Mort subite

Dr Laurent Fauchier

Cardiologie, CHU Trousseau, TOURS.

Objectifs

- Reconnaître les causes de mort subite (MS)

- (Changements dans la prise en charge en aigu de la mort subite)

- Comprendre la prise en charge diagnostique, pronostique et thérapeutique des arythmies à risque létal

- Mise à jour et perspectives sur l'utilisation du DAI dans la MS.

ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Clinical Cardiology: New Frontiers

Sudden Cardiac Death

Douglas P. Zipes, MD; Hein J.J. Wellens, MD

Sudden cardiac death describes the unexpected natural death from a cardiac cause within a short time period, generally ≤1 hour from the onset of symptoms, in a person patients in the convalescent phase after a large myocardial infarction experience sudden cardiac death in the year thereafter, overall they account for a small number of the total

Circulation 1998;98:2334-51.

Mort subite d'origine cardiaque

- **Def : décès < 1 heure, hors de l'Hôpital, chez un patient préalablement stable**

- **Incidence : 400 000 – 500 000 / an aux U.S.A. (0.2 % / an ; 60 % du total des DC)**

- **Seulement 2% - 15% arrivent à l'hôpital**

- **> 50 % décèdent avant la sortie**

- **Taux de récidive élevé**

Causes of Sudden Cardiac Death

Ischemic Heart Disease

- CAD with MI or angina
- coronary artery embolism
- nonathogenic coronary artery disease
- coronary artery spasm

Nonischemic heart disease

- CAD without MI or angina
- cardiomyopathy - obstructive, nonobstructive, nonischemic
- valvular heart disease
- congenital heart disease
- prolonged QT syndrome
- preexcitation syndrome
- complete heart block
- arrhythmogenic RV dysplasia

Nonischemic Heart Disease (con't)

- myocarditis
- acute pericardial tamponade
- acute myocardial rupture

Noncardiac Disease

- sudden infant death syndrome
- drowning
- Pickwickian syndrome
- pulmonary embolism
- drug-induced
- airway obstruction
- no structural heart disease - primary electrical disease, chest wall trauma (commotio cordis), "Brugada's syndrome" (right bundle branch block and ST segment elevation V1 to V3)
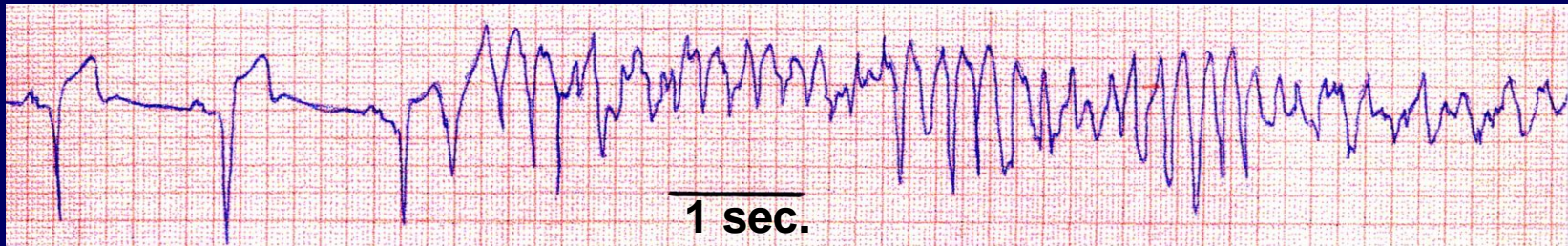
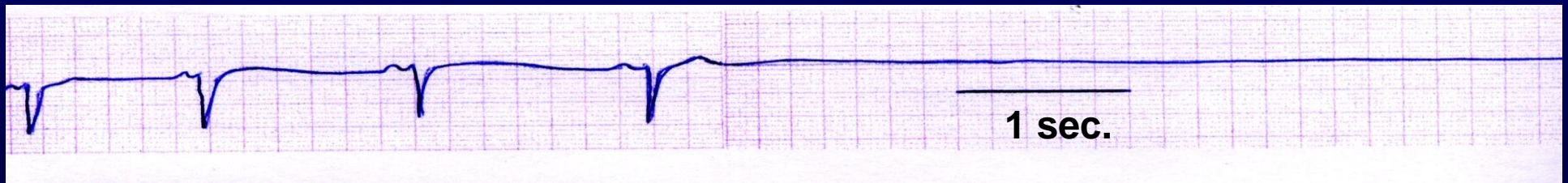# Underlying Arrhythmia of Sudden Death

**Bradycardia
17%**

**Torsades
de Pointes
13%**

**Primary VF
8%**

**VT
62%**
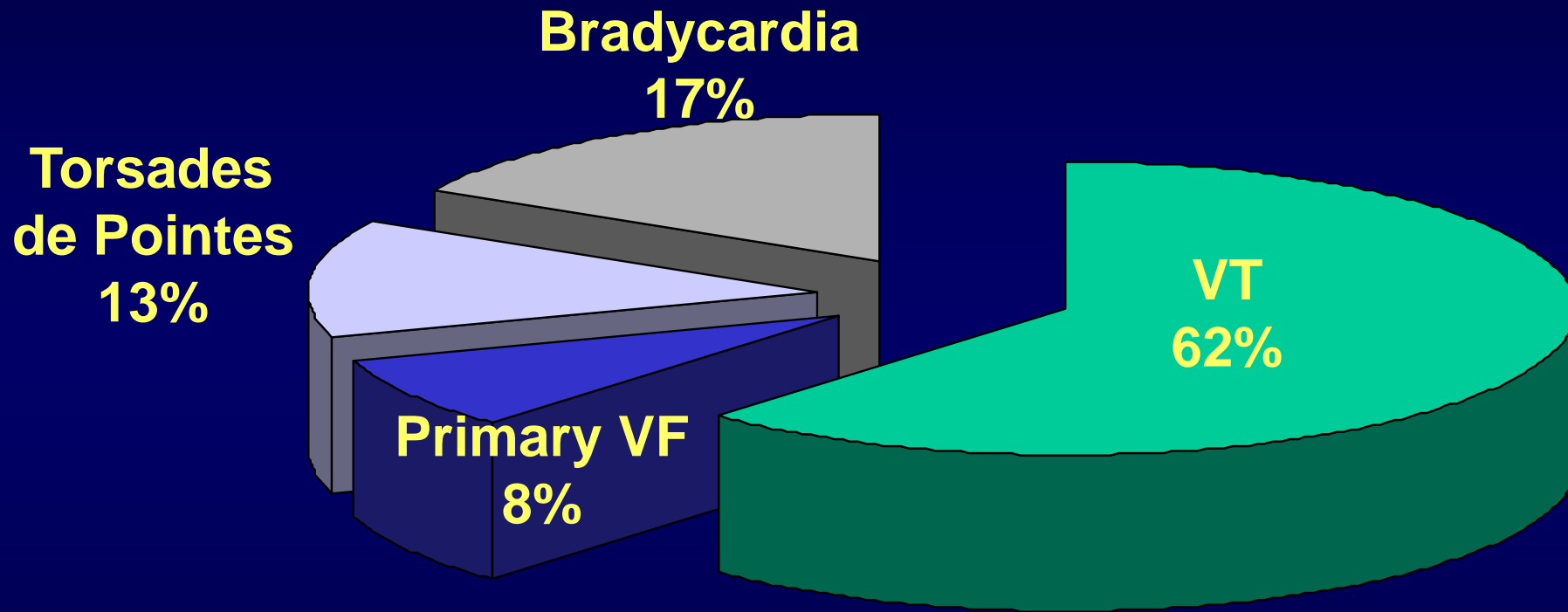
Mechanisms of sudden death in heart failure

Ventricular tachycardia / Fibrillation (60 %)

1 sec.

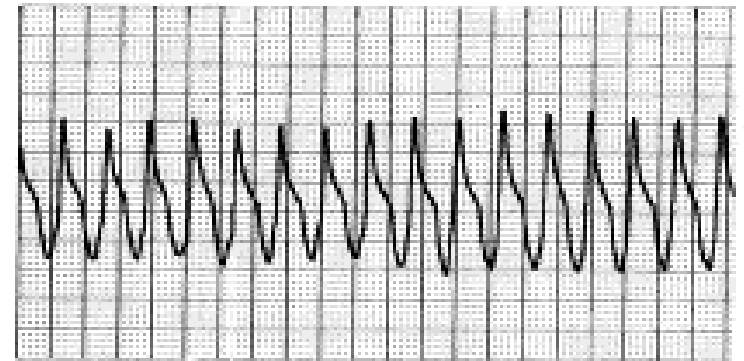## Bradycardia - Electromechanical dissociation (40 %)
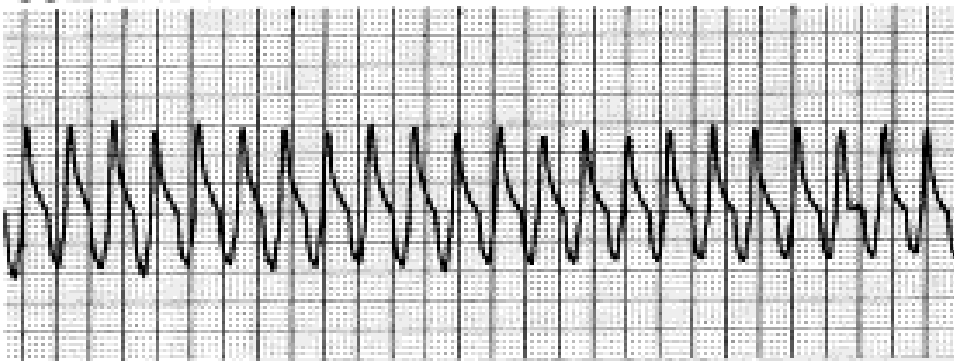

1 sec.

Intérêt du DAI
Traitement symptomatique
des troubles du rythme ventriculaire : TV et FV

Sous -groupes à haut risque nécessitant évaluation

- Rescapés de mort subite

- Post-IDM, FE abaissée, et/ou ESV

- Syncopes répétées inexpliquées

- CMD idiopathique avec syncope ou TV

- CMH avec syncope ou TV

- Cardiomyopathie arythmogène VD

- Syndrome QT long

Evaluation of the survivor of sudden cardiac death

- Discontinue drugs (especially antiarrhythmics) if possible
- Correct metabolic and electrolyte abnormalities
- Evaluate for precipitating factors
- Optimize left ventricular function
- Control symptoms of active ischemia
- Systematic evaluation of antiarrhythmic drugs (Holter, EPS)
- Consider alternative therapy for drug-refractory patients

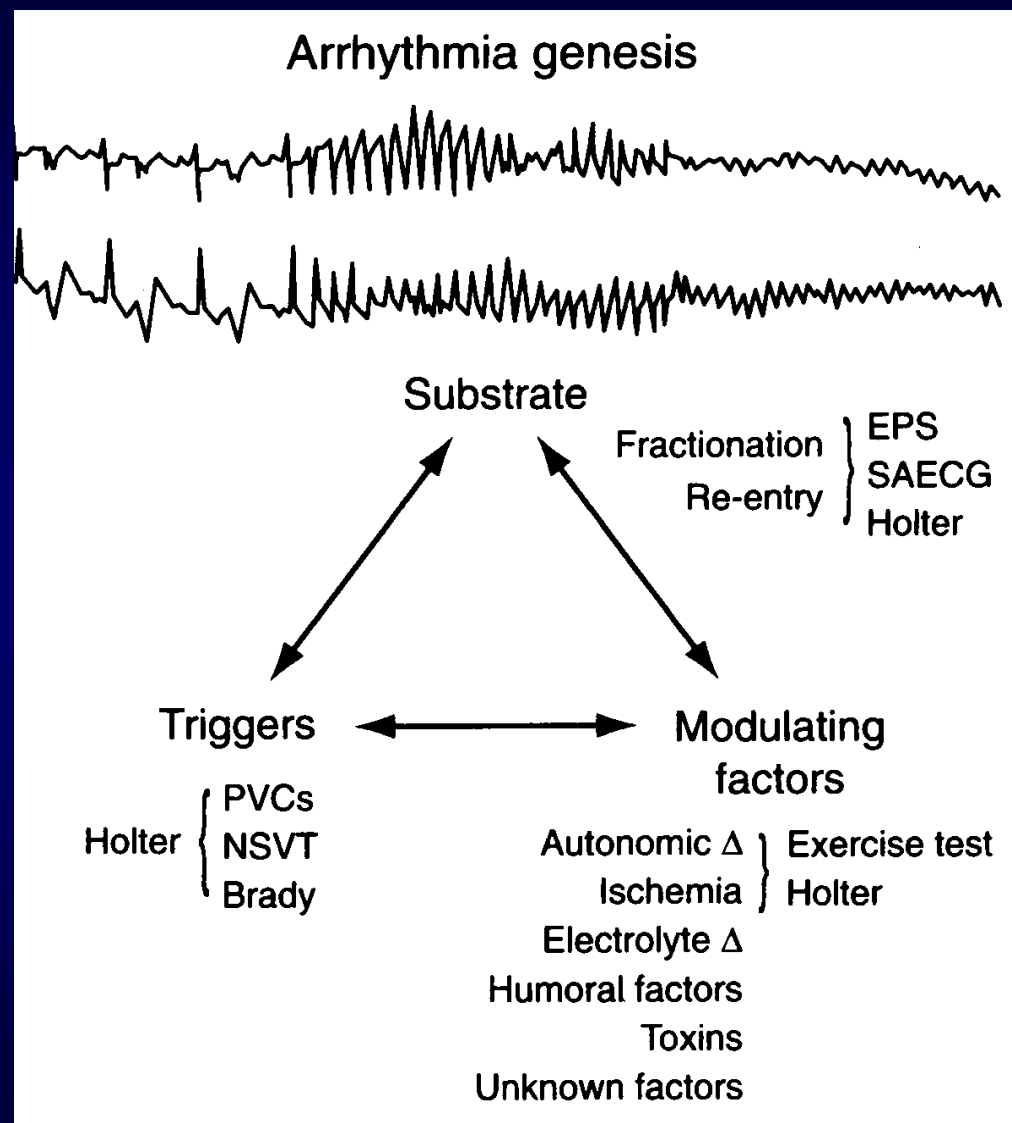# Methods of Evaluating Patients for Risk of Ventricular Arrhythmias

- History and physical
- 12-Lead ECG
- Signal-averaged ECG
- Holter monitor

- Echocardiogram
- Exercise test
- Cardiac catheterization
- Electrophysiology study

Le triangle de l'arythmogénèse

1. Substrat

2. Trigger

3. Modulateurs

Holter

Avantages

- largement accessible et non invasif
- interprétation facile
- facile à répéter au cours du suivi

Inconvénients

- valeur prédictive négative limitée
- critère d'efficacité d'une drogue ?
- différence entre l'effet d'une drogue (suppression ESV) et son efficacité (prévention de TVS ou FV)

Signal Averaged - ECG
ACC Expert Consensus

- Stratification du risque de survenue de TV soutenue en post-IDM avec QRS < 120 ms

- Identification des patients avec CMI et syncope inexpliquée qui ont une probabilité élevée de TV inductible.

Explo. Electrophysiologique

Avantages

- variabilité arythmie modeste
- peut documenter arythmie clinique et risque de MS
- localisation foyer arythmique

Inconvénients

- équipement, coût
- bcp de patients non inductible
- reproductibilité incertaine
- valeur de l'efficacité AA incertaine

Patient avec probabilité pre-test élevée d'EP + :

- **↓ Fraction ejection VG**
- **TVNS**
- **PVT +**

Cardiopathies : marqueurs de MS

- **CMI chronique** **ESV, TVNS, FEVG < 30%**

- **CMH** **Syncope, TVNS, hypoTA d'effort, ATCD fam de MS, HVG > 25-30 mm**

- **CMD** **TVNS (?), FEVG basse, VRS basse, QRS> 120 ms**

- **CMA VD** **Dilat. VD, TVNS, forme familiale**

- **HTA** **HVG, FEVG basse, Tb cond IV**

- **Amylose** **FEVG abaissée, Tb cond IV, ESV**
  Sarcoidose
  Dystrophie & Myop

Cœur « sain » : Marqueurs de MS

Anomalies de repolarisation

- **QT long**   **QTc > 460 ms**

- **Familial**   **Syncope, ATCD fam MS**

- **Acquis**   **TV polym, TdP**

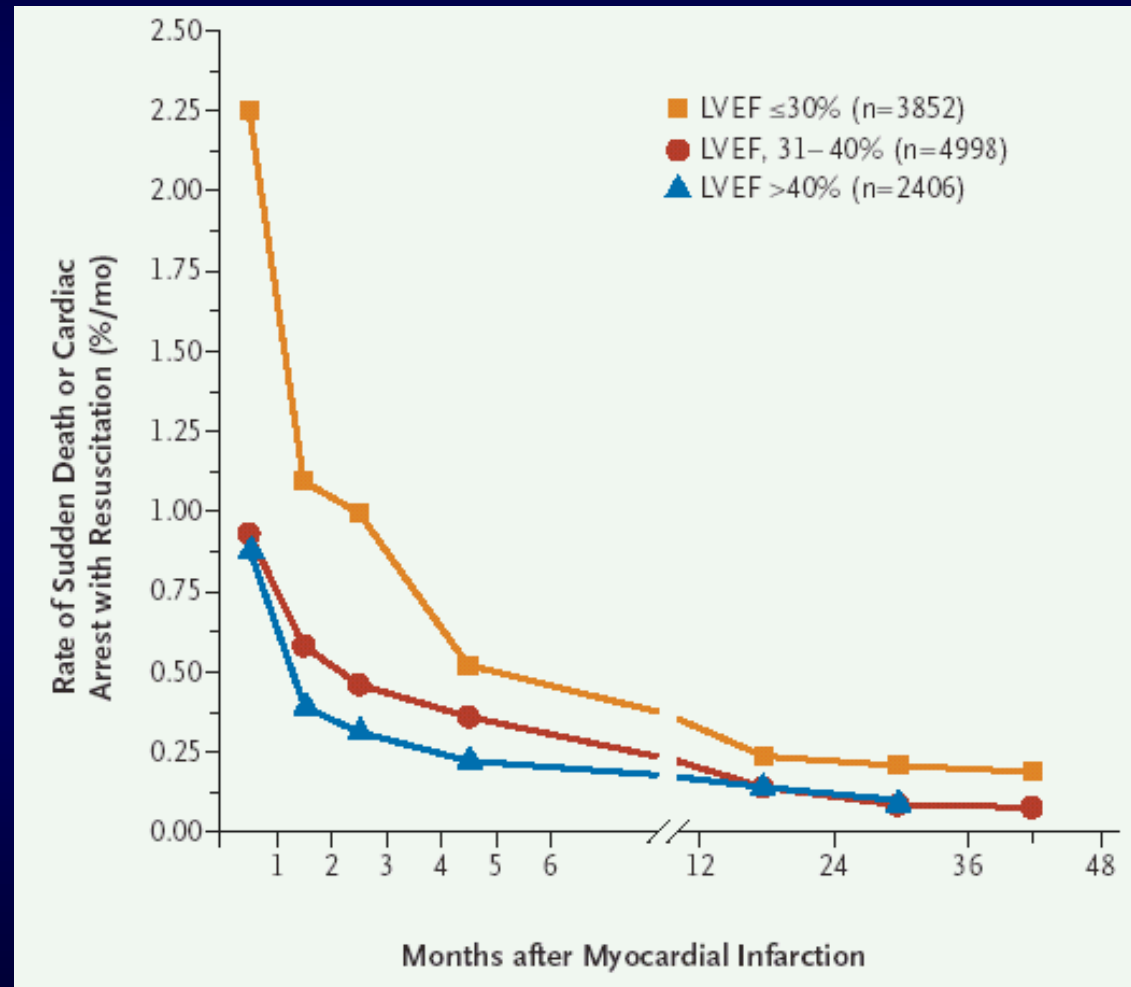- **Brugada**   **Syncope, ATCD fam MS, EP?**

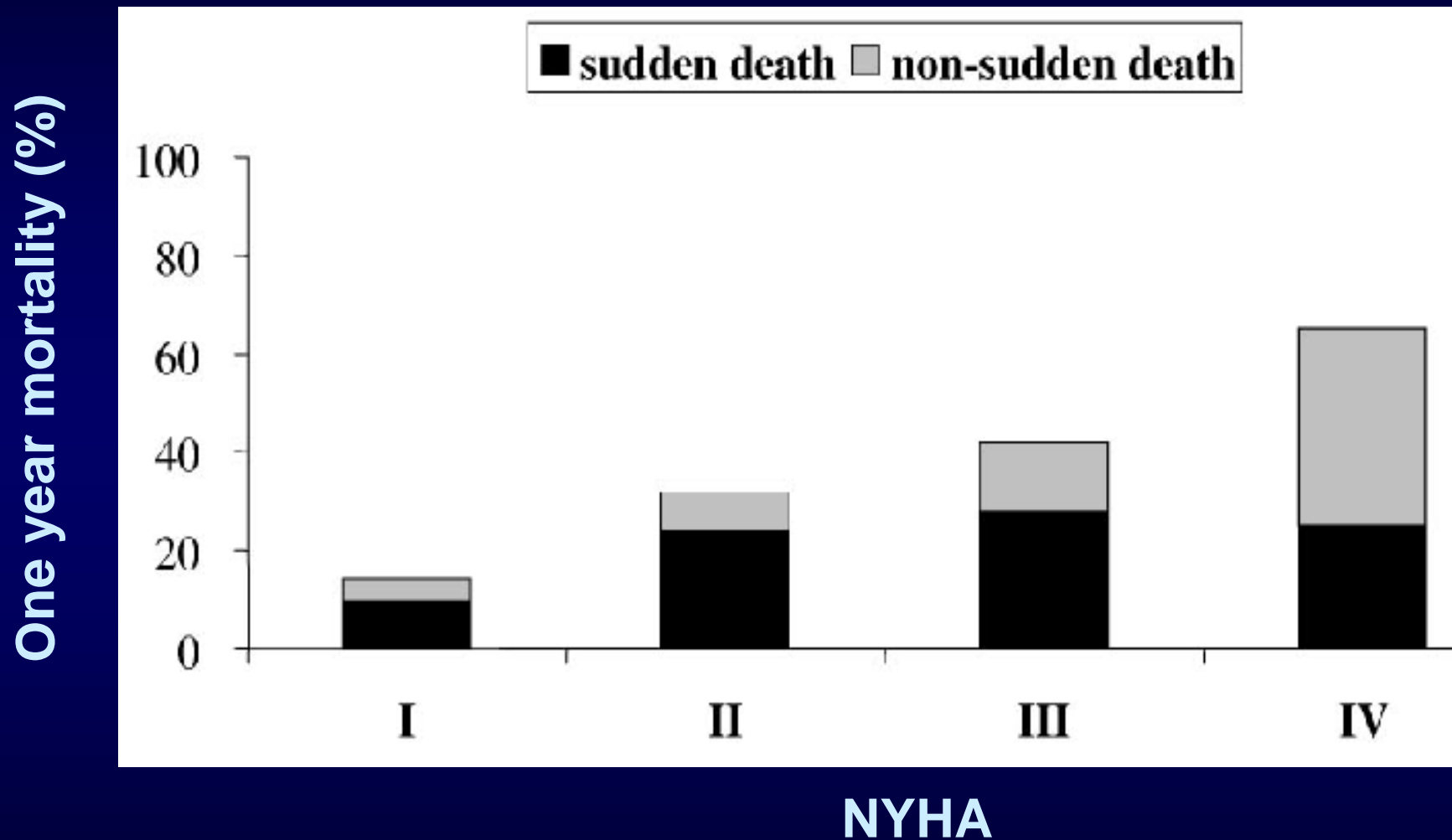*Préexcitation V*

- **WPW**   **WPW, syncope, FA rapide**

Clinical Substrates Associated with VF Arrest

- **Coronary artery disease**
- Idiopathic cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome
- RV dysplasia
- Rarely: WPW syndrome
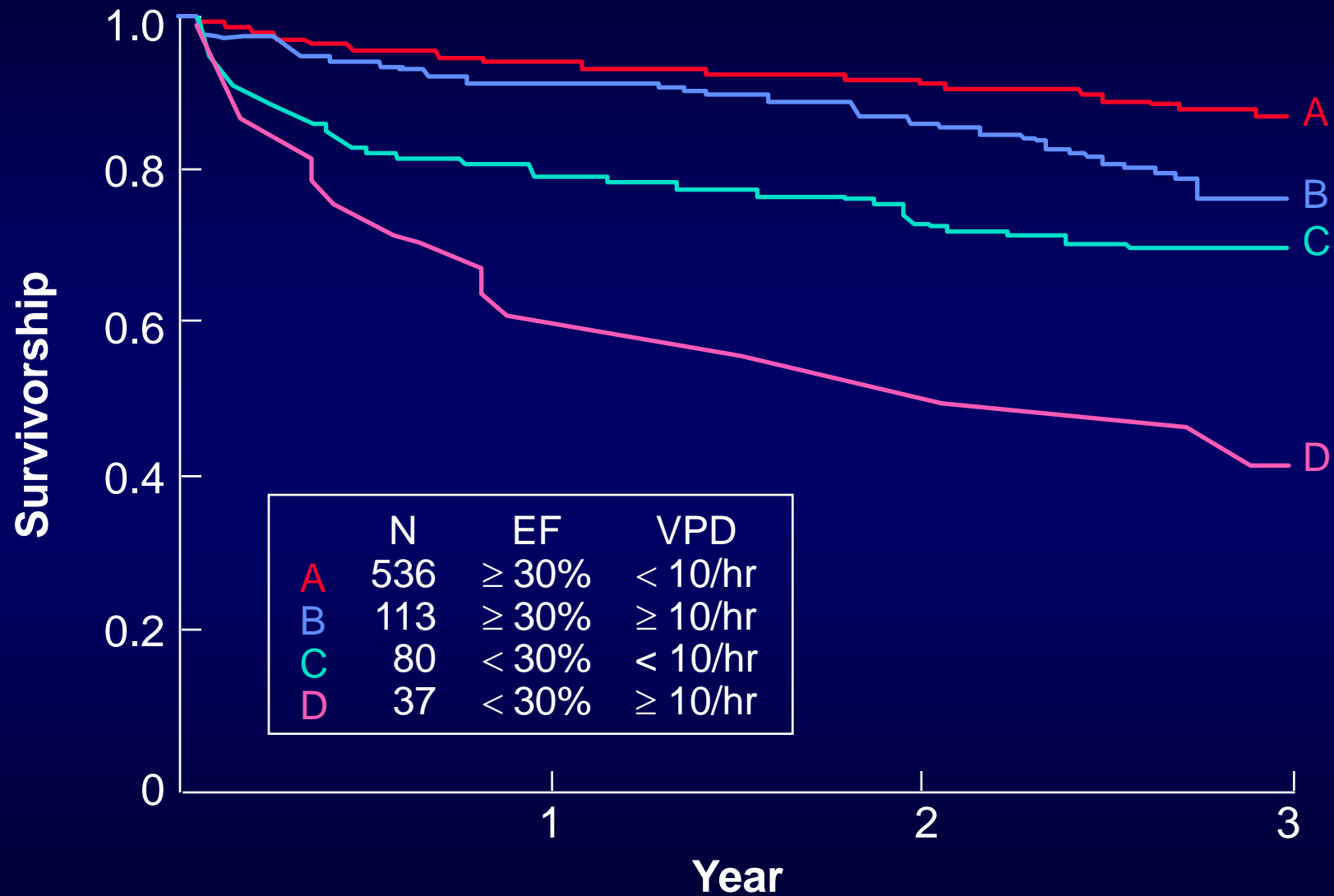
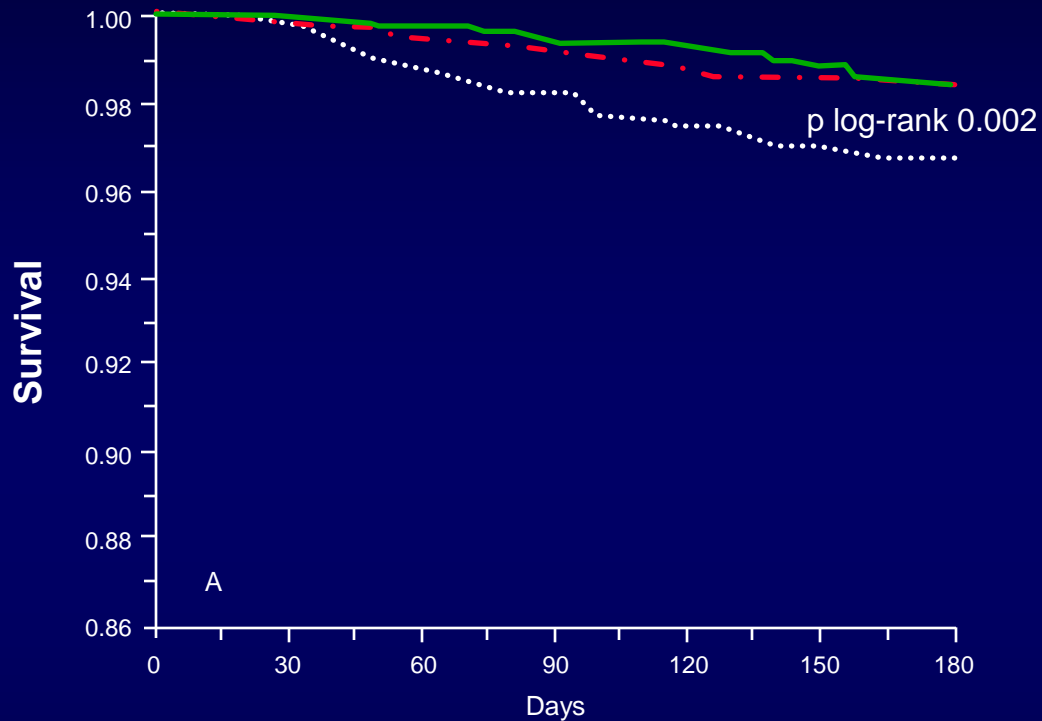# VALIANT. Solomon et al, *NEJM 2005*

Annual Mortality in Heart Failure

Do all pts with HF require ICD to prevent sudden death?
Hsia et al. *Curr Control Trials Cardiovasc Med 2000*
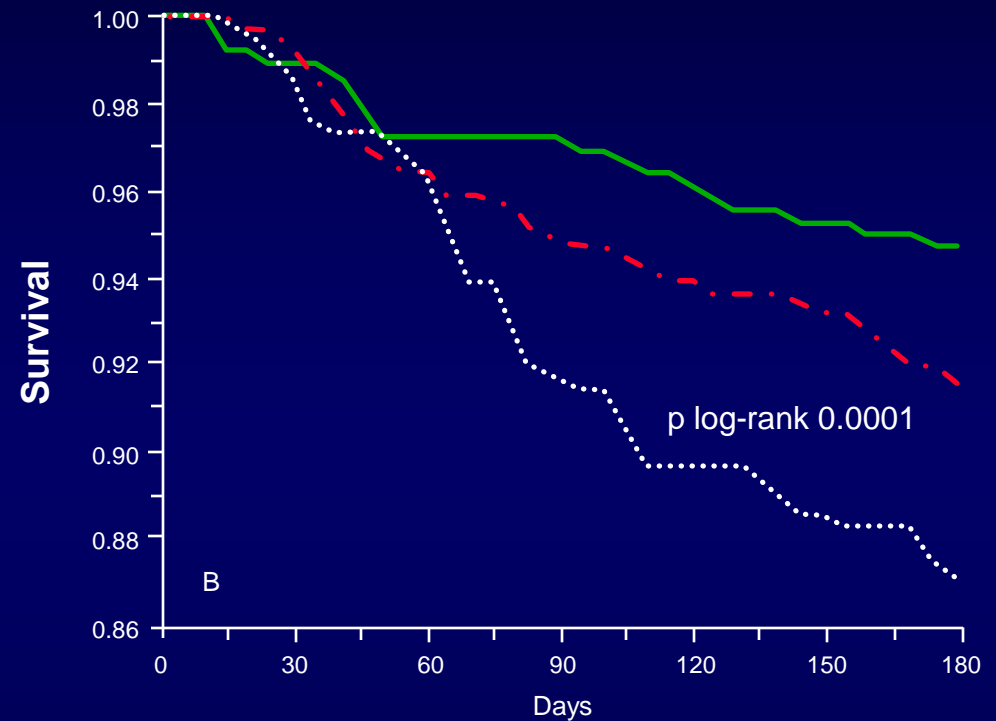
Survival After Acute MI

	N	EF	VPD
A	536	$\geq 30\%$	< 10/hr
B	113	$\geq 30\%$	≥ 10/hr
C	80	$< 30\%$	< 10/hr
D	37	$< 30\%$	≥ 10/hr

Survivorship

Year

Bigger JT. Am J Cardiol. 1986;57:12B.

Risk of Sudden Death: Data from GISSI-2 Trial

Patients without LV Dysfunction

Patients with LV Dysfunction

— No PVBs

-·- 1-10 PVBs/h

···· > 10 PVBs/h

Maggioni AP. Circulation. 1993;87:312-322.
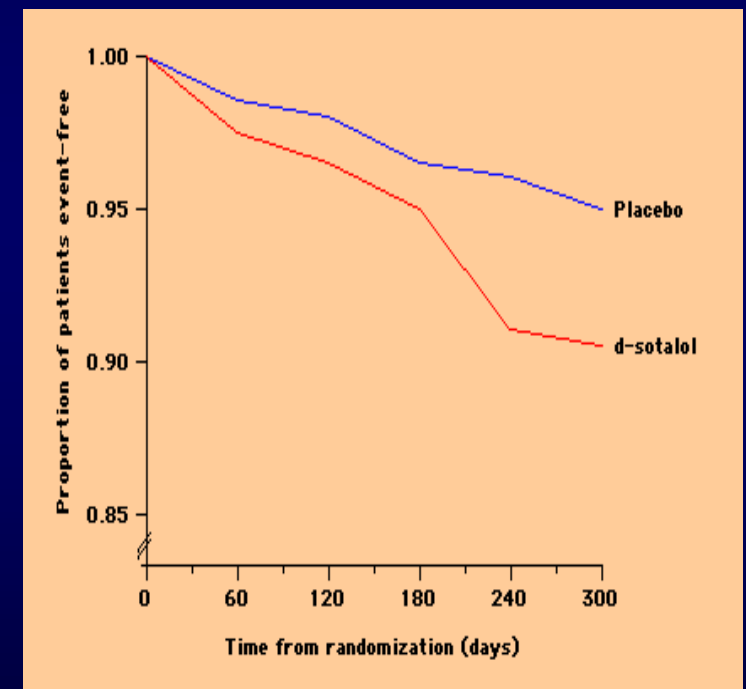
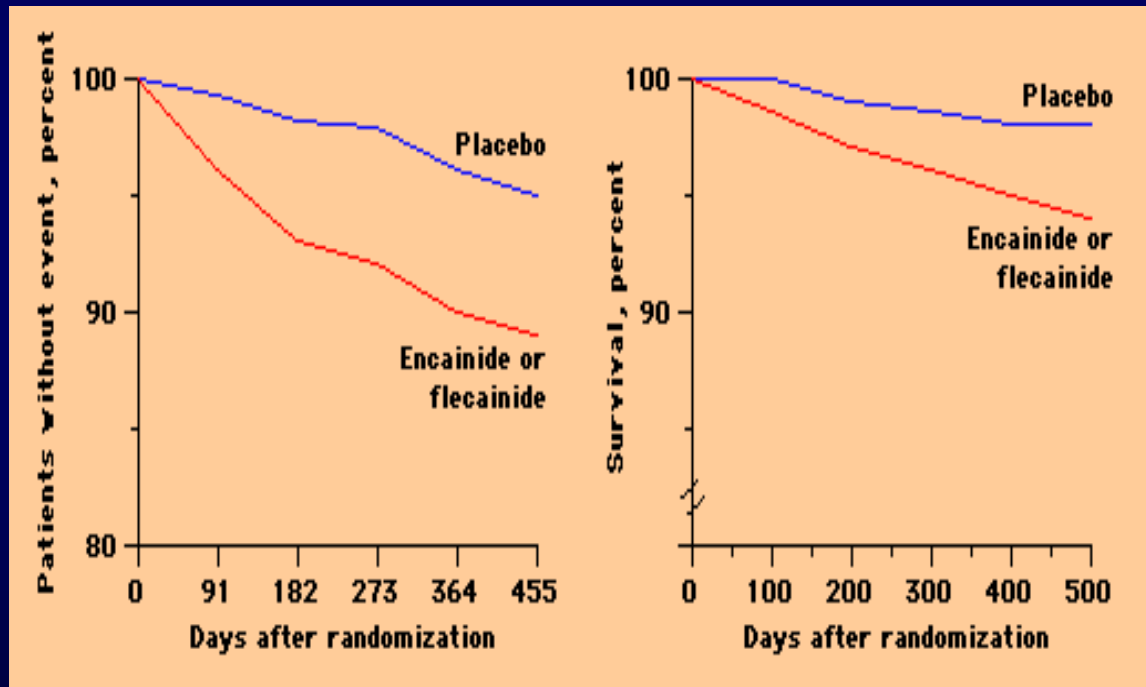# Prévention primaire de la MS

- **Beta bloqueurs**

- **IEC**

- **Revascularisation**

- **DAI**

Antiarrhythmic agents after MI CAST and SWORD Trials
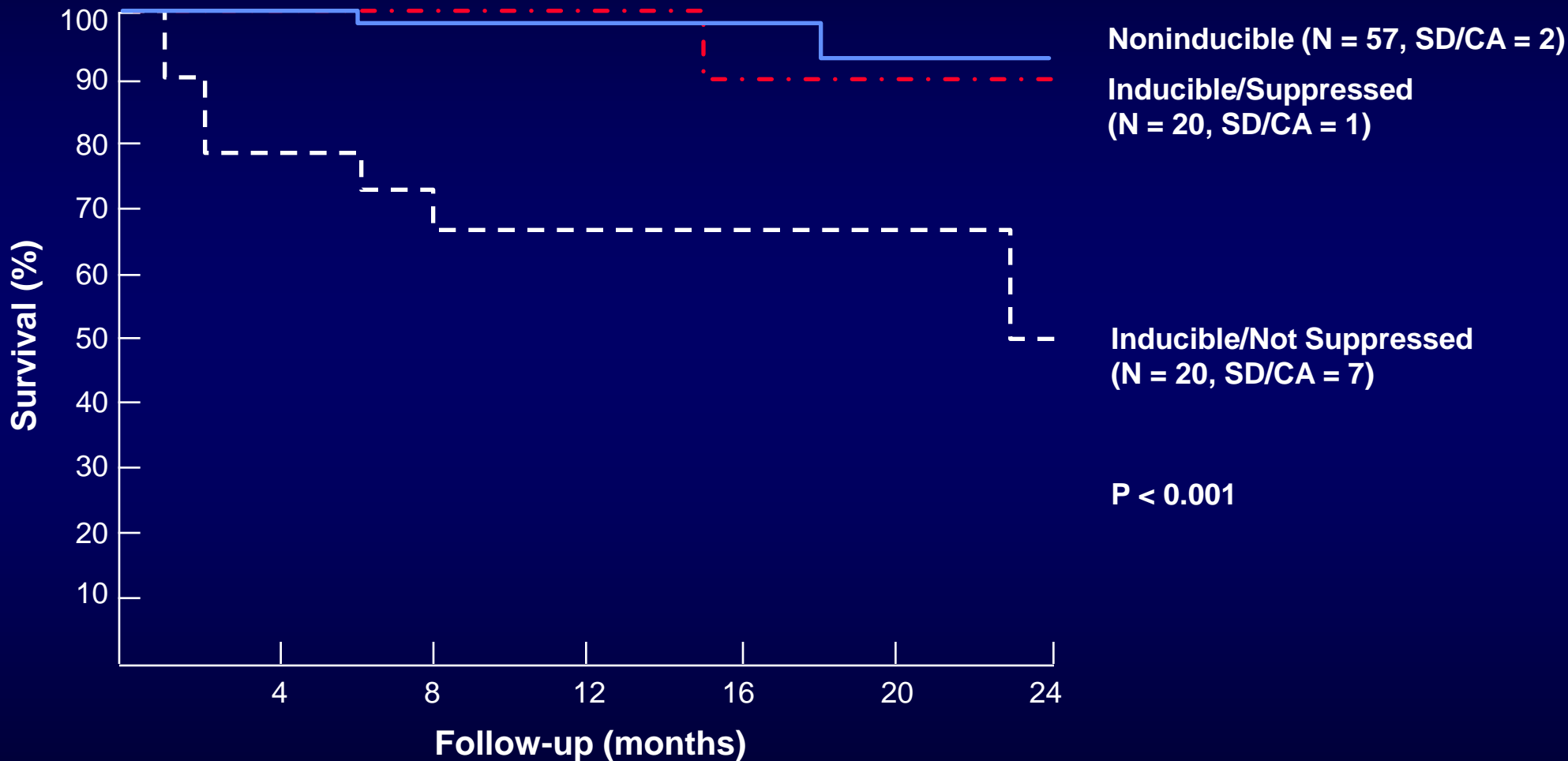
Death or RCA   Death   Death

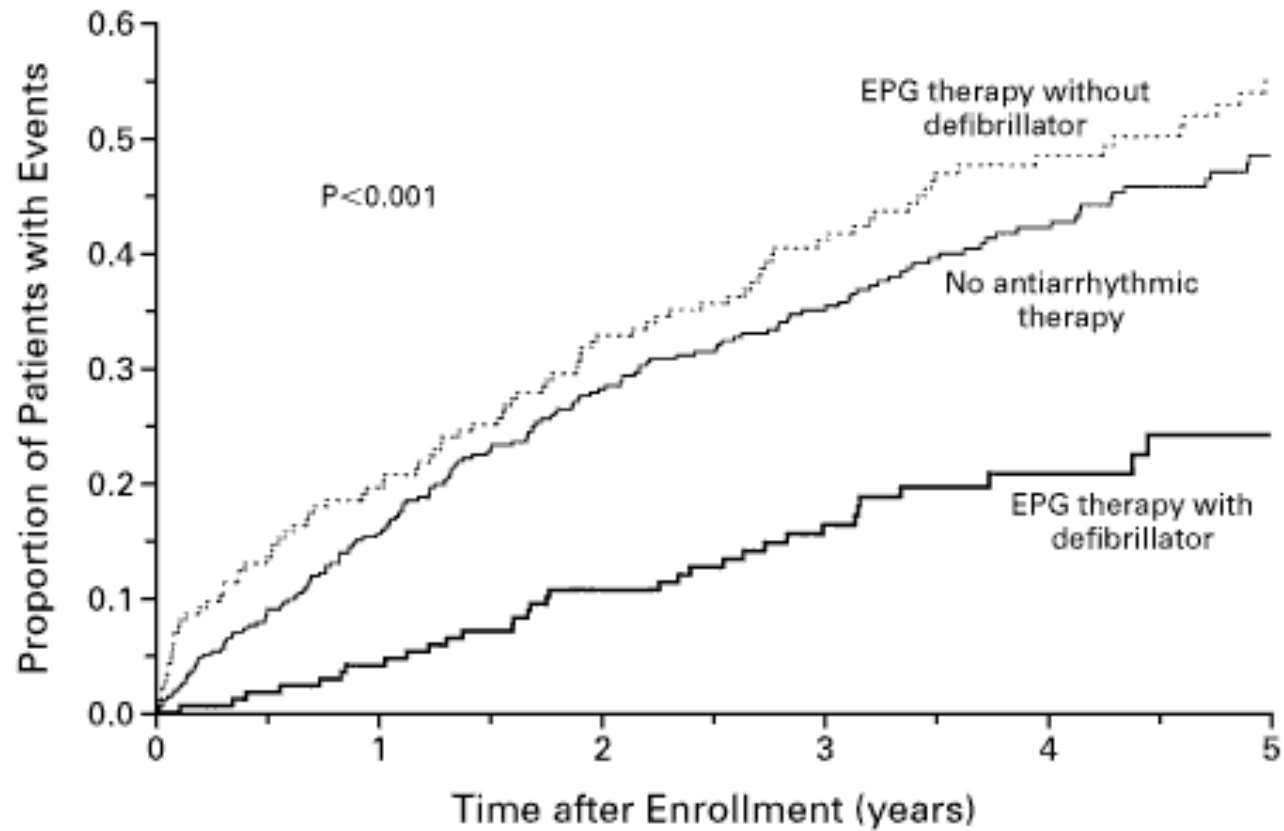N Engl J Med 1991; 324:781   Lancet 1996; 348:7.

Outcome of EP-Guided Antiarrhythmic Drug Therapy in Sudden Death Survivors

Noninducible (N = 57, SD/CA = 2)

Inducible/Suppressed (N = 20, SD/CA = 1)

Inducible/Not Suppressed (N = 20, SD/CA = 7)

P < 0.001

Survival (%)

Follow-up (months)

Wilber DJ. Circulation. 1990;82:350-358.

MUSTT, *NEJM 1999*

ATMA, Lancet 1997
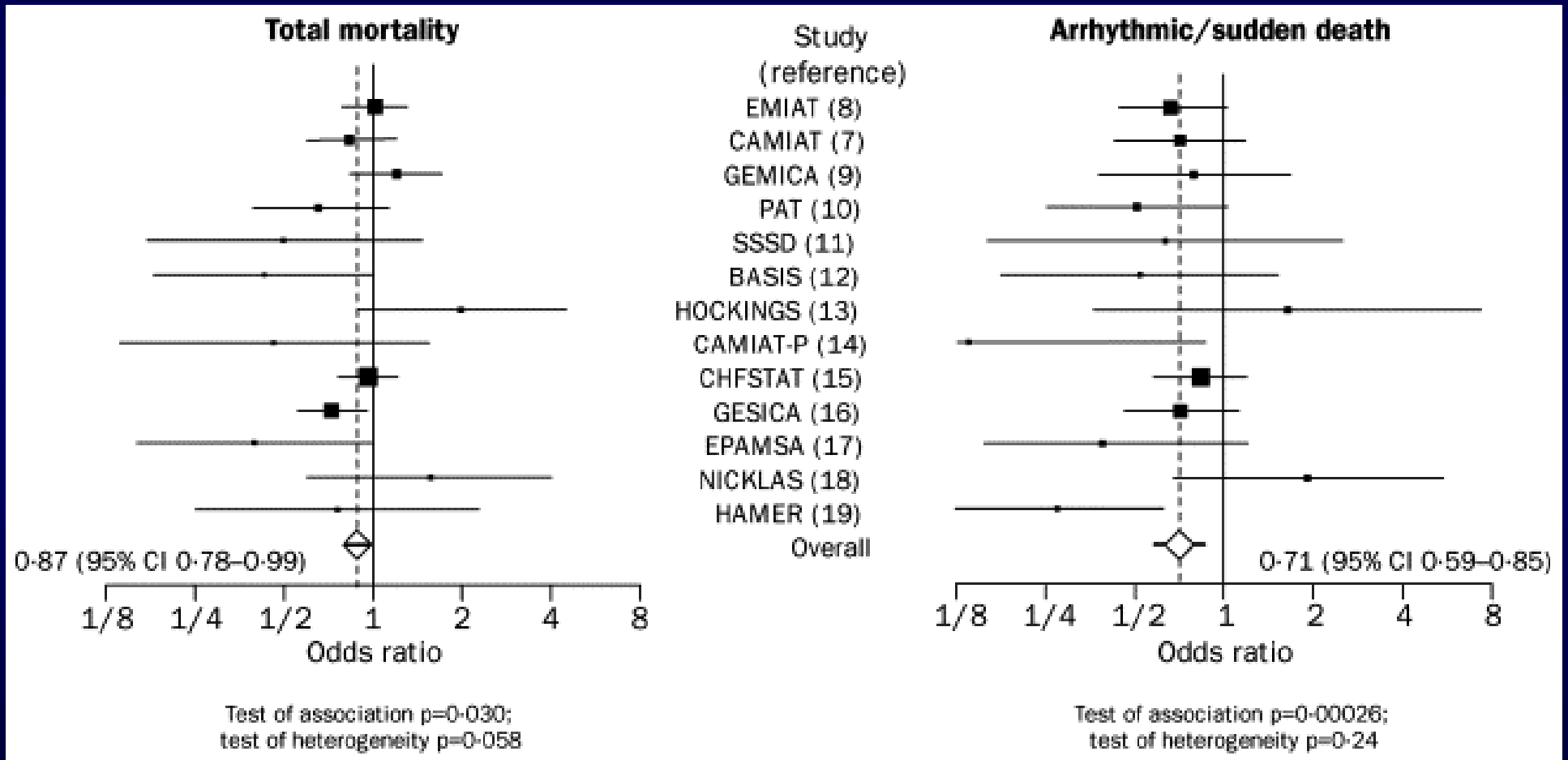
ATMA, Lancet 1997
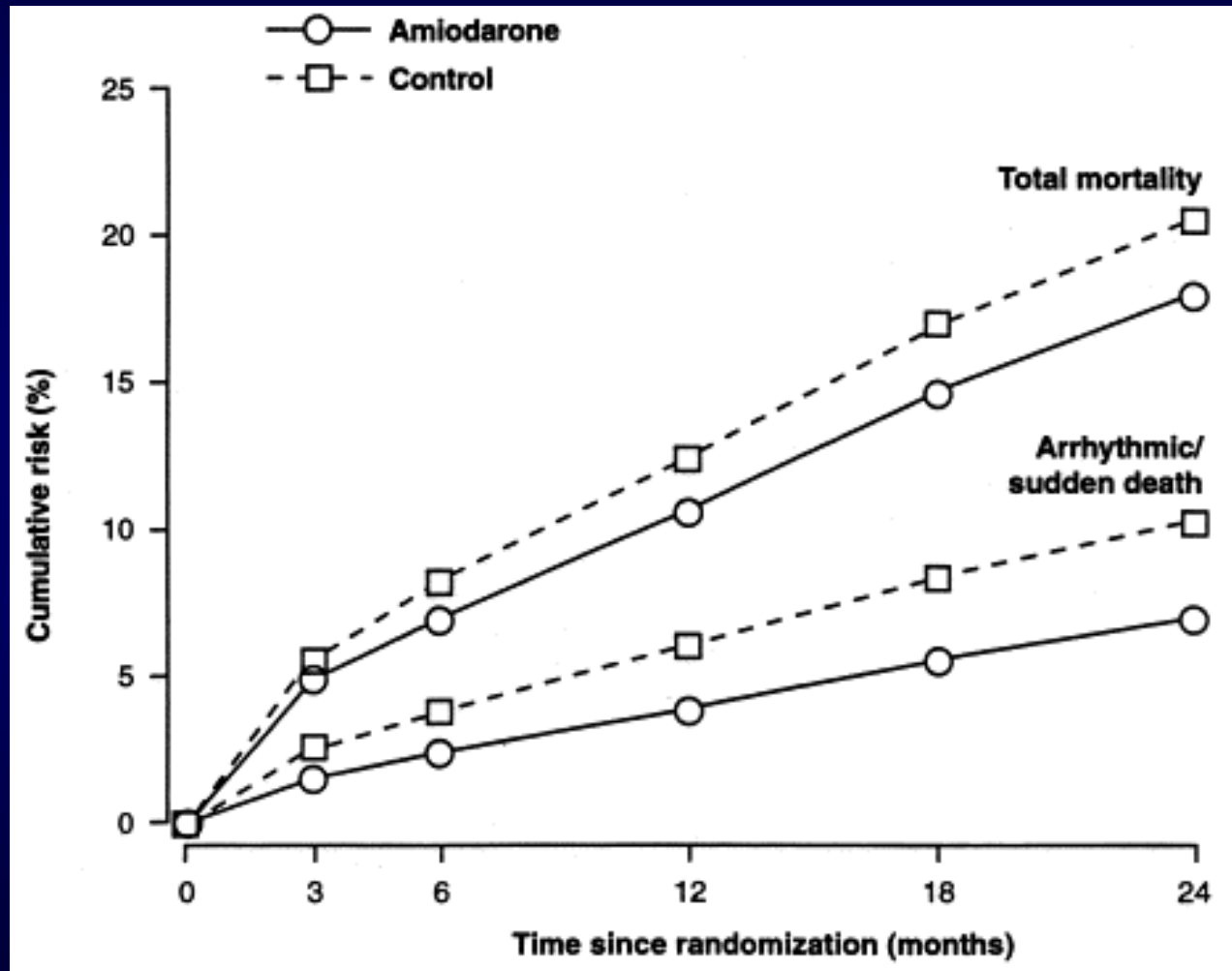
Amiodarone

- **Toxicity**
  - Pulmonary fibrosis
  - Hypo- or hyper-thyroidism
  - Liver failure
  - Bone marrow suppression
  - Renal failure
  - Photosensitivity
  - Corneal deposits

- **Side effects**
  - Myalgias
  - Gait disturbance
  - Insomnia
  - Prolongation of coagulation time (PT) (need to reduce coumadin dosage)
  - Digoxin toxicity (need to reduce digoxin dosage)

SCD Heft, *NEJM 2005*
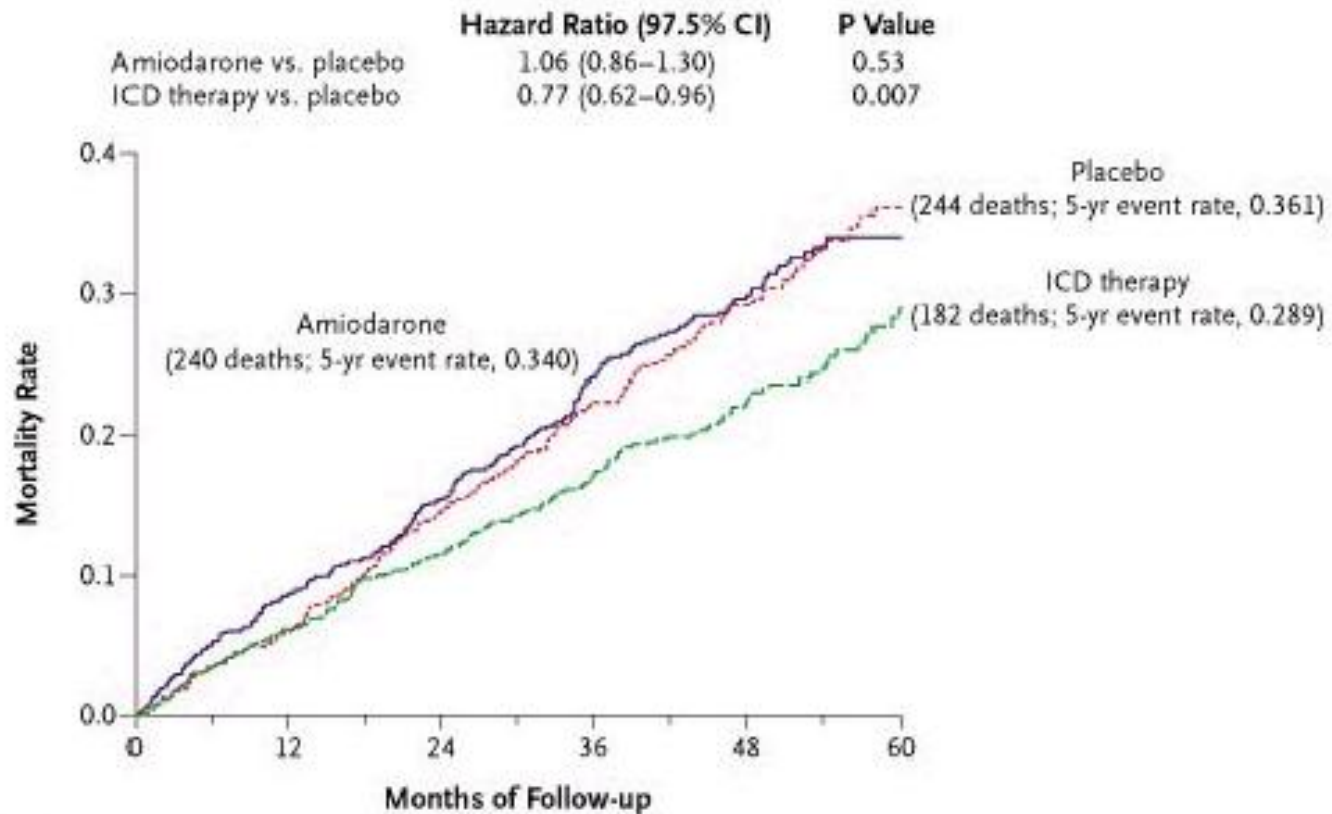
CHF - STAT, *NEJM 1995*
Amiodarone in HF Patients
with frequent ventricular arrhythmia.

OPTIC, *JAMA 2006*

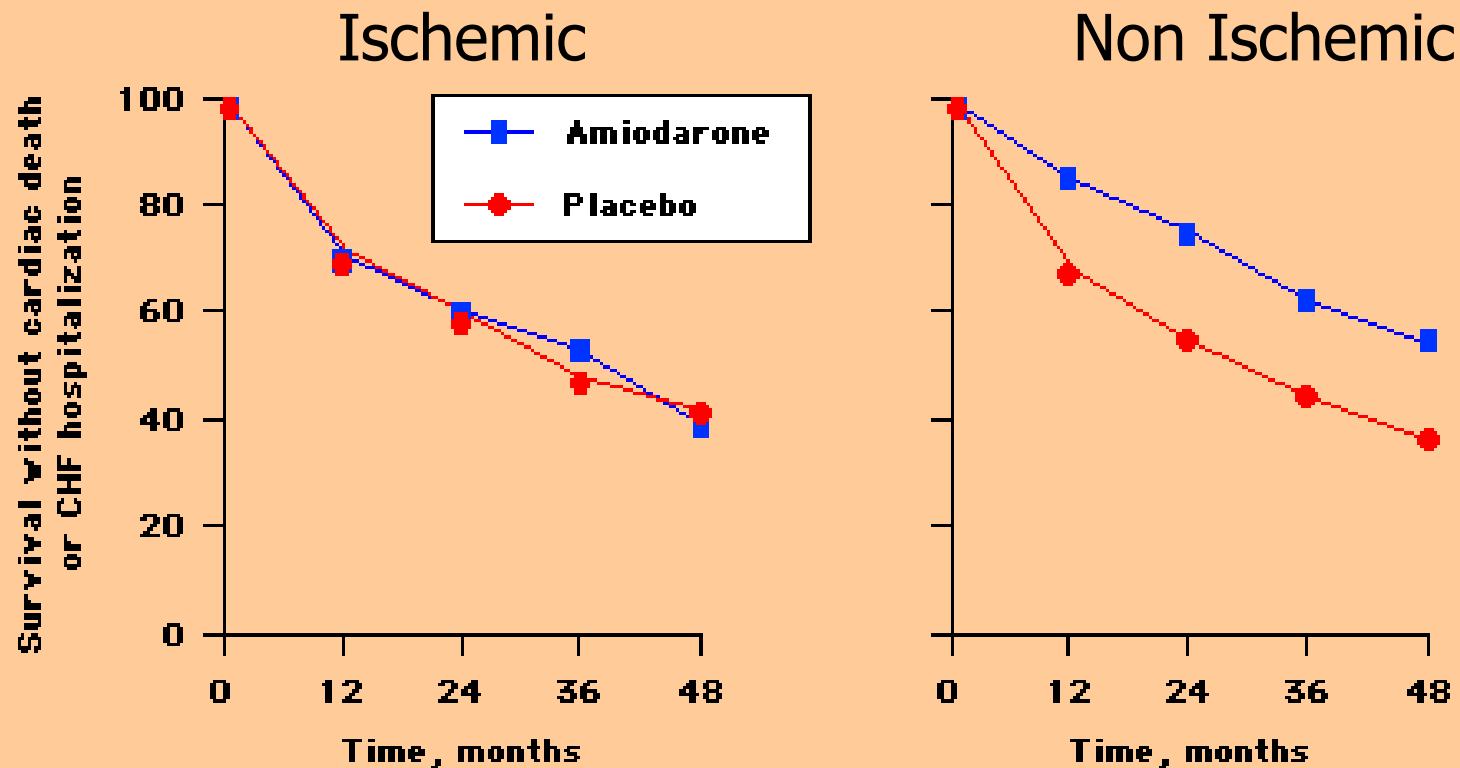|	Beta-blocker (n = 138)	Amiodarone + Beta-blocker (n = 140)	Sotalol (n = 134)
Any shock:			
Rate/year (%)	38.5	10.3	24.3
Hazard ratio		0.27	0.61
95% CI		0.14-0.52	0.37-1.01
P value		< .001	.055

	Beta-blocker (n = 138)	Amiodarone + Beta-blocker (n = 140)	Sotalol (n = 134)
Appropriate shock (%)			
Rate/year (%)	22.0	6.7	15.1
Hazard ratio		0.30	0.65
95% CI		0.14-068	0.36-1.24
P value		.0035	.18
Inappropriate shock			
Rate/year (%)	15.4	3.3	9.4
Hazard ratio		0.22	0.61
95% CI		0.07-0.64	0.29-1.20
P value		.0055	.20

Ttt médical préventif de la mort subite

- Amiodarone : seul AA diminuant la mort subite (totale ??). Peut-être équivalent au DAI chez patient avec FE >35 %.

- Tous les autres AA sont inefficaces et/ou délétères pour diminuer la mortalité

- Traitements non AA apportant le plus de bénéfice pour réduire la mortalité :
    - Béta bloqueurs
    - IEC
    - Spironolactone
    - Huile de poisson (?)
    - Statines

Beta Blockers and Risk of Death in HF

Table 5. Summary of Mortality Across Trials and Best Comparison Subgroup*

	CIBIS-II	COPERNICUS	MERIT-HF	BEST	BCG
n	2647	2289	3991	2708	1668
Number of deaths	384 (14.5%)	320 (14.0%)	362 (9.1%)	860 (31.8%)	494 (30.0%)
Average length of follow-up (years)	1.3	0.87	1.0	2.0	2.1
Annual placebo mortality (%)	13.2	19.7	11.0	16.7	16.1
Hazard ratio and 95% confidence interval					
Mortality	0.66 (0.54–0.81)	0.65 (0.52–0.81)	0.66 (0.53–0.81)	0.90 (0.78–1.02)	0.77 (0.65–0.92)
	$P < .0001$	$P = .0014$	$P < .0001$	$P = .1024$	$P = .0041$
Cardiovascular death	0.71 (0.56–0.90)	N/A	0.62 (0.50–0.78)	0.86 (0.74–0.99)	0.71 (0.58–0.86)
	$P = .0049$		$P = .00003$	$P = .041$	$P = .0005$
Sudden death	0.56 (0.39–0.80)	N/A	0.59 (0.45–0.78)	0.88 (0.72–1.07)	0.77 (0.59–0.999)
	$P = .0011$		$P = .0002$	$P = .206$	$P = .0488$
Pump failure death	0.74 (0.48–1.14)	N/A	0.51 (0.33–0.79)	0.85 (0.67–1.08)	0.64 (0.45–0.91)
	$P = .17$		$P = .0023$	$P = .188$	$P = .0127$

BEST, β-Blocker Evaluation of Survival Trial; BCG, BEST Comparison Subgroup; CIBIS-II, Cardiac Insufficiency Bisoprolol Study-II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; MERIT-HF, Metoprolol Intervention Trial in Congestive Heart Failure Trial; N/A, not ap-

Domanski et al, *J Card Fail 2003*

Beta Blockers in SCD

The mode of action of beta blockers is not completely understood, but includes:

- Direct sympathetic blockade

- A membrane stabilizing effect

- A reduction in ischemic potential

- An increase in heart rate variability and baroreflex sensitivity

- A shorter corrected QT interval

- Prevention of stress-induced hypokalemia

IEC et prévention de MS en post IDM
Domanski et al, *JACC 1999*

	Sample Size		Sudden Cardiac Death		
	ACE	Placebo	ACE	Placebo	OR (95% CI)
Mortarino[26]	10	11	0	0	1.10 (0.02–60.30)
Oldroyd[24]	49	50	4	4	1.02 (0.26–4.02)
Nabel[17]	20	18	0	1	0.29 (0.27–7.44)
Sharpe[25]	50	50	3	2	1.43 (0.27–7.61)
SMILE[14]	772	784	4	11	0.39 (0.13–1.18)
EDI[20]	47	42	0	0	0.90 (0.02–46.09)
ECCE[18]	104	104	1	0	3.03 (0.12–75.22)
CONSENSUS 2[15]	3044	3046	86	88	0.98 (0.72–1.32)
SAVE[5]	1115	1116	105	125	0.83 (0.63–1.08)
AIRE[7,16]	1004	982	89	121	0.69 (0.52–0.93)
PRACTICAL[19]	150	75	5	4	0.60 (0.17–2.16)
Søgaard[21]	29	29	1	0	3.11 (0.12–79.43)
CATS[22]	149	149	3	4	0.77 (0.19–3.18)
TRACE[6]	876	873	105	133	0.76 (0.58–1.00)
EDEN[23]	239	117	1	0	1.48 (0.06–36.56)
Overall	7658	7446	407	493	0.80 (0.70–0.92)
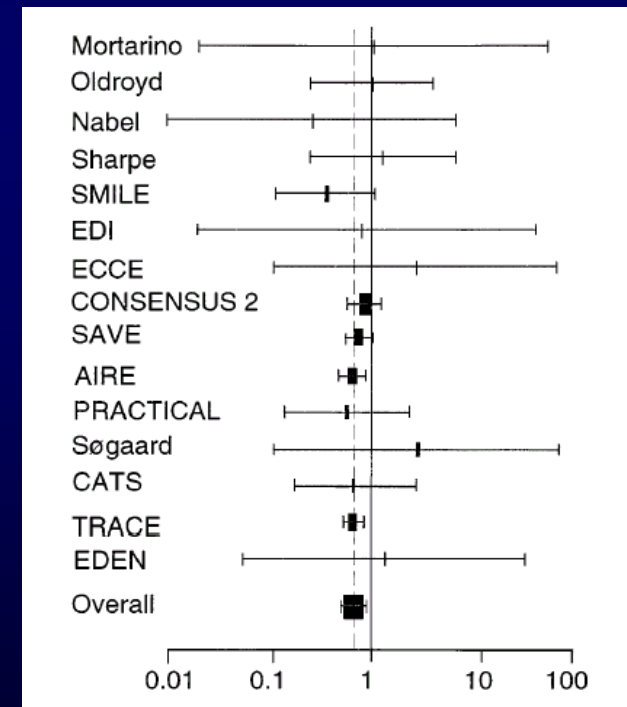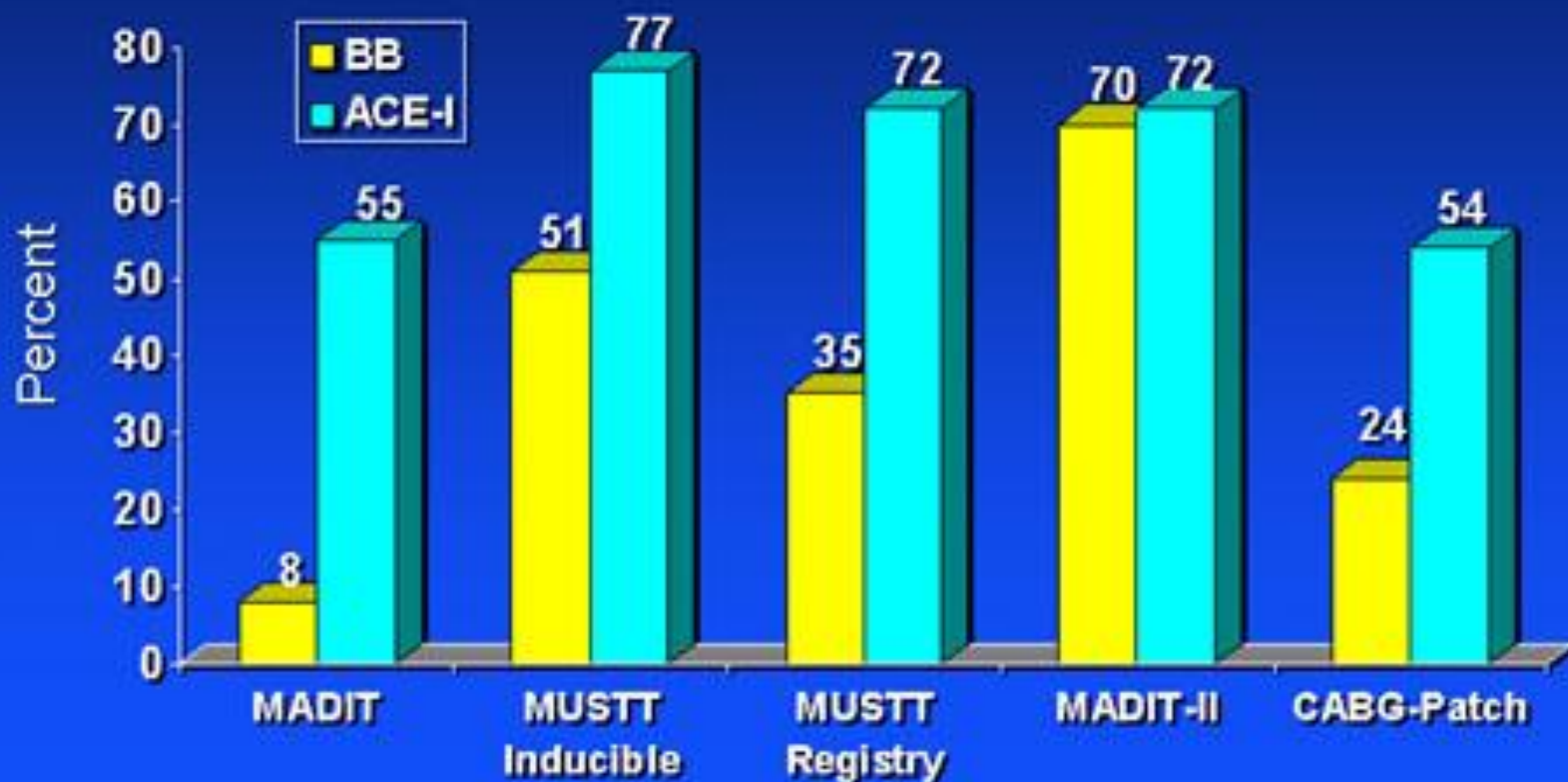
GISSI-Prevenzione trial. *Lancet 1999*

	All (n=11 324)	n-3 PUFA (n=5666)	Control (n=5668)	Relative risk (95% CI)
		Two-way analysis		
Main endpoints				
Death, non-fatal MI, and non-fatal stroke	1500 (13·3%)	715 (12·6%)	785 (13·9%)	0·90 (0·82–0·99)
Cardiovascular death, non-fatal MI, and non-fatal stroke	1155 (10·2%)	547 (9·7%)	608 (10·8%)	0·89 (0·80–1·01)
Secondary analyses				
All fatal events	1017 (9·0%)	472 (8·3%)	545 (9·6%)	0·86 (0·76–0·97)
Cardiovascular deaths	639 (5·6%)	291 (5·1%)	348 (6·2%)	0·83 (0·71–0·97)
Cardiac death	520 (4·6%)	228 (4·0%)	292 (5·2%)	0·78 (0·65–0·92)
Coronary death	479 (4·2%)	214 (3·8%)	265 (4·7%)	0·80 (0·67–0·96)
Sudden death	286 (2·5%)	122 (2·2%)	164 (2·9%)	0·74 (0·58–0·93)
Other deaths	378 (3·3%)	181 (3·2%)	197 (3·5%)	0·91 (0·74–1·11)
Non-fatal cardiovascular events	578 (5·1%)	287 (5·1%)	291 (5·1%)	0·98 (0·83–1·15)

GISSI-Prevenzione trial. *Lancet 1999*

Pharmacological therapy

Antiplatelet drugs

Baseline	2601 (92·2%)
6 months	2308 (88·2%)
42 months	1707 (83·4%)

Angiotensin-converting-enzyme inhibitors

Baseline	1298 (46·0%)
6 months	1033 (39·5%)
42 months	788 (38·5%)

β-blockers

Baseline	1237 (43·9%)
6 months	1092 (41·7%)
42 months	807 (39·4%)

Cholesterol-lowering drugs

Baseline	124 (4·4%)
6 months	782 (28·6%)
42 months	1003 (46·0%)

Revascularisation procedures*

CABG or PTCA

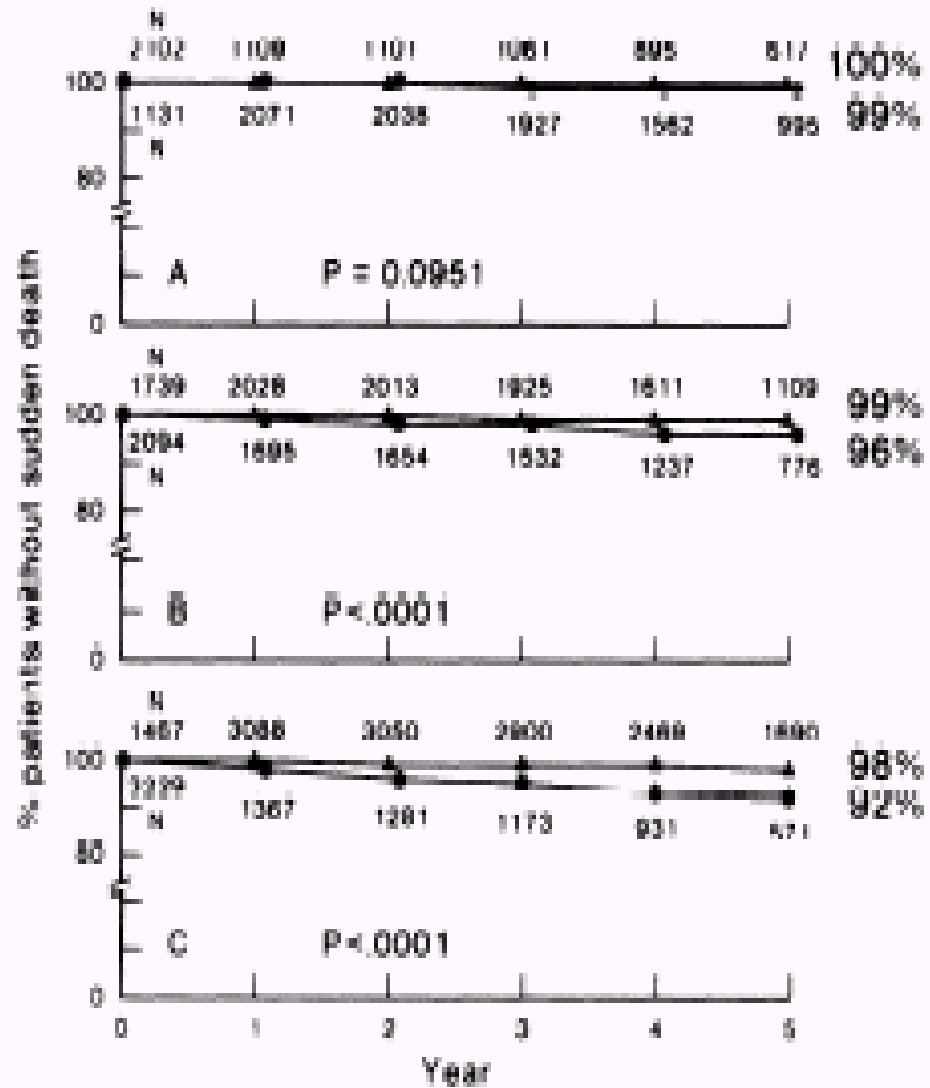|	
Baseline	135 (4·8%)
6 months	433 (15·3%)
42 months	689 (24·3%)

Revascularisation

- La revasculariation (par pontage) ne diminue pas l'incidence de récidive de TV / FV sauf en cas de relation directe documentée d'un événement avec l'ischémie.
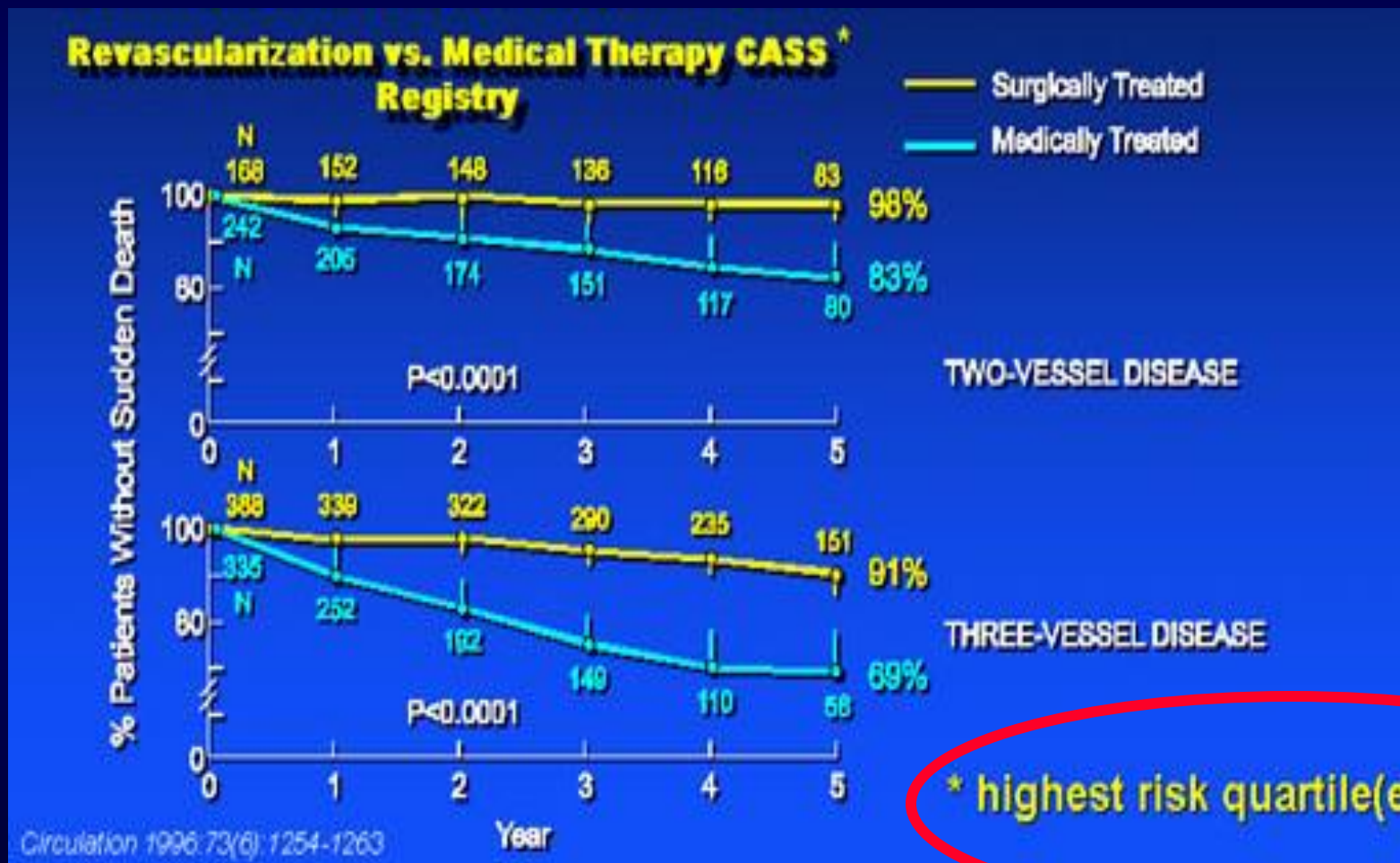
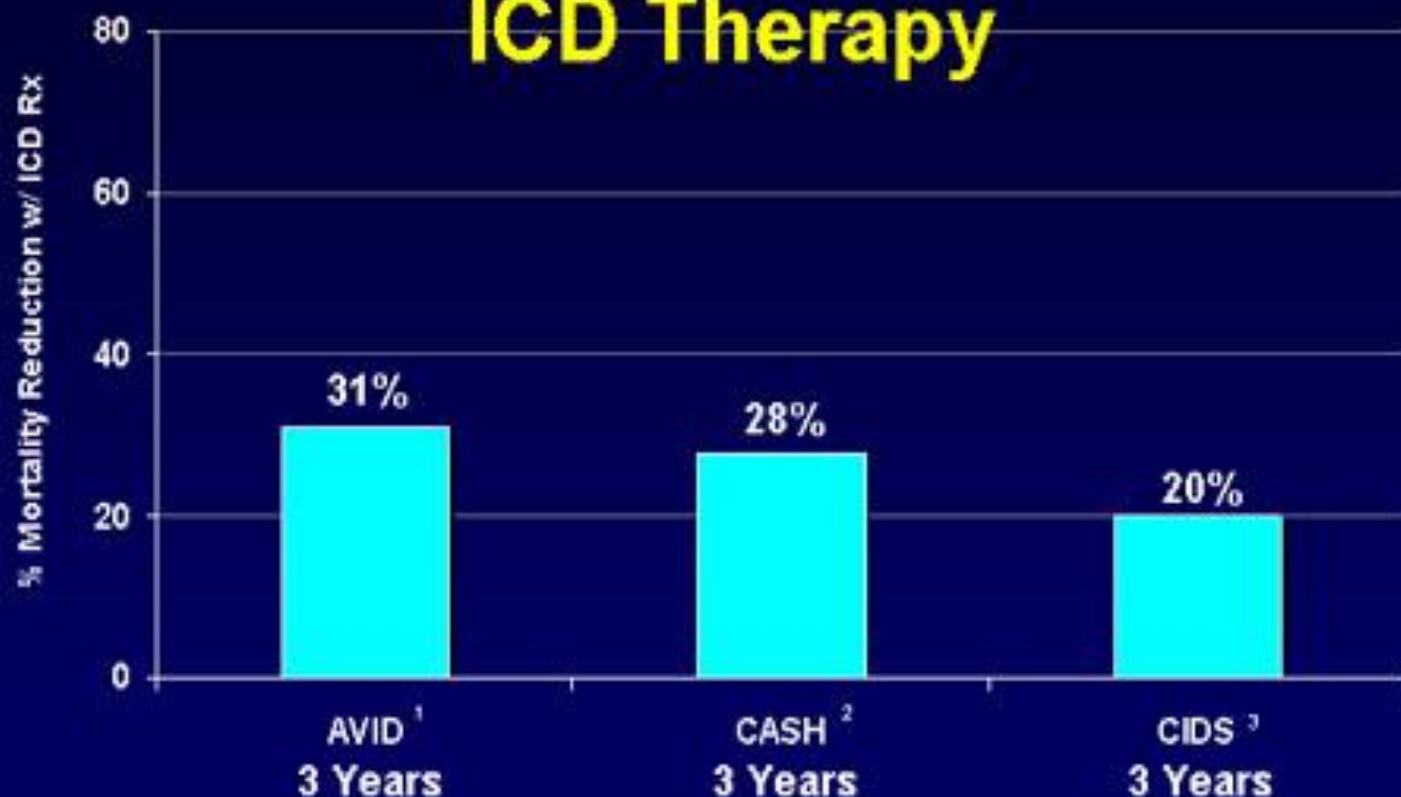# CASS Registry *Circulation 1986*

1 trc

2 trc

3 trc

CASS : Coronary Artery Surgery Study

Revascularization vs. Medical Therapy CASS * Registry

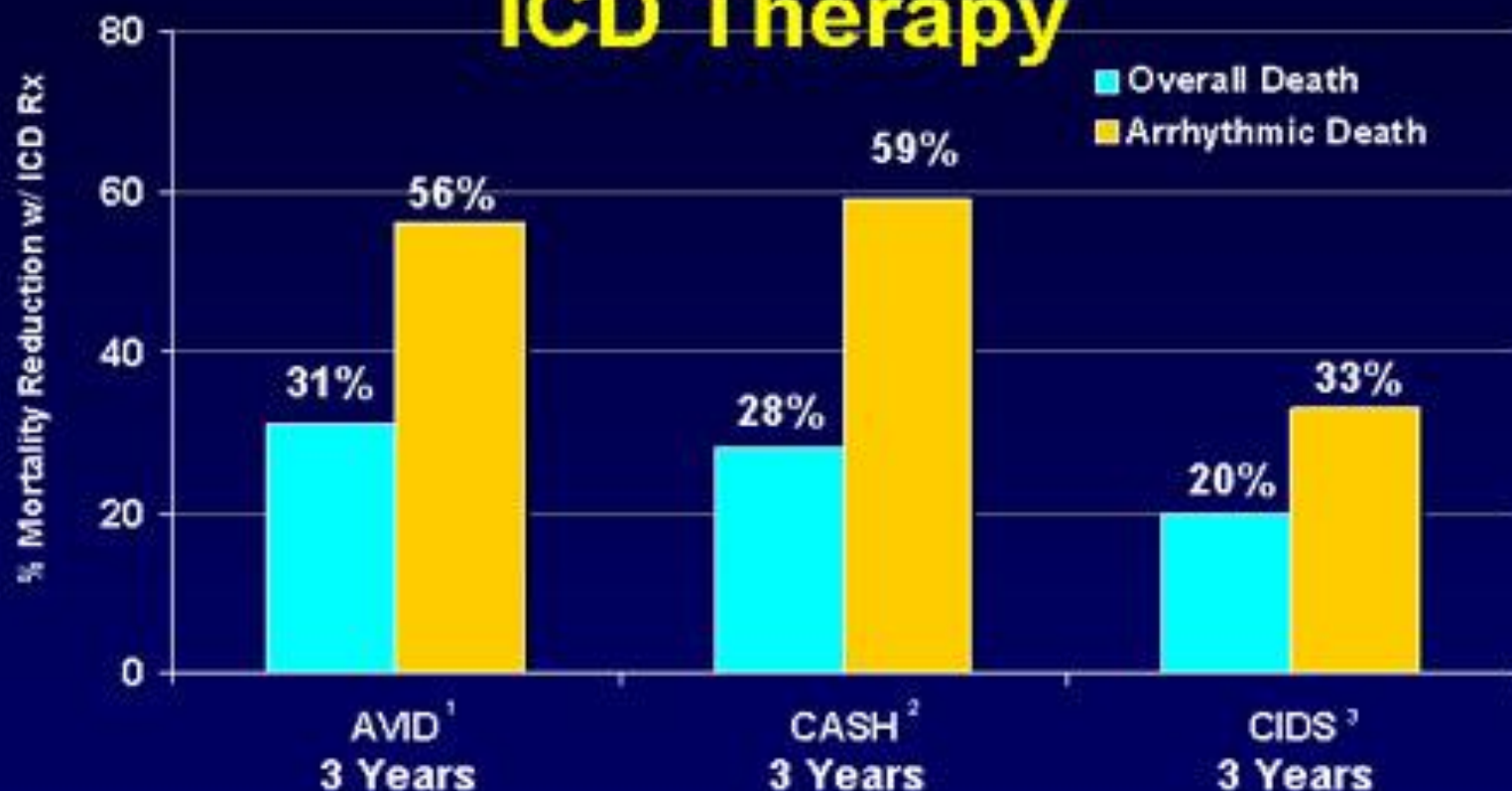Secondary Prevention Trials: Reduction in Overall Mortality with ICD Therapy

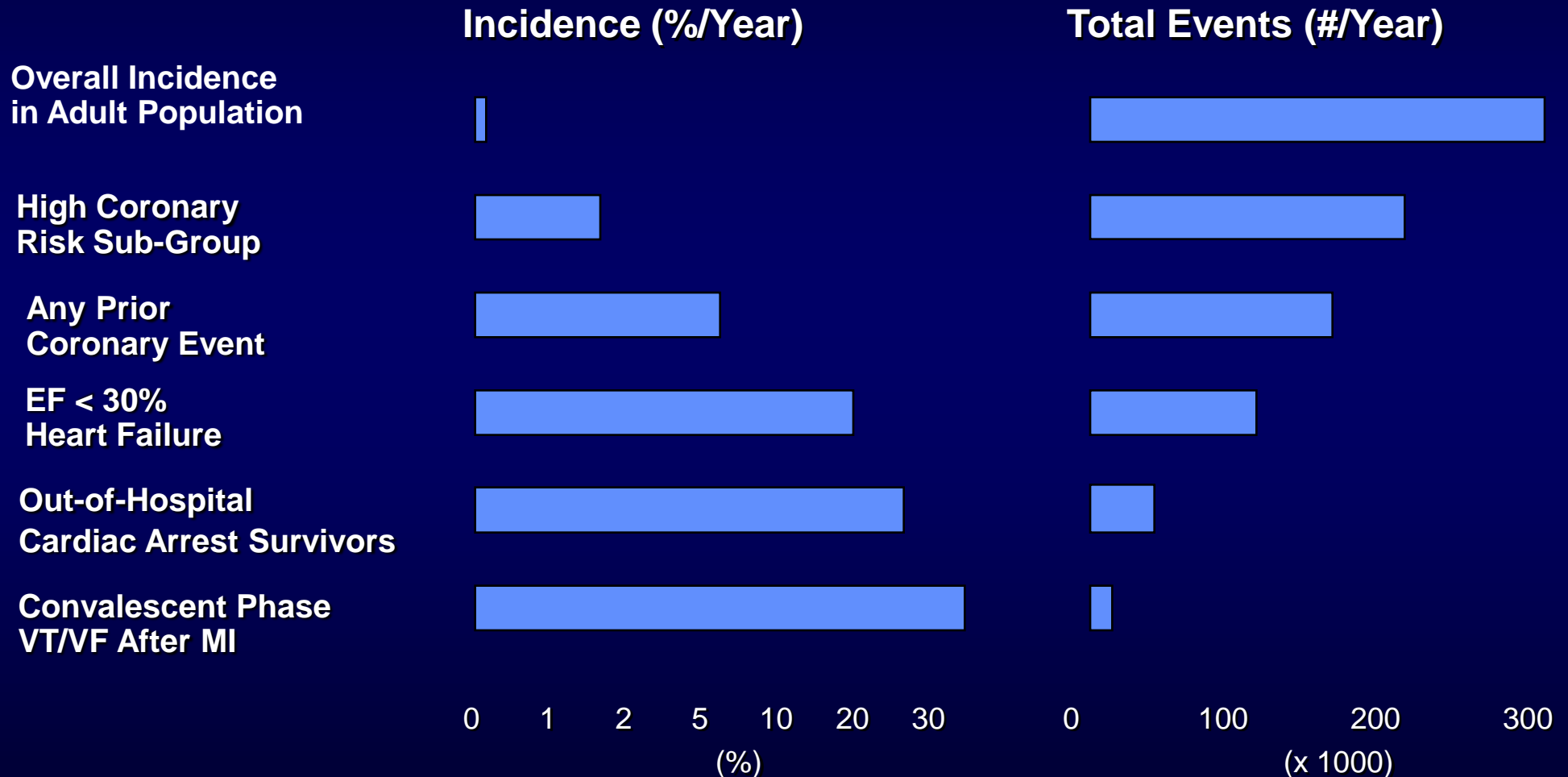[1] The AVID Investigators. N Engl J Med. 1997;337:1576-83.
[2] Kuck K. Circ. 2000;102:748-54.
[3] Connolly S. Circ. 2000;101:1297-1302.

Secondary Prevention Trials: Reduction in Mortality with ICD Therapy

"Climat" au début des études de prévention primaire avec DAI (1990...)

- Incertitude sur le bénéfice du DAI (vs chirurgie des TV, EEP sériées sous AA...)

- DAI épicardique (mortalité op. 4-5 %)

- Etudes de prévention secondaire non publiées

- Etudes de prévention primaire jugées non éthiques par beaucoup

Sudden Cardiac Death
Incidence and Total Events

Incidence (%/Year) **Total Events (#/Year)**

Overall Incidence
in Adult Population

High Coronary
Risk Sub-Group

Any Prior
Coronary Event

EF < 30%
Heart Failure

Out-of-Hospital
Cardiac Arrest Survivors

Convalescent Phase
VT/VF After MI

	0	1	2	5	10	20	30

(%)

	0	100	200	300

(x 1000)

Source: Myerburg RJ. Circulation. 1992;85(suppl I):I-2 – I-10.

MADIT / MUSTT / MADIT II / CABG-Patch

Patient Inclusion Criteria	MADIT	MUSTT	MADIT-II	CABG-Patch
CAD/Post-MI	X	X	X	X
Low LVEF	X (≤35%)	X (≤40%)	X (≤30%)	X (≤36%)
SAECG				X
NSVT	X	X		
Inducible VT on EPS	X	X		
Inducible, non-suppressible VT on EPS	X			

CABG Patch Trial (*Bigger Jr, NEJM 1997*)
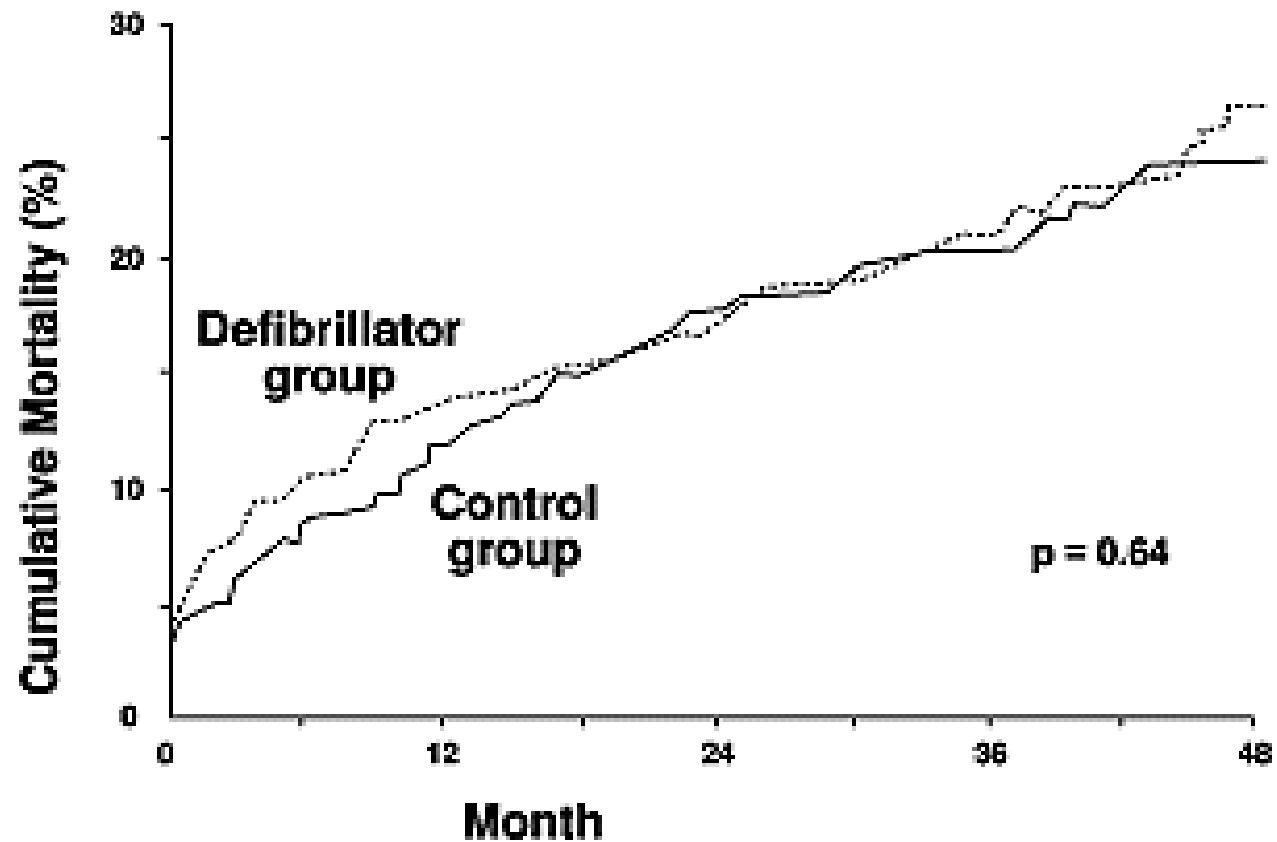
Defibrillator group	446	384	313	213	61
Control group	454	389	308	199	57

CABG Patch Trial (*Bigger Jr, NEJM 1997*)
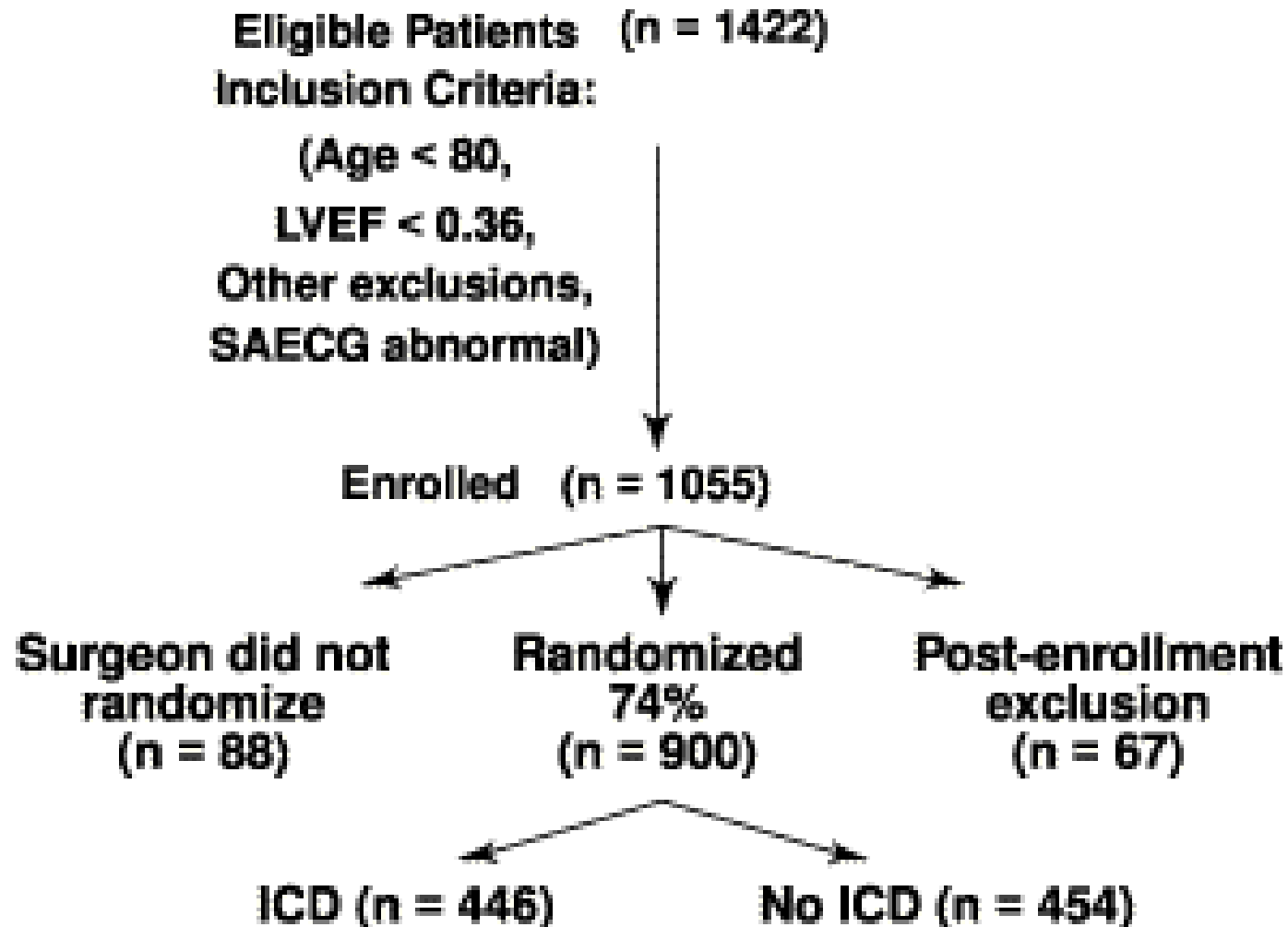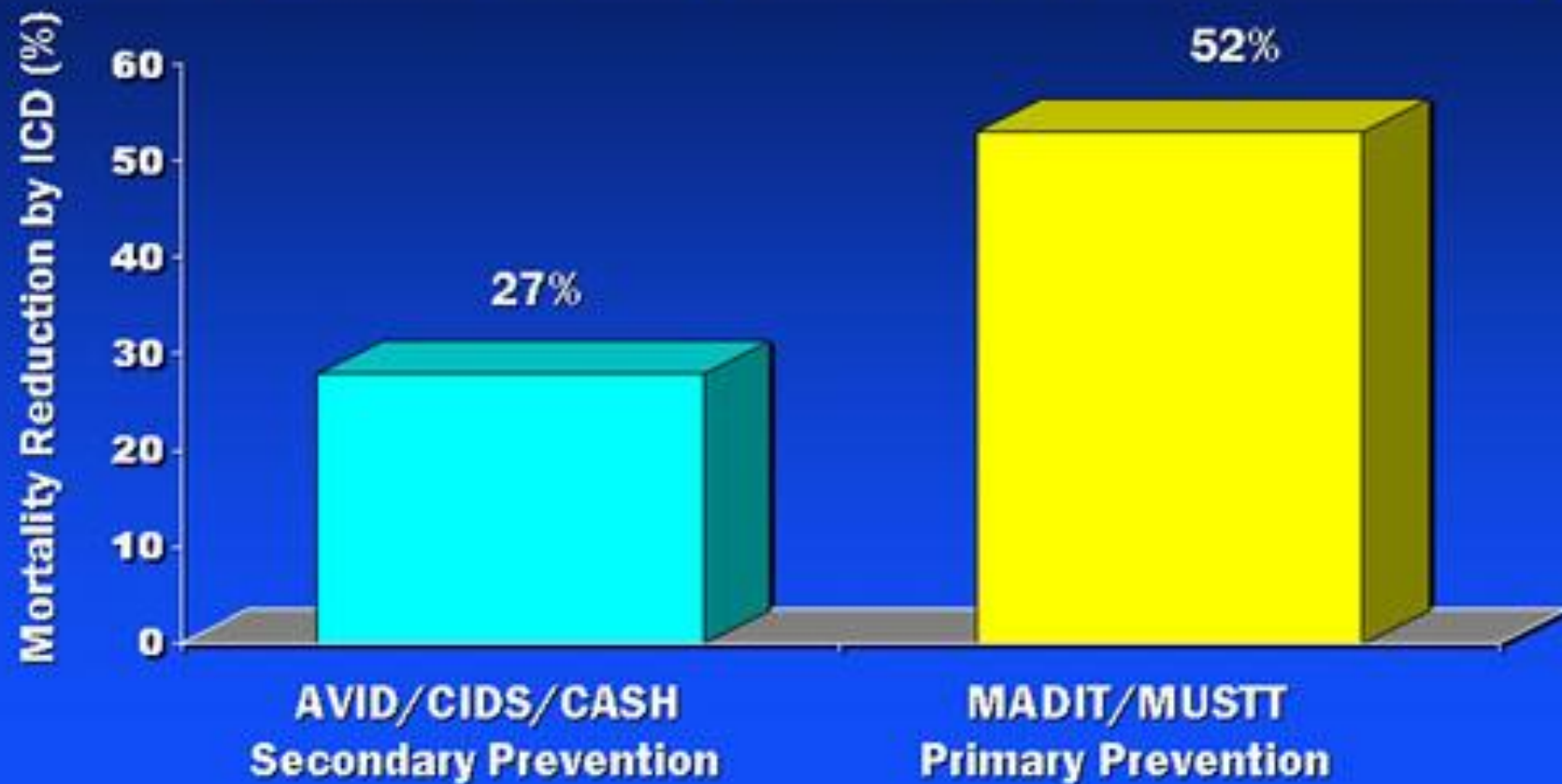
SCD HeFT: Design

- Enrollment Criteria:
  - Ejection Fraction <36%
  - Ischemic or idiopathic Dilated Cardiomyopathy
  - Class II, III CHF

- Randomization:
  - Standard CHF Therapy + Placebo
  - Standard CHF Therapy + Amiodarone
  - Standard CHF Therapy + ICD

- Statistical Assumptions:
  - Mortality with conventional therapy 25%
  - Planned enrollment 2500 pts; fixed sample size
  - 2.5 yr follow-up

SCD Heft, *NEJM 2005*
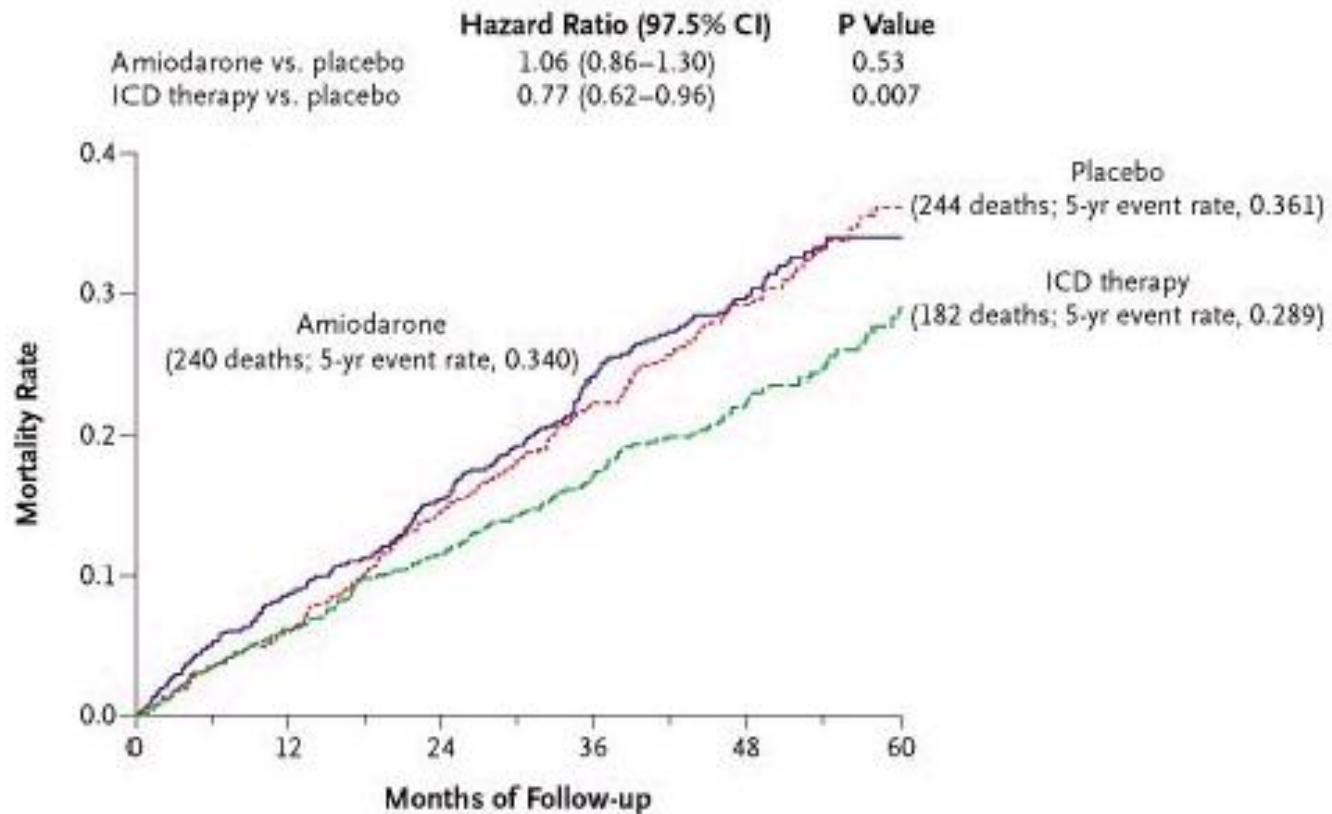
Sanders, *NEJM 2005*

Table 1. Health and Economic Outcomes of the Prophylactic Implantation of an ICD as Compared with Control Therapy.*

Trial and Strategy	Cost	Increase in Cost Related to ICD	Life Expectancy	Increase in Life Expectancy Related to ICD	QALY	Increase in QALY Related to ICD	Incremental Cost-Effectiveness		
							$/Life-Yr	Baseline Efficacy	High Efficacy
	$			year					$/QALY
MADIT I									
Control	38,300		4.06		2.98				
ICD	130,400	92,100	7.70	3.64	5.62	2.64	25,300	34,900	27,000
CABG Patch									
Control	78,600		8.41		6.13				
ICD	134,400	55,700	8.01	(0.40)	5.84	(0.29)	Dominated	Dominated	84,200
MUSTT									
Control	44,300		4.72		3.46				
ICD	145,800	101,500	8.86	4.14	6.45	2.99	24,500	34,000	28,800
MADIT II									
Control	57,500		6.16		4.51				
ICD	136,900	79,400	8.20	2.03	5.98	1.47	39,000	54,100	37,200
DEFINITE									
Control	84,400		9.03		6.57				
ICD	184,900	100,500	11.75	2.73	8.53	1.96	36,800	51,300	34,500
DINAMIT									
Control	88,300		9.44		6.87				
ICD	147,200	58,800	8.96	(0.48)	6.53	(0.34)	Dominated	Dominated	70,900
COMPANION									
Control	37,800		4.01		2.95				
ICD	106,100	68,300	5.88	1.87	4.31	1.36	36,500	50,300	36,100
SCD-HeFT									
Control	57,800		6.19		4.53				
ICD	128,800	71,000	7.59	1.40	5.54	1.01	50,700	70,200	45,600

Données épidémiologiques
Insuffisance cardiaque

Insuffisance Cardiaque
Prévalence 1 à 2 %
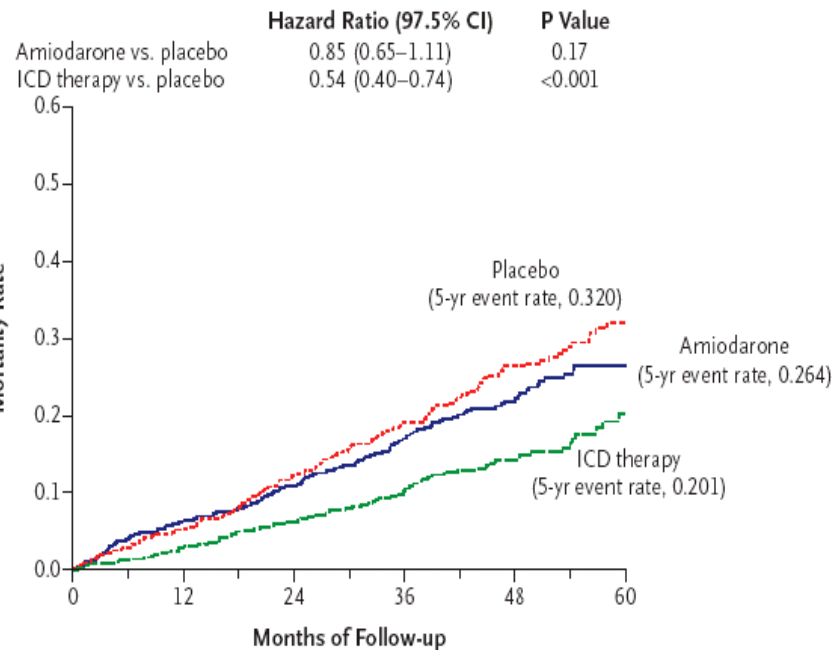
Mortalité annuelle
12 - 15 % classe I - 60 % classe IV

Mortalité rythmique
50 à 60 % classe I - II - 20 à 30 % classe IV
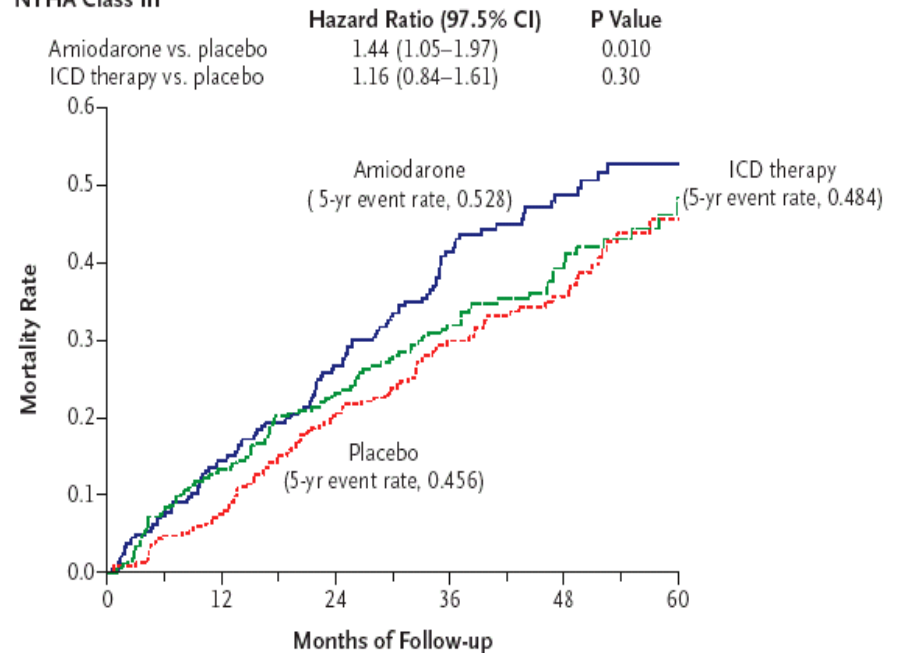
SCD Heft, *NEJM 2005*

SCD Heft, *NEJM 2005*

Other Noninvasive Evaluations

- **QT or JT dispersion** - measured as interlead variability of QT or JT intervals on the surface ECG

- **Repolarization (T wave) alternans (RPA)** - refers to a variability in the timing or morphology of repolarization that occurs in alternate beats on the surface electrocardiogram

- **Heart rate (RR) variability** - measurements provide a low-cost, widely-available method for assessing the status of the parasympathetic/sympathetic nervous system

Identification des patients à risque de mort subite dans l'insuffisance cardiaque

Paramètres	Analyse univariée	Multivariée	Controversée
Maladie coro.	X	X	X
Syncope	X	X	
TVS/FV doc.	X		
TVNS	X	X	X
Variabilité sinusale	X	X	X
Dispersion QT	X	X	X
Dispersion QRS	X	X	
Alternance onde T	X	X	
Hyponatrémie	X	X	X
FeVG	X	X	X
Index cardiothorac.	X		

DINAMIT

. IDM < 6-30 j, FE VG < 35%,

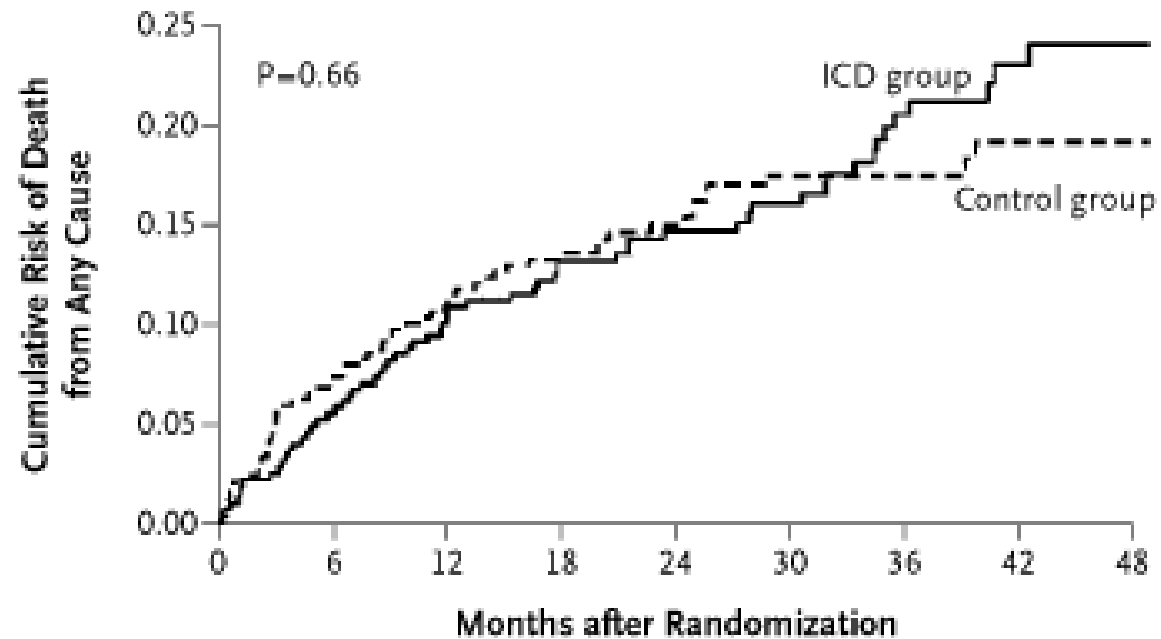. FC > 80/ ' ou SDNN < 70ms,

ttt med_   ttt med
(IEC, Beta B…)   + Def AI

. Critère principal : mortalité globale

Critères 2^{aires} : coûts, qualité de vie,...

. N > 625, suivi > 2 ans
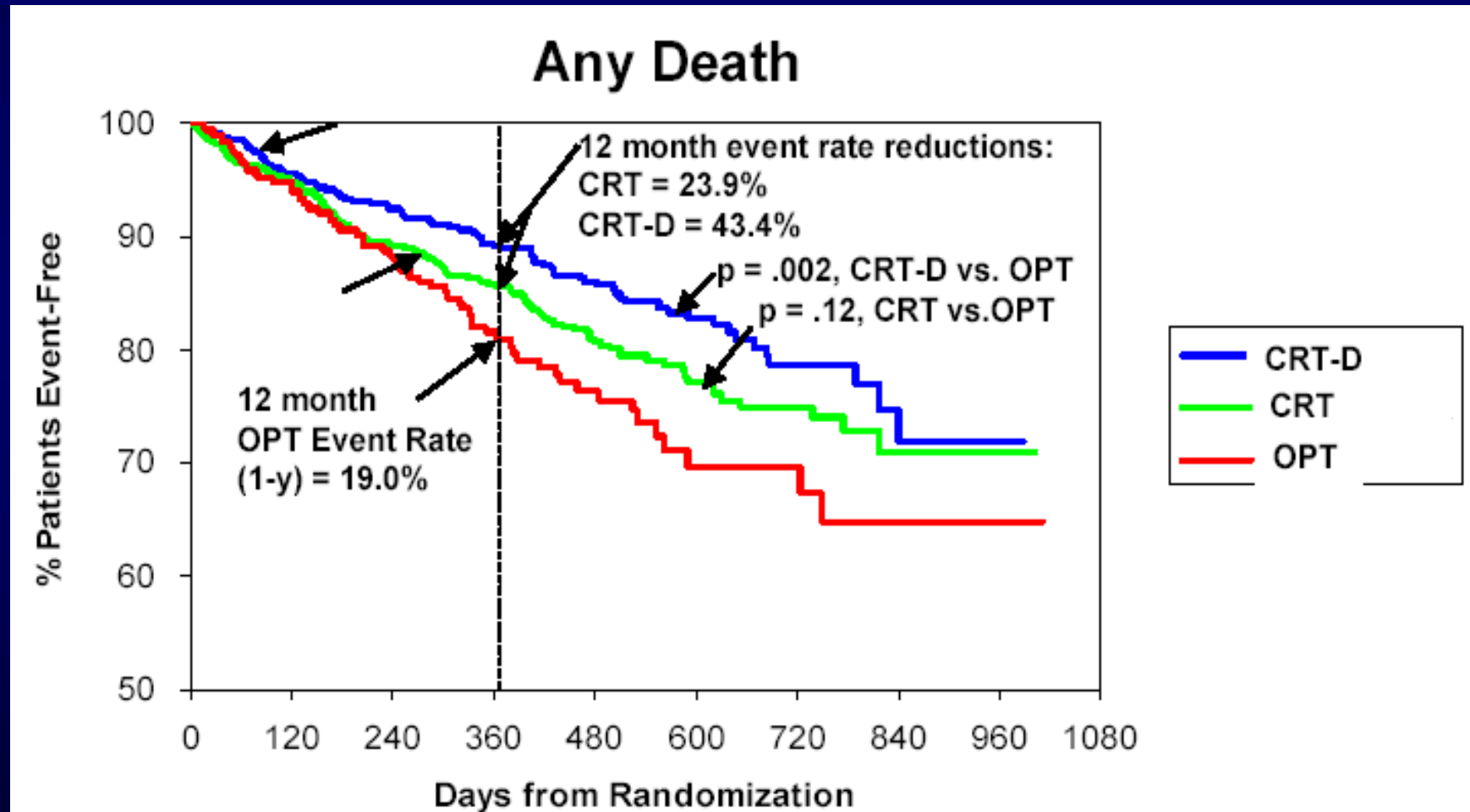
DINAMIT - *NEJM 2004*

P=0.66

Cumulative Risk of Death from Any Cause (y-axis: 0.00 to 0.25)

ICD group

Control group

Months after Randomization (x-axis: 0 to 48)

No. at Risk								
ICD group	315	299	258	211	172	123	82	25
Control group	318	305	272	217	172	124	79	31

COMPANION, 2003

Implantable Cardioverter Defibrillator in High-Risk Long QT Syndrome Patients
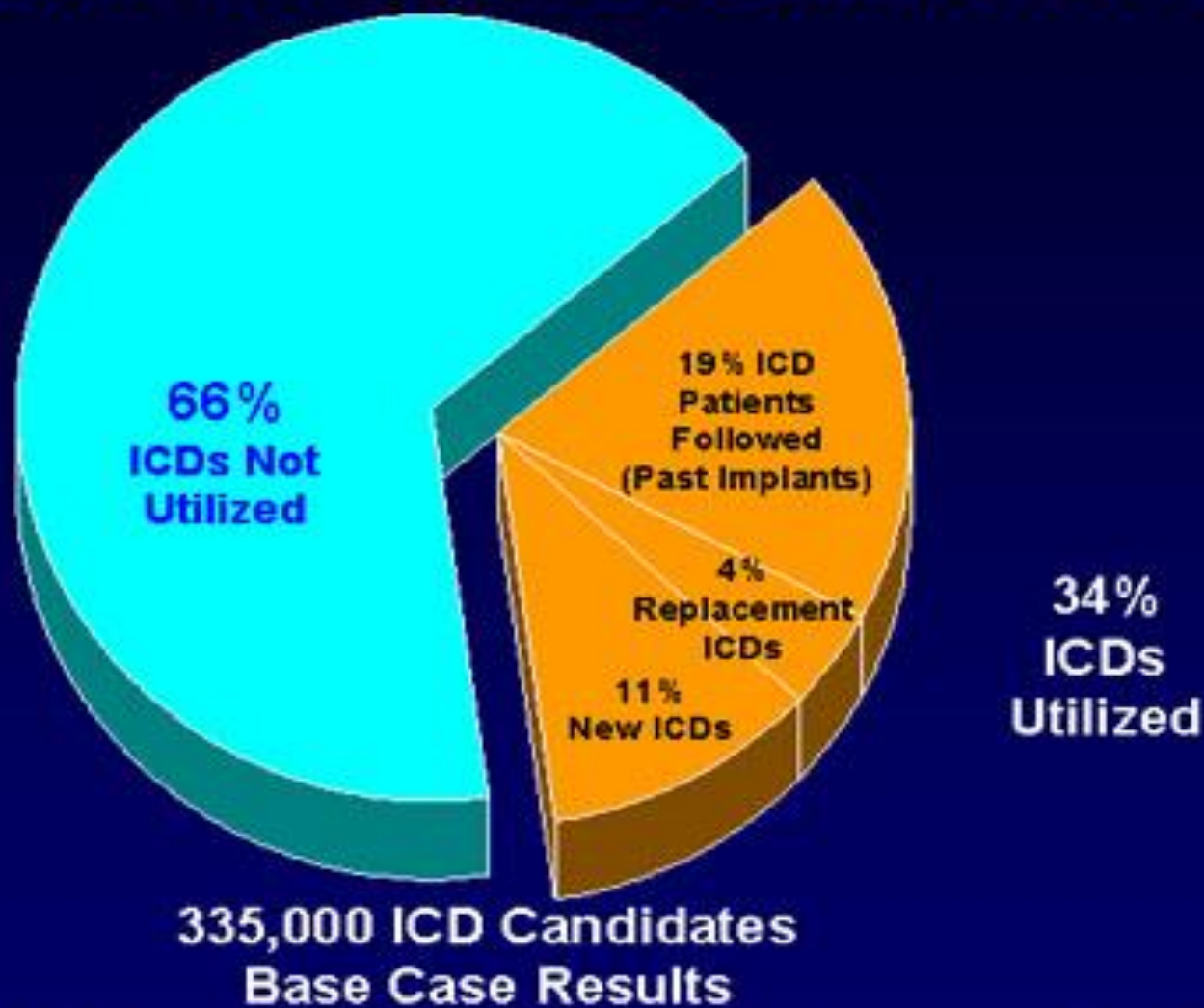
Zareba et al JCE 2003; 14:337

- 125 LQTS patients with ICDs: 54 with CA and 19 with recurrent syncope despite BB = 73

- Compared to 161 LQTS patients with similar indications but no ICD: 89 CA, 72 syncope

- 1 death in ICD group (1.3%) over 3 years, and 26 deaths (16%) in non-ICD group over 8 years (p=.07)

Defibrillator v. ß-Blockers for Unexplained Death in Thailand (DEBUT)

Nademanee et al Circulation 2003; 107:2221

- 86 survivors of SUDS

- Randomized to ICD v beta blocker

- 3 year follow up had 7 deaths in beta blocker group, none in ICD (p=.02)

- 12 ICD patients received shocks for VF

Overall U.S. ICD Utilization

66% ICDs Not Utilized

19% ICD Patients Followed (Past Implants)

4% Replacement ICDs

11% New ICDs

34% ICDs Utilized

335,000 ICD Candidates
Base Case Results

Ruskin JN, Hallstrom AP, Zipes DP, Camm AJ, McGrory-Usset ME. ICD Utilization Based on Discharge Diagnoses from Medicare and Managed Care Patients J Cardiovasc Electrophysiol 13:38-43, 2002

Estimated ICD Utilization
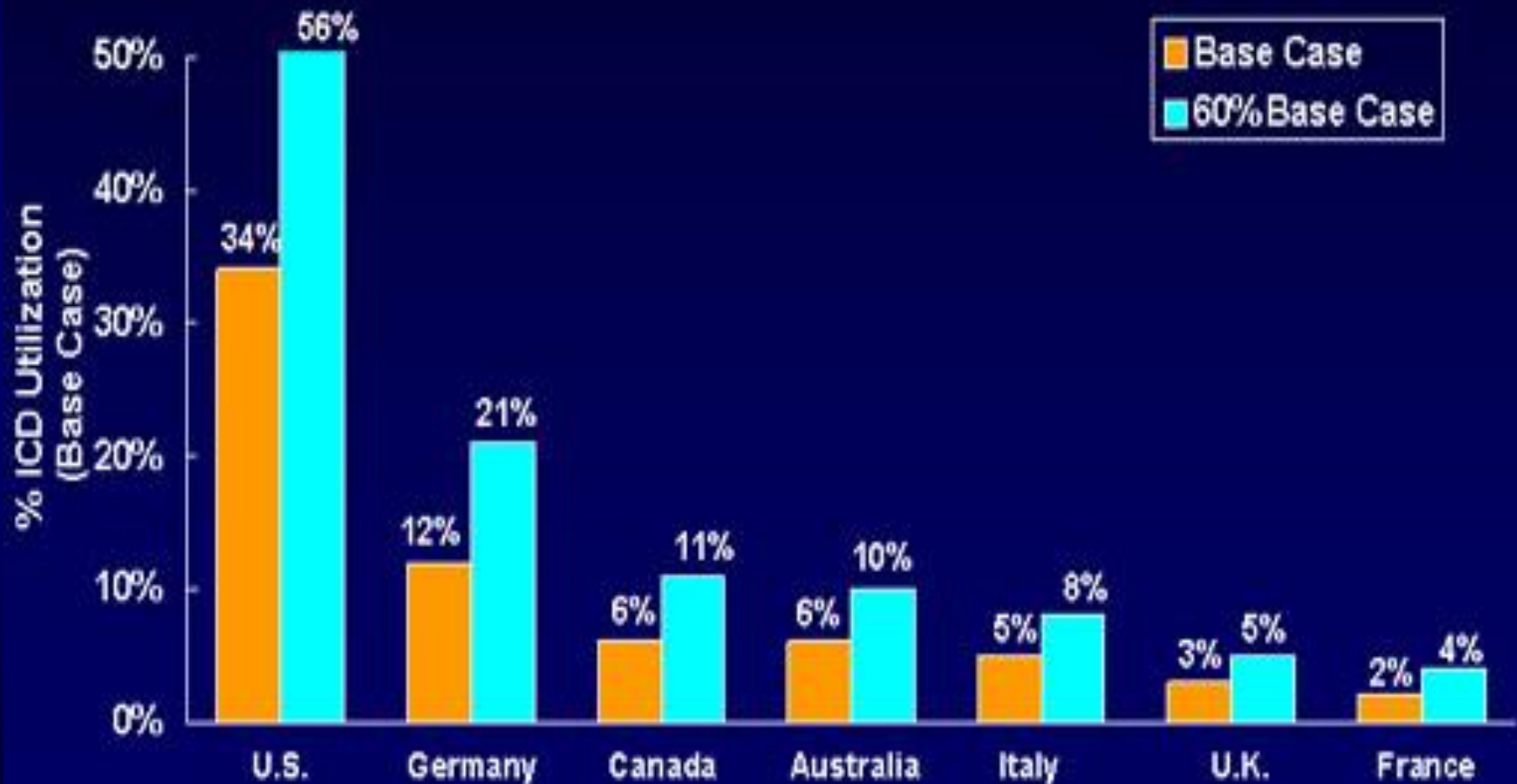
Conclusions

- Le DAI est plus efficace que le traitement médical pour diminuer le risque de mort subite

- Le bénéfice est particulièrement net en cas de FEVG basse

- Le DAI reste sous-utilisé

- Baisse des prix du DAI pour élargir son utilisation ?

- Définir des populations ciblées qui bénéficient du DAI ?
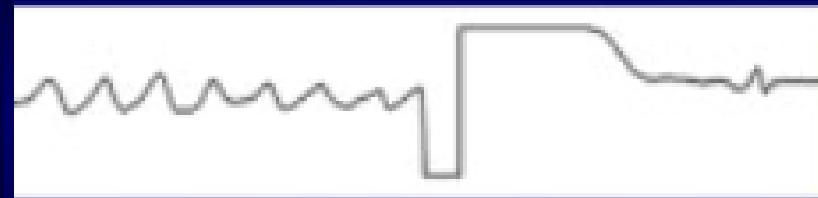
- M 68, aéroport Indianapolis
- FdRCV : Tabac, HTA

• Appel 911 : 0' 54"

• Manœuvres Ressuscitation : 2' 10"

• Défibrillation : 3' 43"

- Réveil J1
- Coro : 3 tronculaire
- + dysfonction VG
- PAC + amiodarone
- Sortie J14
- DAI J45
- Reprise W 6h / j à J60

Save Sudden Cardiac Death Victims

Hungarian National Heart Foundation

Mais …

- **80 % à 90 % des arrêts cardiaques extra-hospitaliers surviennent à domicile**

- **De l'intérêt d'une prévention primaire performante.**