Clinical Trials In Cardiac Rhythm Management

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Question 1

If a patient has an EF of 27% and past history of 2 MI's but no documented arrhythmia which study would indicate an ICD should be implanted?

- DAVID
- CASH
- CIDS
- MADIT II
- AVID

Clinical Trials

- Pacemakers
- ICD’s
- CRT
- AF

Lots to choose from!

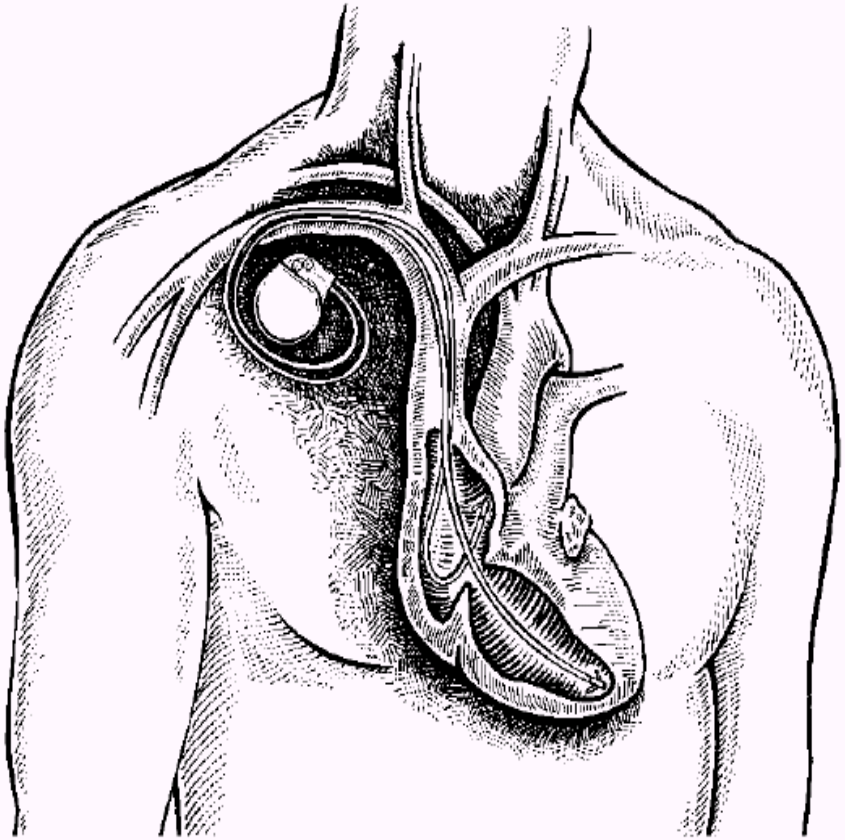
- ADEPT
- ANDROMEDA
- ATHENA
- AVID
- CARE-HF*
- CASH
- CHADS-VASc*
- CIDS
- COMPANION*
- CTOPP*
- DANISH I*
- DANISH II*
- DAVID*
- DEFINITE
- EMPIRIC
- MIRACLE
- MADIT I*
- MADIT II & MADIT II 8y FU*
- MADIT CRT
- MIDAS 9
- MOST
- MUSTT
- Pain FREE I,II
- PAVE
- PREPARE*
- REVERSE
- SAVE PACe
- SCD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

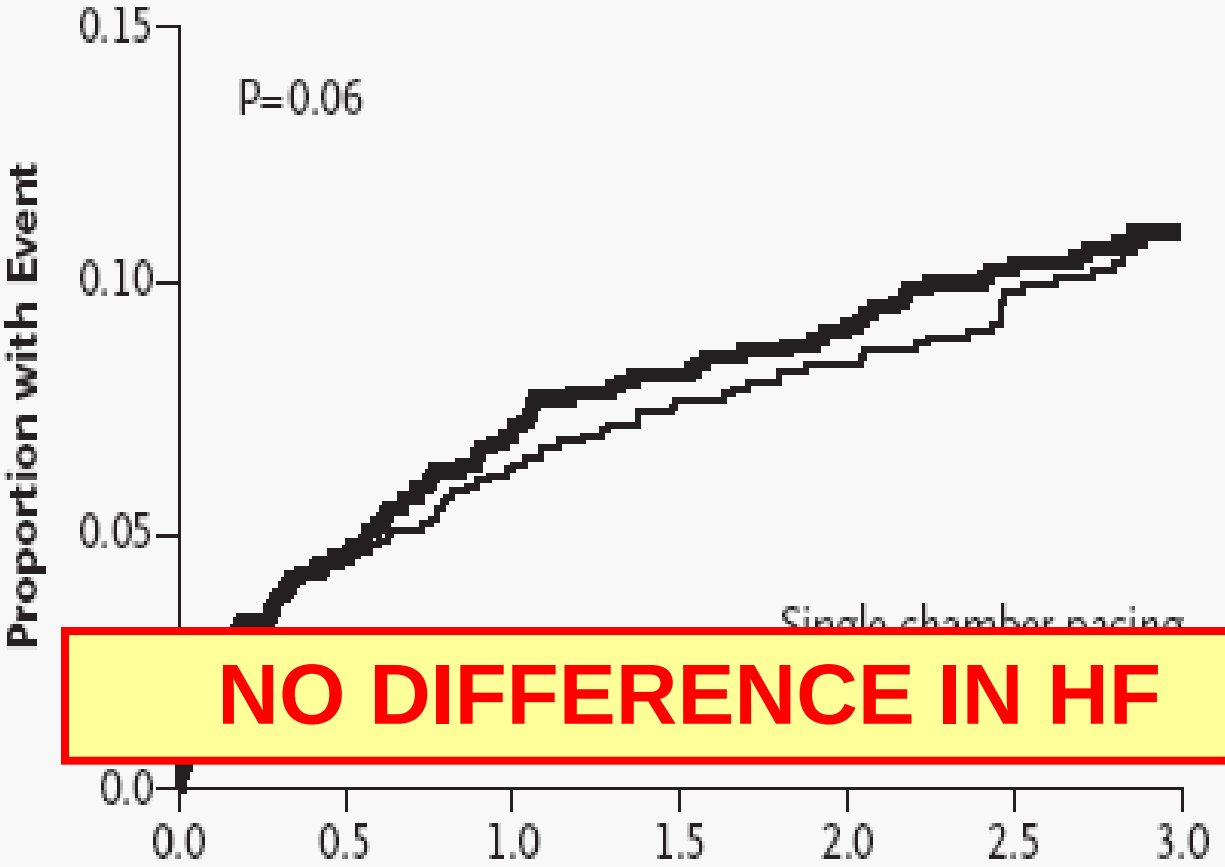
The Major Pacing Trials have Shown Little Benefit to Support 'Physiologic Pacing'

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

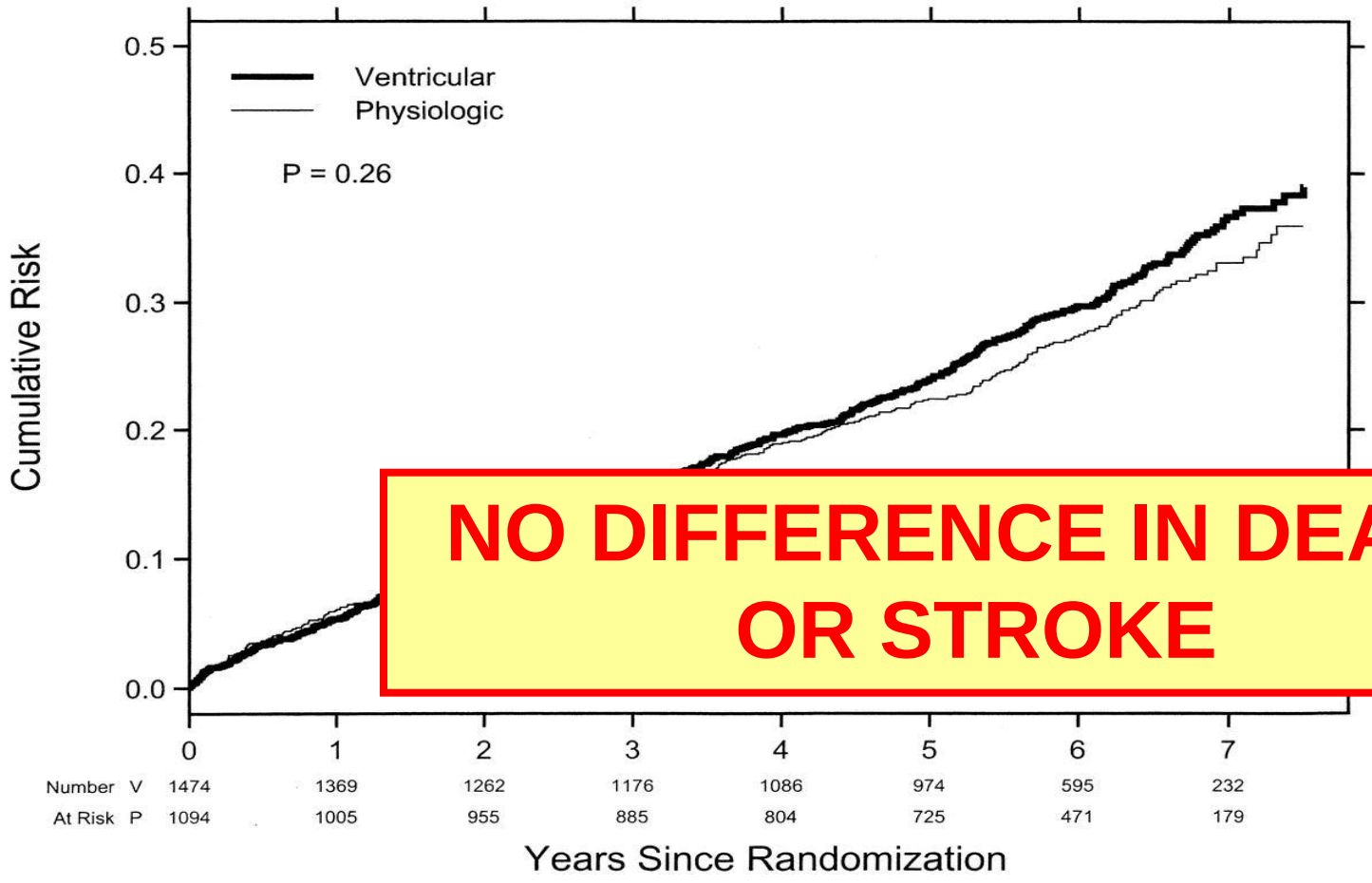
UKPACE: 2,021 AVB pts DDD/R vs. VVI/R
Heart Failure at 5 years



NO DIFFERENCE IN HF

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

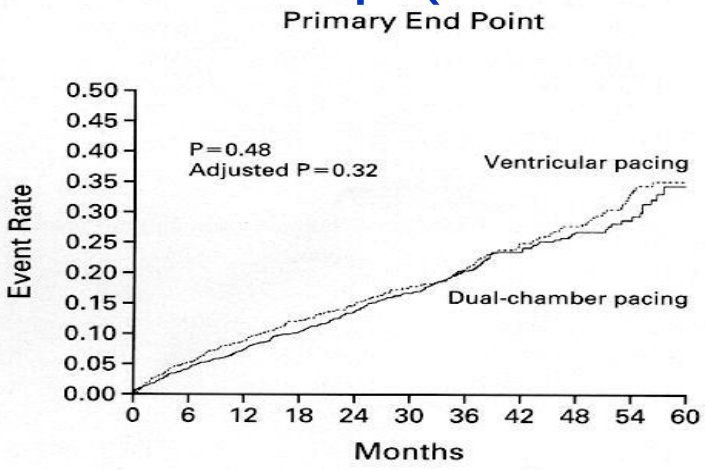
CTOPP: 2,568 pts DDDR vs. VVIR
Death or Stroke at 6.4 years



NO DIFFERENCE IN DEATH OR STROKE

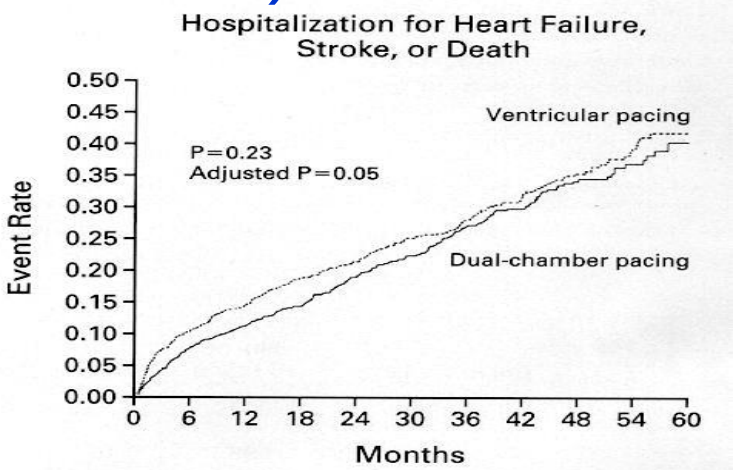
Skanes A, et al. Progression to Chronic Atrial Fibrillation After Pacing: The Canadian Trial of Physiologic Pacing. J Am Coll Cardiol 2001;38:167-72.

MOST: 2,010 SSS pts, DDDR vs.VVIR
6 year Follow-up (Mode selection trial)



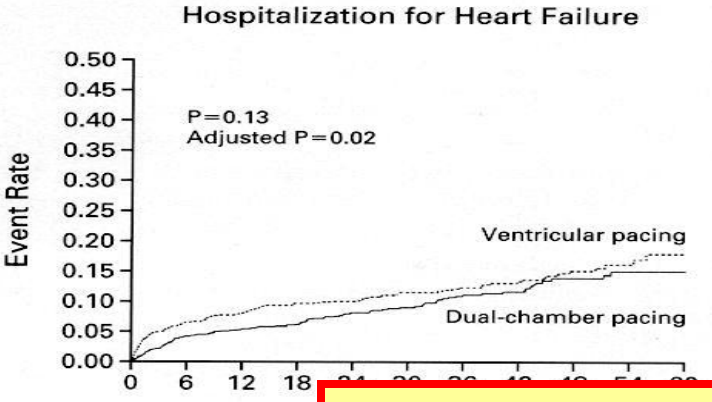
No. at Risk

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



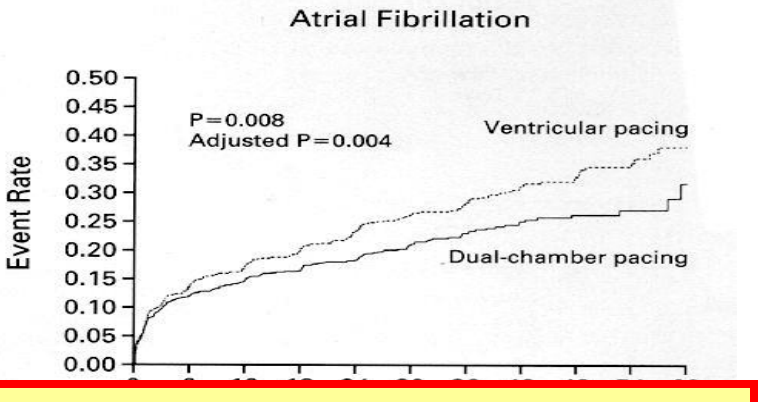
No. at Risk

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

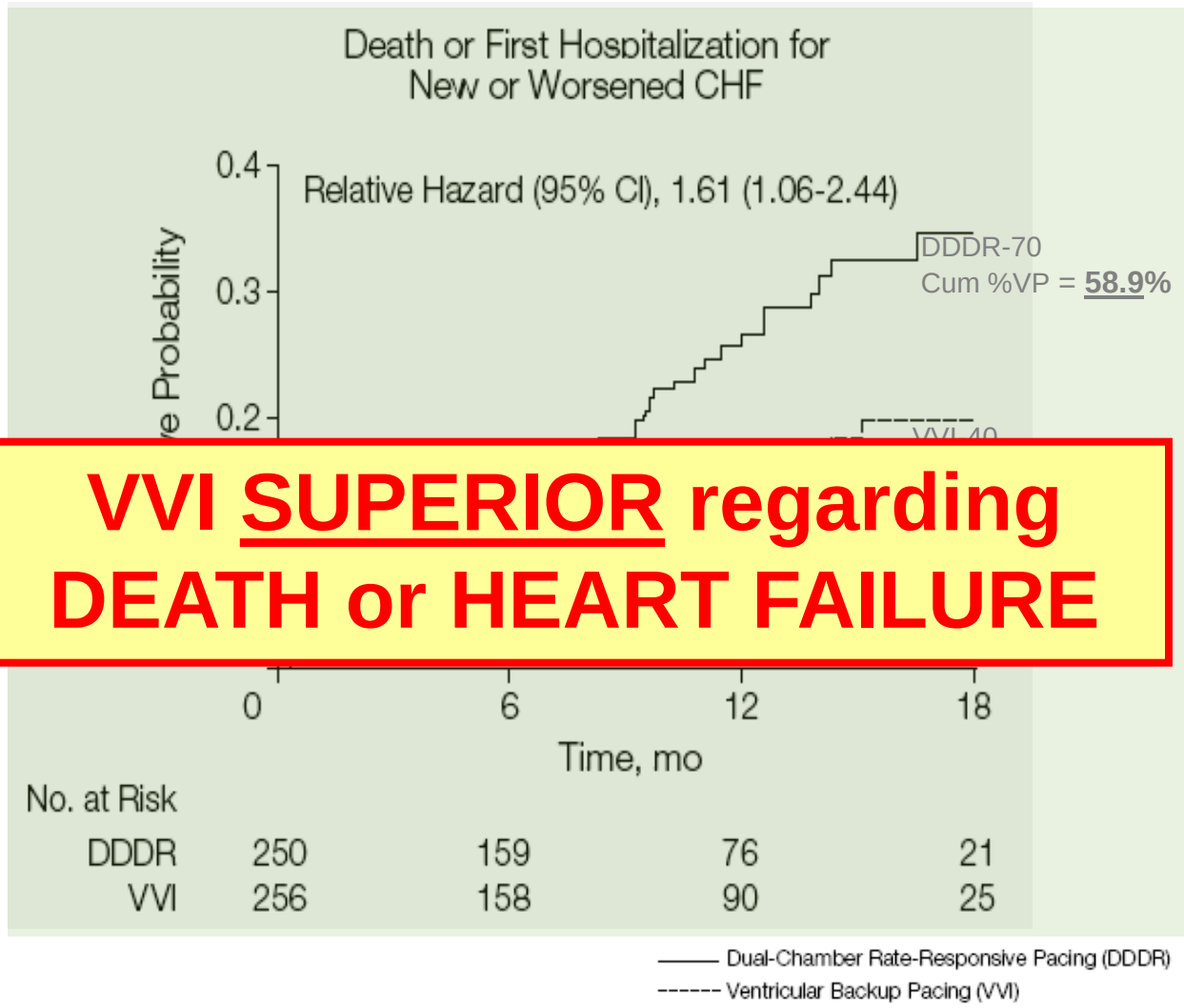
Sweeney M, Hellkamp A, Ellenbogen K, et al. Adverse
Trial of Pacemaker Therapy for Sinus Node Dysfunctio

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?

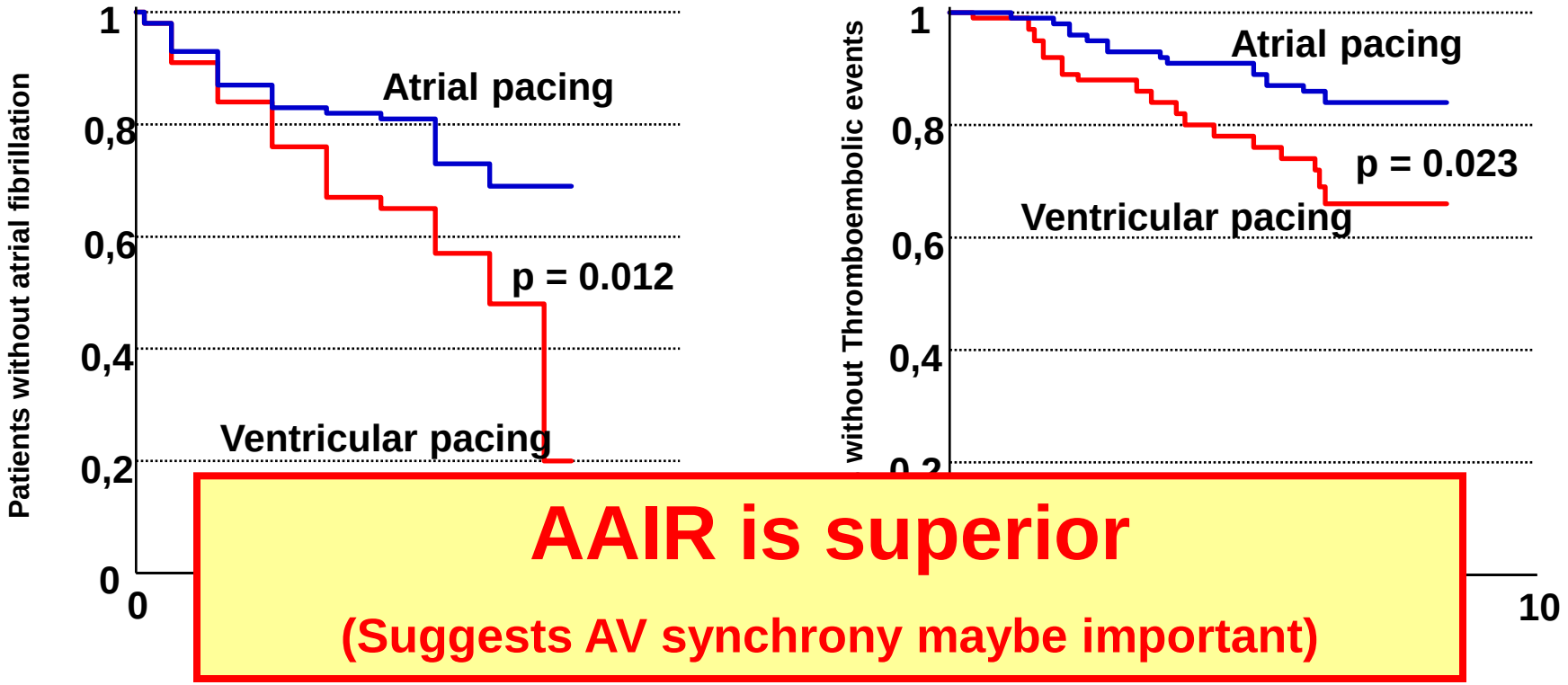
Should we avoid it in SSS patients?

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

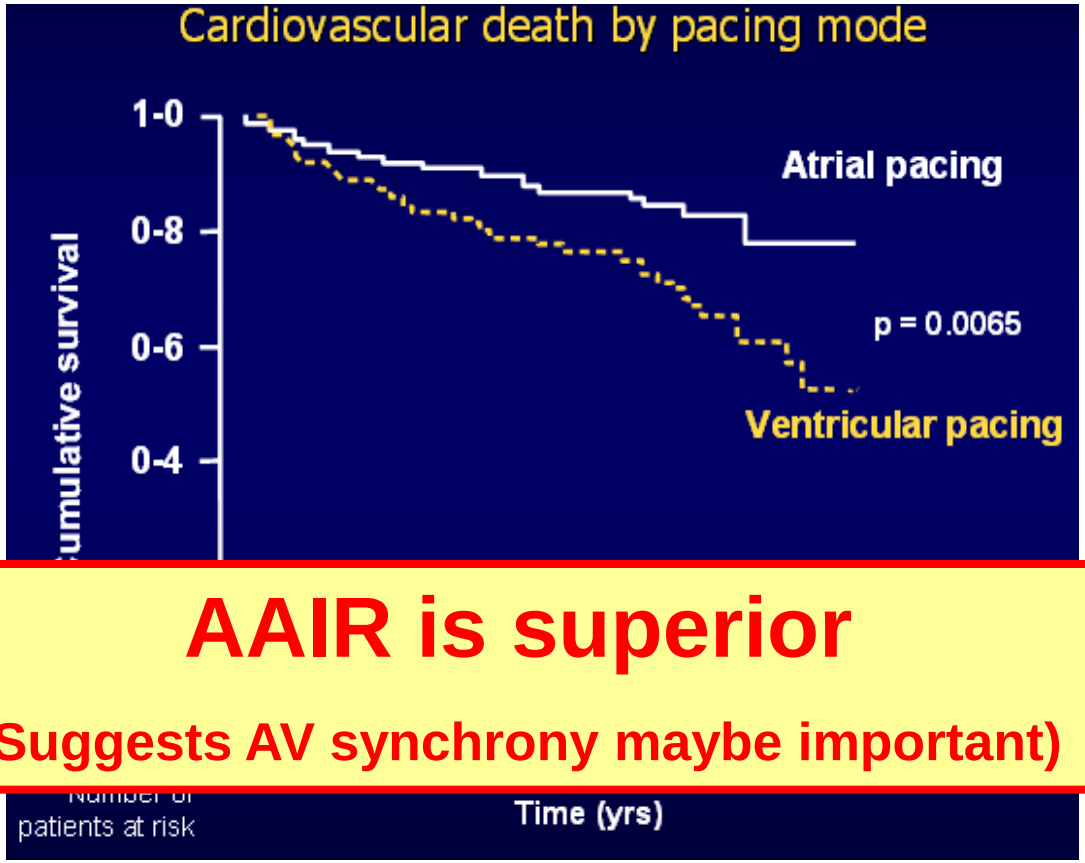
(Suggests AV synchrony maybe important)

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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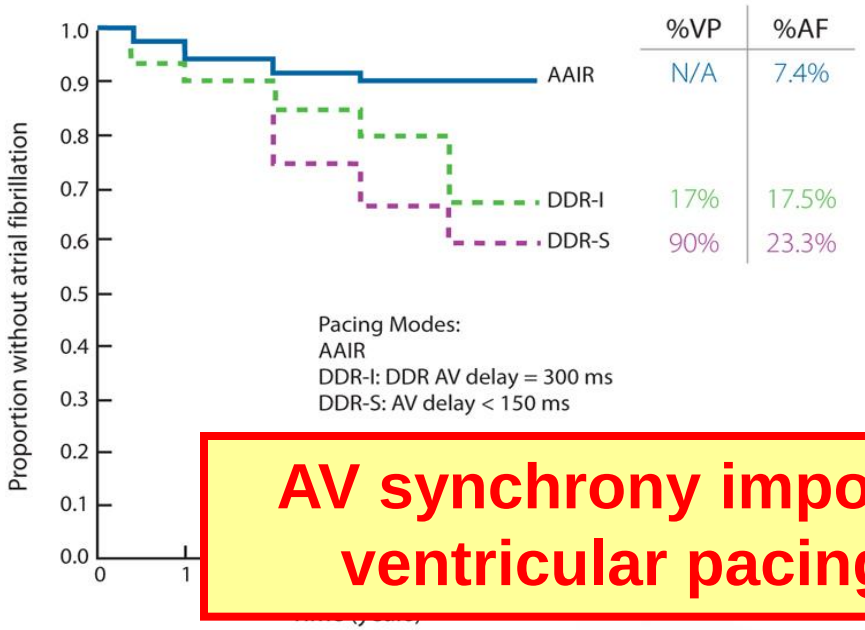
Insight from Danish II: Pace Less to reduce AF

- 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]

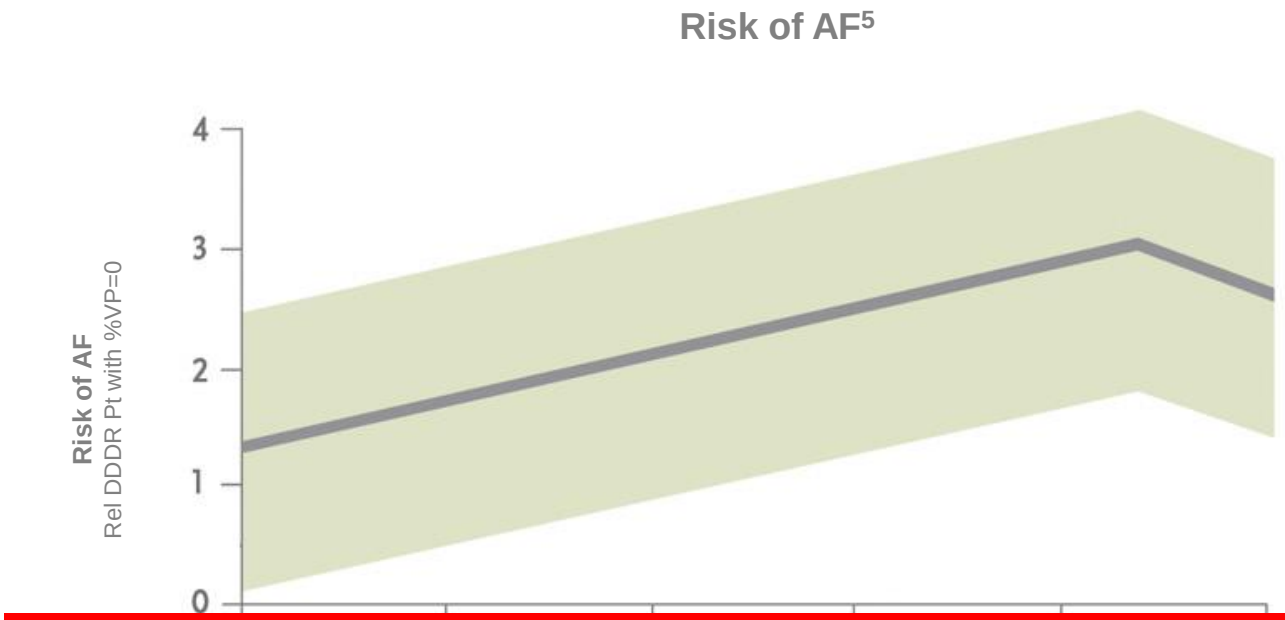
AV synchrony important but unnecessary ventricular pacing maybe detrimental

[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.



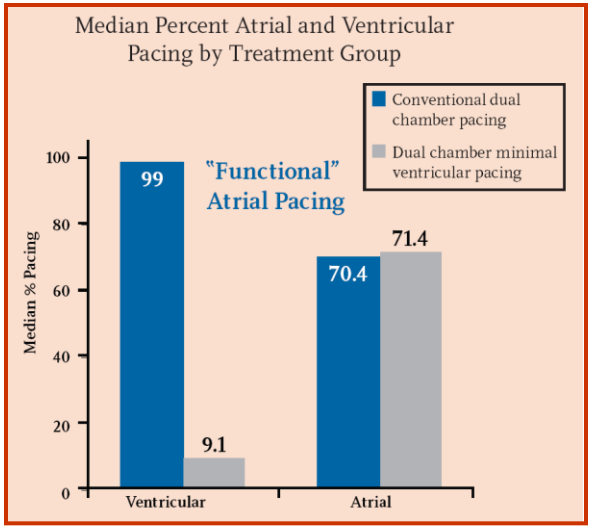
Each 1% increase RV pacing increases the risk of AF by 1% (up to 85%)

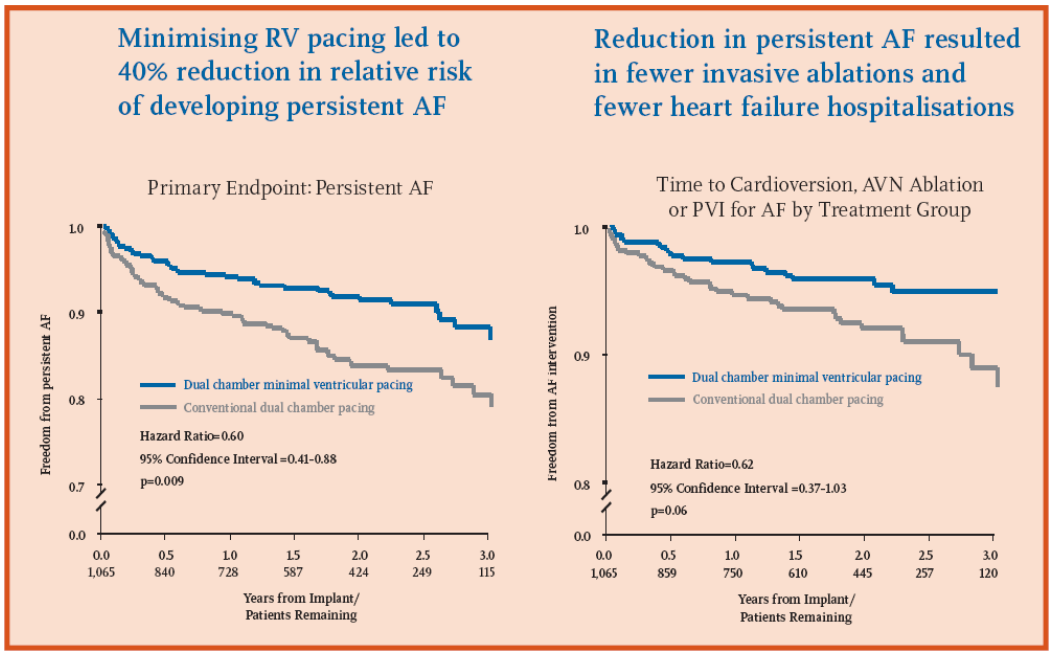
Sweeney MO, et al. Circulation 2003;23:2932-2937

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



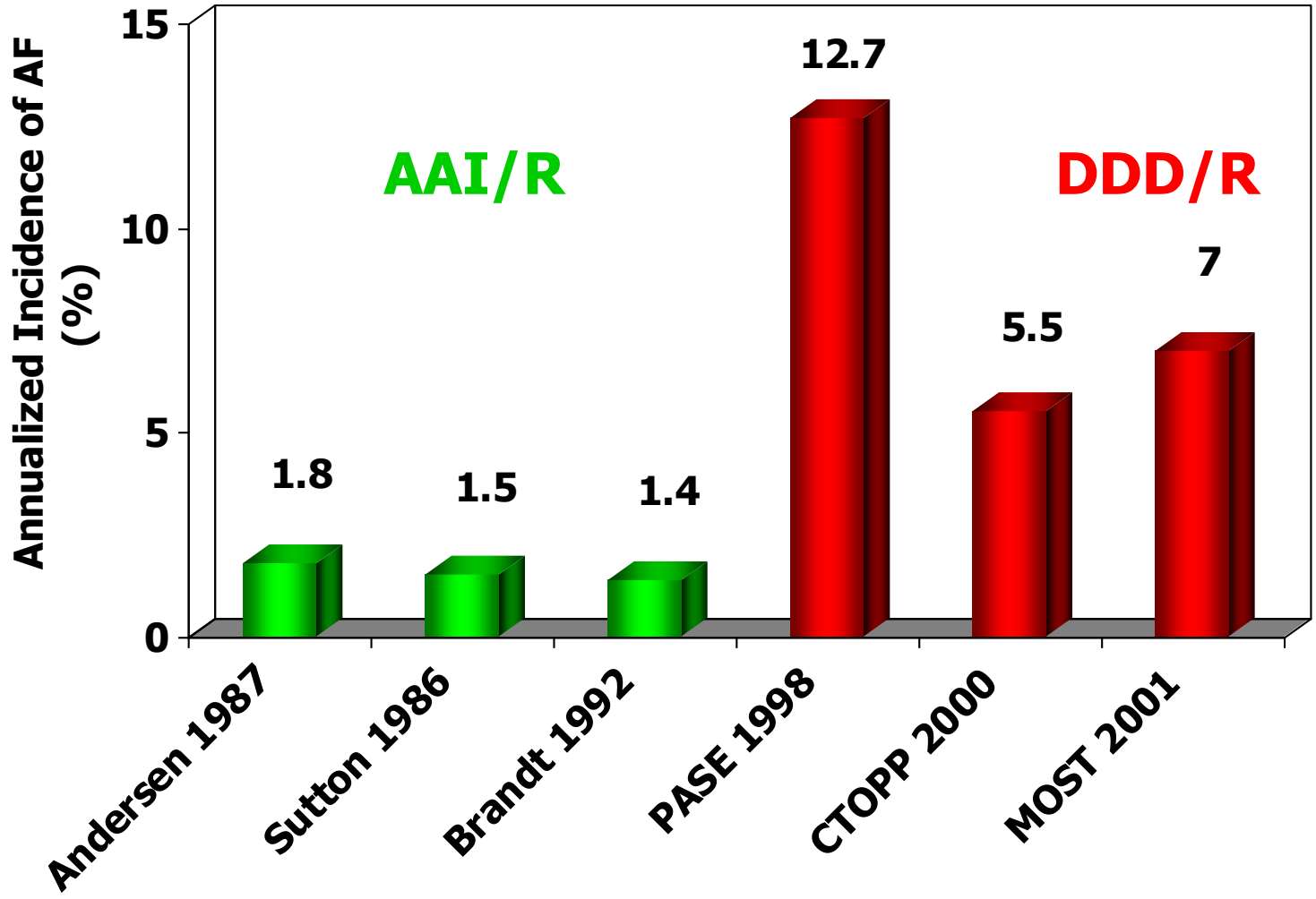


Reference

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

The annual risk of AF in PPM studies has been reported as being dependant on the pacemaker mode



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

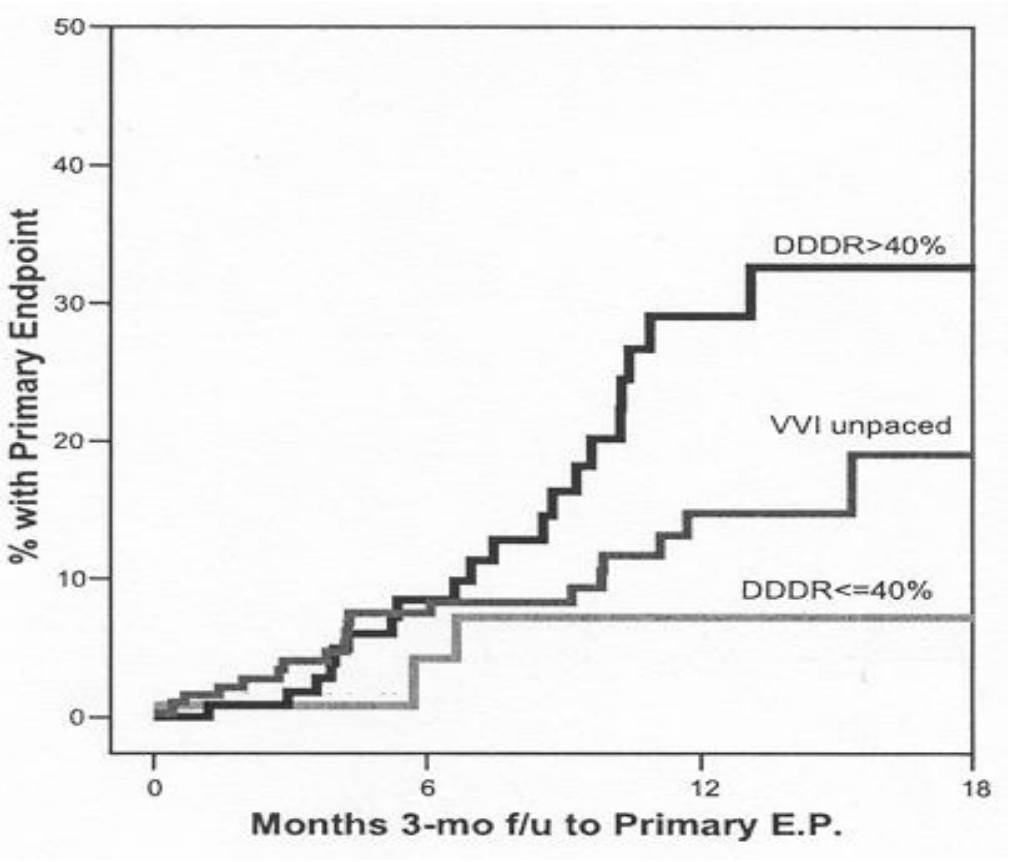
Wilkoff B, et al. on behalf of the DAVID Trial Investigators. JAMA 2002;288:3115-3123.

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

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

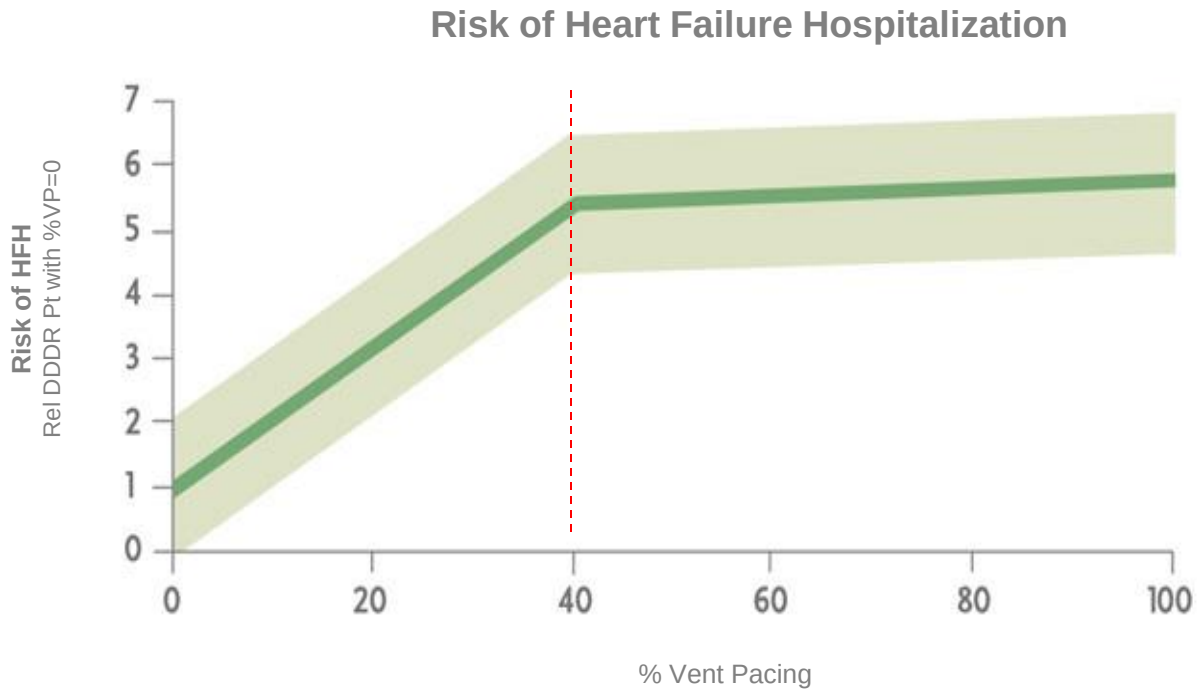
- Conclusion

  For patients with standard indications for ICD therapy, no indication for cardiac pacing, and an LVEF of 40% or less, dual-chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end point of death or hospitalization for heart failure.

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%.



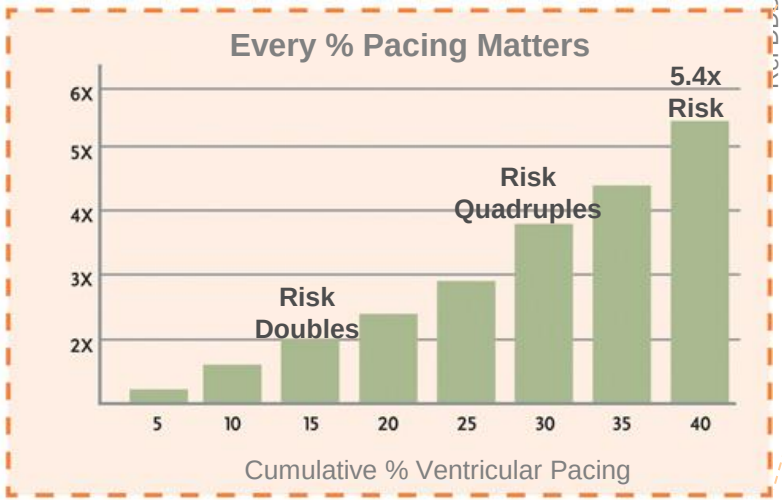
Sweeney MO, et al. Circulation 2003;23:2932-2937

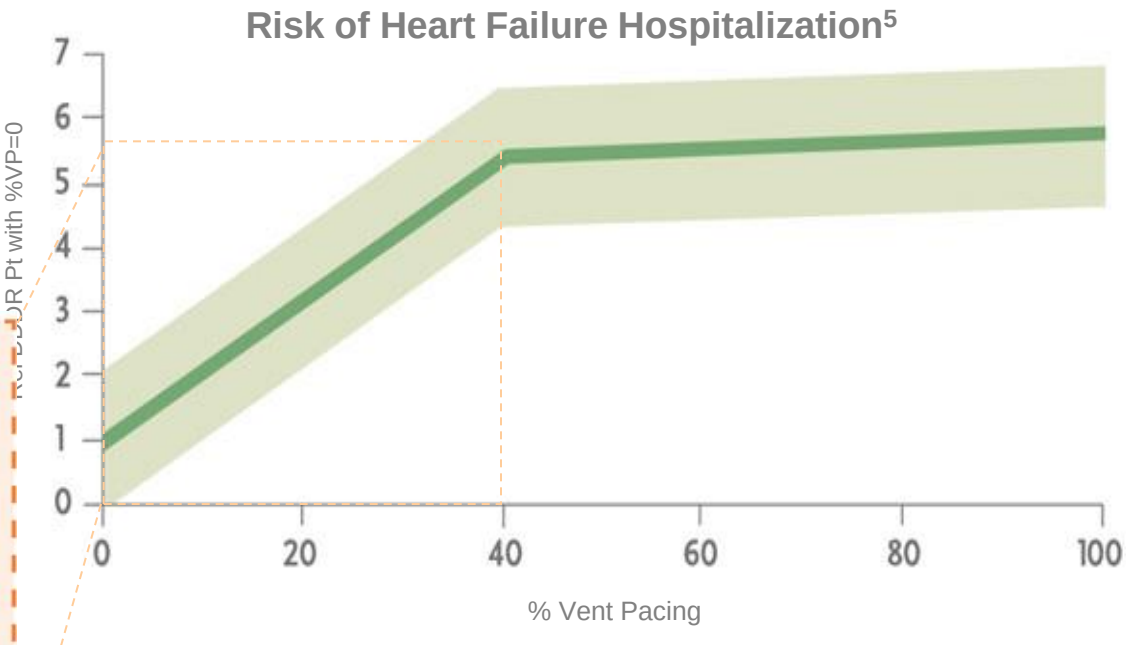
To Minimize Heart Failure You Need to Minimise RV Pacing

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%).

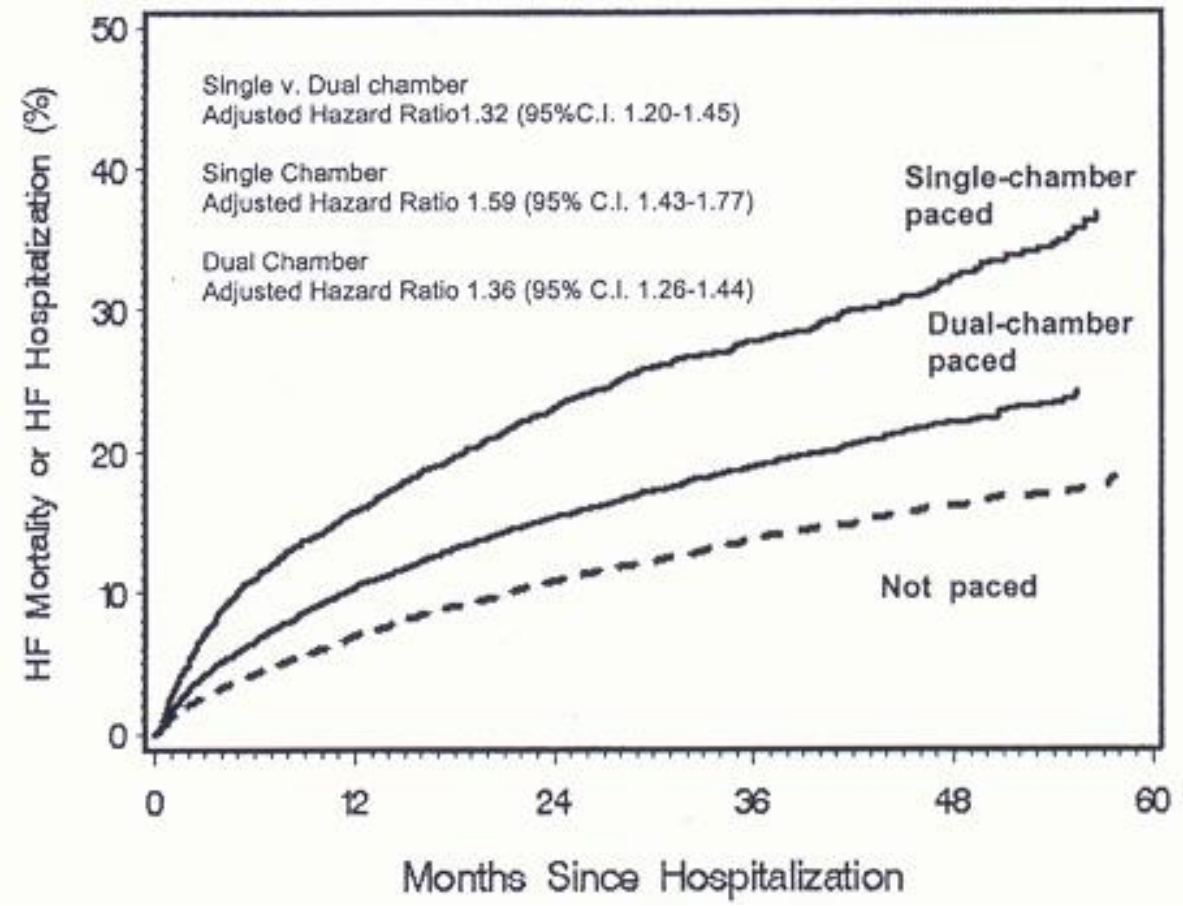




Pace less to reduce HF and mortality, but benefit from dual chamber pacing

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

Question 2

In the DAVID study which of the following statements is true

1. The DDDR arm of the study had an increase in AF
2. VT was the most common rhythm in the VVIR arm
3. Patients randomised to DDDR pacing had an increase risk of HF or death
4. There was no difference in percentage pacing between the DDDR and VVIR arms
5. The endpoint of the study was AF

ICD

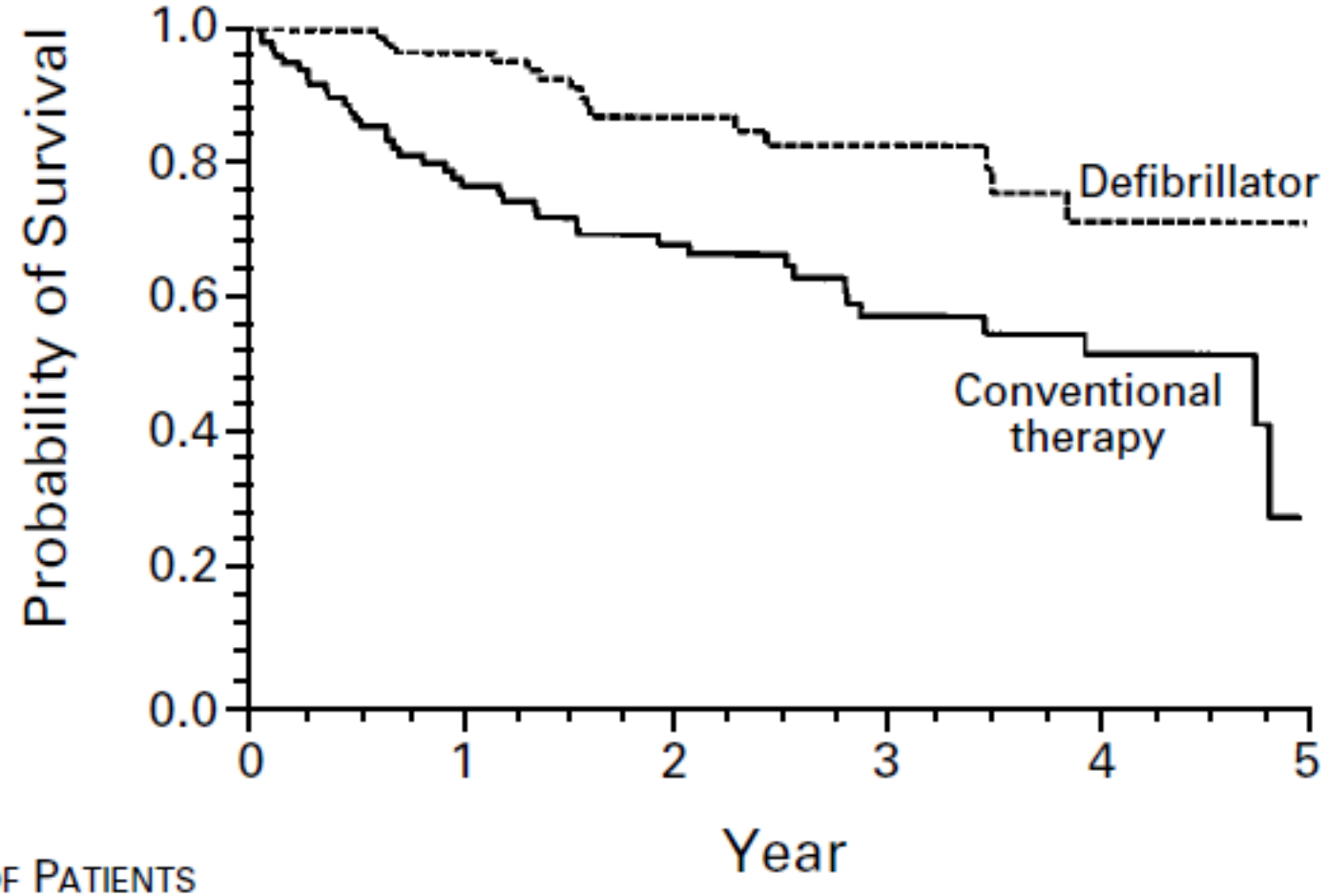
Multicentre Automatic Defibrillator Implantation Trial

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

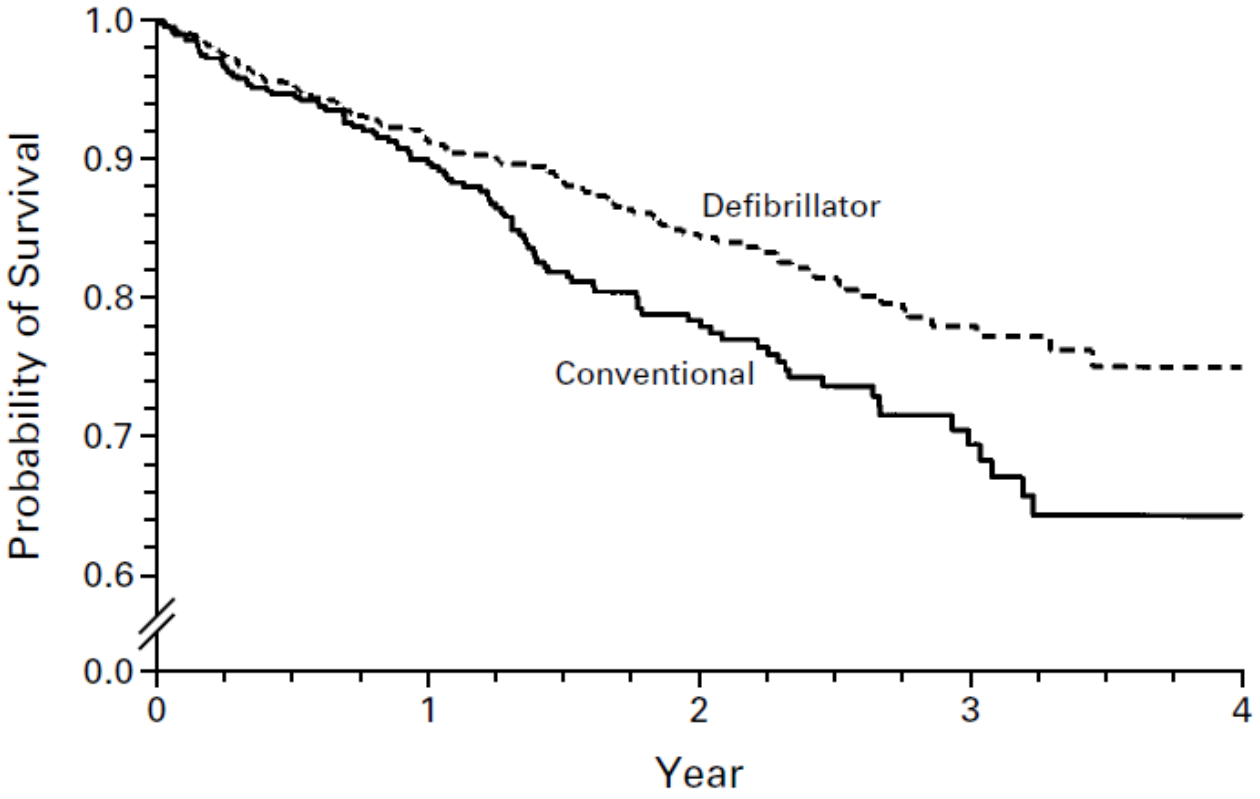


No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

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

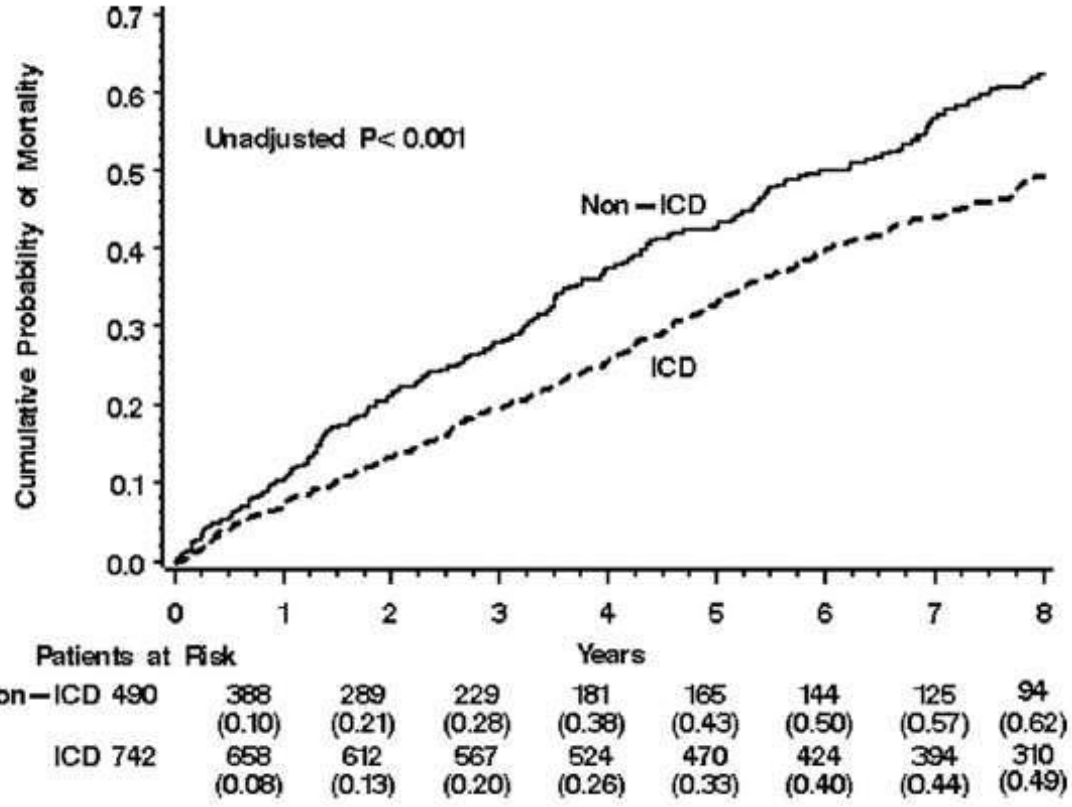
Figure 2. Kaplan–Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy.

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

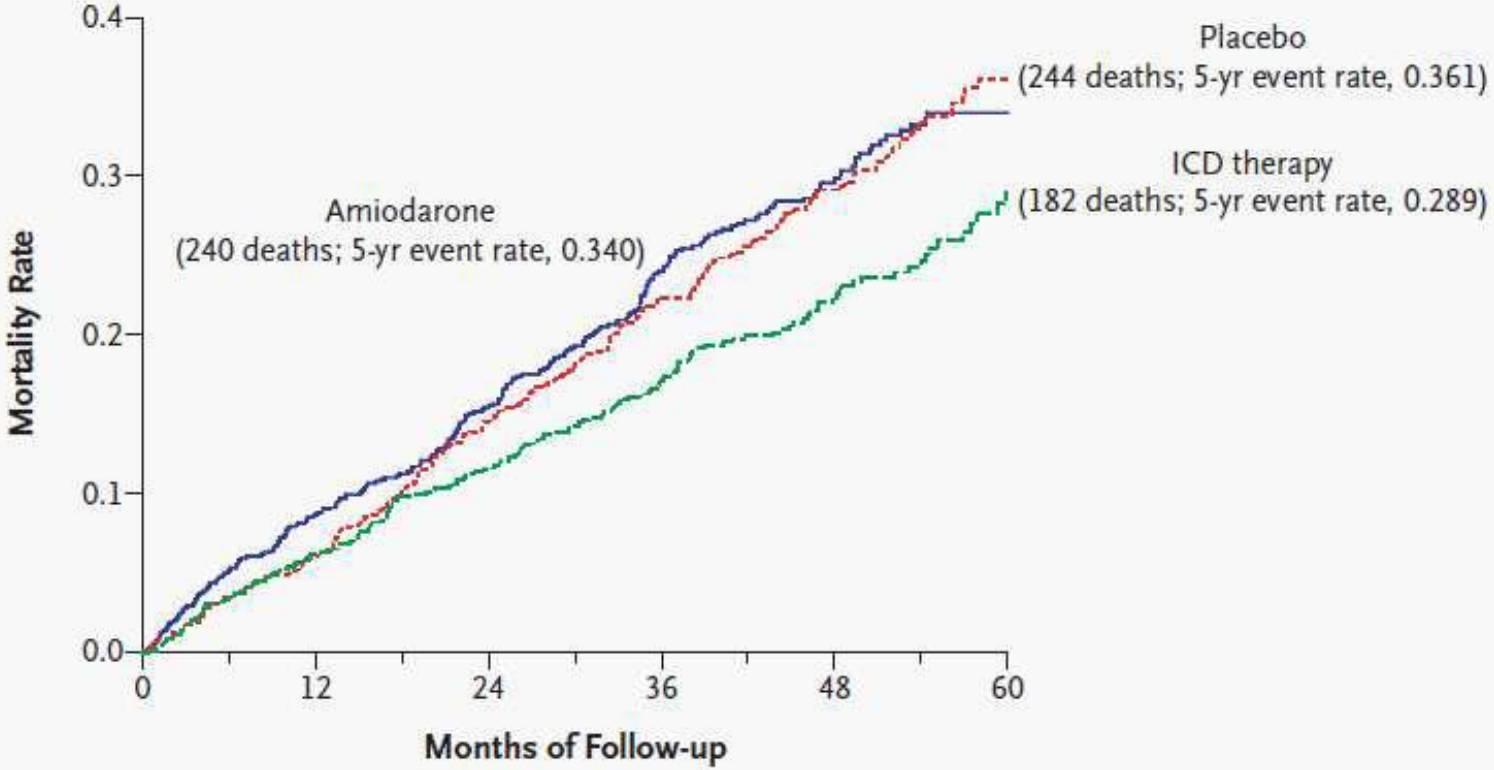
SCD-HeFT

- 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

	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



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

DANISH

- **BACKGROUND**
- The benefit of an implantable cardioverter–defibrillator (ICD) in patients with symptomatic systolic heart failure caused by coronary artery disease has been well documented. However, the evidence for a benefit of prophylactic ICDs in patients with systolic heart failure that is not due to coronary artery disease has been based primarily on subgroup analyses. The management of heart failure has improved since the landmark ICD trials, and many patients now receive cardiac resynchronization therapy (CRT).
- **METHODS**
- In a randomized, controlled trial, 556 patients with symptomatic systolic heart failure (left ventricular ejection fraction, ≤35%) not caused by coronary artery disease were assigned to receive an ICD, and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. The secondary outcomes were sudden cardiac death and cardiovascular death.

DANISH cont'd

- **RESULTS**
- After a median follow-up period of 67.6 months, the primary outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (P=0.005). Device infection occurred in 27 patients (4.9%) in the ICD group and in 20 patients (3.6%) in the control group (P=0.29).

- **CONCLUSIONS**
- In this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. (Funded by Medtronic and others; DANISH ClinicalTrials.gov)

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

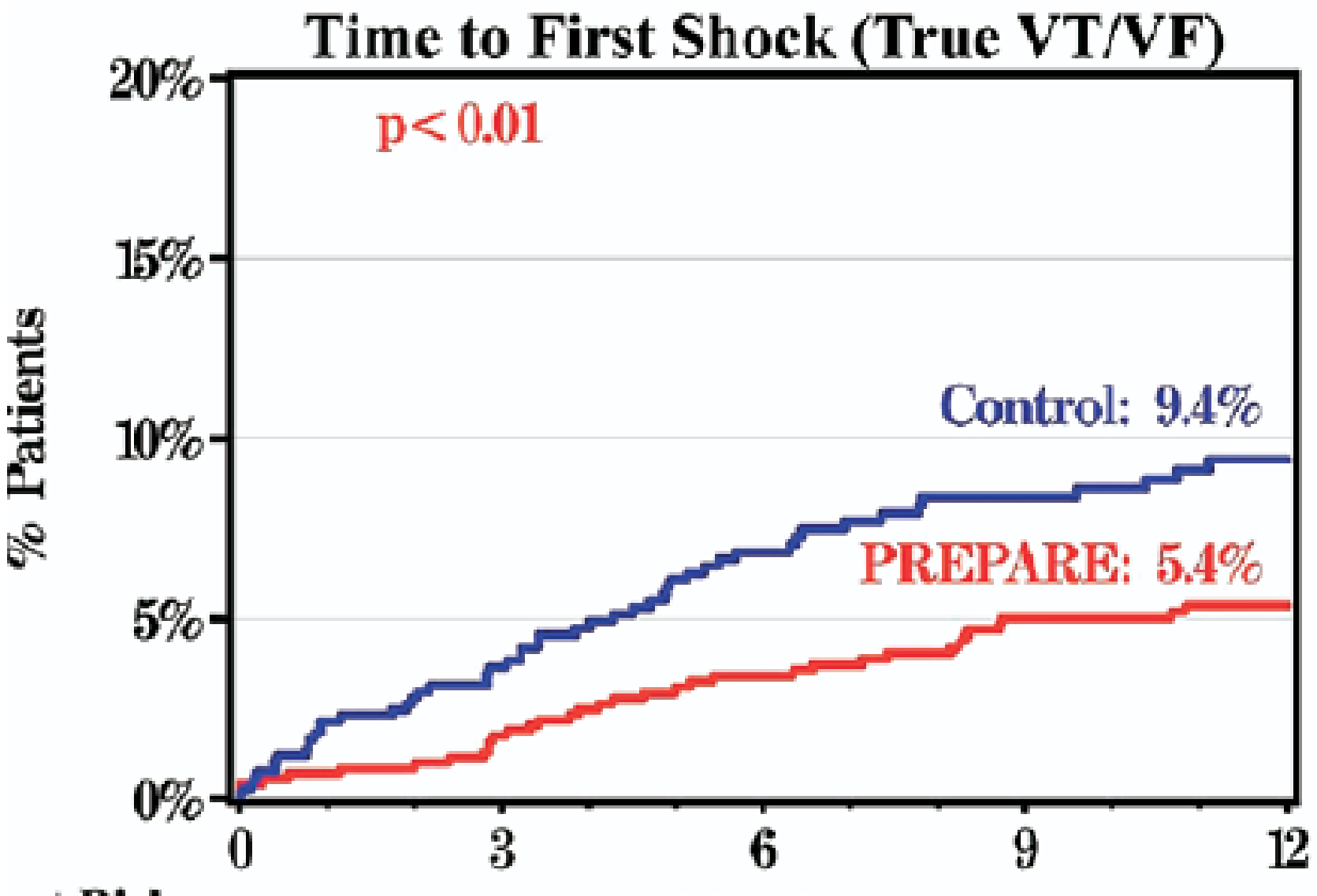
Supraventricular tachycardia criteria on (dual chamber, biventricular implantable cardioverter-defibrillator): atrial fibrillation/flutter, sinus tachycardia (1:1 VT-ST boundary = 66%); supraventricular tachycardia criteria on (single chamber): wavelet morphology discrimination (match threshold = 70%); 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.

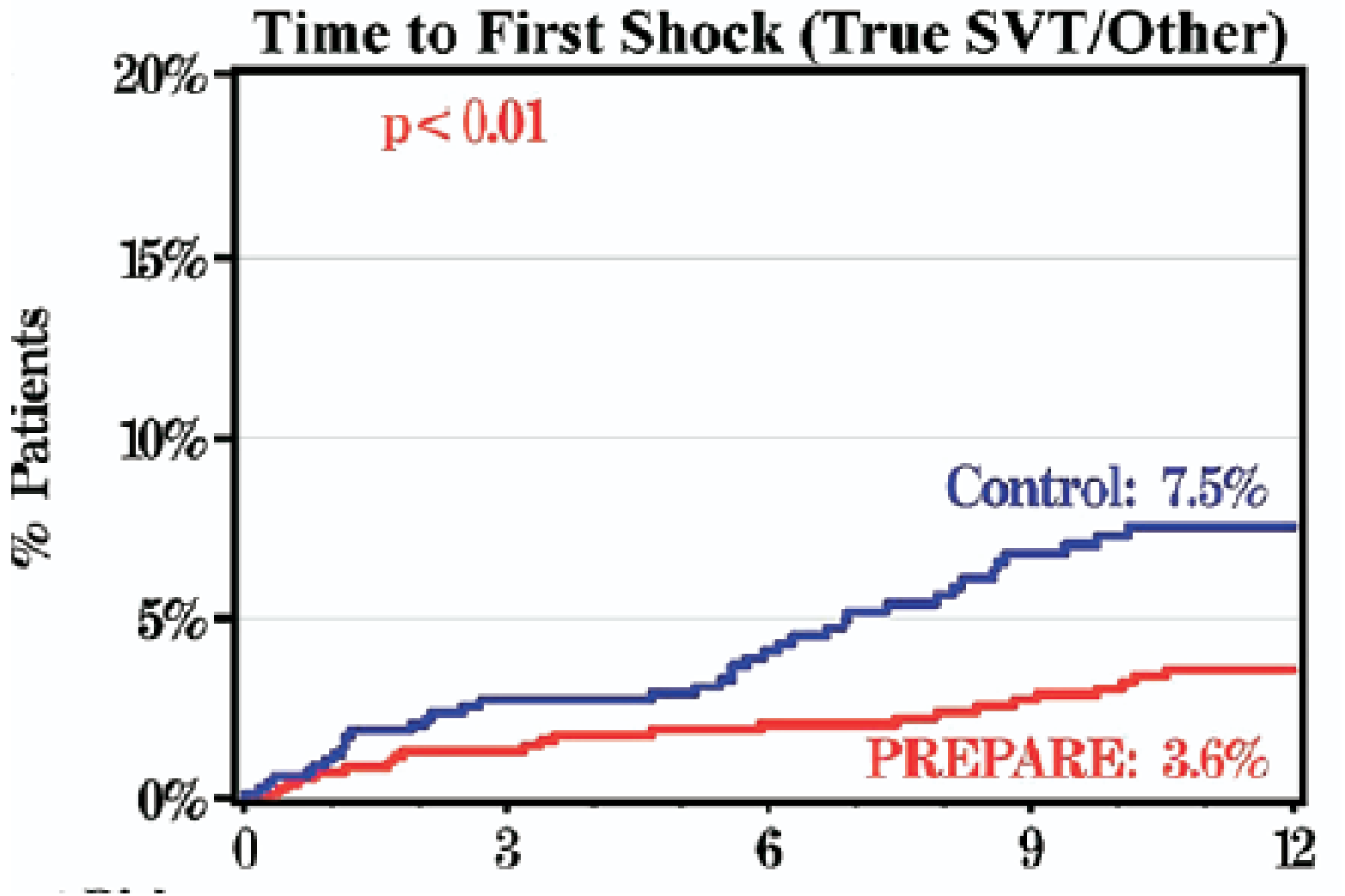
PREPARE

- 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

MADIT-RIT

Three Treatment Arms (abbreviated)*

Arm A (Conventional)	Arm B (High-rate)	Arm C (Duration-delay)
Zone 1:	Zone 1:	Zone 1:
≥170 bpm, 2.5s delay	170 bpm	**≥170 bpm, 60s delay**
Onset/Stability Detection Enhancements ON	Monitor only	Rhythm ID® Detection Enhancements ON
ATP + Shock		ATP + Shock
SRD 3 min initial		SRD Off
Zone 2:	Zone 2:	Zone 2:
≥200 bpm, 1s delay	**≥200 bpm, 2.5s delay**	**≥200 bpm, 12s delay**
Quick Convert™ ATP Shock	Quick Convert™ ATP Shock	Rhythm ID® Detection Enhancements ON ATP + Shock
		SRD Off
		Zone 3 :
		≥250 bpm, 2.5s delay
		Quick Convert™ ATP + Shock

*All programming is within approved labeling. Rhythm ID® and Quick Convert™ are trademarks of Boston Scientific Corporation

MADIT-RIT

Summary

Improved ICD programming to high-rate (>200 bpm) or 60sec duration-delay is associated with:

1) ~75% reduction in 1st inappropriate therapy;
2) ~50% reduction in all-cause mortality

You Should Also Know

- AVID (ANTIARRHYTHMICS VERSUS IMPLANTABLE DEFIBRILLATORS TRIAL)
- MADIT RIT - Randomized Trial to Reduce Inappropriate Therapy
- MIRACLE

- CASH (THE CARDIAC ARREST STUDY HAMBURG)

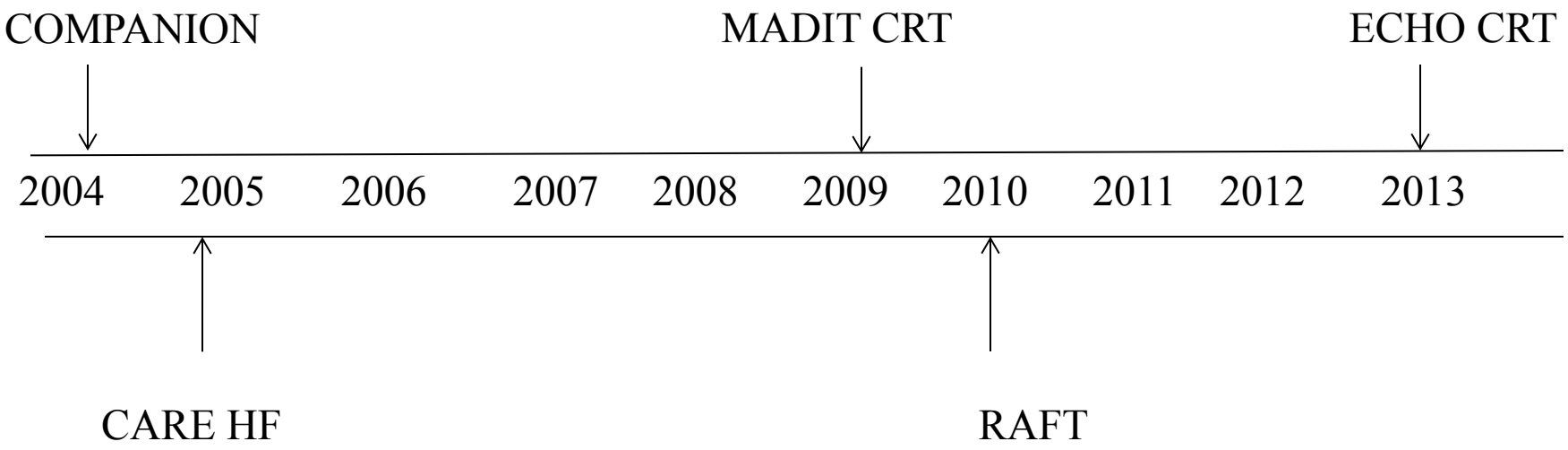
- CIDS - (CANADIAN IMPLANTABLE DEFIBRILLATOR STUDY)
- ADVANCE III

CRT

Quiz Question

- A 71 year old male – IHD, LBBB (QRS 118ms), EF 20% NYHA III NYHA
- Which clinical trial indicated a CRT- D device should be implanted?
- A MADIT CRT
- B COMPANION
- C SCD-HeFT
- D CARE HF
- E A CRT-D is not indicated

CRT – Landmark Studies



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

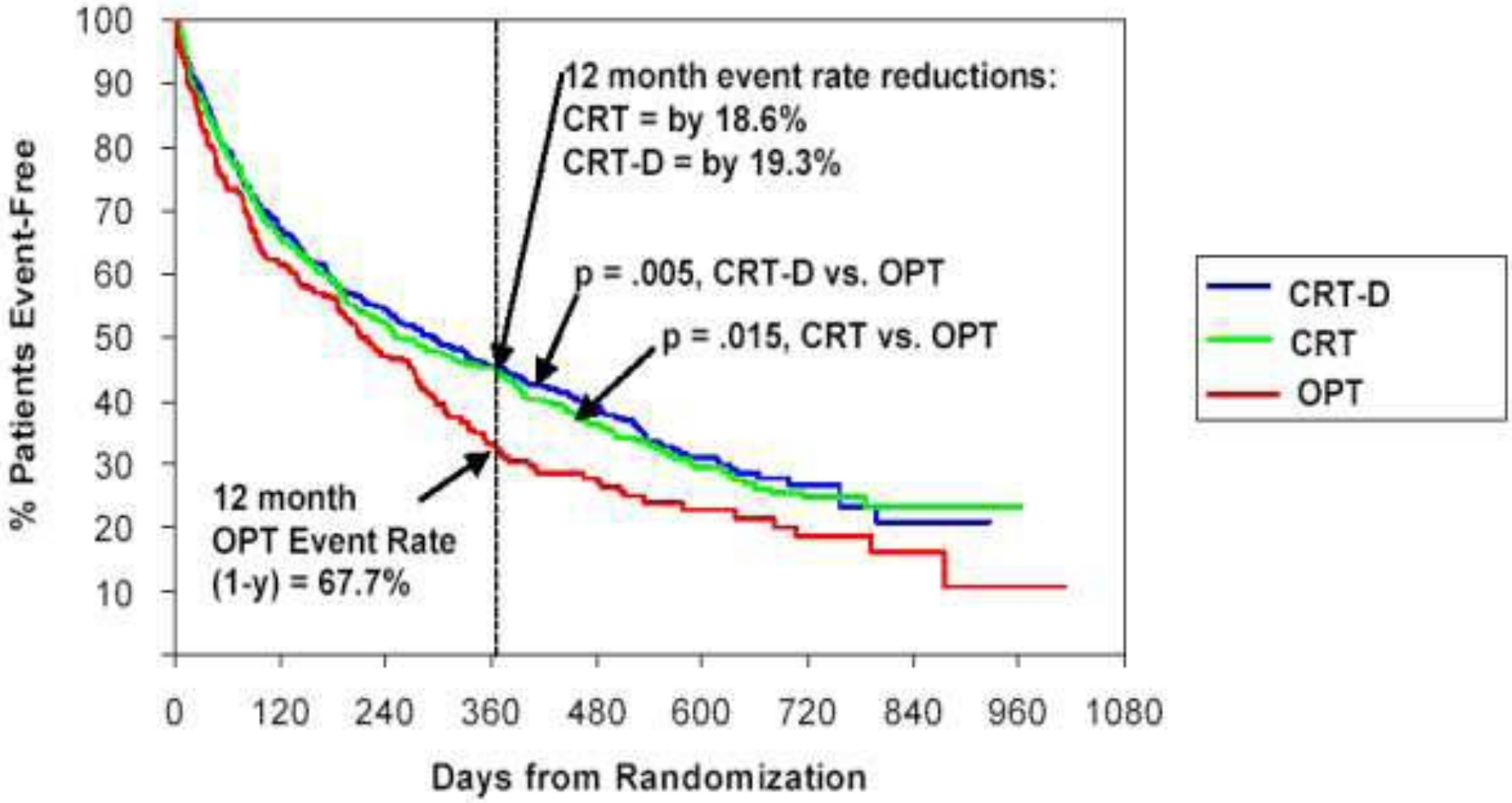
Bristow MR et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140-50

COMPANION

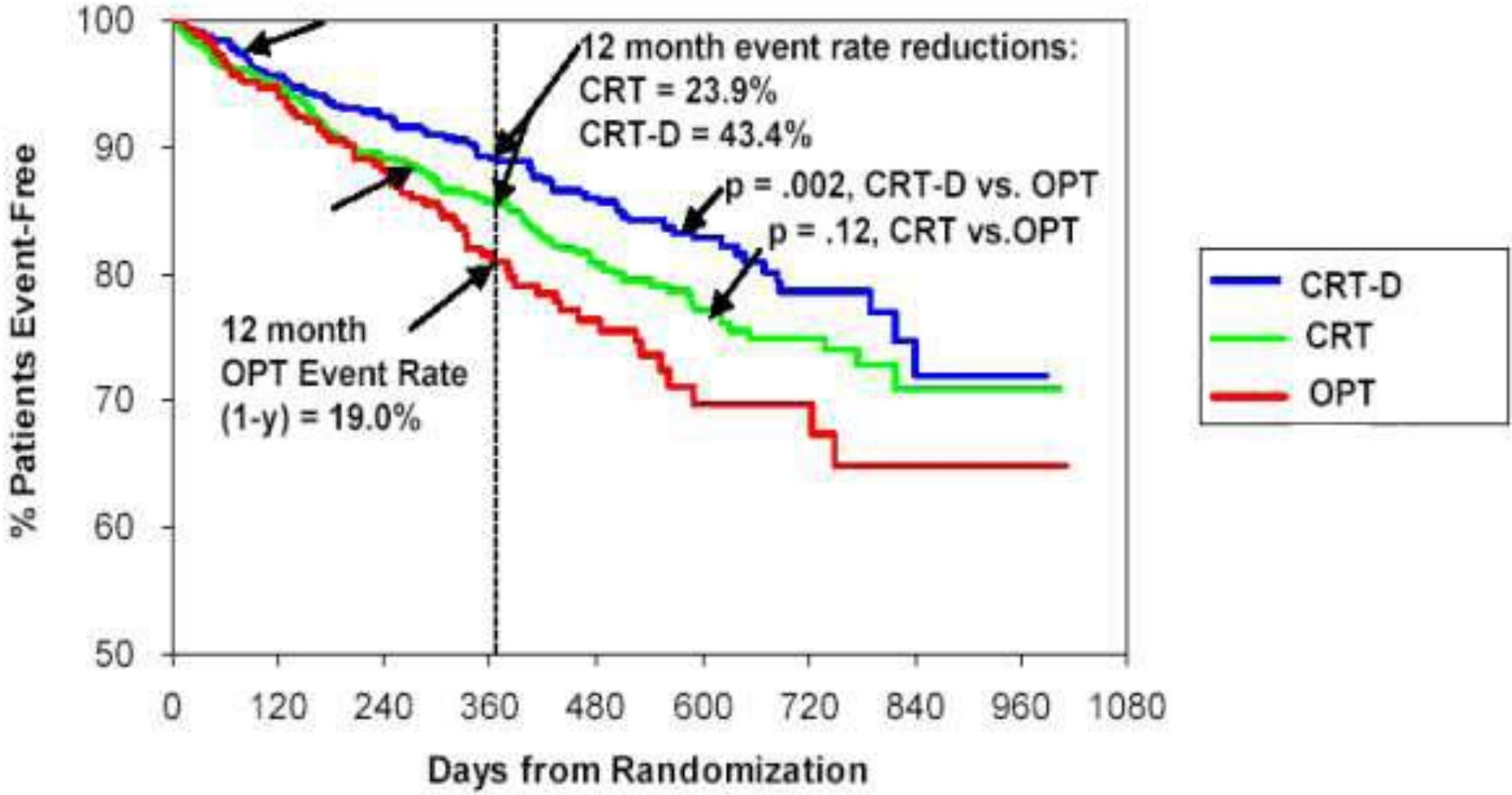
Randomised To 3 Arms

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

COMPANION
Primary End Point
(Death + Hospitalisation)



COMPANION
Secondary End Point
(All Cause Mortality)



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Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex

BACKGROUND

Cardiac-resynchronization therapy (CRT) reduces morbidity and mortality in chronic systolic heart failure with a wide QRS complex. Mechanical dyssynchrony also occurs in patients with a narrow QRS complex, which suggests the potential usefulness of CRT in such patients.

RESULTS

On March 13, 2013, the study was stopped for futility on the recommendation of the data and safety monitoring board. At study closure, the 809 patients who had undergone randomization had been followed for a mean of 19.4 months. The primary outcome occurred in 116 of 404 patients in the CRT group, as compared with 102 of 405 in the control group (28.7% vs. 25.2%; hazard ratio, 1.20; 95% confidence interval [CI], 0.92 to 1.57; P=0.15). There were 45 deaths in the CRT group and 26 in the control group (11.1% vs. 6.4%; hazard ratio, 1.81; 95% CI, 1.11 to 2.93; P=0.02).

CONCLUSIONS

In patients with systolic heart failure and a QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality. (Funded by Biotronik and GE Healthcare; EchoCRT ClinicalTrials.gov number, NCT00683696.)

Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction

Anne B. Curtis, M.D., Seth J. Worley, M.D., Philip B. Adamson, M.D., Eugene S. Chung, M.D., Imran Niazi, M.D., Lou Sherfesee, Ph.D., Timothy Shinn, M.D., and Martin St. John Sutton, M.D., for the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block **(BLOCK HF)** Trial Investigators

- In patients with AVB and LV dysfunction (LV <50%) BI V pacing compared to RV pacing leads to a significant 26% reduction in motality and HF related urgent care and an increase in LVESI

RAFT

- RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial)
- Objective: Determine whether the addition of cardiac resynchronization therapy (CRT) to optimal pharmacological therapy and implantable cardioverter-defibrillator (ICD) is effective in reducing mortality and morbidity in patients with moderate HF
- • Population and treatment: 1798 patients with NYHA class 2 or 3 HF, LVEF <30%, and a QRS duration >120 ms (or paced QRS >200 ms)
- Randomized to ICD therapy alone or an ICD with CRT (CRT-D)—40-month mean follow-up
- • Primary outcome: All-cause death or number HF admissions

You Should Also Know

- MADIT - CRT
- MADIT - RIT
- CARE-HF (CArdiac REsynchronisation Heart Failure)
- SCD-HeFT Sudden Cardiac Death in Heart Failure Trial
- 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

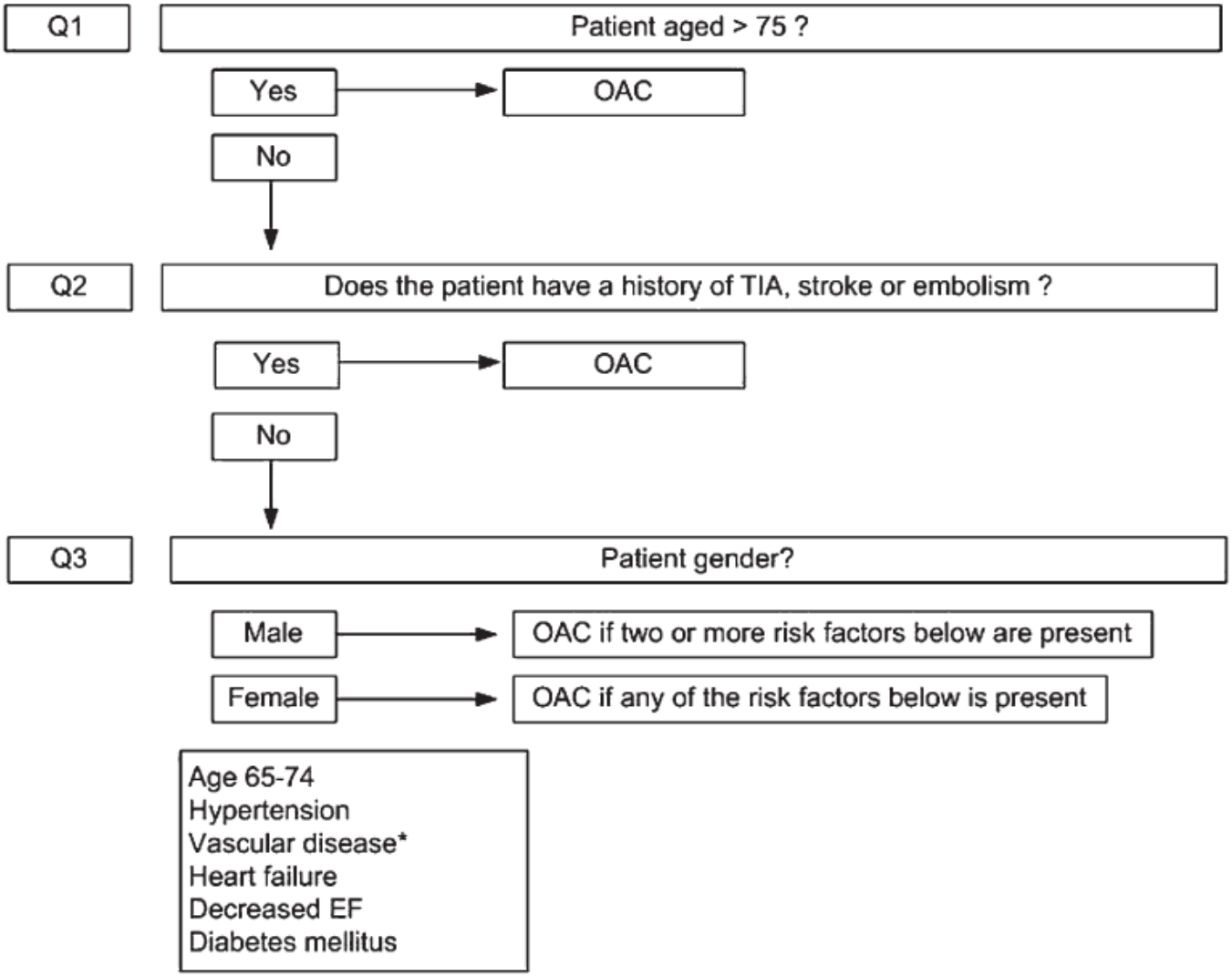
Lip GYH, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. Chest 2010; 137: 263-72.

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

- 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

Quz Question

In the MOST study which of the following is true?

1. Hospitalisation due to HF was not an end point
2. Percentage pacing had no significant effect of HF hospitalisations
3. Symptomatic HF was an inclusion criteria
4. RV pacing of >40% was associated with a increase in HF hospitalisations
5. Only patients with EF <50% were included

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

Stuart.allen@cmft.nhs.uk

NOAC studies

Dabigatran

- Patients under 80 years -150mg bd
- Patients ≥80 years -110mg bd
- Consider 110 mg bd when stroke risk low and bleeding risk is high or patients weigh <50kg

Dabigatran: RE-LY

18,113 patients with AF at increased risk of stroke

50% of patients naïve to oral anticoagulants.

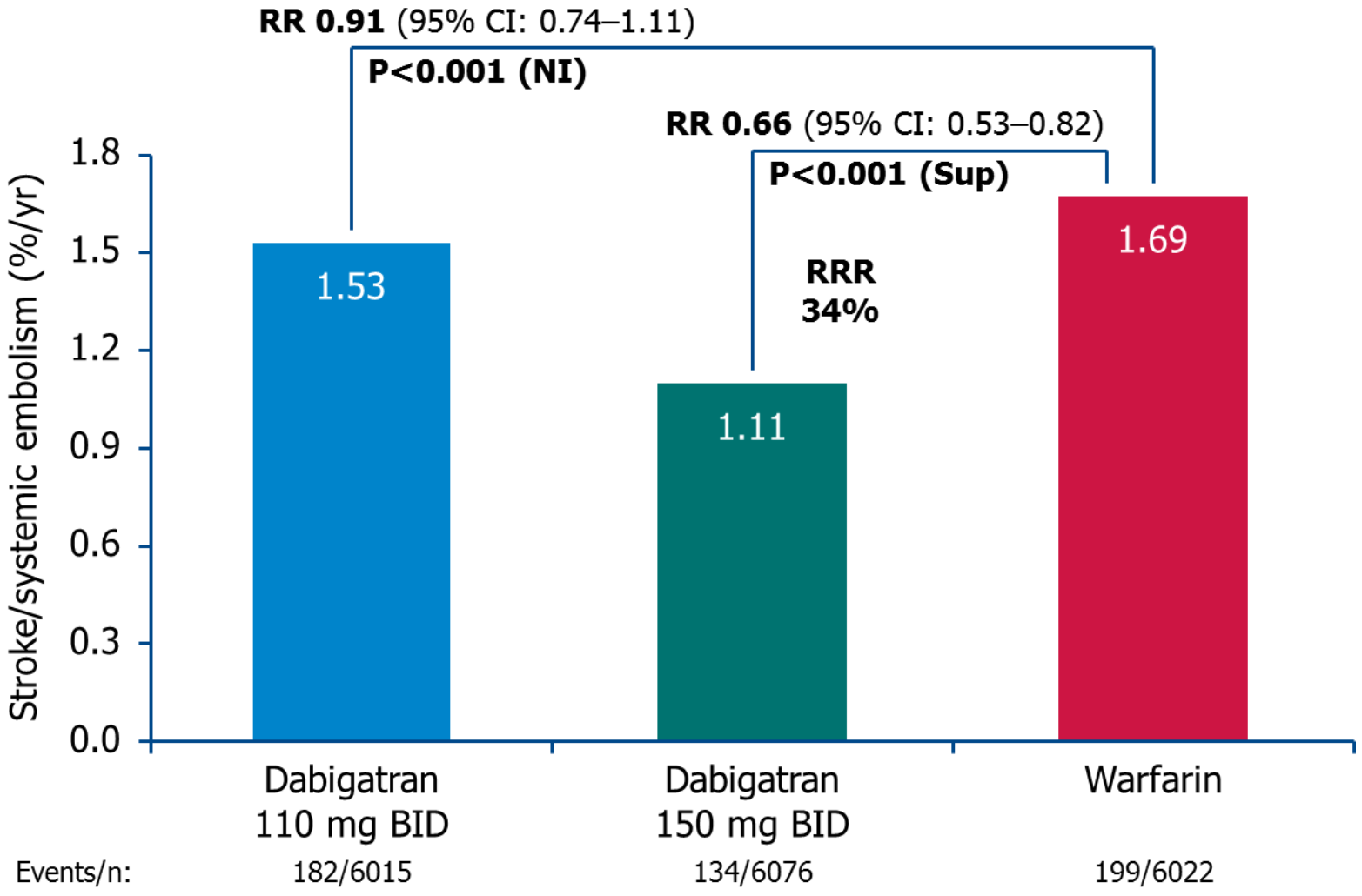
Prospective, open-label, blinded endpoint

Patients with bleeding risks excluded

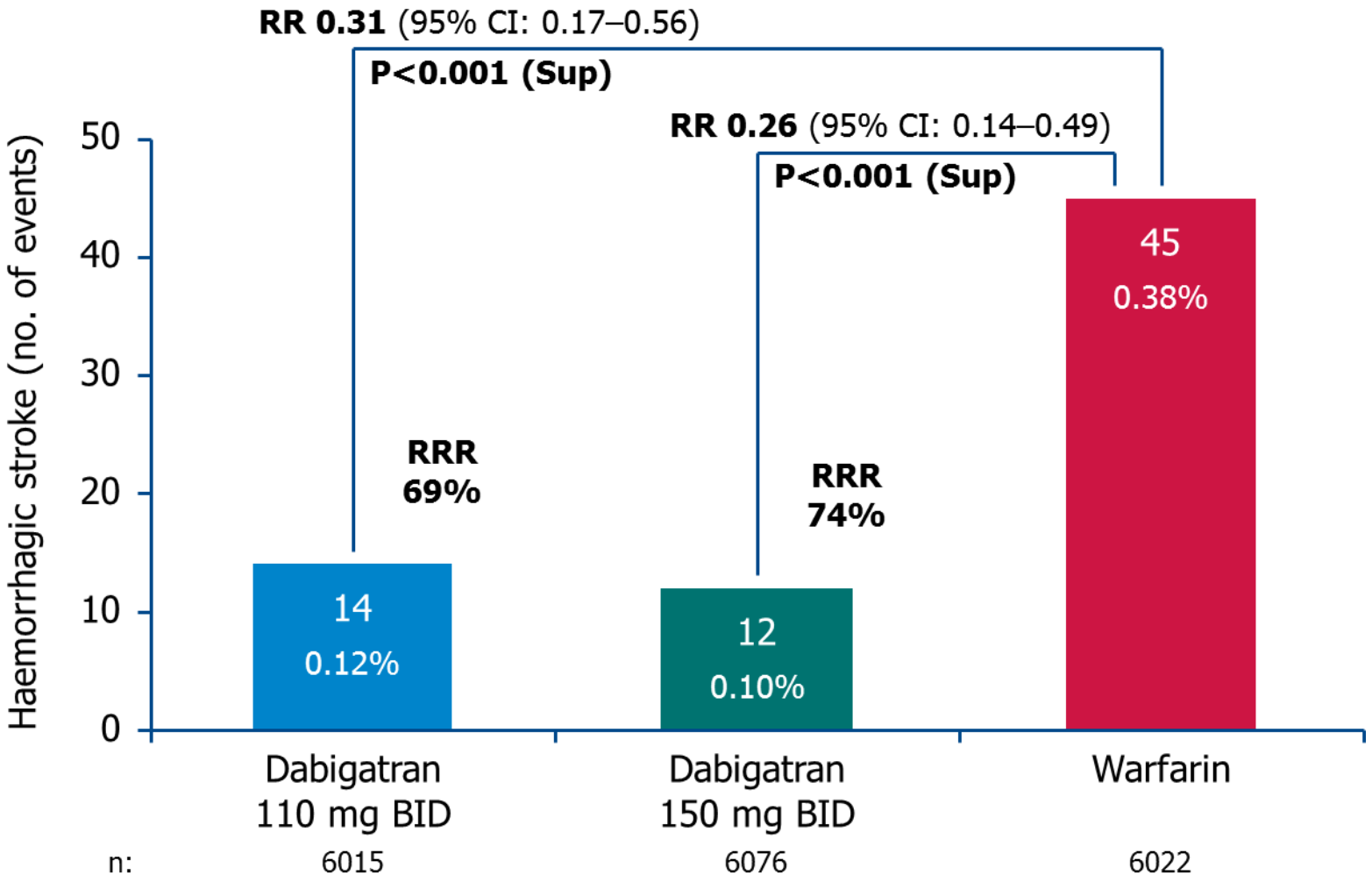
Dabigatran

- Patients under 80 years -150mg bd
- Patients ≥80 years -110mg bd
- Consider 110 mg bd when stroke risk low and bleeding risk is high or patients weigh <50kg
- INR monitoring not helpful

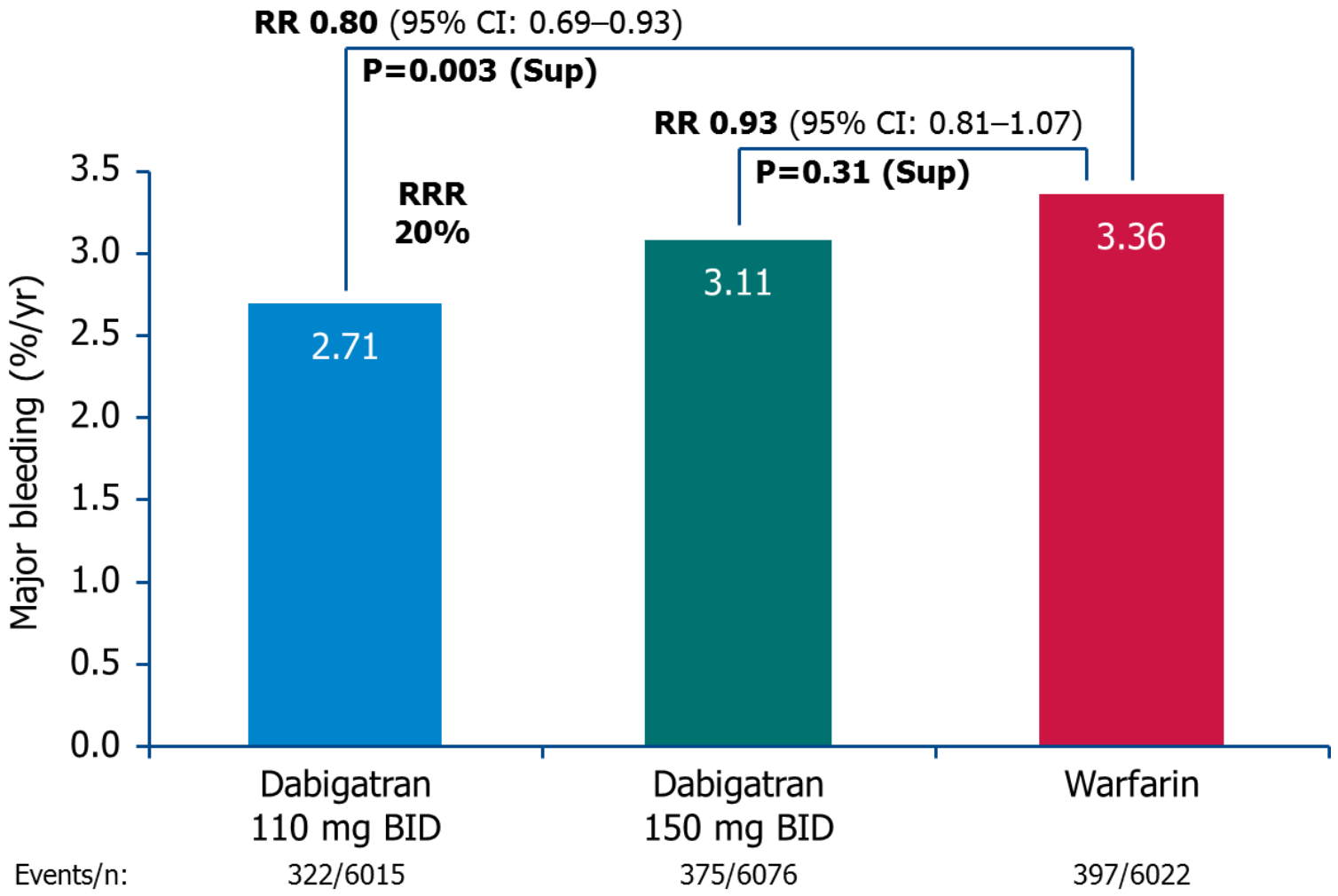
RE-LY Study: Stroke or Systemic Embolism



RE-LY Study: Intracranial Haemorrhage



RE-LY Study: Major Bleeding



RE-LY Study: Major Bleeding

110 mg dose vs. warfarin

- Comparable rates of stroke/systemic embolism
- Statistically significant reduction in haemorrhagic stroke
- Statistically significant reduction in major bleeding rates
- Significant reduction in total bleeds, life-threatening bleeds and intracranial bleeds

150 mg dose vs. warfarin

- Statistically significant reduction in stroke/systemic embolism
- Statistically significant reduction in haemorrhagic stroke
- Statistically significant reduction in vascular mortality
- Comparable rates of major bleeding rates
- Significant reduction in total bleeds, life-threatening bleeds and intracranial bleeds

Rivaroxaban

Usual dose 20mg od

Reduce to 15mg od when CrCl is 15-49ml/min

Extra caution is required if CrCl is 15-29mls/min

10mg od for post operative prophylaxis.

Cannot be used if CrCL <15ml/min

Rivaroxaban: ROCKET-AF

Double-blind randomized trial

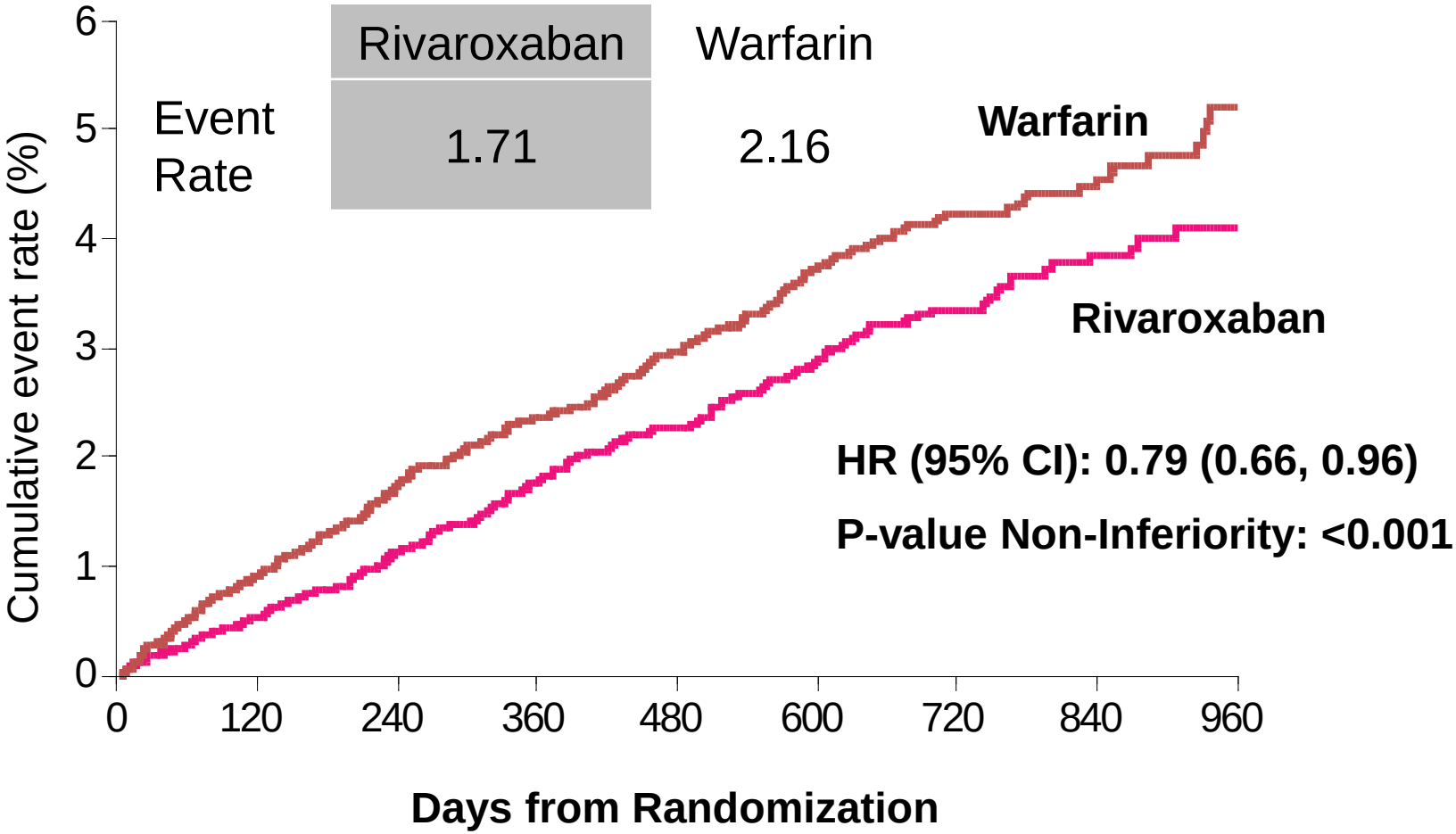
14,264 patients at moderate to high stroke risk

(CHADS2 $\geq$2)

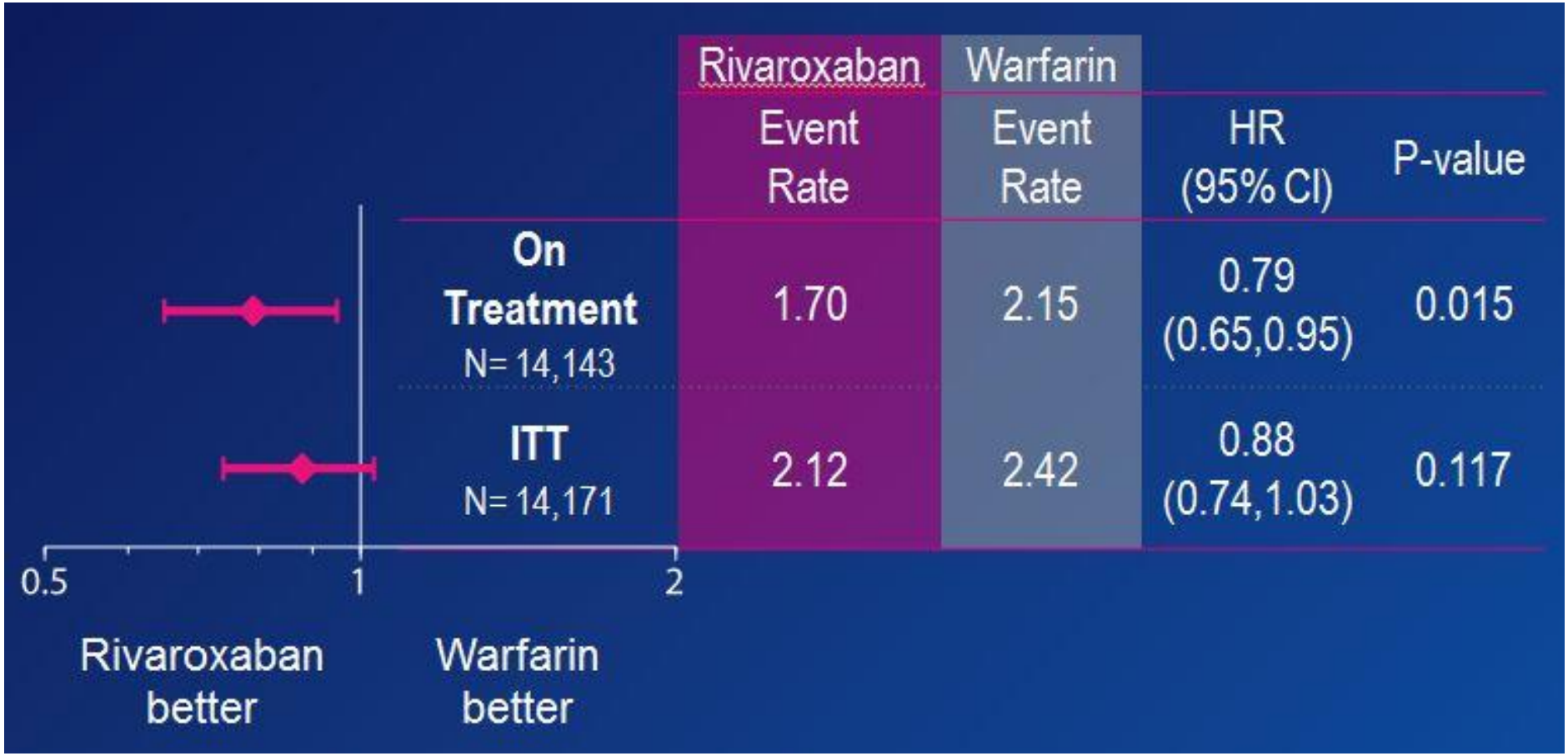
Rivaroxaban 20mg daily vs warfarin with INR 2-3

Dose reduced to15mg od if CrCl 30-49mls/min

ROCKET-AF: Stroke or Systemic Embolism



ROCKET-AF: Stroke or Systemic Embolism



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

ROCKET-AF: Bleeding

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

Greater Manchester CCG NOAC Guidelines

- At least 3 month trial of VKA expected
- Reasons for switching to NOACs
  - <65% in therapeutic range (INR 2-3) with VKA
  - INR >5 on 2 unrelated occasions in past 12 months
  - Unable to tolerate warfarin, sinthrome or dindevan

Apixaban

Direct factor Xa inhibitor

25% renal excretion

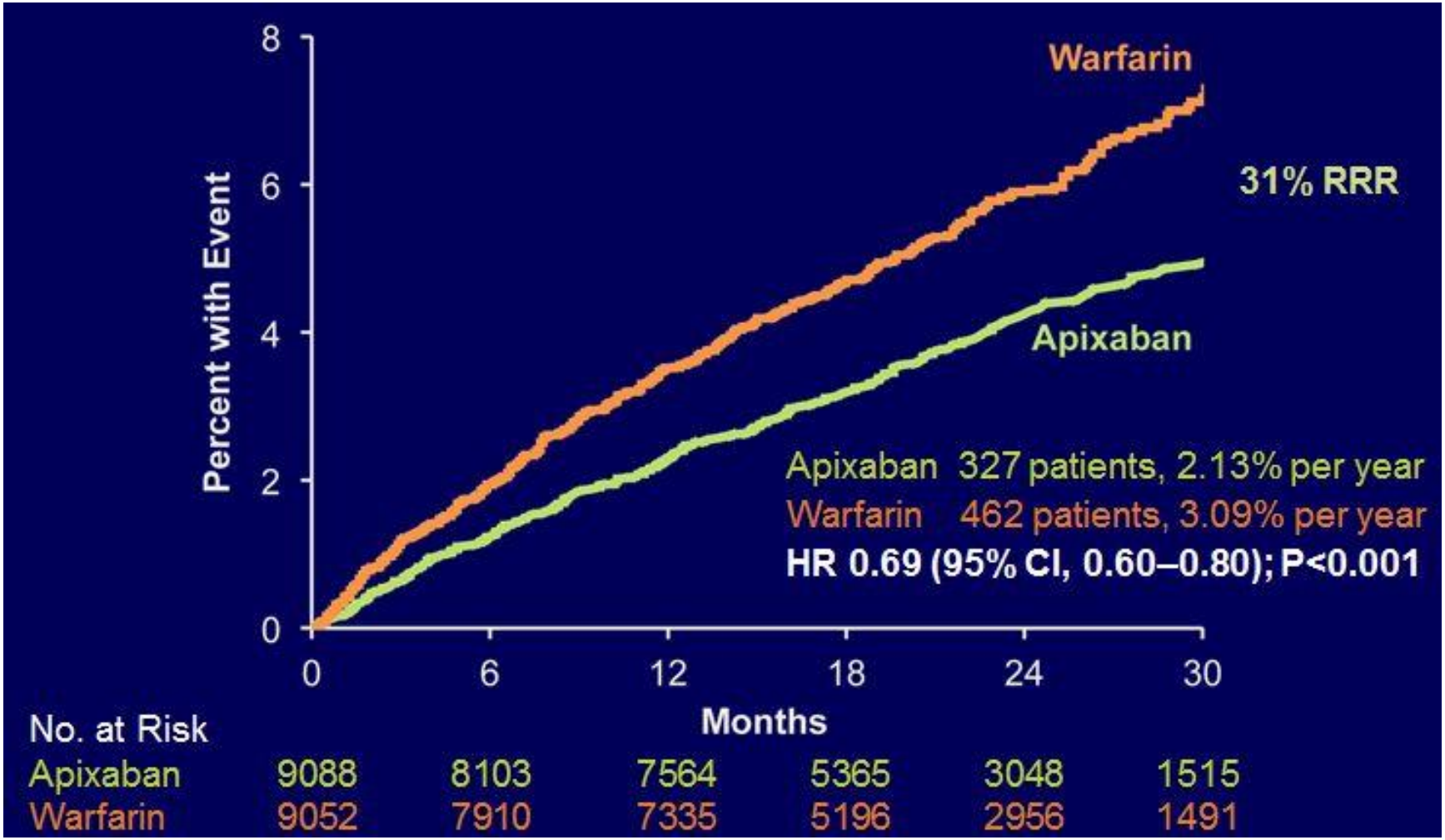
Dose 5 mg bd

Reduced to 2.5mg twice bd in high risk patients (2 of age 80 or over, weight 60kg or less and reduced CrCl)

Apixaban:

- Double-blind randomized trial
- 18,201 patients with nonvalvular AF and at least one additional risk factor for stroke
- Apixaban vs warfarin (target INR 2.0-3.0)

Aristotle Study: Major Bleeding



Aristotle Study: Major Bleeding

Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) Event Rate (%/yr)	HR (95% CI)	P Value
Primary safety outcome: ISTH major bleeding*	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61, 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35, 0.60)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46, 0.70)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68, 0.75)	<0.001

Aristotle Study: Major Bleeding