Clinical Trials In Cardiac Rhythm Management

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HR-UK
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Clinical Trials

- Pacemakers
- ICD’s
- CRT
- AF

Lots to choose from!

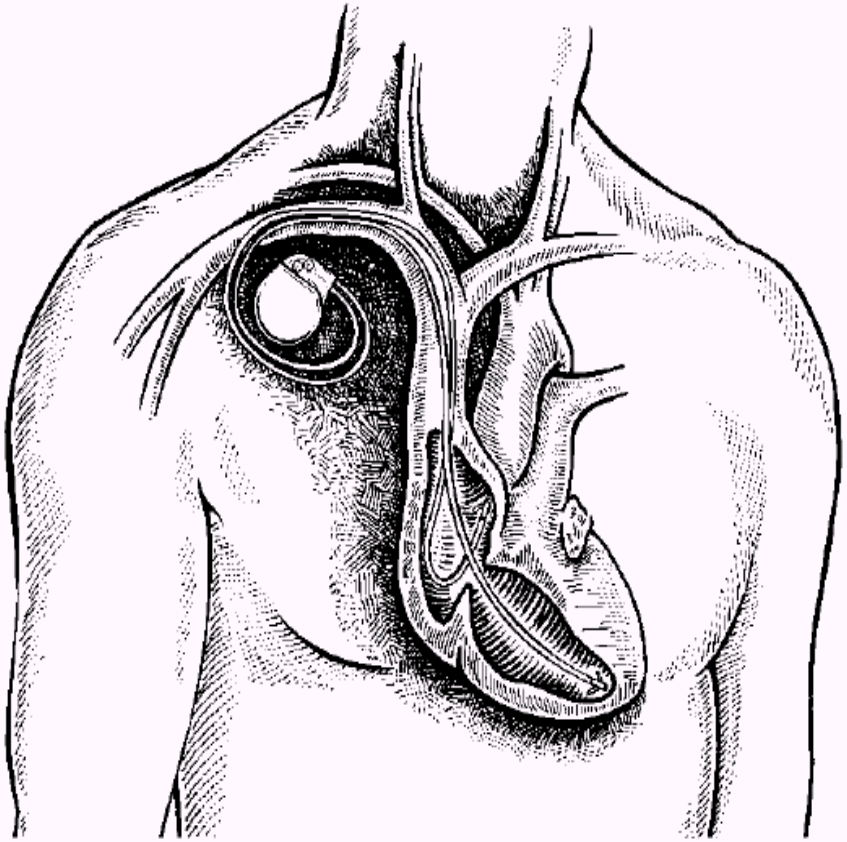
- ADEPT
- ANDROMEDA
- ATHENA
- AVID
- CARE-HF*
- CASH
- CHADS-VASc*
- CIDS
- COMPANION*
- CTOPP*
- DANISH I*
- DANISH II*
- DAVID*
- DEFINITE
- EMPIRIC
- MIRACLE
- MADIT I*
- MADIT II & MADIT II 8y FU*
- MADIT CRT
- MIDAS 9
- MOST
- MUSTT
- Pain FREE I,II
- PAVE
- PREPARE*
- REVERSE
- SAVE PACe
- SCD HeFT*
- UKPACE*
- VAST

.....etc, etc!

Pacing

Physiologic Pacing Trials

- Widespread acceptance that physiologic pacing (i.e. dual chamber pacing with normal short AV from the RV apex) was the universal mode despite lack of clinical evidence.
- Unquestioned for 30 years
- Successful model for all practical purposes (safe and beneficial for patients)
- Accepted by scientific community
- Intuitively clear – i.e. mimics normal AV conduction



But.....what do the studies say?

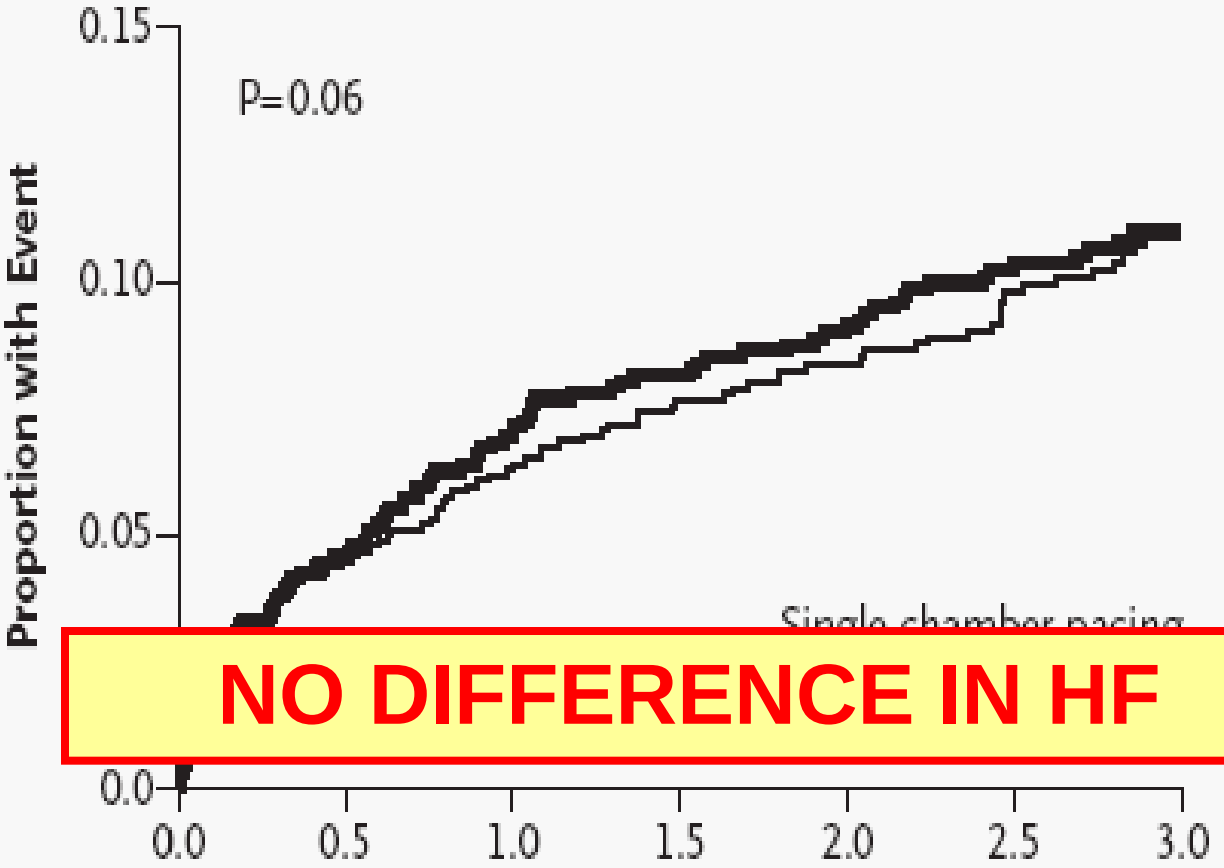
The Major Pacing Trials have Shown Little Benefit to Support 'Physiologic Pacing'

Randomized trials involving >10,000 patients with SND (MOST, CTOPP), AVB (UKPACE) or no indication for bradycardia pacing (DAVID) have reached consensus.

- **There is no advantage in mortality, stroke, heart failure or QOL in DDDR vs. VVIR pacing.**
- **DDDR pacing might reduce AF but you must treat large numbers of patients for at least several years to demonstrate this.**

	Mortality	Hospitalization for CHF	Atrial Fibrillation	Stroke
Danish AAIR vs. VVIR; All SND pts	—	↓ But not until after 3 years FU	↓ Acute & Chronic	NS
CTOPP Physiologic vs. ventricular pacing; ~40% of pts had SND	—	—	↓ But not until 2 years FU	—
MOST Dual-chamber vs. single chamber; All SND pts	—	↓ But still 10% at 36 months	↓ But still 24-25% at 36 months	—
DAVID **No indication for pacing**	↑ Composite Endpoint		NS	NS

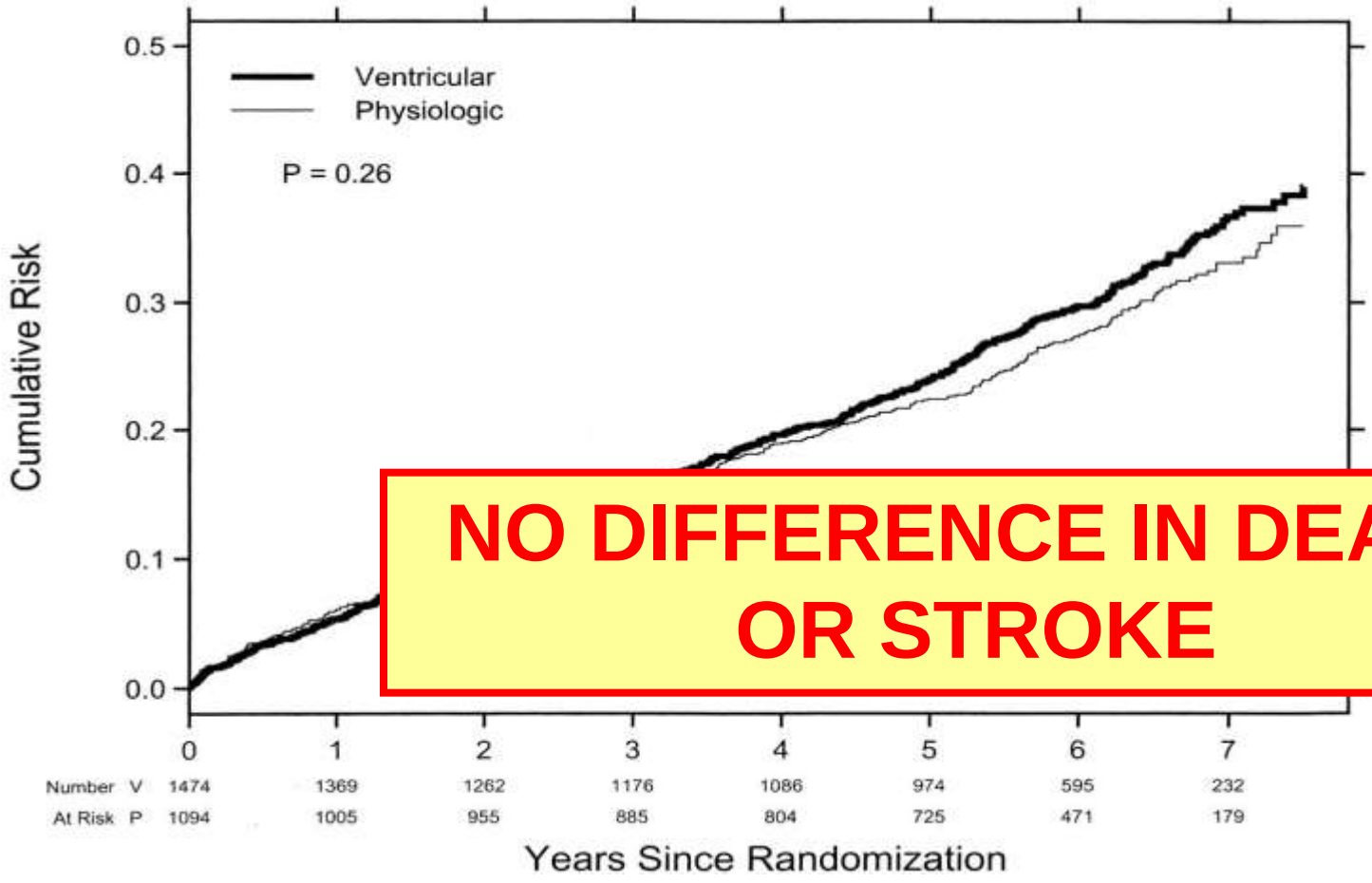
UKPACE: 2,021 AVB pts DDD/R vs. VVI/R
Heart Failure at 5 years



NO DIFFERENCE IN HF

Toff WD et al. N Engl J Med 2005;353:154-155

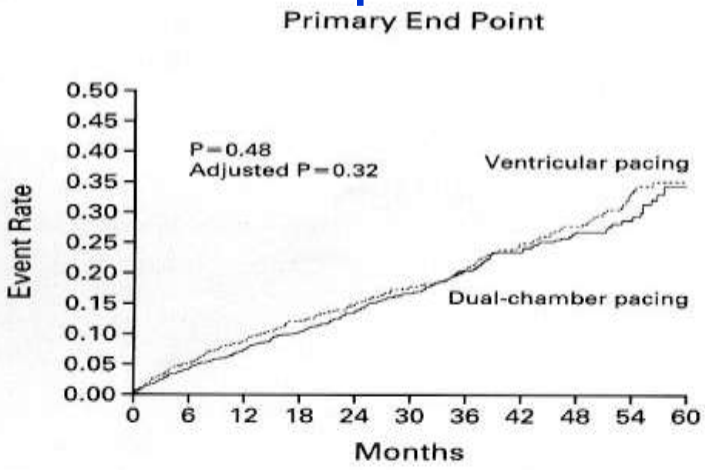
CTOPP: 2,568 pts DDDR vs. VVIR
Death or Stroke at 6.4 years



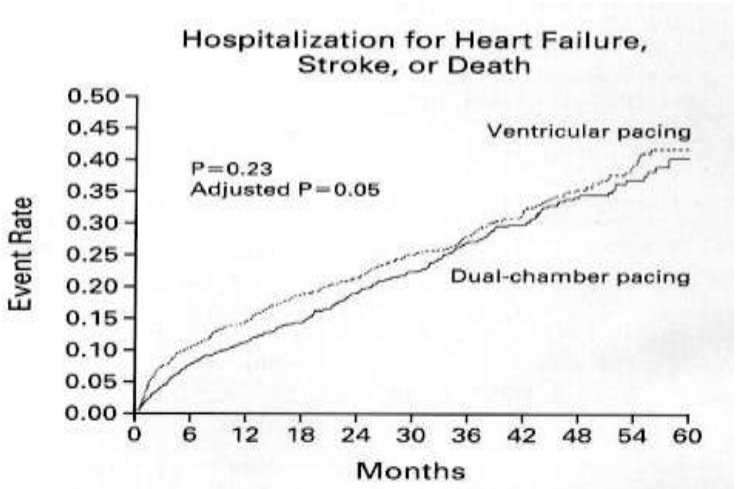
NO DIFFERENCE IN DEATH OR STROKE

Skanes A, et al. Progression to Chronic Atrial Fibrillation After Pacing: The Canadian Trial of Physiologic Pacing. J Am Coll Cardiol 2001;38:167-72.

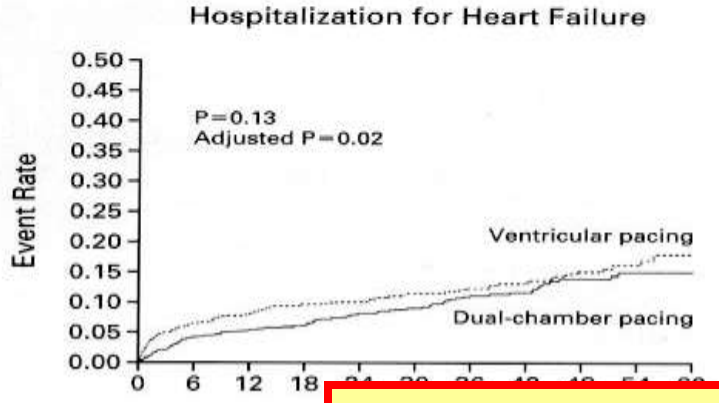
MOST: 2,010 SSS pts, DDDR vs.VVIR
6 year Follow-up



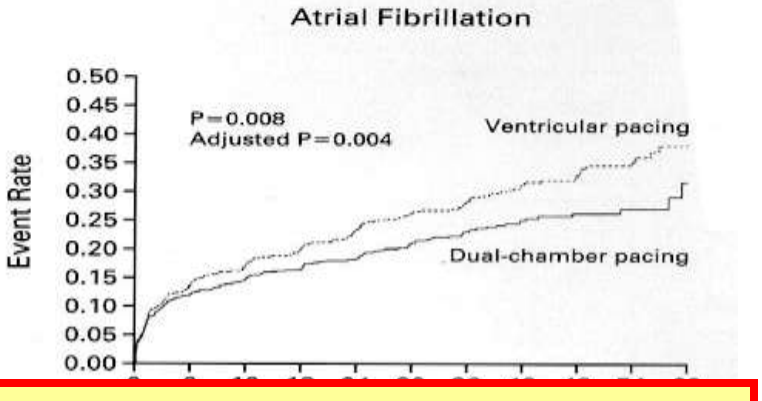
No. at Risk											
Ventricular pacing	996	934	897	813	678	557	431	320	218	125	39
Dual-chamber pacing	1014	963	930	833	693	555	431	328	214	120	28



No. at Risk											
Ventricular pacing	996	880	839	752	624	504	388	287	193	110	35
Dual-chamber pacing	1014	926	889	793	649	518	394	297	188	105	26



No. at Risk				
Ventricular pacing	996	890	855	766
Dual-chamber pacing	1014	932	894	801



NO DIFFERENCE IN DEATH, STROKE, or HEART FAILURE

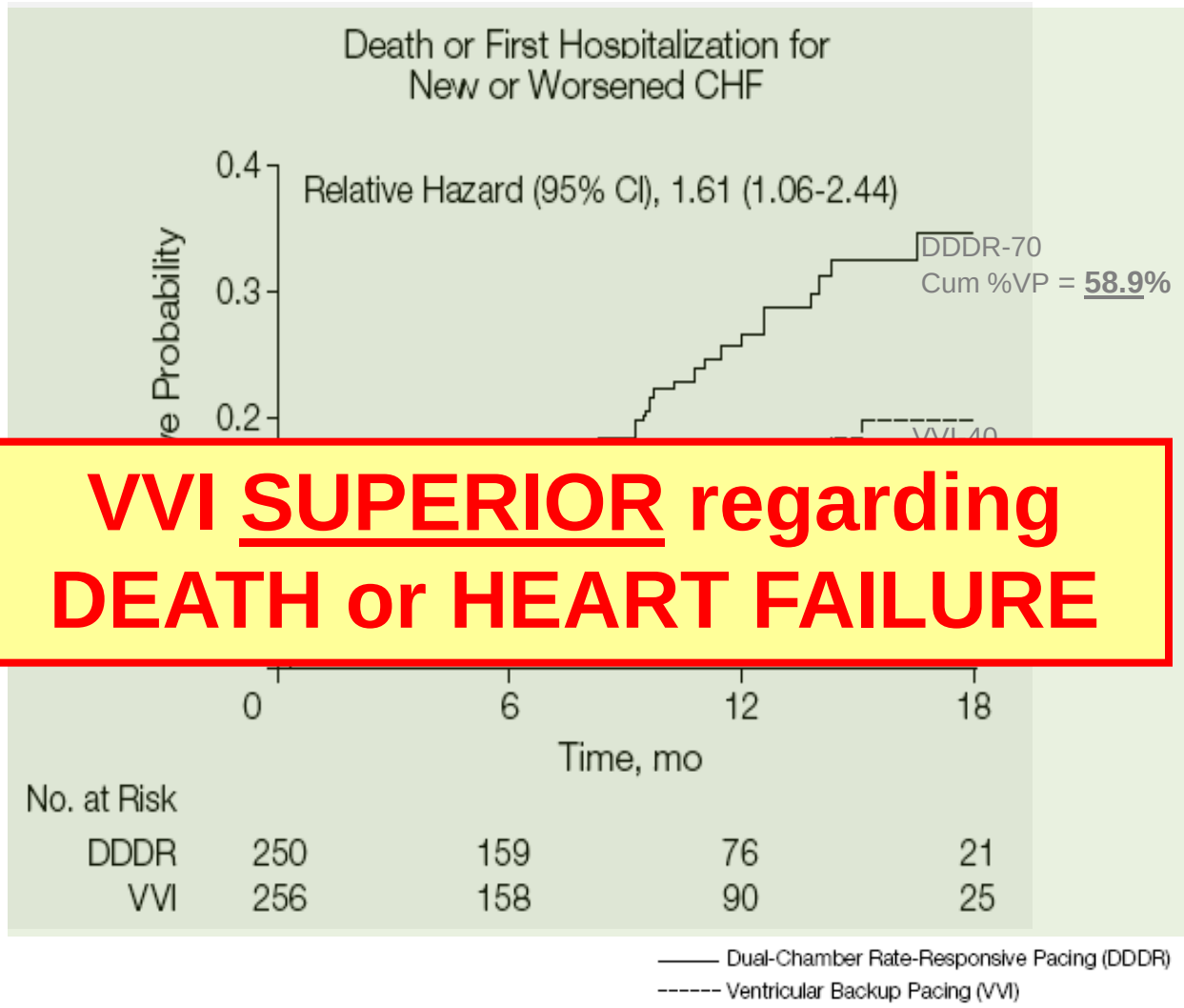
Sweeney M, Hellkamp A, Ellenbogen K, et al. Adverse
Trial of Pacemaker Therapy for Sinus Node Dysfunctio

DAVID: 380 ICD patients: DDDR vs.VVIR
3 year follow up

David Trial

- Randomized DDDR-70 (58.9% Ventricular Pacing) vs VVI-40 (3.5% Ventricular Pacing)

- Patient programmed to receive DDDR pacing had a higher risk of Heart Failure or death.



VVI SUPERIOR regarding DEATH or HEART FAILURE

Wilkoff B, et al. on behalf of the DAVID Trial Investigators. JAMA 2002;288:3115-3123.

So
Is RV Pacing Bad For You?

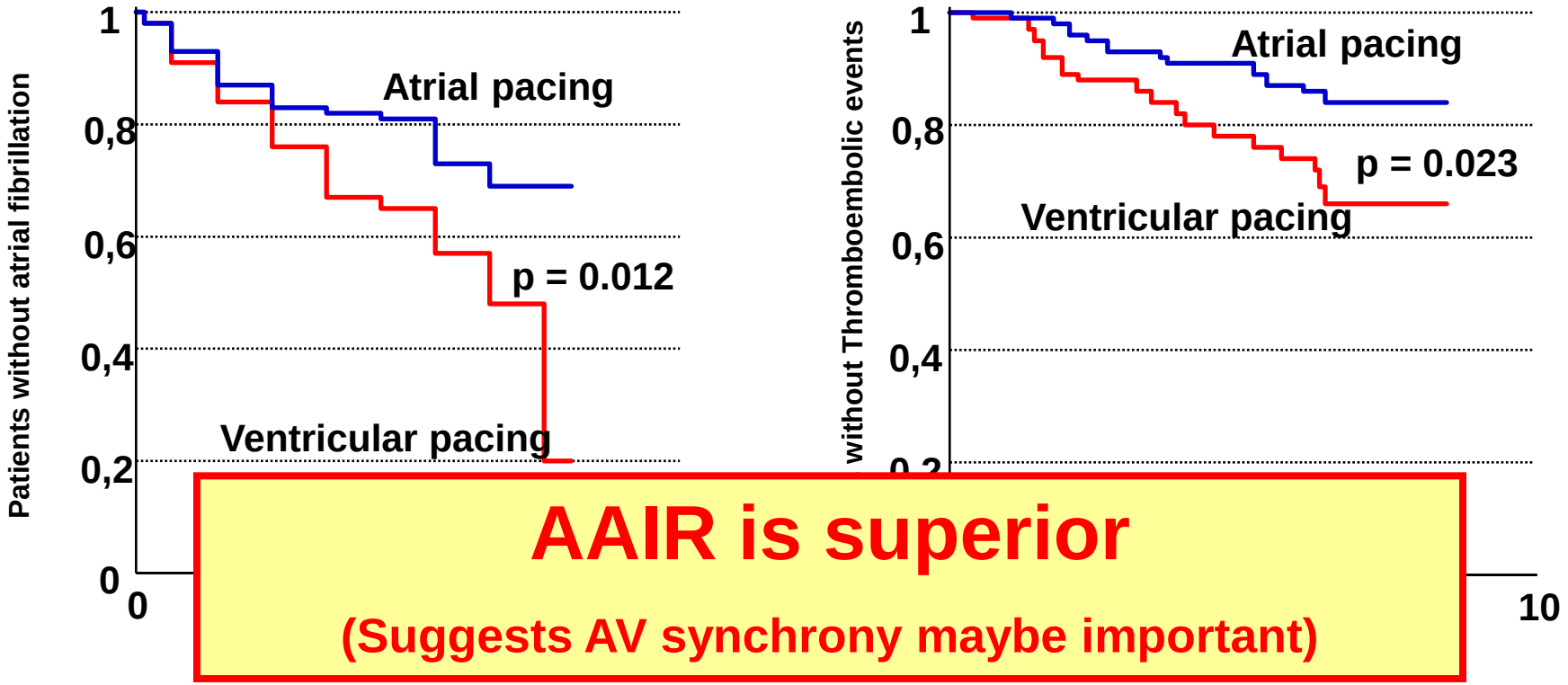
Should we avoid it in SSS patients?

What do the studies say?

Danish I: AAIR better than VVIR in SSS patients

Comparison between 225 Patients with sick sinus syndrome
(110 AAIR-, 115 VVIR-pacemakers)

Atrial only pacing was associated with less AF and Thomboembolic events



AAIR is superior

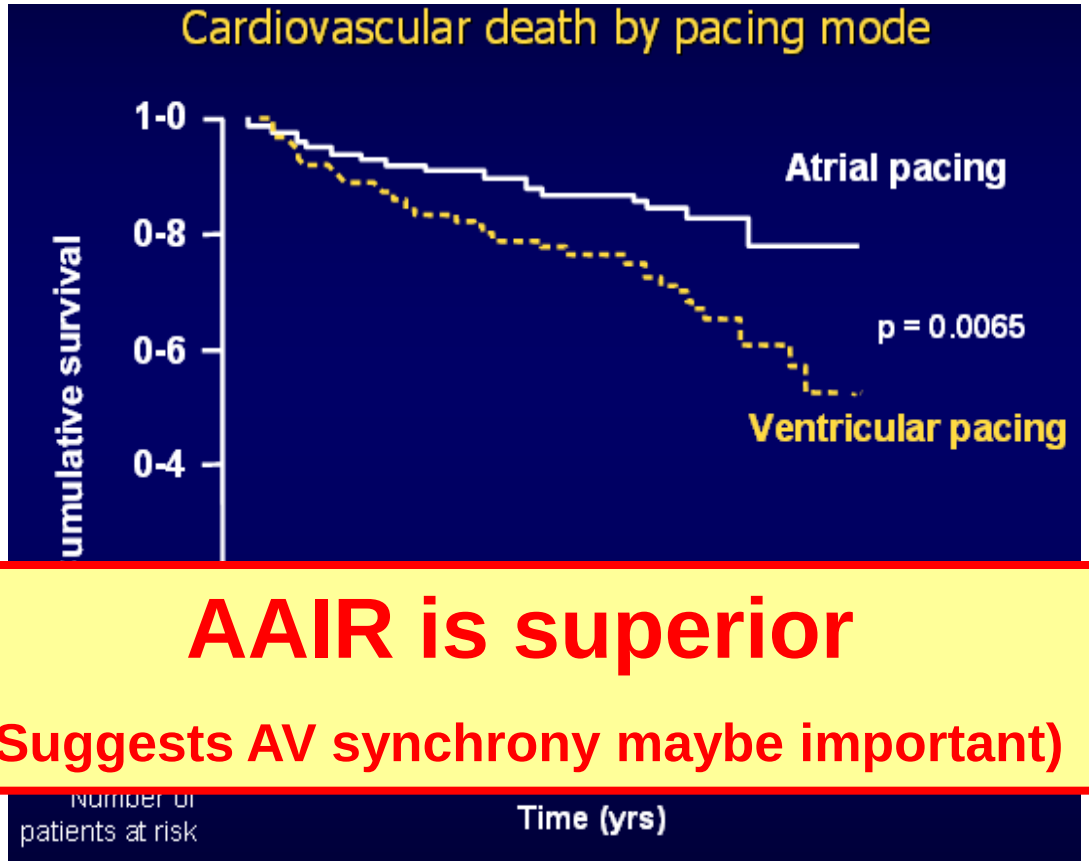
(Suggests AV synchrony maybe important)

Andersen et al., Lancet 1997
Nielsen J, Kristensen L, Andersen H, et al. A Randomized Comparison of Atrial and Dual-Chamber Pacing in 177 Consecutive Patients with Sick Sinus Syndrome. J Am Coll Cardiol 2003;42:614-23.

Insight from Danish I: AAIR better than VVIR in SSS pts

Comparison between 225 Patients with sick sinus syndrome
(110 AAIR-, 115 VVIR-pacemakers)

Atrial only pacing was associated with less cardiovascular death



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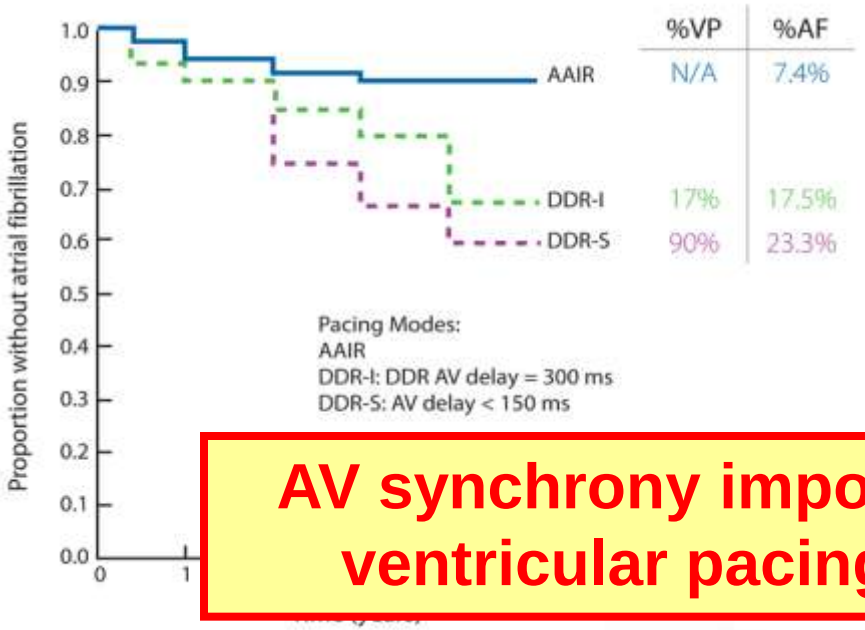
Insight from Danish II: Pace Less to reduce AF

- Comparison between AAIR versus DDDR (with short or long AV interval) - 177 SSS patients

- At 3 years the results for the incidence of AF are
  - AAIR group: 7.4% (p=0.03)
  - DDDR with long AV: 17.5%
  - DDDR with short AV: 23.3%



AAIR pacing had a lower proportion of AF than DDDR **with and without** extended AV delays[2]

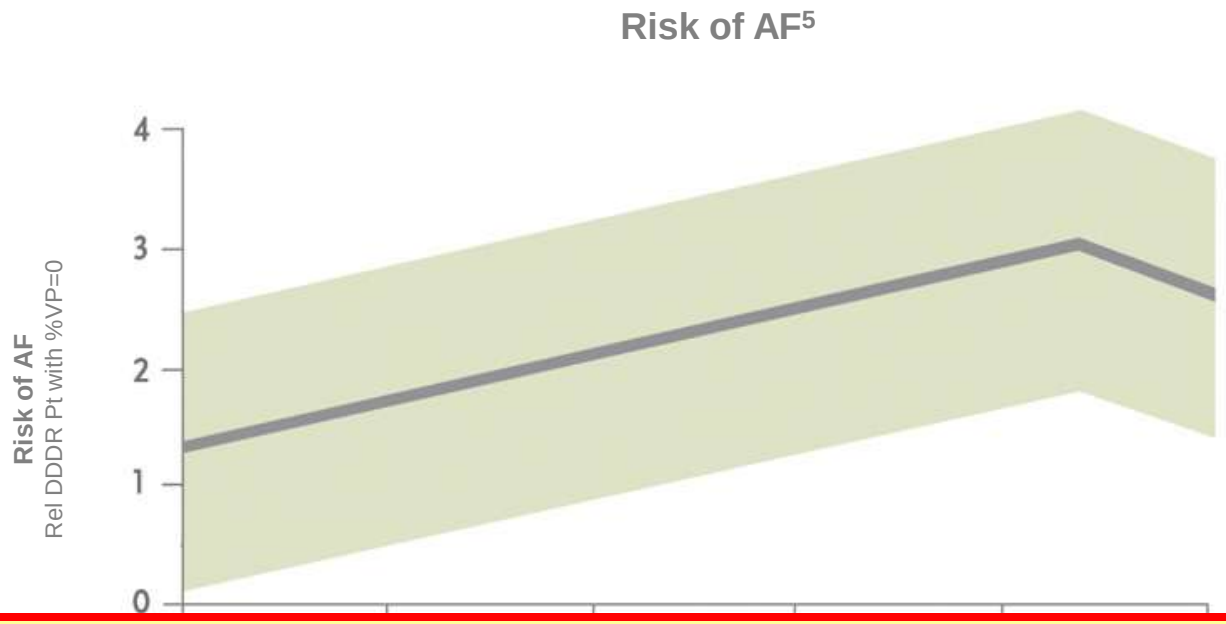
AV synchrony important but unnecessary ventricular pacing maybe detrimental

[1] Epstein AE, et al. *J Am Coll Cardiol*. 2008;51:e1-62.
[2] Nielsen JC, et al. *J Am Coll Cardiol*. 2003;42:614-623.

Insight from MOST: Pace Less to reduce AF

MOST trial:

- Comparison of VVIR with DDDR in 2010pts
- Analysis of 1332pts in which the percentage ventricular pacing could be measured.



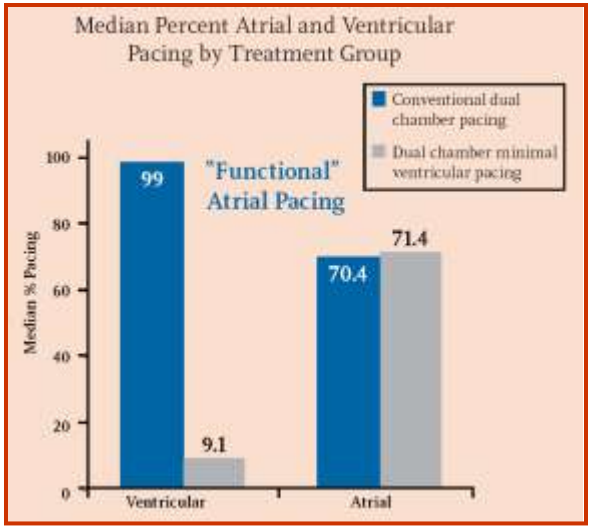
Each 1% increase RV pacing increases the risk of AF by 1% (up to 85%)

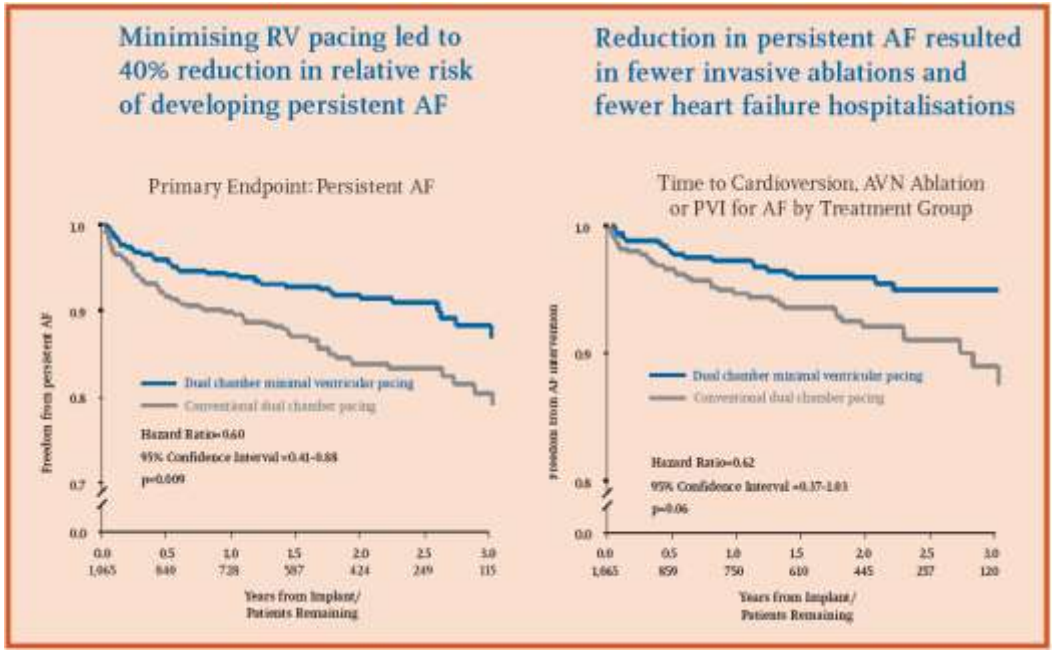
Sweeney MO, et al. Circulation 2003;23:2932-2937

Insight from SAVE PACe – Pace Less to Reduce AF

- Randomised 1065 pts with SND to “conventional dual chamber pacing” OR “dual chamber plus a strategy of minimal ventricular pacing”

A strategy of minimization of ventricular pacing (VP=9.1%) lead to a 40% reduction in the relative risk of developing persistent AF

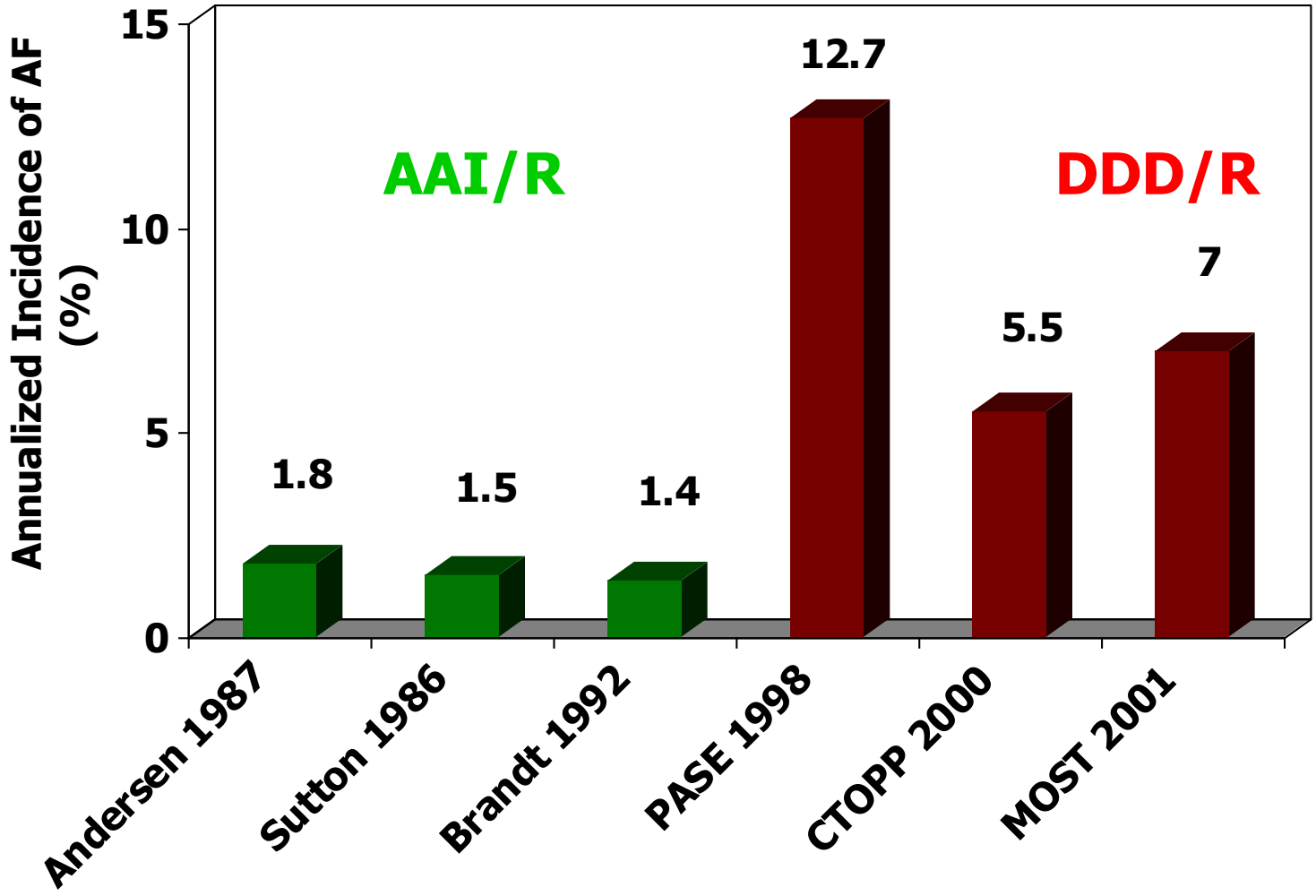




Reference

Sweeney MO, Bank AJ, Nsah E, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med*. September, 2007; 357(10):36-44.

Pace the ventricle less to reduce AF



DAVID Trial: DDDR associated with an increases in the risk of CHF or Death

David Trial

- 380 ICD pts randomized DDDR-70 vs VVI-40
- 3yr follow up
- Pt programmed to DDDR pacing had a higher risk of HF or death.

VVIR SUPERIOR regarding DEATH or HEART FAILURE

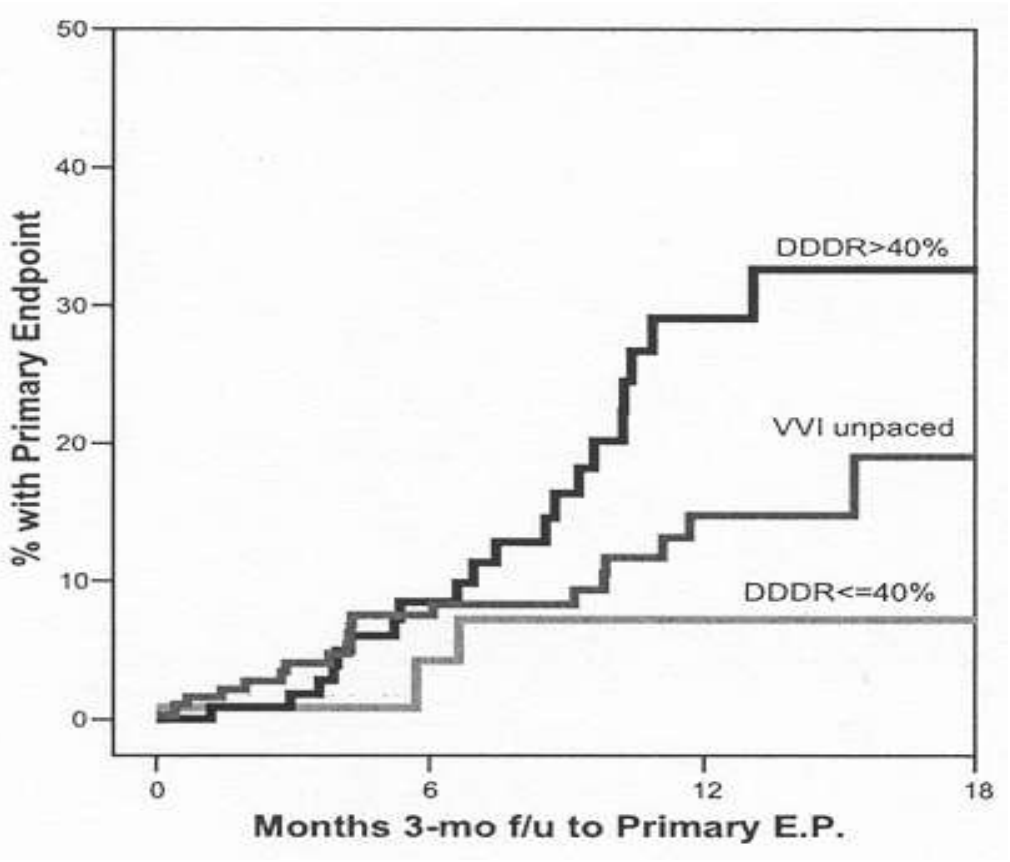
Wilkoff B, et al. on behalf of the DAVID Trial Investigators. JAMA 2002;288:3115-3123.

But ...

Review of DAVID data

- DDDR 70 with less than 40%VP had better outcome than VVI 40 group

- Patients with >40%VP had a 4.4x increased risk of death and heart failure hospitalisation



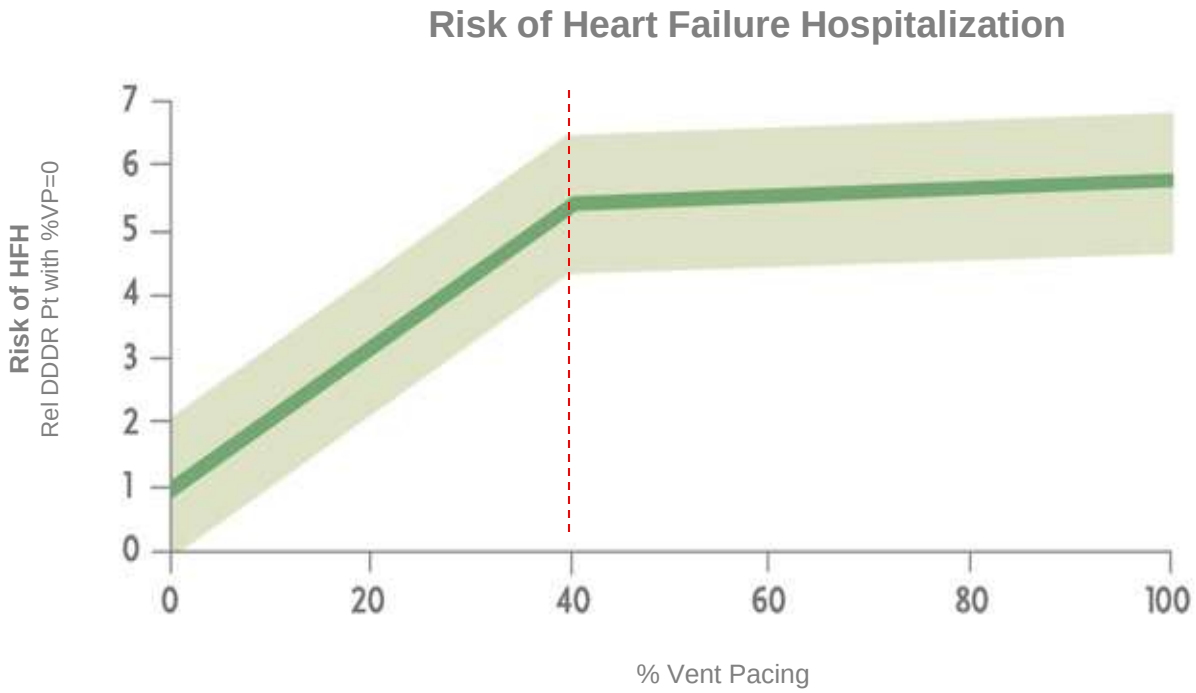
Vent Pace less to reduce HF and mortality, but maintaining AV synchrony important

Sharma AD et al "Percent right ventricular pacing predicts outcomes in the DAVID trial; Heart Rhythm 2; 8; 2005

Pace Less to reduce HF hospitalisation

MOST trial:

- RV pacing > 40% of the time in DDDR mode was associated with a 2.6 fold risk of CHF compared with pacing < 40%.



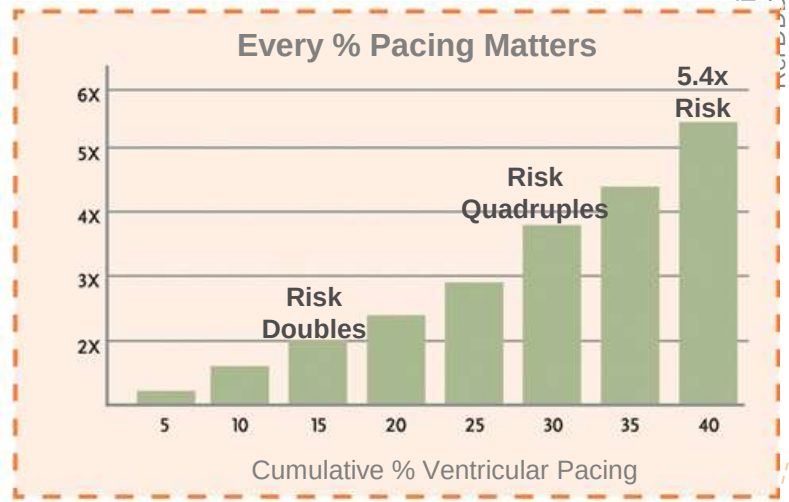
Sweeney MO, et al. Circulation 2003;23:2932-2937

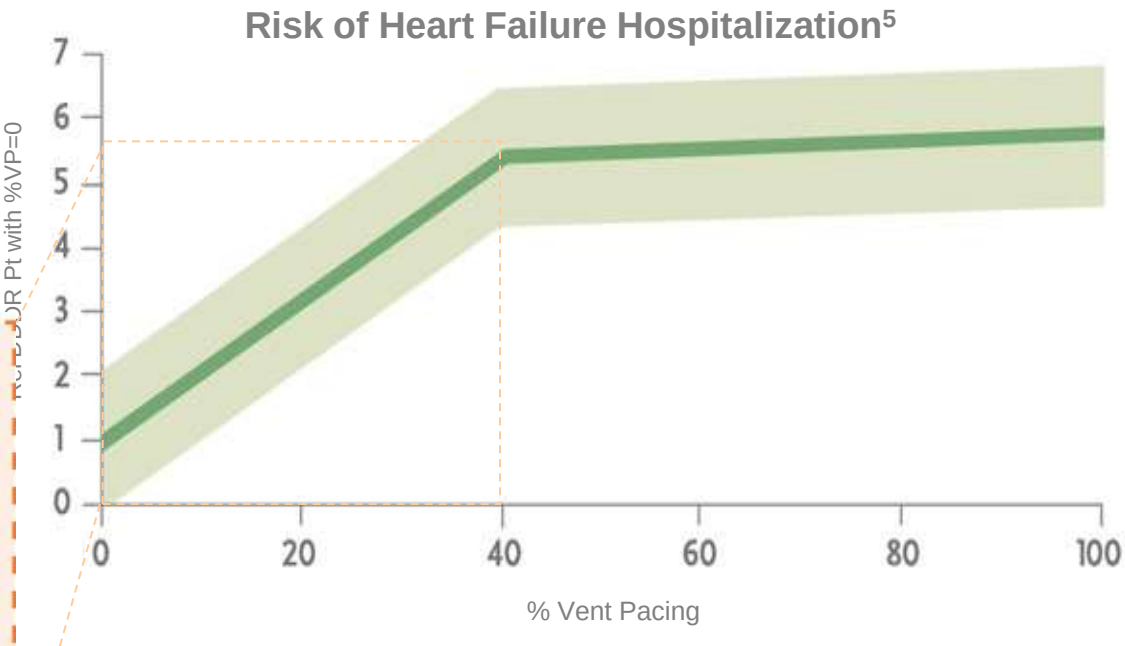
To Minimize Heart Failure You Need to Minimise RV Pacing

MOST trial:

Comparison of VVIR with DDDR in 2010pts (%VP could be measured in 1332pts)

Each 10% increase RV pacing increased the risk of HF by 54% (up to 40%).

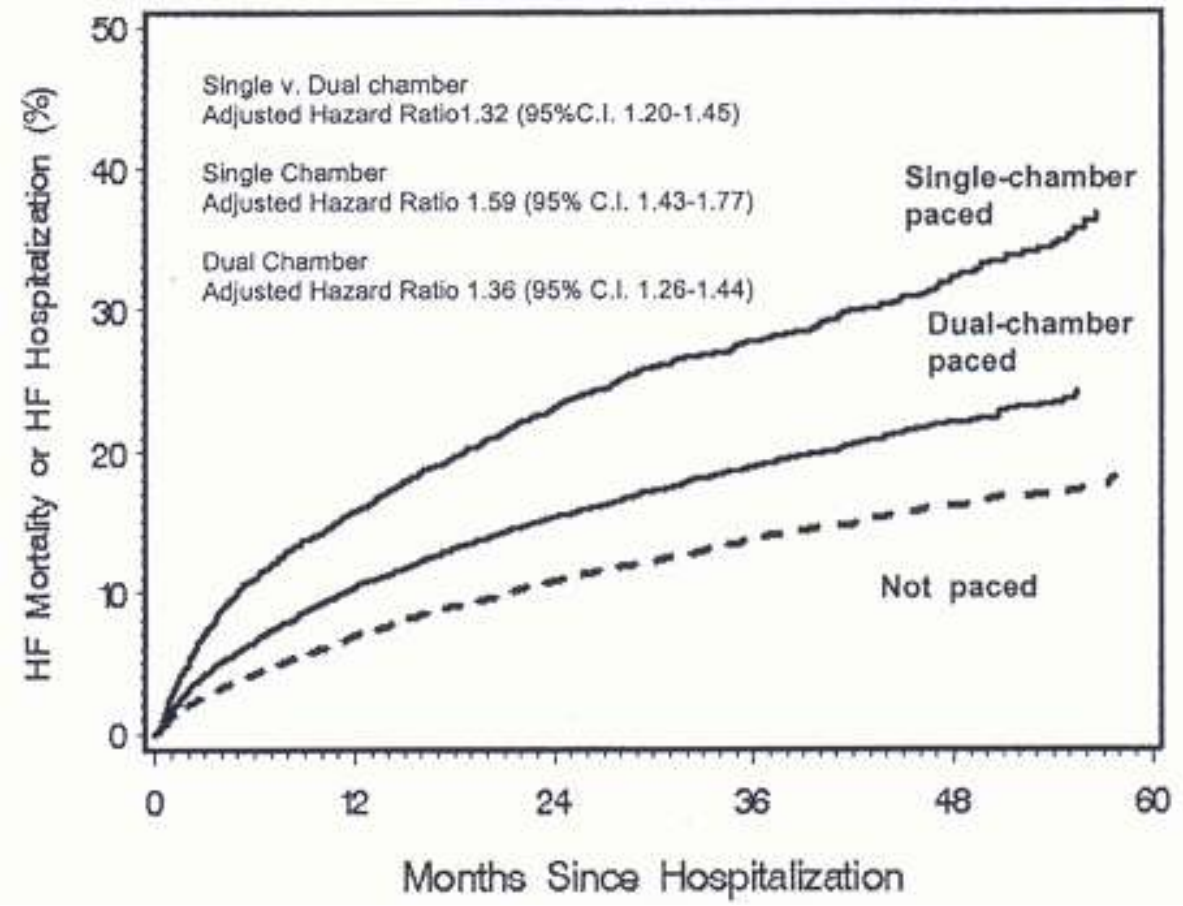




Pace less to reduce HF and mortality, but benefit from dual chamber pacing

MIDAS 9

- Population based comparison of 11,426 pacemaker patients without history of HF with a matched control group without pacing
- Matched regarding age, gender, MI history, race, hypertension and diabetes
- Significant higher risk of HF hospitalisation and HF related death in the paced population



Freudenberger RS et al; Am J Cardiol 95; 671-674; 2005

Development of Chronic AF in SND

Study	Pacing Mode	Mean Follow-up Time	Incidence of AF	Annualized Incidence
Andersen 1997[4]	AAI	5 years	8.8%	1.8%
Sutton 1986[6]	AAI	3 years	4.5%	1.5%
Brandt 1992[5]	AAI	5 years	7.0%	1.4%
PASE 1998[14]	DDDR only	18 months	19.0%	12.7%
CTOPP 2000[15]	DDDR/ VVIR	3 years	16.6%	5.5% (DDDR)

2 Rosenqvist M, Obel IW. Atrial pacing and the risk for AV block: is there a time for change in attitude? PACE 1989;12(1, Part 1):97-101.

3 Kristensen L, Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. AV block and changes in pacing mode during long-term follow-up of 399 consecutive patients with sick sinus syndrome treated with an AAI/AAIR pacemaker.PACE 2001;24(3):358-365.

4 Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet. October 25, 1997;350(9086):1210-1216.

5 Brandt J, Anderson H, Fahraeus T, Schuller H. Natural history of sinus node disease treated with atrial pacing in 213 patients: implications for selection of stimulation mode. J Am Coll Cardiol. September 1992;20(3):633-639.

6 Sutton R, Kenny RA. The natural history of sick sinus syndrome. PACE 1986;9(6, Part 2):1110-1114.

7 Rosenqvist M, Brandt J, Schuller H. Atrial versus ventricular pacing in sinus node disease: a treatment comparison study. Am Heart J. February 1986;111(2):292-297.

8 Rosenqvist M, Vallin H, Edhag O. Clinical and electrophysiologic course of sinus node disease: five-year follow-up study. Am Heart J. March 1985;109(3, Part 1):513-522.

9 Hayes DL, Furman S. Stability of AV conduction in sick sinus node syndrome patients with implanted atrial pacemakers. Am Heart J. April 1984;107(4):644-647.

You Should Also Know

- ADEPT - Impact of rate-modulated pacing on quality of life and exercise capacity

ICD

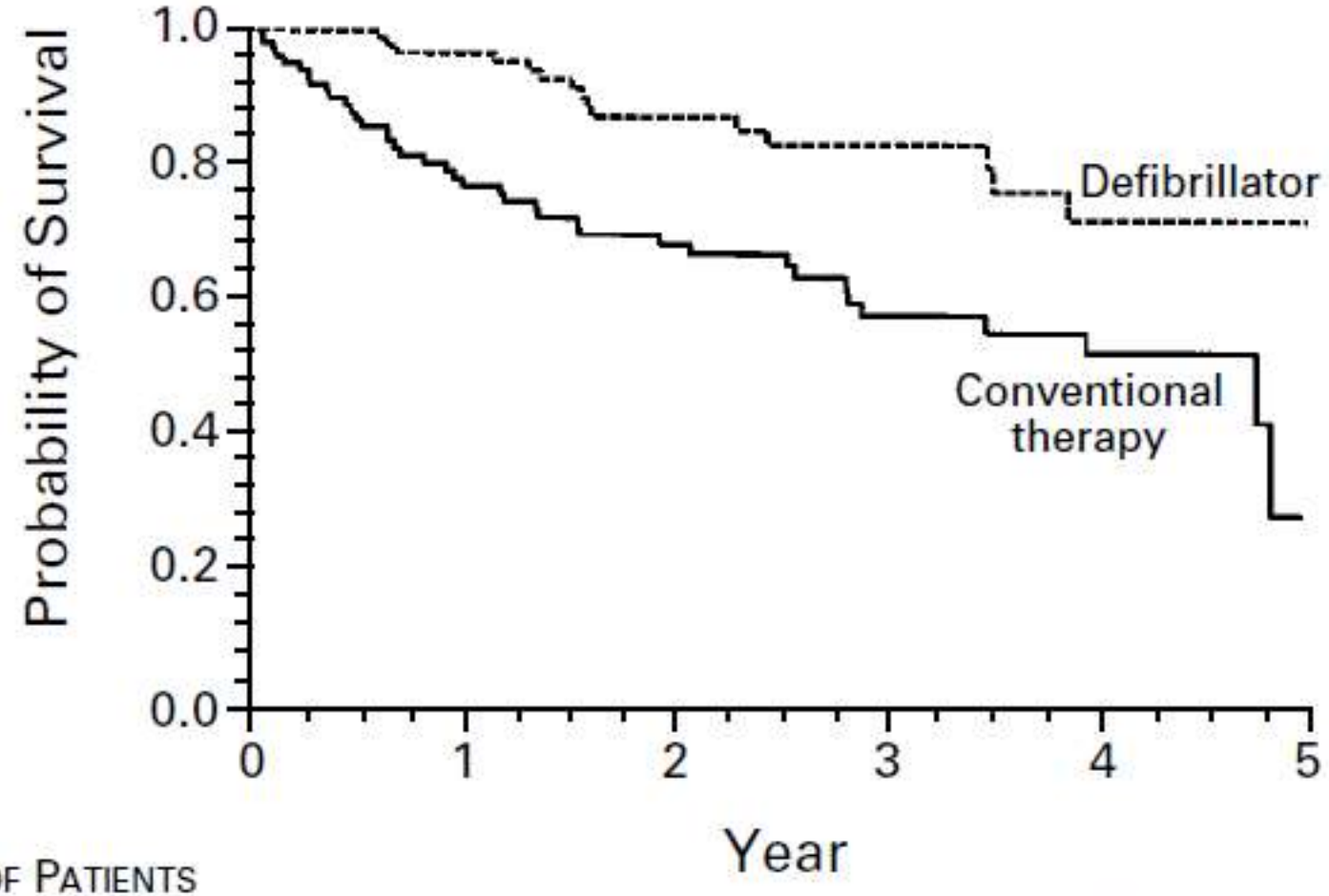
Multicentre Automatic Defibrillator Implantation Trial

MADIT

- 196 patients, NYHA class I-III
- Previous MI LVEF ≤35%, documented non-sustained VT (holter), inducible VT (EPS) not suppressed by procainamide
- At 27 months follow-up reduction in cardiac mortality from 27% to 11% (p=0.009)

Moss AJ, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. New Eng J Med 1996; 335: 1933-40

MADIT I

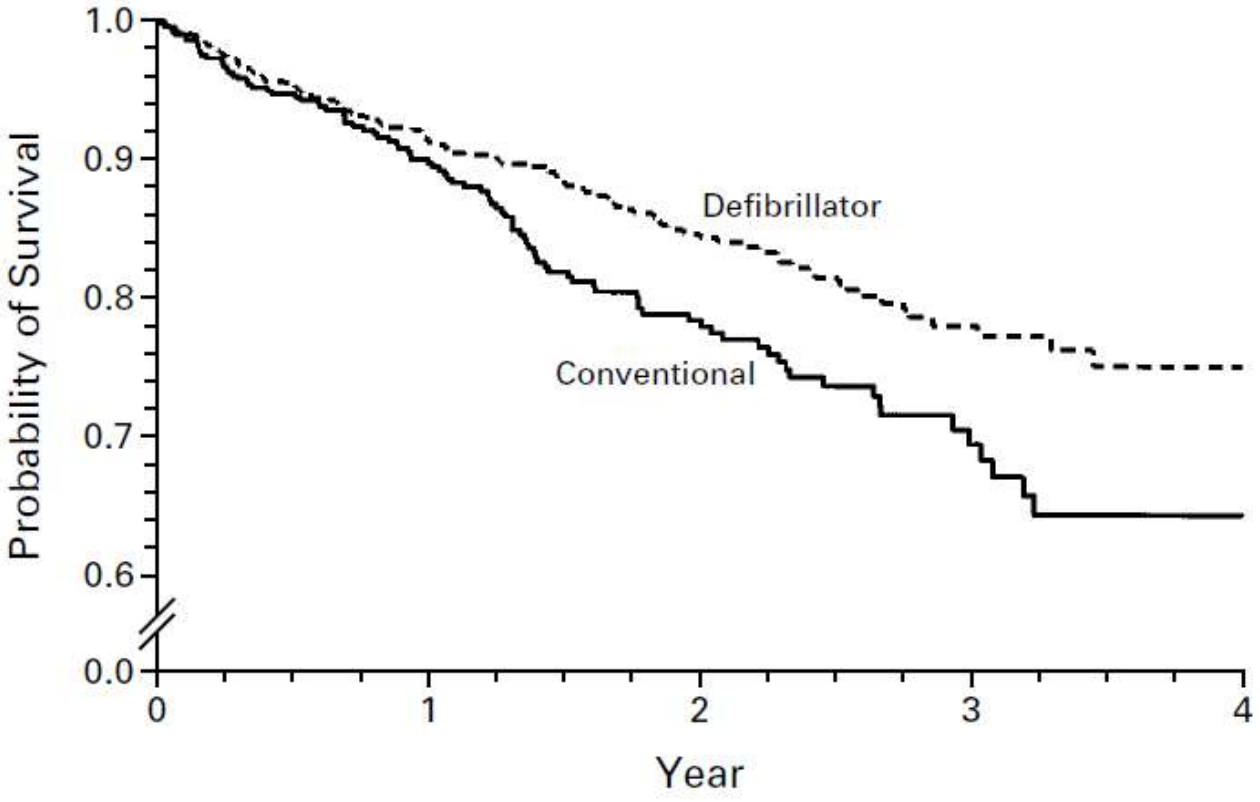


No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

MADIT II

- 1232 patients, NYHA class I-III, MI (greater than one month), LVEF ≤30%
- At 20 months follow-up reduction in cardiac mortality from 20% to 14% (p=0.016)

MADIT II



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

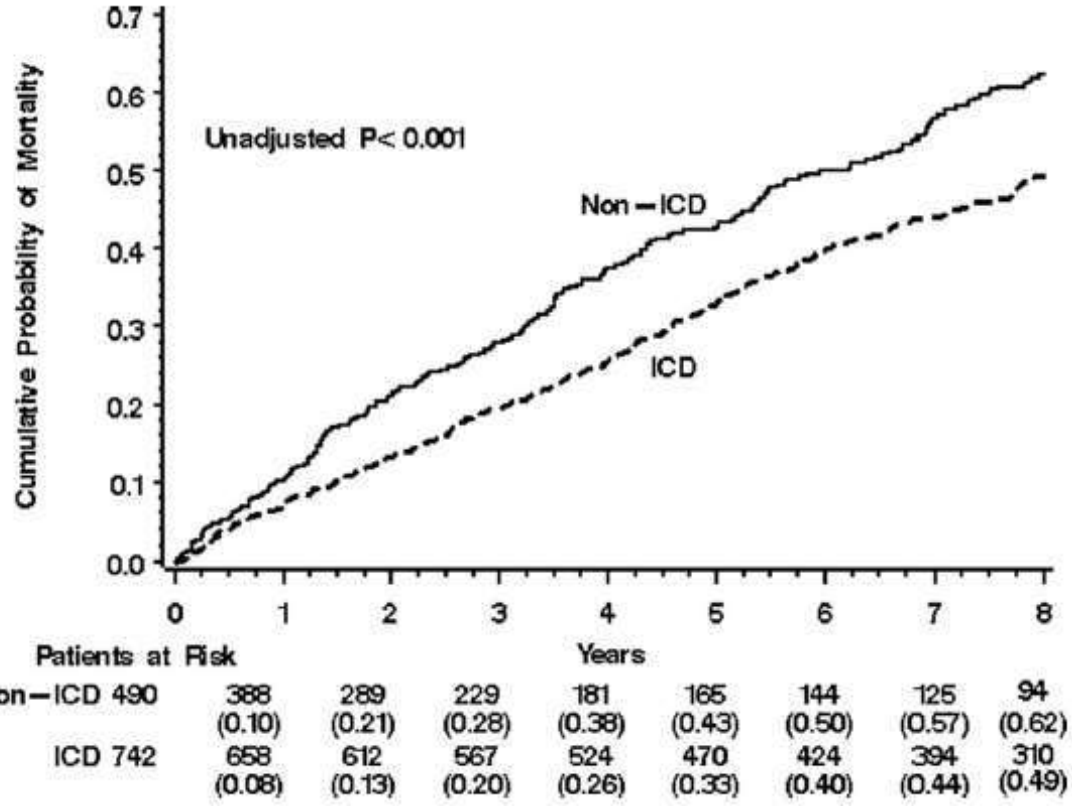
Figure 2. Kaplan–Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy.

The difference in survival between the two groups was significant (nominal P=0.007, by the log-rank test).

MADIT II 8 Year Follow Up

8 year follow-up after termination of MADIT-II trial in 2001.1232 pts followed-up
Primary end-point was all cause mortality

- 34% reduction in mortality over 8 yrs
- 6 pts need to be treated for 8 yrs to save one life
- Benefit greater (45% reduction) in those who do not develop heart failure



Goldenberg I, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator. An extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II Circ 2010; 122: 1265-71.

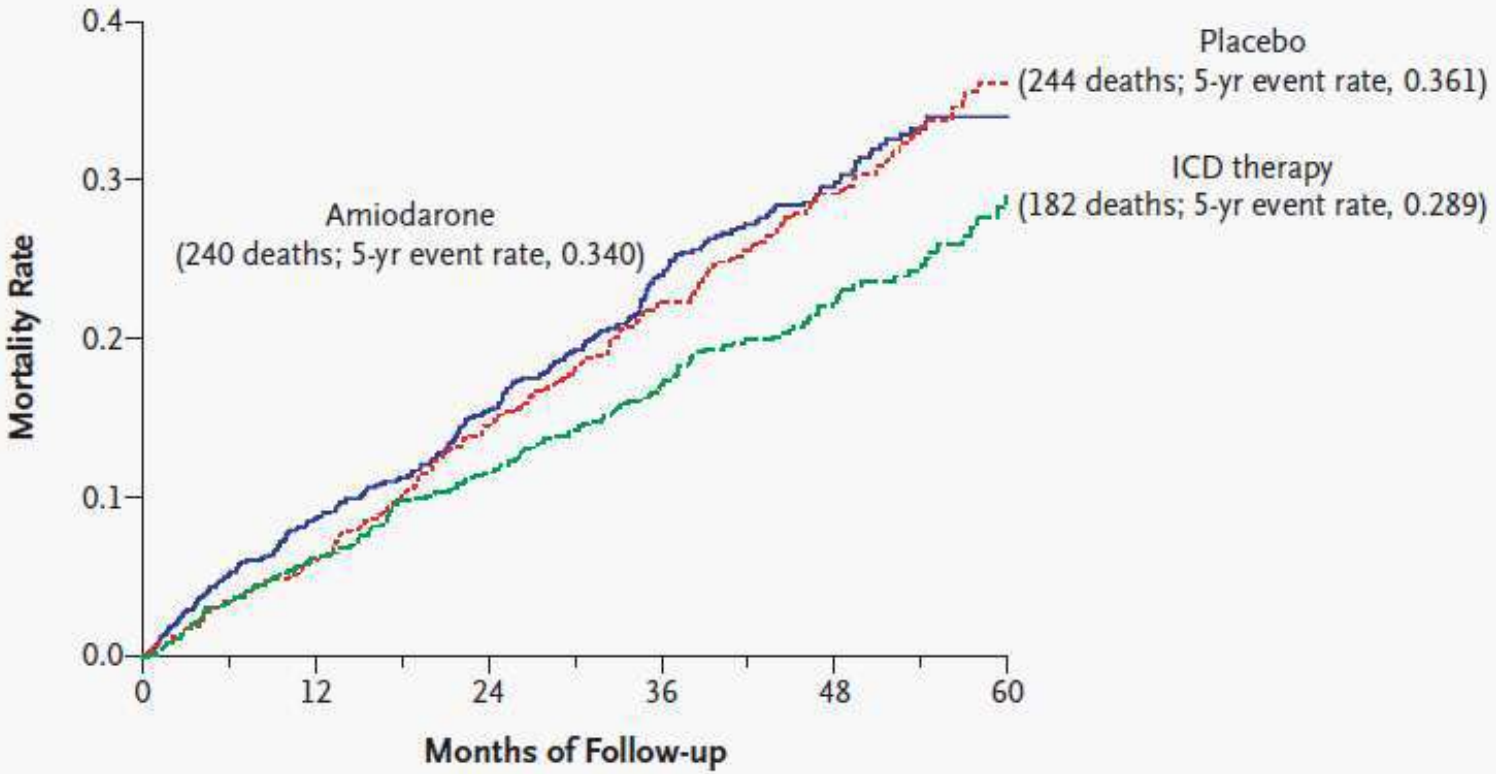
Sudden Cardiac Death in HEart Failure Trial

SCD-HeFT

- 2521 patients, NYHA II or III, LVEF ≤35% (52% ischaemic, 48% non-ischaemic)
- Randomised to placebo, amiodarone or single lead ICD
- Primary end-point was all cause mortality
- Mean follow-up 45.5 months
- No difference in mortality between amiodarone and placebo (28% v 29%)
- Significant mortality reduction in ICD group (29% to 22%, p=0.007); 23% risk reduction

Bardy GH, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. New Eng J Med 2005; 352: 225-37

SCD-HeFT



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

Primary Prevention ParAmeteRs Evaluation PREPARE

- 700 patients (primary prevention) VT/VF >182bpm 30/40 beats

Table 1 PREPARE VT/VF Programming Parameters

Detection		Threshold	Beats to Detect	Therapies
VF	On	250 beats/min	30 of 40	30 to 35 J (max output) × 6
FVT	via VF	182 beats/min	30 of 40	Burst (1 sequence), 30 to 35 J (max output) × 5
VT	Monitor	167 beats/min	32	Off

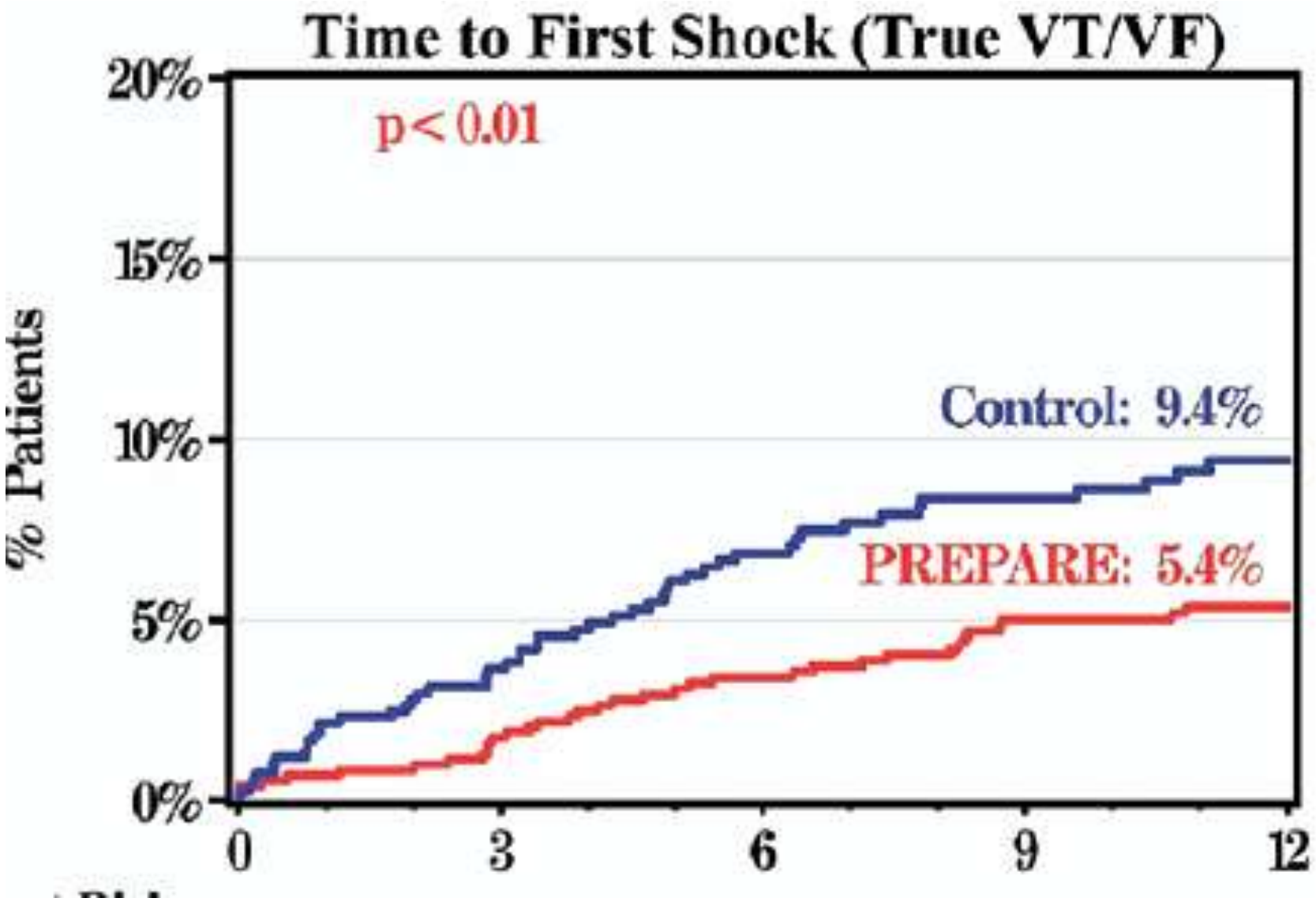
Supraventricular tachycardia criteria on (dual chamber, biventricular implantable cardioverter-defibrillator): atrial fibrillation/flutter, sinus tachycardia (1:1 VT-ST boundary = 66%); supraventricular tachycardia criteria on (single chamber): wavelet morphology discrimination (match threshold = 70%); supraventricular tachycardia limit = 300 ms; burst antitachycardia pacing: 8 intervals, pacing cycle length = 88% of tachycardia cycle length

FVT = fast ventricular tachycardia; PREPARE = Primary Prevention Parameters Evaluation study; VF = ventricular fibrillation; VT = ventricular tachycardia; VT-ST = ventricular tachycardia-sinus tachycardia.

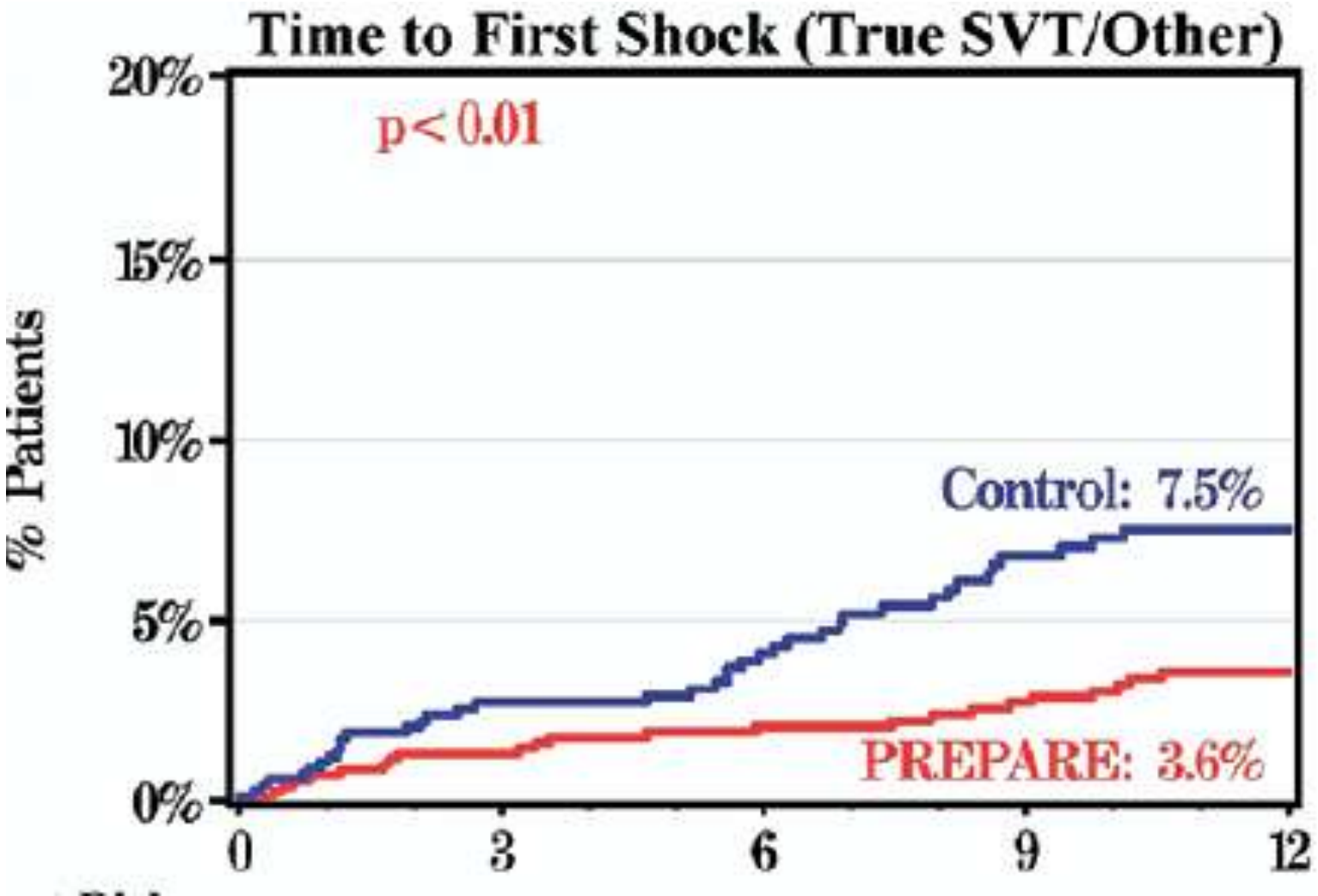
PREPARE

- Control group 689 patients from EMPIRIC/ MIRACLE ICD
- The PREPARE study patients were less likely to receive a shock in the first year compared with control patients (9% vs. 17%, $p<0.01$)
- PREPARE programming significantly reduced morbidity 0.26 vs 0.69
- The incidence of untreated VT and arrhythmic syncope was similar between the PREPARE study patients and the control cohort.

PREPARE


Time to First Shock (True VT/VF)
20%
15%
10%
5%
0%
% Patients
p < 0.01
Control: 9.4%
PREPARE: 5.4%
0
3
6
9
12

PREPARE

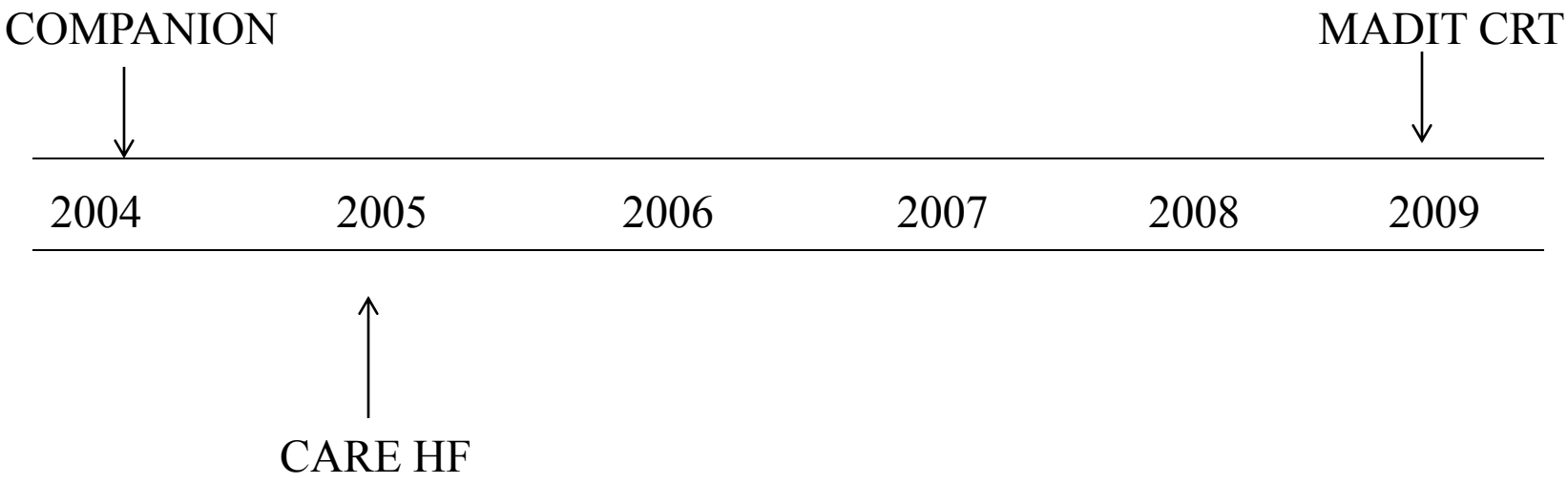

Time to First Shock (True SVT/Other)
20%
15%
10%
5%
0%
% Patients
p< 0.01
Control: 7.5%
PREPARE: 3.6%
0
3
6
9
12

You Should Also Know

- AVID (ANTIARRHYTHMICS VERSUS IMPLANTABLE DEFIBRILLATORS TRIAL)
- CASH (THE CARDIAC ARREST STUDY HAMBURG)
- CIDS - (CANADIAN IMPLANTABLE DEFIBRILLATOR STUDY)
- EMPIRIC
- PainFREE Rx1
- PainFREE RxII

CRT

CRT – Landmark Studies



2012.....?RECCOVVER - **R**andomised trial of **E**arly **C**ombined **C**RT, **V**olume status assessment and **V**entricular **R**hythm therapy

COMPANION

- 1520 patients; NYHA Class III or IV
- Sinus rhythm, QRS 120ms, PR 150ms LVEF 35%, LVEDD 60mm
- Optimal pharmacological therapy (OPT) B-blocker (for at least 3 months), Diuretic, ACEI, spironolactone (1 month) +/- digoxin
- History of HF hospitalisation <12 months, >1months prior to enrollment

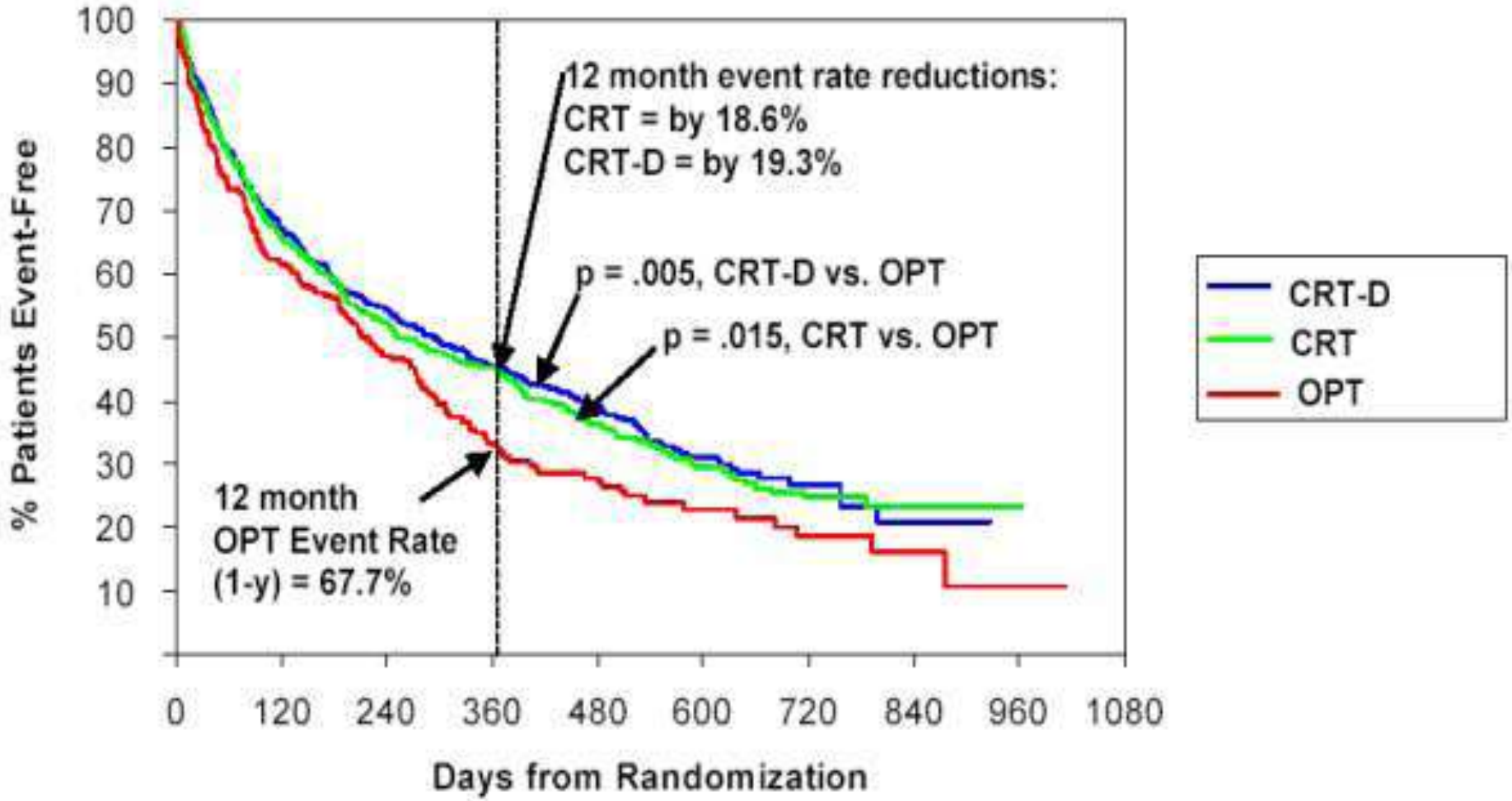
Bristow MR et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140-50

COMPANION

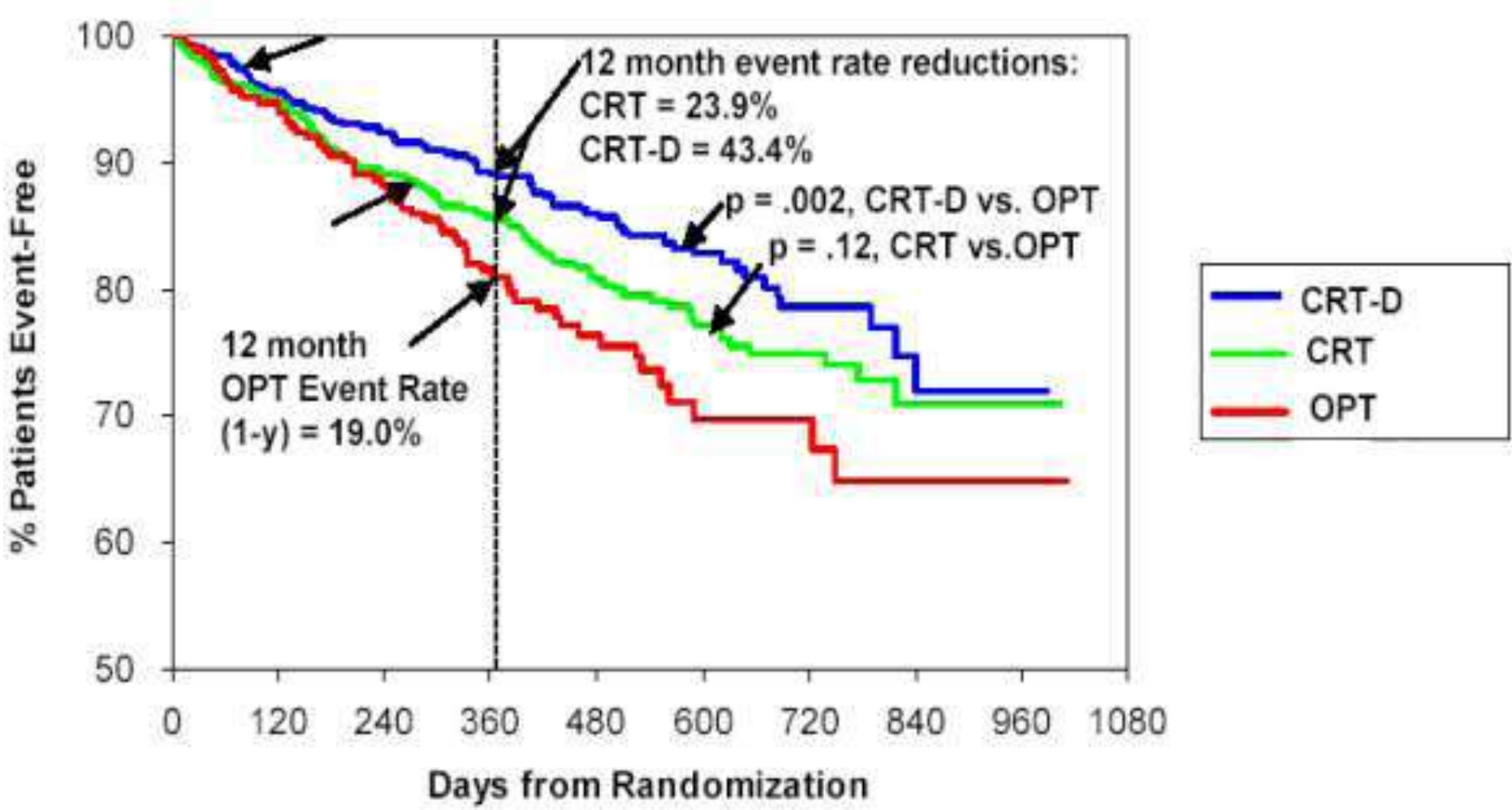
Randomised To 3 Arms

- Optimal Medical Therapy Alone (OPT)
- OPT + CRT-P
- OPT + CRT-D

COMPANION
Primary End Point
(Death + Hospitalisation)



COMPANION
Secondary End Point
(All Cause Mortality)



You Should Also Know

- MADIT-CRT
- CARE-HF (CArdiac REsynchronisation Heart Failure)
- PAVE (Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation)
- REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction

AF

STROKE RISK: CHA_2DS_2-VASc

Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke / TIA	2
Vascular disease (MI, PVD)	1
Age 66-74	1
Sex Category (i.e. female)	1

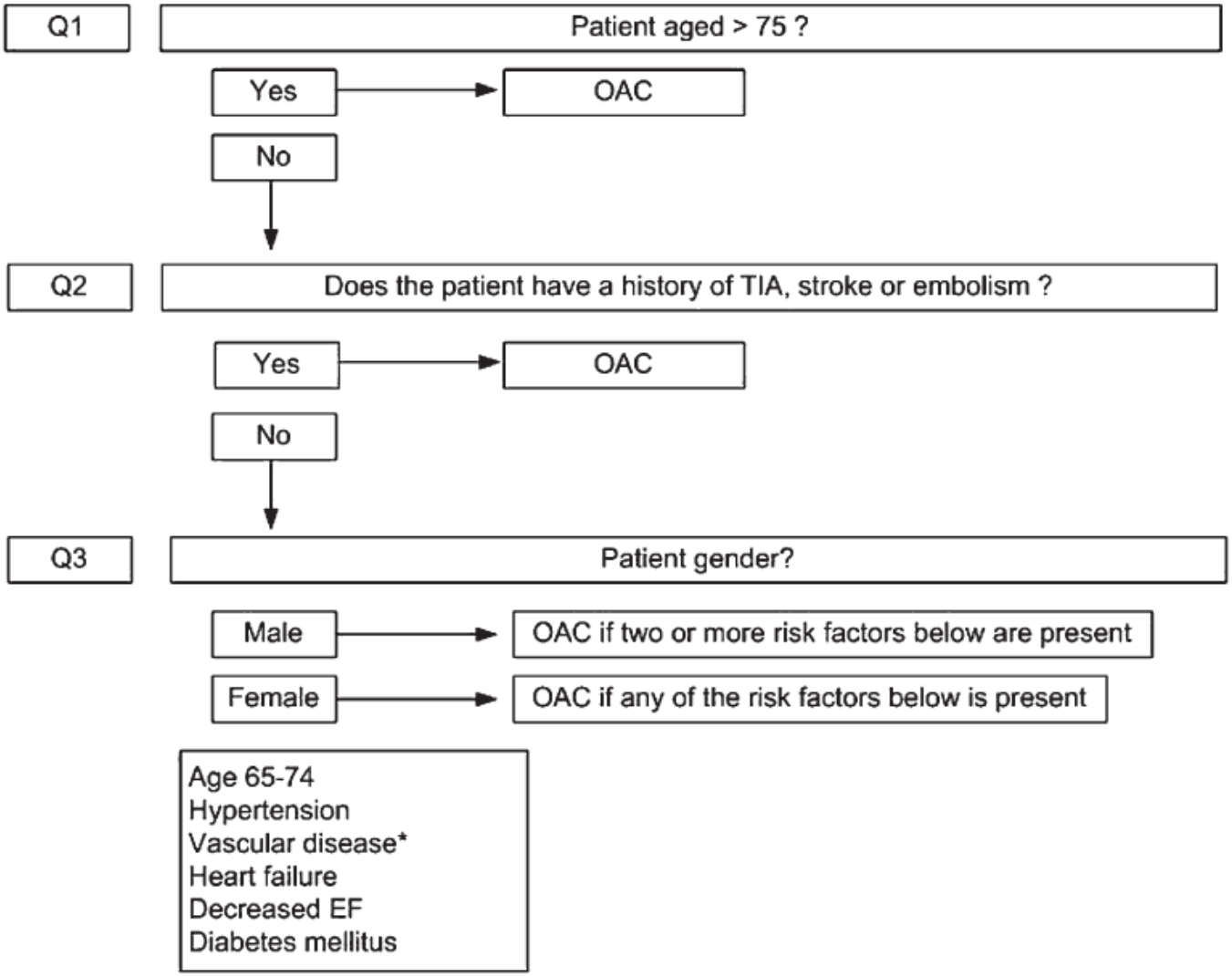
Lip GYH, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. Chest 2010; 137: 263-72.

CHA_2DS_2-VASc Scoring

Score	OAC	Annual Stroke Risk %
0		1.9
1		2.8
2		4.0
3		5.9
4		8.5
5		12.5
6		18.2

M > 1 OAC
F > 2
} Aspirin/ Warfarin/ Aspirin + Warfarin

STROKE RISK – CHA_2DS_2-VASc



*Myocardial infarction, peripheral artery disease or aortic plaque

You should Also Know

- AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Managment)

- Dronedarone trials
  - ANDROMEDA - NYHA III/IV Stopped!
  - ATHENA – NYHA I/II
- Dabigatran
  - RE-LY – low dose (100mg bd) as good as Warfarin with less bleeding, larger dose better protection than Warfarin with same bleeding risk

Conclusions

- Know your major trials
- NICE guidance AF, T-LOC, CRT
- ESC guidance AF, Pacing & CRT (especially minimising VP in SND)

Thank You
&
Good Luck

This presentation and links to all the clinical trials referenced can be found at
www.cardiologyhd.com

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