Unresolved Issues in CRT Therapy for Heart Failure: A Case Based Approach

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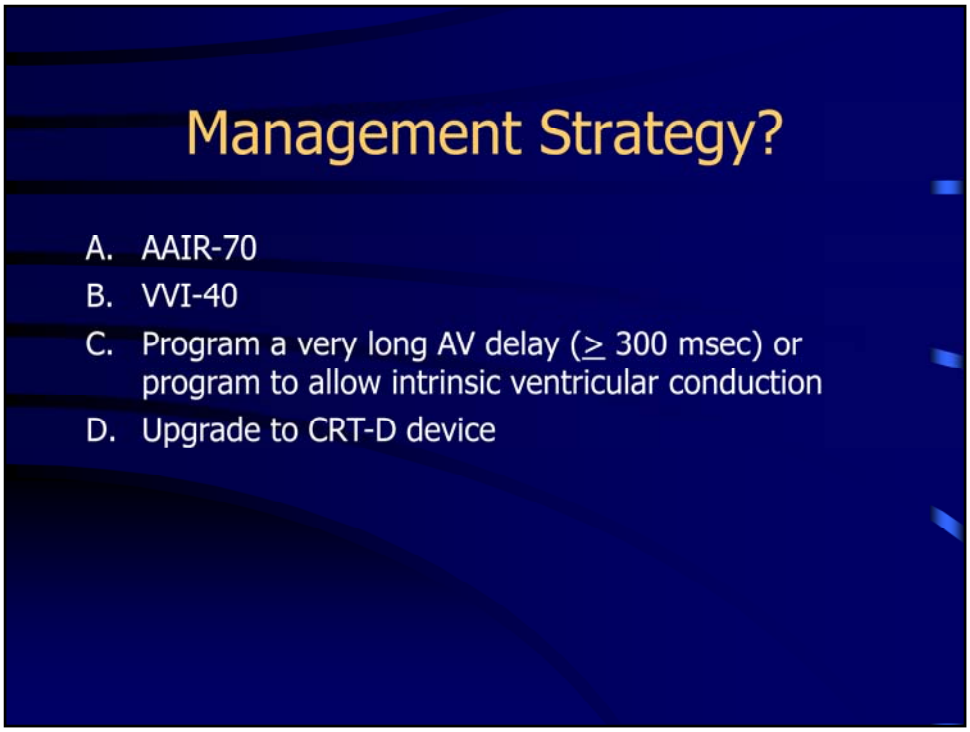
Conflict of Interest Disclosure

None

Case 1

- 61 year old sudden cardiac arrest survivor
- Dual chamber ICD implanted following his cardiac arrest – Device programmed DDDR 60-120 ppm
- Echocardiogram done after his arrest showed an ejection fraction of 40%
- 6 months later he had worsening heart failure despite optimal medical therapy with an EF of 20%
- Baseline ECG (without pacing) shows the following:
  - Sinus bradycardia at 48 bpm
  - PR interval: 260 msec
  - QRS interval: 100 msec
- Interrogation of his ICD showed: 90% atrial and ventricular pacing

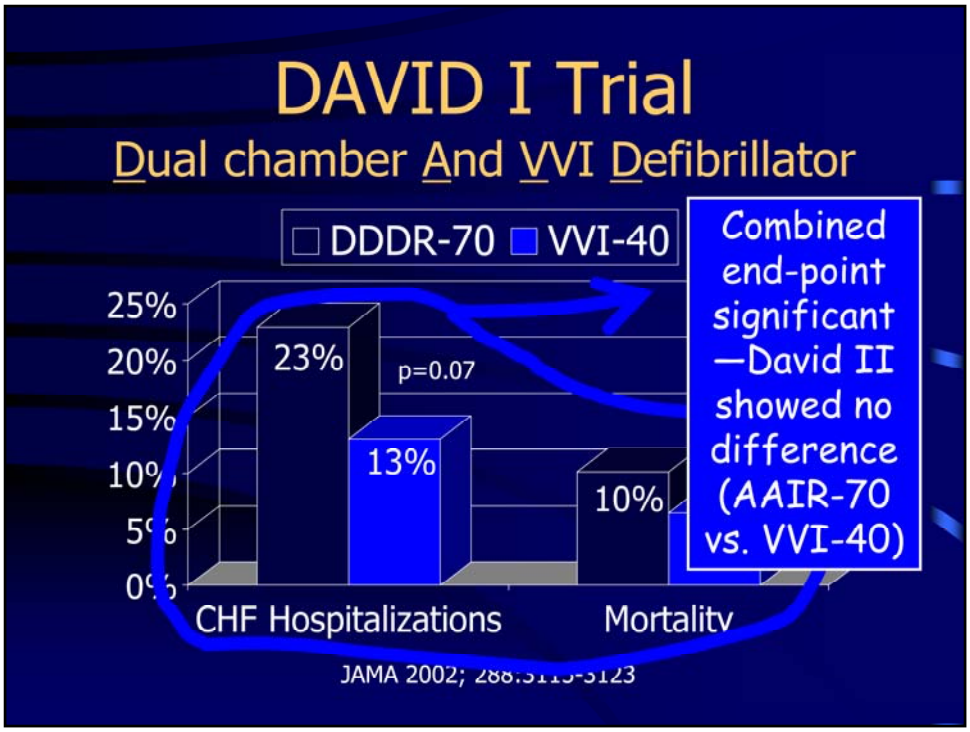


Option A would be a very reasonable strategy based on the DAVID II Study. This would allow treatment of his underlying sinus bradycardia while avoiding RV pacing.

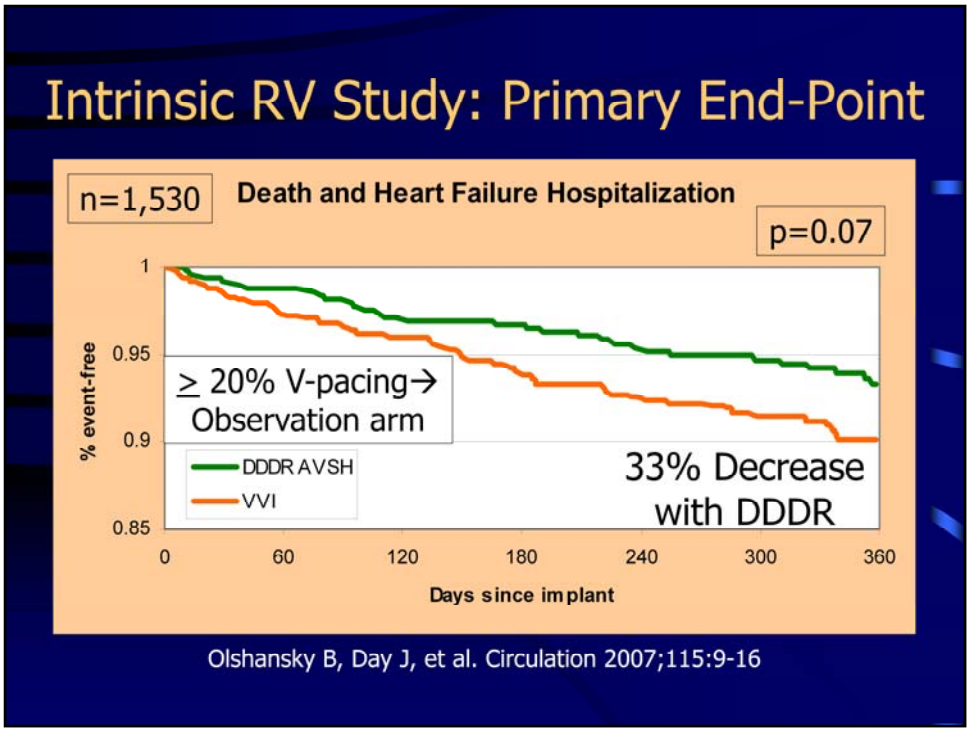
Option B would be very reasonable as well based on the DAVID I and DAVID II Studies as RV pacing could be avoided. However, the patient does appear to have sinus bradycardia and may potentially experience some functional limitations from chronotropic incompetence.

Option C would allow treatment of his probably sinus node dysfunction and potentially avoid unnecessary RV pacing. Unfortunately, given his long PR interval depending on the manufacturer/model RV pacing may or may not be avoided.

Option D would allow treatment of his sinus node dysfunction and allow a physiologic AV delay without RV pacing. However, this is not a current recommended indication for a CRT device and would be an off-label use.

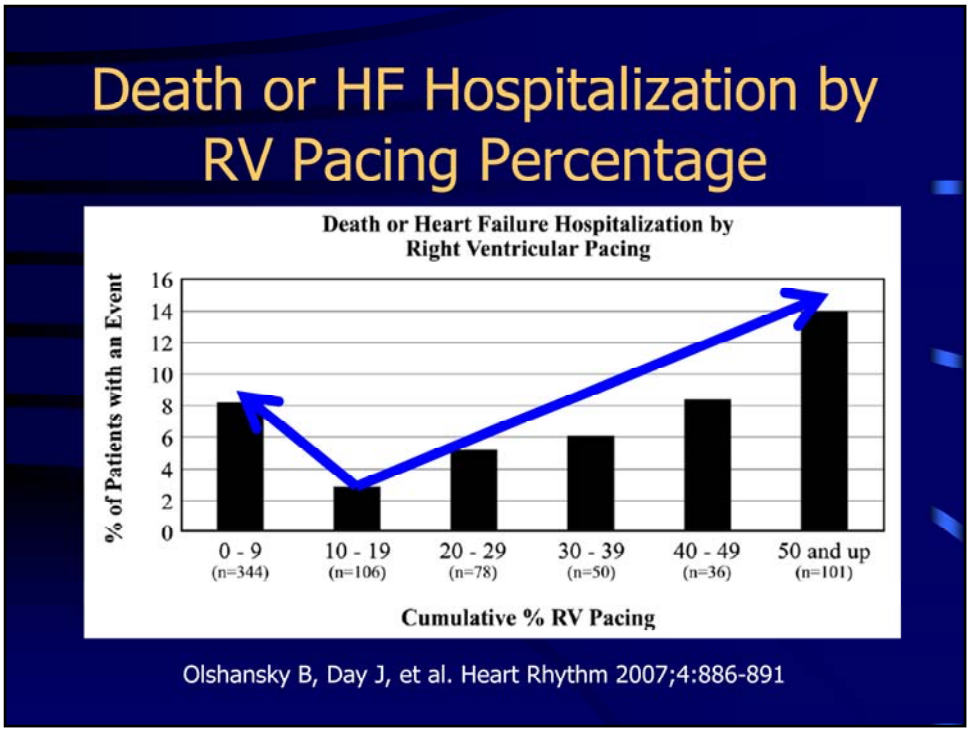


The David I Trial compared a DDDR-70 versus VVI-40 pacing mode for ICD patients WITHOUT a standard pacing indication. As predicted, the percentage of right ventricular pacing was dramatically higher in the DDDR-70 group. This unnecessary right ventricular pacing lead to the study being terminated early due to excessive heart failure hospitalizations and mortality in the DDDR-70 group. Interestingly, the DAVID II Trial was recently completed which showed no statistical difference in heart failure hospitalizations or mortality in ICD patients randomized to either AAIR-70 or the VVI-40 pacing modes.



The Intrinsic RV Study was a large multi-center ICD trial which enrolled 1,530 patients and randomized them to the DDDR-60 versus VVI-40 pacing modes. In this study, there was a 1 week wash-out period. During this period of time all patients were programmed DDDR-60 with the AV Search Hysteresis feature activated allowing intrinsic AV conduction up to 300 msec. If there was more than 20% RV pacing during this wash-out phase patients were placed in the observational arm. In patients that had less than 20% RV pacing they were then randomized to DDDR-60 or the VVI-40 pacing modes and followed for 1 year for heart failure hospitalizations or mortality.

Shown here are Kaplan-Meier curves which illustrate this result. The top line shows outcomes in the DDDR with AV Search hysteresis arm, below which are the outcomes in the VVI arm. The curves separated early and maintained that separation throughout follow up.



This was an interesting sub-study published from the Intrinsic RV Study. In this study, we evaluated the development of heart failure hospitalization or mortality based on the percentage of RV pacing.

As expected, the risk of death or heart failure hospitalization increased with increasing percentages of RV pacing. Unexpectedly, in patients with no RV pacing the risk of heart failure hospitalization or death was increased. This could potentially be explained by a lack of AV synchrony in these patients with long PR intervals.

Case 1 Outcome

- We initially programmed around RV pacing by extending the AV delay to 300 msec (maximum AV delay allowed by his device)
- Unfortunately, avoiding RV pacing only modestly improved his heart failure symptoms
- Over time he developed underlying complete heart block and was upgraded to a CRT-D device
- With CRT he did have a significant improvement in his heart failure status
- This case demonstrates that unnecessary RV pacing and AV dyssynchrony may exacerbate heart failure patients

Our Approach to RV Pacing in Dual Chamber ICD Patients: 1

- We prefer dual chamber ICDs over single chamber ICDs
  - We will program long AV delays to avoid unnecessary right ventricular pacing
  - We prefer the benefits of a dual chamber device
    - Atrial support pacing
    - Better rhythm discrimination between SVTs and VTs
  - If the sinus node intact and we cannot program around RV pacing in an ICD (uncommon) we will use the AAI or VVI-40 pacing modes

Our Approach to RV Pacing in Dual Chamber ICD Patients-2

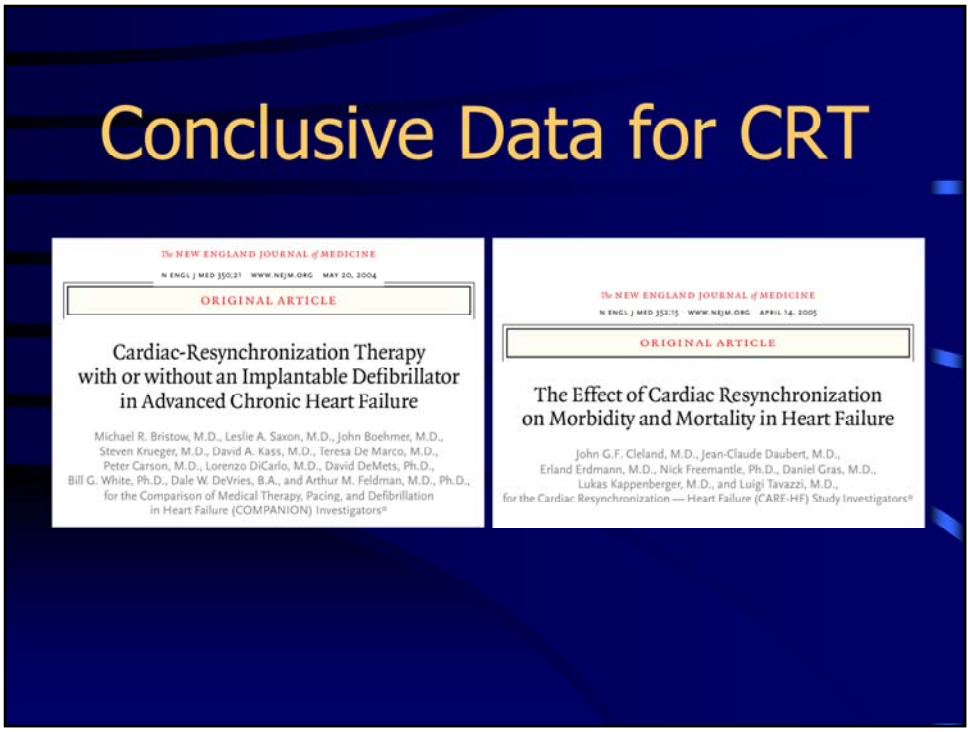
- One concern is that are we creating iatrogenic AV dyssynchrony by allowing excessively long AV intervals in order to avoid RV pacing?
- If a heart failure patient with a low ejection fraction requires ventricular pacing we will use a CRT device

Case 2

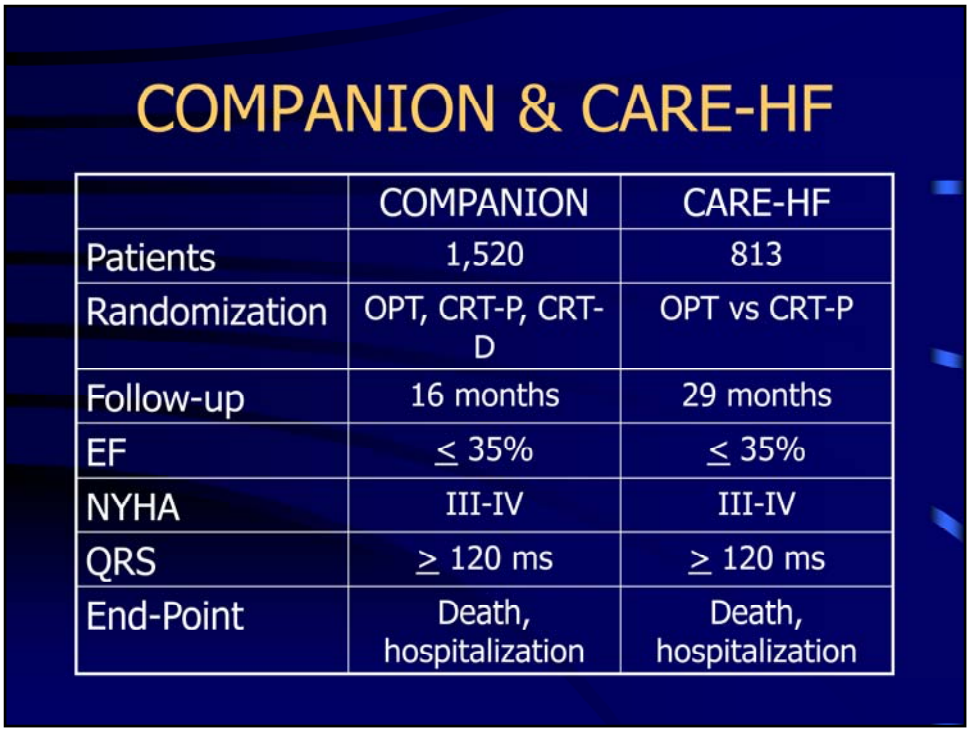
- 68 year old man with non-ischemic heart failure for 3 years
- Ejection fraction of 30%
- NYHA class III heart failure despite optimal medical therapy
- Left bundle branch block with a QRS width of 150 ms
- He is frequently hospitalized for heart failure exacerbations—every time he goes to his mountain cabin at 8,000 feet elevation he is flown by helicopter to our facility for treatment of acute pulmonary edema
- He has no history of ventricular arrhythmias or syncope

Option A is not indicated as the patient has clear indication for CRT therapy; chronic long-standing heart failure with an ejection fraction less than or equal to 35%, NYHA class III heart failure despite optimal medical therapy, and a QRS greater than or equal to 120 msec.

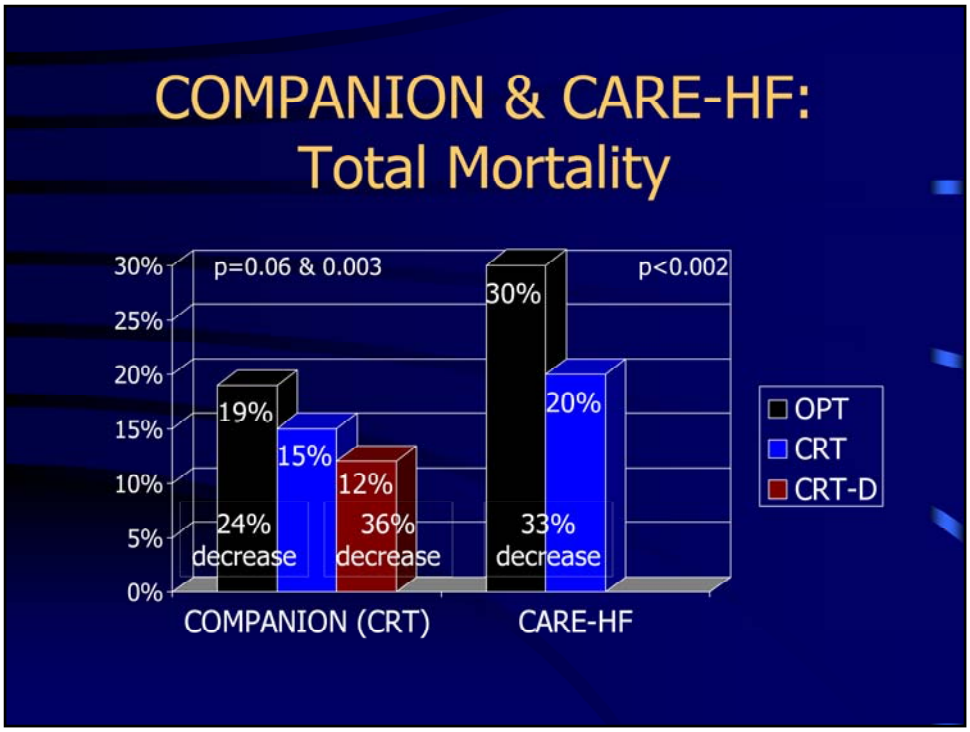
Option B would not be the best choice for the U.S. given his indication for ICD therapy. The SCD-HeFT Study showed that patients with an ejection fraction less than or equal to 35% with at least NYHA class II heart failure benefited from ICD therapy.



This slide shows the 2 large multi-center trials establishing the role of CRT therapy.



This slide shows the number of patients in both of these trials, how they were randomized (OPT=optimal pharmacologic therapy), the length of follow-up, ejection fraction, NYHA status, QRS width, and the primary end-point of the study.

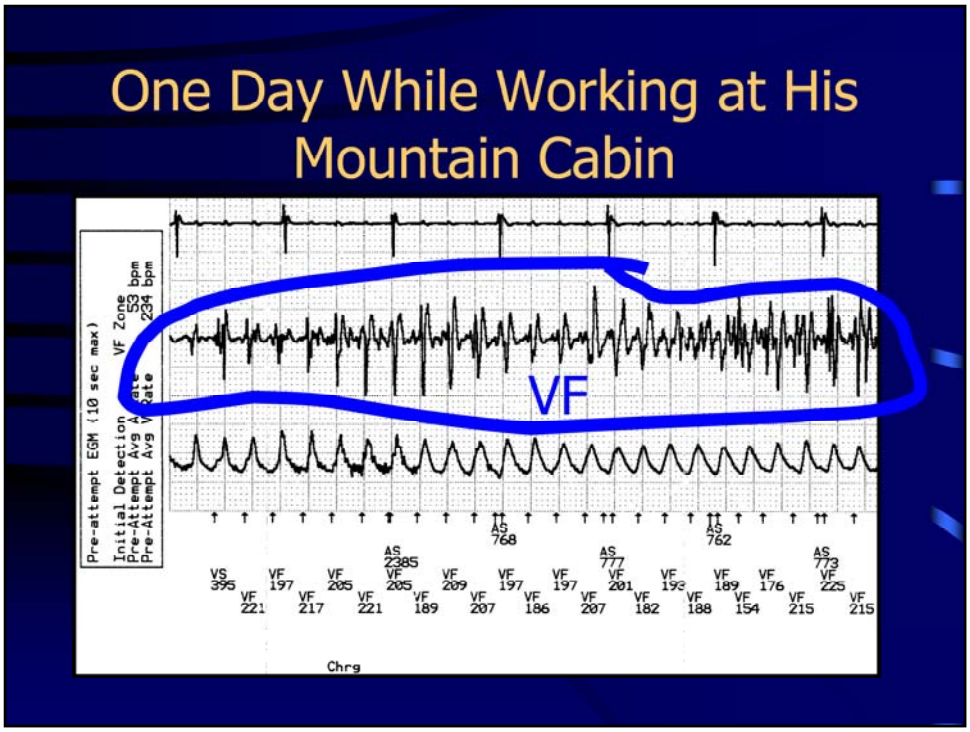


This slide compares the total mortality reduction achieved with CRT therapy. In the Companion Trial, there was a statistically significant mortality reduction in the CRT-D arm when compared to optimal pharmacologic therapy (OPT). The CRT-P arm in Companion failure to reach statistical significance when compared to optimal pharmacologic therapy.

In the CARE-HF Study, there was a statistically significant mortality reduction with CRT-P alone.

Case 2 Outcome

- At the time of this case it was 2001 and there was no ICD indication at that time (prior to the MADIT II and SCD-HeFT Trials)—the CRT devices were not yet market approved in the U.S.
- This patient was enrolled into the COMPANION Study and was randomized to the CRT-D arm
- With CRT therapy he had complete resolution of his heart failure symptoms (NYHA I)
- As he was feeling so well he was again able to return to his mountain cabin at 8,000 feet without pulmonary edema



Given that he felt so good with CRT therapy, he was performing hard physical labor at his mountain cabin (8,000 feet above sea level). While working he unexpectedly found himself on the ground (the CRT-D shock did not occur until after syncope had occurred). Not knowing how he got to the ground he got back up and continued working on his mountain cabin.

He went on to have several more episodes of VF all while working at his mountain cabin. Each episode was successfully terminated with 1 shock. Since he stopped performing hard physical labor at his mountain cabin he has had no further episodes of VF.

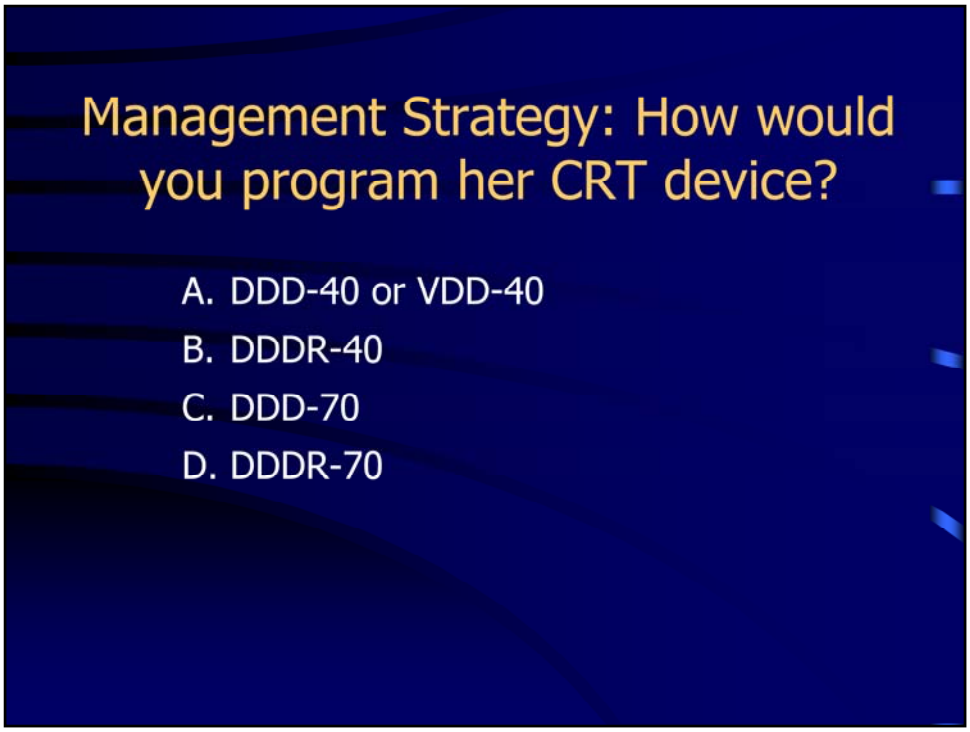
This case shows that while CRT may dramatically improve heart failure symptoms these patients are still at significant risk for sudden cardiac arrest.

Our Approach to CRT in Heart Failure Patients

- We follow current CRT guidelines: EF $\leq$ 35%, QRS $\geq$ 120 msec, NYHA 3 despite OPT
- We generally do not implant CRT-P devices as these patients generally qualify for ICD therapy—the exception is in special situations where patients want to feel better but do not want their lives artificially prolonged by a shock for VT/VF
- We routinely upgrade patients with pacemakers or ICDs who require RV pacing and have low ejection fractions and heart failure symptoms

Case 3

- A 60 year old woman with sinus node dysfunction
- Her baseline sinus rate is 45 bpm on beta-blocker therapy for heart failure
- Her peak heart rate on a treadmill was 122 bpm
- She had a myocardial infarction 2 years ago
- Her ejection fraction is 30%
- She has a left bundle branch block with a QRS width of 130 msec
- She has had frequent hospitalizations for heart failure exacerbations

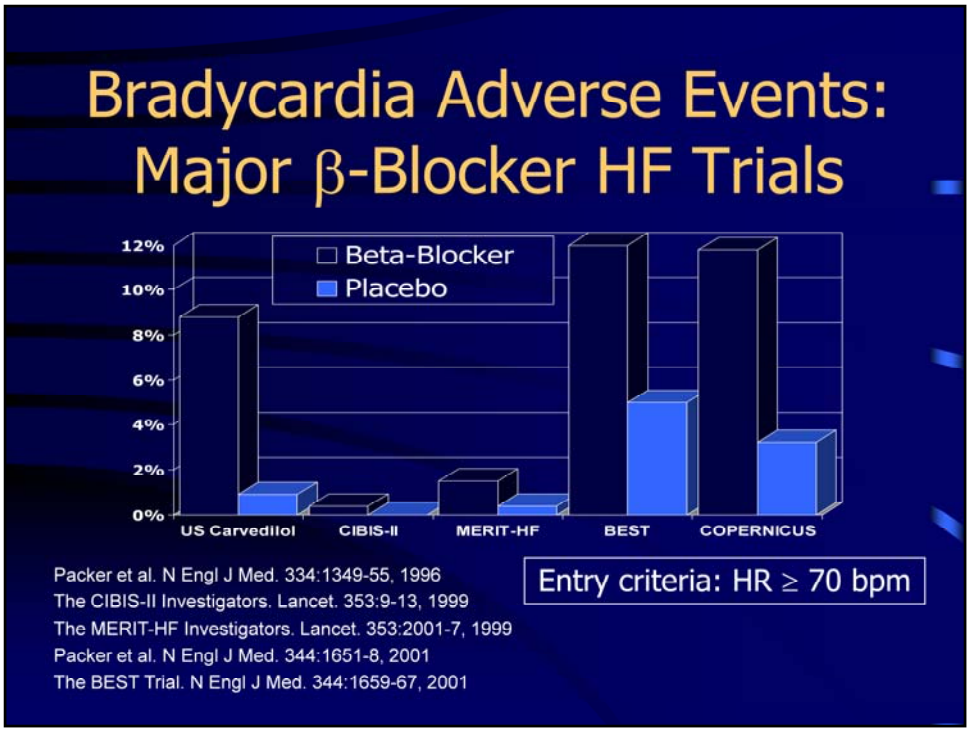


Option A would be based on the large multi-center clinical trials which established the efficacy of CRT. In these studies, atrial pacing was avoided and thus the DDD-40 or VDD pacing modes were selected to sense the atrium and provide biventricular pacing. Unfortunately, option A does not address his sinus node dysfunction and chronotropic incompetence.

Option B would give him rate responsive pacing which would help his chronotropic incompetence but he may have symptoms from sick sinus syndrome at rest.

Option C would correct his resting sinus bradycardia but he would still have chronotropic incompetence.

Option D would optimally treat him from a physiologic stand point. However, there is no data establishing the efficacy of CRT in patients with sinus node dysfunction who require atrial support pacing. Thus, it is unclear if this option would decrease his risk of heart failure hospitalization or death.



This slide shows the significance of sinus node dysfunction in the major beta-blocker trials for heart failure. Most of these landmark studies required a resting sinus heart rate of at least 70 bpm to even be entered into the study. Of note, significant bradycardia from beta-blocker therapy was a significant adverse event in most of these studies when compared to placebo. It remains unclear how to best treat heart failure patients with sinus node dysfunction.

What is the role of atrial support pacing in heart failure? We were all taught in medical school that the cardiac output was equal to the heart rate times the stroke volume. In heart failure patients where you may not be able to significantly improve the stroke volume it makes sense that perhaps their outcomes could be improved by increasing their heart rate and thereby their cardiac output.

However, a recently published study shows that right atrial pacing may potentially impair cardiac function during CRT therapy.

The role of atrial support pacing in heart failure patients remains unresolved…

Outcome?

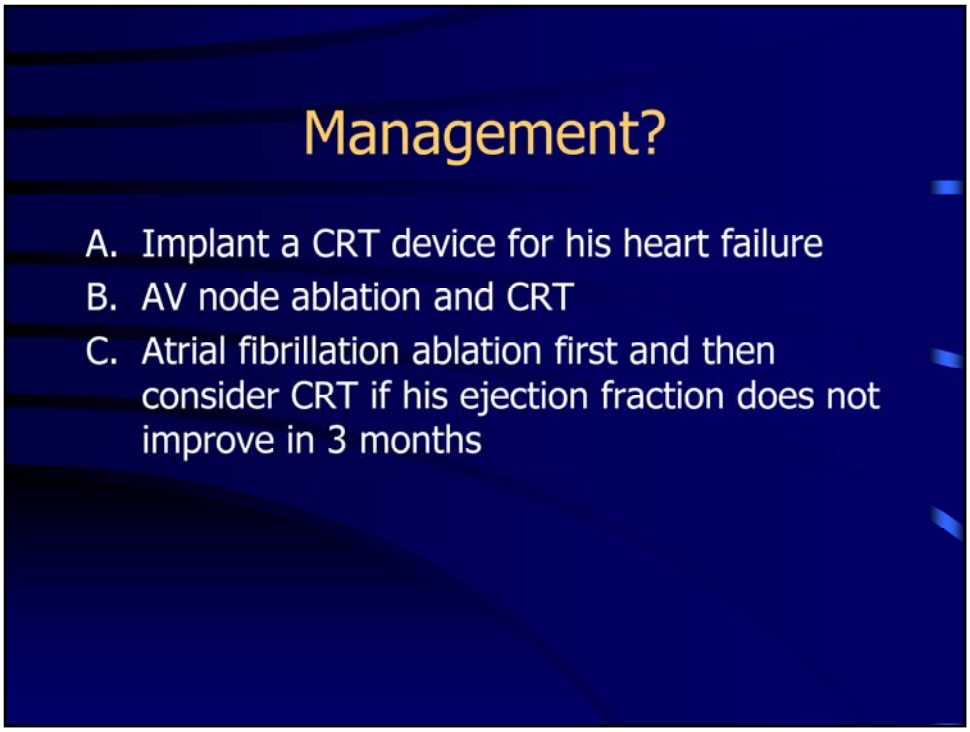
- She was enrolled in the PEGASUS CRT Trial and was randomized to the DDD-70 arm
- With CRT therapy she has done well and is now a NYHA functional class II with no further heart failure hospital admissions

The Role of Atrial Support Pacing in CRT???

- The PEGASUS CRT trial just finished enrollment in December, 2007 with nearly 1,600 patients enrolled
- In the PEGASUS CRT Trial patients with CRT indications were randomized to the following 3 pacing modes:
  - DDD-40 → based on established efficacy of CRT
  - DDDR-40 → to evaluate the role of rate response
  - DDD-70 → to evaluate the role of a higher lower rate limit in HF
- There is a 1 year clinical follow-up with a primary end-point of the heart failure clinical composite score (based on heart failure hospitalizations, mortality, and overall assessment)

Case 4

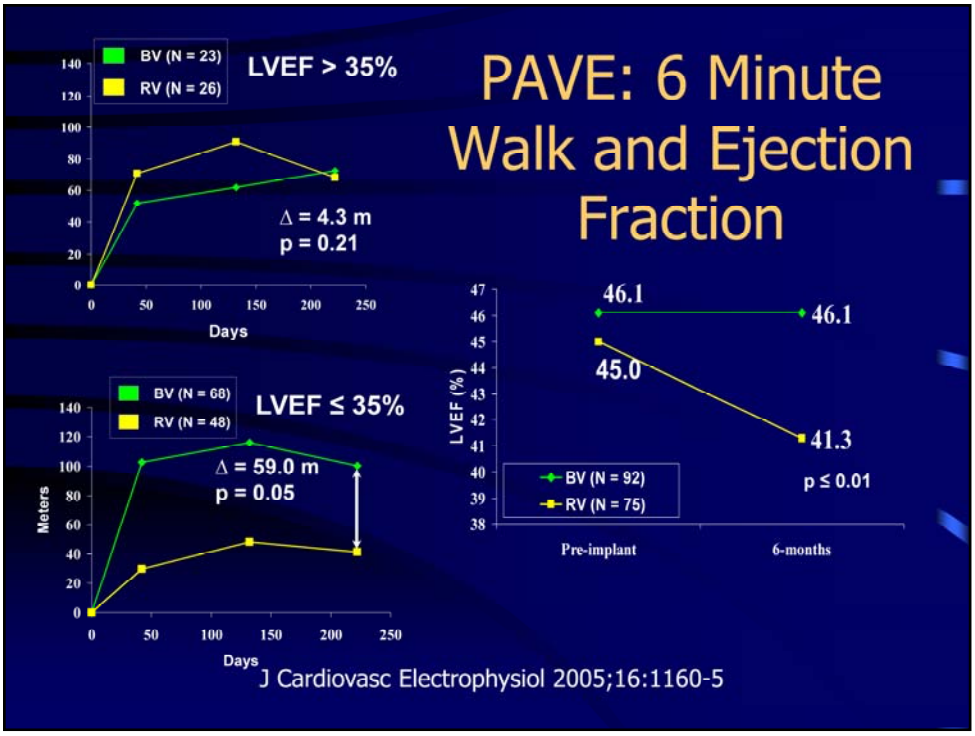
- 71 year old man with a non-ischemic cardiomyopathy for 3 years
- His ejection fraction is 35%
- He has NYHA class III heart failure despite optimal medical therapy
- He has a left bundle branch block with a QRS of 160 msec
- He has had long-standing symptomatic persistent atrial fibrillation for 2 years which has been refractory to amiodarone and cardioversions
- He has had good rate control of his atrial fibrillation
- His echo shows moderate left atrial enlargement with mild right atrial enlargement



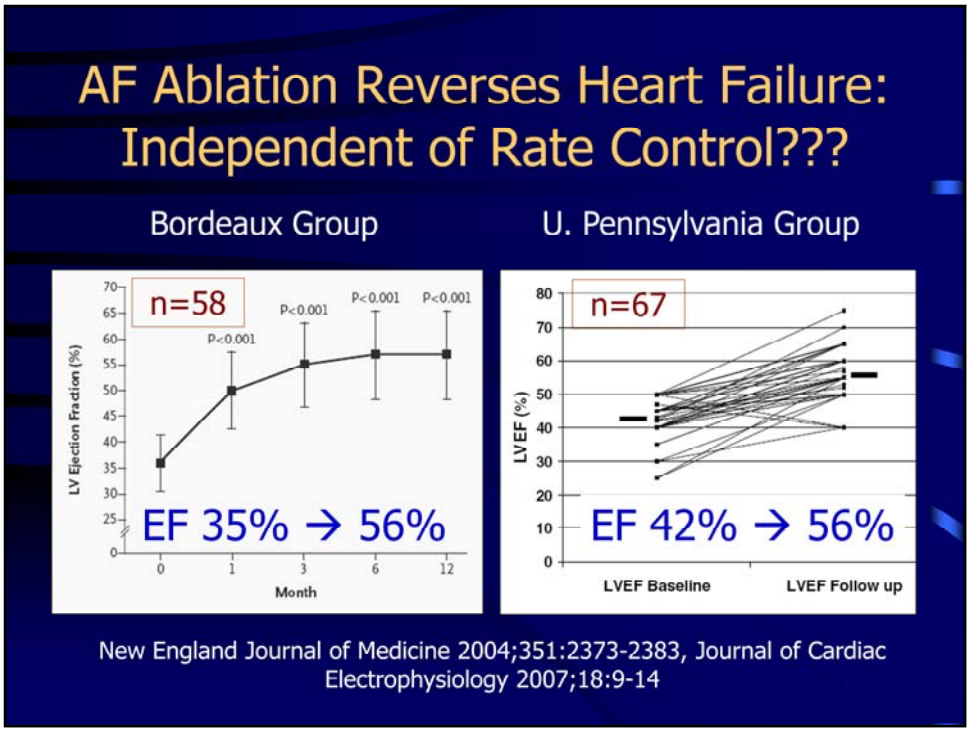
Option A is reasonable given his chronic heart failure, EF of 35%, LBBB, and NYHA class III heart failure status despite optimal medical therapy. While the landmark clinical trials establishing CRT therapy did not include chronic atrial fibrillation patients there have now been many studies showing that atrial fibrillation patients also benefit from CRT.

Option B may not be best given that he currently has excellent rate control of his atrial fibrillation with beta-blocker therapy for his heart failure. AV nodal ablation could render him pacemaker dependent which could create additional problems at a future date.

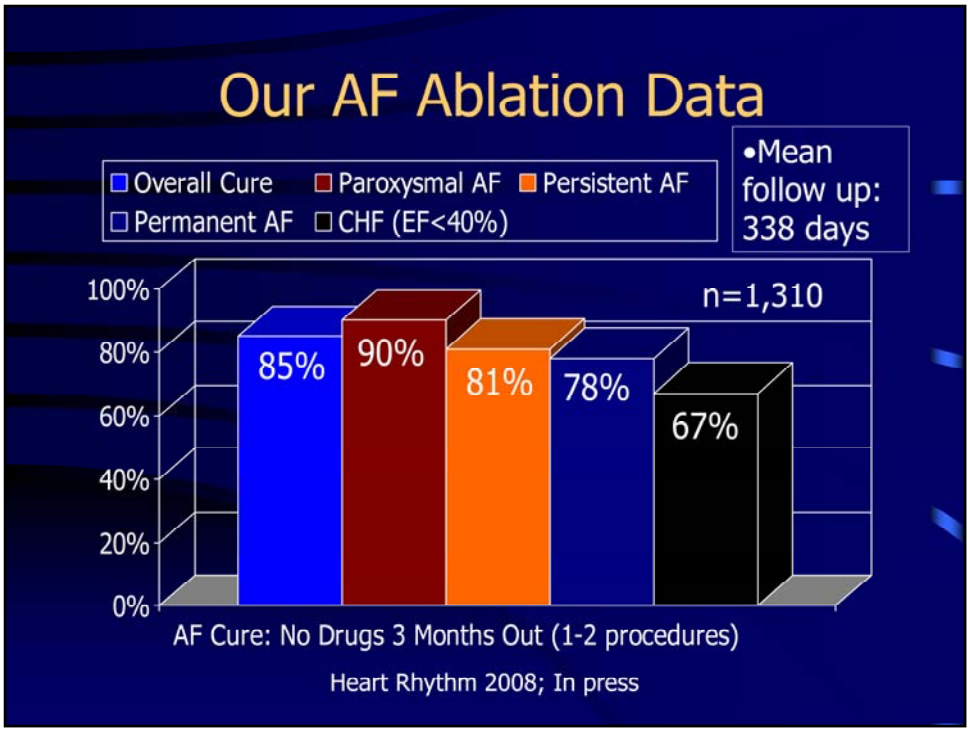
Option C is a reasonable option at centers with extensive AF ablation experience. As he has symptomatic AF refractory to anti-arrhythmic therapy he has an indication for AF ablation. Several studies have now suggested that AF is a cause of heart failure independent of the heart rate. In fact, several studies have now shown that with AF ablation the EF may increase independent of heart rate control.



The PAVE Study compared RV to biventricular pacing in patients with AF who underwent AV nodal ablation. In this study, patients with an impaired EF benefited from CRT over RV pacing following their AV nodal ablation.



These 2 studies demonstrated dramatic improvements in the EF after AF had been successfully ablated.



In our experience of more than 1,500 cases now, AF can be successfully eliminated in most patients. Unfortunately, in heart failure patients with an EF 40% or lower the success rate is not as high as our patients with paroxysmal AF.

Outcome?

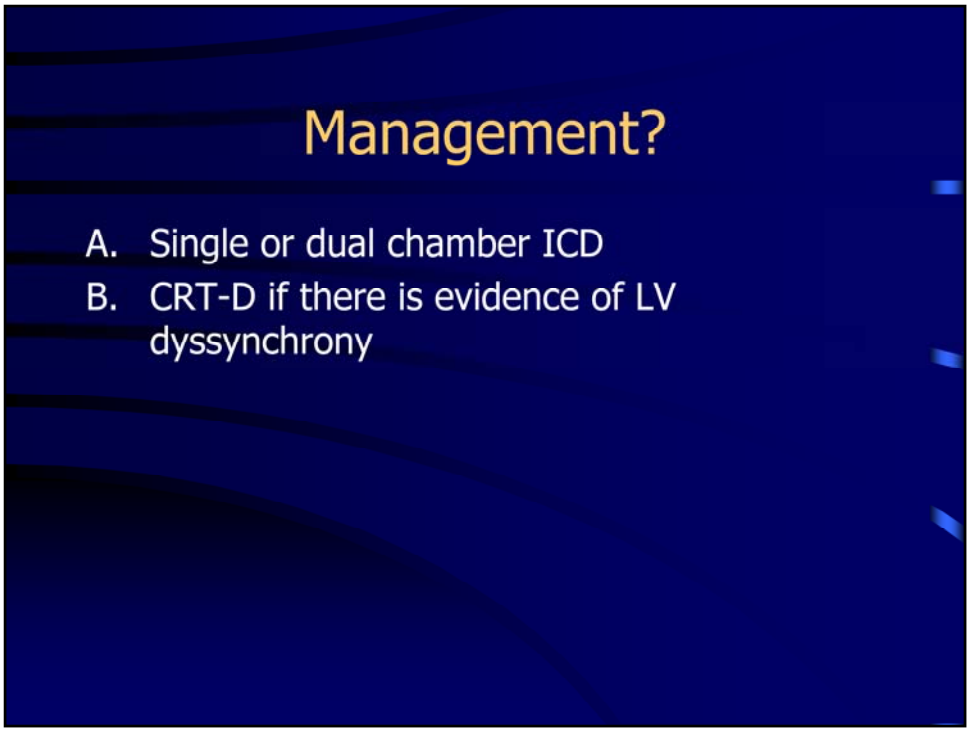
- His atrial fibrillation was eliminated with an AF ablation procedure
- 3 months after AF ablation his EF had increased to 50% with resolution of all heart failure symptoms
- A CRT device was not implanted

Our Approach to Afib and CRT

- We will implant CRT devices in AF patients
- CRT patients may experience less AF due to better treatment of their heart failure
- Key is to maintain Bi-V pacing while in AF
  - AV nodal blockers (beta-blockers or digoxin)
  - AV nodal ablation in patients who have failed medical therapy and are not candidates for AF ablation
- We aggressively maintain sinus rhythm in our heart failure patients

Case 5

- 62 year old man with end-stage heart failure (EF 10%) on the heart transplant list
- He has non-ischemic heart failure with no history of VT and a narrow QRS
- He is hospitalized for an episode of unexplained syncope
- Based on his blood type, there will likely be a 2-3 year wait for a donor heart
- The referring cardiologist is concerned that he may die suddenly before transplantation and refers the patient for ICD implantation…



Option A is very reasonable as it would help to improve his survival to cardiac transplantation. Given his expected 2-3 year wait on the transplant list an ICD would be very reasonable.

Option B was felt by many to be a reasonable approach until several recent studies showed that patients with a narrow QRS and mechanical evidence of LV dyssynchrony did not benefit from CRT therapy.

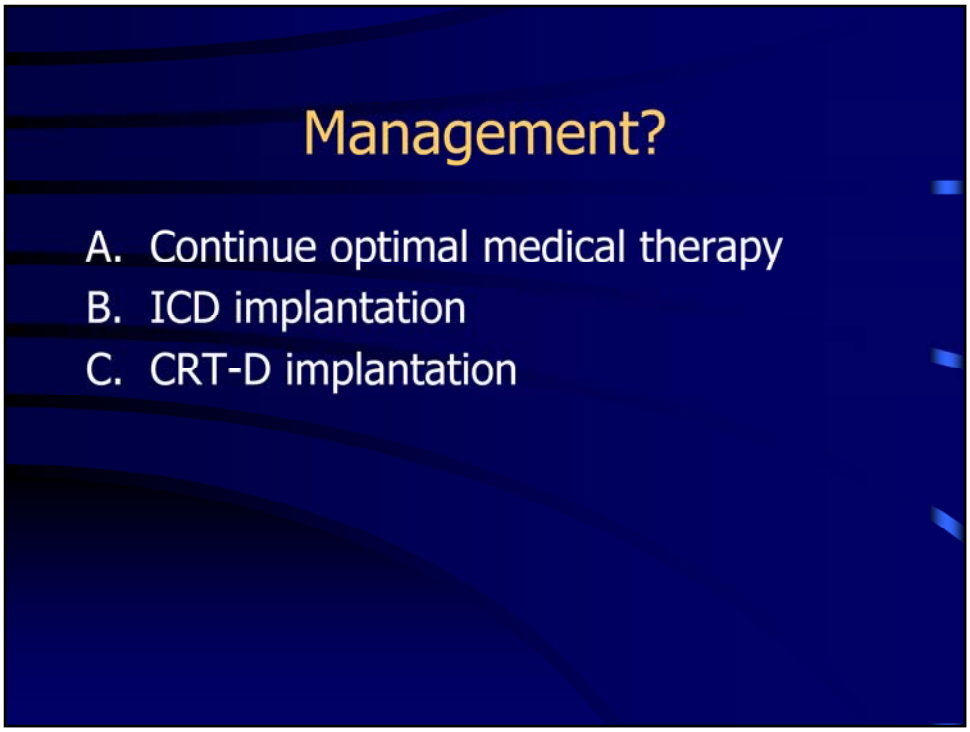
The recently presented PROSPECT and RETHINQ Trials showed that CRT did not benefit heart failure patients with a narrow QRS and mechanical LV dyssynchrony. Thus, based on these 2 large multi-center clinical trials we no longer implant CRT devices in patients with narrow QRS complexes and echo evidence of mechanical dyssynchrony.

Outcome?

- LV dyssynchrony present on echo
- At the time, CRT-D was not yet approved in the U.S. and so an ICD was implanted
- 8 days after ICD implantation he had had a successful shock for VF
- He had 2 more episodes of VF with syncope that were successfully defibrillated by his ICD
- He had worsening heart failure and a left ventricular assist device (LVAD) was placed as a bridge to transplantation
- After 1 year with an LVAD he underwent cardiac transplantation (he had no further shocks after the LVAD was placed)

Case 6

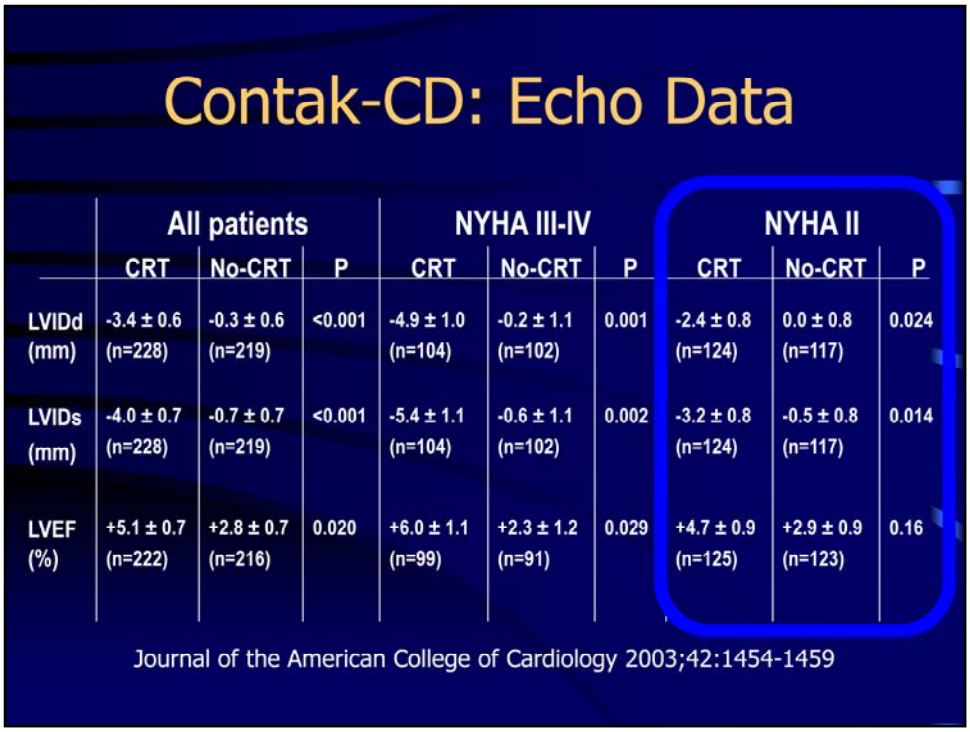
- 61 year old man with a prior myocardial infarction 5 years ago
- On optimal medical therapy
- Left ventricular ejection of 35%
- Left bundle branch block with a QRS width of 145 msec
- NYHA class I heart failure (asymptomatic)
- No history of ventricular arrhythmias or syncope



Option A would be very reasonable given that he does not meet current ICD guidelines given his EF of 35% and only NYHA class I heart failure. The SCD-HeFT trial showed a benefit for patients with an EF of 35% or less and at least NYHA class II heart failure.

Option B: See explanation for option A above

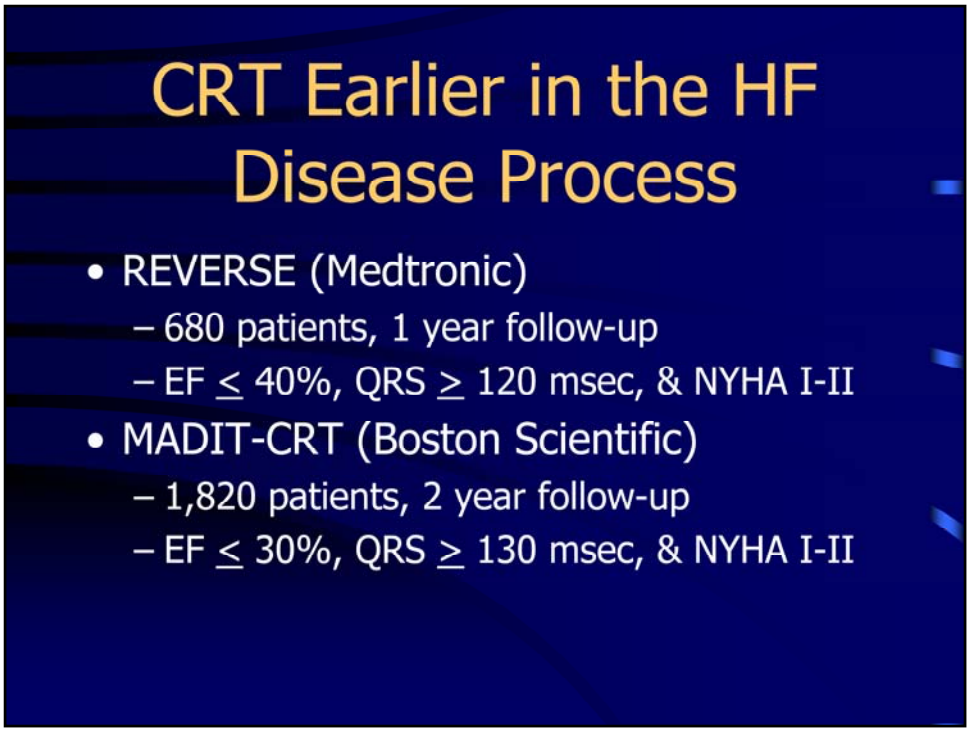
Option C: While the patient does have a wide QRS with a LBBB, he is only NYHA class I heart failure. Current indications for CRT therapy include at least class III NYHA status.



The Contak-CD trial showed a modest benefit of CRT in NYHA II patients although the benefit was not as great as was seen in class III and IV patients.

Outcome

- He was enrolled in the REVERSE Trial which is evaluating the role of CRT in patients with an EF $\leq$ 40%, QRS $\geq$ 120 msec, and NYHA class I or II heart failure



There are 2 ongoing trials evaluating the role of CRT in NYHA class I and II patients.