Cardiac Resynchronization: Future Indications

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FDA Indications 2009

- For CRT
  - NYHA functional class III or IV
  - Stable and optimized medical regimen
  - LVEF ≤ 35%
  - QRS duration ≥ 130 ms
  - Normal sinus rhythm
- For CRT-D
  - CRT indications, plus
  - QRS duration ≥ 120 ms
  - Accepted ICD indication (primary or secondary prevention)

Non-Indications 2009

- Normal QRS duration (ie < 120 ms), even if dyssynchrony demonstrated by TDI
- Diastolic heart failure (with normal systolic function)
- NYHA functional class I or II heart failure (despite all other CRT criteria)
- CRT as a routine substitute for standard RV pacing and conventional bradycardia indications

Peering Into the Future

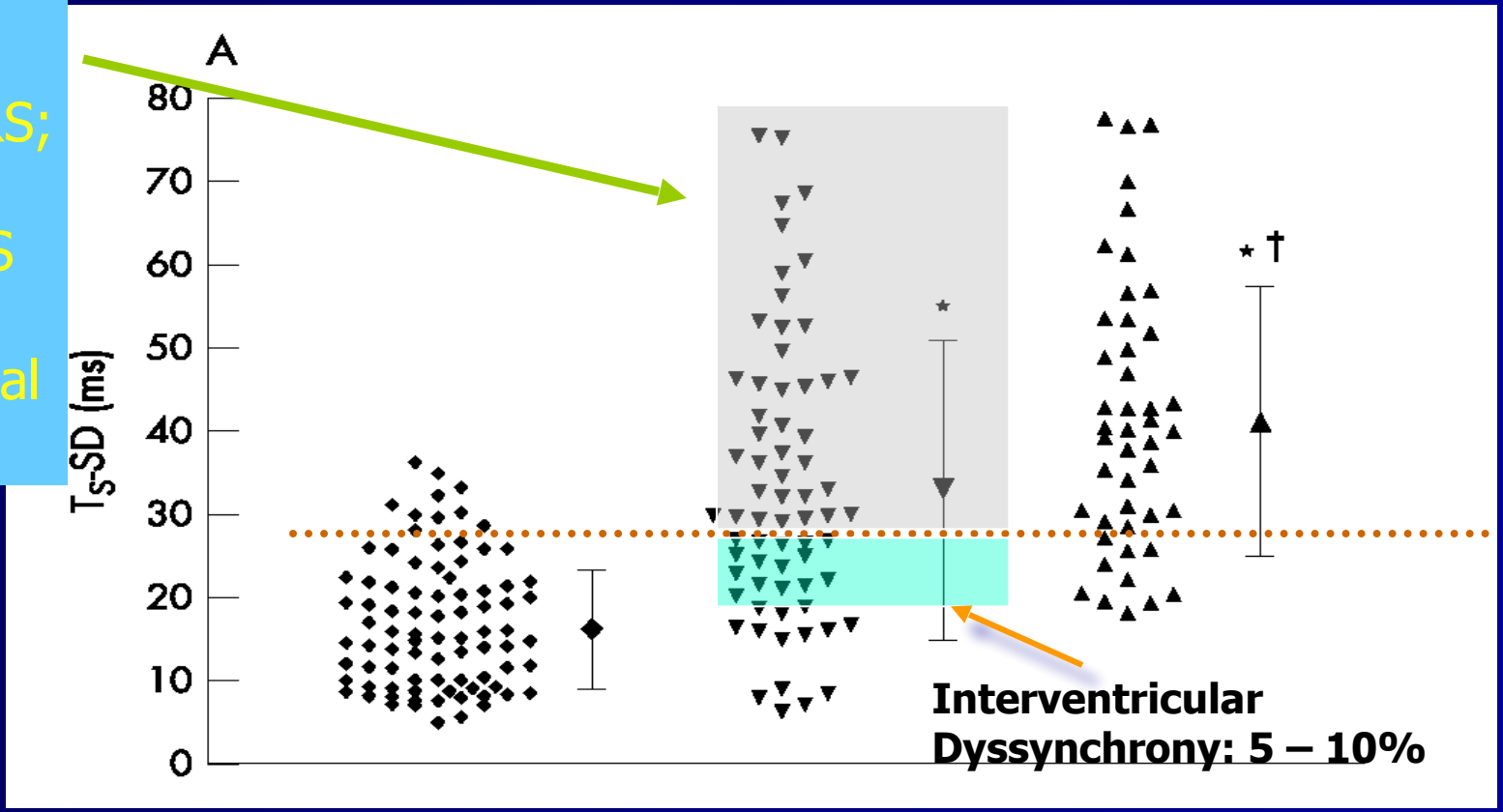
- CRT for narrow QRS
- CRT for NYHA Class I-II heart failure
- Atrial fibrillation and AVN ablation
- CRT for routine bradycardia indications

Can patients with narrow QRS benefit from CRT in similar manner to patients with wide QRS?

Mechanical Dyssynchrony With Narrow QRS Duration

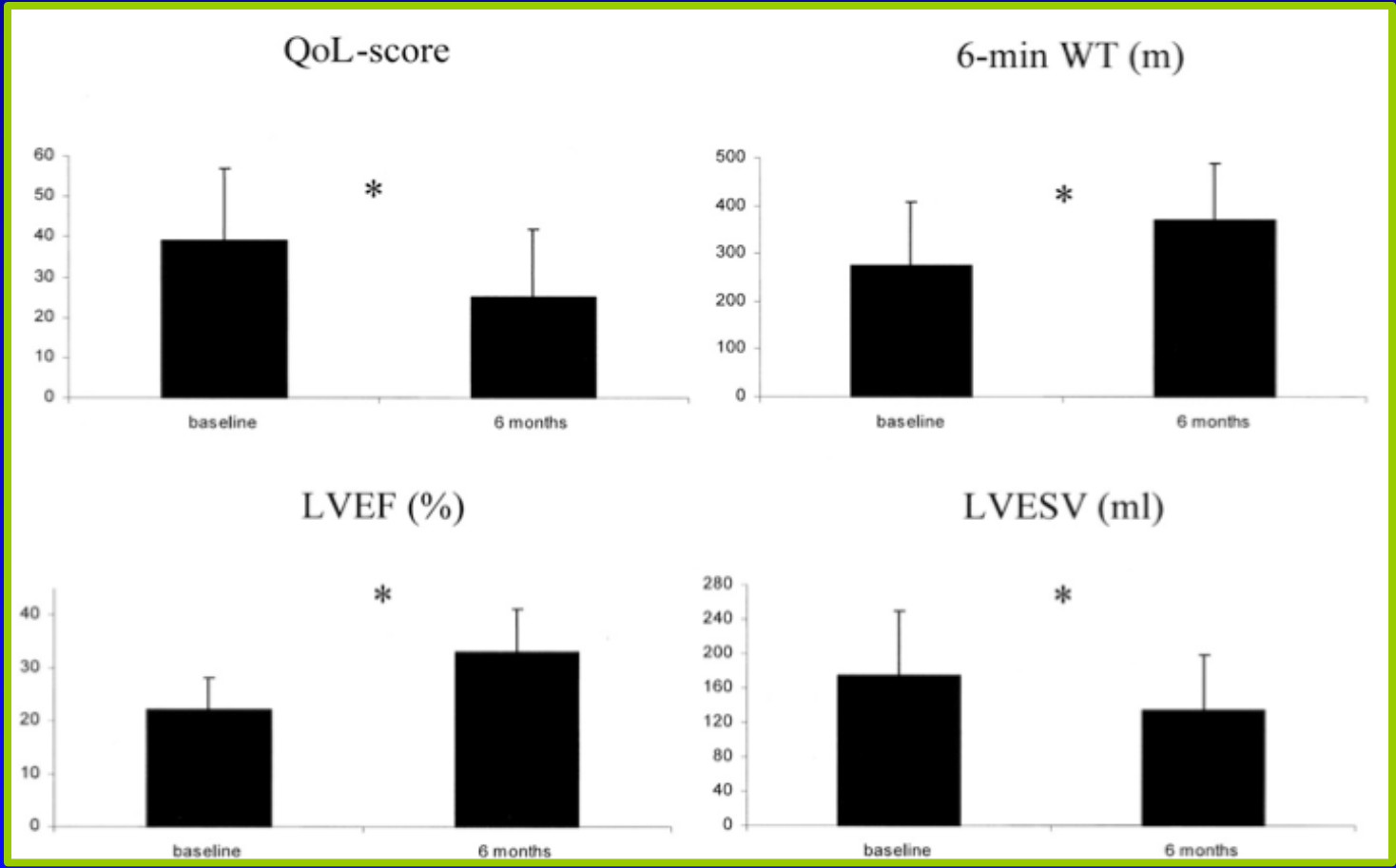
Normal <120 ms >120 ms

46% of patients with nQRS; less than wide QRS but substantial minority



CM Yu et al. Heart 2003

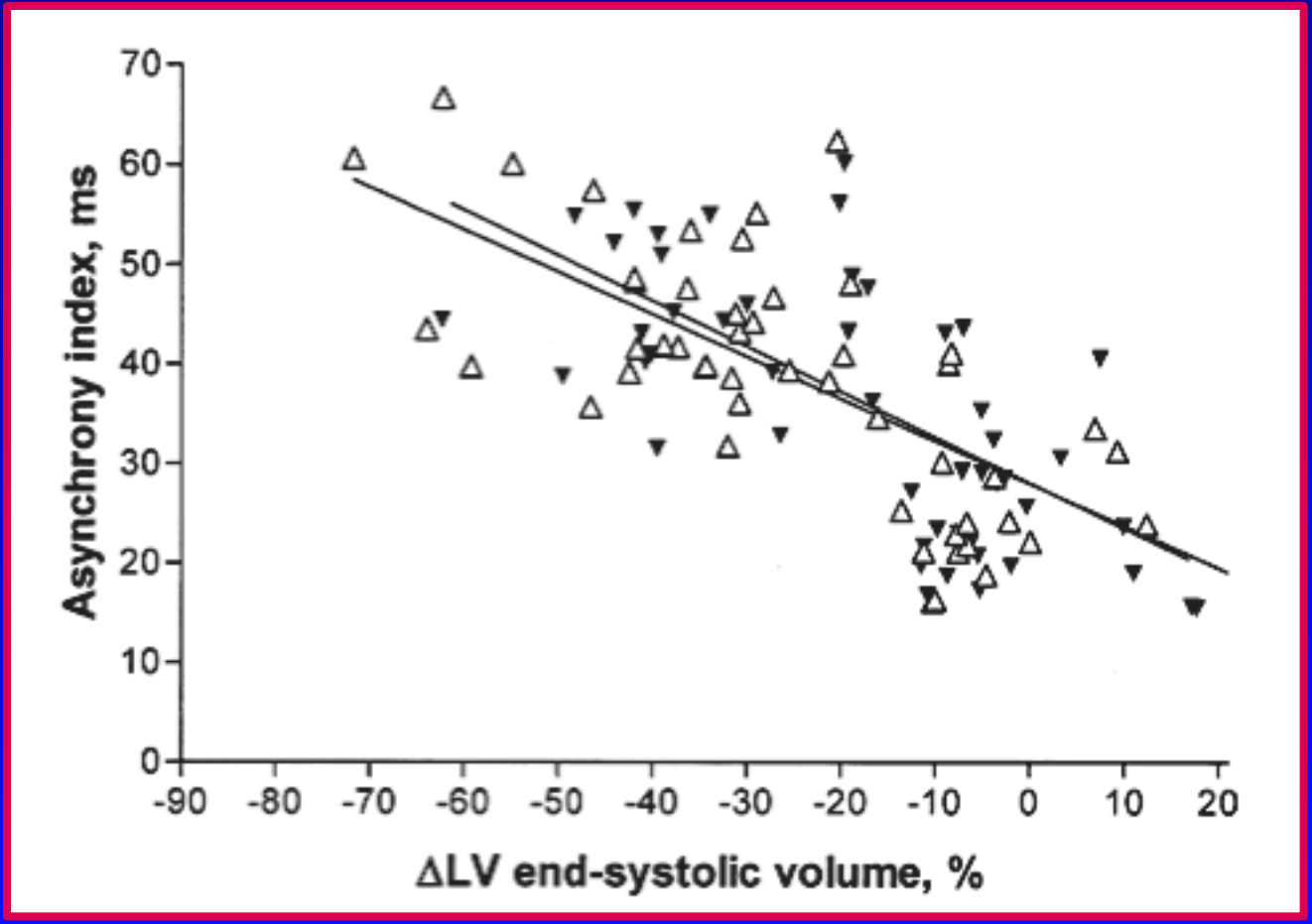
Preliminary Favorable Results in Patients with Narrow QRS



Septal-lateral Delay > 85ms required

Bleeker et al, JACC 2006

Reverse Remodeling Is Dependent Upon Dyssynchrony in Both Narrow and Wide QRS Patients



SD > 65ms required

Yu et al, JACC 2006

Cardiac Resynchronization in Patients With Heart Failure and Narrow QRS (RethinQ)

- Only randomized clinical trial comparing ICD vs CRT-D; 156 patients with NYHA Class III
- Echo criteria for dyssnchrony required for eligibility
- Primary endpoint (peak O_2 consumption) not different at 6 mos (p = 0.63)
- Secondary endpoints largely not different
  - Change in QoL, 6 min walk test
  - Change in EF, EDV, ESV and MR on echo (reverse remodeling)
- More patients with CRT-D increased ≥1 NYHA class (54% vs 29%; p = 0.006)
- Fewer patients required IV rx for HF (16% vs 22%; p = NS) in CRT-D group

Beshai et al, NEJM 2007

Any Hope for Narrow QRS Based on RethinQ?

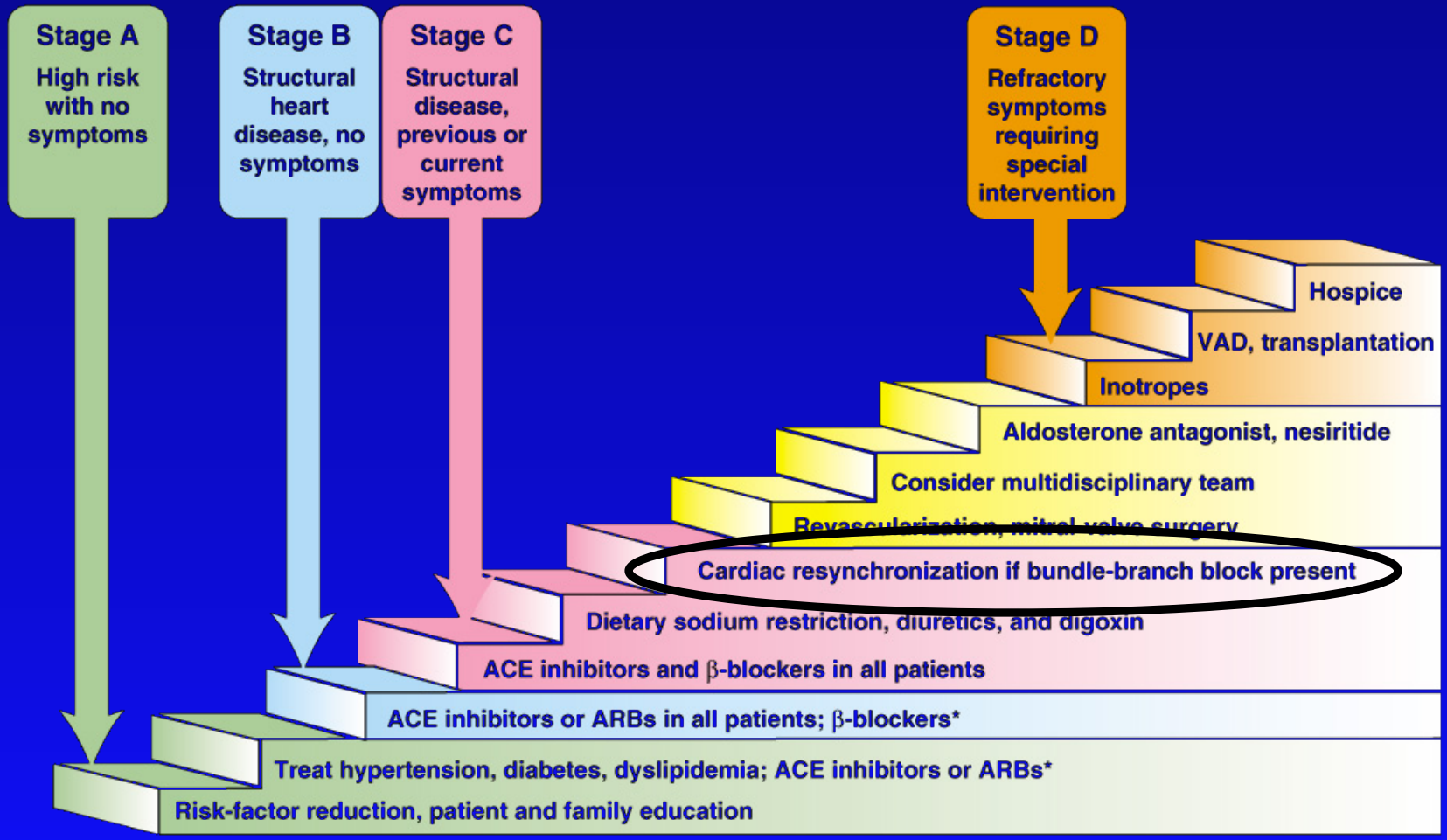
- Trial may have been underpowered for primary and important secondary endpoints
- Different primary endpoint may have been more relevant
- Longer study duration probably important
- Echo criteria not specific
- Select secondary endpoints were positive

Relevent Clinical Trial

- Echo-CRT: CRT vs conventional rx; HF hospitalization or mortality
  - –Narrow QRS, echo-based dyssyncchrony, LVEF ≤ 35%, NYHA III-IV
  - –N = 1258

Does implementation of BVP in early phase of HF in patients with severe LV dysfunction prevent progression to overt HF?

ACC/AHA Stages of Systolic HF and Treatment Options



*In appropriate patients

Jessup M, Jessup M, Brozena S. *N Engl J Med*. 2003;348:2007-18.

Justification to Investigate CRT Prevention of HF Progression

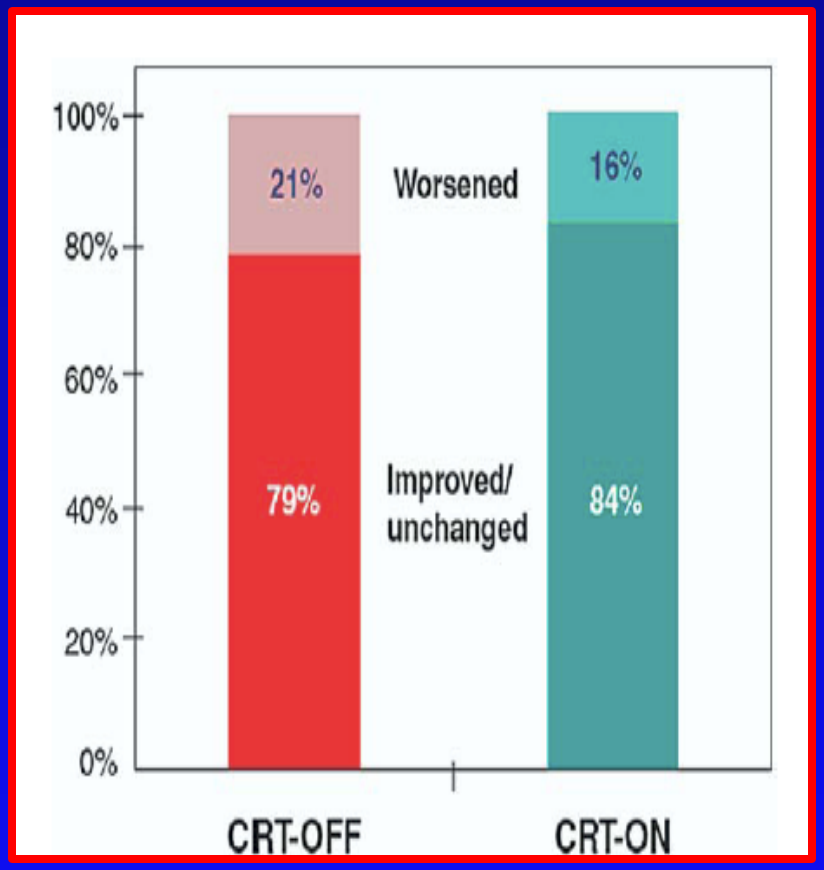
- In the MADIT II Study of patients with EF < 30% and class I-II heart failure, 30% developed new or worsening heart failure over 21 mos.
- In the CONTAK CD Study of 263 class I-II heart failure patients treated with CRT, there was improvement in LV dimensions but not symptoms nor exercise capacity over 6 mos.
- In the MIRACLE II Study of 186 class II heart failure patients treated with CRT, there was improvement in LV dimensions and EF, but no change in 6 min walk or QoL over 6 mos.

REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE)

- Obective: To determine the effects of CRT on disease progression in patients with asymptomatic or mildly symptomatic heart failure and ventricular dyssynchrony
- Randomized double-blind parallel-controlled clinical trial
- 610 patients randomized

Linde et al, JACC 2008

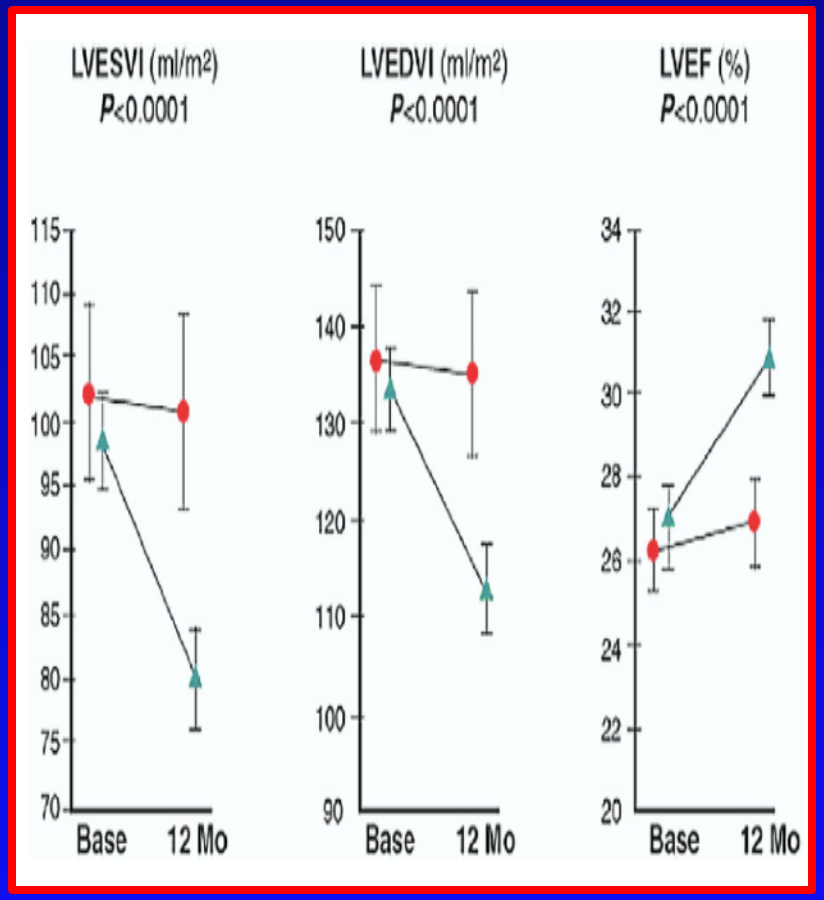
Primary Endpoint of REVERSE



- CRT was slightly more effective than control at reducing the likelihood for worsening heart failure but was statistically NS (p=0.10) at 1 year

Linde et al, JACC 2008

Hopeful Findings in REVESE



- Prominent reverse remodeling was observed in the CRT group
- However no improvement in functional findings and death rates
- There was a reduction in heart failure hospitalization by about 50% in the CRT group

Relevent Clinical Trials: Results Available in 1-2 Years

- MADIT-CRT: CRT-D vs ICD; all-cause mortality or HF
  - ICM and EF ≤ 30%, QRS ≥ 130 ms, NYHA I-II
  - NICM and EF ≤ 30%, QRS ≥ 130 ms, NYHA II
  - N = 1820
- RAFT: CRT-D vs ICD; all-cause mortality or HF
  - CM and EF ≤ 30%, QRS ≥ 120 ms, NYHA II
  - N = 1800

Should AF patients who qualify for CRT all receive AV junctional ablation?

Chronic Atrial Fibrillation

- Only 1 randomized clinical trial of CRT (MUSTIC-AF) involving 48 patients
- PAVE trial of AVJ ablation plus RV vs BiV pacing
- Several inherent impediments to consistent effective CRT

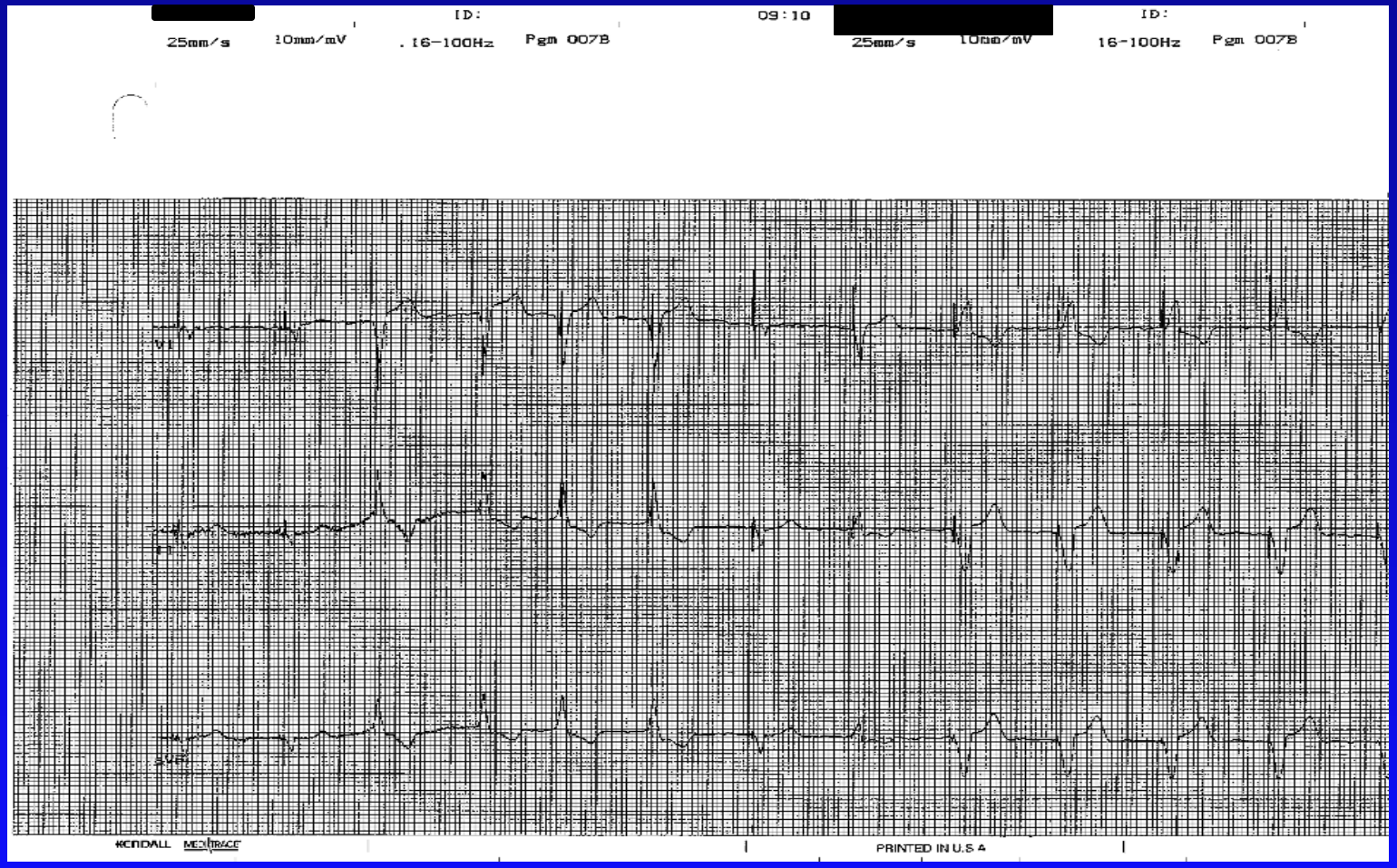
CRT in Heart Failure and AF: MUSTIC - AF

- N = 59
- Class III HF, LVEF < 35%
- Chronic AF and “slow” ventricular rate
- 6 month randomized crossover design: RVP vs BVP; 1o endpoint = 6 min walk
- Only 39 pts completed study
- No difference in 6 min walk: 341m vs 359m, respectively, and no difference in QoL
- More pts preferred BVP

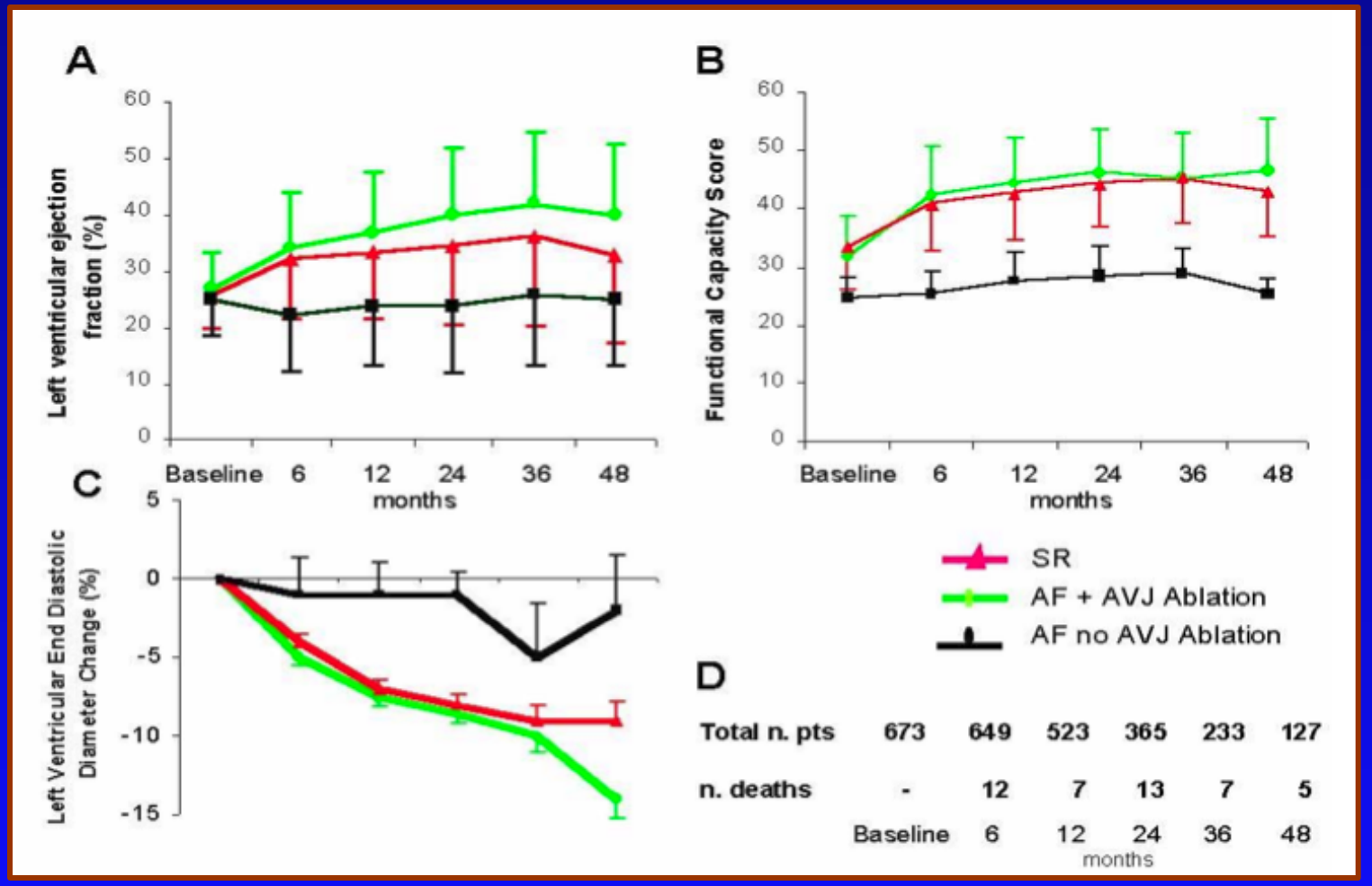
Challenges to Achieving Consistent BV Capture in Patients With AF

- Higher intrinsic heart rate necessitates higher programmed pacing rate
- Frequent fusion beats
- Frequent pseudofusion beats
- Inaccurate assessment of BV capture by device counters

Example of Problematic BV Pacing

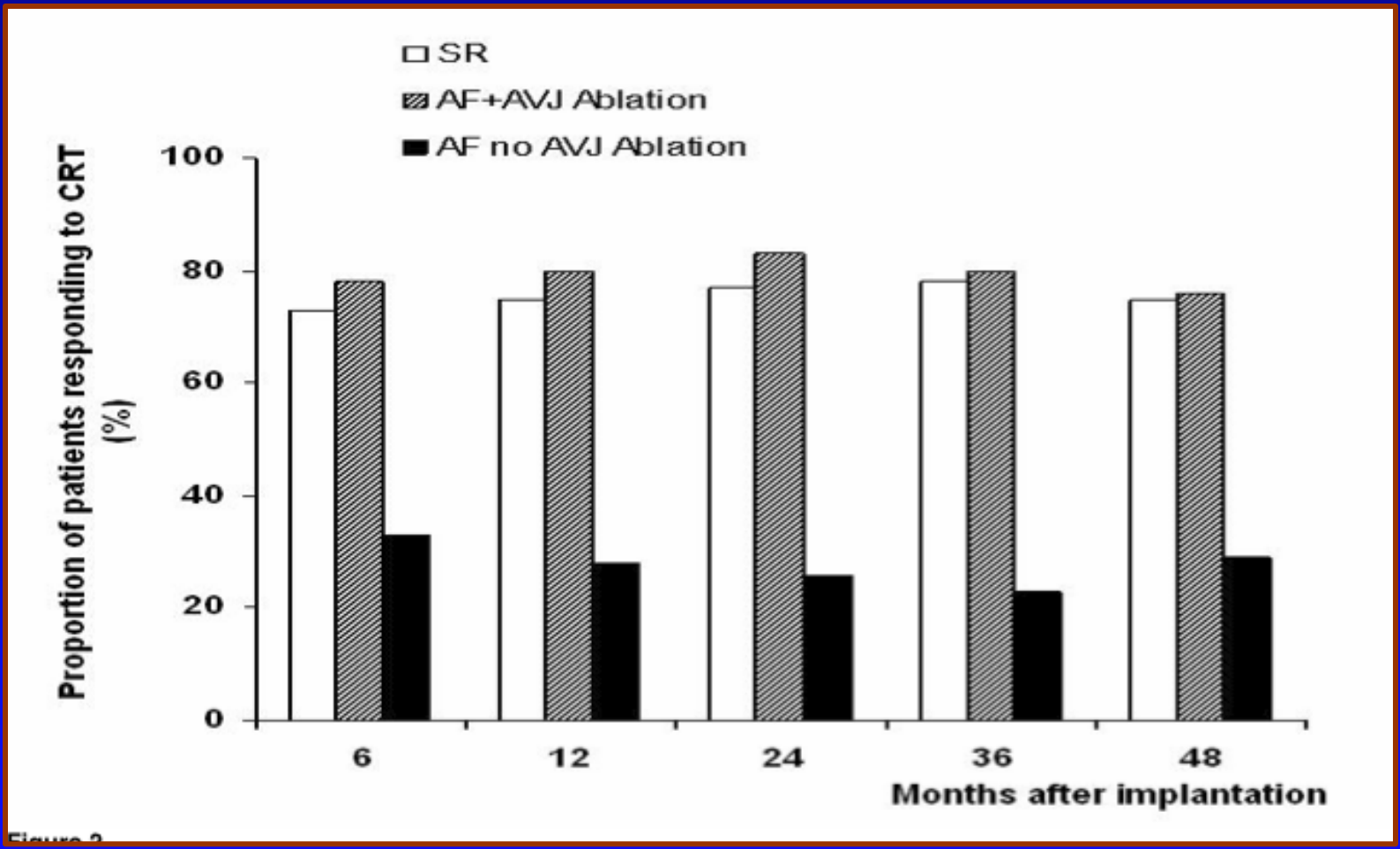


CRT Employed in AF: Outcomes From Observational Study



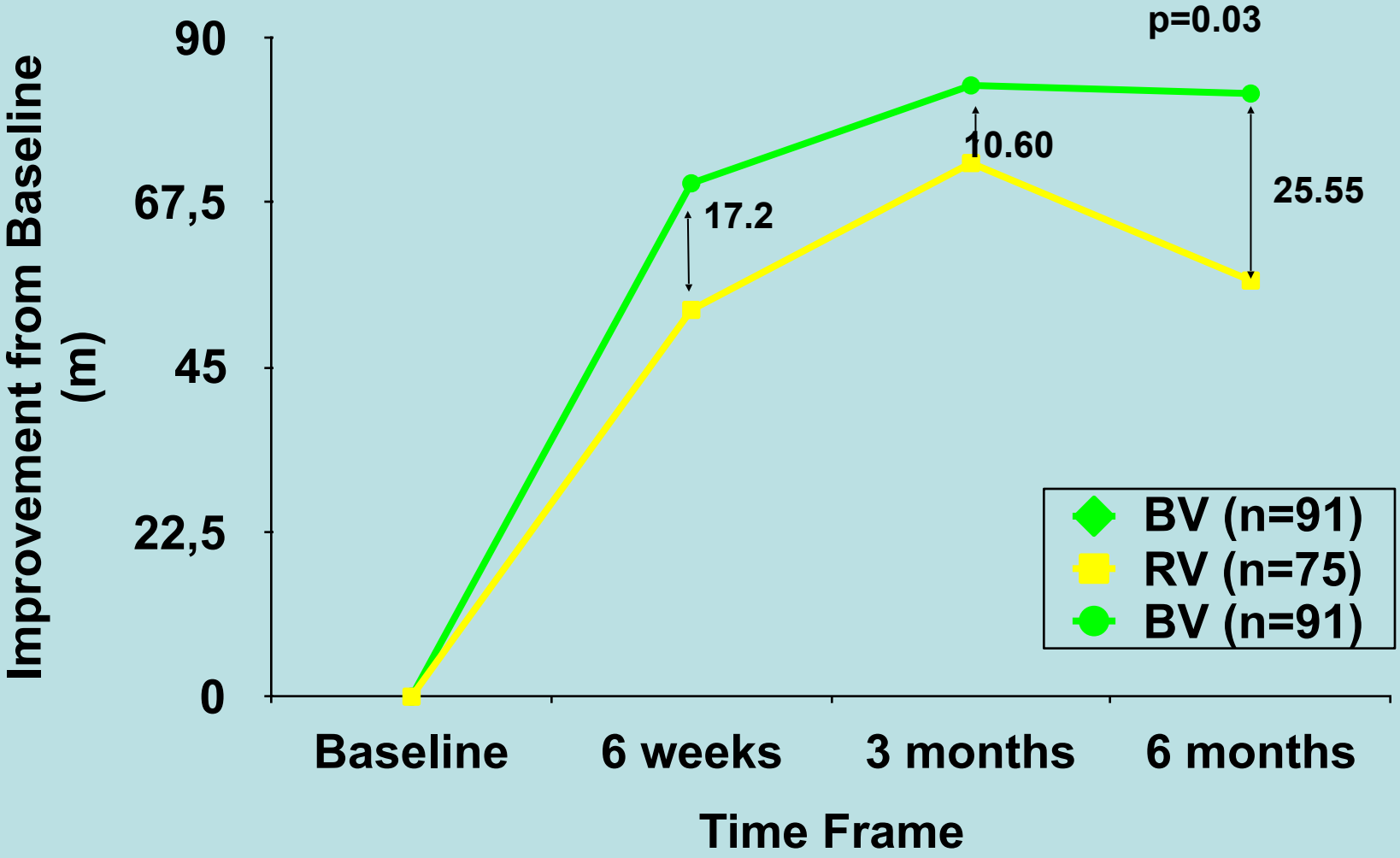
Courtesy of Gasparini et al

CRT Employed in AF: Outcomes From Observational Study

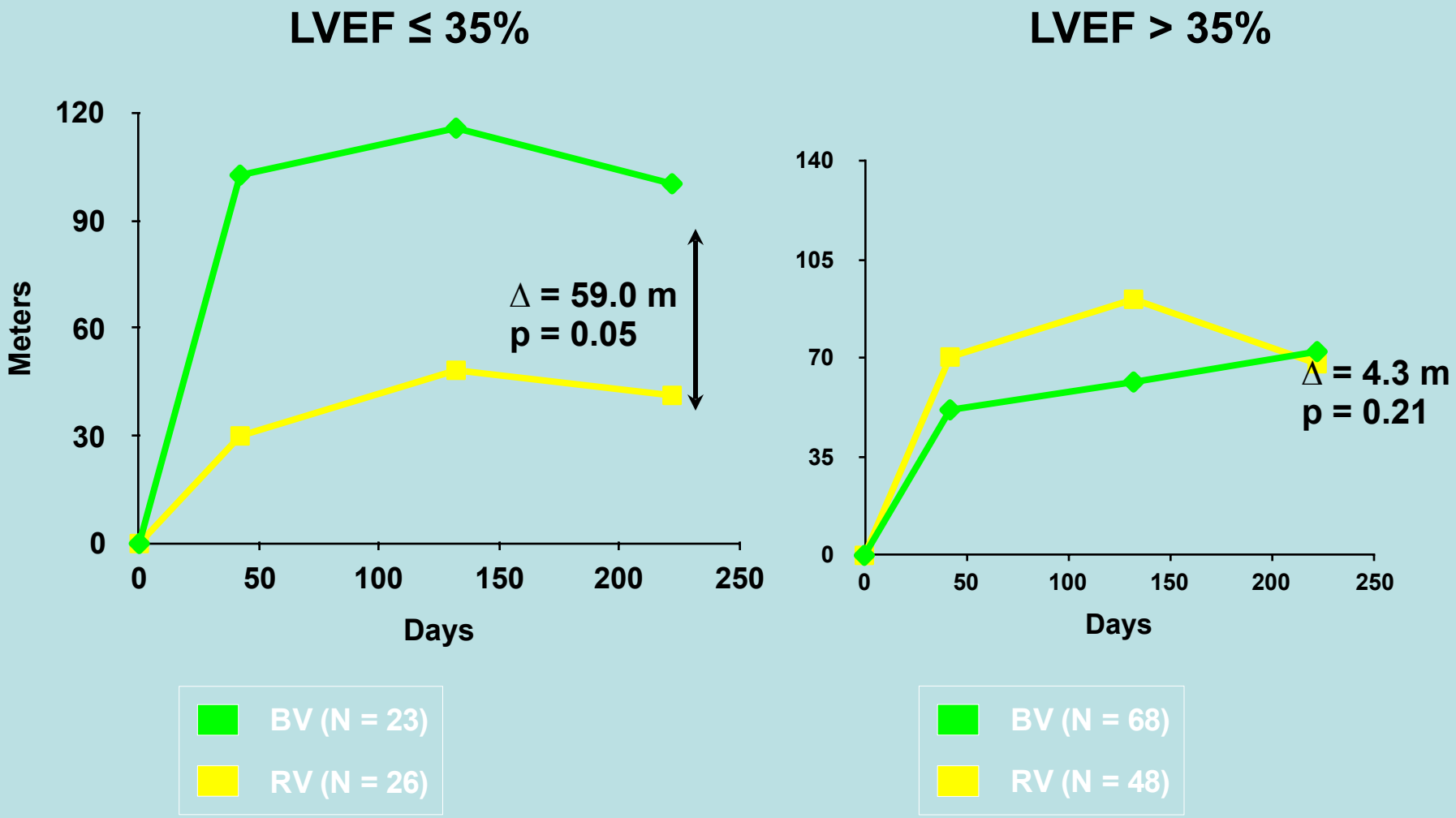


Courtesy of Gasparini et al

PAVE: 6-Minute Walk Test

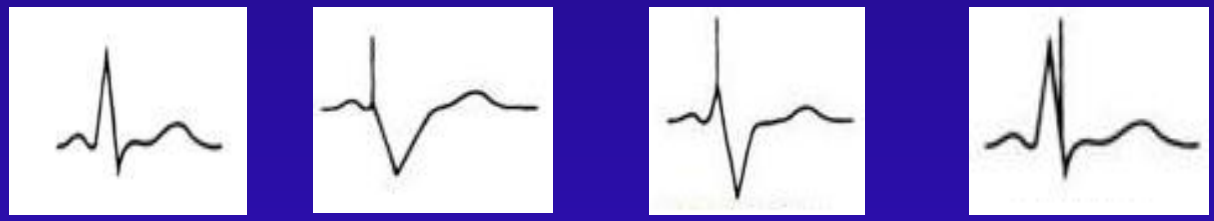


PAVE: Results of 6-Minute Walk Relative to LVEF



Can 12-Lead Holter Predict Response to CRT in Patients with Permanent AF and Apparent Rate Control?

- Patients were instructed to wear an ambulatory 12-Lead Holter for 24 hours
- Template matching analysis software was used to record percentages of fusion, pseudofusion and complete capture beats



Intrinsic Paced beat Fusion beat Pseudofusion beat

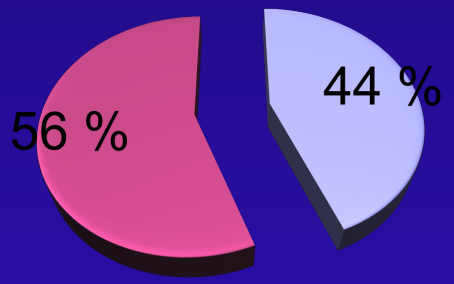
Kamath, Steinberg et al, JACC (in press)

Endpoint Definitions

- Effective pacing
  - > 90% complete capture beats as identified by Holter analysis program
- Ineffective pacing
  - < 90% complete capture beats as identified by Holter analysis program
  - Further breakdown based on pattern of ineffective pacing, eg fusion or pseudofusion beats, or others

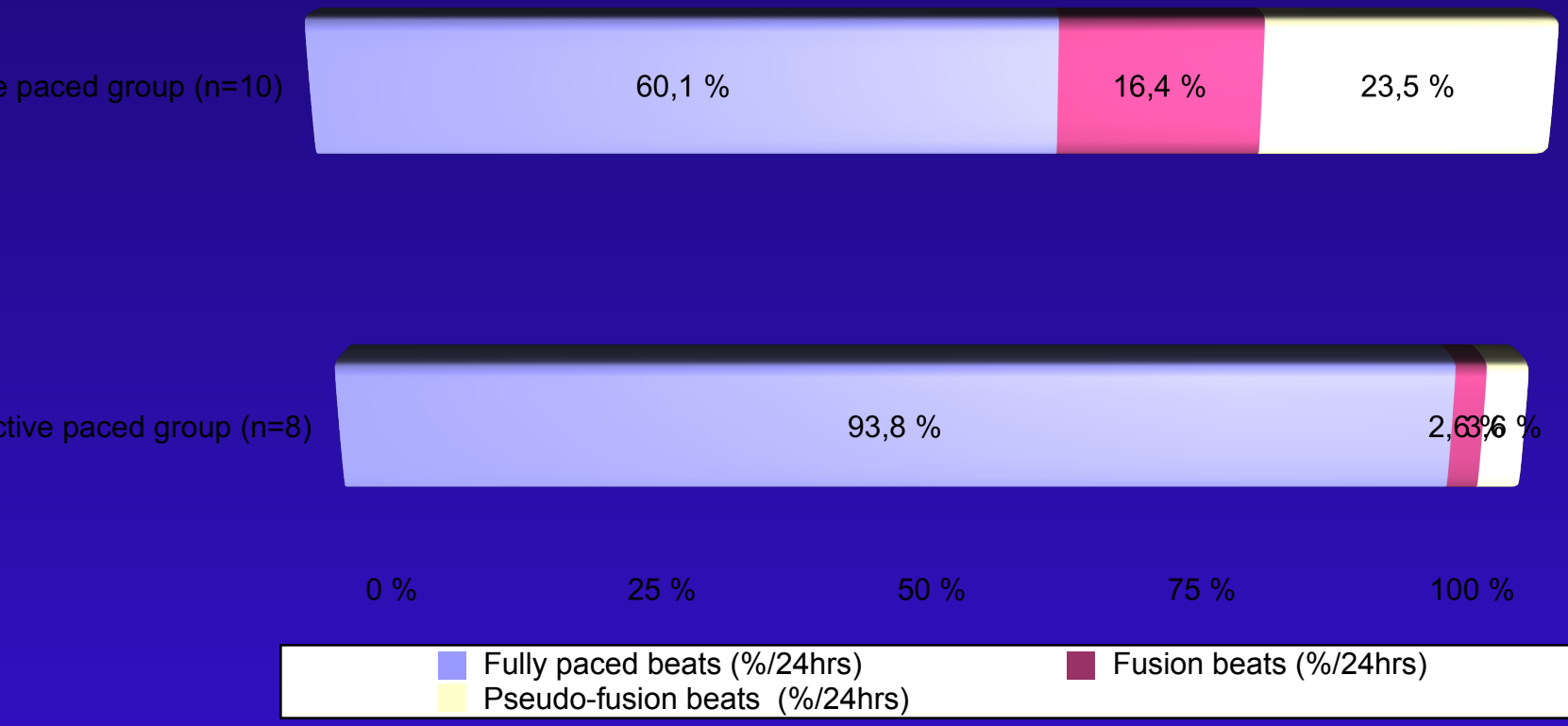
Kamath, Steinberg et al, JACC (in press)

Holter Data Analyses



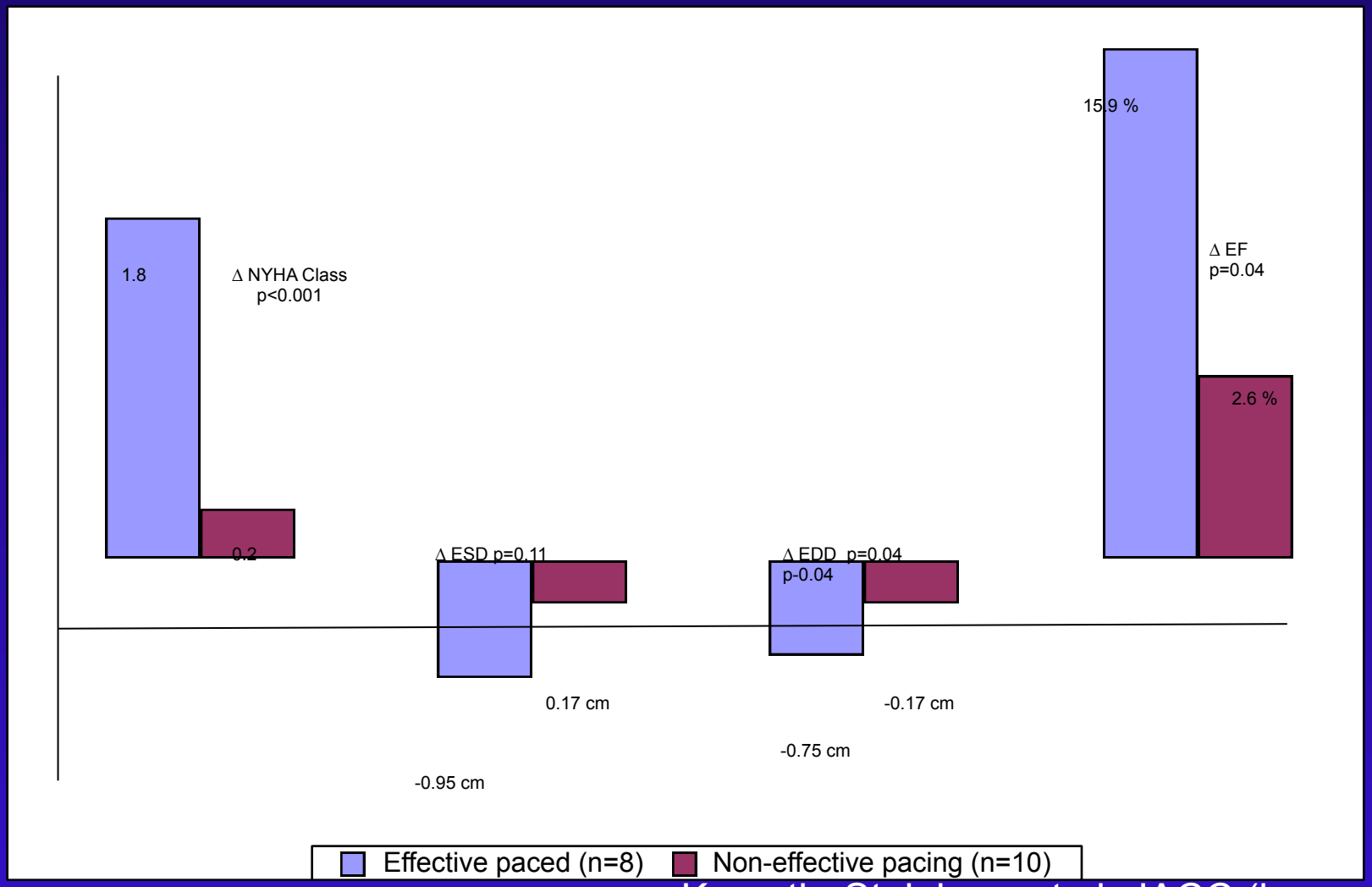
Kamath, Steinberg et al, JACC (in press)

Holter Results:
Comparison of Pacing Groups



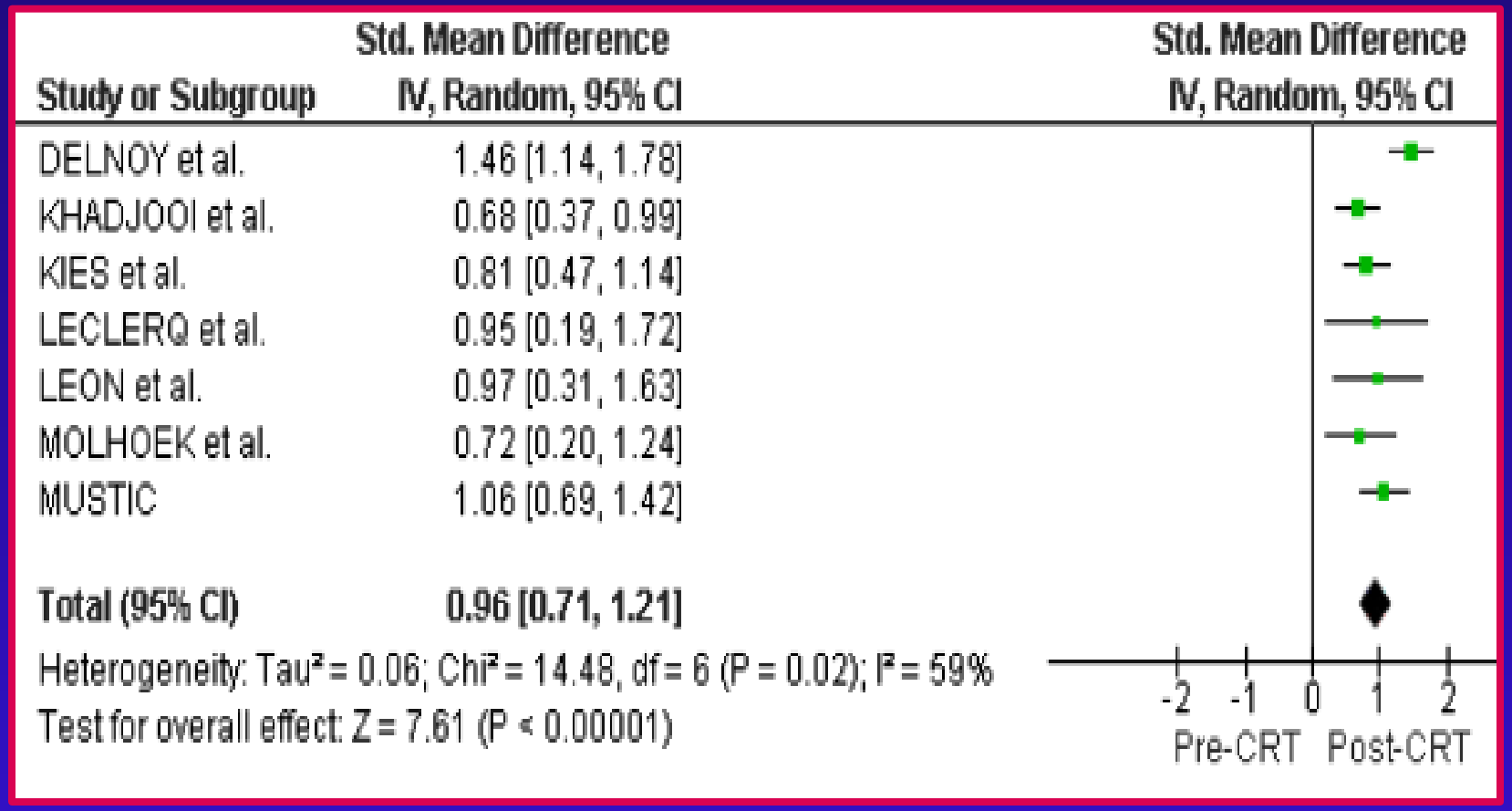
Kamath, Steinberg et al, JACC (in press)

Effective Pacing and Outcomes



Kamath, Steinberg et al, JACC (in press)

Our Meta-Analysis Indicates That Patients with AF Benefit From CRT



Use of CRT in AF Patients

- More challenging than for sinus rhythm patients
- Benefit over time may be similar to that seen for NSR patients but more challenging to achieve and less consistent
- The importance of AVJ ablation to facilitate response is provocative but not yet proven

Relevent Clinical Trial

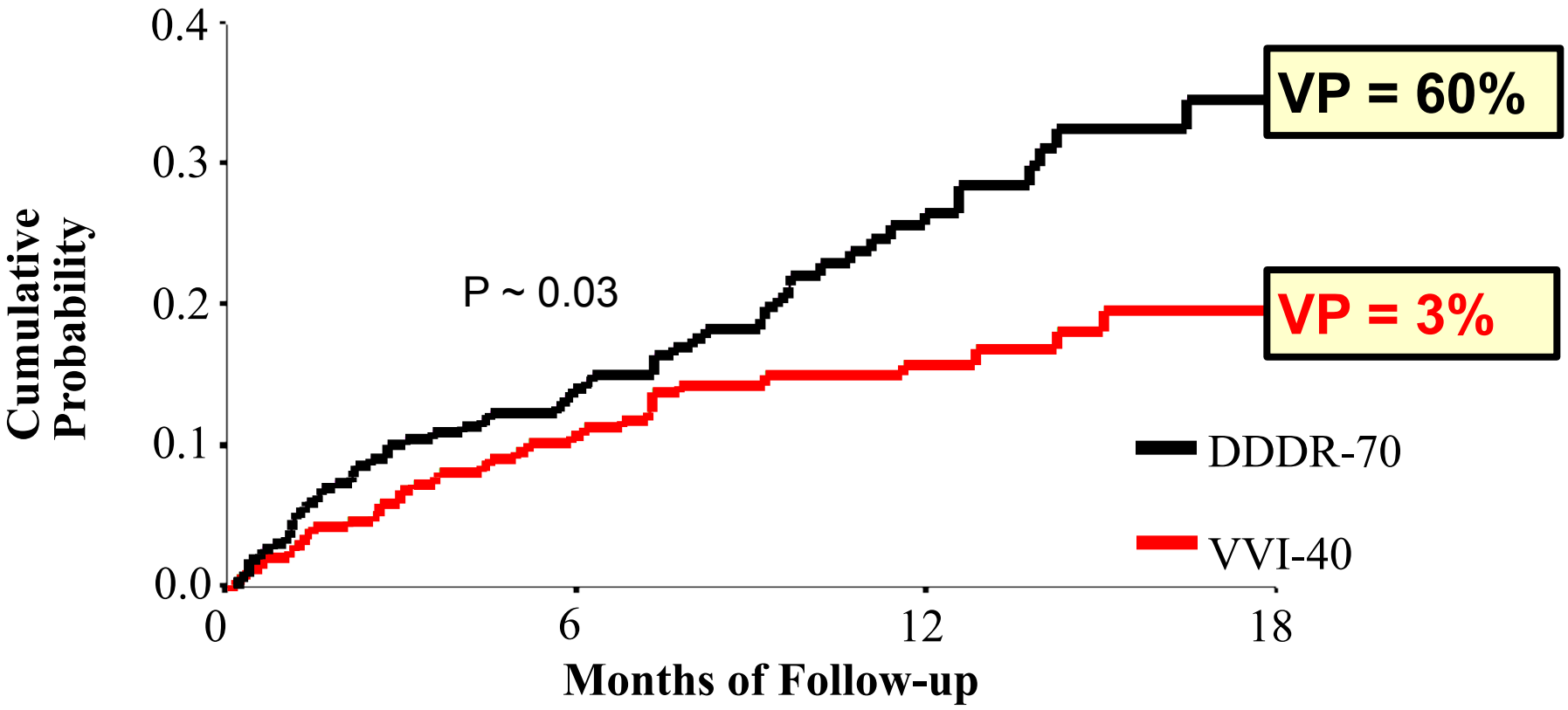
- AVERT-AF: AVJ+CRT vs med rx; ETT duration
  - –Permanent AF, ICD indication, LVEF ≤ 35%, NYHA II-III, maximum med rx for AF and HF

Should BVP replace RVP as the routine configuration in all or most patients who will require majority ventricular pacing?

Summary of 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
- Increased atrial fibrillation
- Left atrial dilation
- Promotion of ventricular arrhythmias
- Activation of sympathetic nervous system

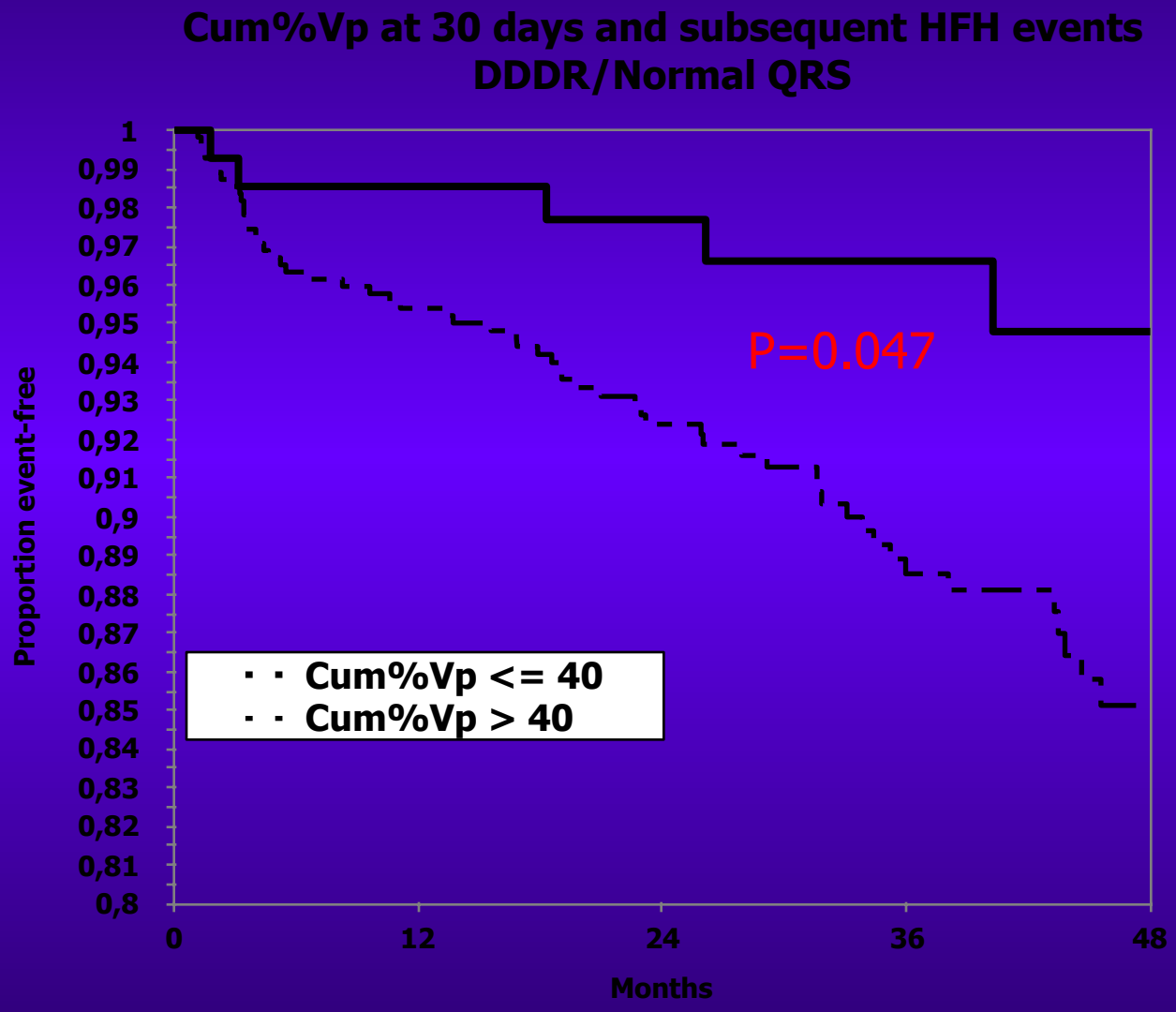
DAVID Trial: Death or First Hospitalization for New or Worsened CHF



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

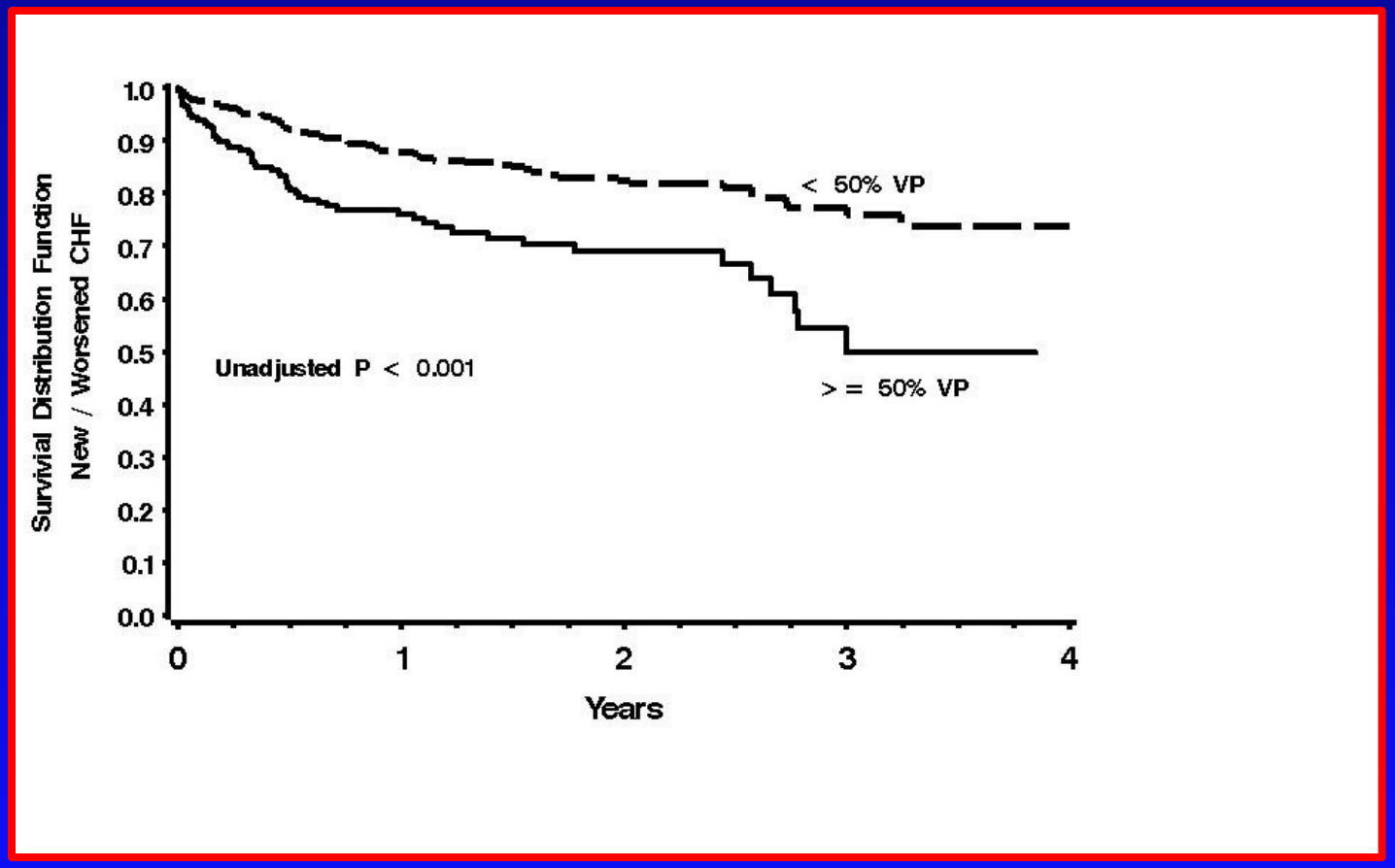
Wilkoff B, et. al. Cardiac Electrophysiology Review 2003;7:468–472

MOST Substudy: DDDR Mode



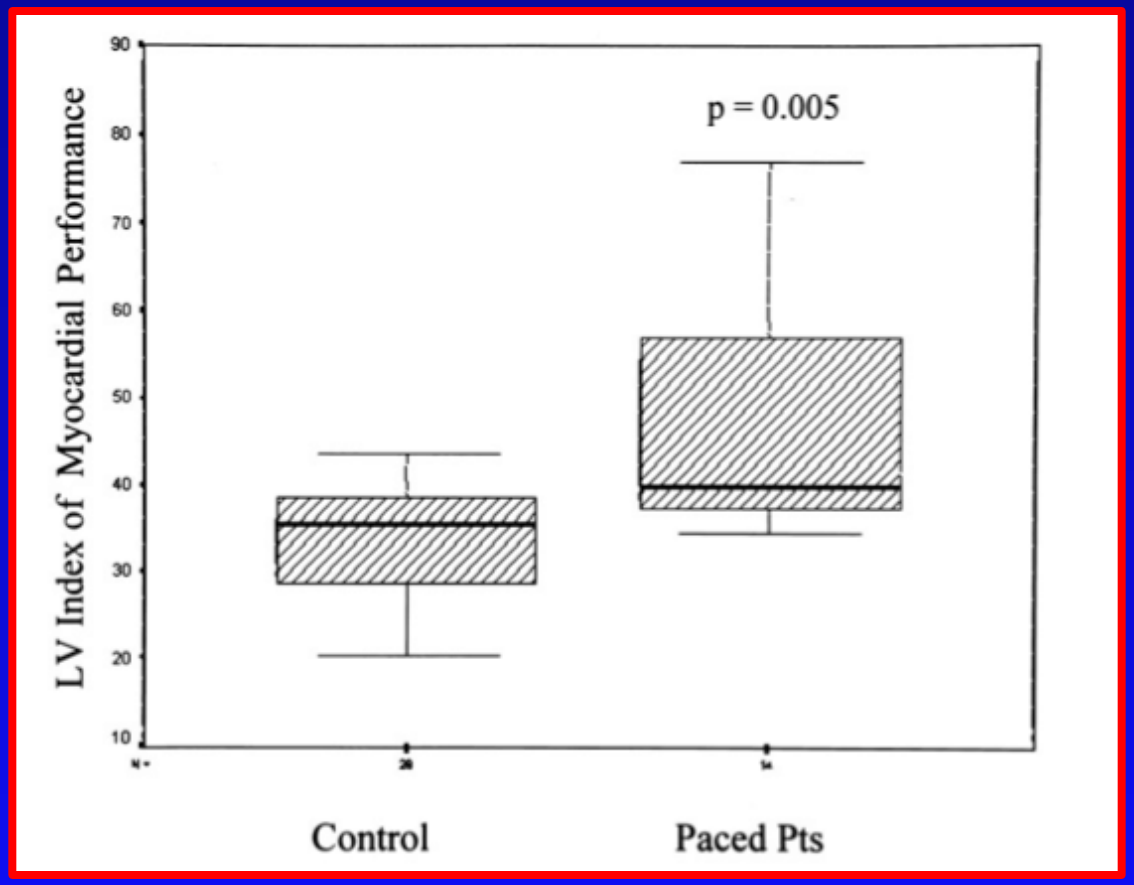
Sweeney et al, Circulation 2003

Relationship of Ventricular Pacing to New/Worsened Heart Failure Outcome



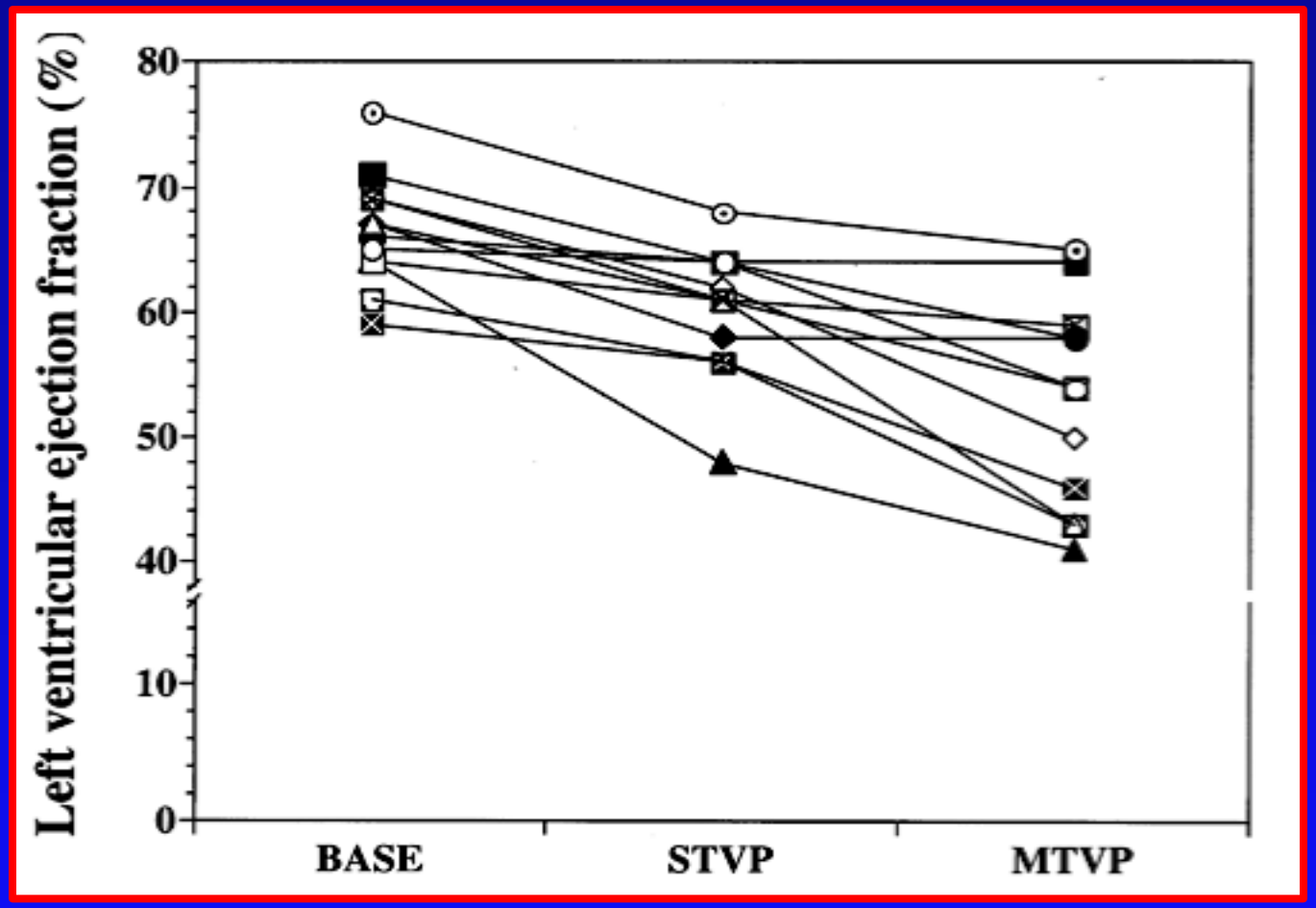
Steinberg et al, JCE 2005

Long-term Deleterious Effect on LV Performance



Tantengco et al, JACC 2001

Decline in Normal Ventricular Function With RVP



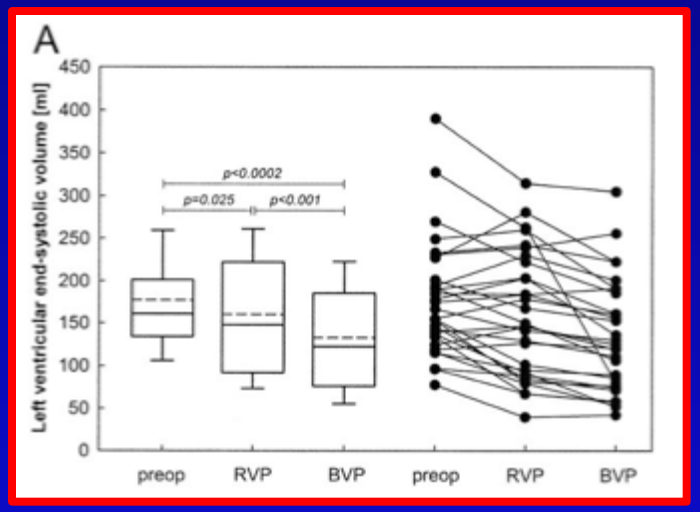
Nahlawi et al, JACC 2004

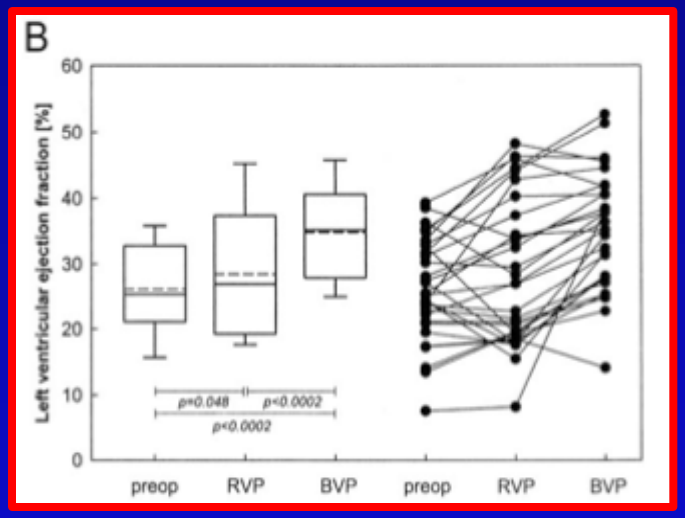
OPSITE Trial

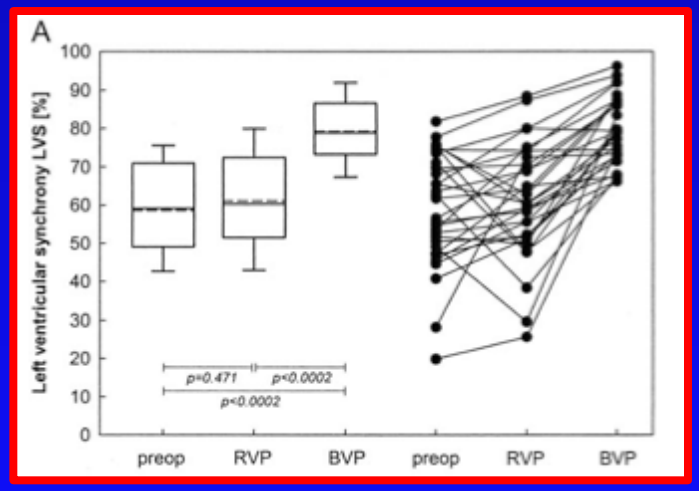
- Crossover comparison of RVP with BVP in 41 patients with AF after AVJ ablation
- No difference between RVP and BVP in
  - NYHA class
  - QoL score
  - 6 min walk distance
  - Ejection fraction
  - LV volume

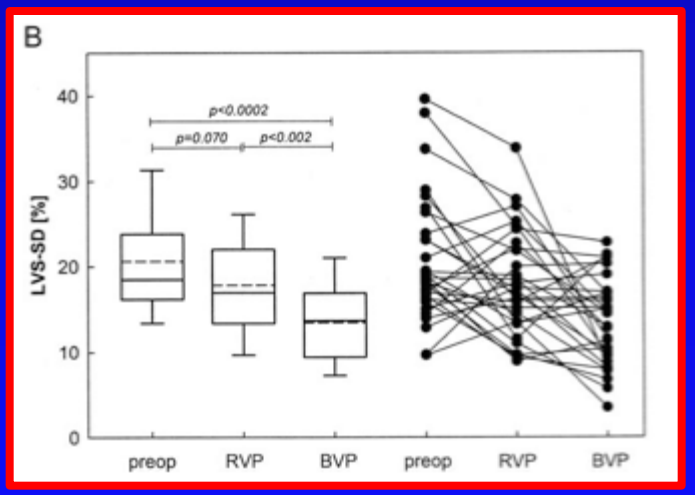
Brignole et al, Eur Heart J 2005

HOBIPACE Trial: Comparison of RV and BiV Pacing in Patients With LV Dysfunction









Kindermann et al, JACC 2006

Relevent Clinical Trial

- BLOCK-HF: CRT (D) vs PPM (ICD); HF composite
  - –Heart block requiring PPM
  - –EF ≤ 50%, NYHA I-III