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Biventricular Pacing and Non-responders

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Introduction

- Pharmacologic therapy for HF, based principally on inhibition of the renin-angiotensin-aldosterone system and β-blockade, has dramatically improved the outcomes of patients with systolic HF.
- Despite widespread implementation of GDMT, the prognosis of patients with HF remains poor.
- ***Cardiac Resynchronization Therapy*** (CRT) has proved to be one of the most important breakthroughs in the treatment of HF.

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Response & Outcomes Studied in CRT Trials

Measure	*Endpoints*
Functional status	Quality of life (QOL) 6-minute walk distance Cardiopulmonary exercise test
Heart failure progression	Left ventricular ejection fraction (LVEF), ventricular volume Mitral valve regurgitation Serum catecholamines, brain natriuretic peptide Heart rate variability
Heart failure outcome	Hospitalization Mortality

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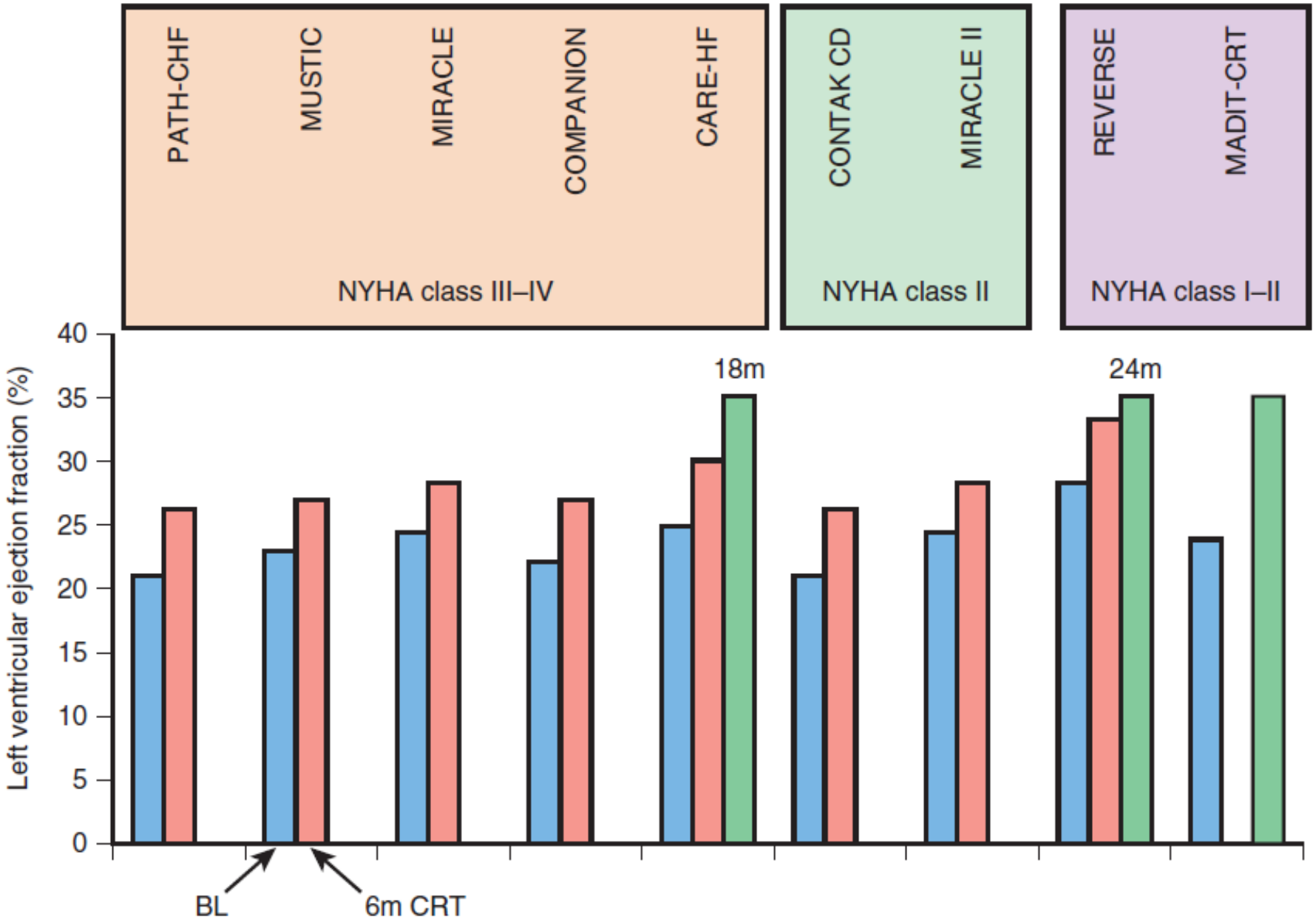
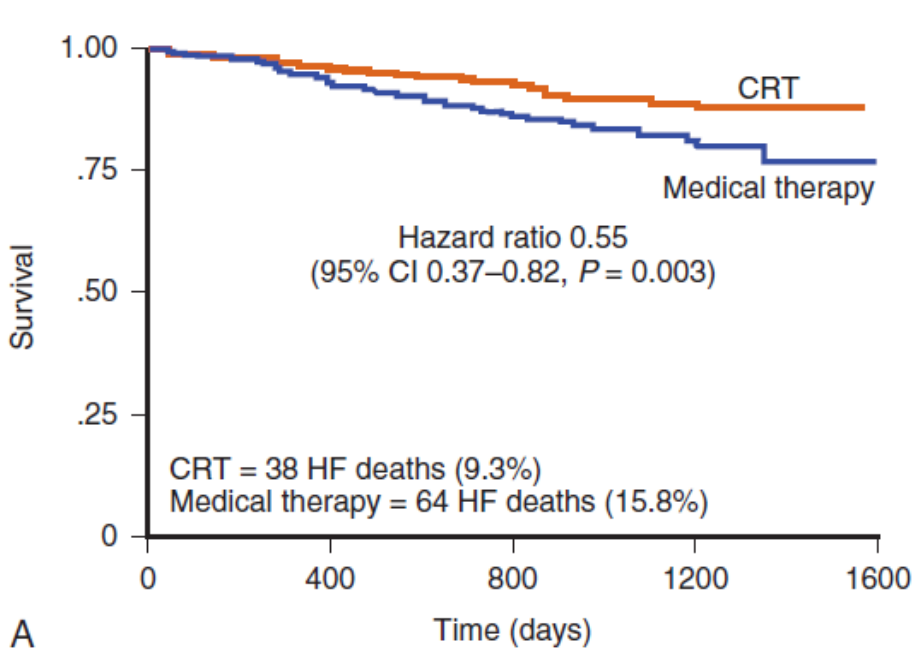
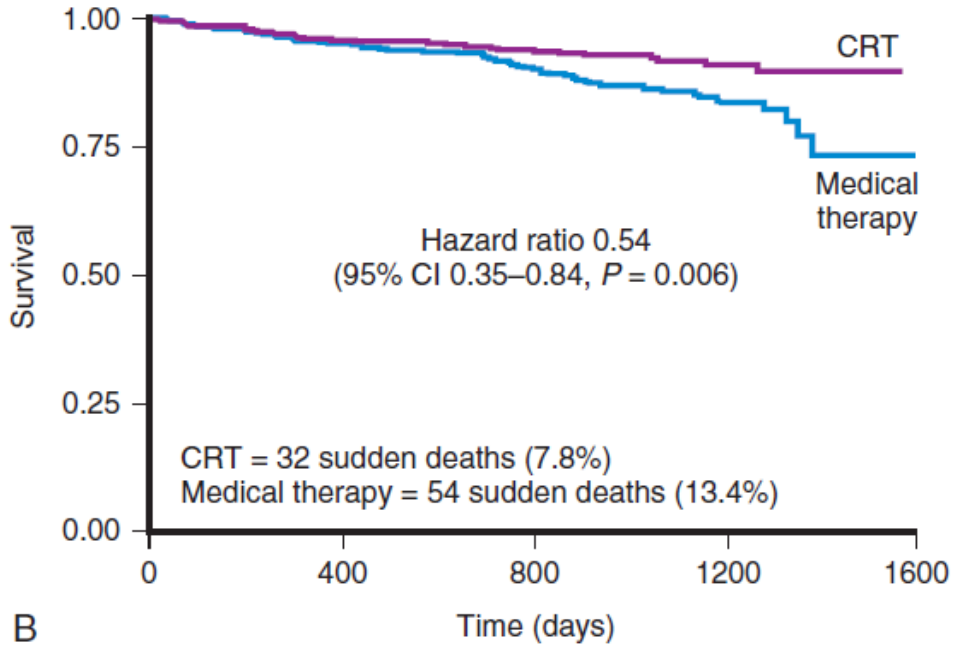

PATH-CHF
MUSTIC
MIRACLE
COMPANION
CARE-HF
NYHA class III–IV
CONTAK CD
MIRACLE II
NYHA class II
REVERSE
MADIT-CRT
NYHA class I–II
Left ventricular ejection fraction (%)
40
35
30
25
20
15
10
5
0
18m
24m
BL
6m CRT

CARE HF Trial





Cleveland JGF, Daubert JC, Erdmann E, et al: Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 27:1928-1932, 2006.

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Who is a Responder to CRT?

- Fornwalt et al demonstrated that in the PROSPECT study that the response rate ranged from 32% to 91% based on 15 different response criteria used in many CRT clinical studies.
- The criteria include changes in:
  - Various echocardiographic parameter changes, such as volumes, EF, and stroke volume.
  - Changes in clinical parameters, such as NYHA classification, 6-minute walk distance and QOL.
  - A combination of changes in echocardiographic and clinical measures.

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What is the importance of CRT response?

- Non-responders are exposed to the detrimental effects of HF
  - Their projected survival is poor .
  - They also have more frequent hospitalizations.
  - They also have poor QOL.

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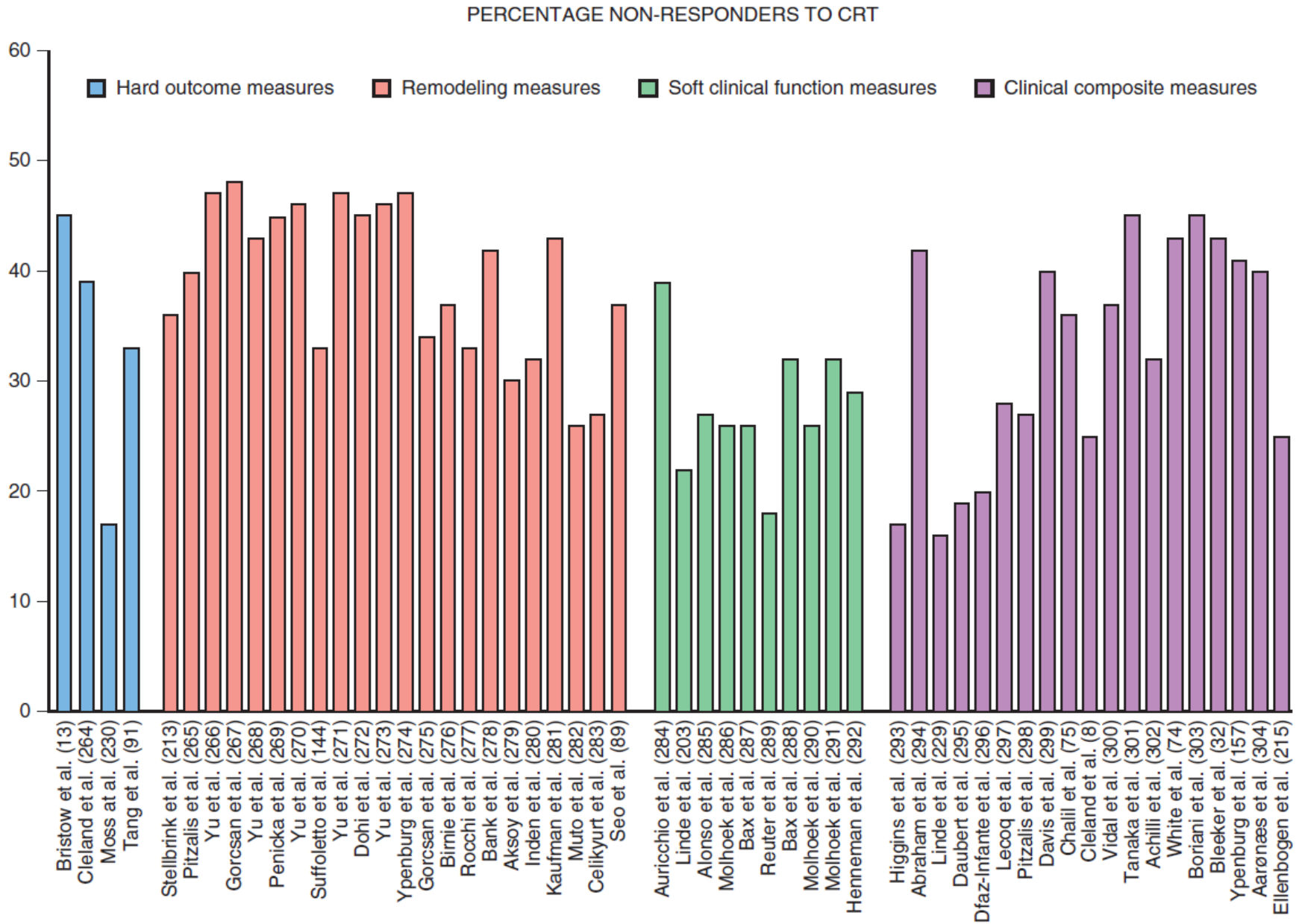

From Daubert JC, Saxon L, Adamson PA, et al: 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace* 14:1236-1286, 2012

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Non-responders and Outcomes

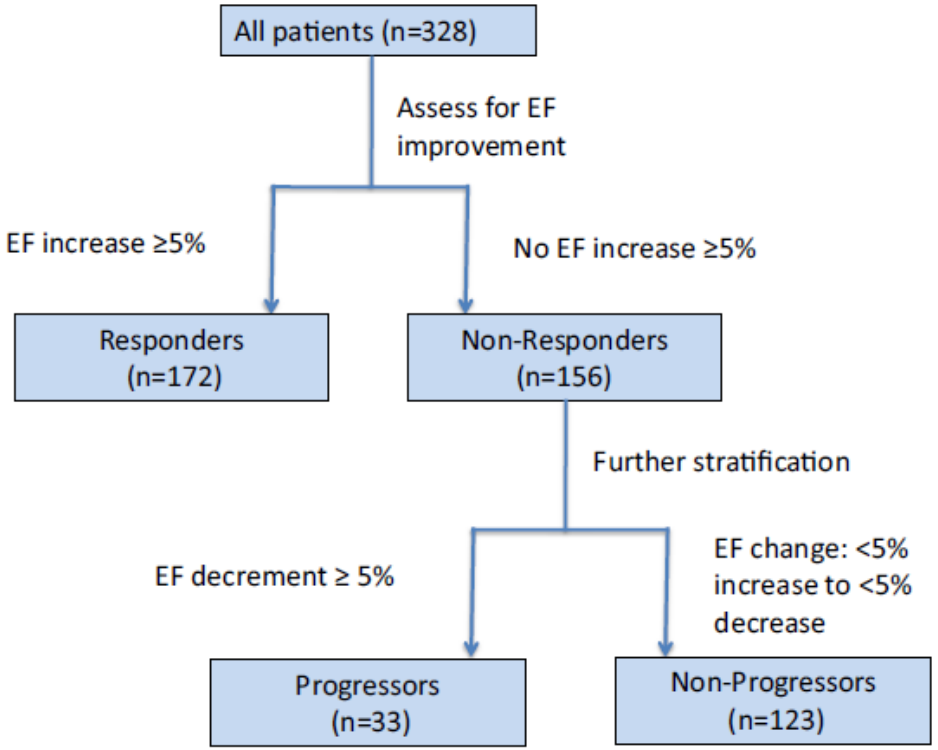

Table 3 Baseline predictors of progressive worsening of ventricular function despite cardiac resynchronization therapy

Variable	Odds ratio	95% CI	*P*
Univariate analysis			
Hypertension	2.9	1.0–8.6	.0498
Valve surgery	2.8	1.3–6.1	.01
EF	1.07	1.02–1.13	.01
Aldosterone antagonist	0.24	0.08–0.69	.008
LBBB	0.52	0.24–1.13	.099
QRS duration	0.99	0.97–1.00	.06
Previous VT/VF	1.93	0.89–4.21	.097
Chronic AF	1.98	0.94–4.17	.07
Multivariate analysis[*]			
Aldosterone antagonist	0.23	0.08–0.67	.008
Valve surgery	3.3	1.4–7.7	.005
QRS duration	0.98	0.967–0.996	.02

Friedman et al; Heart Rhythm 2014;11:1991–1998

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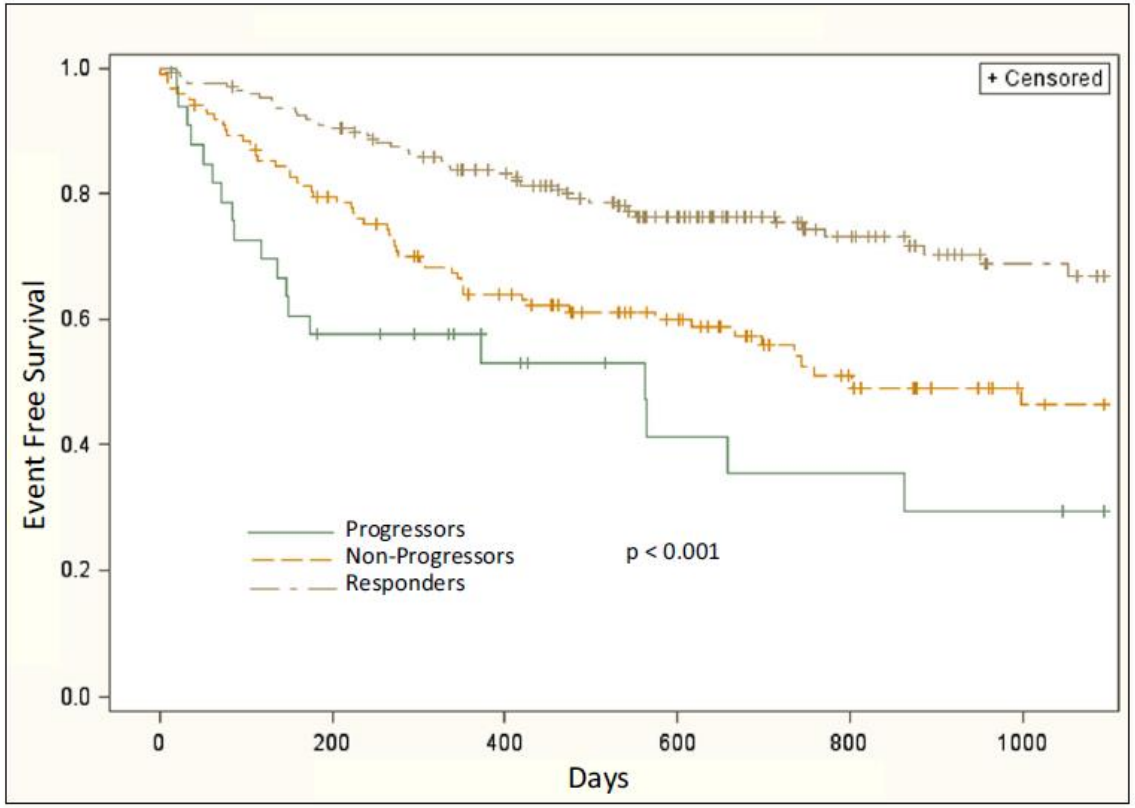

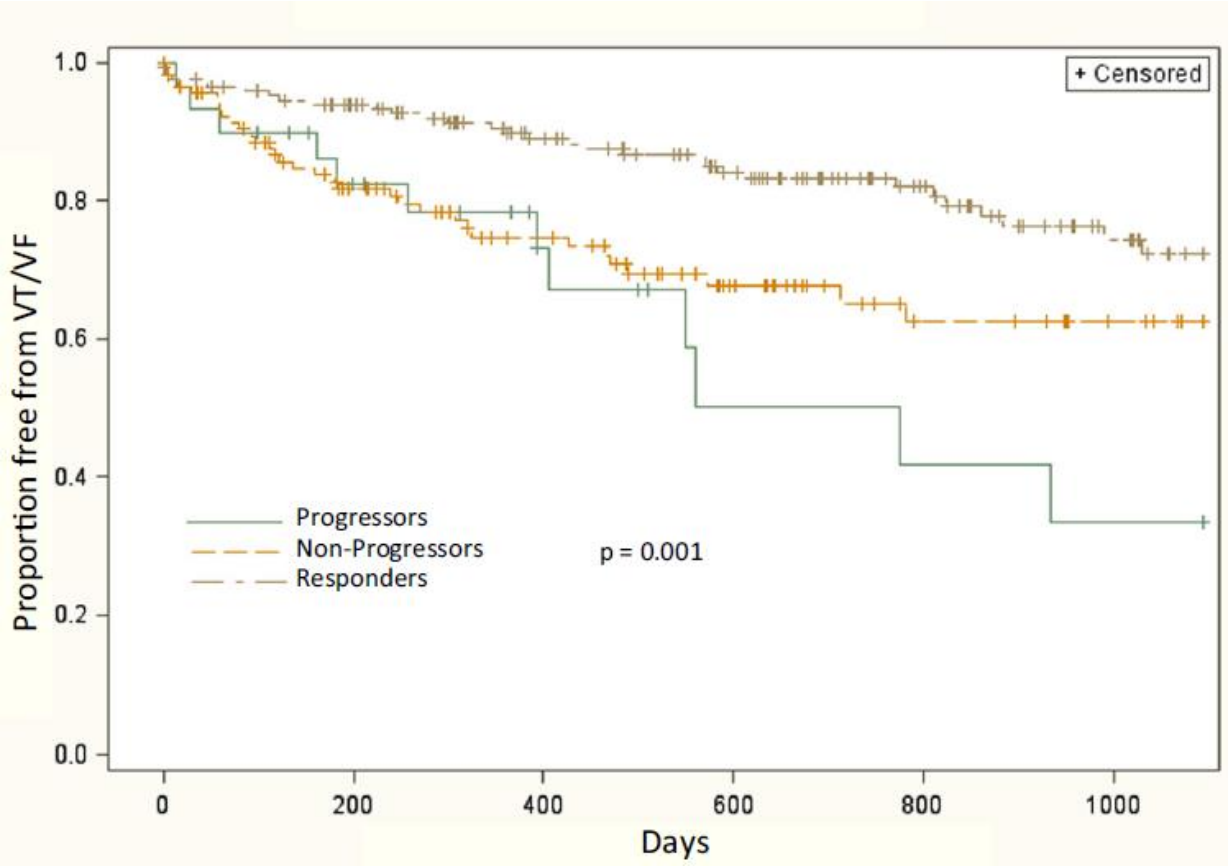

Friedman et al; Heart Rhythm 2014;11:1991–1998

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How do we approach CRT Non-responders?

- A systematic approach and a multidisciplinary approach are important to help the patient
- This requires collaboration between Electrophysiology and Heart failure specialists.
  - Is the patient BIV pacing? If so, is there enough fusion?
  - Does the patient have arrhythmias?
  - Is the patient compliant with medications?
  - Is the patient on optimal GDMT?
  - Treat comorbidities (COPD, OSA…)
  - Echocardiographic guided optimization for AV and VV timing .

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Is the Patient BIV pacing?

- Check the ECG.
- Check CXR.
- Optimize AV and VV timing electrically to have the optimal response.
- Avoid anodal capture.

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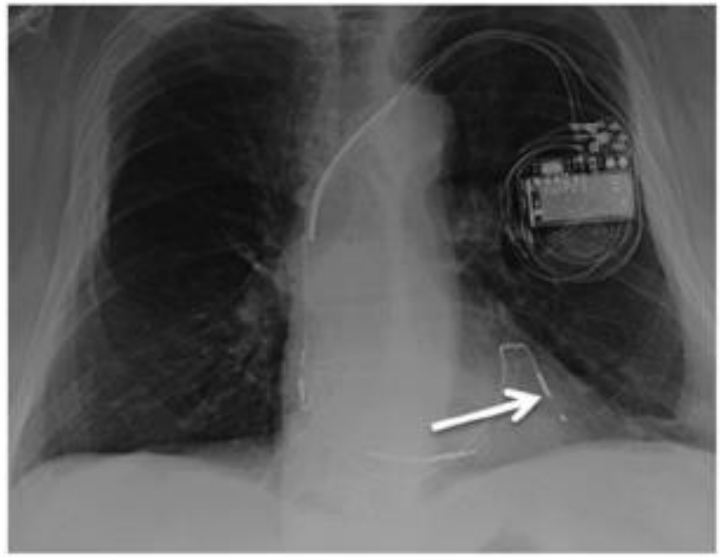
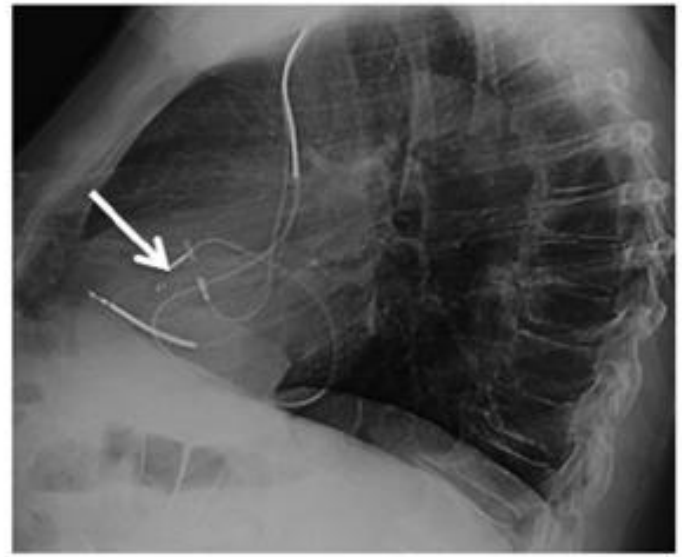
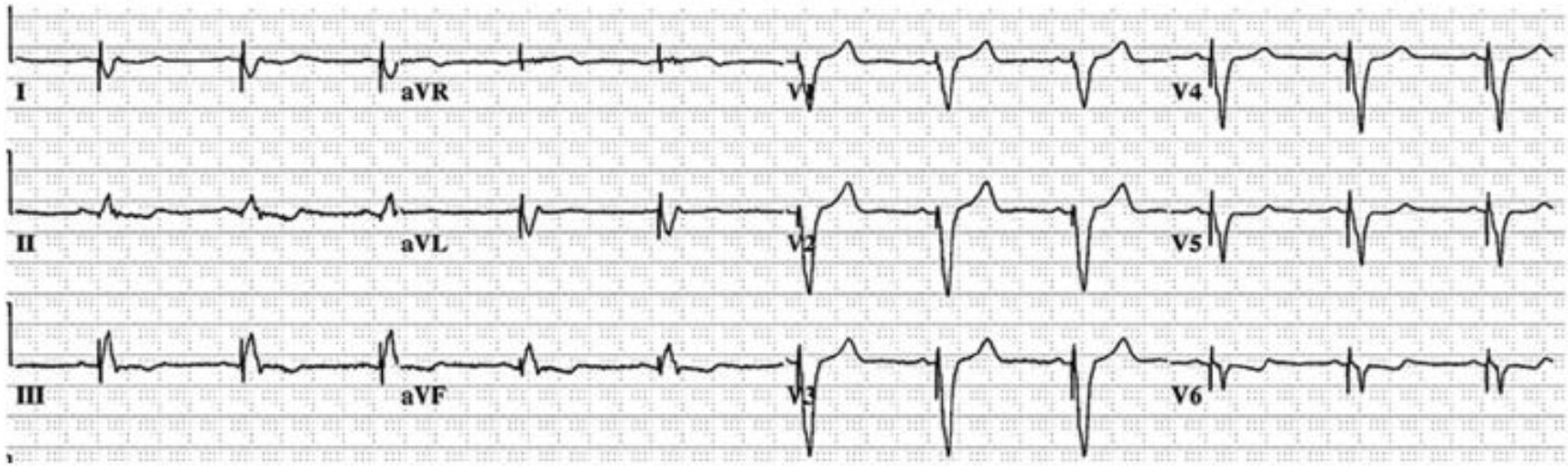
Anterior Interventricular Vein







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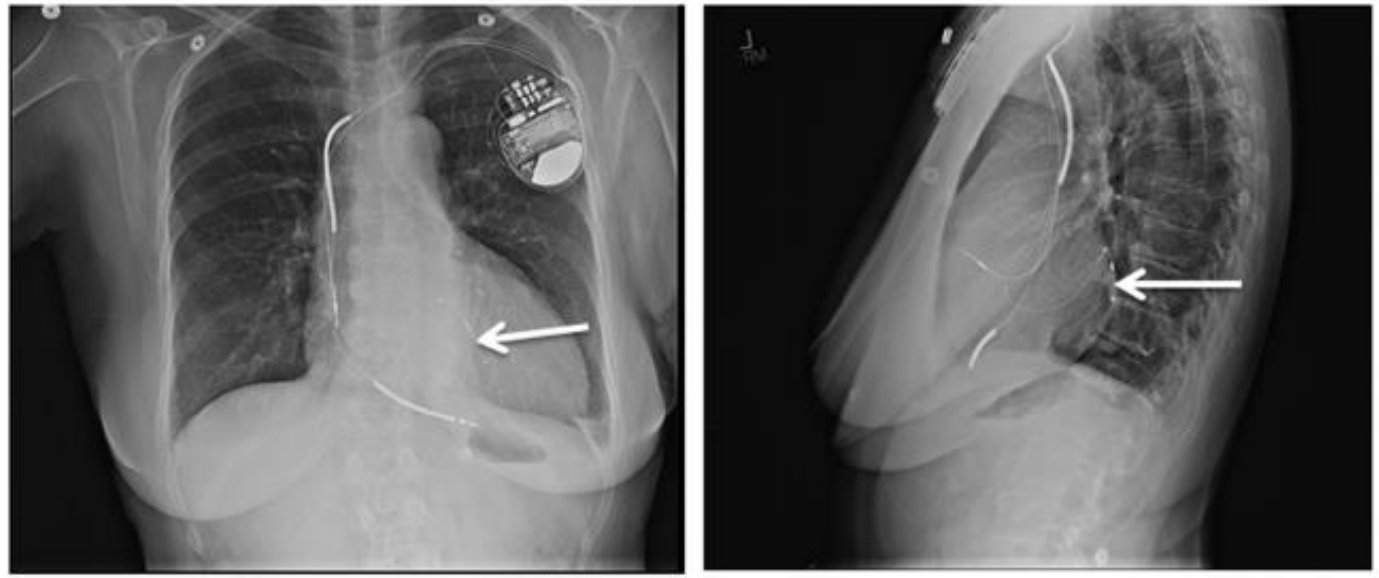
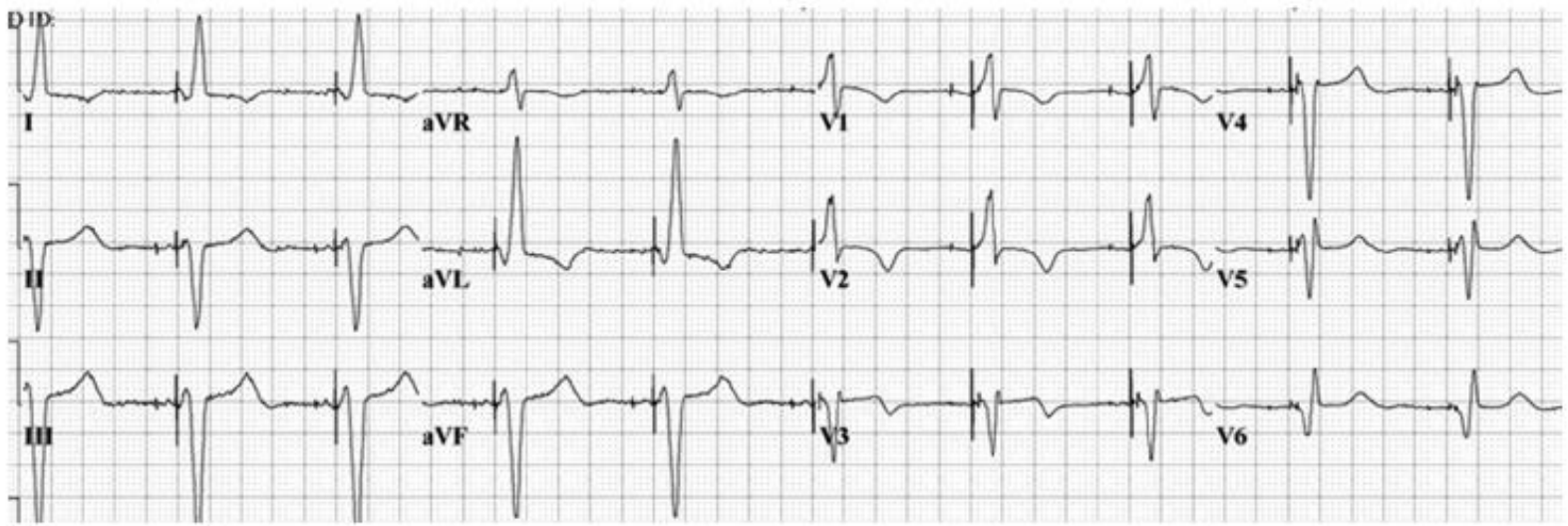
D Posterolateral coronary sinus branch





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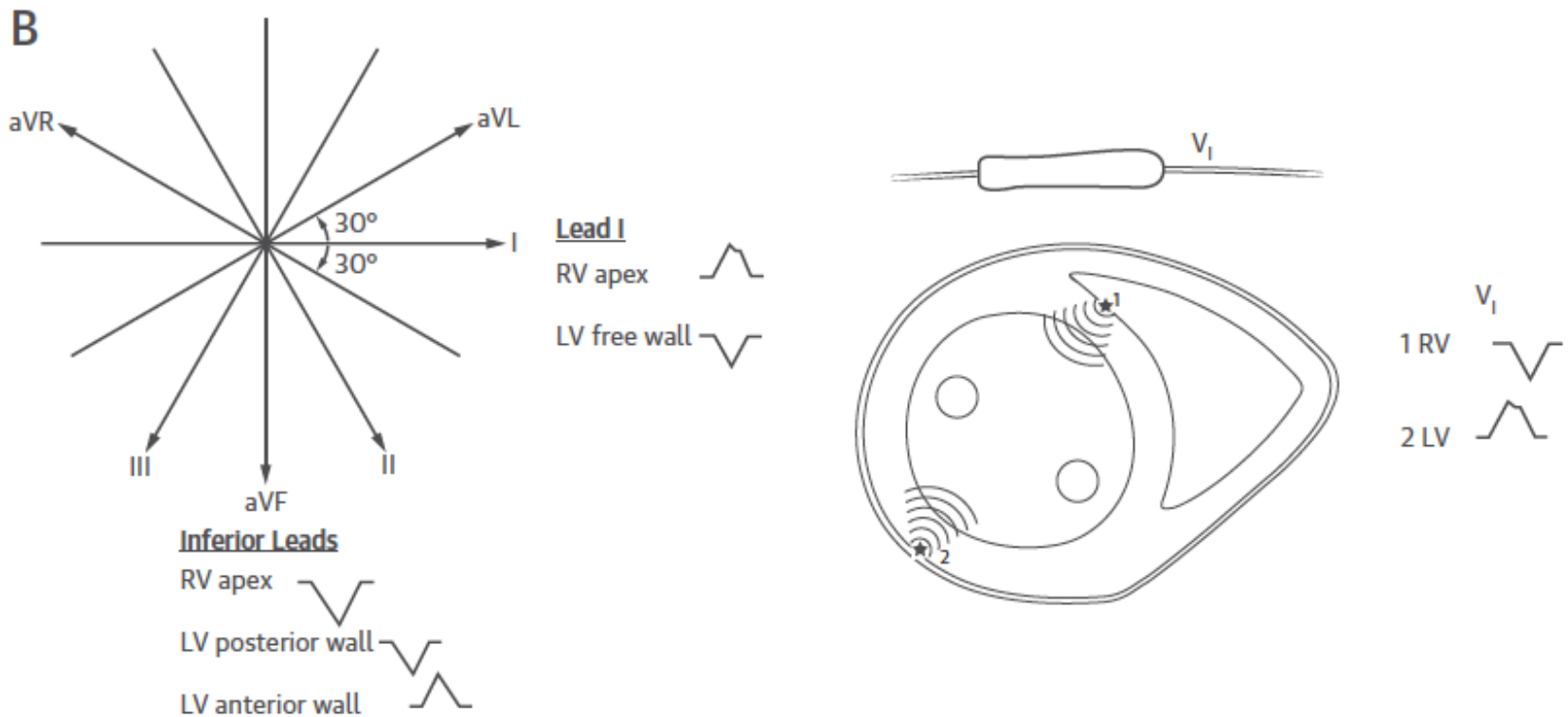
B
aVR
aVL
I
30°
30°
III
II
aVF
Inferior Leads
RV apex
LV posterior wall
LV anterior wall
Lead I
RV apex
LV free wall
V1
1
2
V1
1 RV
2 LV

Optimizing VV Timing: Simultaneous

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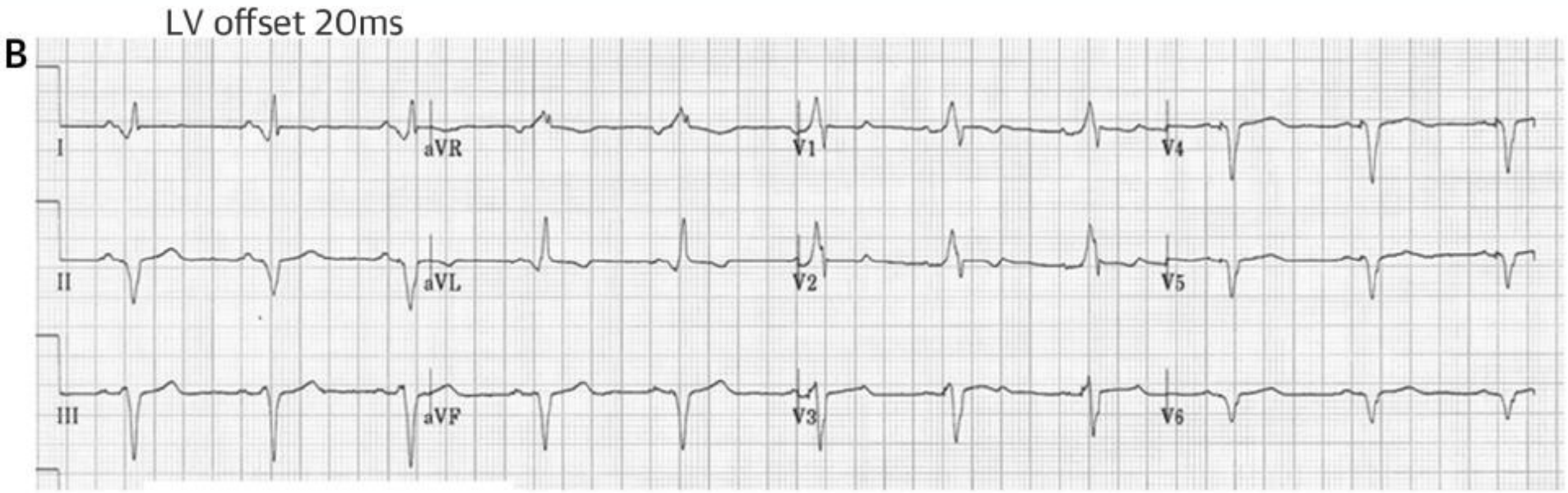
LV earlier by 20 msec



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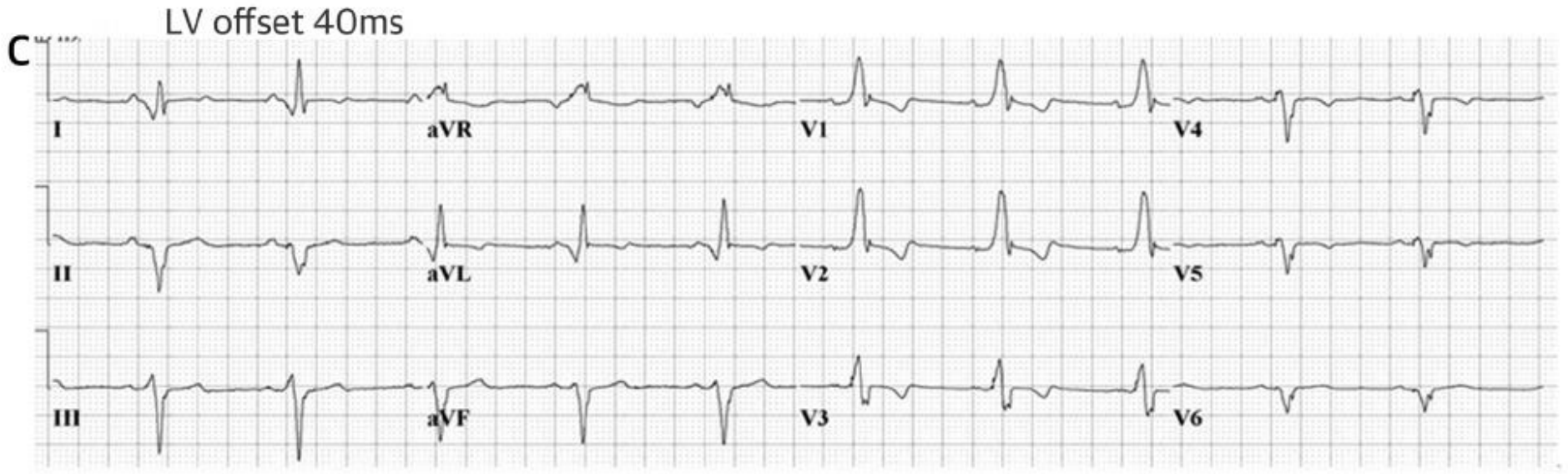
LV earlier by 40 msec



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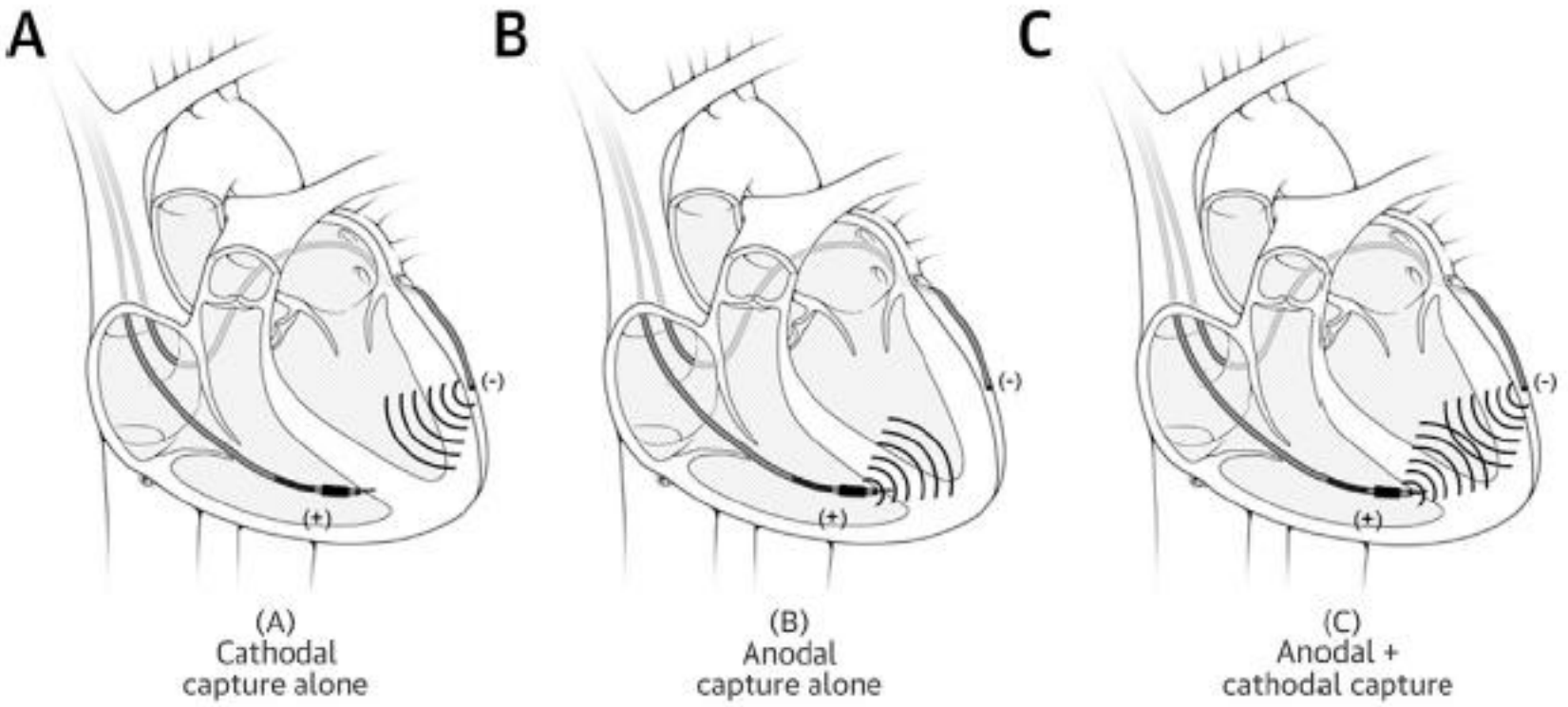
Anodal Capture



(A)
Cathodal
capture alone

(B)
Anodal
capture alone

(C)
Anodal +
cathodal capture

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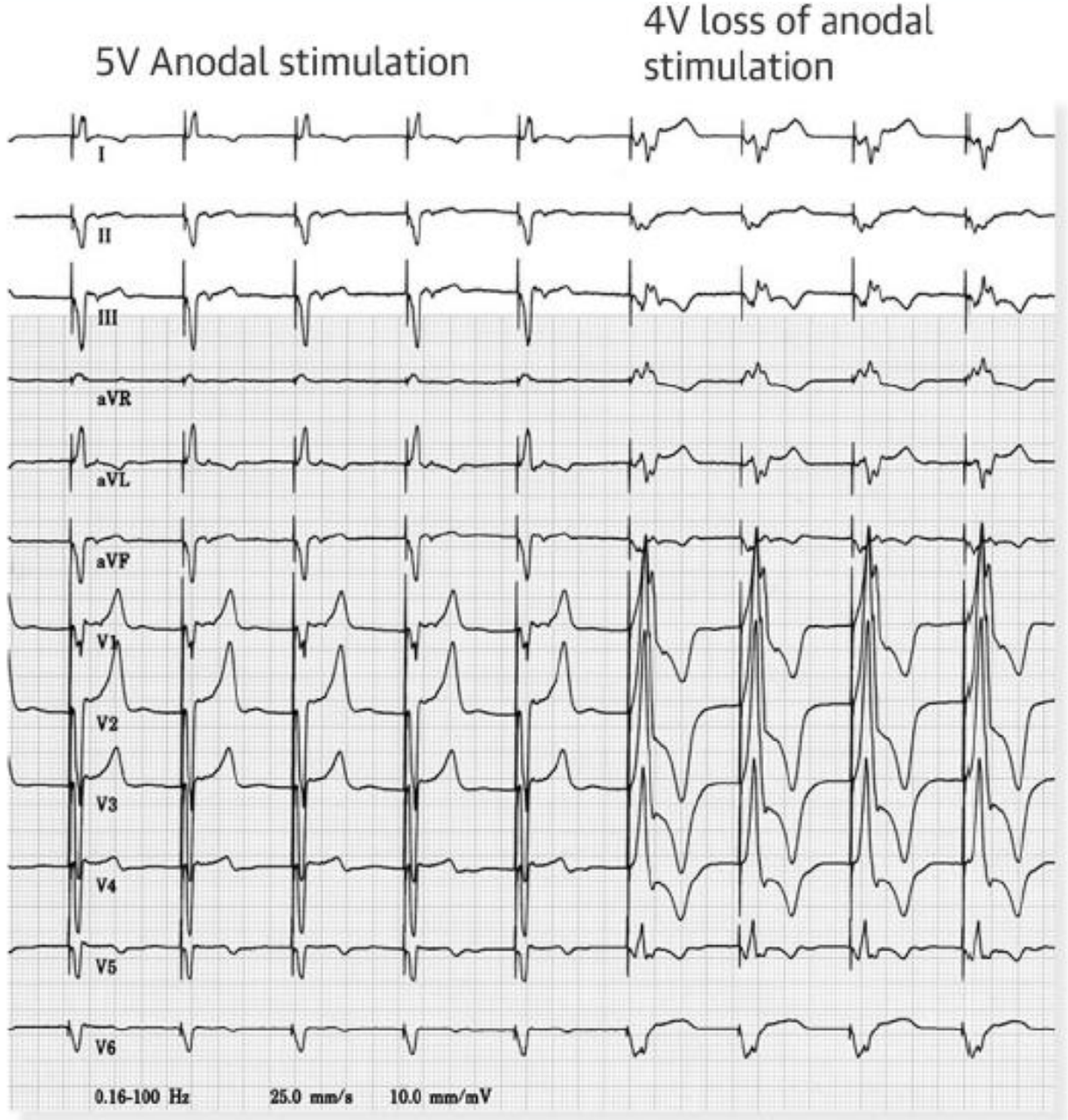
D



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Does the Patient have any arrythmias?

- BIV pacing < 95% of the time leads to reduces survival.
- This could be from high thresholds: check CXR and confirm LV capture by ECG too.
- AF has detrimental effects even in patients who previously responded to CRT.
- PVCs can lead to loss of BIV pacing. Treat them aggressively.

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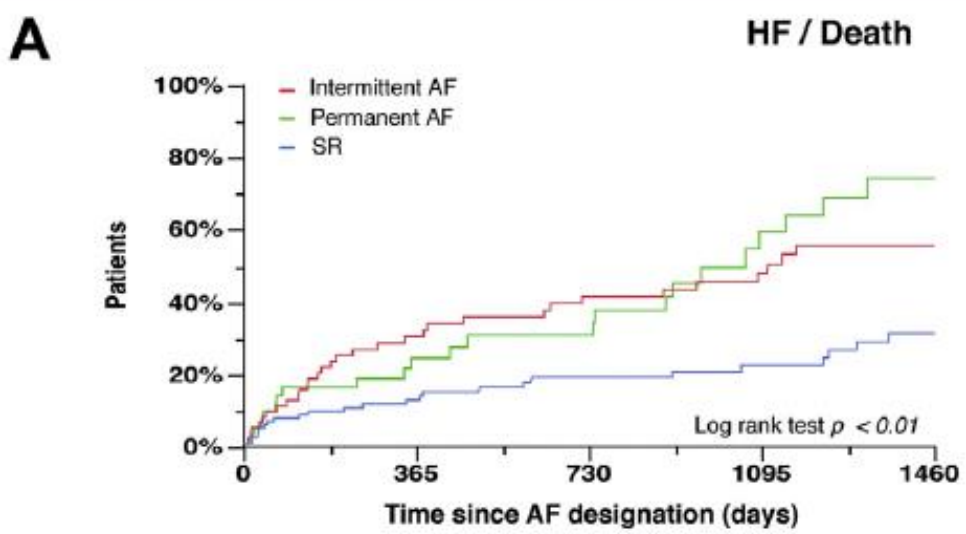
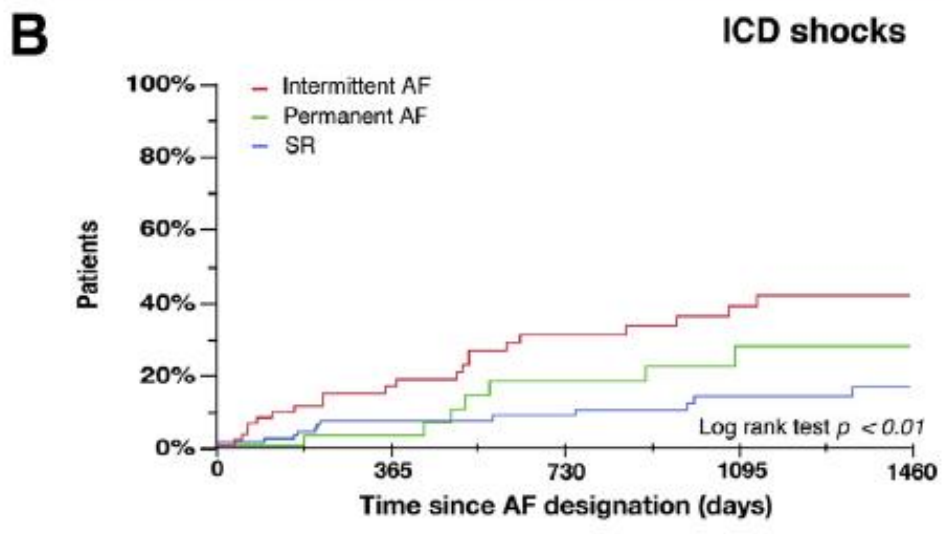
AF and HF Hospitalizations



Patients at risk

SR	113	82	59	44	25
Intermittent AF	67	42	34	25	13
Permanent AF	47	31	21	10	3



Patients at risk

SR	113	84	62	44	27
Intermittent AF	67	46	32	24	16
Permanent AF	47	32	22	15	5

Nakajima, et al J Am Coll Cardiol EP 2018;4:1227–34)

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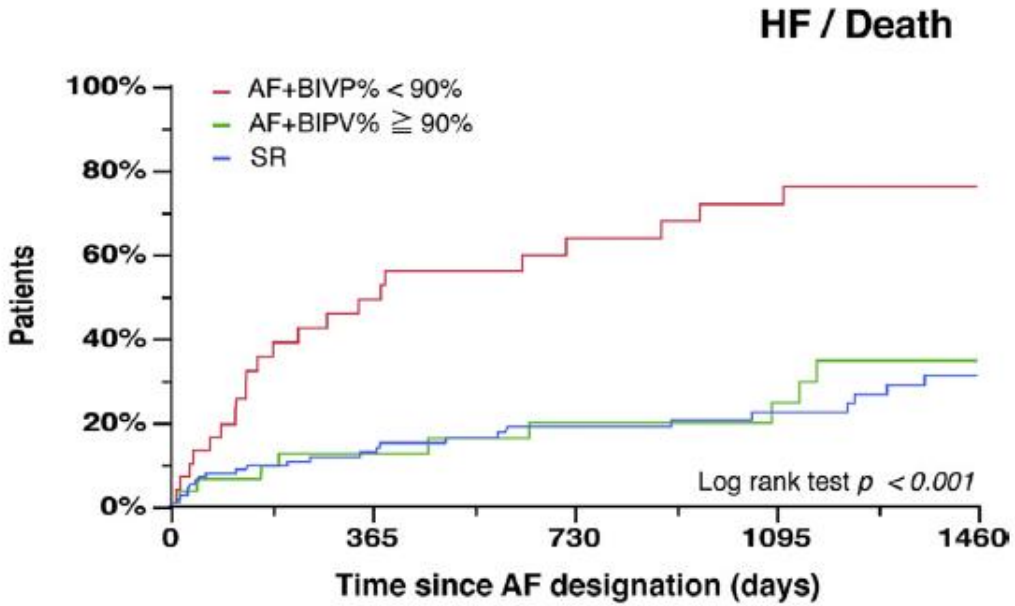
AF-percentage BIV Pacing and Outcomes



Patients at risk

SR	113	82	59	44	25
AF+BIVP% ≧ 90%	35	26	23	18	8
AF+BIVP% < 90%	32	17	12	8	5

Nakajima, et al J Am Coll Cardiol EP 2018;4:1227–34)

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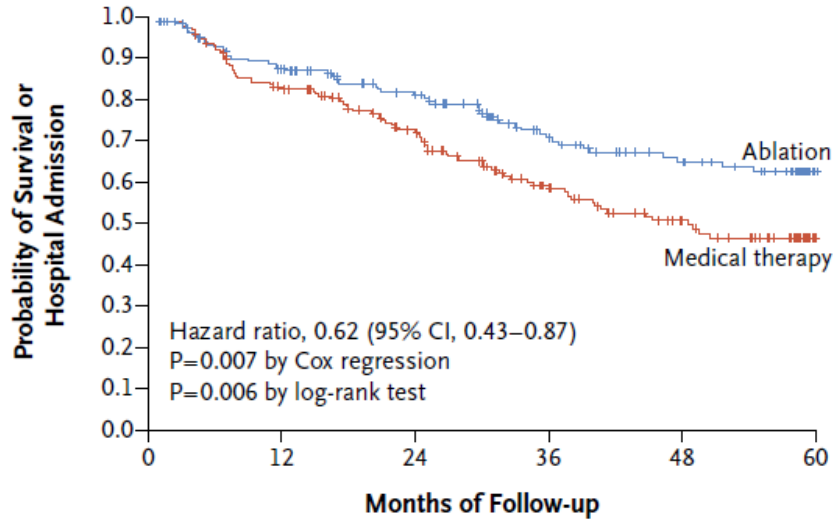
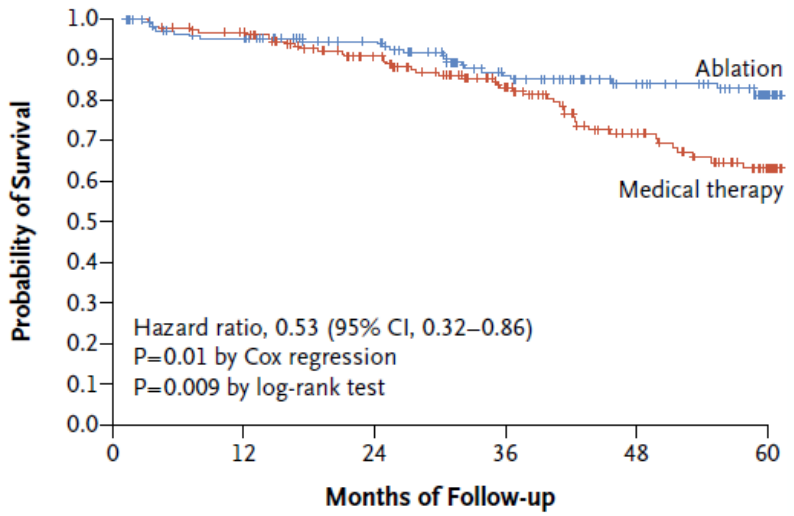
AF Ablation vs AAD for HF Patients

A Death or Hospitalization for Worsening Heart Failure



No. at Risk						
Ablation	179	141	114	76	58	22
Medical therapy	184	145	111	70	48	12

B Death from Any Cause



No. at Risk						
Ablation	179	154	130	94	71	27
Medical therapy	184	168	138	97	63	19

CASTLE AF trial. N Engl J Med 2018;378:417-27.

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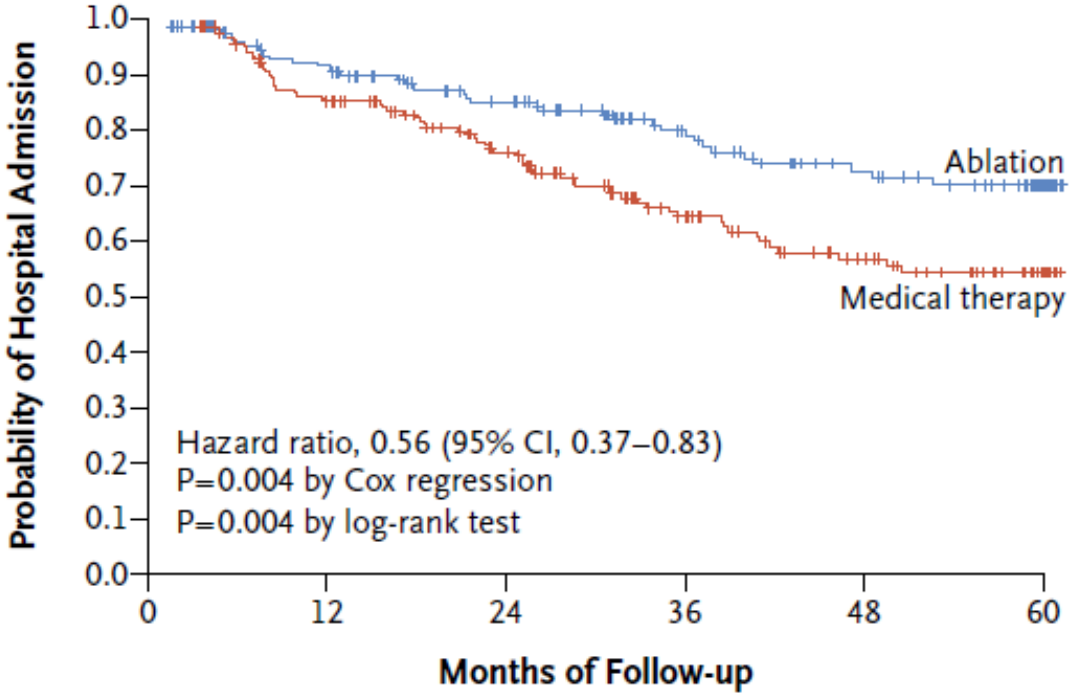
C Hospitalization for Worsening Heart Failure



No. at Risk

Ablation	179	141	114	76	58	22
Medical therapy	184	145	111	70	48	12

CASTLE AF trial. N Engl J Med 2018;378:417-27.

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Treatment of PVCs in Patients with CRT

- Increase β blockers as tolerated.
- Consider increasing LRL.
- Consider AAD.
- Consider Ablation if PVC burden is high and they are unifocal.

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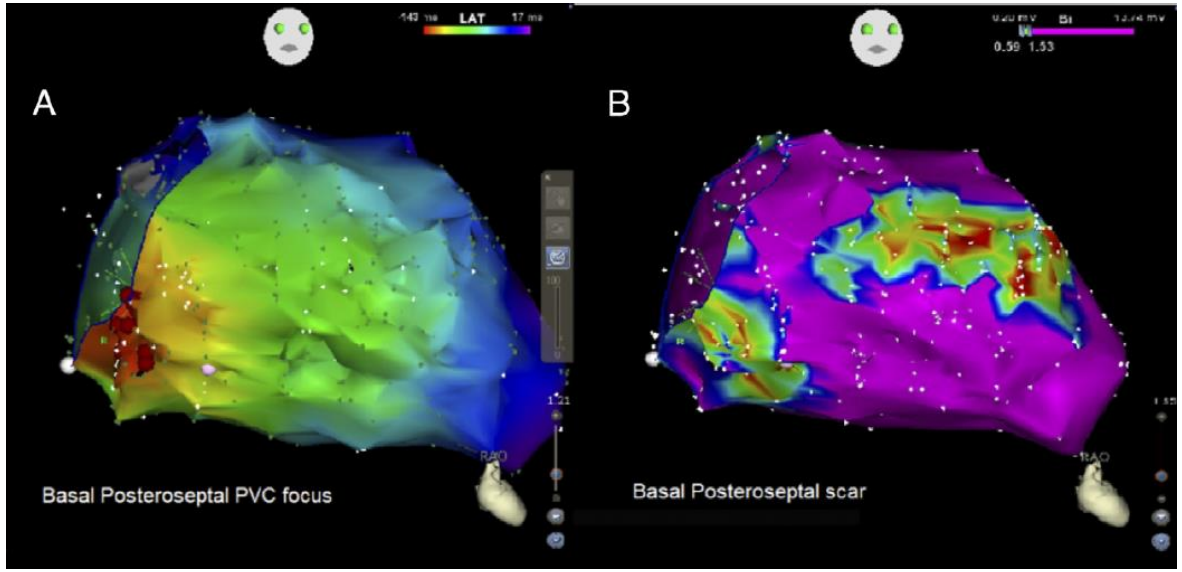
Treatment of PVCs in Patients with CRT

Change in Echo Parameters	Pre-Ablation	Post-Ablation	Mean Improvement	p Value
Δ EF	26.2 ± 5.5	32.7 ± 6.7	6.42 ± 5.26	<0.001
Δ LVEDD	6.83 ± 0.83	6.51 ± 0.91	−0.32 ± 0.26	<0.001
Δ LVESD	5.83 ± 0.55	5.62 ± 0.32	−0.31 ± 0.23	<0.001
Δ LVESV	178 ± 72	145 ± 23	−33.17 ± 22.94	<0.001
Δ LVEDV	242 ± 85	212 ± 63	−30.65 ± 21.63	<0.001

Change in Echo Parameters	Pre-Ablation PVC Ablation		Independent *t* Test p Value
	≤22.0%, n = 33	>22.0%, n = 32	
Δ EF	4.79 ± 7.25	12.66 ± 7.54	<0.001
Δ LVEDD	−0.18 ± 0.18	−0.47 ± 0.24	<0.001
Δ LVESD	−0.17 ± 0.19	−0.46 ± 0.18	<0.001
Δ LVESV	−18.7 ± 15.4	−48.1 ± 19.8	<0.001
Δ LVEDV	−16.0 ± 17.8	−45.8 ± 13.2	<0.001
Δ NYHA class	−1.00 (−1.00, 0.00)	−1.0 (−1.00, 0.00)	0.525*



Lakkireddy et al; J Am Coll Cardiol 2012;60:1531–9)

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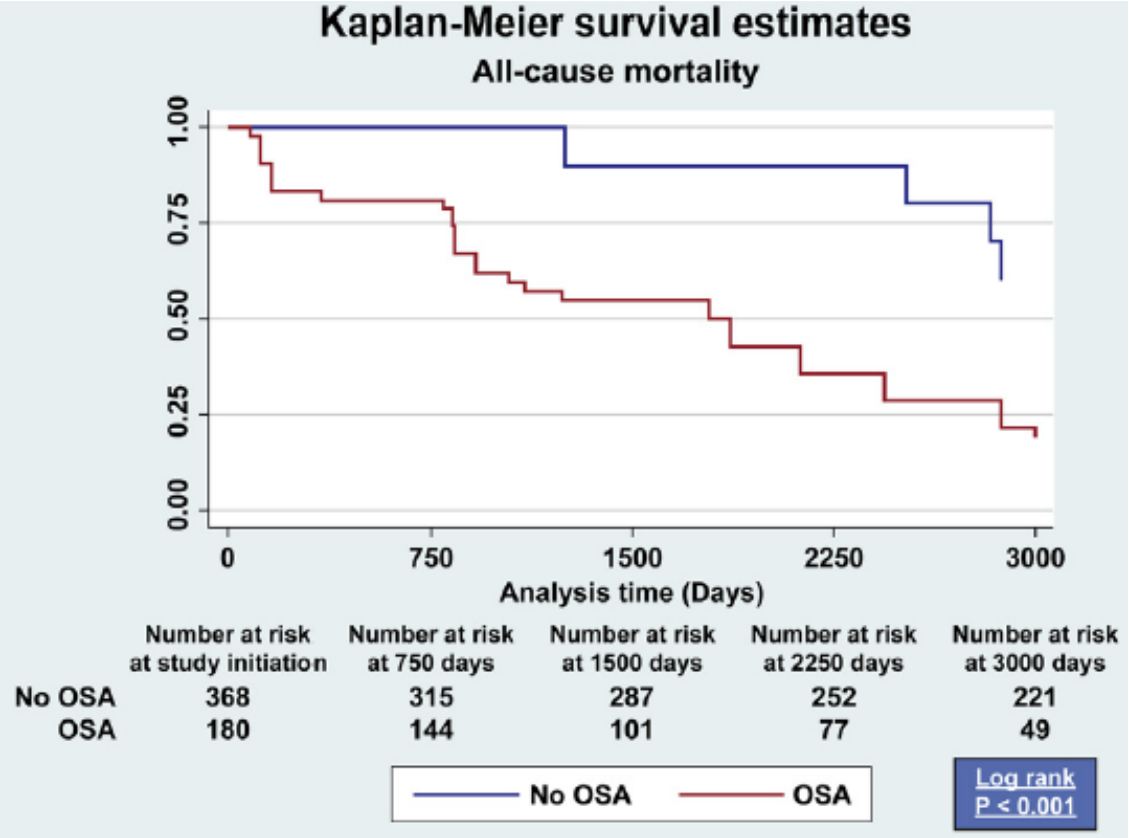
CRT and OSA

- Obstructive sleep apnea (OSA) is prevalent in 35% of patients with HF.
- After effective CRT, patients with OSA improved their EF, improved cardiac output, and subsequently improved their AHI.
- It was inferred that an improvement in cardiac output resulted in better perfusion and a reduction in circulation time.
  - These hemodynamic improvements result in synonymous perfusion to the ventilator chest muscles and the ventilator centers in the brain.

Stanchina et al The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: a pilot study. Chest 2007; 132:433–439.

Treatment of Obstructive Sleep Apnea

Variable	Hazard ratio (95% confidence interval); *P*
Hazard ratio of the chance of improvement in ejection fraction	
Unadjusted analysis	0.71 (0.60–0.89); $P < .001$
Adjusted analysis	0.72 (0.63–0.91); $P < .001$
Restricted to CPAP-compliant patients in the OSA group	0.74 (0.58–0.91); $P = .027$
Nonischemic cardiomyopathy cohort	0.71 (0.53–0.87); $P < .001$
Ischemic cardiomyopathy cohort	0.98 (0.70–3.90); $P = .276$
Hazard ratio of all-cause mortality	
Unadjusted analysis	3.6 (2.5–5.3); $P < .001$
Adjusted analysis	3.7 (2.5–6.8); $P < .001$
Restricted to CPAP-compliant patients in the OSA group	2.1 (1.3–3.9); $P = .001$
Nonischemic cardiomyopathy cohort	4.2 (2.7–6.5); $P < .001$
Ischemic cardiomyopathy cohort	1.2 (0.6–6.3); $P = .752$



Shantha et al, Heart Rhythm 2018;15:1283–1288

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- Although the programming of the AV and VV intervals of CRT devices appears to be an important factor in determining the CRT response.
- Recent multicenter trials (FREEDOM, SMART-AV) failed to provide support for the idea that either echocardiographic or algorithm-based optimization is of long-term benefit compared with using default settings .

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Multi-disciplinary care vs Conventional Care

Table 1 Baseline characteristics

Variable	Multidisciplinary care (n = 254)	Conventional care (n = 173)	P-value
Age (SD)	68 ± 13	69 ± 12	0.41
Male (%)	205 (81)	142 (82)	0.80
QRS (ms)[a]	160.4 ± 29	159.4 ± 28	0.73
NYHA class IV[a] (%)	23 (10)	16 (18)	0.05
HTN (%)	186 (73)	130 (75)	0.73
DM (%)	102 (40)	70 (40)	1.00
Atrial fibrillation (%)	149 (59)	110 (64)	0.32
Ischaemic cardiomyopathy (%)	140 (55)	111 (64)	0.07
CAD (%)	162 (64)	127 (73)	0.045
Post-CABG (%)	124 (49)	107 (62)	0.01
Valve surgery (%)	40 (16)	26 (15)	0.89
Creatinine >2 prior to implant (%)	41 (18)	33 (22)	0.29
Loop diuretics (%)	217 (85)	161 (93)	0.02
Aldosterone antagonist (%)	90 (35)	57 (33)	0.68
Digoxin (%)	92 (36)	100 (58)	<0.0001
Beta-blockers (%)	228 (90)	147 (85)	0.17
ACE inhibitors/AR blockers (%)	209 (82)	136 (79)	0.38
New implant (%)	149 (59)	102 (59)	1.00
Transvenous (%)	237 (93)	160 (93)	1.00
Apical lead location[a] (%)	55 (22)	25 (16)	0.12
Non-lateral lead location[a] (%)	36 (15)	42 (26)	0.004
Baseline ejection fraction (%)[a]	24.2 ± 6.8	22.5 ± 7.2	0.02
Baseline end-systolic diameter[a]	54.9 ± 9.1	54.1 ± 9.1	0.47
Baseline end-diastolic diameter[a]	62.9 ± 8.9	62.0 ± 8.5	0.32

Altman et al; European Heart Journal (2012) 33, 2181–2188

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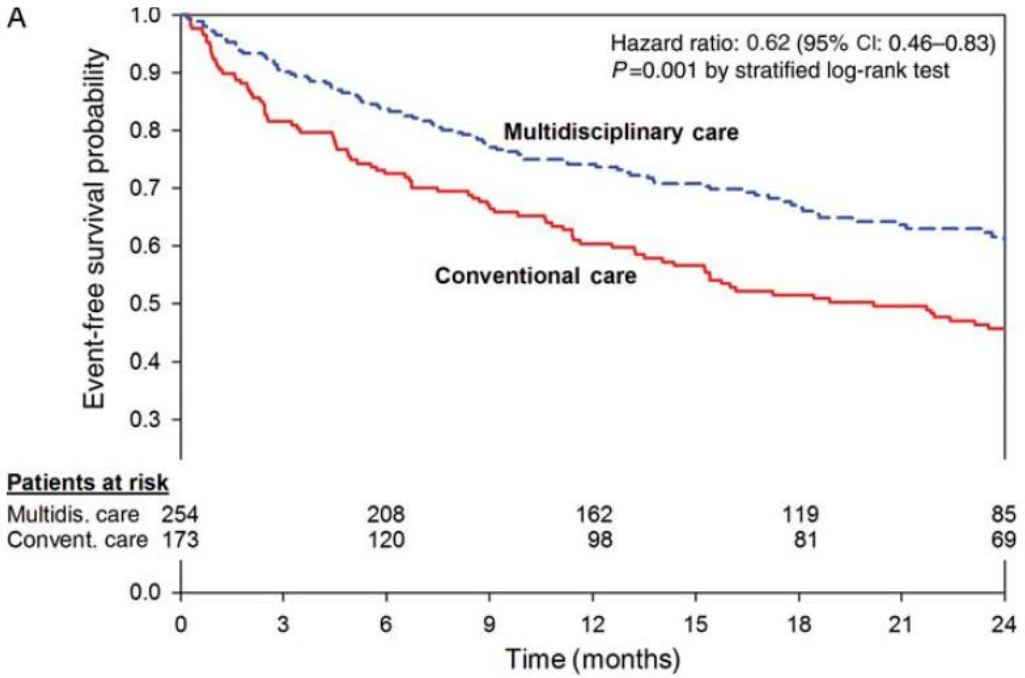
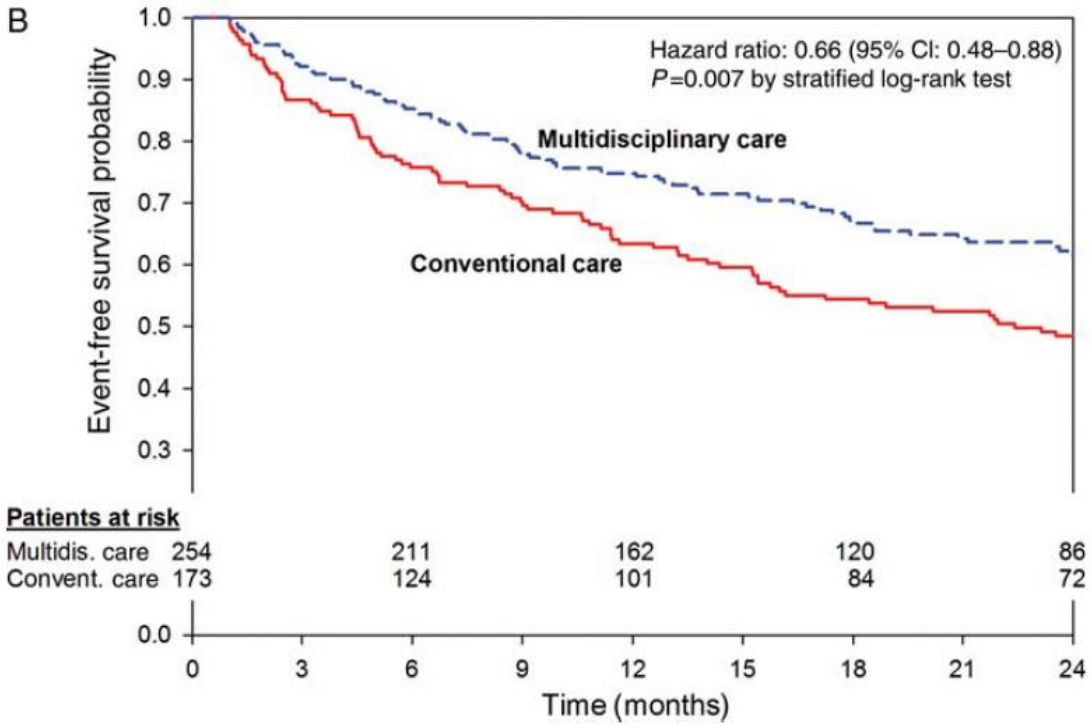
Multi-disciplinary care vs Conventional Care





Altman et al; European Heart Journal (2012) 33, 2181–2188

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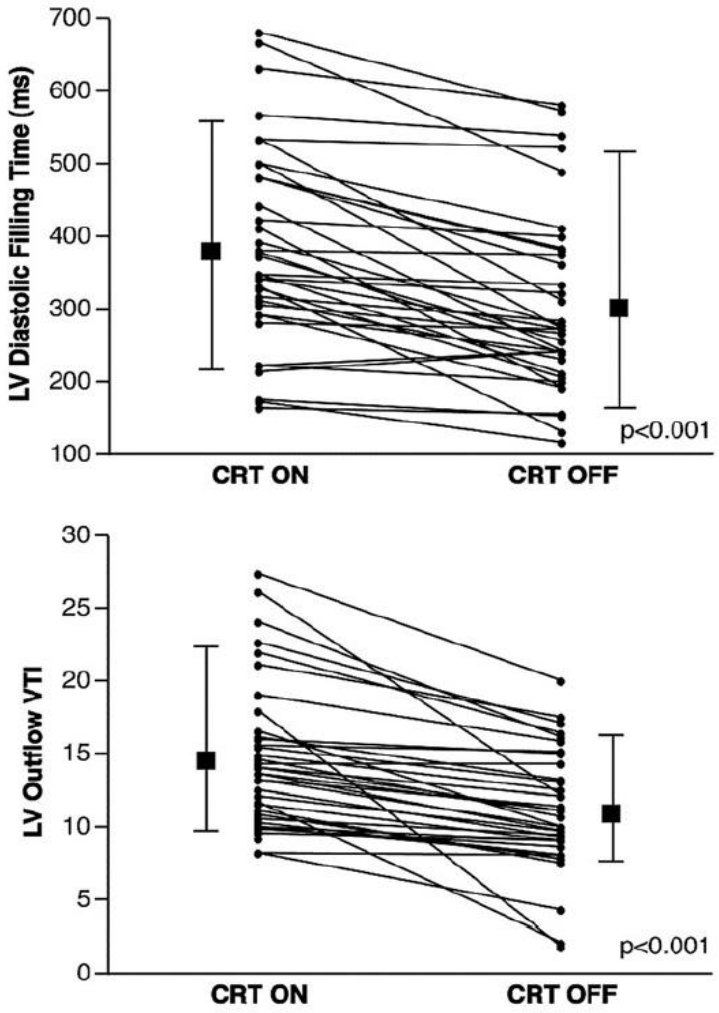
Persistent HD Benefits of CRT Despite Progression

Table 1 Subject Characteristics (n = 40)

Demographics	
Age (yrs)	62 (53–67)
Men (%)	71
Weight (kg)	88 (70–103)
Comorbidities (%)	
Hypertension	68
Hyperlipidemia	71
Diabetes	24
Heart failure etiology (%)	
Idiopathic dilated	60
Ischemic	40
Medications (%)	
ACE inhibitors/ARB	60
Beta-blockers	72
Spironolactone	60
Loop diuretic	92
Digoxin	36
Hydralazine	42
Isosorbide dinitrate	44
Sodium nitroprusside	50
Inotropic drugs	32
Laboratory data	
Hemoglobin (g/dl)	11.6 (10.4–13.6)
Creatinine (mg/dl)	1.4 (1.0–2.2)
B-type natriuretic peptide (pg/ml)	580 (269–1,469)



Willkoff et al. J Am Coll Cardiol 2009;53:600–7)

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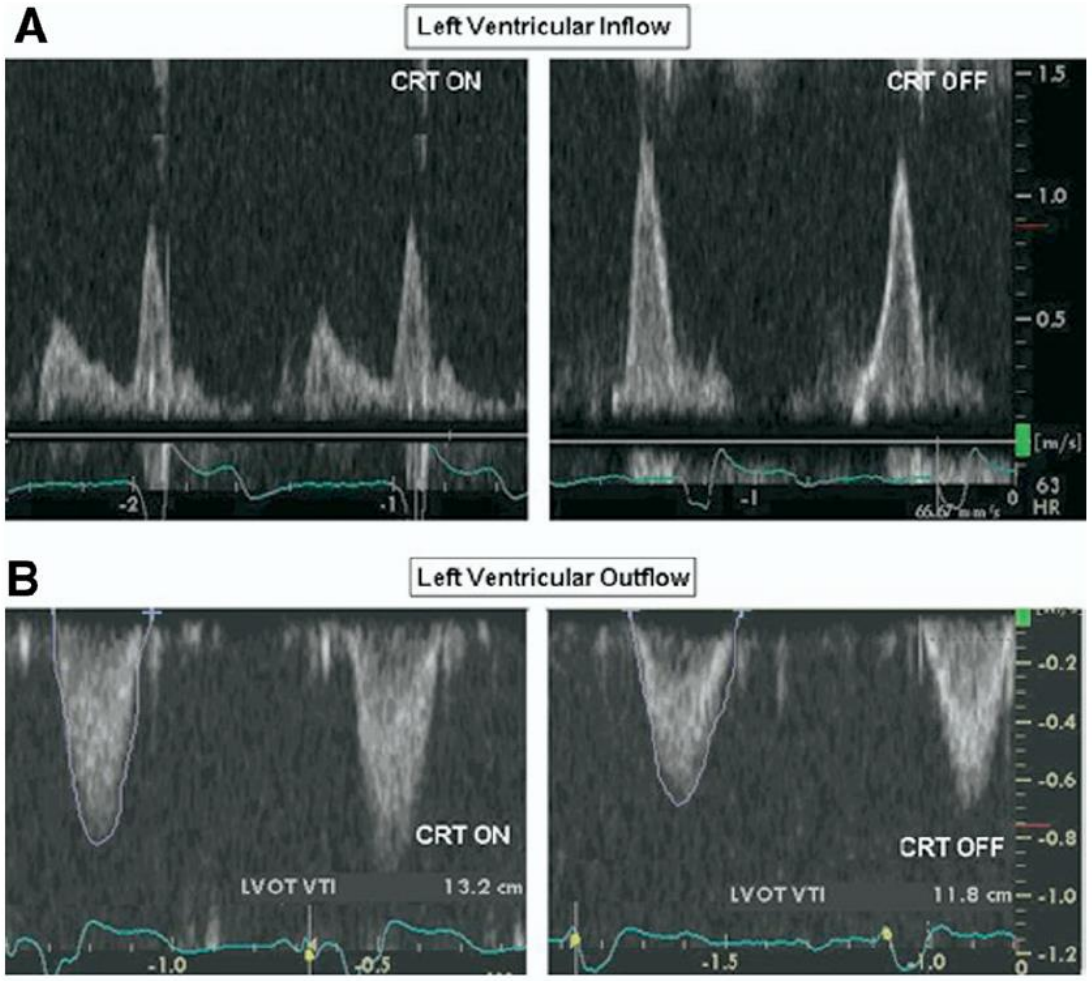

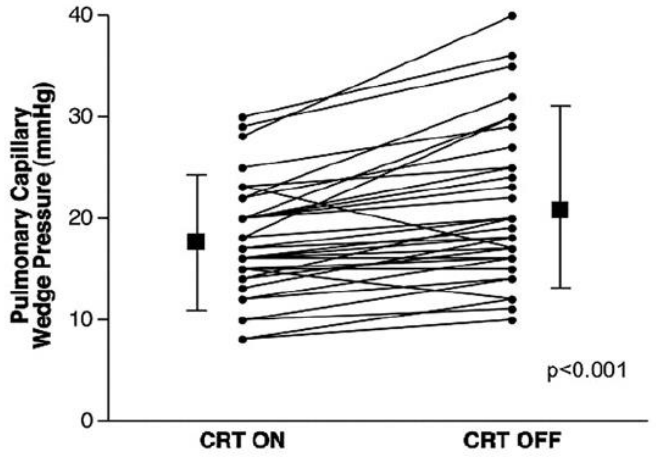

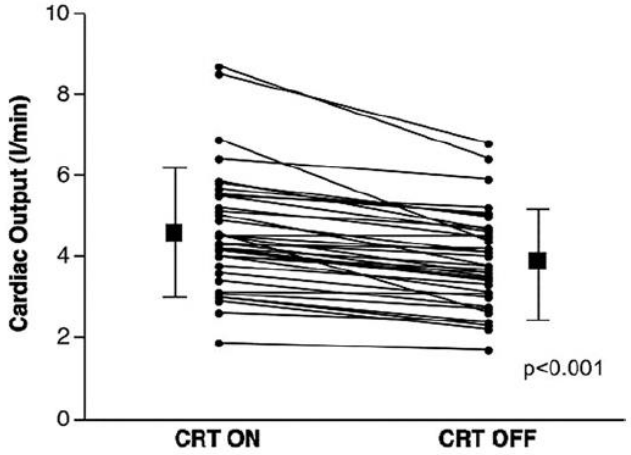

Willkoff et al. J Am Coll Cardiol 2009;53:600–7)

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- Despite progressive cardiac remodeling and decompensation, chronic CRT continues to provide HD augmentation in the failing heart in most patients.

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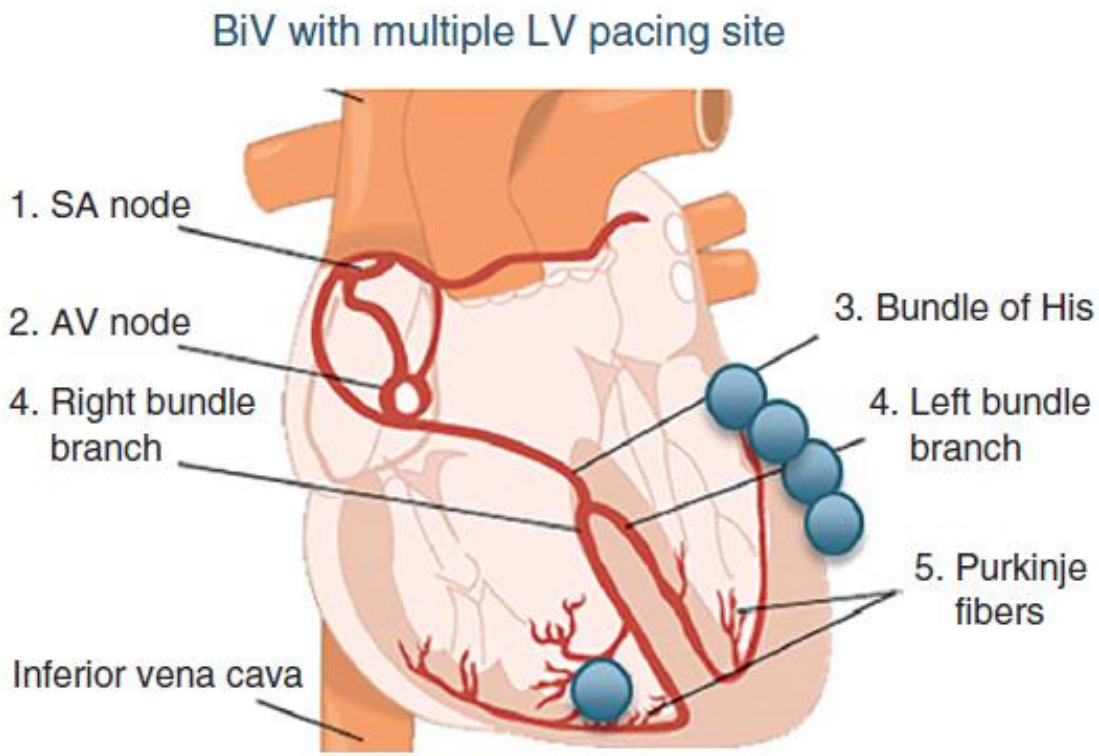
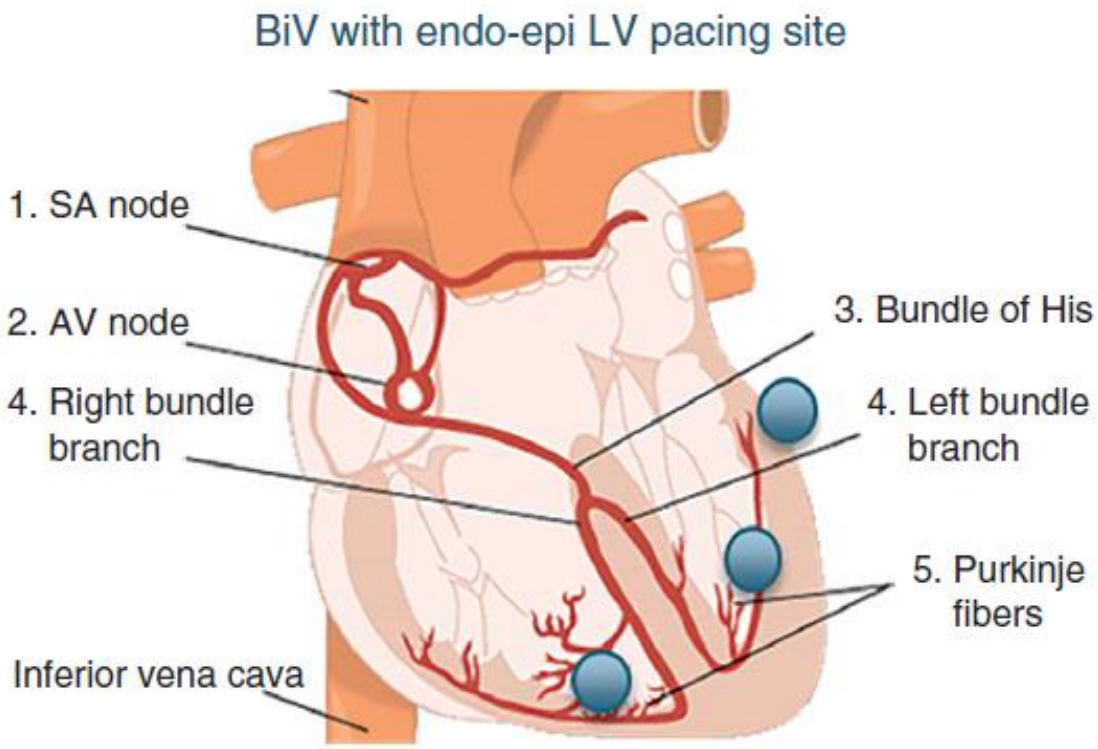
New Modalities: Multipoint Pacing





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