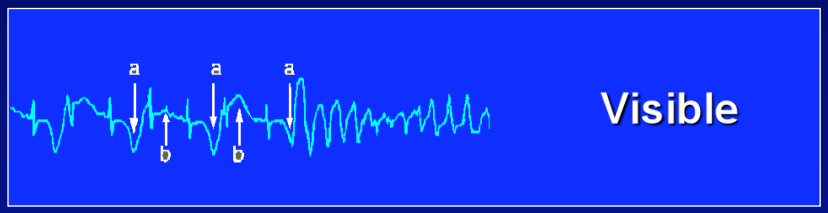
Sensitivity of PCS in ischaemic heart disease is acceptable, but its PPA is poor.



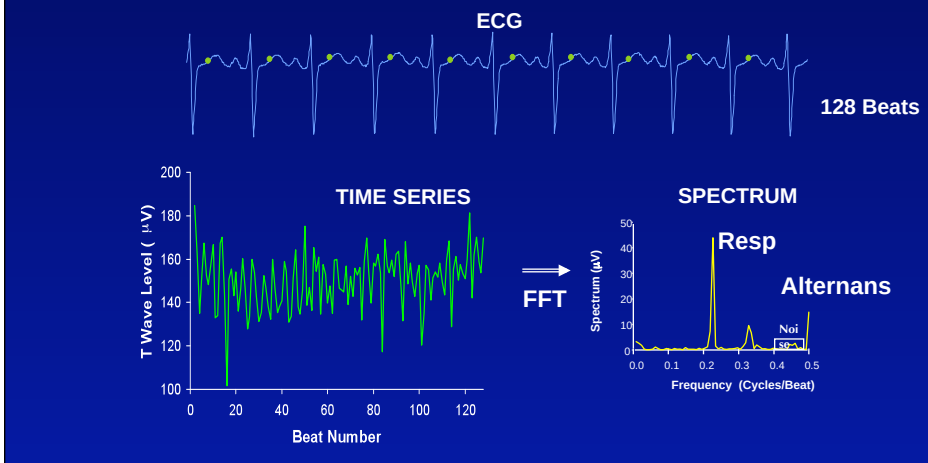
PCS: Limitations

- Sensitivity of PCS in ischaemic heart disease is acceptable, but its PPA is poor.
- In non-ischaemic CM, there is up to 40% incidence of clinical arrhythmic events in “non-inducible” group.
- There are no reproducible data to justify its clinical utility in HCM.
- Not applicable in “channelopathies”, except for Brugada Syndrome.

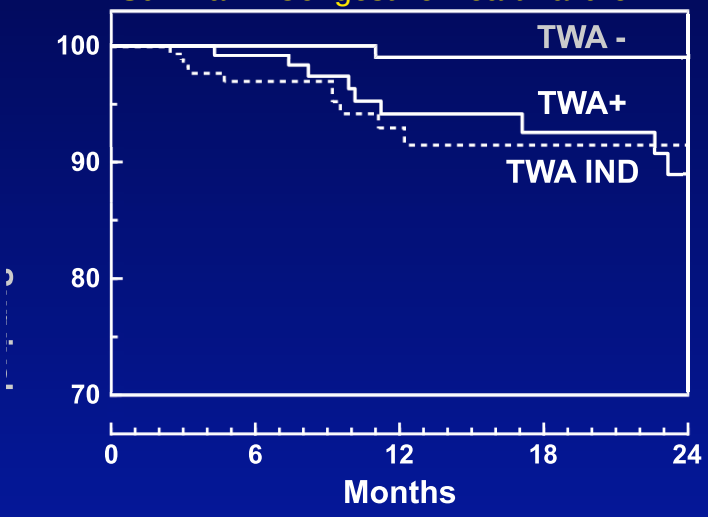
SCD RISK STRATIFICATION IN CHF
T-Wave Alternans



Spectral Method Detects Microvolt T Wave Alternans



Survival in Congestive Heart Failure



542 patients
EF <=40%
NSR, no prior arrhythmias

Total number of subjects at risk:

TWA -	186	95	41
TWA +	161	83	49
IND	195	66	38

Bloomfield DM, et al. ACC 2003.

SURVIVAL IN NON-ISCHEMIC CARDIOMYOPATHY

ALPHA Investigators JACC 2007;50:1896

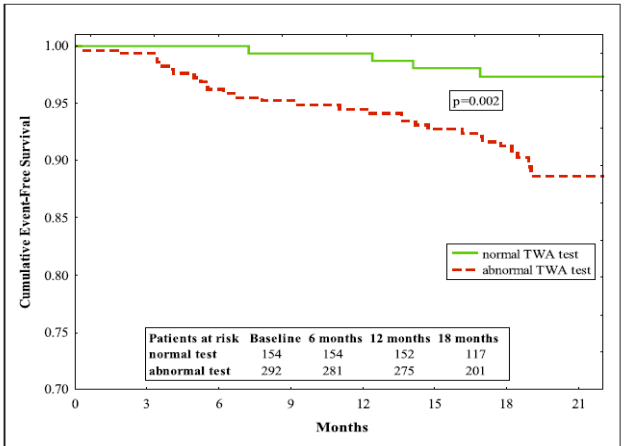


Figure 1 Freedom From Cardiac Death + Life-Threatening Arrhythmias

SCD
TREATMENT & PREVENTION

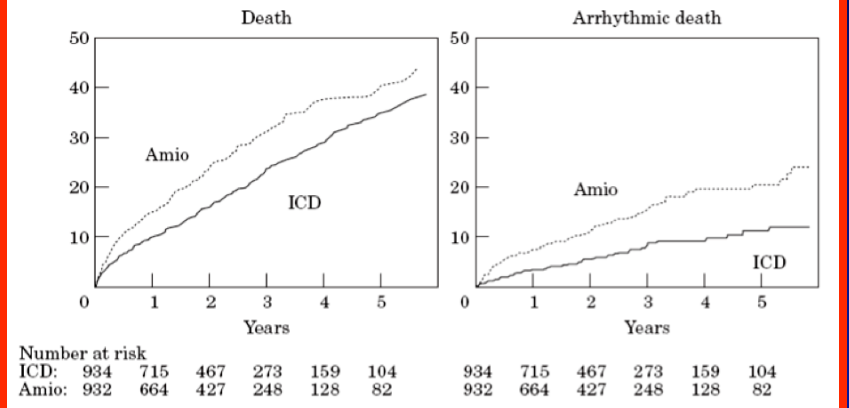
SCD: SECONDARY PREVENTION
Treating survivors of out-of-hospital cardiac arrest with documented VT/VF

There are no controlled studies with placebo or no-treatment arm

Randomized trials: Implantable Cardioverter/Defibrillator (ICD) vs Antiarrhythmic Drugs (AADs)

- Three randomized trials have shown that ICD therapy is superior to AAD (mostly amiodarone) therapy

AVID/CIDS/CASH Metanalysis



Number at risk

ICD:	934	715	467	273	159	104	934	715	467	273	159	104
Amio:	932	664	427	248	128	82	932	664	427	248	128	82

Figure 1 Cumulative risk of fatal events or the amiodarone (. . . .) and ICD (—) treatment arms.

Primary Prevention vs. Secondary Salvage

- Salvage rate for patients with sudden cardiac arrest is < 2%
- Therefore the major task is to identify patients at risk **prior to** the event
  - focus on primary prevention
  - identify and treat

SCD: PRIMARY PREVENTION

ANTIARRHYTHMIC DRUG (AAD) TRIALS

None of the several prospective, controlled, AAD trials, except for one, in high-risk patients (post-MI, cardiomyopathy,CHF) showed any survival benefit with AAD

SCD
TREATMENT & PREVENTION

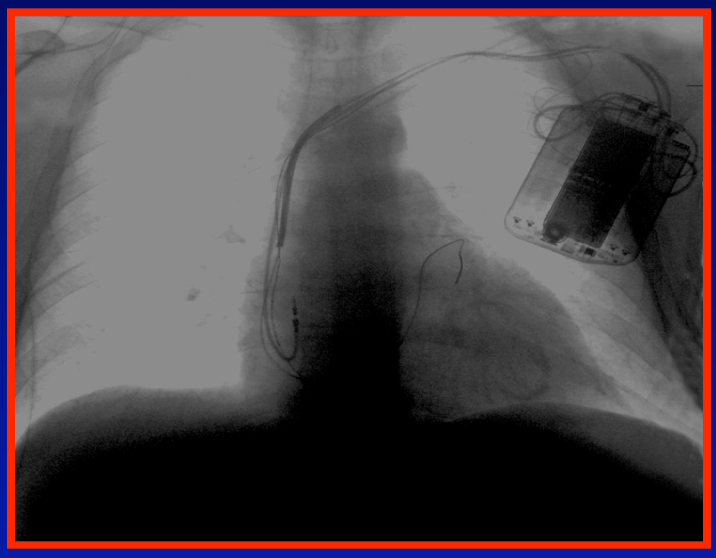
I) IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) THERAPY

II) DRUG THERAPY (Beta blocker therapy)

III) CATHETER ABLATION (WPW syndrome)

IV) SURGERY (Anomalous coronary arteries, severe CAD, e.g. LMCA stenosis)

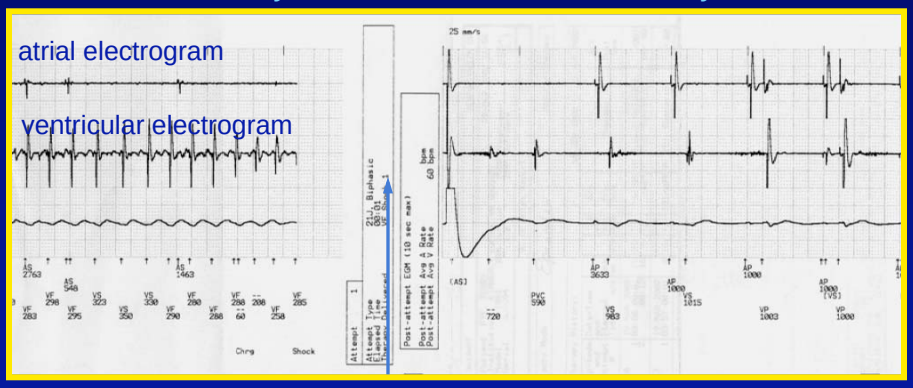
Implantable Cardioverter Defibrillator



DETECTION & TERMINATION OF VT BY ICD

Ventricular Tachycardia

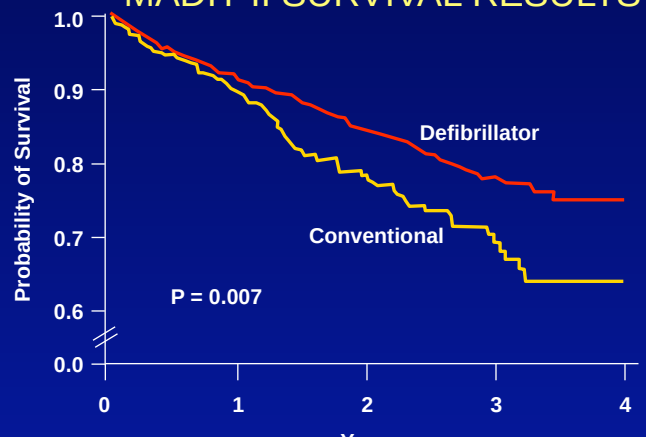
Sinus Rhythm



SCD: PRIMARY PREVENTION
ICD THERAPY

- 4 randomized, prospective trials showed survival benefit with ICD in:
  - Ischaemic heart disease and non-sustained VT (MUSTT)
  - Ischaemic heart disease and depressed LV function (MADIT I, MADIT II)
  - CHF and depressed LV function (ischaemic or non-ischaemic) (SCD-HeFT)
- ICD-related survival benefit not established in:
  - Patients undergoing surgical coronary revascularization
  - Implantation immediately after acute MI

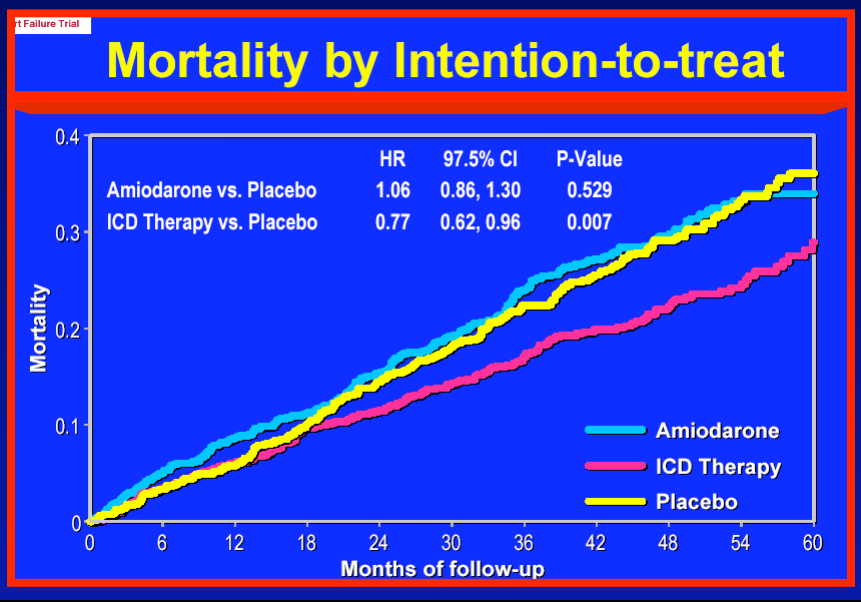
PRIMARY PREVENTION OF SCD
MADIT-II SURVIVAL RESULTS



No. At Risk					
Defibrillator	742	502 (0.91)	274 (0.94)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Moss AJ. *N Engl J Med.* 2002;346:877-83.

SCD-HeFT STUDY



ICD THERAPY IN ISCHAEMIC CARDIOMYOPATHY OR CHF: INDICATIONS

Chronic ischaemic heart disease with LVEF<40%, documented non-sustained VT, and electrically inducible VT/VF

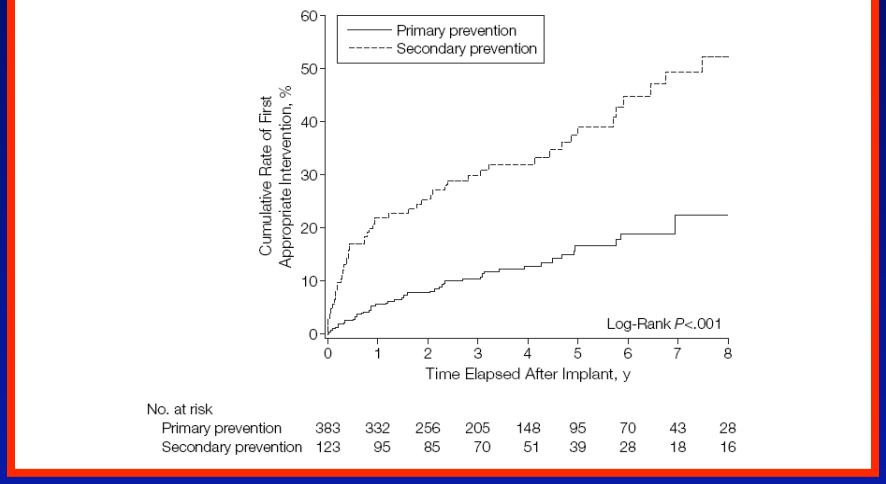
Chronic/subacute ischaemic heart disease with LVEF<35%, and electrically inducible VT/VF

Chronic/subacute ischaemic heart disease with LVEF<30%

Ischaemic or non-ischaemic cardiomyopathy with LVEF<35%, and Class II or III congestive heart failure

Cumulative Rates for First Appropriate ICD Intervention in Patients Who Had Received Devices for Primary (n=383) and Secondary (n=123) Prevention

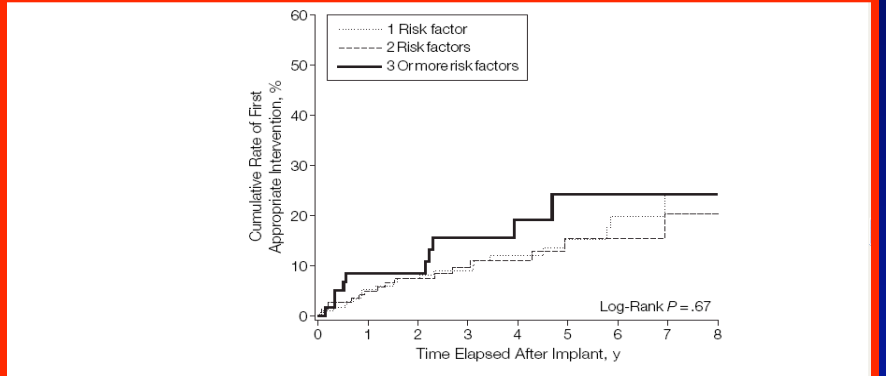
Maron BJ et al. JAMA 2007;298:405



No. at risk									
Primary prevention	383	332	256	205	148	95	70	43	28
Secondary prevention	123	95	85	70	51	39	28	18	16

Cumulative Rates for First Appropriate ICD Intervention in Patients with 1,2, 3 or More Risk Factors Who Had Received Devices for Primary Prevention

Maron BJ et al. JAMA 2007;298:405



No. at risk									
1 Risk factor	173	150	119	98	70	48	31	18	16
2 Risk factors	143	123	95	71	53	34	28	16	6
3 Or more risk factors	59	52	38	32	23	11	9	8	6

ICD THERAPY IN HCM: INDICATIONS

- Survivors of cardiac arrest (VT/VF)
- Spontaneous sustained VT
- Unexplained syncope
- Family history of premature SCD
- Maximum LV thickness ≥ 30 mm (controversial in absence of any other risk factor)
- Abnormal BP response to exercise
- Non-sustained VT
- Certain mutations in individuals (specific beta-myosin heavy chain and troponin T mutations)

ICD THERAPY IN ARVC/D

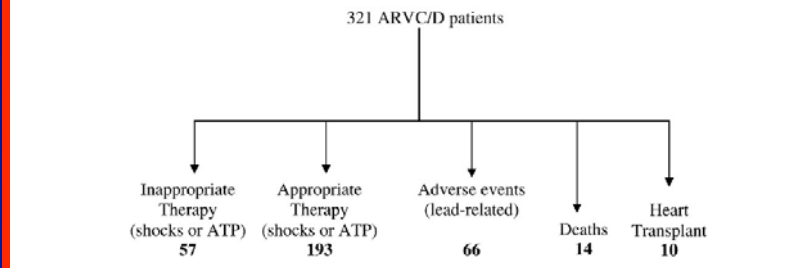
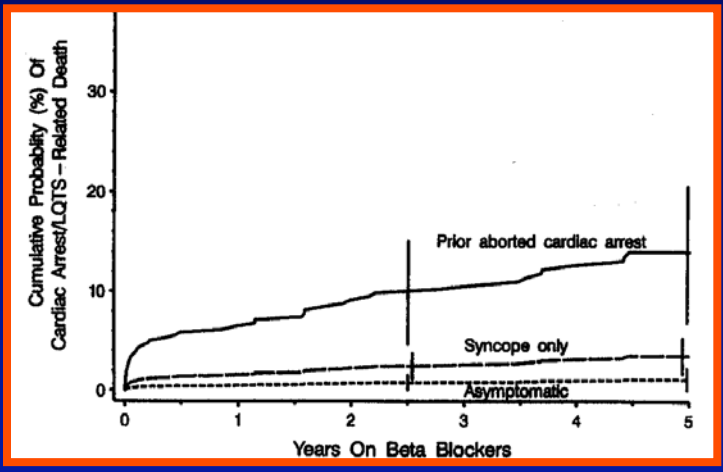


Fig 1. Diagram summarizing the results of 321 patients with ARVC/D implanted with an ICD, with a mean follow-up of 37 ± 20 months.[16,17,19-23]

RECOMMENDATIONS FOR ICD THERAPY IN ARVD/C

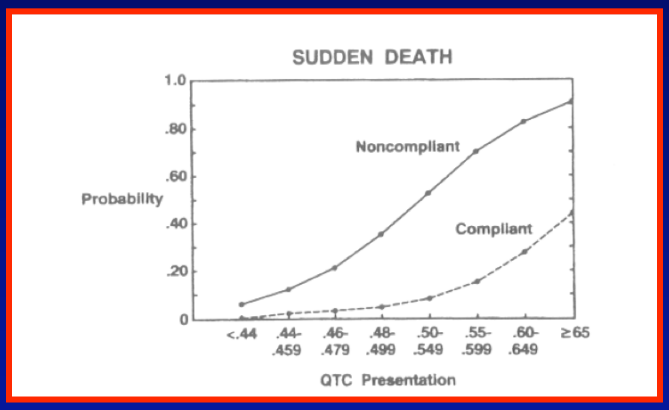
- Patients with syncope, heart failure, or LV involvement
- As secondary prevention therapy in patients with documented sustained VT and hypotension

EFFECTIVENESS OF BETA BLOCKER THERAPY IN LQTS



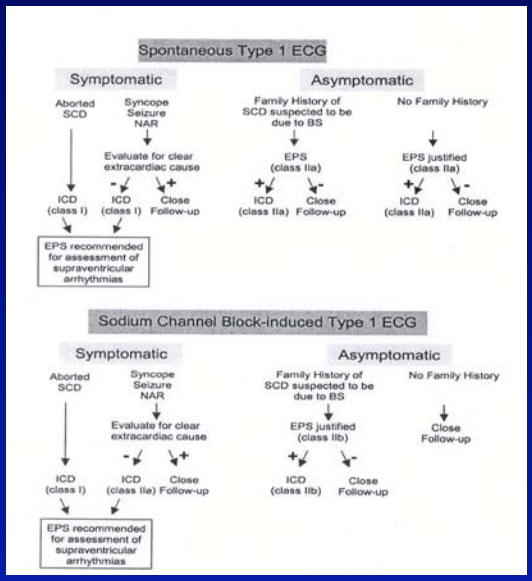
Arthur J. Moss et al. Circulation 2000;101:616

PROBABILITY OF SUDDEN DEATH IN CHILDREN WITH LQTS: RELATION TO QT_C



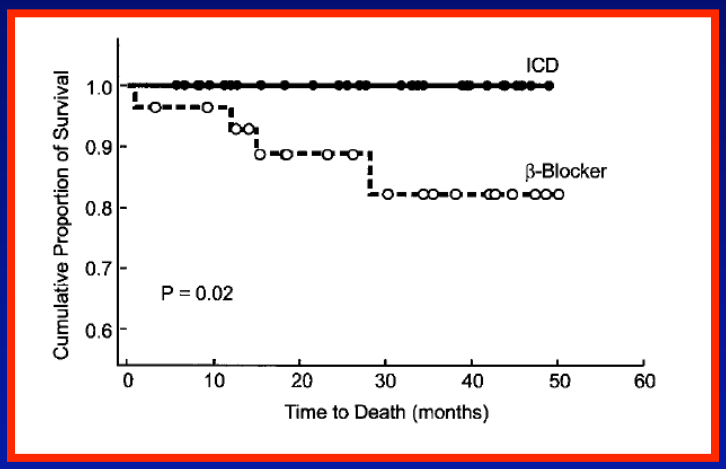
Garson et al. Circulation 1993;87:1866-1872

Risk Profile & Treatment Algorithm: Brugada Protocol

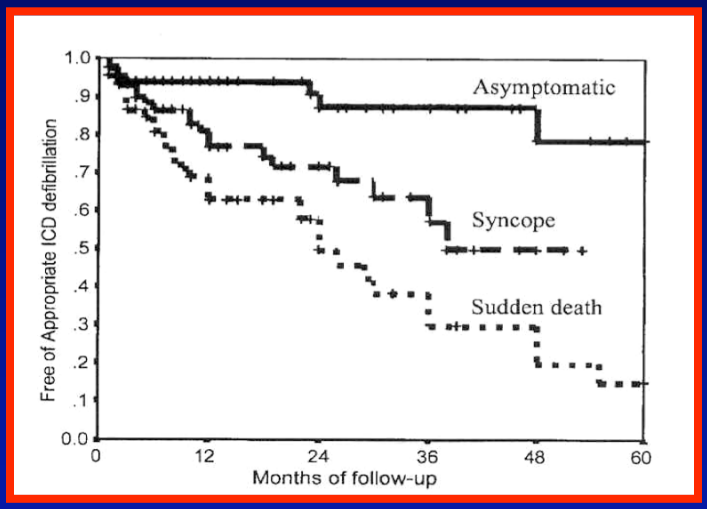


DEBUT Trial

Nademanee et al. Circulation 2003;107:2221



BRUGADA SYNDROME: EFFECTIVENESS OF ICD THERAPY IN 258 PATIENTS WITH BRUGADA PATTERN ON ECG



ICD THERAPY IN "CHANNELOPATHIES": INDICATIONS

- LQTS PRESENTING WITH CARDIAC ARREST
- LQTS WITH
  - RECURRENT SYNCOPE ON BETA BLOCKER Rx
    POSITIVE FAMILY Hx FOR SUDDEN DEATH
  - CHILD WITH MARKEDLY PROLONGED QT AT BASELINE
- IDIOPATHIC VF
  - PATIENTS WITH SPONTANEOUS BRUGADA PATTERN WHO ARE SYMPTOMATIC OR HAVE A POSITIVE FAMILY HISTORY
  - PATIENTS WITH INDUCED (SODIUM CHANNEL BLOCKERS) BRUGADA PATTERN WHO ARE SYMPTOMATIC
  - THE ROLE OF PCS IS CONTROVERSIAL

Drug therapy in CPVT

Table 1 Prognosis in relation to drug treatment

	β Blocker	Ca blocker	Na blocker	Total
Alive	17	3	1	21
Dead	4	0	3	7
Total	21	3	4	28

Ca blocker, calcium channel blocker; Na blocker, sodium channel blocker.

TABLE 3. Events at Follow-Up in CPVT Patients According to Genotype

	RyR2-CPVT	Nongenotyped CPVT	*P*
Follow-up, mo	40±29	52±30	NS
sVT/VF on β-blockers	7/19	11/20	NS
ICD*	6	6	NS
ICD follow-up, mo	21±10	19±5	NS
ICD shock†	1/6	5/6	NS

Values are presented as mean±SD, n, or n/N. sVT indicates sustained ventricular tachycardia; and VF, ventricular fibrillation.
*ICD was implanted in 3 patients with cIVF and in 9 patients with pVT/bTV.
†Appropriate shocks as assessed by ICD-stored electrogram analysis.

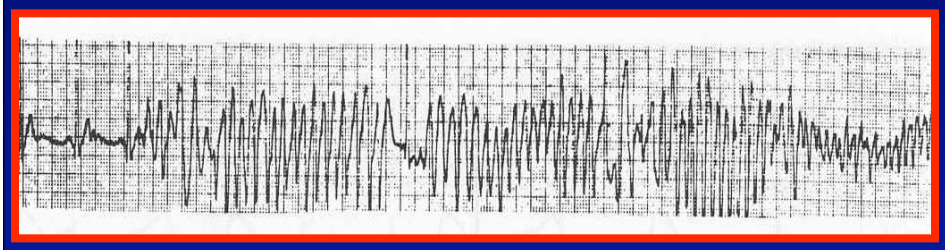
Treatment of CPVT

- Beta blocker therapy strongly indicated in all CPVT patients. About 30% of the patients with CPVT treated with beta blockers still develop cardiac arrhythmias over long-term follow-up
- ICD therapy in survivors of cardiac arrest
- ICD therapy in patients with documented CPVT or syncope during maximally tolerated doses of beta blocker therapy

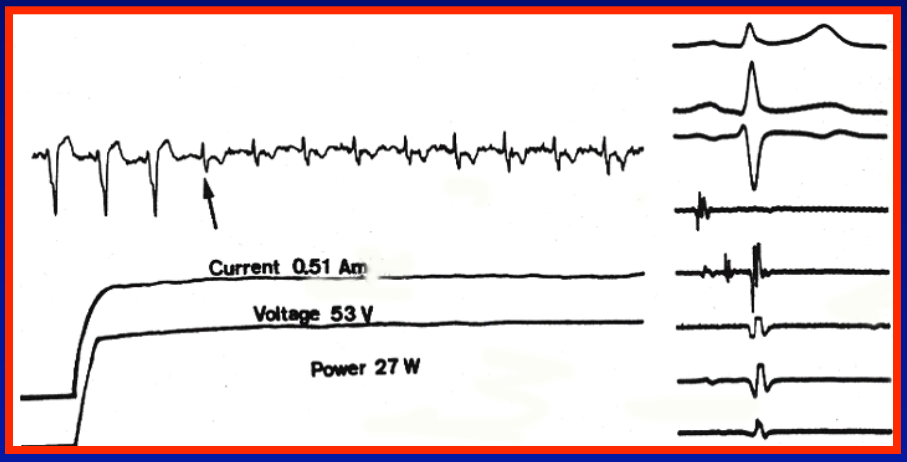
Management of Patient with ARCA or ALCA

- All ALCA patients require surgical repair
- ARCA patients with well-defined symptoms or studies indicating myocardial ischemia require surgical repair
- Asymptomatic ARCA patients risk-benefit dilemma
- ICD consideration only if a satisfactory repair is not possible

AF TRANSFORMING TO VF IN A PATIENT WITH WPW SYNDROME
Rare form of SCD curable with catheter ablation



WPW Syndrome: Disappearance of Ventricular Pre-excitation during RF Application



SCD: Difficulties with Primary Prevention

- Large numbers of patients at risk
  - Need for simple, inexpensive, non-invasive tests with high sensitivity
- Low incidence of sudden cardiac death among patients with known heart disease
  - Post myocardial infarction mortality rates ~5%
  - Low specificity of the tests for risk stratification

CONCLUSIONS

- Overall the vast majority of SCD results from VT/VF in patients with advanced organic heart disease with poor ventricular function
- The majority of SCD in young patients results from congenital cardiomyopathies or more rarely congenital electrical disturbances in the absence of structural heart disease
- There is no effectively preventive drug therapy for SCD
- ICD therapy remains the only known effective method for protection of patients at high risk