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

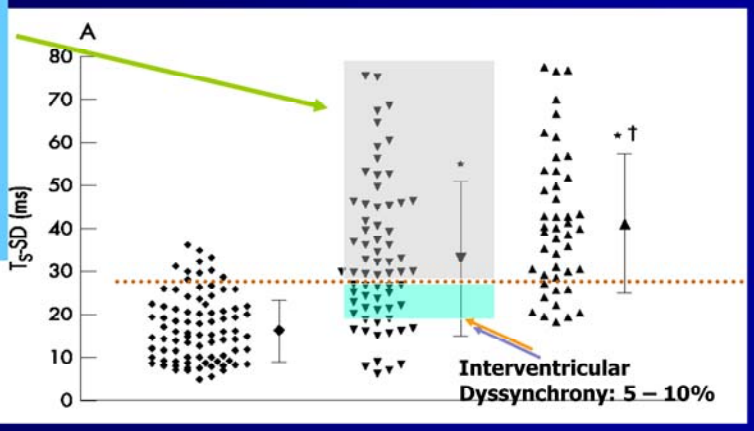
- CRT for narrow QRS
- CRT for NYHA Class I-II heart failure
- Atrial fibrillation and AVN ablation
- CRT for routine bradycardia indications

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

Mechanical Dyssynchrony With Narrow QRS Duration

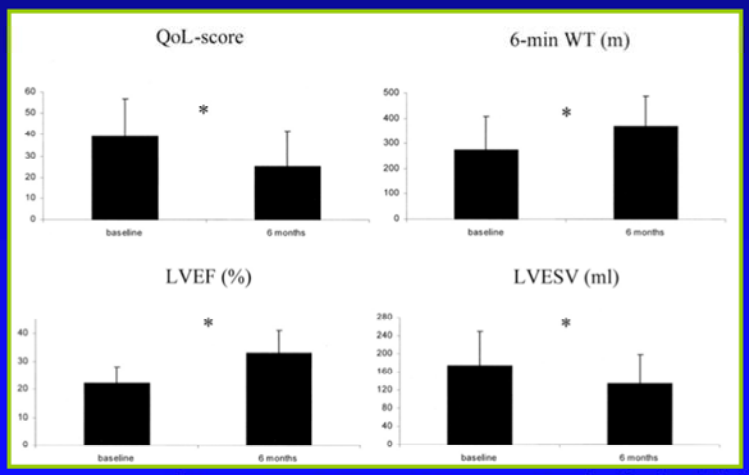
Normal <120 ms >120 ms

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



CM Yu et al. Heart 2003

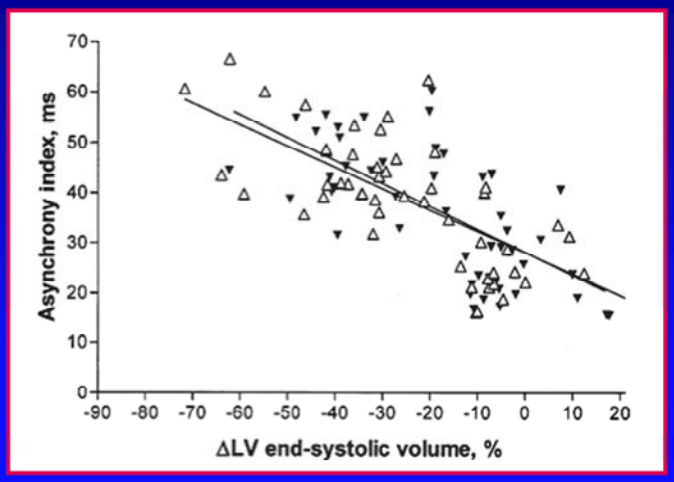
Preliminary Favorable Results in Patients with Narrow QRS



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

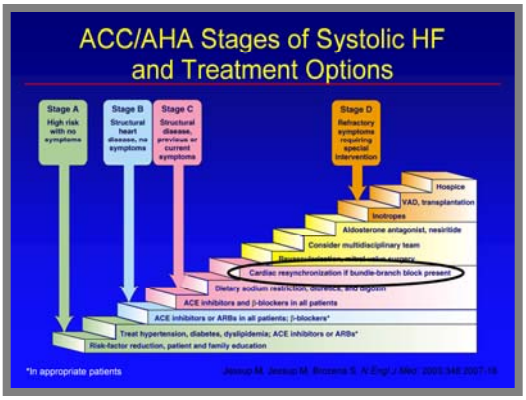
Any Hope for Narrow QRS Based on RethinQ?

- 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?



- Current ACC/AHA chronic HF guidelines emphasize that each stage of HF is associated with unique options for treatment.[1,2]
- *Stage A*: Treatment should include risk-factor reduction and patient and family education. Hypertension, dyslipidemia, and diabetes should be targeted, and ACE inhibitors or ARBs are also recommended in appropriate patients.
- *Stage B*: ACE inhibitors or ARBs are recommended in all patients; β-blockers are recommended in appropriate patients.
- *Stage C*: All patients should receive ACE inhibitors and β-blockers. Other treatments may include dietary sodium restriction, diuretics, and digoxin.
  - Additional options in appropriate patients include cardiac resynchronization (if bundle-branch block is present), revascularization and mitral-valve surgery, and aldosterone antagonists and nesiritide.
  - A multidisciplinary team approach may be useful.
- *Stage D*: Refractory symptoms require special interventions, which may include inotropes, ventricular assist device (VAD), heart transplantation, and hospice care.

1. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2001;38:2101-2113.
2. Jessup M, Brozena S. Heart failure. *N Engl J Med*. 2003;348:2007-2018

Justification to Investigate CRT Prevention of HF Progression

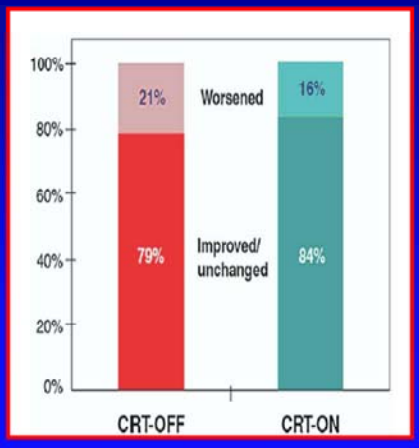
- In the MADIT II Study of patients with EF < 30% and class I-II heart failure, 30% developed new or worsening heart failure over 21 mos.
- In the CONTAK CD Study of 263 class I-II heart failure patients treated with CRT, there was improvement in LV dimensions but not symptoms nor exercise capacity over 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

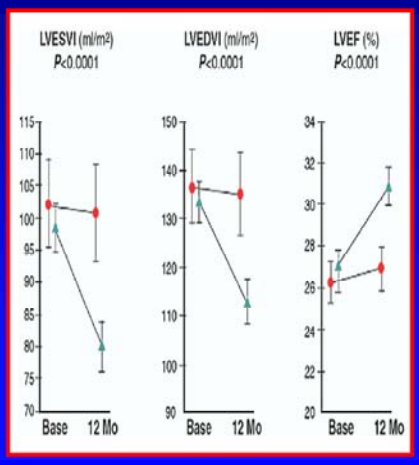
Primary Endpoint of REVERSE



- 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

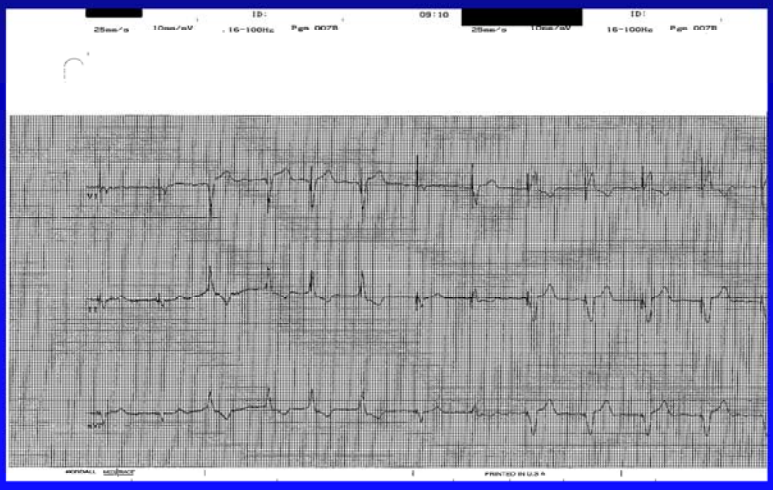
CRT in Heart Failure and AF: MUSTIC - AF

- 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

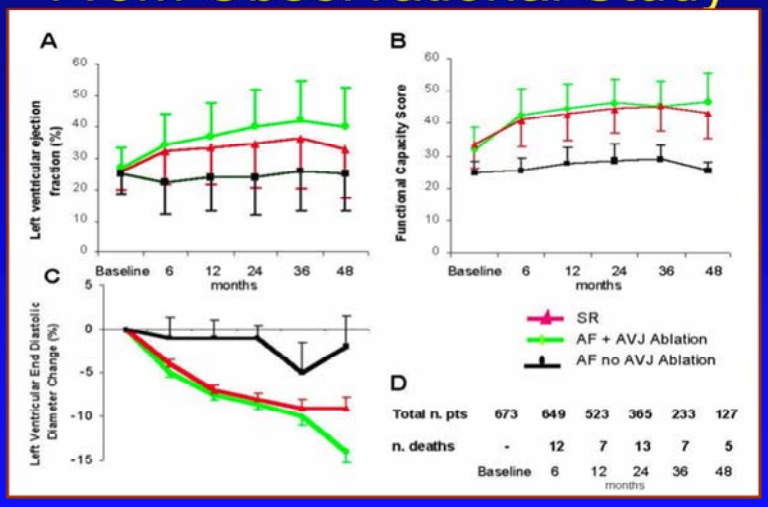
Challenges to Achieving Consistent BV Capture in Patients With AF

- 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

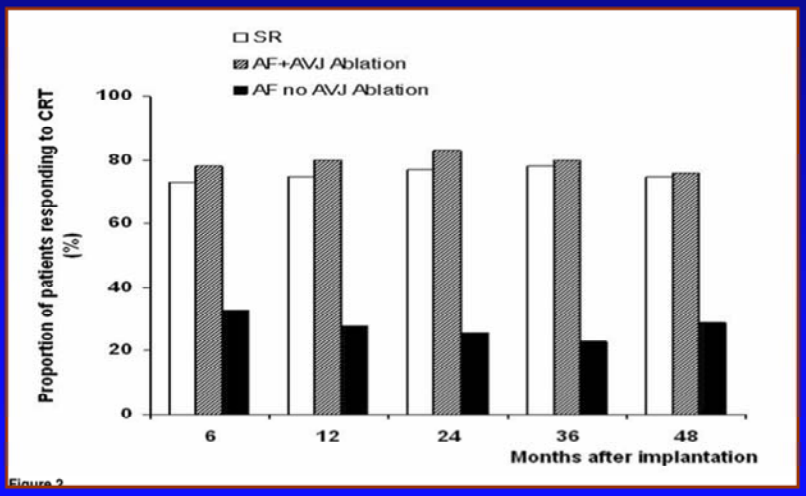


CRT Employed in AF: Outcomes From Observational Study

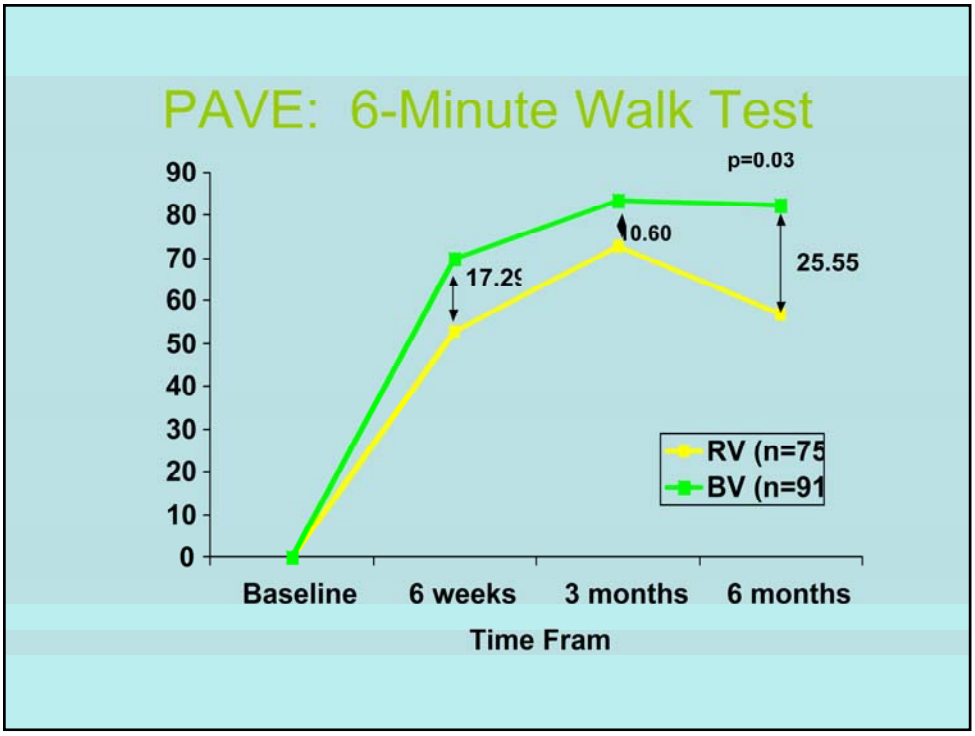


Courtesy of Gasparini et al

CRT Employed in AF: Outcomes From Observational Study

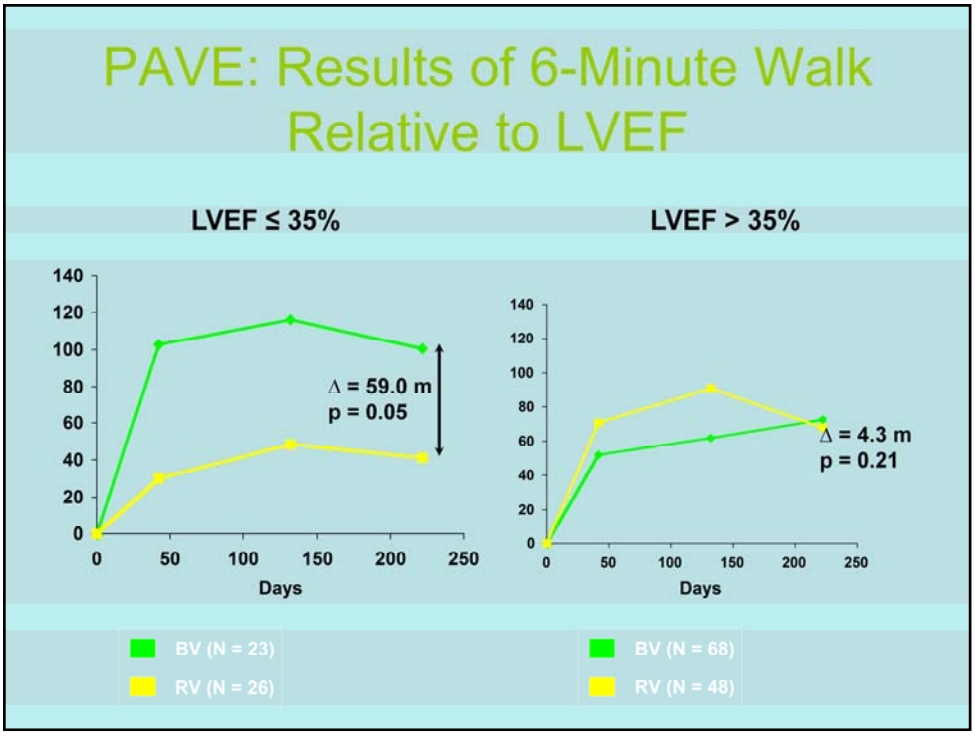


Courtesy of Gasparini et al



I think that it is worth pointing out during the talk that the difference between groups widens after 6 months of pacing because the RV group worsens while the BV group maintains the improvement (rather than because the BV group improves more while the RV group stays the same). This is consistent with the observations from DAVID.

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

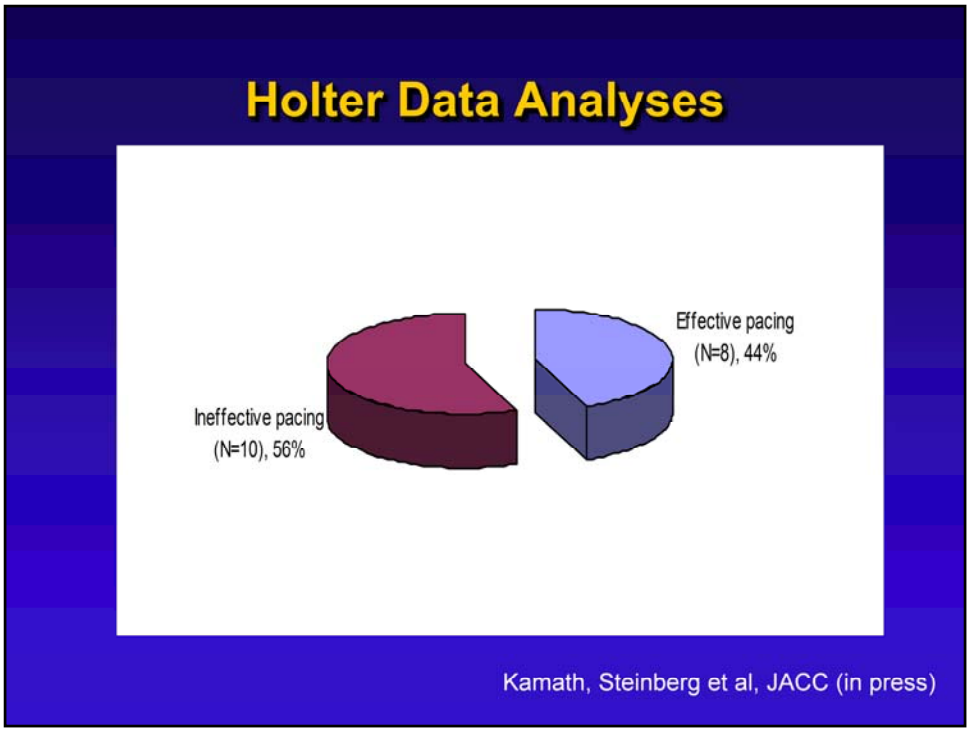
Intrinsic | Paced beat | Fusion beat | Pseudofusion beat

Kamath, Steinberg et al, JACC (in press)

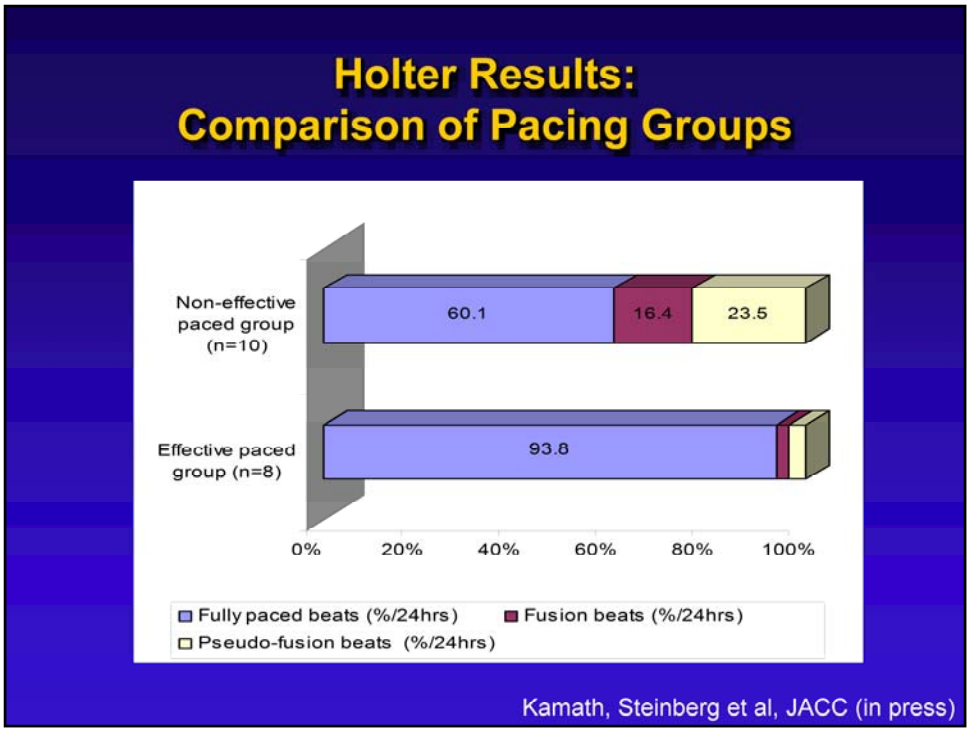
Endpoint Definitions

- 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

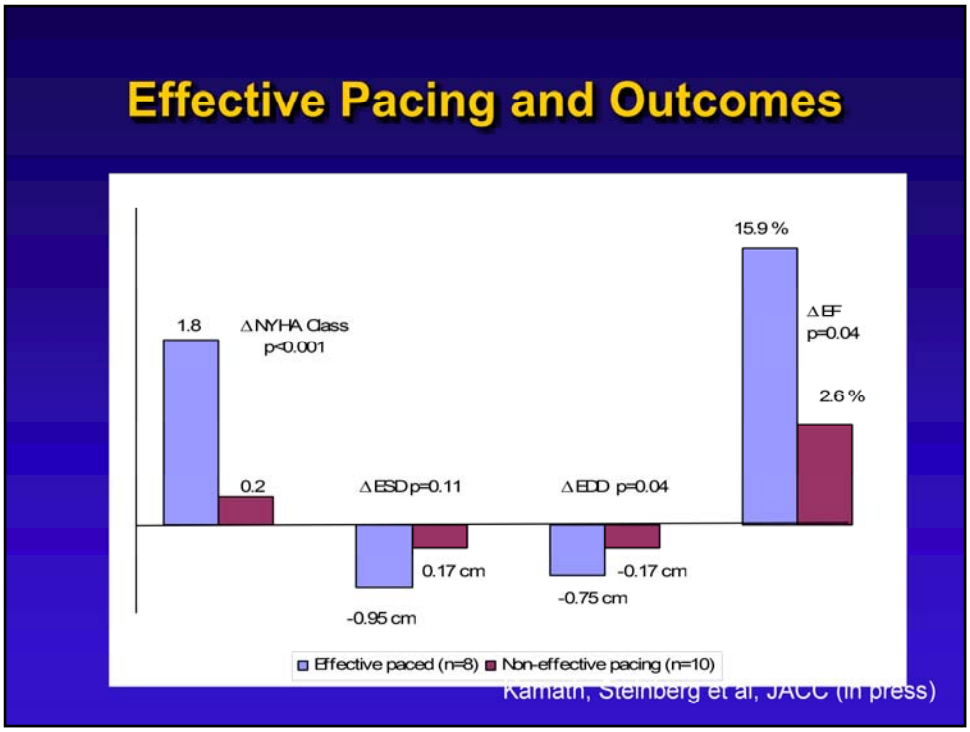
Kamath, Steinberg et al, JACC (in press)



After careful and formal analyses of the Holter using the previously described template matching algorithm, the results indicate that only 8 pts, or 44%, showed evidence of effective pacing. The remaining 10 pts, representing 56% of pts, had ineffective pacing. Please keep in mind that BiV pacing counters always demonstrated more than 90% capture and this finding indicates that many patients had substantial numbers of beats that had incomplete capture.

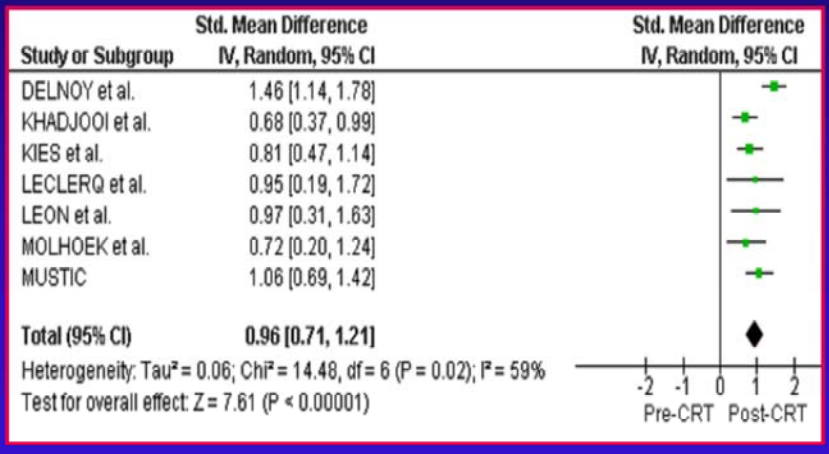


On this slide, we have detailed the Holter analyses in each group. The effective paced group had 93.8% fully paced beats with complete capture. In the ineffective paced group, only 60% of the beats had complete capture. Nearly 40% of the pacing was ineffective from a combination of fusion and pseudofusion beats



Over the 12 months of follow-up, not all patients demonstrated a clinical response. Comparison of the effective and non-effective paced groups showed that only the effective paced group had significant improvement in the NYHA Class.Similarly, only the effective paced group exhibited a decrease in the end-systolic diameter and the end-diastolic diameter, and a marked improvement in the ejection fraction.

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

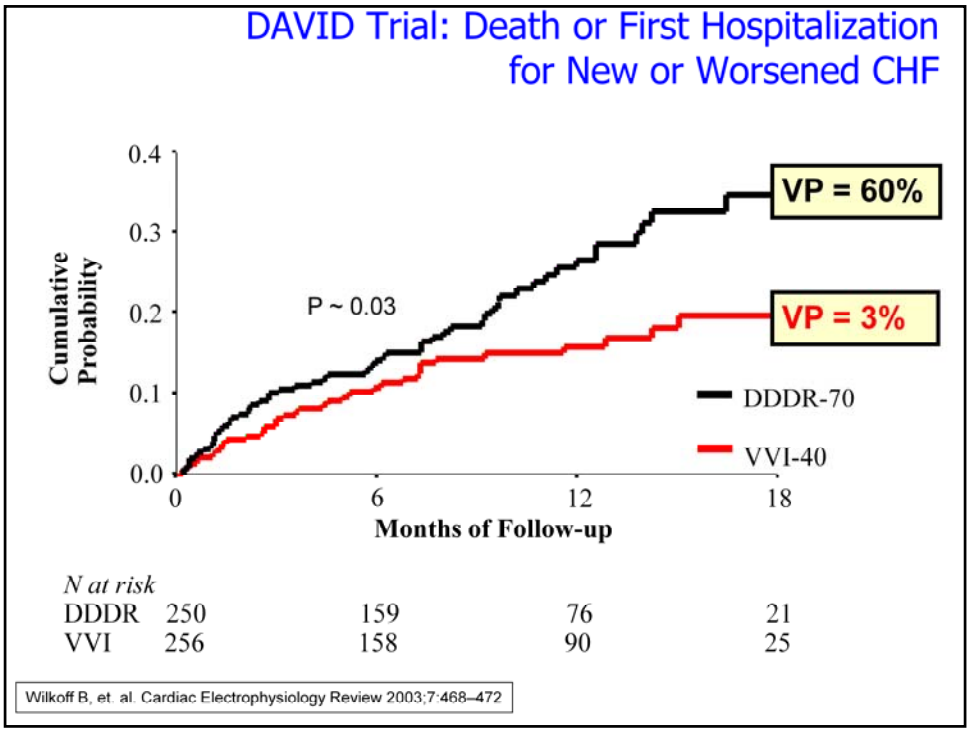
Relevent Clinical Trial

- 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?

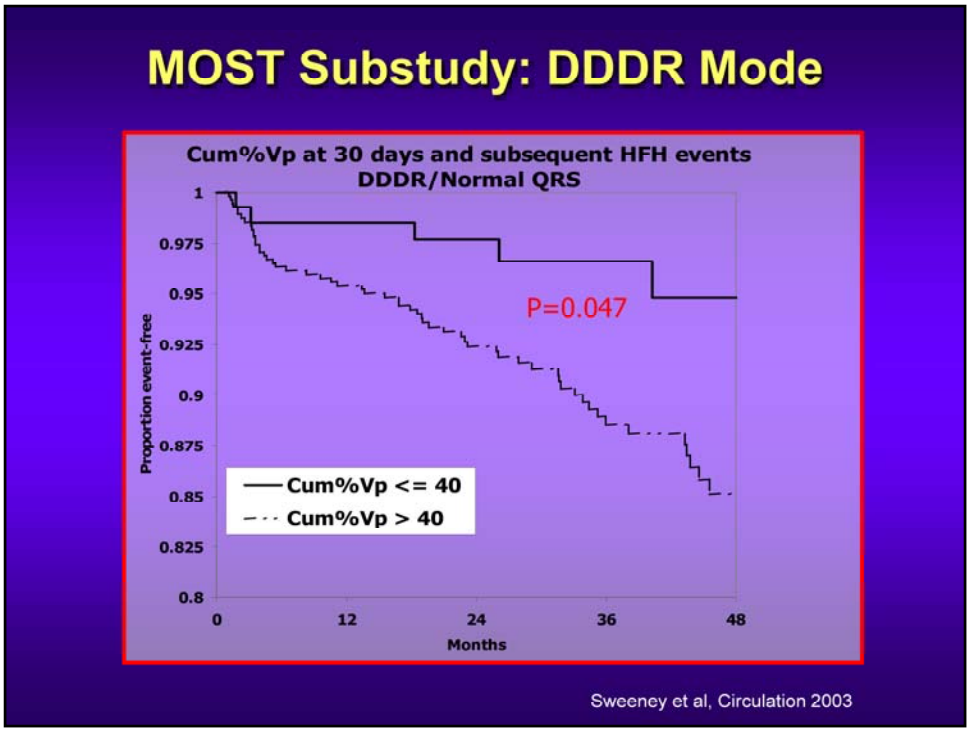
Summary of Deleterious Effects of RV Apical Pacing

- 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



In the DAVID Trial, VVI (Ventricular backup pacing mode) produced less than 3% ventricular pacing and no atrial pacing; while dual chamber pacing produced around 60% of atrial and ventricular paced beats. The p-value of 0.03 is adjusted for sequential monitoring.

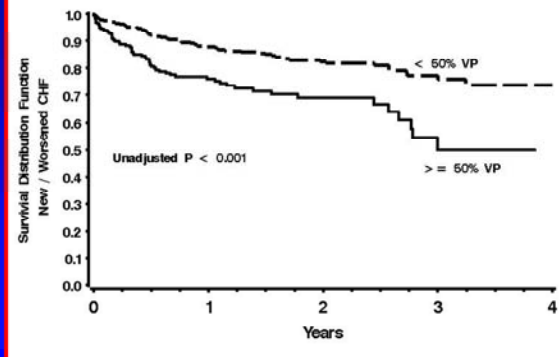
Wilkoff B, et. al. Cardiac Electrophysiology Review 2003;7:468–472



This is a graphic representation of the effect of cumulative percent ventricular paced in the DDDR mode on subsequent incidence of heart failure hospitalization. Analysis showed that cumulative percent ventricular paced at 30 days correlated well with cumulative percent ventricular paced over all of follow-up. This plot shows time to heart failure hospitalization after 30 days, by cumulative percent ventricular paced groups using the binary cutoffs applied to the 30 day value for patients with normal QRS duration.

The plot shows an early, sustained and increasing incidence of heart failure hospitalization amongst DDDR patients with cumulative percent ventricular paced >40% compared to <40%.

Relationship of Ventricular Pacing to New/Worsened Heart Failure Outcome

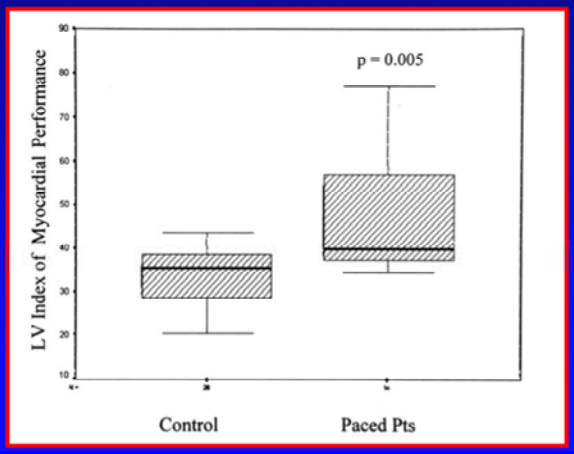


Steinberg et al, JCE 2005

The next serious of slides will be Kaplan-Meier survival plots comparing the outcome of the top quartile of patients who were always paced, shown as a dotted line, with the other 3 quartiles combined, shown as a solid black line. We found that these 3 lower quartiles had similar outcomes.

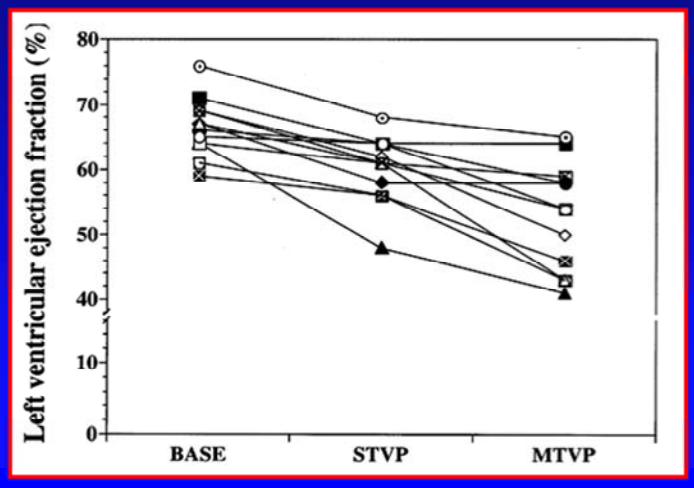
Shown here is the outcome of new or worsened heart failure; the 4th quartile had significantly worse outcome and a greater likelihood of presenting with heart failure throughout follow-up. The unadjusted p value was 0.031.

Long-term Deleterious Effect on LV Performance



Tantengco et al, JACC 2001

Decline in Normal Ventricular Function With RVP



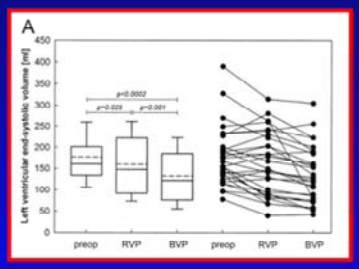
Nahlawi et al, JACC 2004

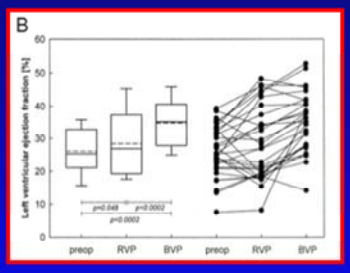
OPSITE Trial

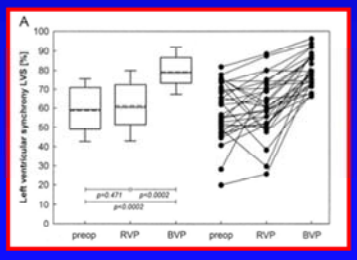
- Crossover comparison of RVP with BVP in 41 patients with AF after AVJ ablation
- No difference between RVP and BVP in
  - NYHA class
  - QoL score
  - 6 min walk distance
  - Ejection fraction
  - LV volume

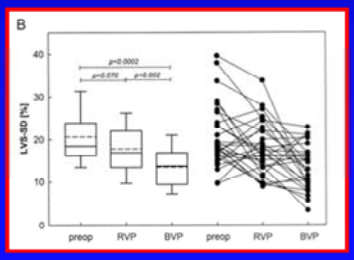
Brignole et al, Eur Heart J 2005

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