De Novo CRT in Patients With Conventional Pacemaker Indications Without Heart Failure

Jonathan S. Steinberg, MD
Director, Arrhythmia Institute
The Valley Health System
Professor of Medicine (adj)
University of Rochester
New York, NY and Ridgewood, NJ, USA

October 16 - 18
14th EDITION 2015

MY CONFLICTS OF INTEREST ARE:

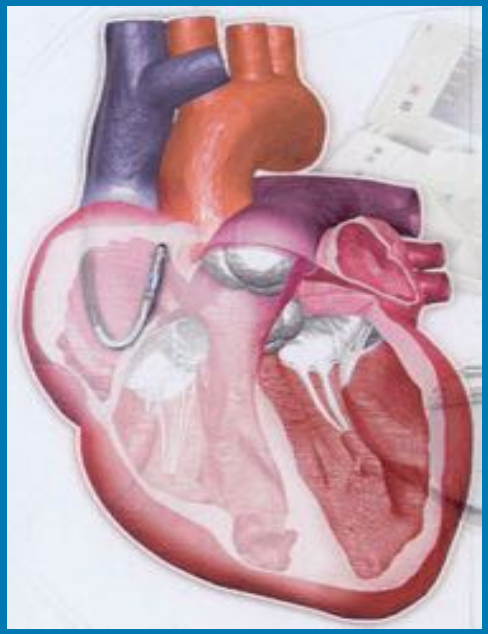
Medtronic, Boston Scientific (consultant); Medtronic (research support); Medtronic (DSMB, Events Committee)

Indications for Permanent Pacing

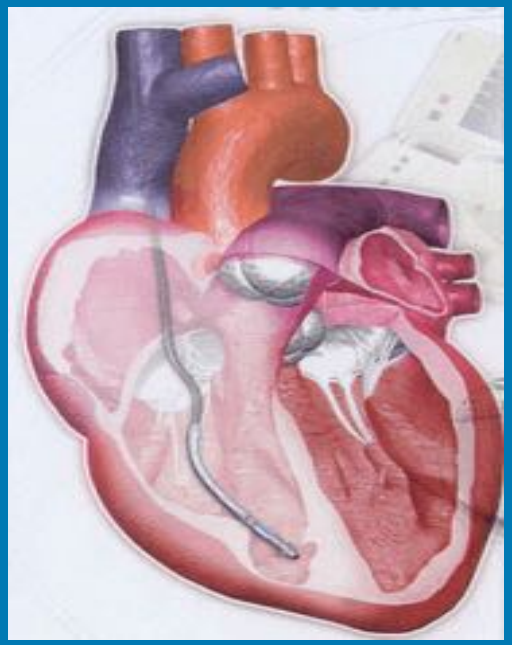
Recommendations	Class [a]	Level [b]
1) Sinus node disease. Pacing is indicated when symptoms can clearly be attributed to bradycardia.	I	B
2) Sinus node disease. Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive.	IIb	C
3) Sinus node disease. Pacing is not indicated in patients with SB which is asymptomatic or due to reversible causes.	III	C
4) Acquired AV block. Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptoms.	I	C
5) Acquired AV block. Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS.	IIa	C
6) Acquired AV block. Pacing is not indicated in patients with AV block which is due to reversible causes.	III	C

Once pacing indicated, does device selection and programming matter?

Conventional Pacing Lead Positions

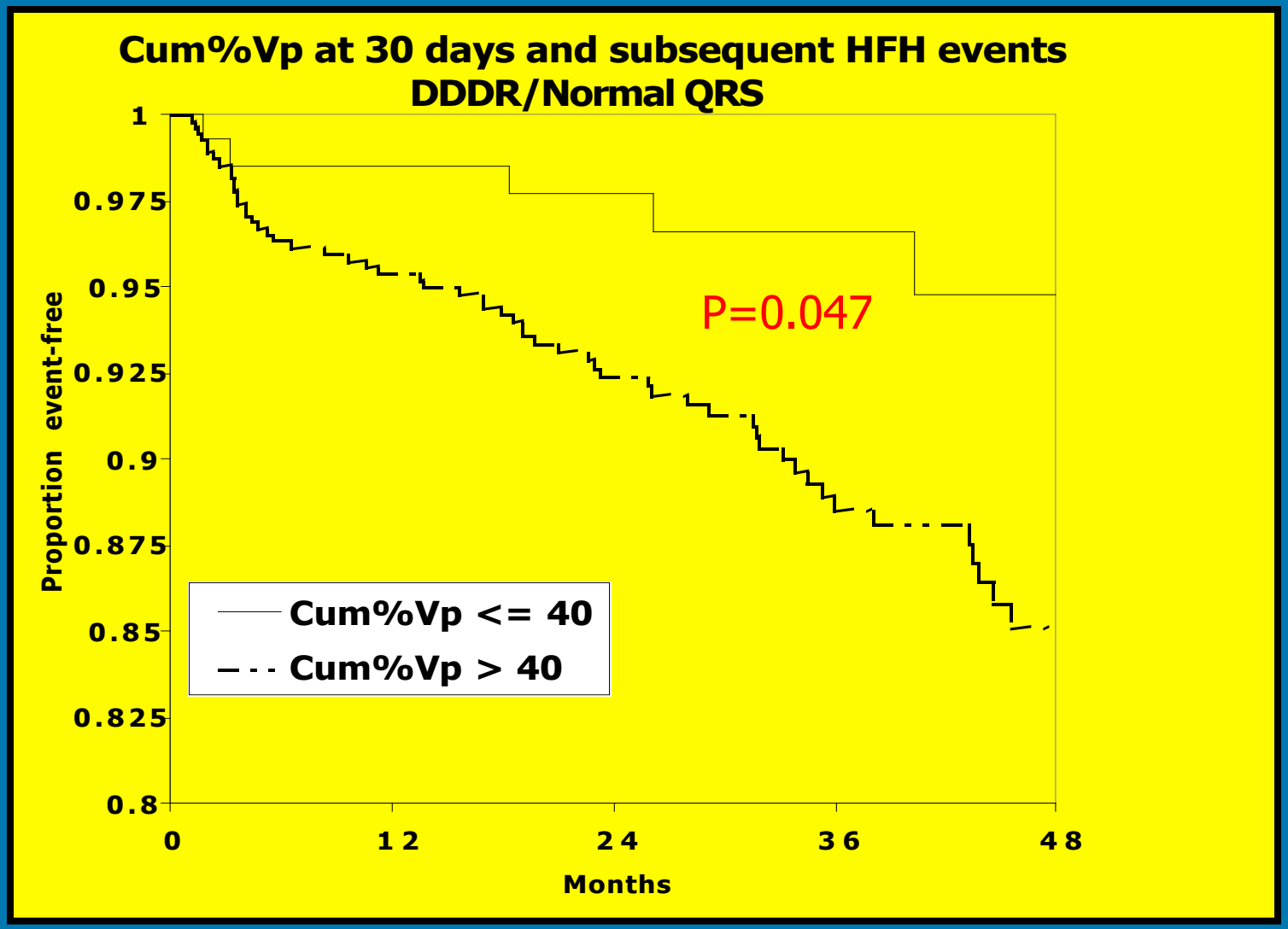


- The first-order pacing goal was resolution of bradycardia – atrial leads were added to establish AV synchrony.



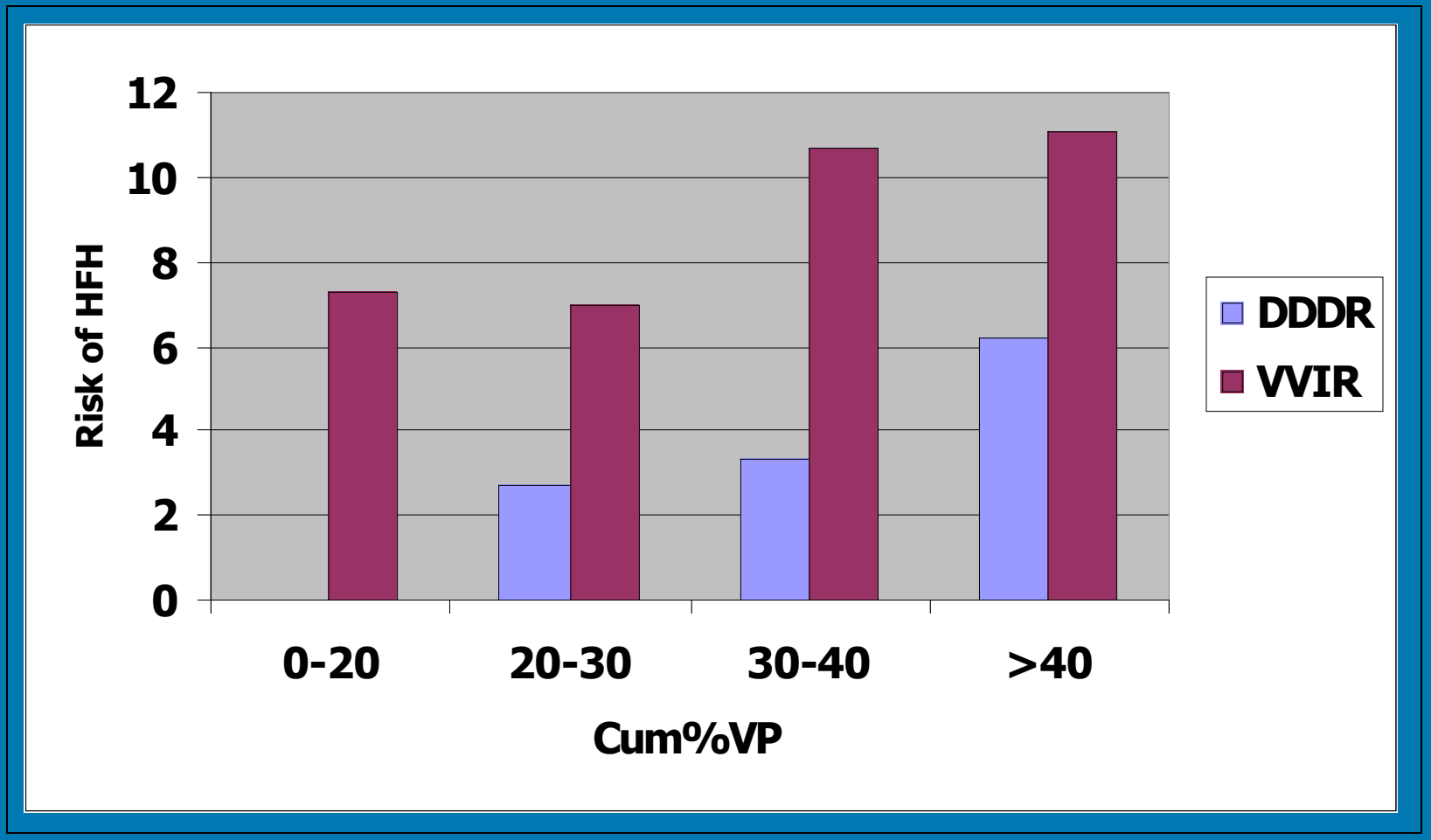
- Pacing leads were designed for easy and reliable delivery to the RV apex, RA appendage – where the position was considered **convenient and stable** after years of clinical practice.

Relationship of Ventricular Pacing to New/Worsened Heart Failure Outcome in SSS PPM Patients (MOST)

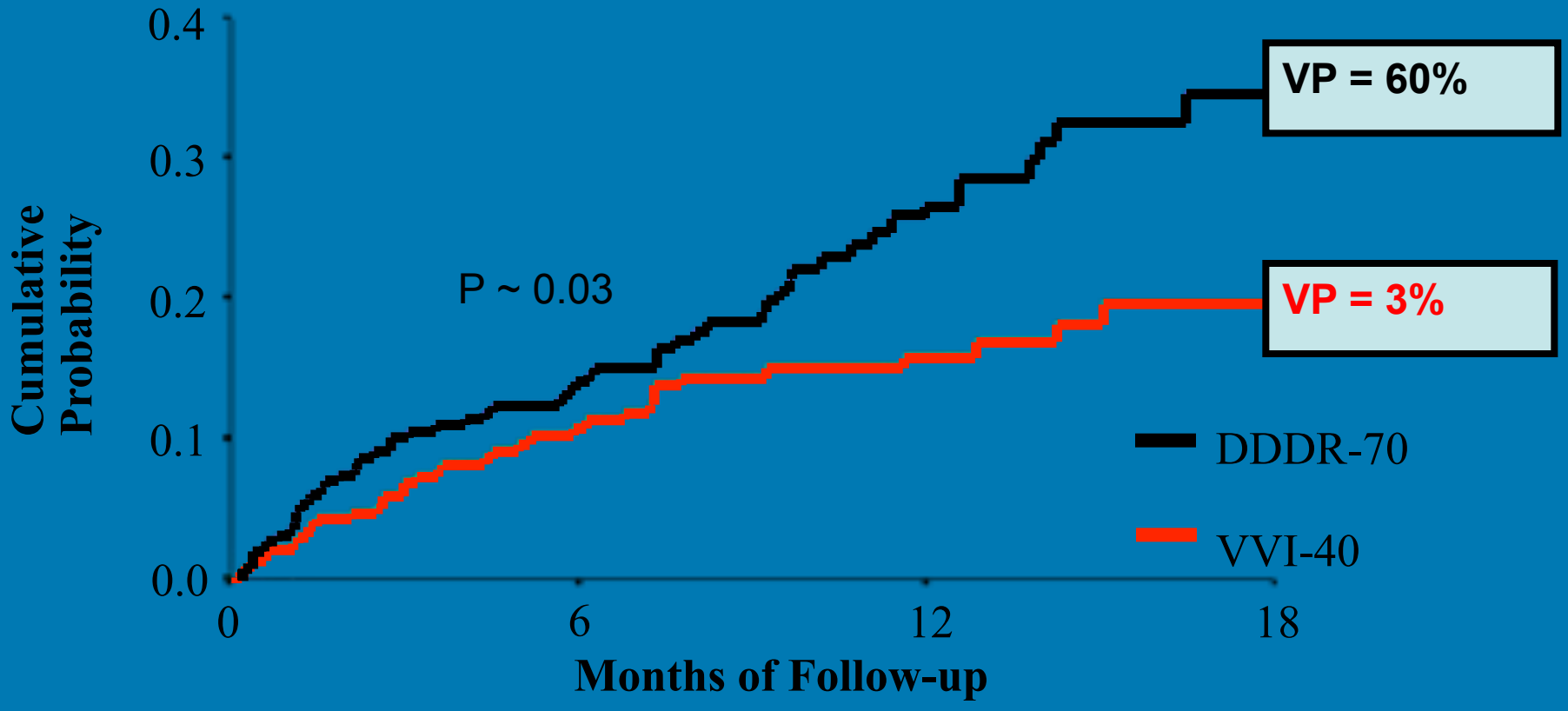


Sweeney et al, Circulation 2003

Risk of HF Relative to Mode/%Pacing (MOST)



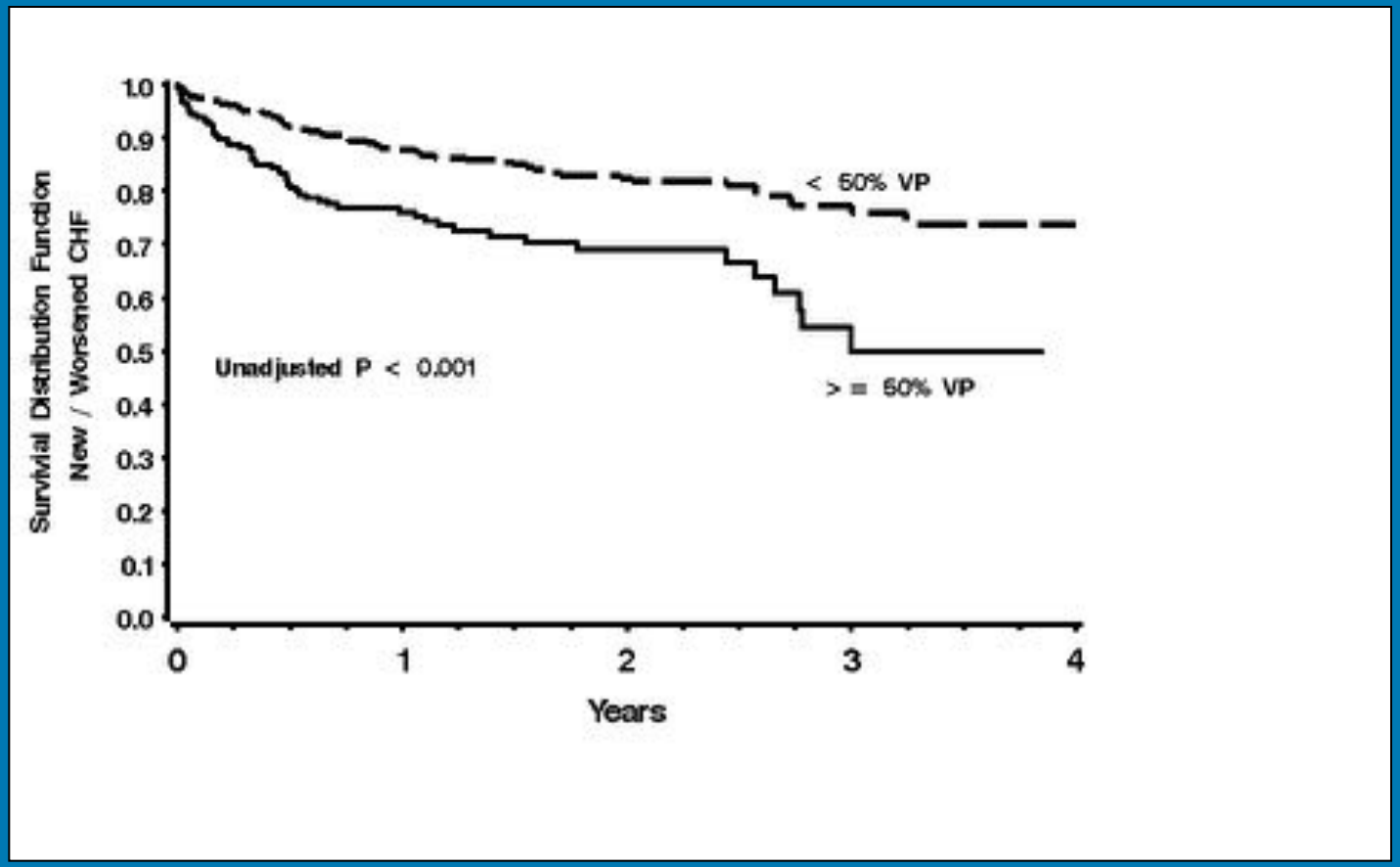
Death or First Hospitalization for New/ Worsened CHF in Diverse ICD Patients (DAVID)



N at risk				
DDDR	250	159	76	21
VVI	256	158	90	25

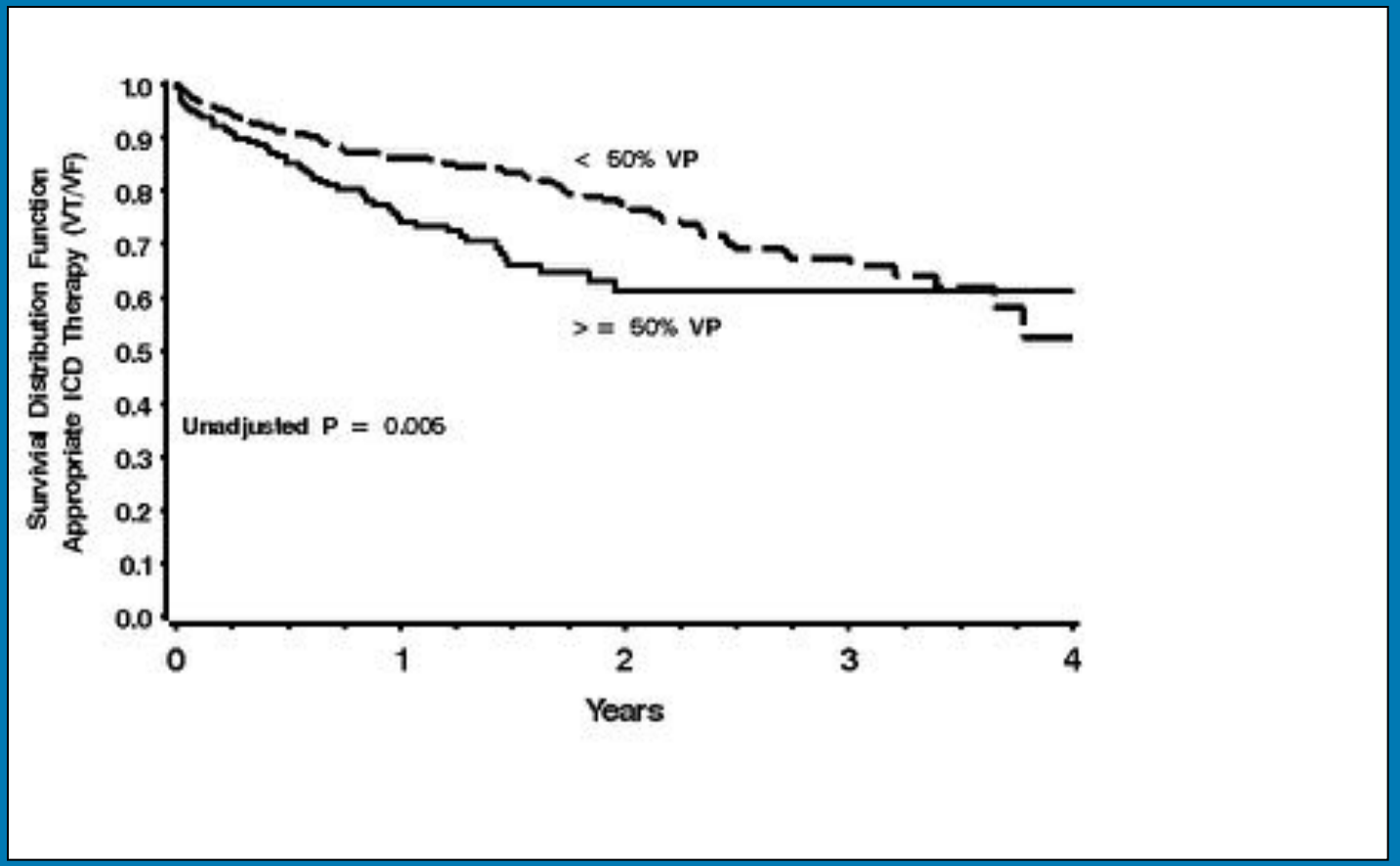
Wilkoff et al, Cardiac Electrophysiology Review 2003

Relationship of Ventricular Pacing to New/Worsened CHF in Primary Prevention ICD Patients (MADIT II)



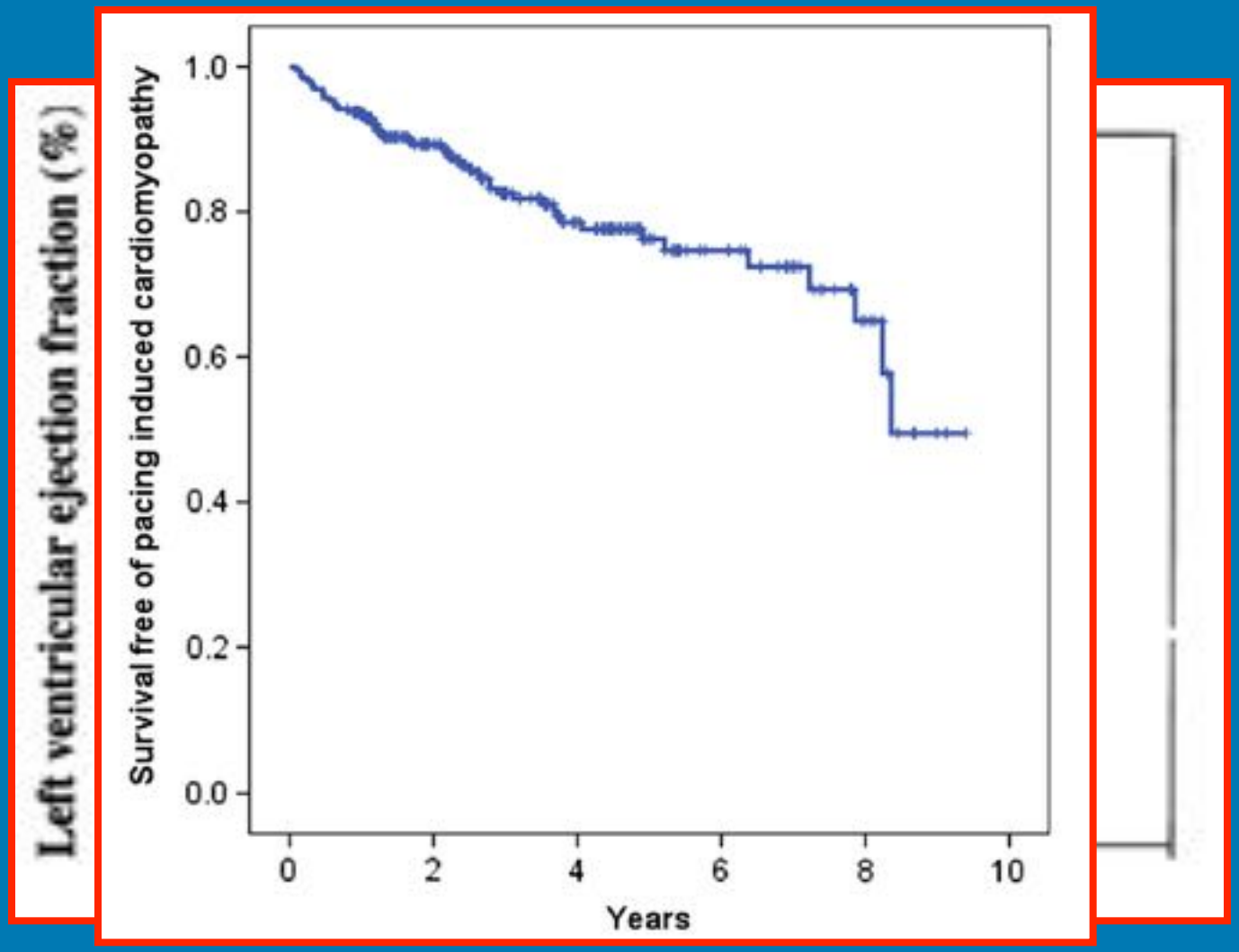
Steinberg et al, JCE 2005

Relationship of Ventricular Pacing to ICD Therapy for VT/VF (MADIT II)



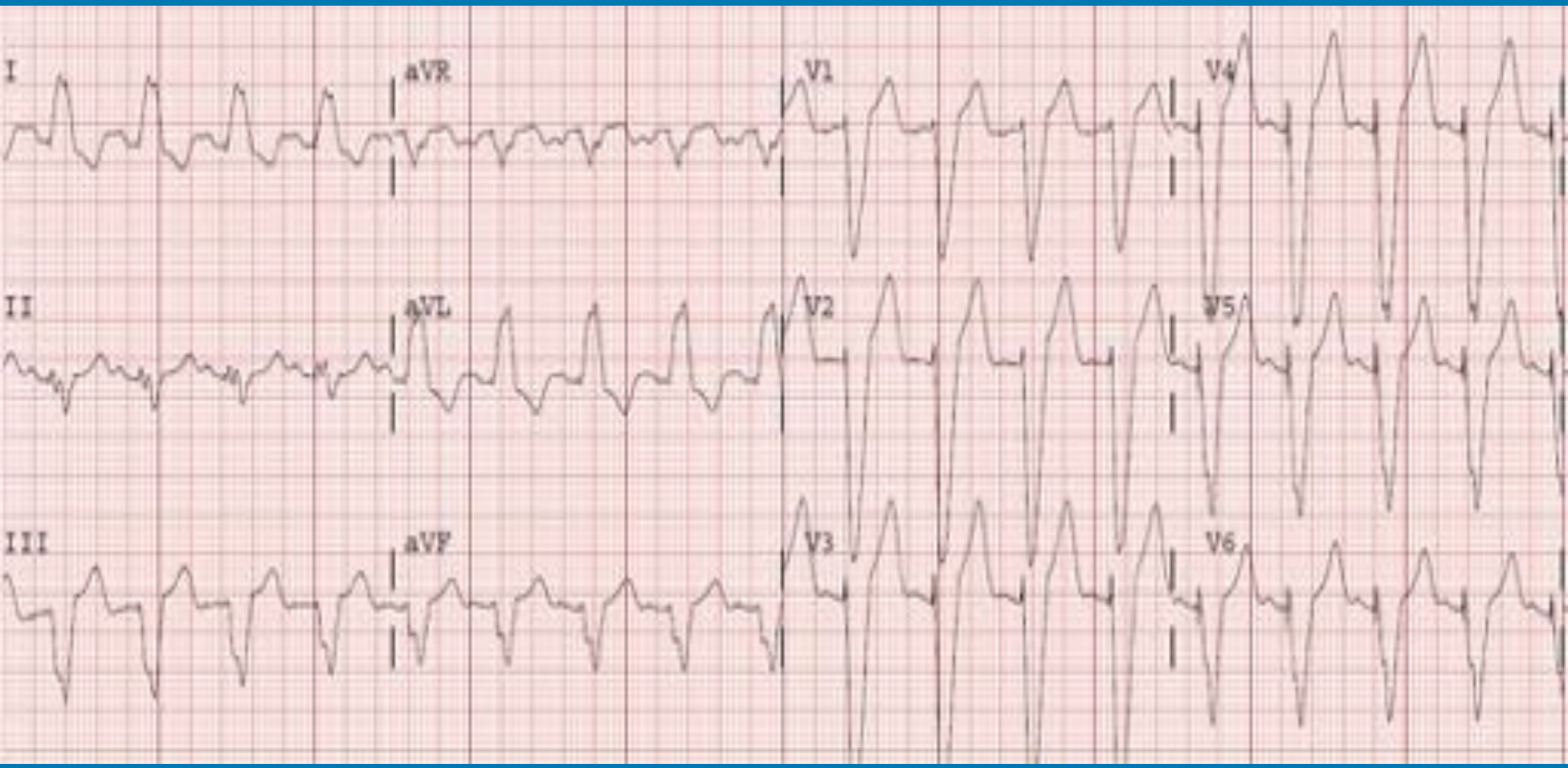
Steinberg et al, JCE 2005

Decline in Normal Ventricular Function With RVP?



Nahlawi et al, JACC 2004; Kurshid et al, Heart Rhythm 2014

ECG of Paced QRS Complex



Mechanisms Underlying the Deleterious Effects of RV Apical Pacing

- Intraventricular conduction delay
- LV mechanical and electrical dyssynchrony
- LV remodeling
- Abnormal myocardial histopathology
- LV systolic dysfunction
- Overt congestive heart failure
- Myocardial perfusion defects
- Mitral regurgitation
- Left atrial dilation
- Increased atrial fibrillation
- Promotion of ventricular arrhythmias
- Activation of sympathetic nervous system

Summary of Potential Harm from Chronic RVP

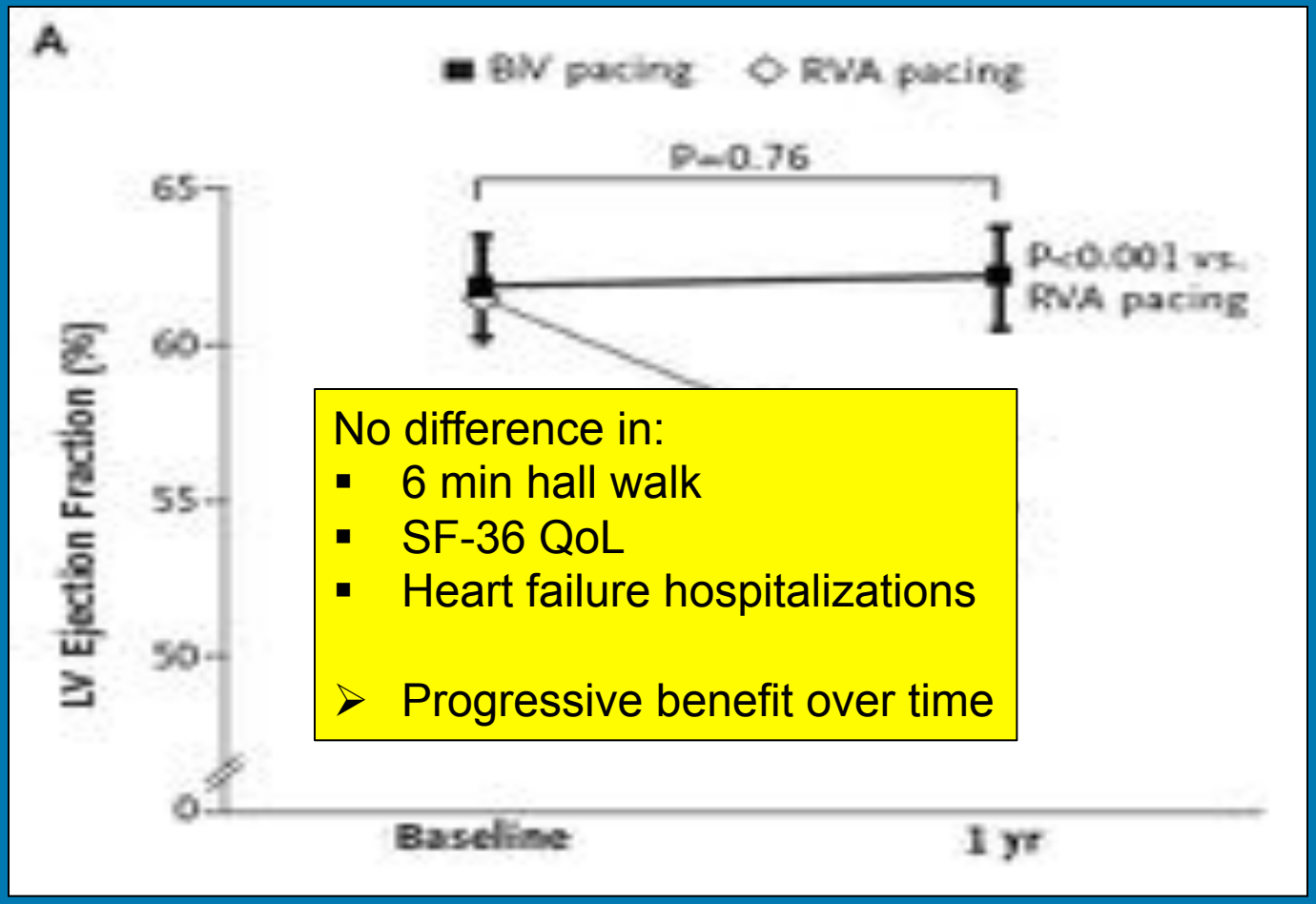
- Observed in diverse patient device groups
- Dose effect, ie more pacing associated with more harm
- Patients with more baseline LV dysfunction most vulnerable
- Multitude of plausible mechanisms for harm, and individuals may be affected differently
- Clinical manifest harm follows preclinical measures of ventricular dysfunction, ie opportunity for preemption

Principles for Device Selection and Programming

- Almost all PPM patients who are not in permanent AF will receive a dual chamber device (RA/RV)
- If AV conduction is intact, avoid unnecessary RV pacing
  - Longer AV intervals
  - Algorithms to avoid RV pacing
  - Back-up pacing only for ICD patients
- In general, avoid programming to AAI(R) mode and/or extremely long AV intervals

But in many patients, continuous ventricular pacing is unavoidable. How can deleterious effects of RVP be mitigated?

PACE Trial



No difference in:

- 6 min hall walk
- SF-36 QoL
- Heart failure hospitalizations

➢ Progressive benefit over time

Yu et al, NEJM 2009; Chan et al, Eur Heart J 2011

Study Purpose and Objectives

Purpose: Biventricular pacing is superior to RV apical pacing in patients with AV block and LVEF ≤50% who require ventricular pacing

Endpoints:

Primary: Composite of:

- All-cause mortality,
- HF-related urgent care, defined as
  - HF hospitalization requiring IV therapy, or
  - Any unplanned visit requiring intravenous HF therapy, and
- Increase in left ventricular end systolic volume index (LVESVI) ≥15%

Key Secondary: All-cause mortality,

All-cause mortality/HF hospitalization,

HF hospitalization

Acknowledgments

Steering Committee

Curtis AB (Principal Investigator), Adamson PB , Chung ES, St. John Sutton MG, Worley SJ

Echo Core Lab

St. John Sutton MG, Plappert T

Adverse Events Advisory Committee

Boehmer JP, Meyer TE(Chair), Smith AL, De Lurgio DB

Data Monitoring Committee

Steinberg JS (Chair), DeMarco T, Elkayam U, Louis TA (Statistician)

Investigators

Canada: Rinne C, Thibault B

United States: Adamson PB, Al-Sheikh T, Andriulli J, Barber MJ, Beau S, Bell M, Borgatta L, Brodine W, Canosa R, Chung ES, Compton S, Curtis AB, Ellison K, Evonich R, Faddis M, Foreman B, Murray C, Guerrero M, Herre J, Hodgkin D, Huang D, Keim S, Kocovic D, Kusmirek SL, Lessmeier T, Levanovich P, Lobban JH, Mackall JA, Manaris A, McBride W, McKenzie J, Mela T, Merliss A, Mitrani R, Mittal S, Mounsey P, Navone A, Niazi I, Obel O, Oren J, Patel P, Patel V, Pickett A, Rao A, Rist K, Rosenblum A, Saba S, Sakaguchi S, Sandler D, Sangrigoli R, Shinn TS, Simmons T, Simonson J, Smith JE, Telfer EA, Tobias S, Tomassoni G, Worley SJ

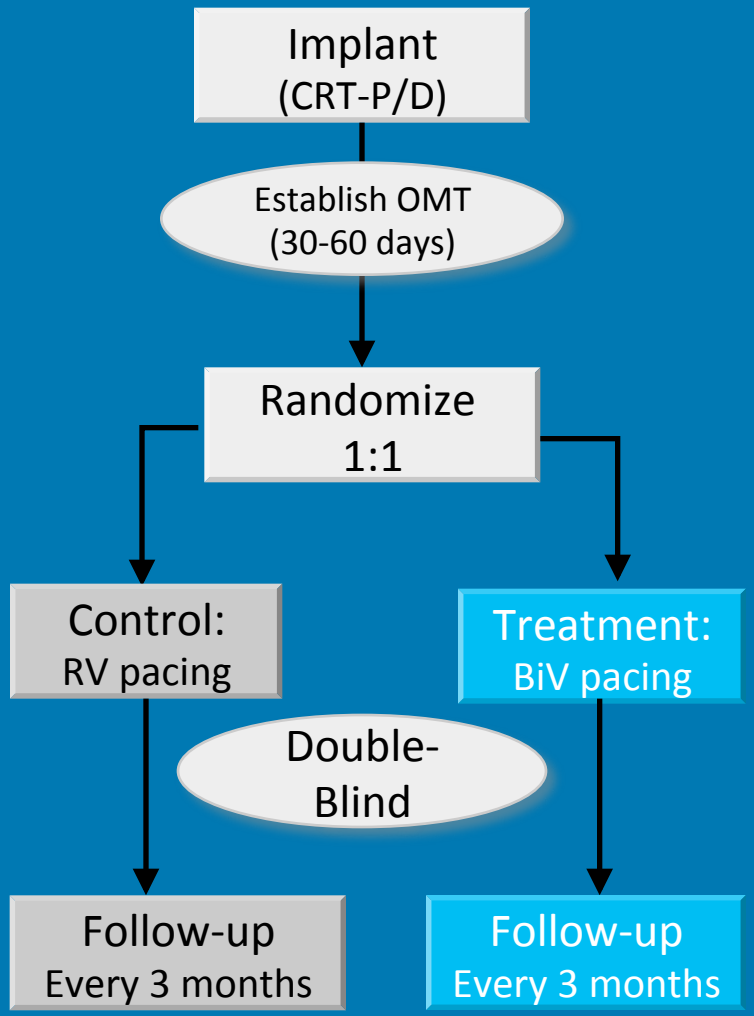
Sponsor

Medtronic Inc.

Clinical Trials.gov Identifier: NCT00267098

Caution: Use of CRT devices for AV block and systolic dysfunction patients without ventricular dyssynchrony is not an approved use in the United States.

Study Design



ELIGIBILITY CRITERIA

- AV block necessitating pacing
- Left ventricular ejection fraction (LVEF) ≤ 50%
- NYHA functional class I, II or III
- Absence of a Class I indication for resynchronization therapy
- No previous pacemaker or implantable cardioverter defibrillator (ICD)

- Echocardiography performed at Randomization, 6, 12, 18 and 24 months

OMT=optimal medical therapy
CRT-P=cardiac resynchronization therapy pacemaker
CRT-D=CRT defibrillator

BLOCK HF

Study Flow Diagram

Enrollment

918 Assessed for eligibility

227 Subjects not randomized:
- 95 Subjects for whom inclusion criteria not met (e.g., AV conduction testing criteria not met prior to implant)
- 14 Subject withdrawals prior to implant
- 51 Unsuccessful implants
- 67 Implanted subjects not randomized

691 Randomized 1:1

Allocation

349 Allocated to Biventricular Pacing
- 346 Received allocated intervention
- 3 Did not receive allocated intervention

342 Allocated to Right Ventricular Pacing
- 342 Received allocated intervention

Follow-up

- 52 Exited/lost to follow-up
- 75 Deaths
- 13 Crossed over to Right Ventricular Pacing
- 3 Met primary endpoint prior to crossover

- 50 Exited/lost to follow-up
- 90 Deaths
- 84 Crossed over to Biventricular Pacing
- 50 Met primary endpoint prior to crossover

Analysis

349 Analyzed
- 83 Censored for primary endpoint due to missing LVESVI data

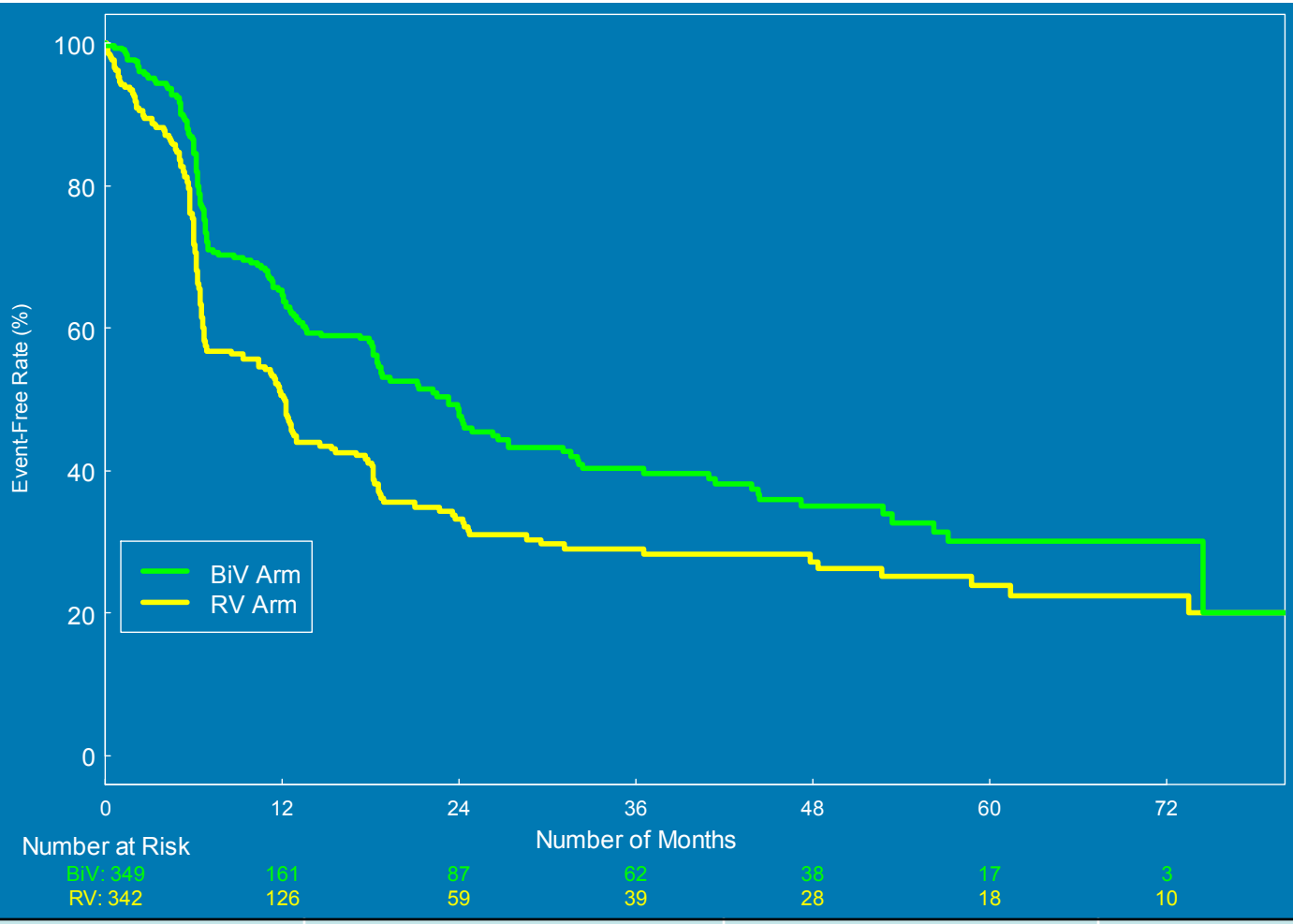
342 Analyzed
- 71 Censored for primary endpoint due to missing LVESVI data

BLOCK HF

Baseline Demographics

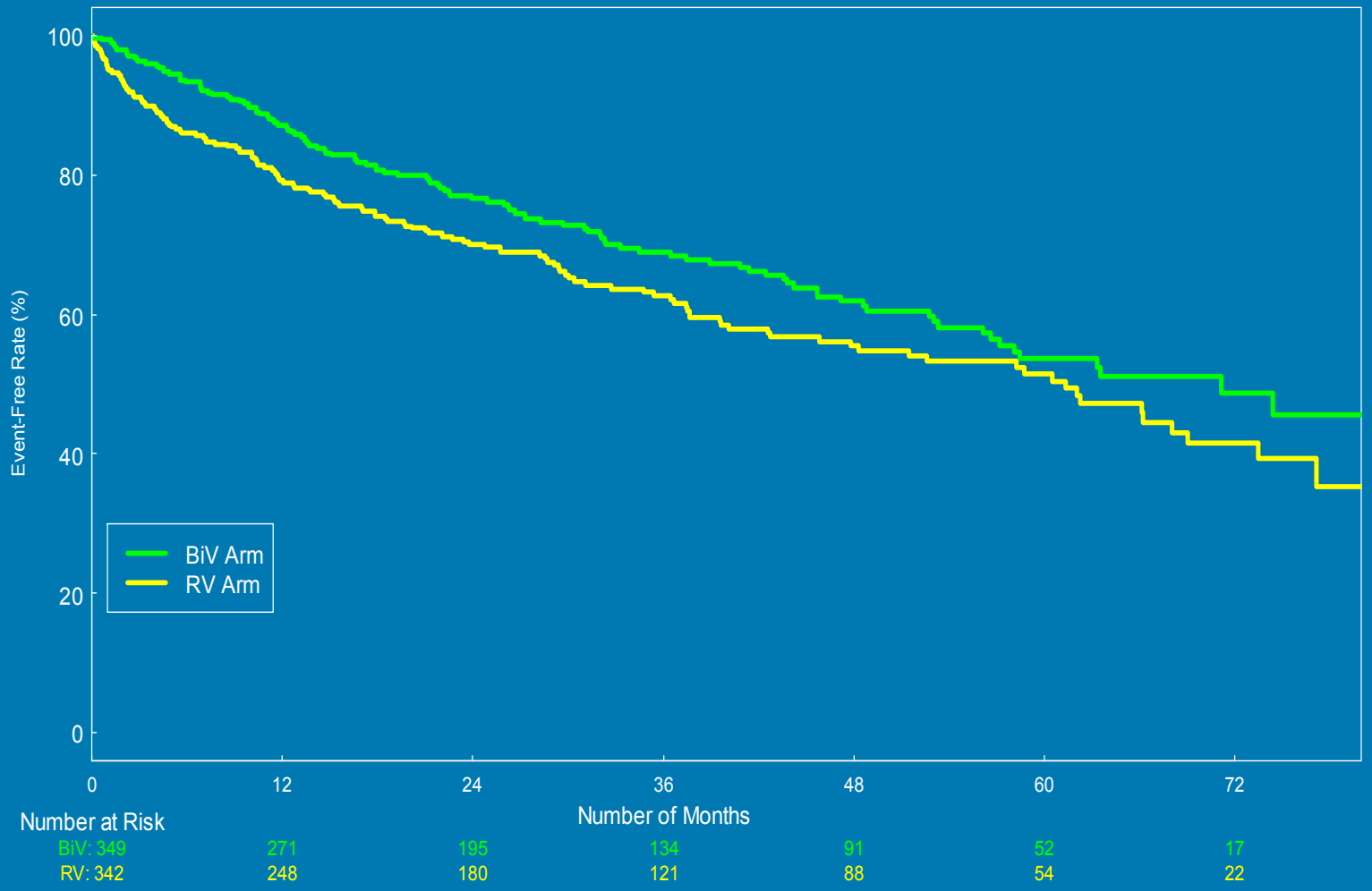
	CRT-P		CRT-D	
	BiV (N=243)	RV (N=241)	BiV (N=106)	RV (N=101)
% Male	75%	70%	82%	80%
Age, years	74 ± 10	74 ± 11	72 ± 9	71 ± 10
LVEF, %	43 ± 7	43 ± 7	33 ± 8	33 ± 8
Heart Rate, beats/min	69 ± 23	69 ± 24	68 ± 17	69 ± 17
QRS Duration, ms	125 ± 33	125 ± 31	123 ± 30	119 ± 30
NYHA I NYHA II NYHA III	14% 58% 27%	20% 52% 28%	10% 63% 26%	16% 57% 27%
Left Bundle Branch Block	35%	31%	35%	27%
Ischemic Heart Disease	39%	38%	63%	58%
1st Degree AV Block 2nd Degree AV Block 3rd Degree AV Block	17% 33% 49%	15% 29% 56%	27% 33% 40%	31% 38% 32%
ACE Inhibitor/ARB at Randomization	71%	74%	83%	88%
Beta Blocker at Randomization	75%	78%	92%	92%
Diuretics at Randomization	64%	66%	72%	70%

Primary Endpoint Results: Mortality/HF Urgent Care/LVESVI



Cohort	Estimated HR (95% CI)	Probability HR < 1	Threshold
All Randomized Subjects	**0.74 (0.60, 0.90)**	**0.9978**	0.9775
CRT-P Only	0.73 (0.58, 0.91)		
CRT-D Only	0.75 (0.57, 1.02)		

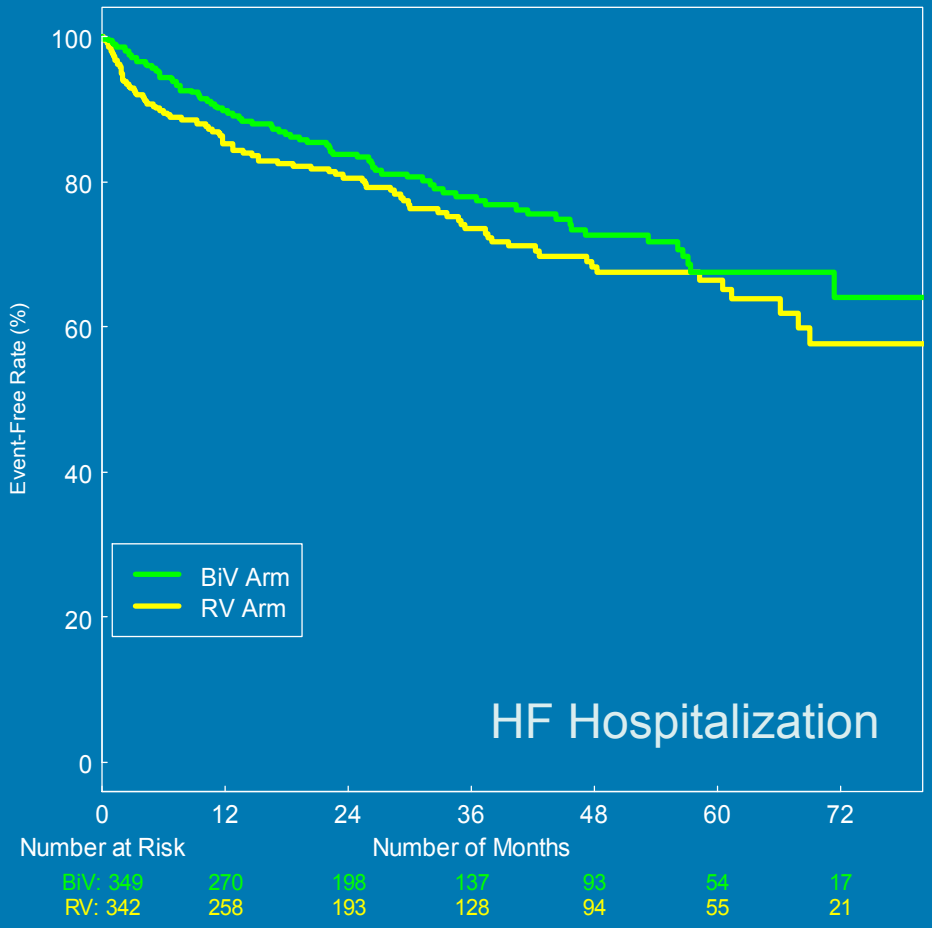
Clinical Components of Primary Endpoint: Mortality/HF Urgent Care Visits

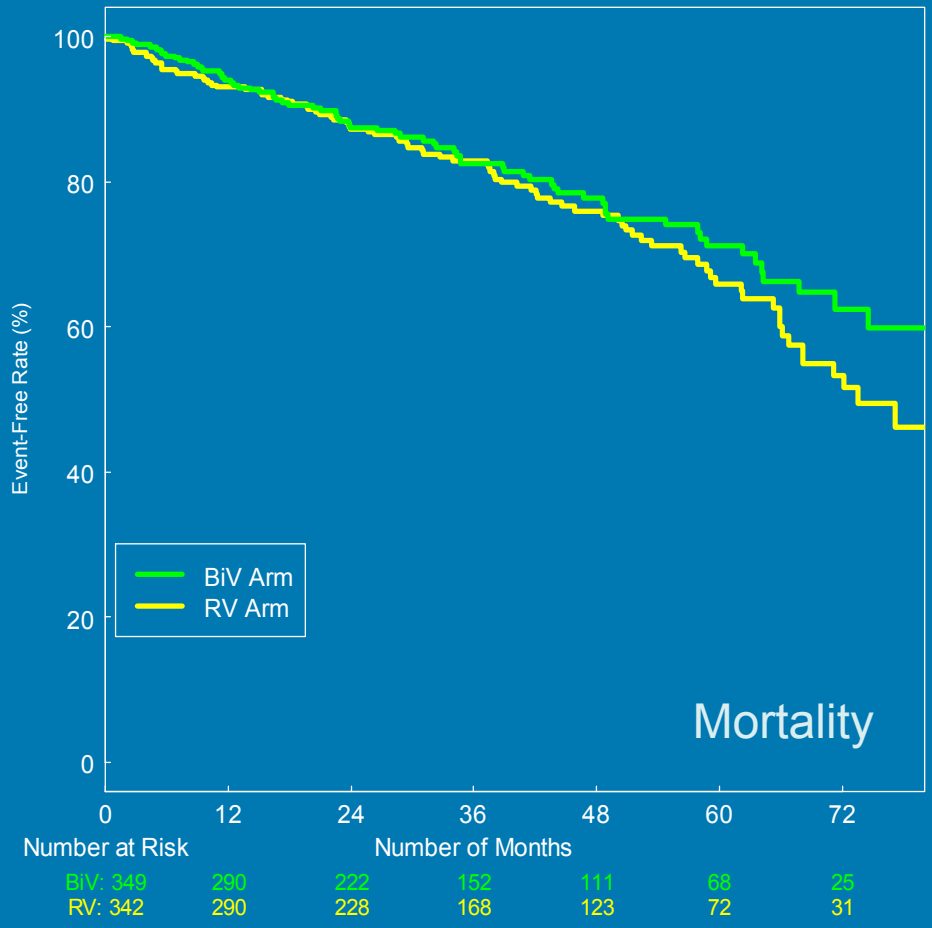


Cohort	Estimated HR (95% CI)	Probability HR < 1	Threshold
All Randomized Subjects	**0.73 (0.57, 0.92)**	**0.997**	N/A
CRT-P Only	0.73 (0.56, 0.94)		
CRT-D Only	0.73 (0.53, 1.02)		

BLOCK HF

Secondary Objective Results: HF Hospitalization and Mortality





Cohort	HF Hospitalization		Mortality		Threshold
	Estimated HR (95% CI)	Probability HR < 1	Estimated HR (95% CI)	Probability HR < 1	
All Randomized Subjects	**0.70 (0.52, 0.93)**	**0.9922**	**0.83 (0.61, 1.14)**	**0.8588**	0.95

BLOCK HF

Strengths and Limitations

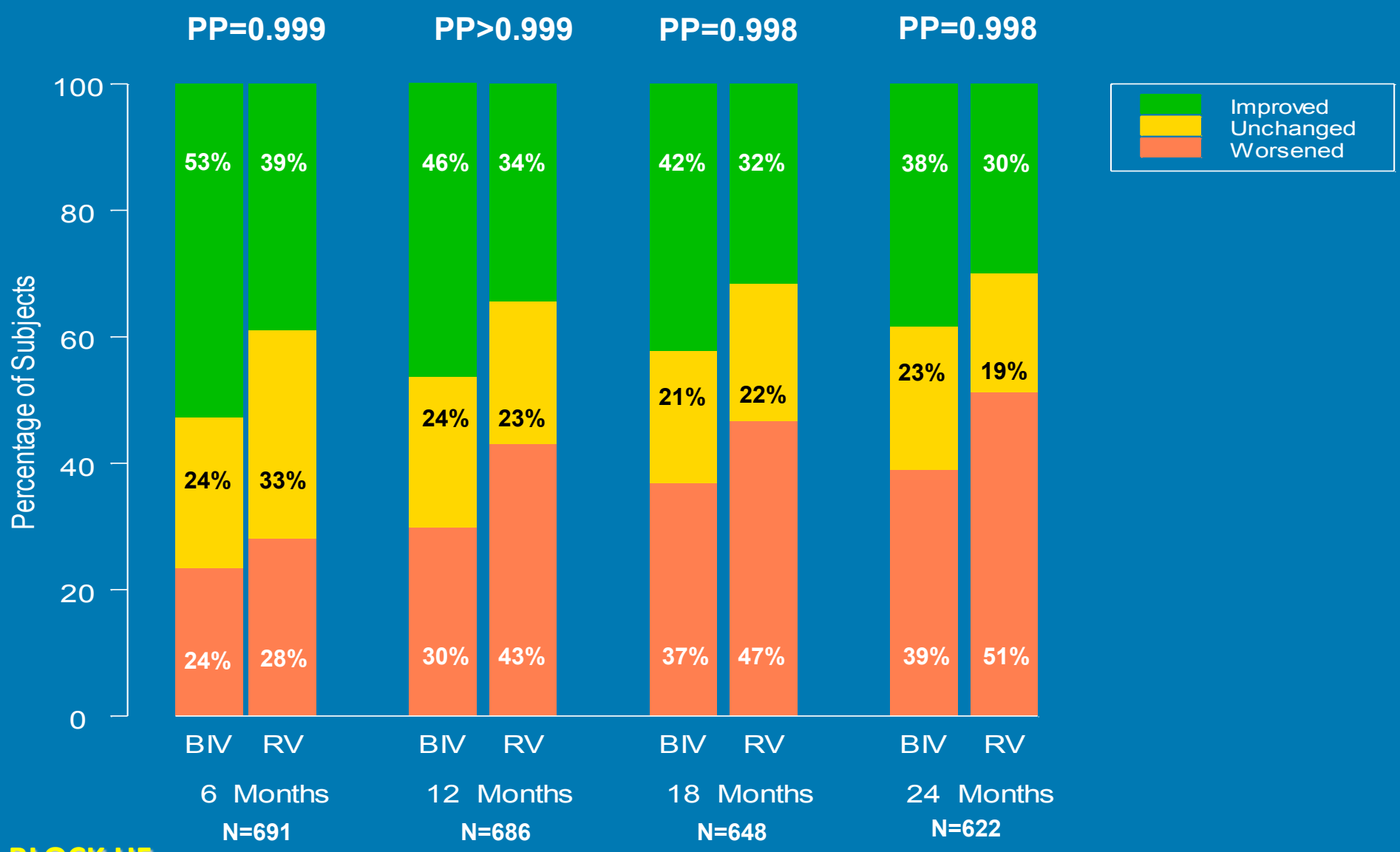
- **STRENGTHS:**
  - Prospective, randomized, double-blind control design
  - Largest, longest follow-up trial to date
  - First to show difference in outcomes in AV block and LV systolic dysfunction patients with BiV vs. RV pacing

- **LIMITATIONS:**
  - Long enrollment duration
  - All patients received CRT systems
  - Censoring due to missing LVESVI in primary objective
  - Crossover imbalance between arms:
    - 24.6% crossed over from RV to BiV
    - 4.6% crossed over from BiV to RV

Conclusions

- In patients with AV block and LV systolic dysfunction (LVEF ≤ 50%), BiV pacing compared to RV pacing leads to a significant 26% reduction in the combined endpoint of mortality, heart-failure related urgent care, and increase in LVESVI.
- Furthermore, there is a 27% relative risk reduction in the composite endpoint of heart-failure urgent care and all-cause mortality.

Packer Clinical Composite Score



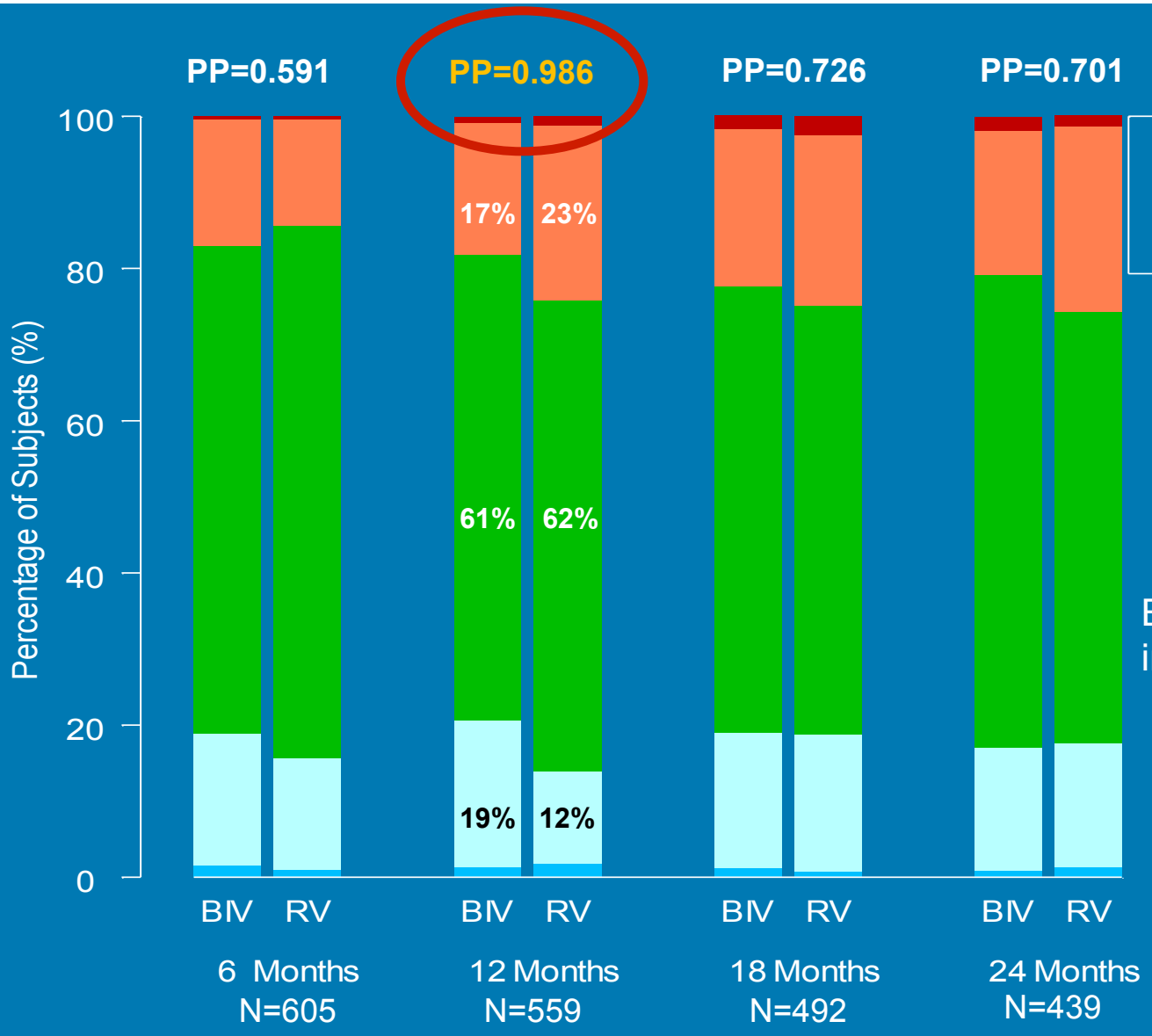
BLOCK HF

Packer Clinical Composite Score at 6 Months

Episode Type	Number(%) of Subjects	
	BIV Arm (N=349)	RV Arm (N=342)
Worsened	**82 (23.5%)**	**96 (28.0%)**
Death	10 (2.9%)	16 (4.7%)
HF Hospitalization	18 (5.2%)	32 (9.4%)
Therapy Discontinuation for Worsening HF	0 (0%)	12 (3.5%)
Worsened NYHA	50 (14.3%)	34 (9.9%)
Moderately/Markedly Worse Global Assessment	4 (1.1%)	2 (0.6%)
Unchanged	**83 (23.8%)**	**113 (33.0%)**
Improved	**184 (52.7%)**	**133 (38.9%)**
Global Assessment & NYHA	37 (10.6%)	26 (7.6%)
Global Assessment Only	126 (36.1%)	91 (26.6%)
NYHA Only	21 (6%)	16 (4.7%)

- RV arm had 18% incidence of x-over to BIV

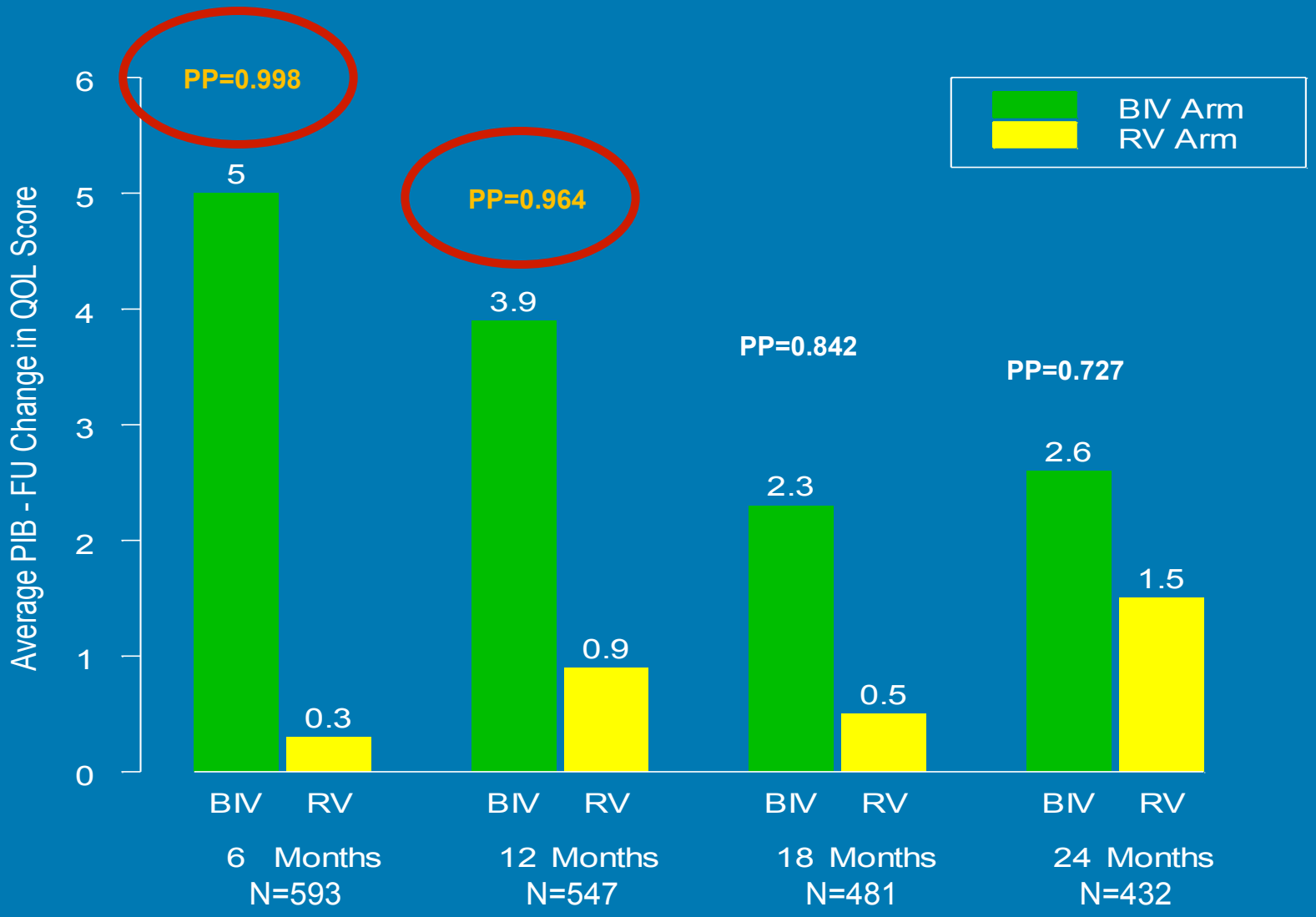
Change in NYHA Class from Baseline



BIV arm had significantly better improvement at 12 months

BLOCK HF

Improvement in Quality of Life from Baseline



BLOCK HF

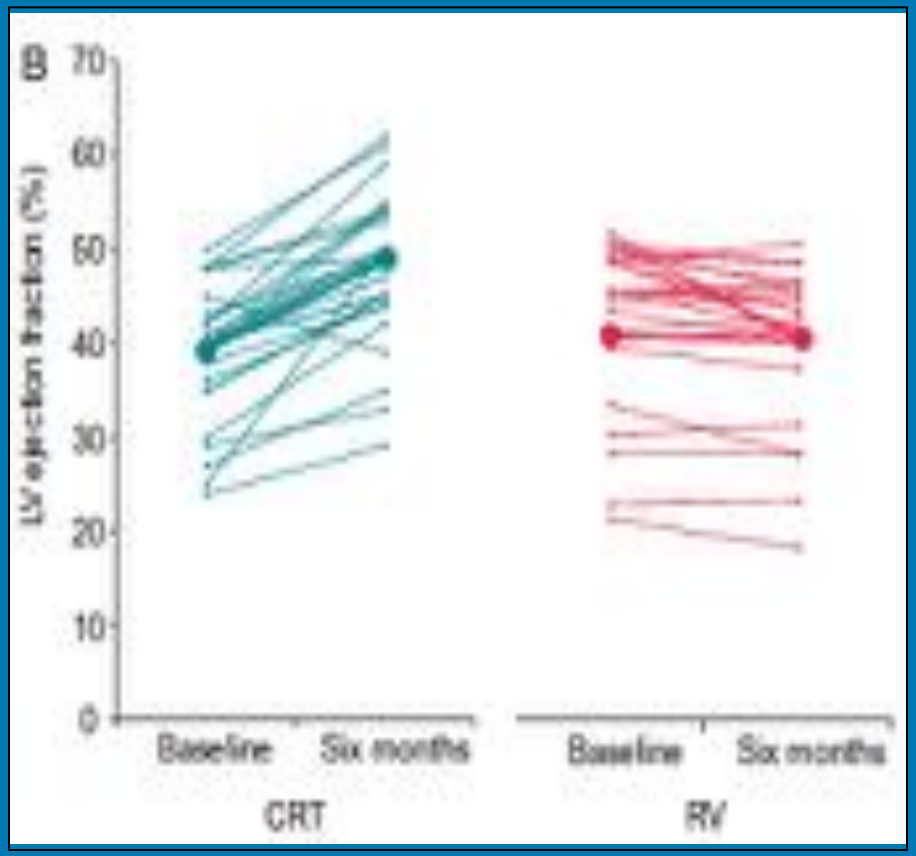
Significant difference seen at 6 and 12 months (PP > 0.95)

Clinical Implications of BLOCK-HF

- For patients with AV block and systolic dysfunction, BIV pacing not only reduces the risk of mortality/morbidity, but also leads to better clinical outcomes and improved patient quality of life and HF status.

What About Patients With Preexisting RV Pacemakers? An Opportunity for Intervention at Generator Change?

- 50 patients with RV PPM and >80% RVP at time of generator replacement
- LVEF < 50% but no CHF
- Randomized to CRT-P upgrade vs simple generator change
- CRT-P patients had better exercise capacity and QoL, lower BNP and fewer hospitalization days
- But required longer procedure and fluoroscopy times



Gierula et al, Europace 2013

FDA Panel Review October 2013

- Based on BLOCK HF and proposed indications, panel voted:
  - 6-1 that CRT-P device is safe
  - 7-0 that CRT-P device is effective
  - But 3-3-1 that benefits outweigh risks
  - Tiebreaker by chairman brought final vote to 4-3-1
  - Panel stipulated that indications should be changed to eliminate patients without AVB and that there be "verifiable confidence that ventricular pacing is needed in this patient most of the time"

What Do the Guidelines Say?

Table 3. Indications for CRT in Patients with Right Ventricular Pacing for Brady Indications

Guidelines, Year	Indication (Excluding Classic CRT Indications for Native QRS >120 ms)	Strength of Recommendation
2013 ACCF/AHA guideline for the management of heart failure[65] and 2012 ACCF/AHA/HRS focused update incorporatedinto the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities[66]	(1) CRT can be useful in patients with atrial fibrillation and LVEF ≤ 35% on recommended medical therapy if • the patient requires ventricular pacing or otherwise meets CRT criteria; and • AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT.	IIA
	(2) CRT can be useful for patients on recommended medical therapy who have LVEF ≤ 35%, and are undergoing placement of a new or replacement device with anticipated requirement for significant (>40%) ventricular pacing	IIA
2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy[44]	(1) CRT is indicated in patients with LVEF <35% and high percentage of RV pacing, who remain in NYHA III or ambulatory NYHA IV despite optimal medical therapy (upgrade).	I
	(2) CRT should be considered in HF patients with reduced LVEF, and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF (de novo implant).	IIA
2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[72]	CRT is indicated in patients with an indication for conventional pacing and no other indication for CRT if:	IIA
	• NYHA III or IV with LVEF ≤ 35% irrespective of QRS duration, to reduce the risk of HF worsening	
	• NYHA II with LVEF ≤ 35% irrespective of QRS duration, to reduce the risk of HF worsening	IIB

Guglin and Barold, ANE 2015

Implications

1. Consider primary CRT-P in patients
   - Who have clinical indication for permanent pacemaker
   - With projected dominant ventricular pacing
   - LVEF < 50%
2. Consider upgrade to CRT-P in patients
   - At time of generator replacement
   - When LV function has significantly declined
   - When no other cause for LV dysfunction is likely
   - Particularly if very wide QRS and HF symptoms
3. In all predominantly paced patients
   - Perform regular assessment of LV function, HF status and QRS duration

Thank you!