Les indications du défibrillateur implantable

N Sadoul, CHU de Nancy

Les indications du DAI

- Médecine basée sur les preuves => Indications du DAI reposent sur les grandes études → Il faut les connaître !!!
- Etudes de prévention primaire
  - Cardiopathies ischémiques : MADIT, MUSTT, CABG, MADIT 2, dinamit …
  - CMD: Amiovirt, CAT, Definite,
  - CHF, NYHA II et III (CMD + CI) : SCD HeFT
  - CHF + QRS larges : Companion et al.
- Etudes de prévention secondaire
  - Cardiopathies ischémiques+++

Post MI pre-event trials before 2000

Trial	Design	Target Population	Therapies randomised	Outcome
MADIT	Randomised, total mortality	n=196; EF<0.35, NSVT EPS inducible PCA refractory	ICD vs conventional Amio(74%)	ICD improved survival by 46% p < 0.02
CATBG Patch	Randomised, total mortality	n = 900, EF<0.36, LPs+ CABG candidate	CABG in all ICD vs no therapy	No survival benefit for ICD
MUSTT	Randomised, total mortality	n = 2204, EF<0.4, NSVT Inducible : 767 (Non induc.:1435)	No EP guided therapy EP guided therapy (AA, ICD if PES+)	27% reduction for patients with EP guided therapy >50% reduction for ICD

MADIT II trial (NEJM 2002;346:873-83)

CAD (MI ≥ 1 month), LVEF ≤ 0.3

1 232 patients : 3 :2 ratio

R*

ICD (742)

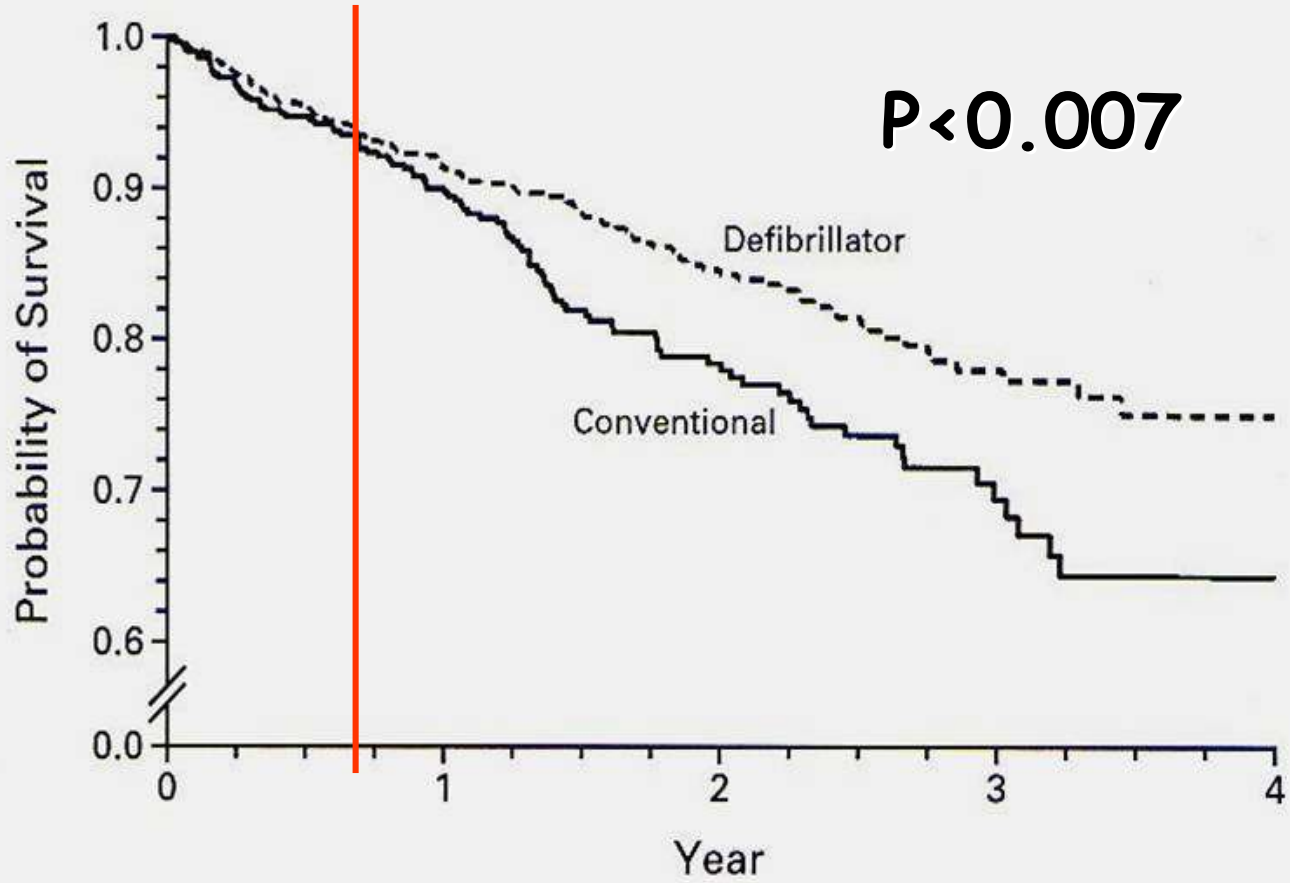
Conventional (490)

+ EEP

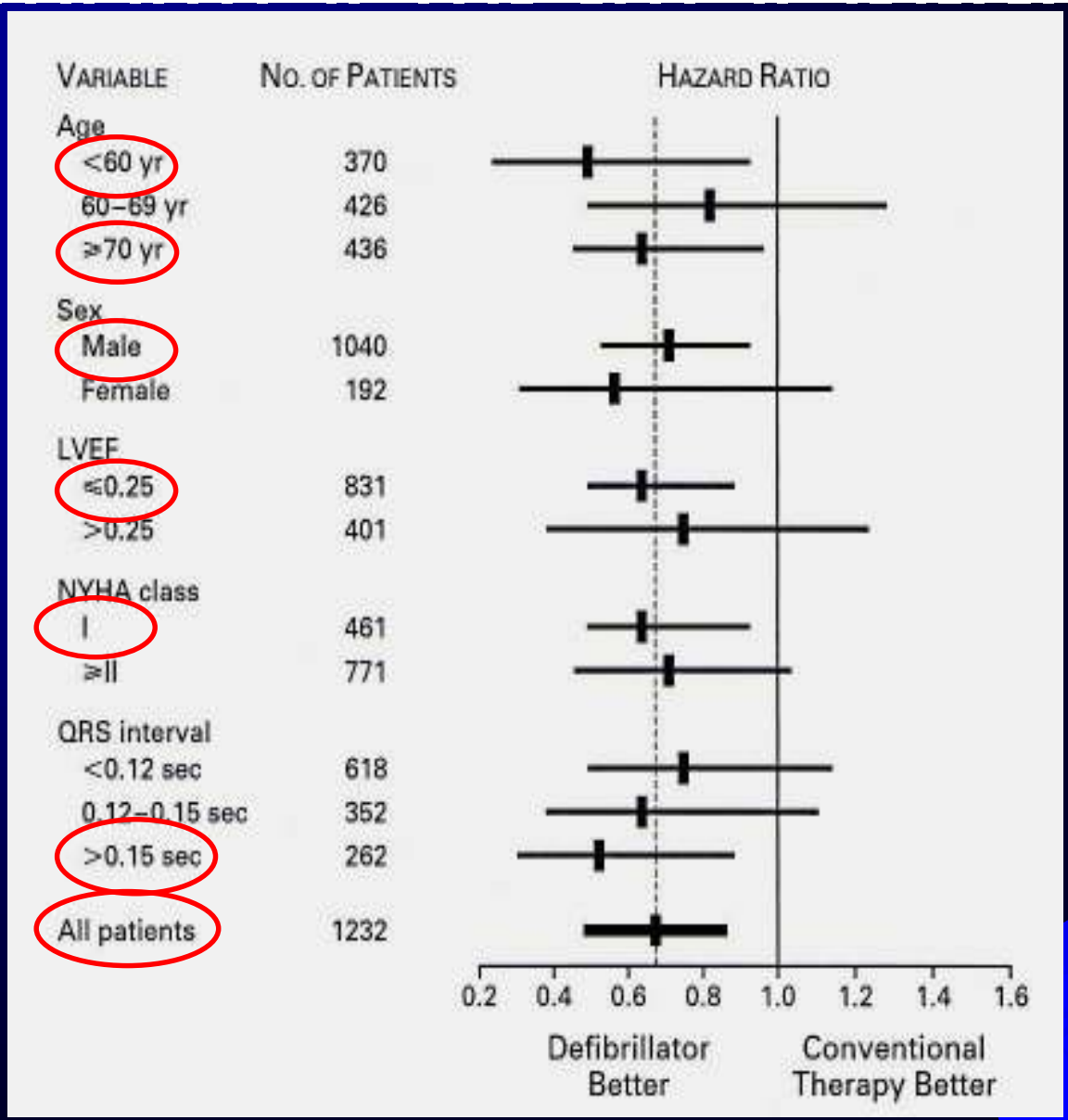
Follow-up
(mean : around 2 years)

β-, ACE inhibitors, no AA

Kaplan Meier estimates of the probability of survival



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3



Hazard ratios and 95% CI for death from any cause

Discussion, conclusions

- ICD improves survival among pts with a prior MI and a LVEF < 0.3 (31% mortality reduction)
- Survival benefit occur only after 9 months
- Beneficial effects of ICD in pts with QRS > 150 ms => Companion
- Need to refine stratification
- 88% of patients with an MI > 6 months
  => Dinamit and SCD HeFT
- Economical considerations : 400 000 new cases per year in the US

Dinamit trial (NEJM 2004;351:2481-8)

CAD (MI < 6 weeks), LVEF ≤ 0.35 + decreased HRV

2348 patients screened
1016 study eligible
674 patients randomised
(342 refused)

R*

ICD
(332)

+ EEP

Conventional
(342)

Follow-up
(mean : 30 months)

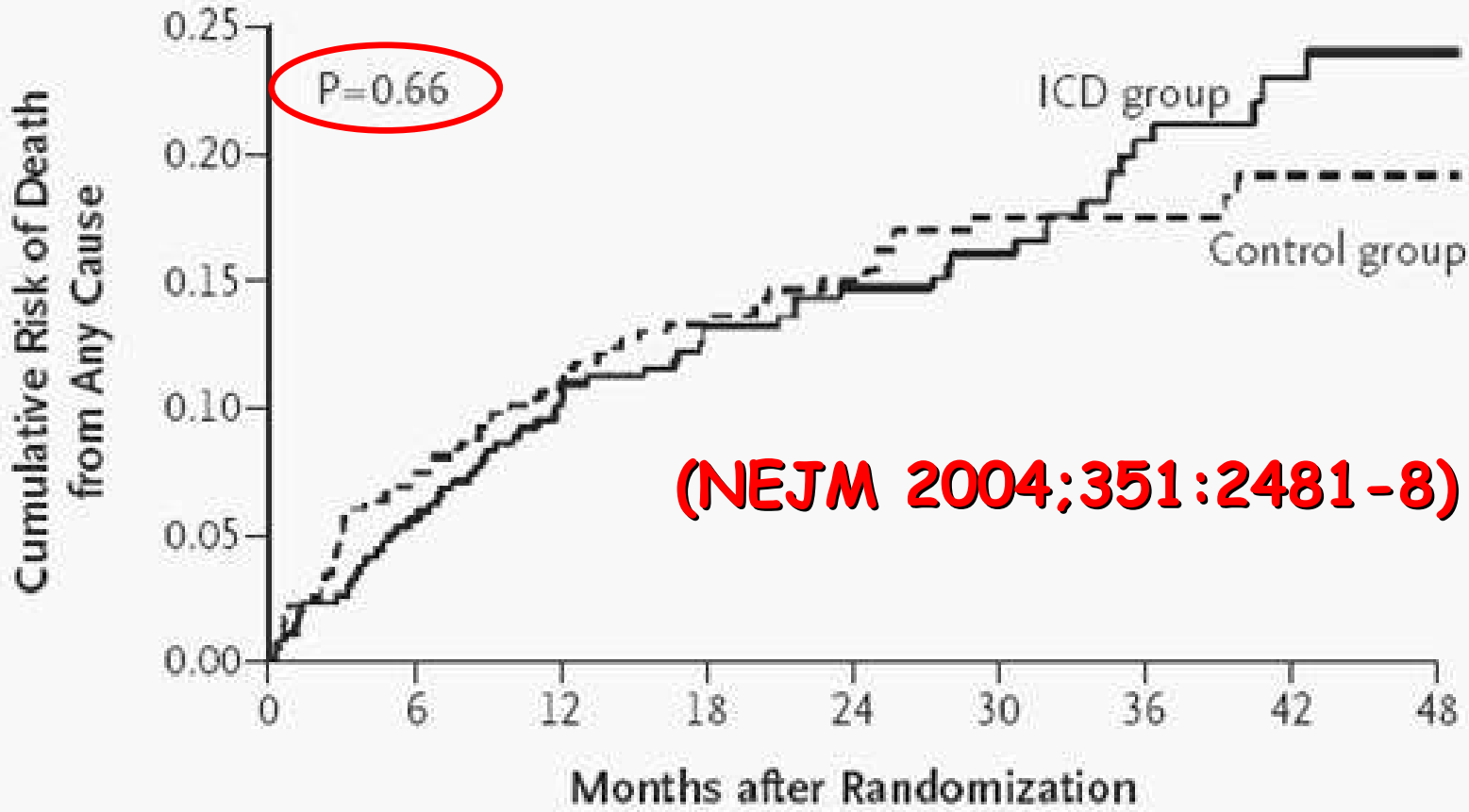
β-, ACE inhibitors, no AA

Dinamit : Patients characteristics

Characteristic	ICD Group (N=332)	Control Group (N=342)
Male sex — no. (%)	252 (75.9)	262 (76.6)
Age — yr	61.5±10.9	62.1±10.6
Beta-blockers — no. (%)	289 (87.0)	296 (86.5)
ACE inhibitors — no. (%)	315 (94.9)	323 (94.4)
Antiplatelet agents — no. (%)	306 (92.2)	315 (92.1)
Lipid-lowering agents — no. (%)	255 (76.8)	272 (79.5)

(NEJM 2004;351:2481-8)

Kaplan Meier estimates of cumulative risk of death from any cause according to study group



(NEJM 2004;351:2481-8)

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

Dinamit : Conclusions

- ICD therapy does not reduce mortality in high risk patients who have recently had a myocardial infarction (< 6 weeks)
- Although ICD therapy was associated with a reduction in the rate of death due to arrhythmia, that was offset by an increase in the rate of death from non-arrhythmic causes
- This study defines a limitation of prophylactic ICD implantation

Les indications du DAI

- Etudes de prévention primaire
  - Cardiopathies ischémiques : MADIT, MUSTT, CABG, MADIT 2, dinamit …
  - CMD: Amiovirt, CAT, Definite,
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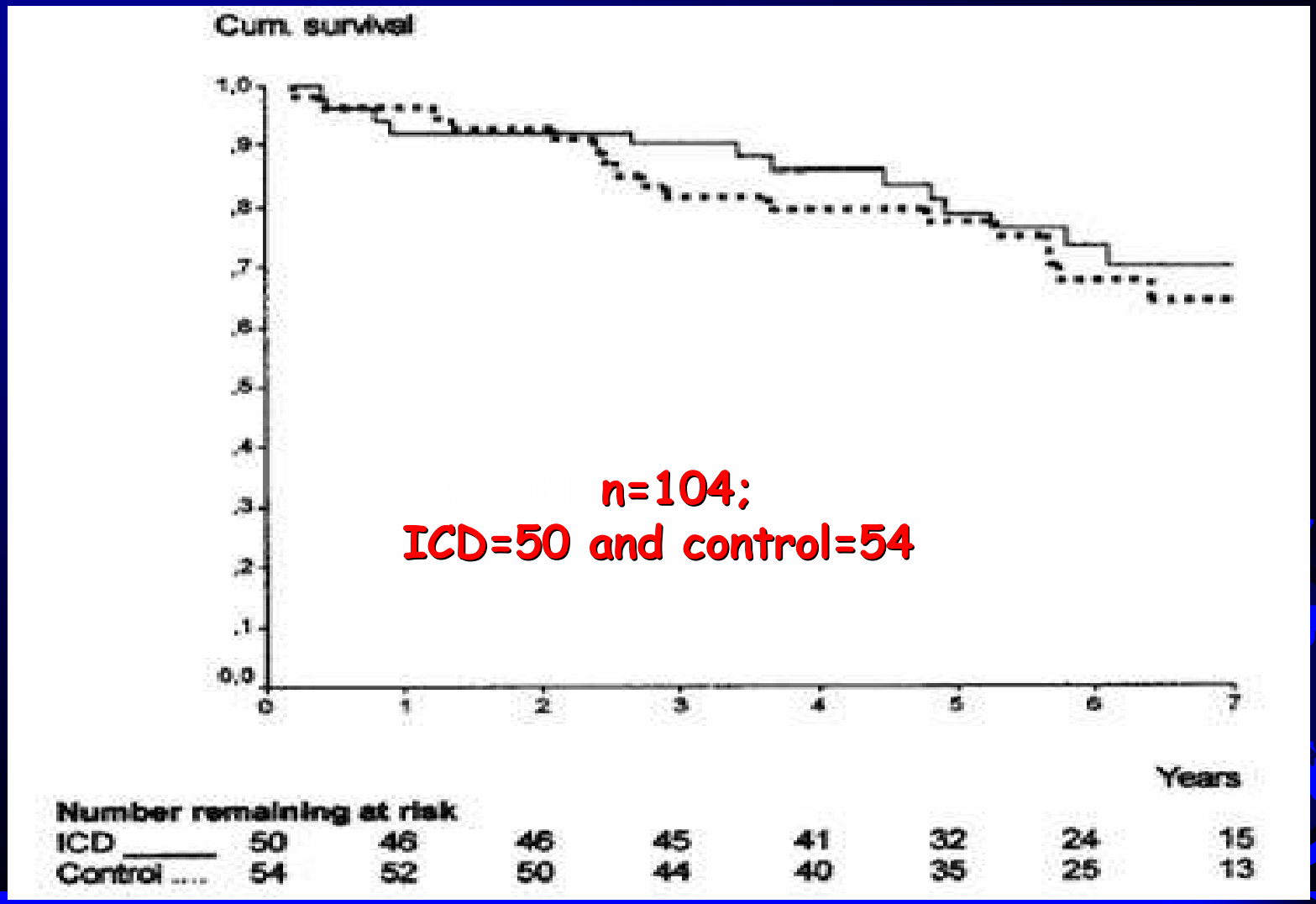
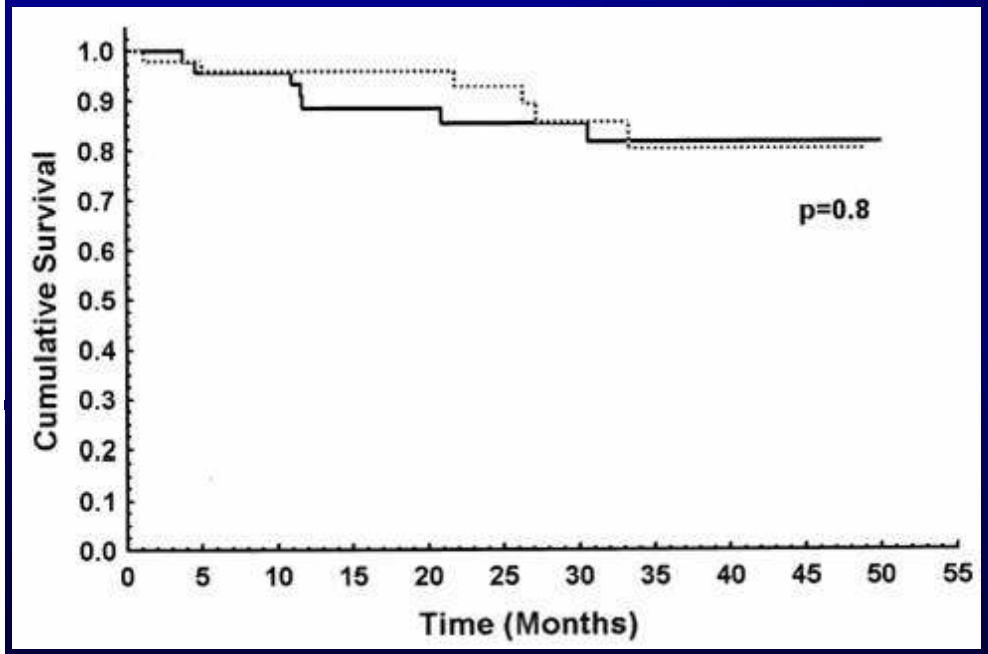
  - CHF + QRS larges : Companion et al.
- Etudes de prévention secondaire
  - Cardiopathies ischémiques+++

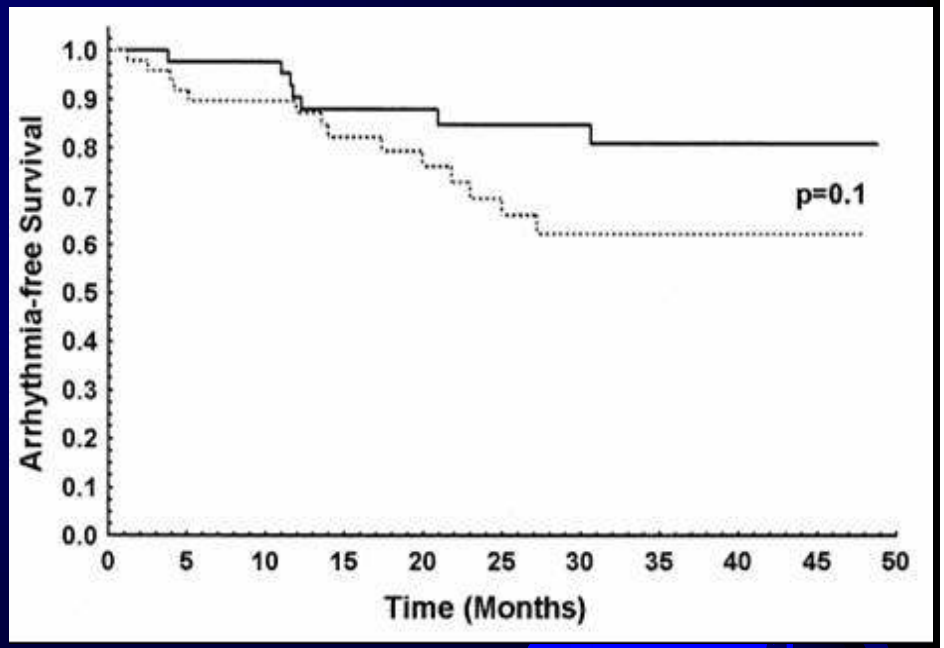
The CArdiomyopathy Trial : CAT JACC 2002

DCM (≤ 9 months), EF ≤ 30 %, Low 1 year mortality rate



AMIOdarone Versus Implantable cardioverter Randomized Trial (AMIOVIRT) (JACC 2003;41:1707-12)



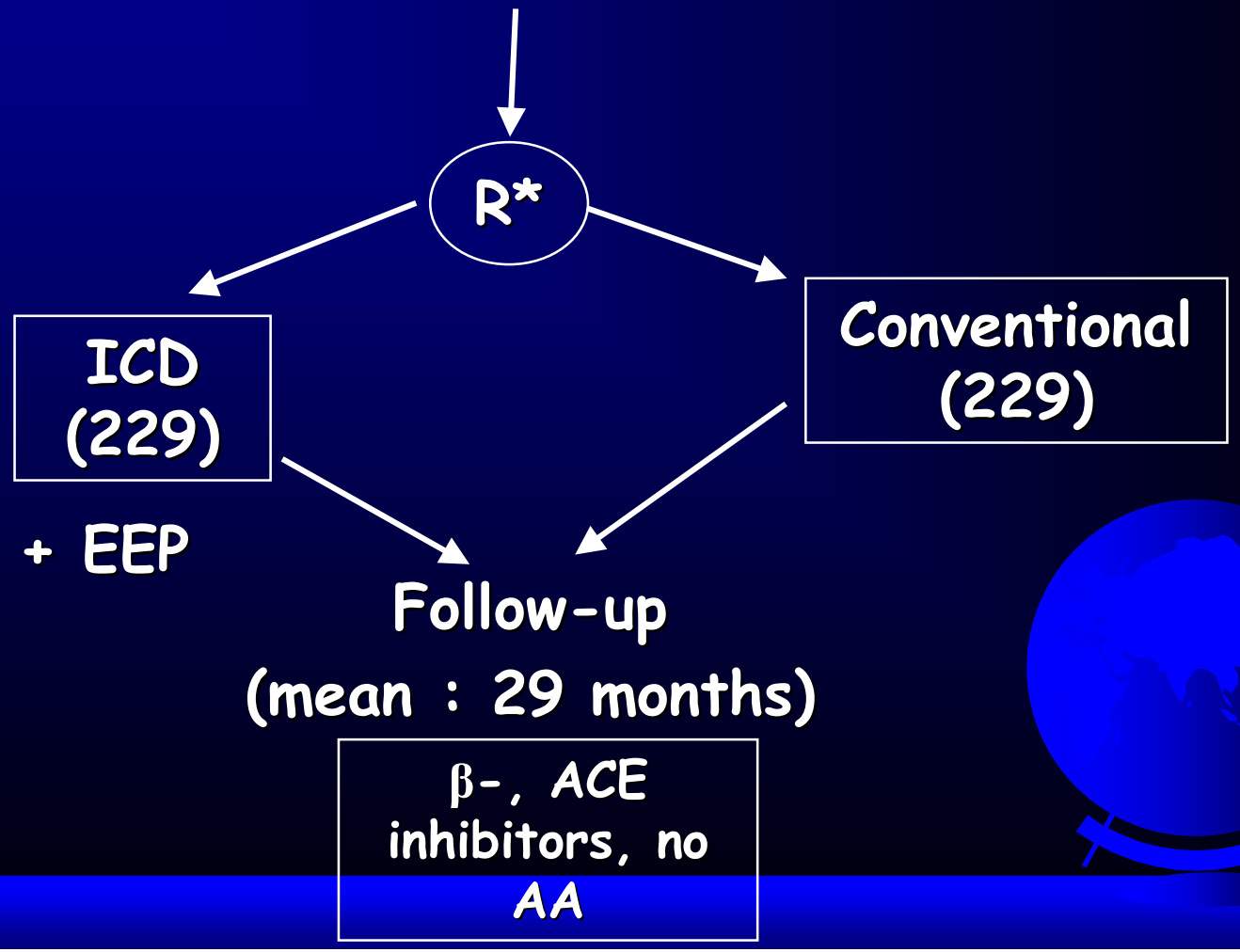


n = 103 ; DCM (non isch.), LVEF ≤ 0.35

NSVT, NYHA I to III, age ≥ 18

DEFINITE : DEFibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation (NEJM 2004;350:2151-8)

NICM (DCM), LVEF ≤ 0.35 + HF history + NSVT or > 10 VPBs on Holter

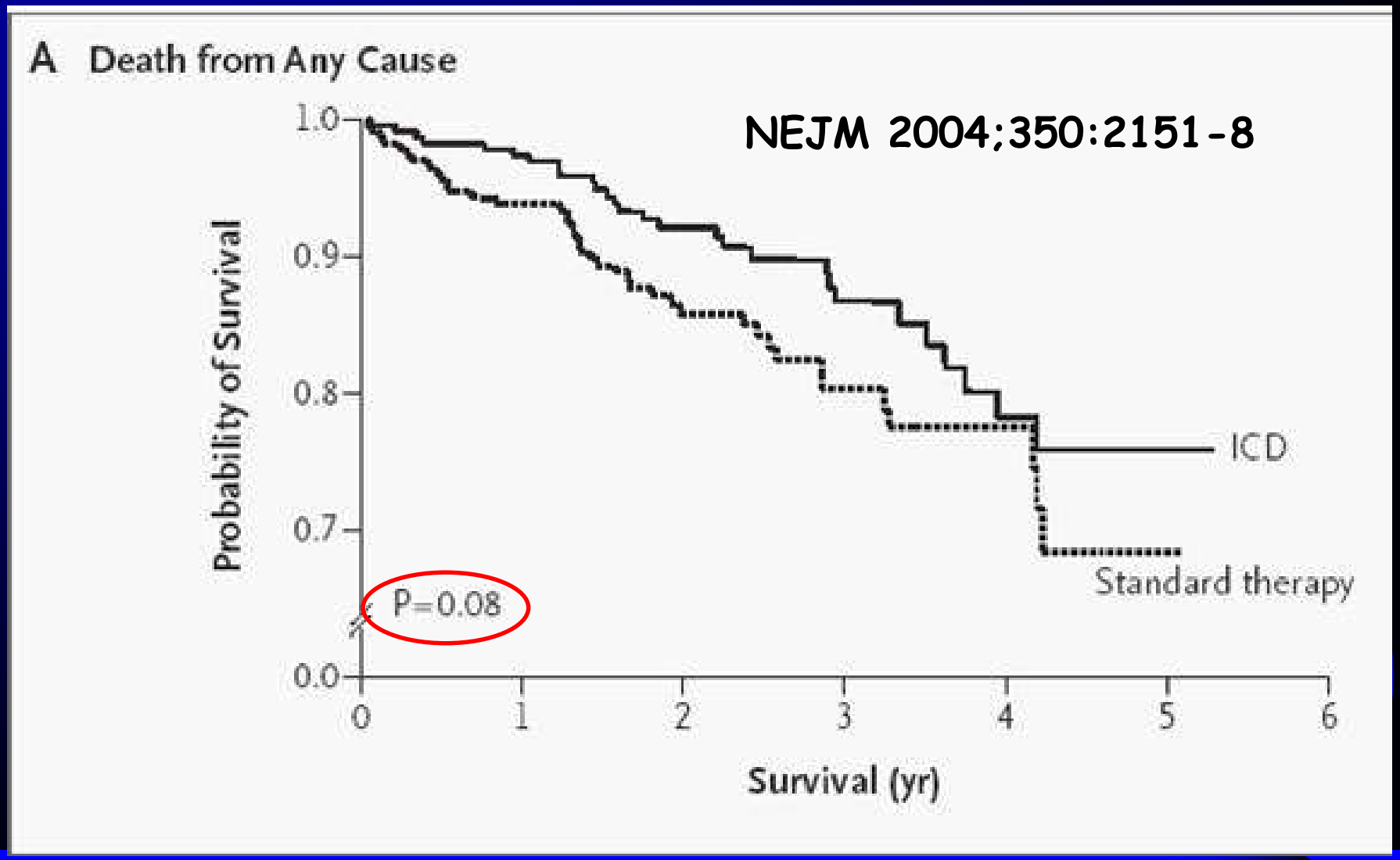


DEFINITE : Patients characteristics

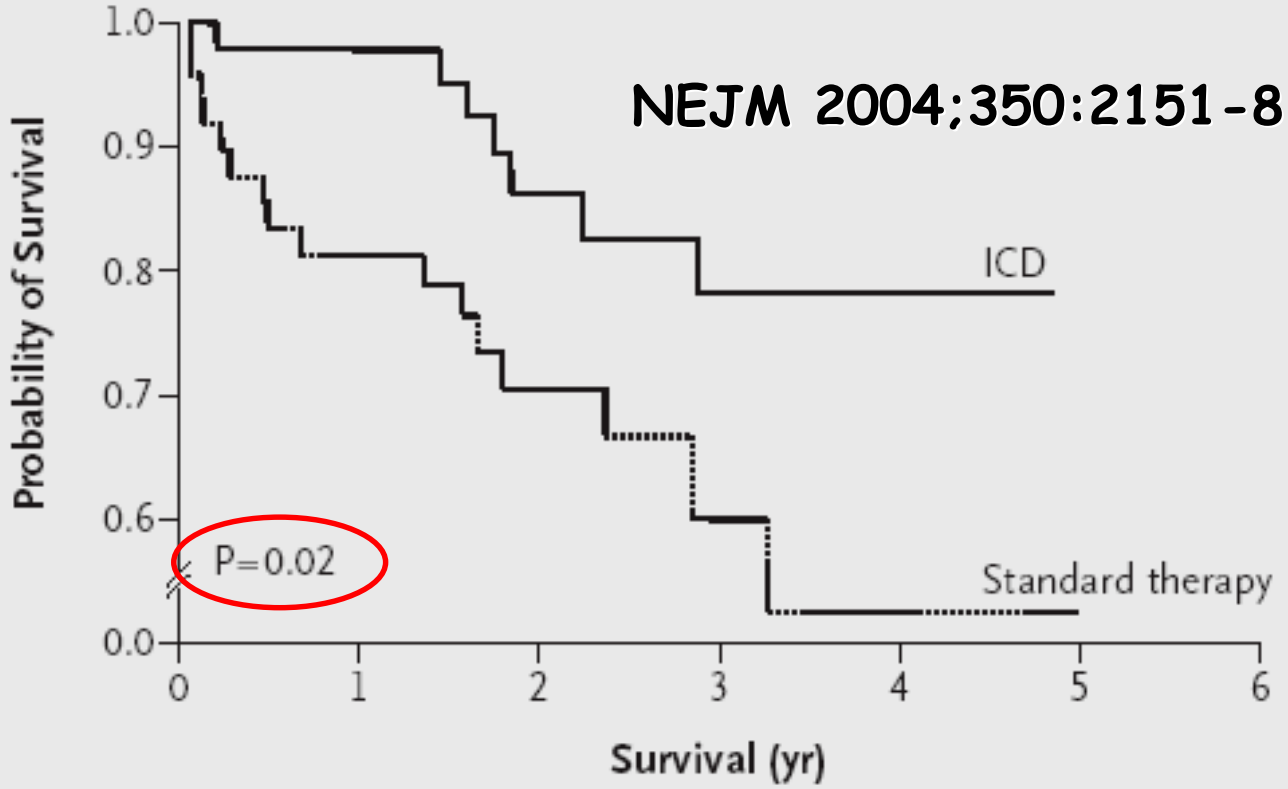
Characteristic	All Patients (N=458)	Standard-Therapy Group (N=229)	ICD Group (N=229)
Age — yr			
Mean	58.3	58.1	58.4
Range	20.3–83.9	21.8–78.7	20.3–83.9
Male sex — no. (%)	326 (71.2)	160 (69.9)	166 (72.5)
LVEF — %			
Mean	21.4	21.8	20.9
Range	7–35	10–35	7–35
Distance walked in 6 min — m			
Mean	319.4	328.3	311.2
Range	18–1317	18–1317	29–1143
NYHA class — no. (%)			
I	99 (21.6)	41 (17.9)	58 (25.3)
II	263 (57.4)	139 (60.7)	124 (54.2)
III	96 (21.0)	49 (21.4)	47 (20.5)

NEJM 2004;350:2151-8

DEFINITE : Kaplan-Meier All cause mortality (NEJM 2004)



DEFINITE (NEJM 2004) : Kaplan-Meier Class III



No. at Risk					
Standard-therapy group	49	38	22	9	5
ICD group	47	45	25	17	10

Figure 3. Kaplan–Meier Survival Curves among Patients with New York Heart Association Class III Heart Failure, According to Whether They Received Standard Therapy or an Implantable Cardioverter–Defibrillator (ICD).

Les indications du DAI

- Études de prévention primaire
  - Cardiopathies ischémiques : MADIT, MUSTT, CABG, MADIT 2, dinamit …
  - CMD: Amiovirt, CAT, Definite,
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  - CHF + QRS larges : Companion et al.
- Etudes de prévention secondaire
  - Cardiopathies ischémiques+++

SCD-HeFT enrollment scheme

DCM ± CAD and CHF

↓

EF ≤ 35%

↓

NYHA Class II or III

↓

6 minutes walk, Holter

R

Placebo (n = 847)

Amiodarone (n = 845)

ICD (n = 829)

SCD-HeFT patients characteristics

Table 1. Characteristics of the Patients at Baseline or at the Last Follow-up Visit.

Characteristic	Amiodarone (N=845)	Placebo (N=847)	ICD Therapy (N=829)
Age — yr			
Median	60.4	59.7	60.1
Interquartile range	51.7–68.3	51.2–67.8	51.9–69.2
Female sex — no. (%)	206 (24)	192 (23)	190 (23)
Nonwhite race — no. (%)	196 (23)	204 (24)	189 (23)
Ejection fraction			
Median	25.0	25.0	24.0
Systolic blood pressure — mm Hg			
Median	118	120	118
Interquartile range	106–130	108–132	104–131
Diastolic blood pressure — mm Hg			
Median	70	70	70
Interquartile range	62–80	62–80	61–80

NEJM 2005;352:225-37

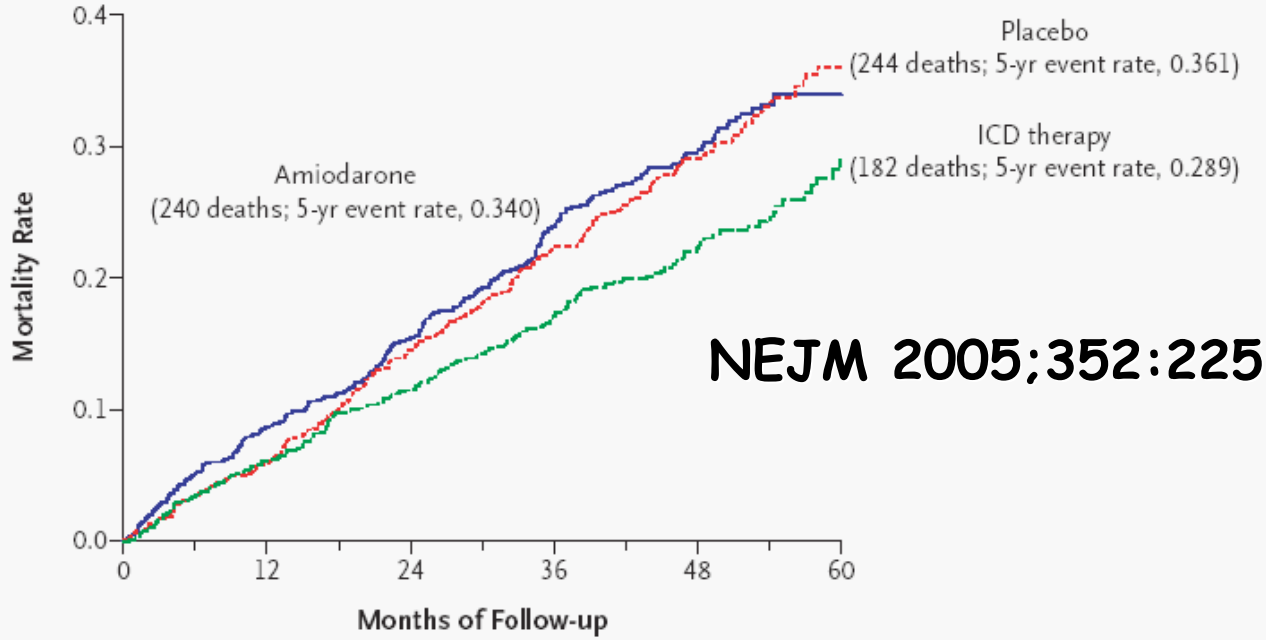
SCD-HeFT: CHF medications

Characteristic	Amiodarone (N=845)	Placebo (N=847)	ICD Therapy (N=829)
Medication use — no. (%)¶			
ACE inhibitor at enrollment	731 (87)	718 (85)	684 (83)
ACE inhibitor at last follow-up	594 (71)	619 (74)	576 (70)
ARB at enrollment	118 (14)	132 (16)	114 (14)
ARB at last follow-up	152 (18)	145 (17)	144 (18)
ACE inhibitor or ARB at enrollment	822 (97)	827 (98)	783 (94)
ACE inhibitor or ARB at last follow-up	718 (85)	740 (88)	706 (86)
Beta-blocker at enrollment	581 (69)	581 (69)	576 (69)
Beta-blocker at last follow-up	605 (72)	662 (79)	672 (82)
Diuretic			
Loop at enrollment	696 (82)	692 (82)	676 (82)
Loop at last follow-up	665 (79)	674 (80)	649 (79)
Potassium-sparing at enrollment	174 (21)	165 (19)	168 (20)
Potassium-sparing at last follow-up	236 (28)	278 (33)	261 (32)
Thiazide at enrollment	52 (6)	60 (7)	63 (8)
Thiazide at last follow-up	95 (11)	88 (11)	80 (10)

NEJM 2005;352:225-37

Mortality by intention-to-treat

	Hazard Ratio (97.5% CI)	P Value
Amiodarone vs. placebo	1.06 (0.86–1.30)	0.53
ICD therapy vs. placebo	0.77 (0.62–0.96)	0.007



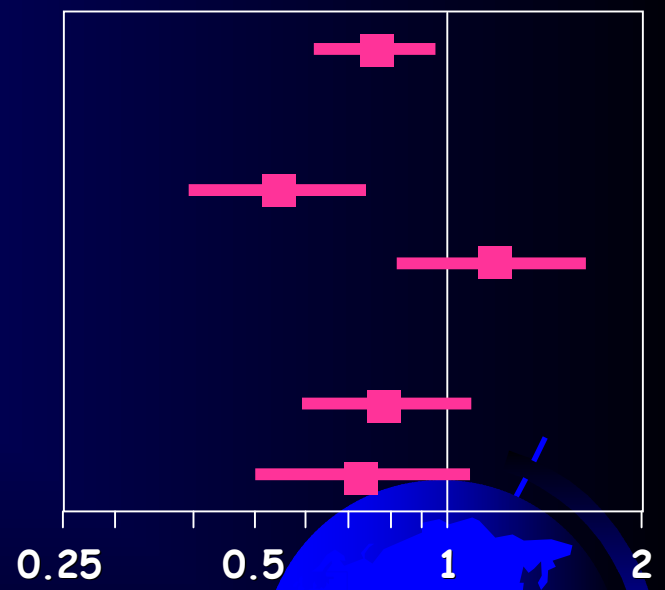
NEJM 2005;352:225-37

No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD therapy	829	778	733	501	304	103

Figure 1. Kaplan–Meier Estimates of Death from Any Cause.

ICD vs Placebo : Hazard Ratios

Patient Group		N	HR	97.5% CI
All Patients		1676	0.77	0.62-0.96
NYHA	Class II	1160	0.54	0.40-0.74
	Class III	516	1.16	0.84-1.61
Etiology	Ischemic	884	0.79	0.60-1.04
	Non-Ischemic	792	0.73	0.50-1.04



SCD-HeFT: Conclusions

- In class II or III CHF patients with EF ≤35% on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years
- Simple, shock-only ICDs decrease mortality by 23%
- Amiodarone, when used as a primary preventive agent, does not improve survival

Les indications du DAI

- Etudes de prévention primaire
  - Cardiopathies ischémiques : MADIT, MUSTT, CABG, MADIT 2, dinamit …
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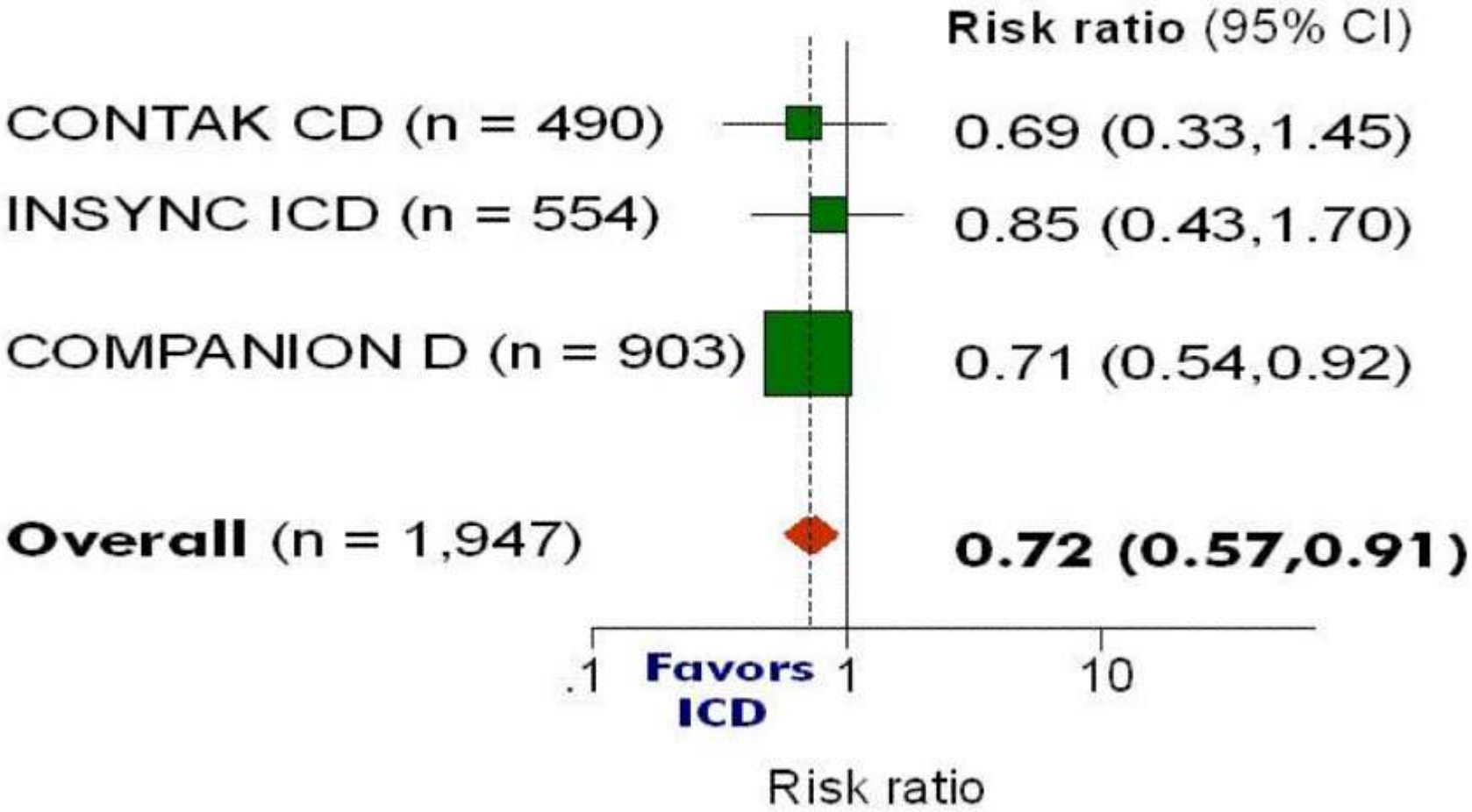
  - Etudes de prévention secondaire
  - Cardiopathies ischémiques+++

CRT ICD Trials: Death



Care HF : n = 813

Bristow, NEJM 2004;350:2140-50
Bradley, JAMA 2003;289:730-40

COMPANION

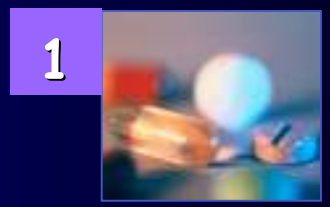
- NYHA III ou IV
- En rythme sinusal
- QRS ≥ 120 ms PR > 150 ms
- FEVG ≤ 35% Diamètre télédiastolique VG ≥ 60 mm
- Traitement pharmacologique optimal

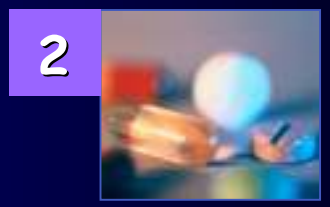
Randomization

1/5
- OPT

2/5
- OPT
- CRT

2/5
- OPT
- CRT-D





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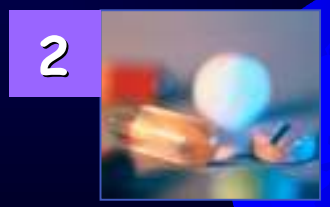

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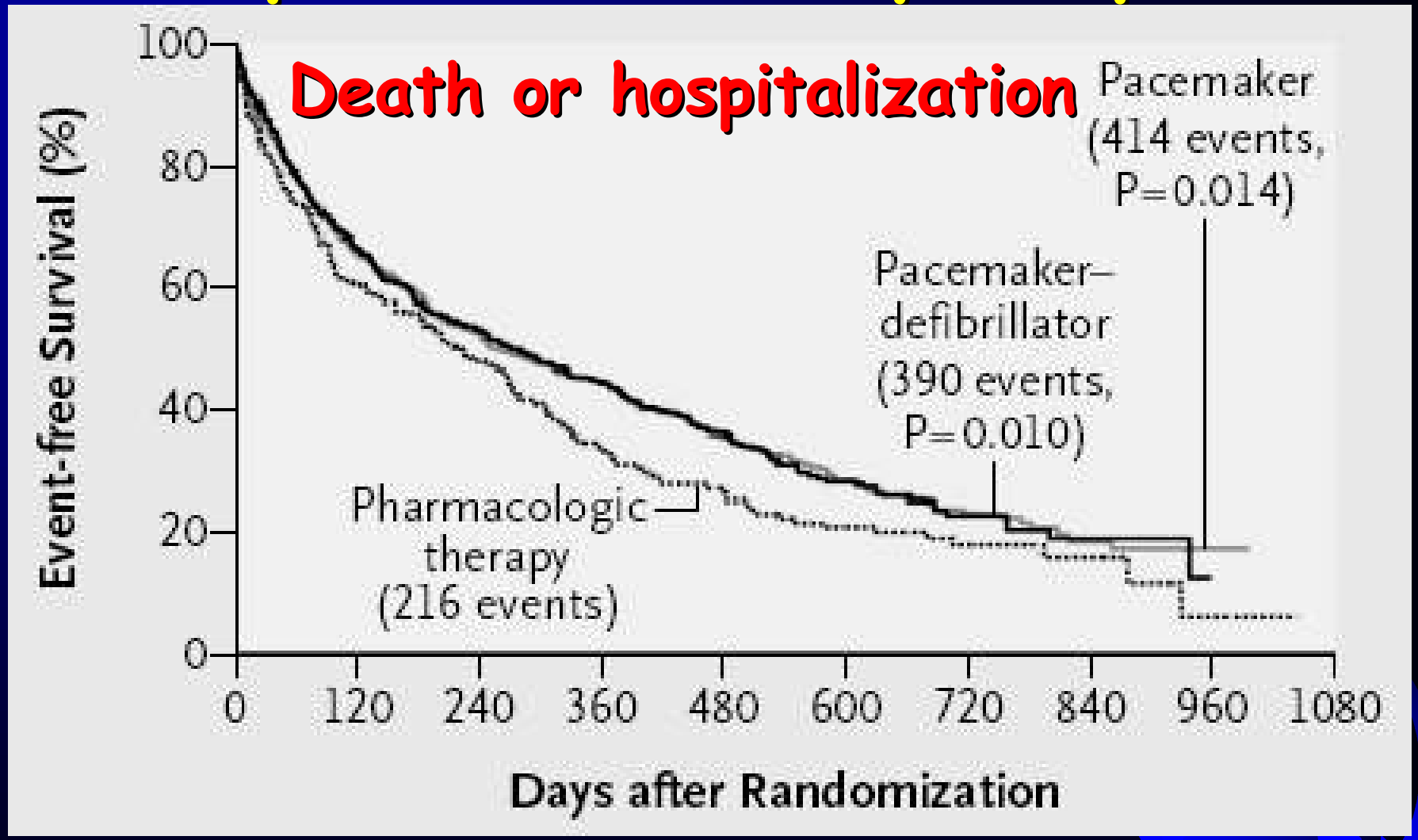
L'analyse en intention de traiter commence au moment de la randomisation

Bristow MR et al. N Engl J Med 2004; 350:2140-50

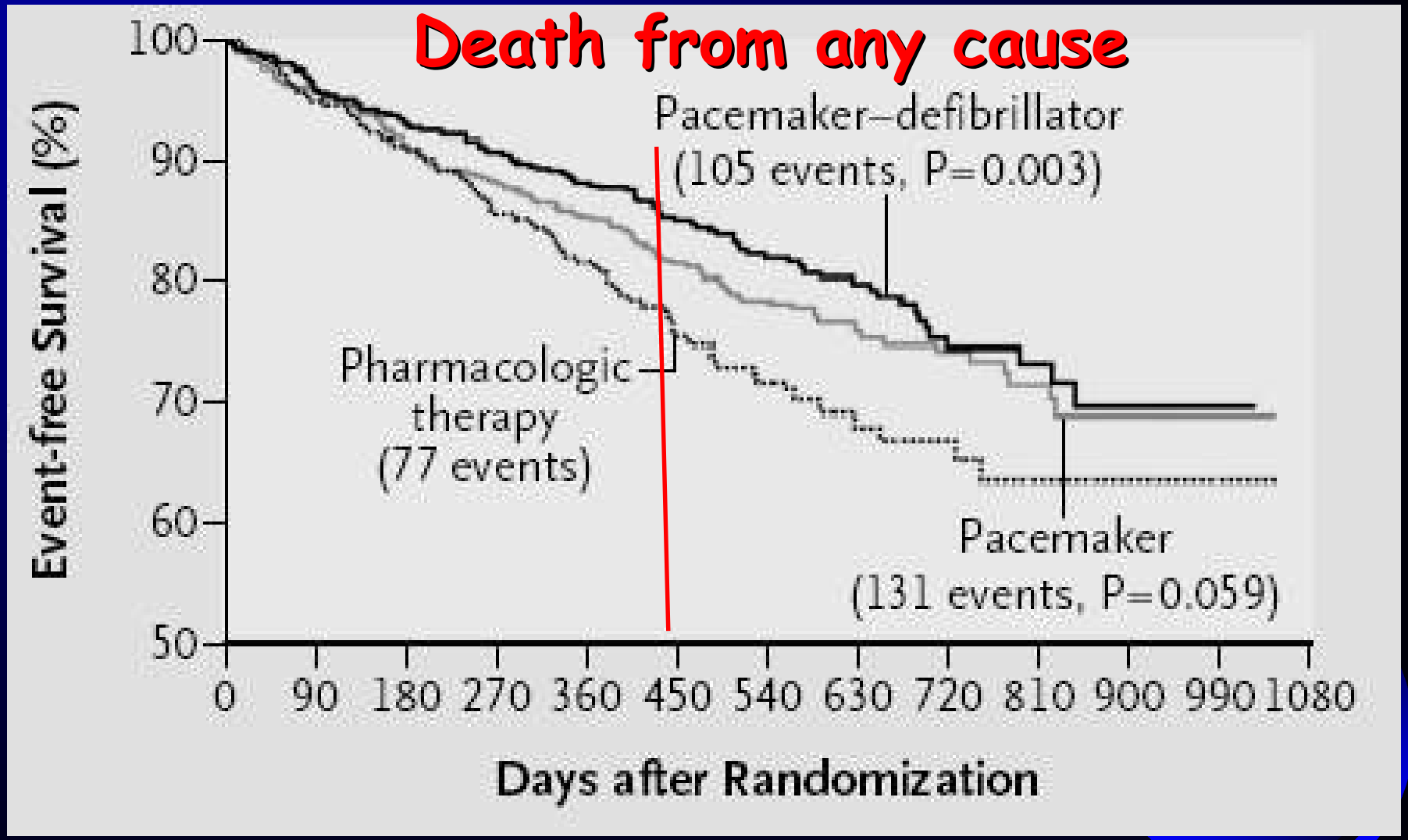
Companion : Primary endpoint



PM + DAI >> ttt pharmacologique optimal

Pas de différence entre PM et DAI

Companion : Secondary endpoint



DAI >> PM mais… étude non conçue pour répondre à cette question

COMPANION : conclusions du NEJM

- Cardiac resynchronisation reduces by 20% the rate of hospitalisation or death in addition to optimal pharmacological therapy (PM=ICD)
- The implantation of a PM was associated with a marginally significant reduction in the risk of death ($p = 0.059$)
- The addition of an ICD reduces the risk of death ($p = 0.003$) as compared with optimal therapy

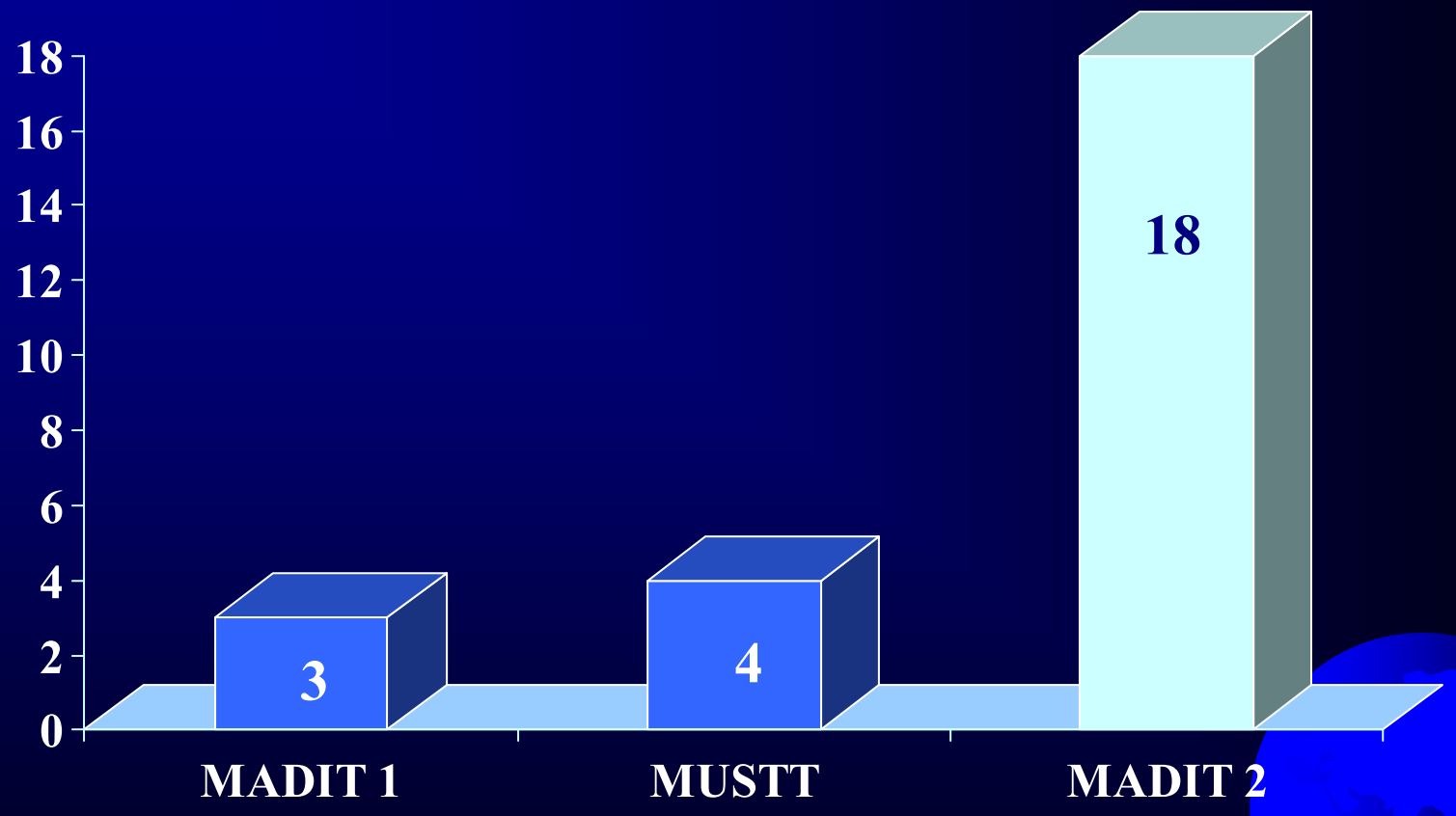
Ongoing pre-event trials

… BEST ICD, PRIDE, NORDIC, REVERSE, MADIT CRT etc)

If results favour the ICD → more convincing

If they do not → more confusing

Nb of patients to treat during 2 years to save 1 life

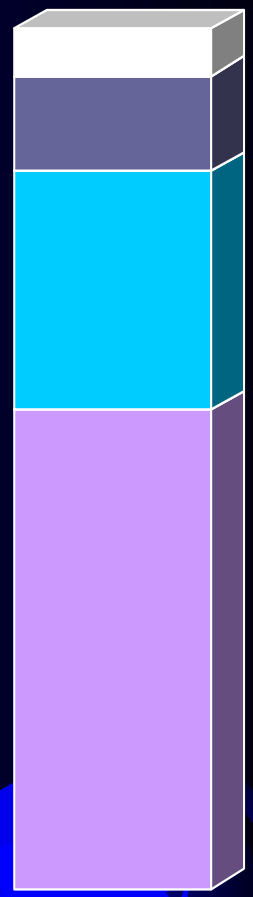


400 ICD/Million to save 22 pts/Million

Ezekowitz AJ et al. Ann Intern Med 2003;138:445-452

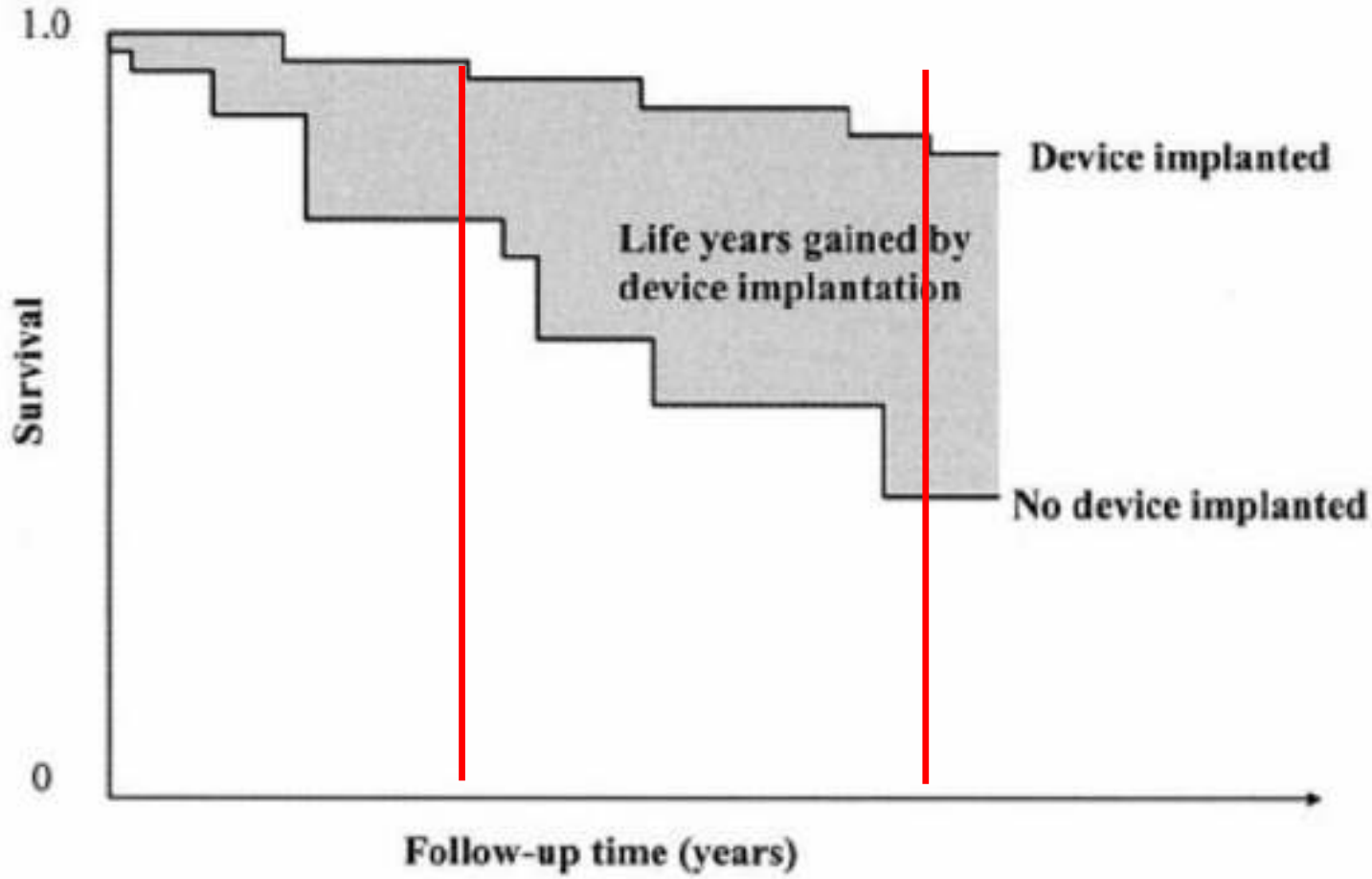
MADIT 2 Population

- 18 patients
  - 1 life saved
  - 2 ICD complications
  - 4-6 patients with inappropriate therapies
  - 10 unuseful ICD without complication



- Some patients will require ICD replacement (ERI, complication)

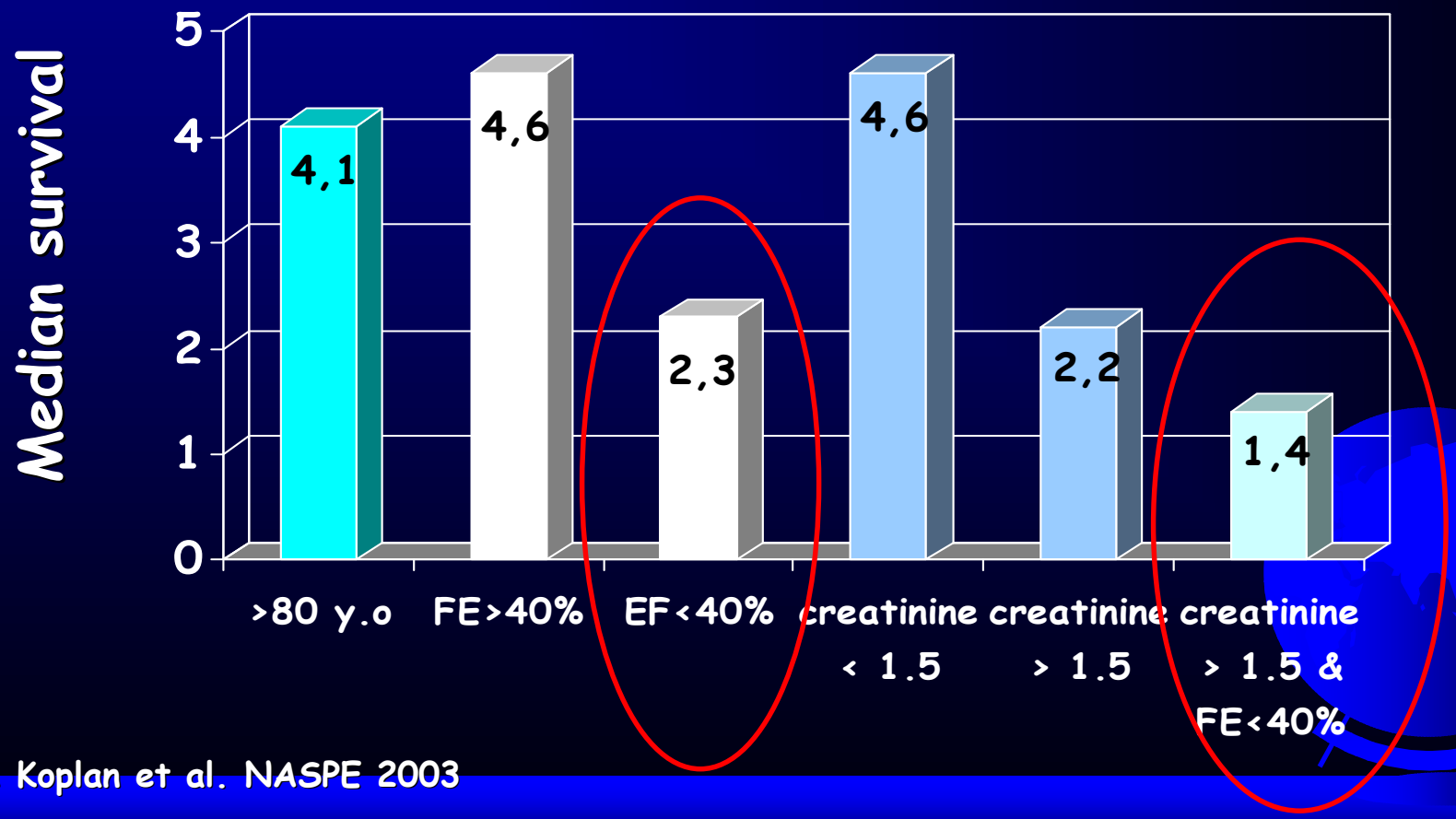
Cost-efficacy from ICD Trials



Salukhe et al. Circulation 2004;109:1848-53

Survival of octogenarian with an ICD

Median survival = 4.1 years in > 80 y group,
Survival was 67% at the same time period in the 60-70 y group



BA Koplan et al. NASPE 2003

Les indications du DAI

- Etudes de prévention primaire
  - Cardiopathies ischémiques : MADIT, MUSTT, CABG, MADIT 2, dinamit …
  - CMD: Amiovirt, CAT, Definite,
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- Etudes de prévention secondaire
  - Cardiopathies ischémiques+++

AVID : Antiarrhythmic Versus Implantable Defibrillator

VF survivors, syncopal VT
SVT with EF<0.4, + symptoms
(near-syncope, CHF, angina)

R → Drugs
R → ICD

R → Empirical amiodarone
R → EP guided sotalol

(NEJM 1997;337:1576-83)

AVID : Antiarrhythmic Versus Implantable Defibrillator (NEJM 1997;337:1576-83)

Mean FU = 18 months

6035 Screened

4621 Registry

1885 Eligible

1016 Randomised

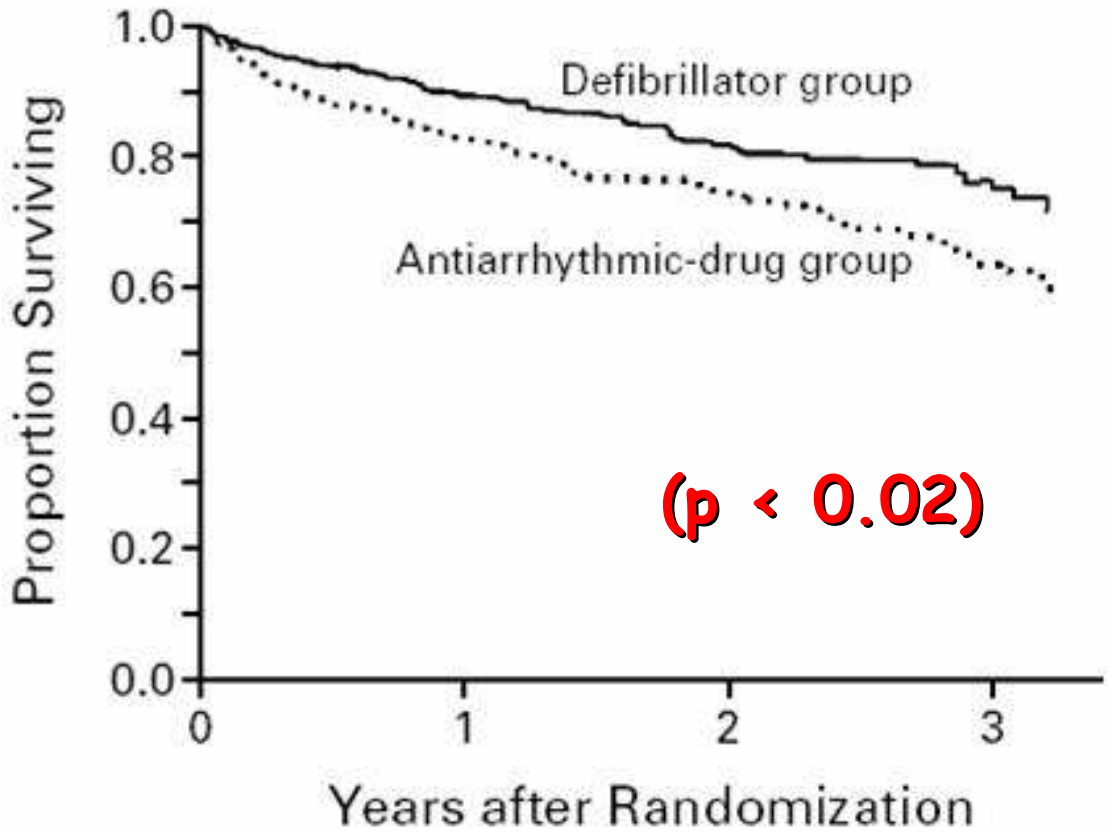
AA (509)

Amio (435)

Sotalol (74)

ICD (507)

AVID : Overall survival (NEJM 1997;337:1576-83)



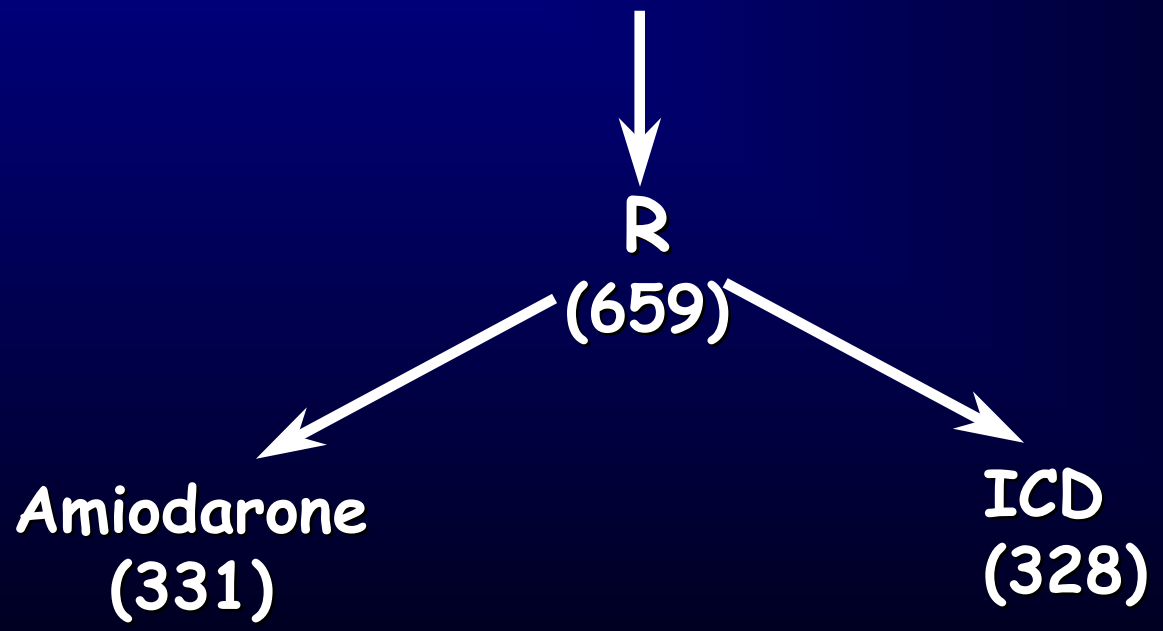
Patients at risk	1016	644	333	104
Percent surviving				
Defibrillator group		89.3	81.6	75.4
Antiarrhythmic-drug group		82.3	74.7	64.1

AVID : Antiarrhythmic Versus Implantable Defibrillator

	I year survival rate	2 year survival rate	3 year survival rate
ICD group	89.3%	81.6%	75.4%
Drug-treated group	82.4%	74.7%	64.1%
Mortality reduction	39%	27%	31%

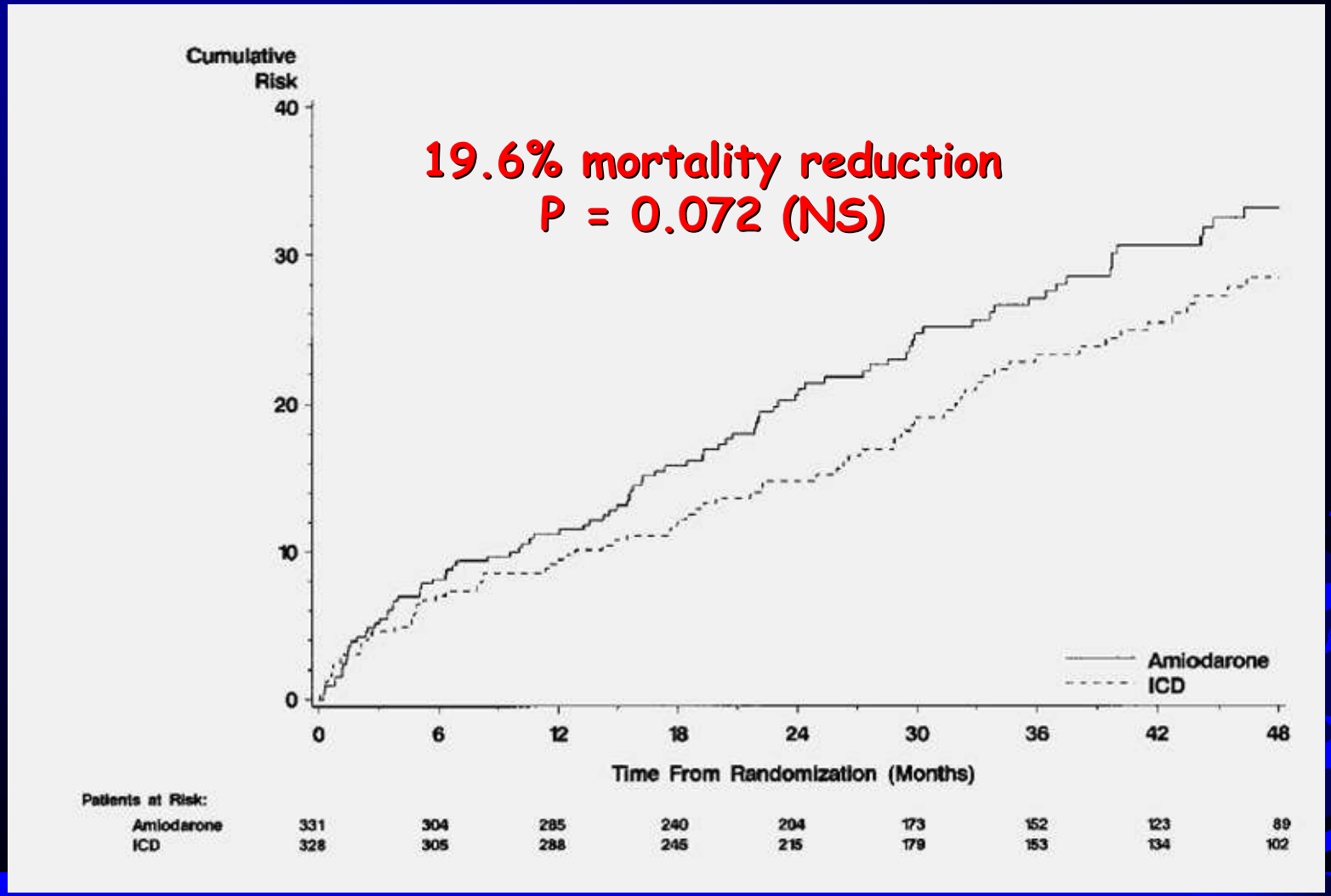
Canadian Impantable Defibrillator Study (CIDS)

VF survivors, cardiac arrest requiring CV
VT>150 bpm with symptoms and EF<0.35,
syncope with VT>10s or induced VT



Canadian Impantable Defibrillator Study (CIDS)

Circulation 2000;101:1297-1302



Canadian Implantable Defibrillator Study (CIDS)

- Non significant 19.6% all cause mortality reduction in the ICD group at 3 years (25% vs. 30%, p = 0.072).
- Analysis on an intention to treat basis with a high crossover rate
  - ICD group took concomitant β- (4 times more than AA group), sotalol and amiodarone (30%)
  - 22% of AA group subsequently received an ICD => Survival overestimation in the amiodarone arm?

Cardiac Arrest Study Hamburg (CASH)

(Circulation 2000;102:748-54)

SCD survivors due to documented VT or VF

346

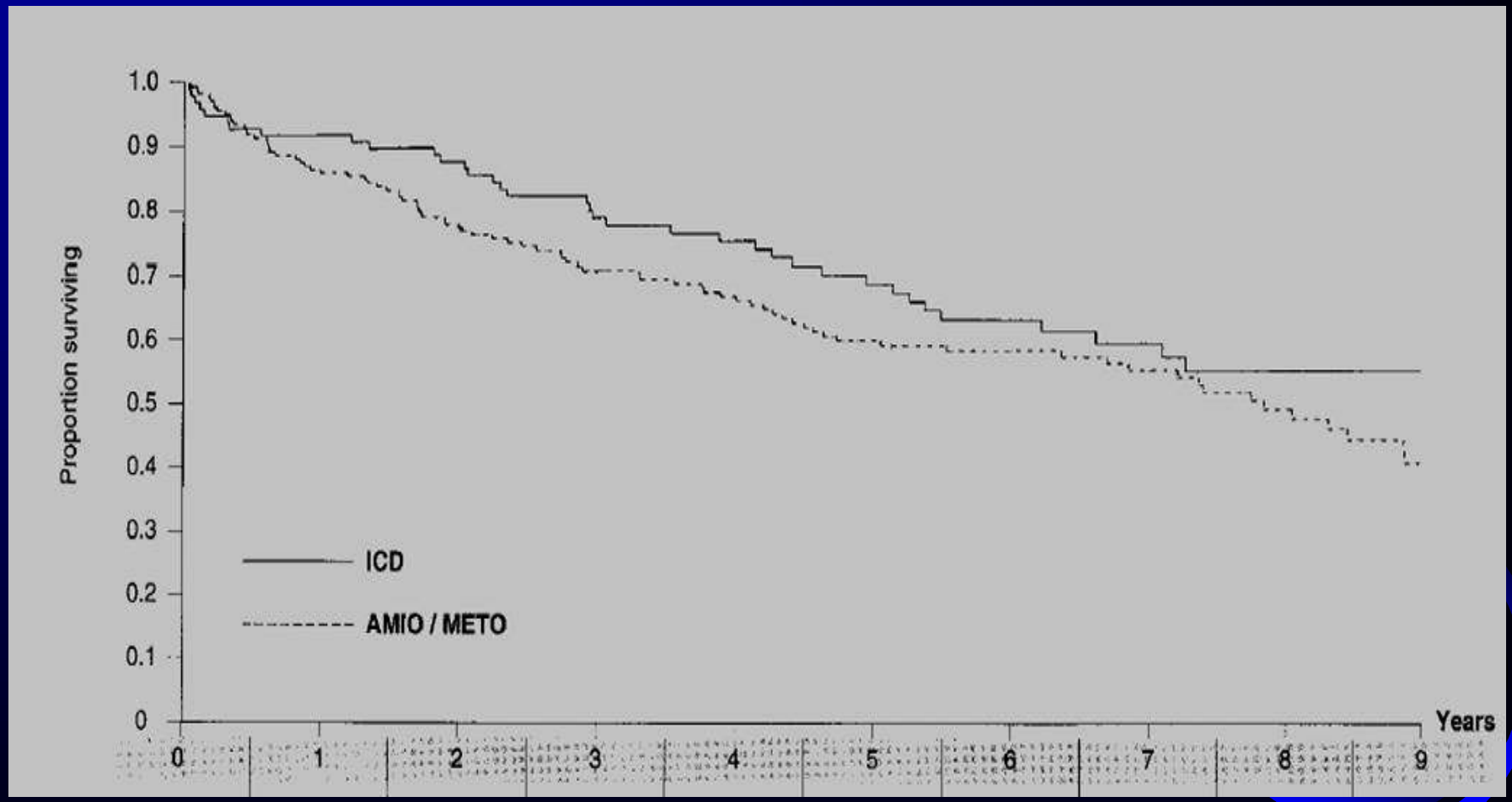
Propafenone (58) stopped in 3/92

ICD (99)

Amiodarone (92)

Metoprolol (97)

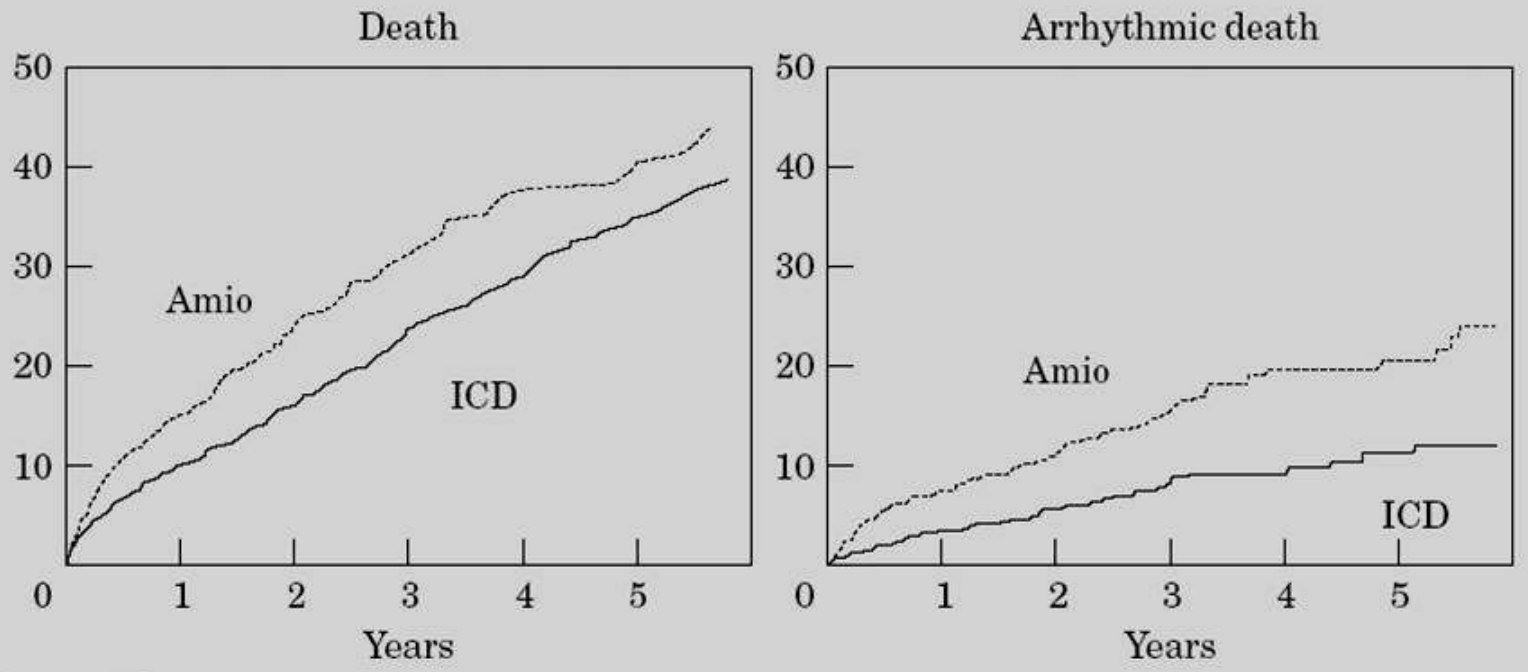
Cardiac Arrest Study Hamburg (CASH) (Circulation 2000;102:748-54)



All cause mortality at 2 years in CASH (Circulation 2000;102:748-54)

- No difference in the metoprolol and amiodarone treatment arms
- ICD : 12.1%
- Metoprolol and amiodarone :19.6%
- => Relative risk reduction : 37% at 2 years (p=0.047)
- Overall mortality reduction = 23% (p = 0.08) and SCD reduction = 61% (p = 0.001) in the ICD group

Meta-analysis of AVID, CASH and CIDS: Connolly EHJ 2000;21:2071-8.



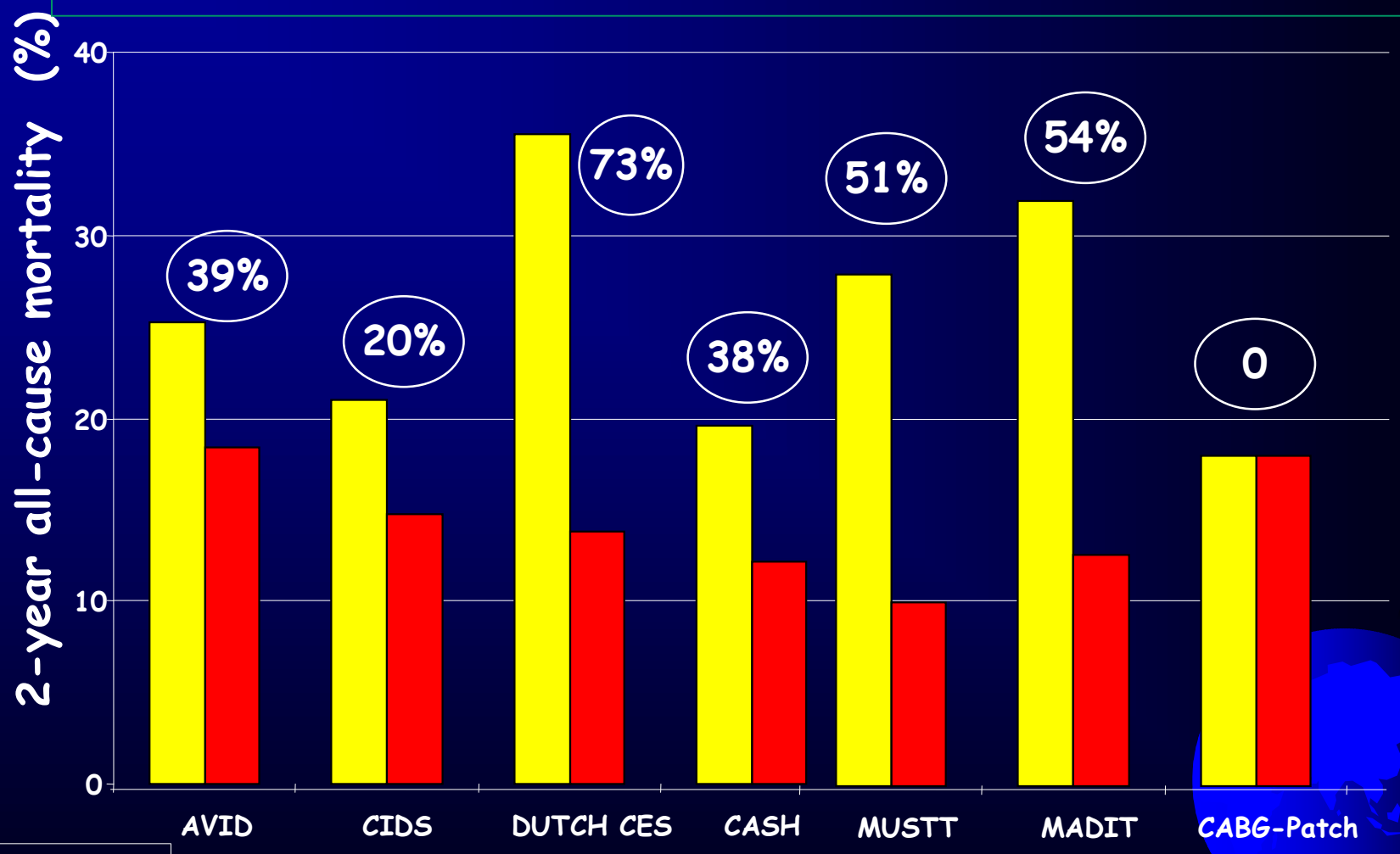
Number at risk

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

Post-event trials

Trial	Design	Target Population	Therapies randomised	Outcome
AVID	Randomised, total mortality	n=1016; VF(455) Sync VT or VT EF<0.4 with Sx (561)	ICD vs Amio(488) or sotalol (13)	ICD ↗ survival by 39% for all arrhythmia classes with EF<0.4 p < 0.02
CIDS	Randomised, total mortality	n=659; VF, Sync VT, presync VT>150/min with EF<0.35	ICD vs amio	ICD improved survival by 20% p = 0.072 (NS)
CASH	Randomised, total mortality	n = 346, VF	ICD vs amio, metoprolol (propafenone)	ICD improved survival by 37% at 2 y, p = 0.047

ICDs reduce mortality by ~ 40%… in secondary and primary prevention



Indications du Traitement par DAI

Extrait des recommandations de la
Société Française de Cardiologie
Janvier 2006
(ESC/ACC/AHA, septembre 2006)

Classification of recommendations

- **Class I :** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful and effective
- **Class II :** Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment
  - **Class IIa :** Weight of evidence/opinion is in favour of usefulness/efficacy
  - **Class IIb :** Usefulness/efficacy is less well established by evidence/opinion
- **Class III :** Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful

Level of evidence

- Level of evidence A : Data derived from multiple clinical trials or meta-analysis
- Level of evidence B : Data derived from a single randomised trial or non-randomised analyses
- Level of evidence C : Only consensus opinion of experts, case studies, or standard-of-care

Indications de classe I

- Arrêt cardiaque par FV ou TV, sans cause aiguë ou réversible : (A)
- Patients coronariens, ± Σtomes IC légère ou modérée (NYHA II ou III), FEVG ≤ 0.3 mesurée 1 mois après un IDM ou 3 mois après un geste de revascularisation : (B)
- TVS spontanée Σtomatique sur cardiopathie : (B)
- TVS spontanée, mal tolérée, en l'absence d'anomalie cardiaque pour laquelle un ttt médical ou une ablation ne peut être réalisé ou a échoué : (B)
- Syncope de cause inconnue avec TV ou FV déclenchable, en présence d'une anomalie cardiaque sous-jacente : (B)

Indications de classe IIa

- Coronariens avec FEVG entre 31 et 35%, mesurée ≥ 1 mois après un IDM et 3 mois après revscularisation avec TV ou FV déclenchable : B
- CMD avec FE ≤ 0.3 et NYHA II ou III : B
- Maladie génétique à haut risque de mort subite par FV sans autre traitement efficace connu : B
- Patients en ICC qui restent Σtomatiques en NYHA III ou IV sous traitement médical optimal avec FEVG ≤ 0.35 et QRS > 120 ms* : B

* : il n'existe pas à cette date d'évidence de la supériorité du DAI biV sur le PM biV

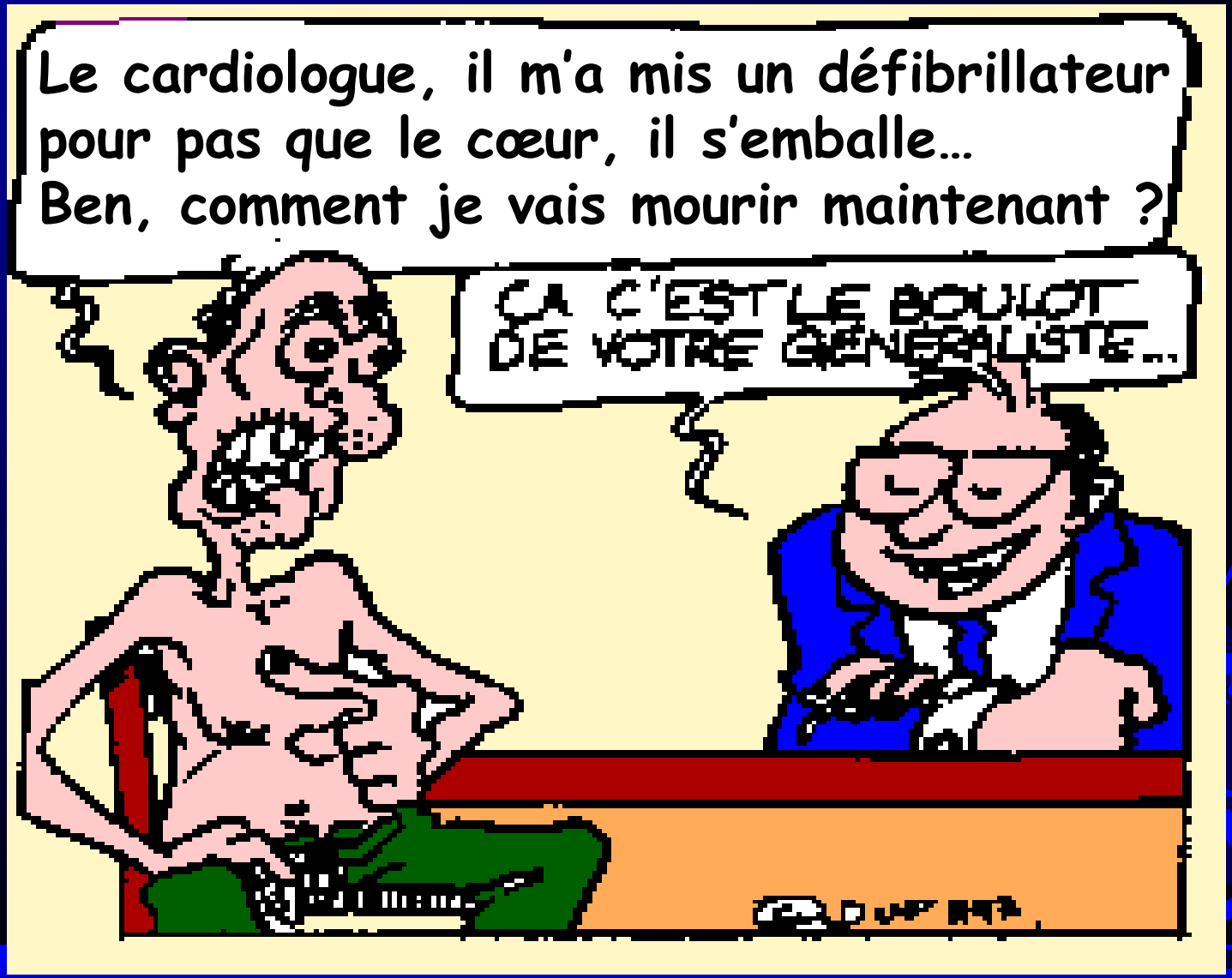
Indications de classe II b

- Patients coronariens avec FEVG entre 0.31 et 0.35 : C
- CMD avec FEVG entre 0.31 et 0.35 : C
- TVS mal tolérée chez un patient en attente de transplantation cardiaque : C

Classe III

Syncope (s) de cause inconnue sans trouble du rythme déclenchable	III	C
TV ou FV incessantes malgré le traitement	III	C
TV ou FV curables par chirurgie ou ablation, ne mettant pas en jeu le pronostic vital (ex : TV fasciculaires, TV infundibulaires…)	III	C
TV ou FV dues à des causes aiguës ou réversibles (ex : ischémie, hypokaliémie…)	III	C
TV ou FV et maladie mentale susceptible d'être aggravée par l'implantation ou d'empêcher le suivi	III	C
Arrêt circulatoire par TV ou FV avec séquelles neurologiques graves	III	C
TV ou FV et maladie terminale avec espérance de vie de moins d'un an	III	C
TV ou FV et insuffisance cardiaque terminale chez un patient non candidat à la transplantation	III	C

Merci pour votre attention



The CABG Patch Trial

1422 eligible
1055 enrolled

900
randomised

Mean follow-up
32 ± 16 months

Hypothesis:
prophylactic ICD implant
at the time of bypass surgery
will improve survival
in pts at high risk of SCD
(EF< 0.36, LP+)

ICD
(n = 466)

Control
(n = 507)

Multicenter Automatic Defibrillator Implantation Trial (MADIT) (NEJM 1996)

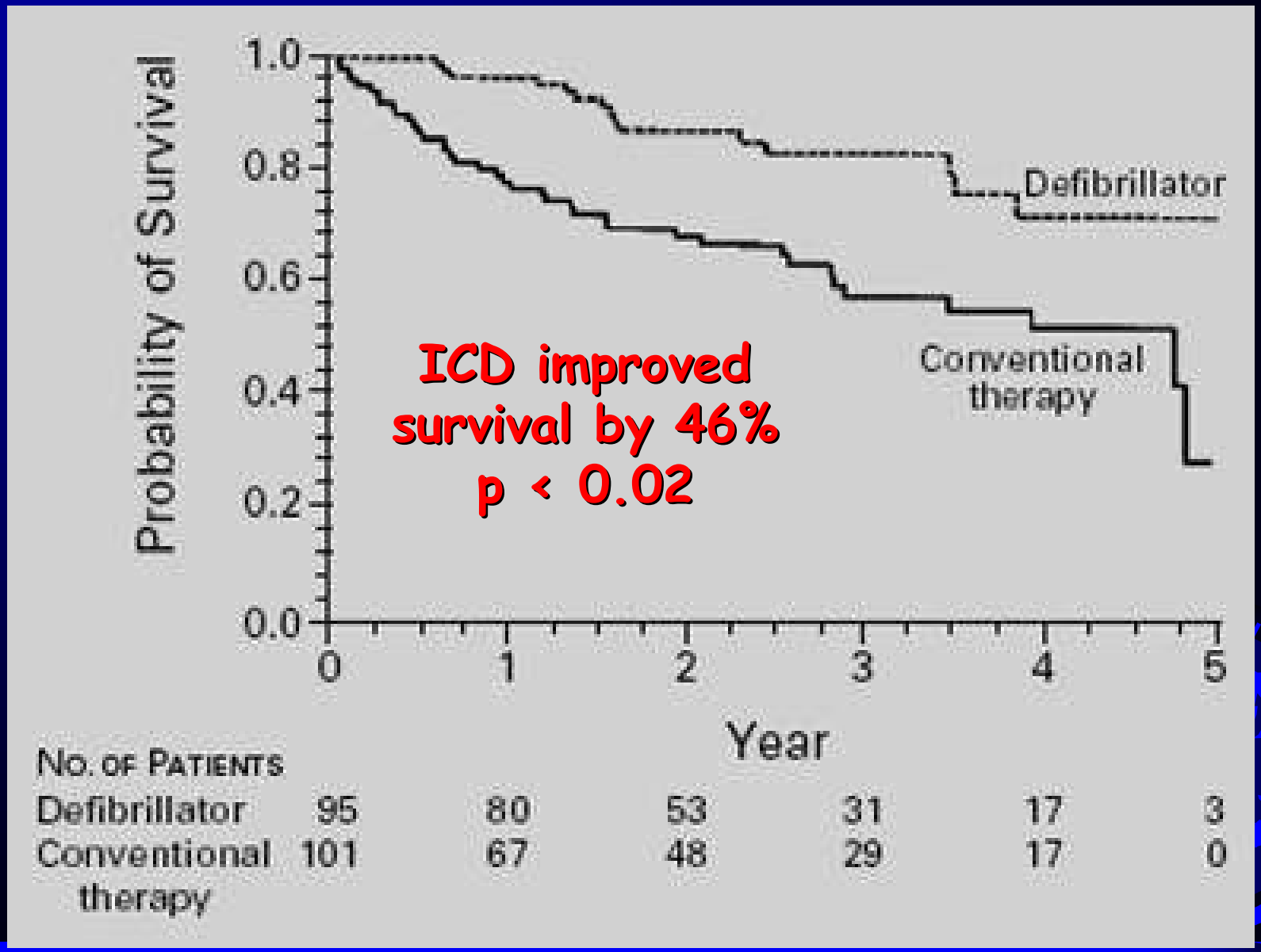
CAD (prior MI, > 3 weeks)
EF<0.35, NYHA I-III, NSVT
Inducible (PES+) off drugs,
PES+ on procainamide

R

Conventional therapy

ICD

MADIT (NEJM 1996;335:1933-40): 196 patients …



MADIT : Limitations, conclusions

- Small number of patients (196 patients in 32 centers in more than 5 years...) => «the typical MADIT patient is rare indeed»
- No placebo arm incorporated
- Randomisation post procainamide failure may have pre-selected drug-failure patients and biased against AA drug therapy
- β- 4 times more frequent in the ICD group

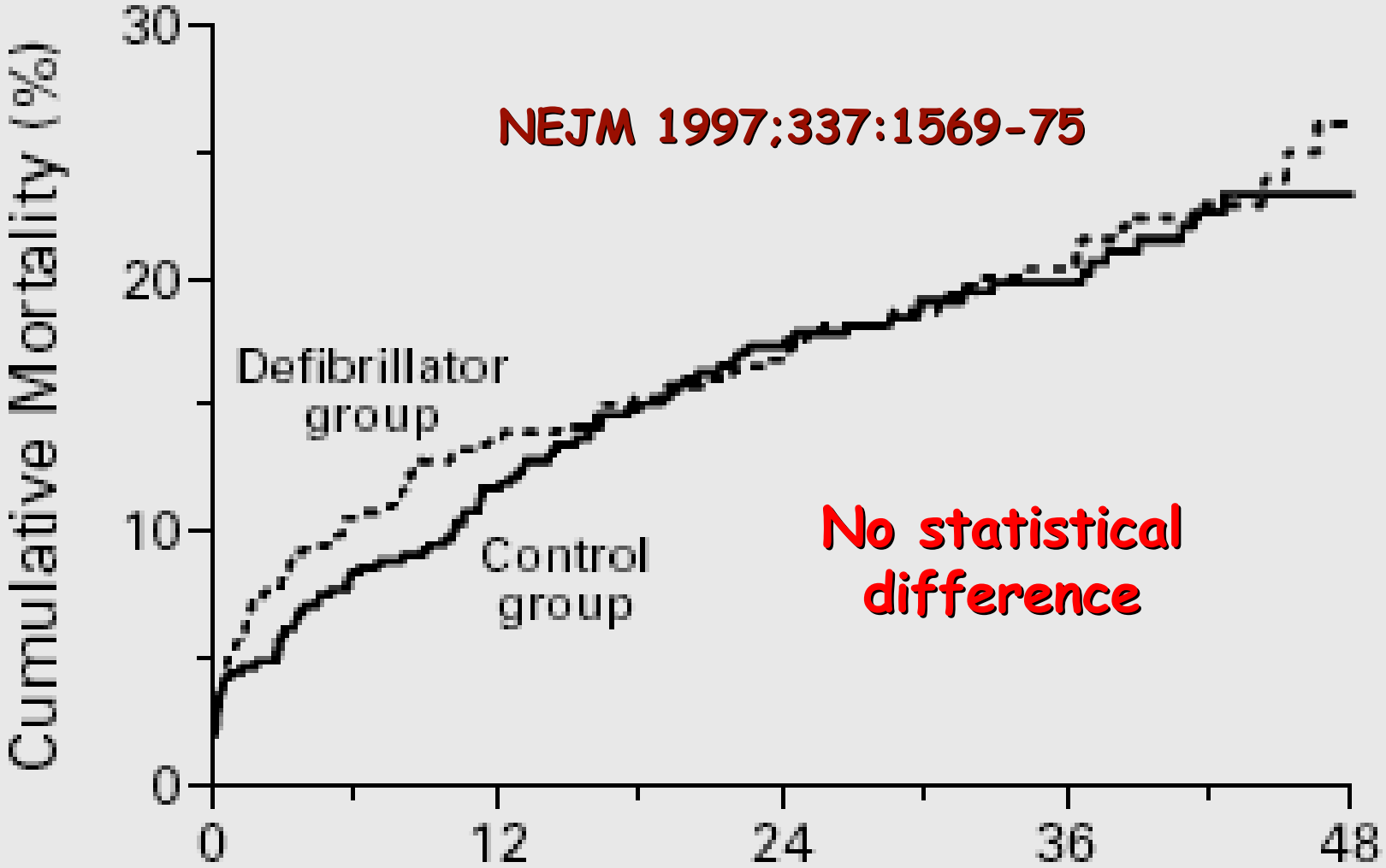
The Coronary Artery Bypass Graft Trial (CABG) Patch Trial (NEJM 1997)

CAD EF<0.36, LPs +,
CABG candidates (900)
Primary endpoint :
Mortality

R

CABG
(n = 446)

CABG + ICD
(n = 454)



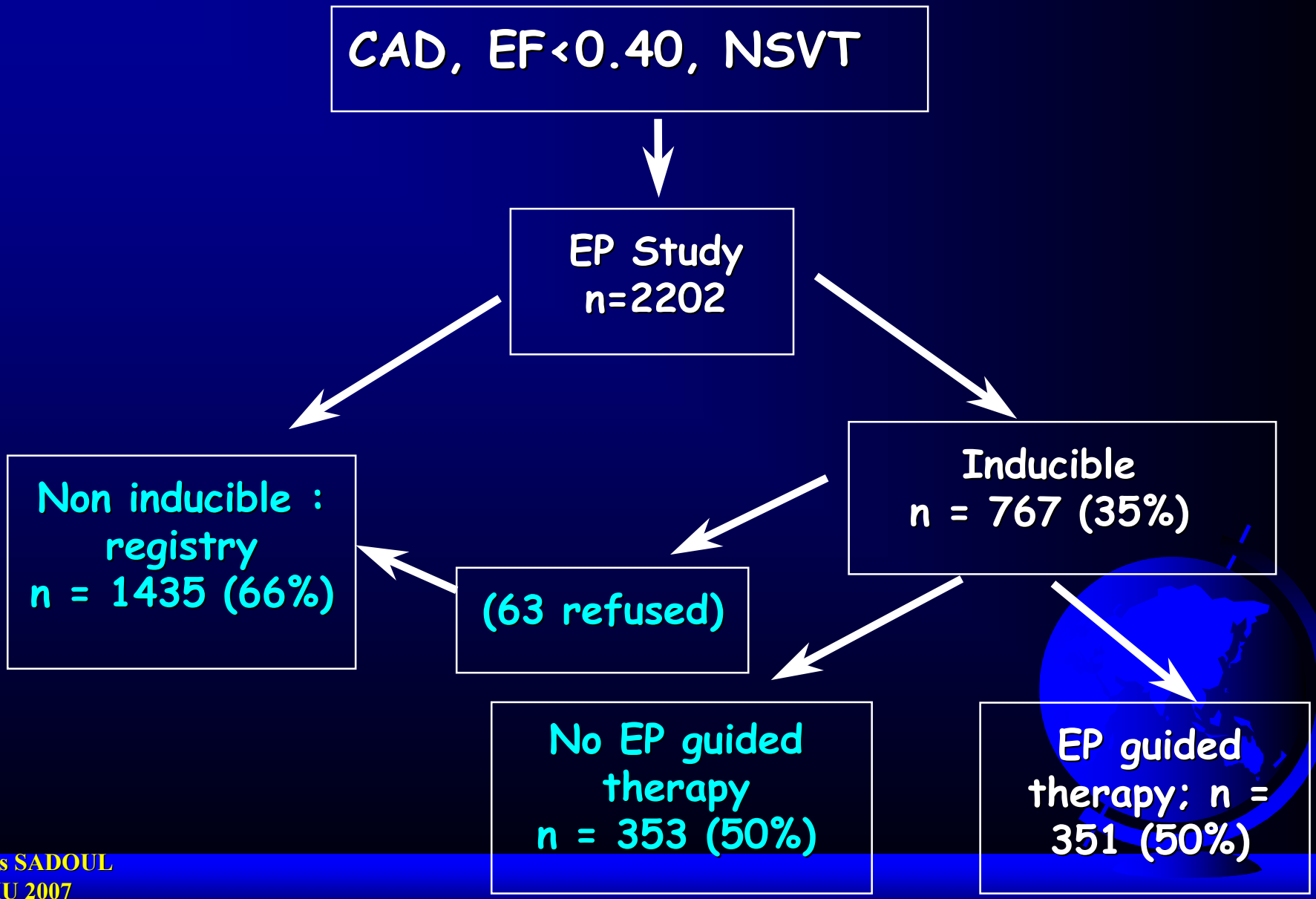
Hypothesis: prophylactic ICD implant at the time of bypass surgery will improve survival in pts at high risk of SCD (EF< 0.36, LP+)

1422 eligible, 1055 enrolled ; 900 randomised; FU = 32 ± 16 months

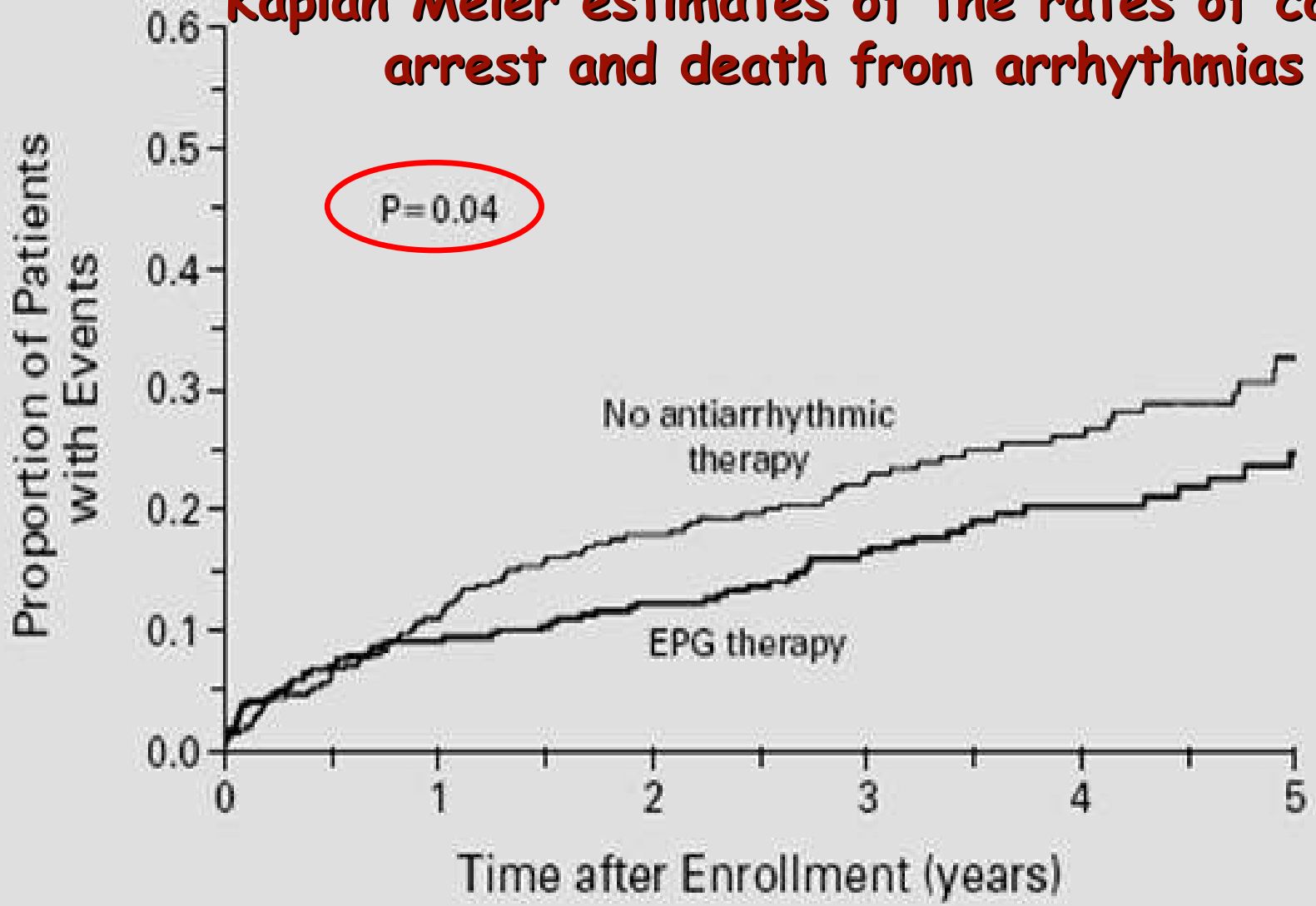
CABG Patch Trial : Limitations, conclusions

- Epicardial systems (morbidity)
- Low mortality rate as compared to MADIT
- Underlines the need for a better identification of high risk patients
- Role of coronary bypass surgery in the prevention of SCD

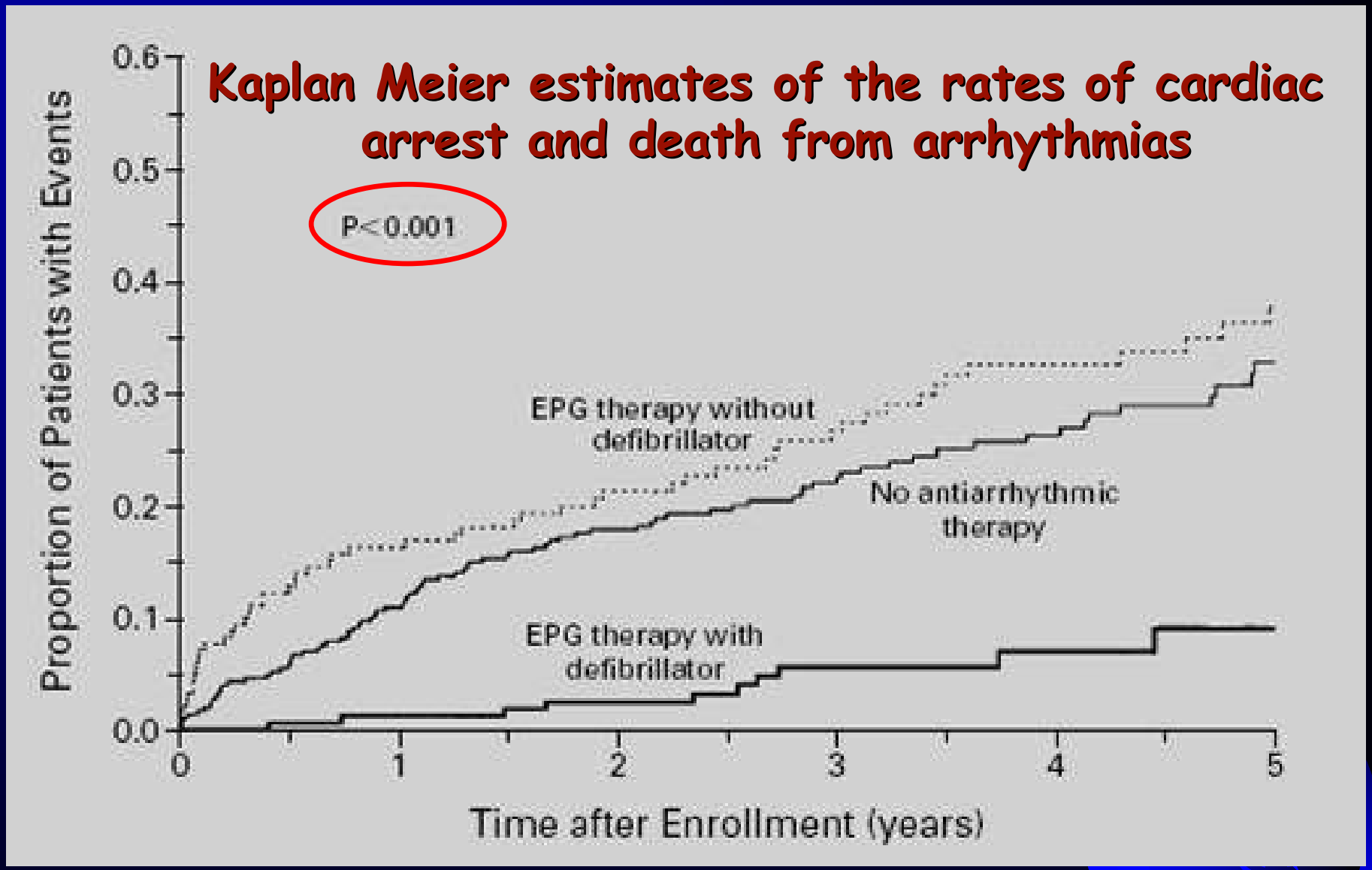
Multicenter UnSustained Tachycardia Trial



Kaplan Meier estimates of the rates of cardiac arrest and death from arrhythmias



27% reduction in arrhythmic death or cardiac arrest for patients receiving EP guided therapy

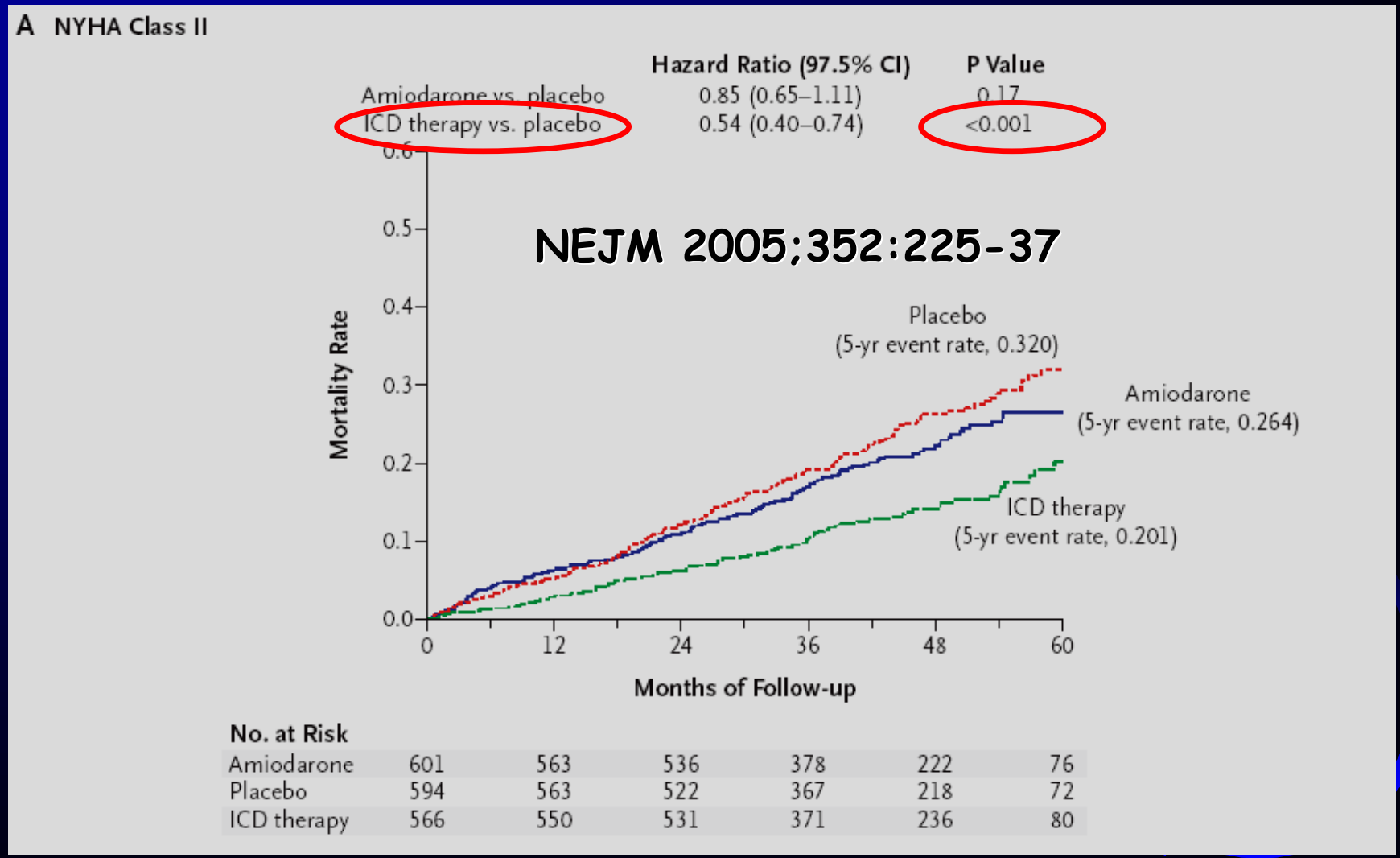


50% or more reduction in arrhythmic death or cardiac arrest for patients receiving ICD therapy

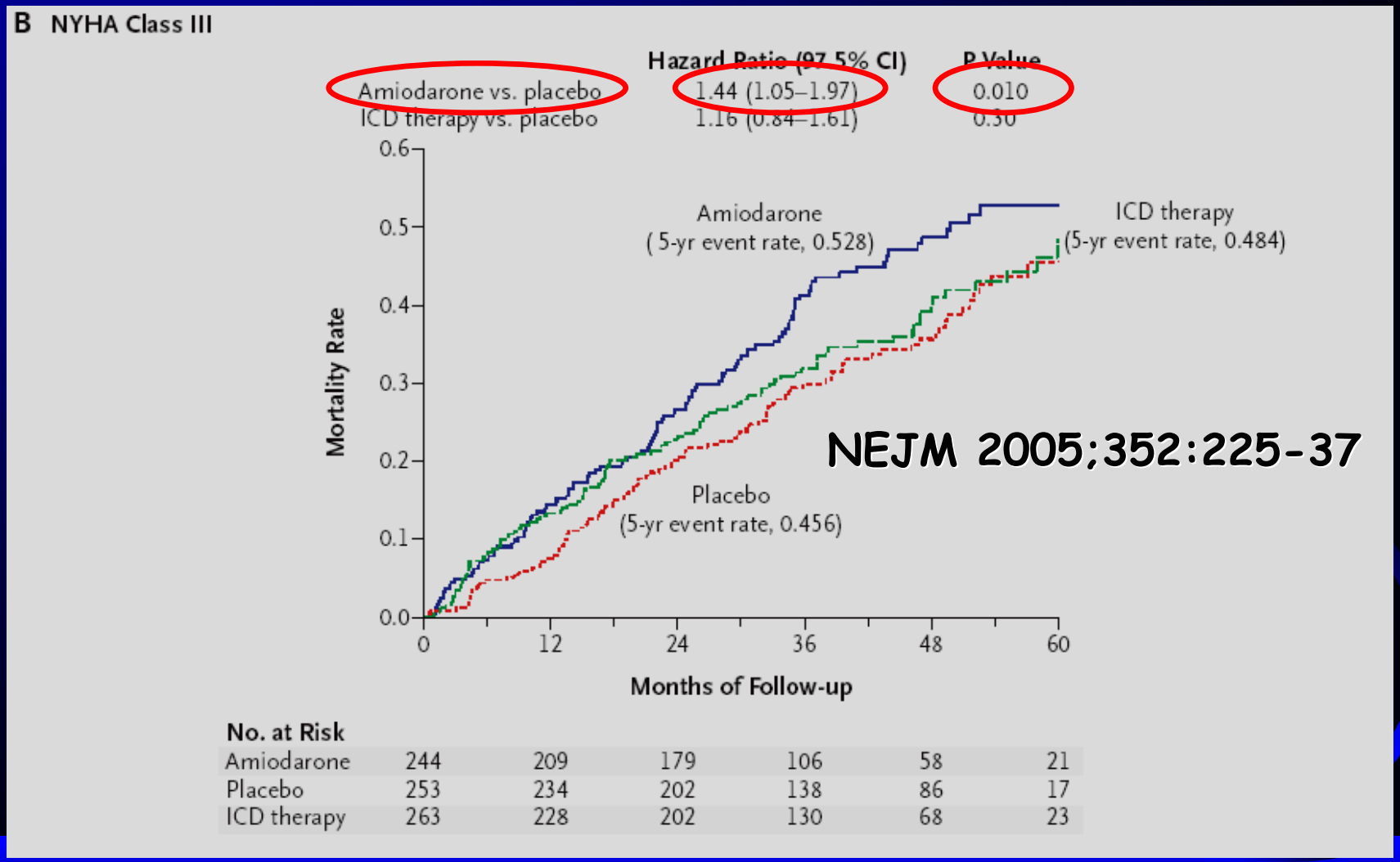
MUSTT: conclusions: NEJM 1999;341:1882-90

- "pts with CAD, LVEF < 0.4, asymptomatic NSVT and inducible sustained ventricular tachyarrhythmia have substantial mortality due to arrhythmia….
- The rate of death is reduced by the use of ICD but not by antiarrhythmic drug therapy…
- It is reasonable to perform EP testing in pts who meet the entry criteria of this trial. If sustained ventricular tachyarrhythmia can be induced, implantation of an ICD is warranted."

KM estimates of death from any cause for the prespecified subgroup of NYHA class II

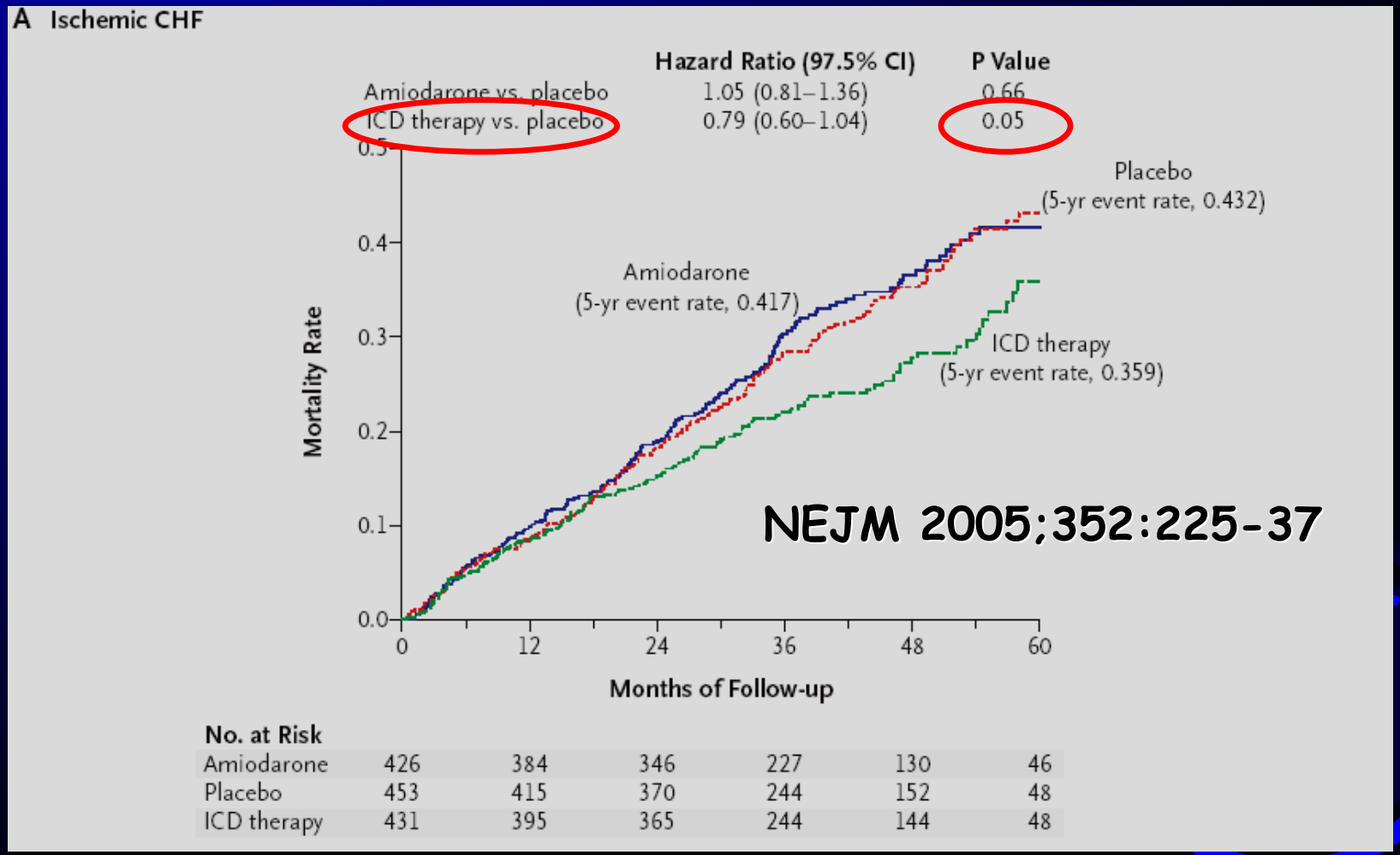


KM estimates of death from any cause for the prespecified subgroup of NYHA class III



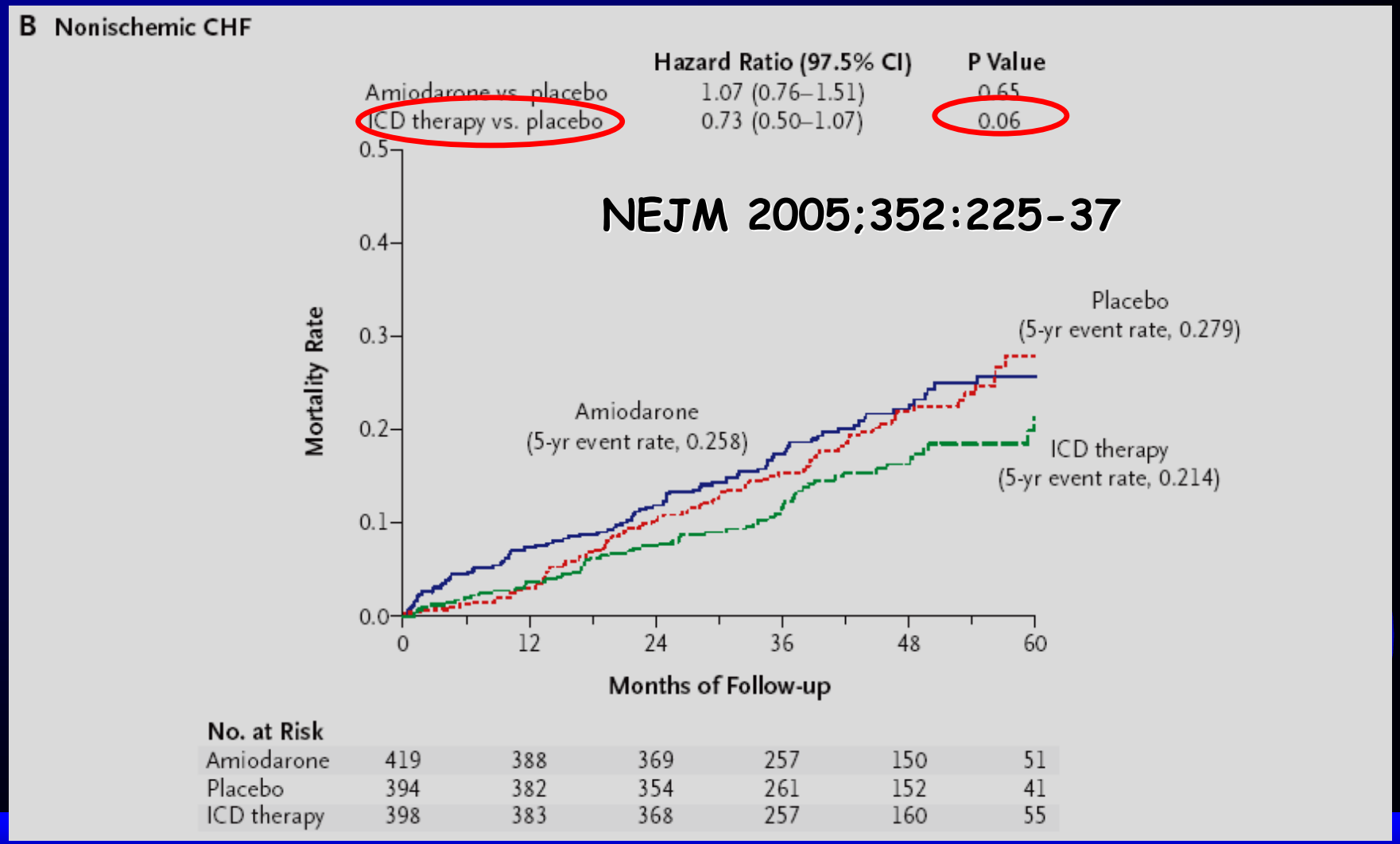
NEJM 2005;352:225-37

KM estimates of death from any cause for the prespecified subgroup of ischemic CHF



NEJM 2005;352:225-37

KM estimates of death from any cause for the prespecified subgroup of non-ischemic CHF



Clinical perspective of AVID, CASH and CIDS

- These trials support the use of ICD therapy as a front-line therapy in patients at high risk of SCD
- Results are confounded by the fact that many of ICD patients took concomitant amiodarone, sotalol and β-
- Although amiodarone, sotalol and β- appear to have a beneficial effect on survival, the lack of placebo-controlled studies raises the question of whether these drugs have a beneficial, neutral or adverse effect on survival