Non-Pharmacologic Treatment in Heart Failure

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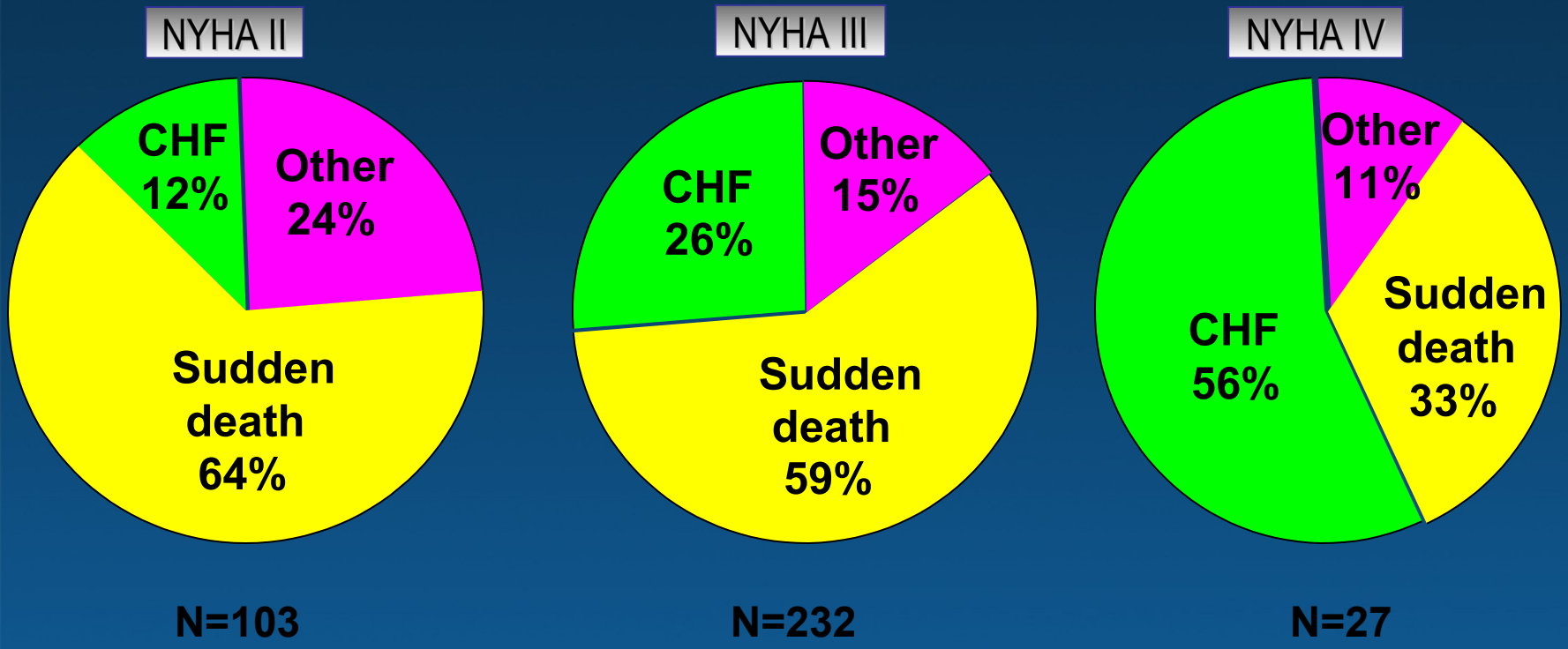
Severity of Heart Failure and Mode of Death



N = number of deaths

MERIT-HF Study Group. Effect of Metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). LANCET. 1999;353:2001-07.

Device-based treatment of heart failure

Function of device	Examples
Monitor heart failure condition	Implantable hemodynamic monitors, home scales, home monitoring systems
Prevent or treat rhythm disturbances	Pacemakers for bradycardia, ICD, LifeWest Wearable AED (LIFECOR, Inc, PA)
Improve mechanical efficiency of the heart	Left ventricular or multisite pacing, Biventricular pacing, CorCap (Accorn, MN) Myosplint (Myocor, MN)
Cardiac replacement therapy	LVAD, BiVAD, TAH

Adapted from Boehmer, Am J Cardiol, 2003

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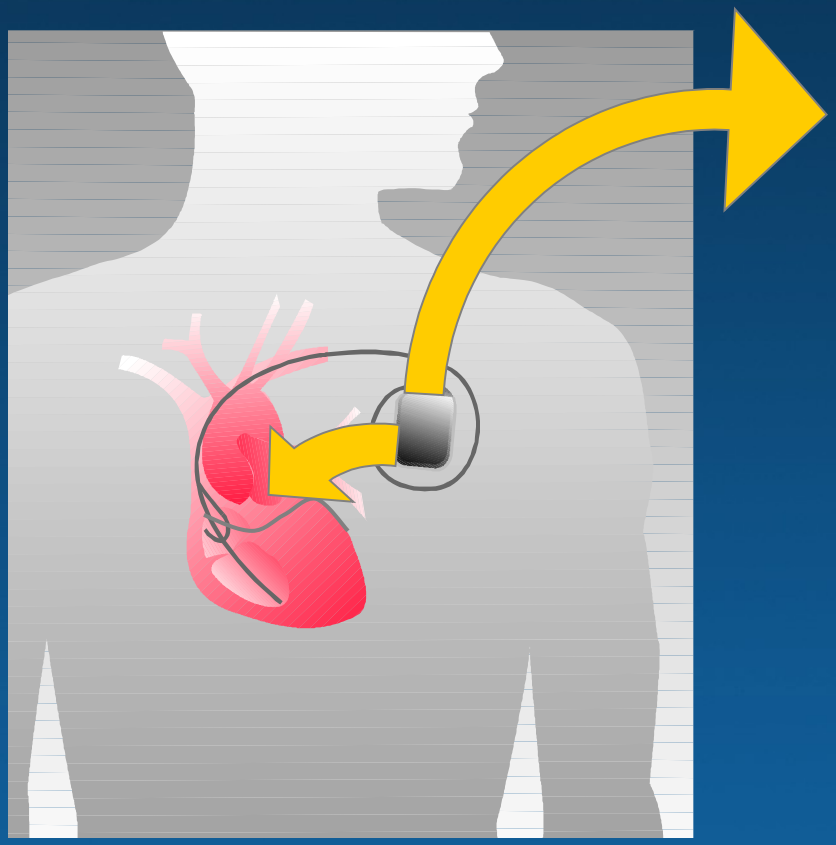
Devices in heart failure



Diagnostic capabilities

- Arrhythmia monitoring
- Heart rate
- Percent pacing
- Physical activity
- Heart rate variability
- Intrathoracic impedance
- RV pressures

The Chronicle®

Implantable continuous hemodynamic monitor (ICHM)

- Heart rate
- Syst RV pressure
- Diast RV pressure
- RV pulse pressure
- ePAD
- pos dP/dt_{max}
- neg dP/dt_{max}
- PEI
- STI
- Activity

External Pressure Reference

Randomized Controlled Trial of an Implantable Continuous Hemodynamic Monitor in Patients With Advanced Heart Failure

The COMPASS-HF Study

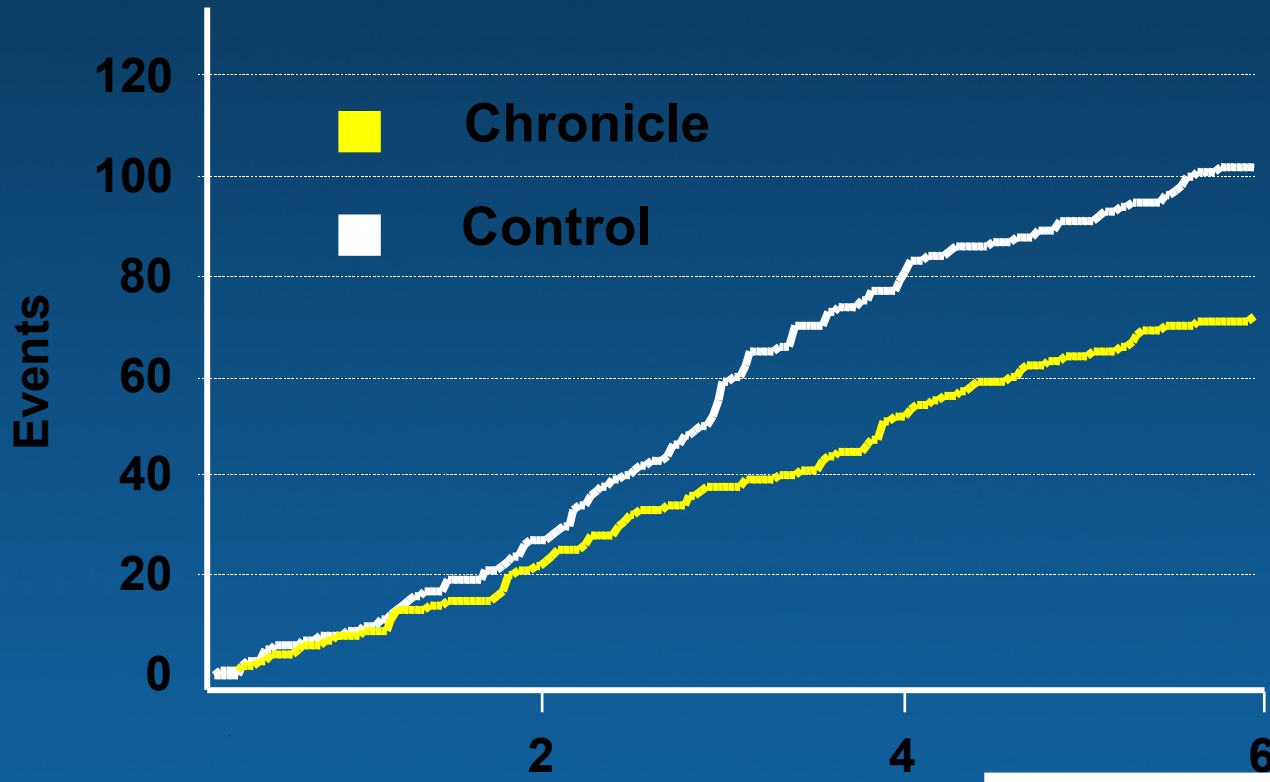
- Primary Effectiveness end-point - the Chronicle group would have a 30% lower rate of combined HF-related events (hospitalizations, emergency department and urgent clinic visits requiring intravenous therapy) compared with the control group.

Bourge et al., JACC, 2008

COMPASS-HF

HF-related Hospitalization

Cumulative Events

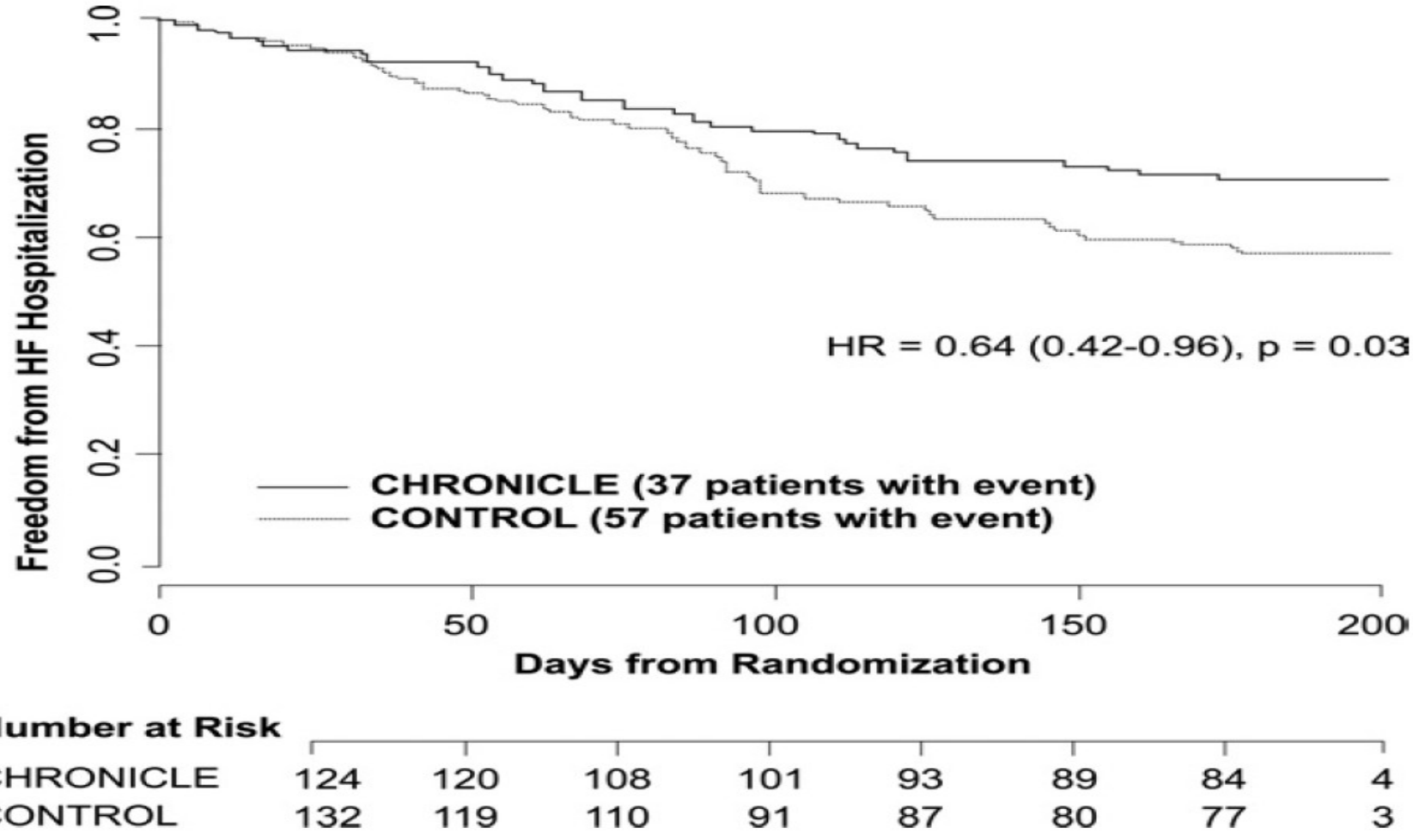


RR: 22%
(p=0.27)

* Hypothesized event rate was 1.2

Bourge et al., JACC, 2008

Reduction in relative risk of a first heart failure related hospitalization



Bourge et al., JACC, 2008

Conclusions

- In patients with moderate to severe HF, the addition of an ICHM to optimal medical management did not significantly reduce the rate of all HF-related events.
- Additional trials will be necessary to establish clinical benefit of ICHM-guided care in this patient population.

Bourge et al., JACC, 2008

Intrathoracic impedance

Dryer lungs

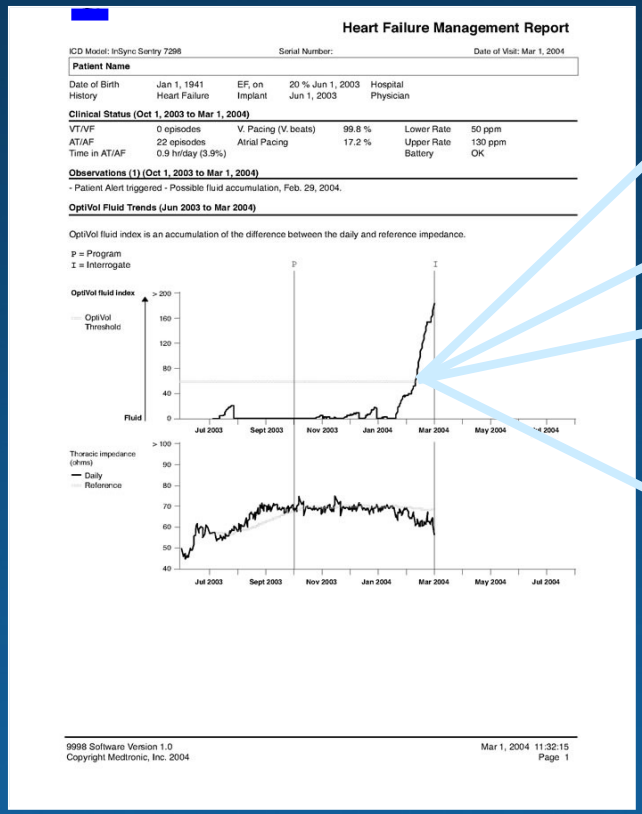
Impedance ↑

Wetter lungs

Impedance ↓

Intrathoracic impedance

Fluid Accumulation Notification Options



Heart Failure Management Report

ICD Model: InSync Sentry 7298 | Serial Number: | Date of Visit: Mar 1, 2004

Patient Name

Date of Birth	Jan 1, 1941	EF, on	20 % Jun 1, 2003	Hospital	
History	Heart Failure	Implant	Jun 1, 2003	Physician	

Clinical Status (Oct 1, 2003 to Mar 1, 2004)

VT/VF	0 episodes	V. Pacing (V. beats)	99.8 %	Lower Rate	50 ppm
AT/AF	22 episodes	Atrial Pacing	17.2 %	Upper Rate	130 ppm
Time in AT/AF	0.9 hr/day (3.9%)			Battery	OK

Observations (1) (Oct 1, 2003 to Mar 1, 2004)

- Patient Alert triggered - Possible fluid accumulation, Feb. 29, 2004.

OptiVol Fluid Trends (Jun 2003 to Mar 2004)

OptiVol fluid index is an accumulation of the difference between the daily and reference impedance.

P = Program
I = Interrogate

OptiVol fluid index
OptiVol Threshold
Fluid
> 200
160
120
80
40
0
Jul 2003 Sept 2003 Nov 2003 Jan 2004 Mar 2004 May 2004

Thoracic impedance (ohms)
Daily
Reference
> 100
90
80
70
60
50
40
Jul 2003 Sept 2003 Nov 2003 Jan 2004 Mar 2004 May 2004 Jul 2004

9998 Software Version 1.0
Copyright Medtronic, Inc. 2004

Mar 1, 2004 11:32:15
Page 1

- Observations with Trends
- Device audible alert
- SentryCheck™

- Patient look ind

European Heart Journal (2007) 28, 1835–1840
doi:10.1093/eurheartj/ehl506

European Heart Journal

EUROPEAN SOCIETY OF CARDIOLOGY®

Clinical research
Heart failure/cardiomyopathy

Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure

- 640 pts with heart failure elligible for CRT-D (InSync Sentry®, Medtronic Inc, USA) implantation were enrolled in 42 countries.
- Lack of FU reports in 267 pts.
- Finally 373 pt files were analyzed.

Vollmann et al., 2008

Main Findings

- The device alert detected HF deterioration with an adjusted sensitivity and an adjusted PPV of 60% each.
- Failure of the alert algorithm to detect clinical HF deterioration was in 55% of the cases associated with an increase of the fluid index that was yet below the programmable alert threshold.
- Half of the false-positive alerts were related to other clinical findings or therapeutic interventions.

Vollmann et al., 2008

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Adapted from Boehmer, Am J Cardiol, 2003

HF Patients:
A Need for a New Therapy

40% of patients are
not suitable for ACE Inibitors Therapy

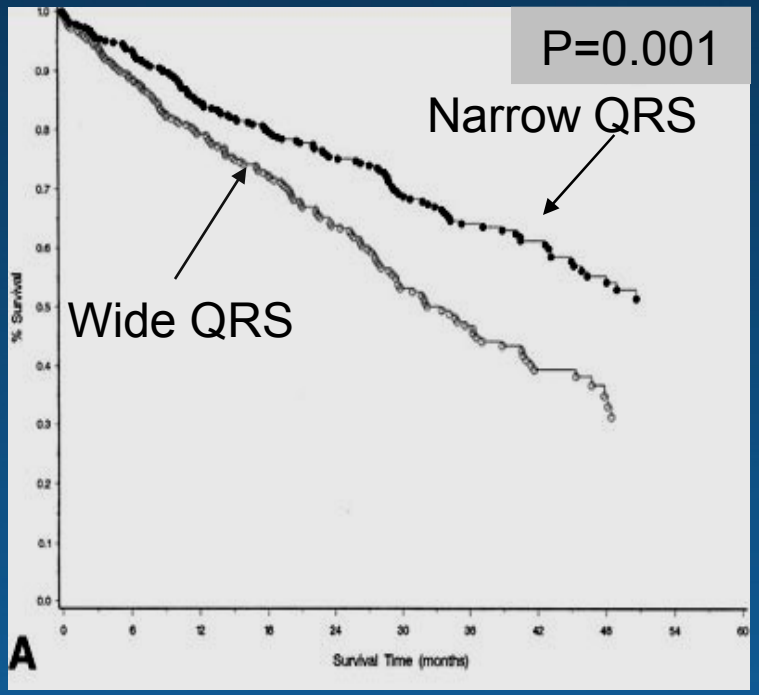
60% of Rehospitalizations
Noncompliance with medications and diet

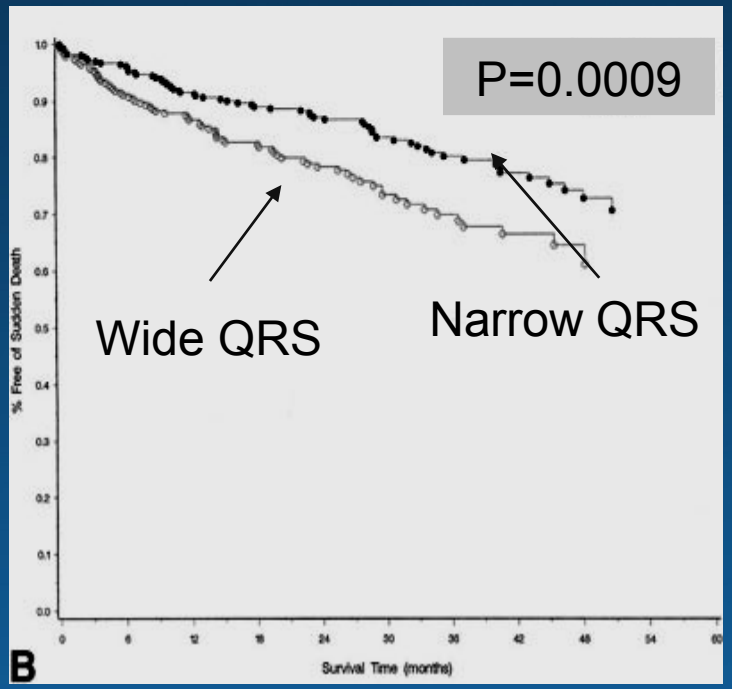
Over 65 yrs of age HF is the leading cause of
Hospitalization

50% of Mortality within five years
for 50% of patients in NYHA Functional Class I throught IV

CHF STAT Trial

QRS Duration and Mortality





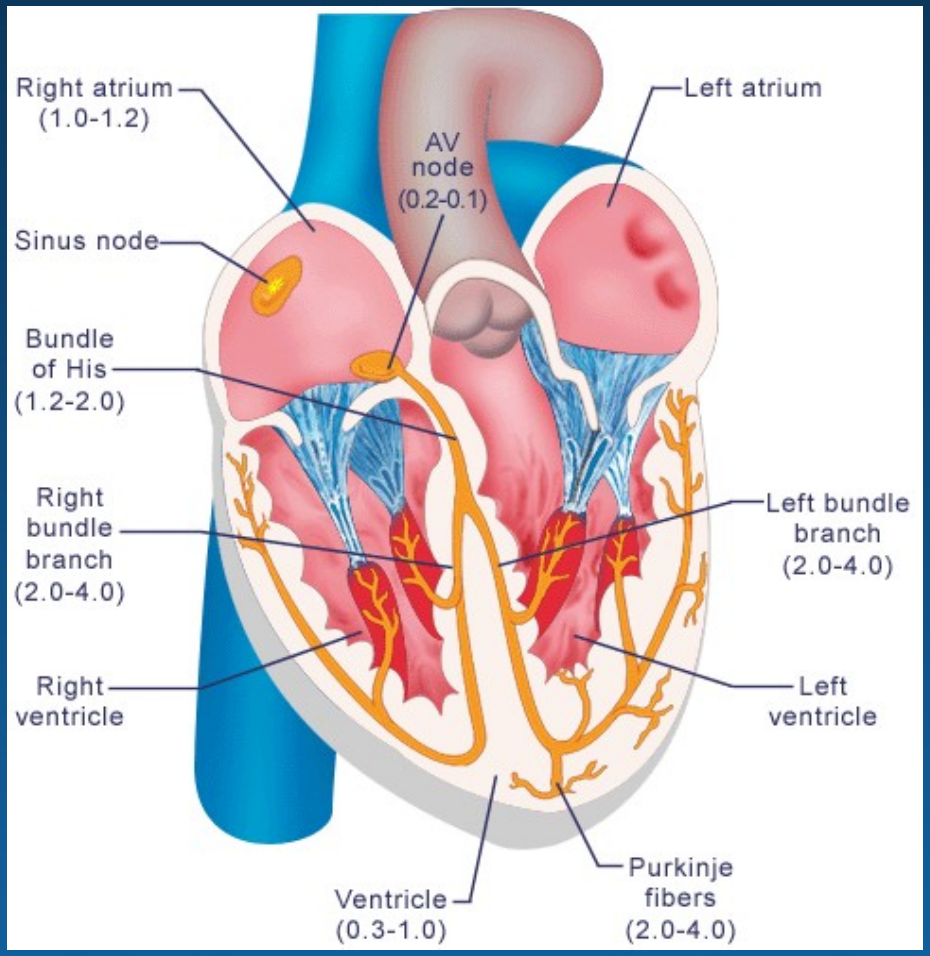
Total Death

Sudden Death

LBBB <u>not</u> RBBB associated with adverse outcomes

Juliano S. Am Heart J 143:1085, 2002

Contraction Depends on Activation

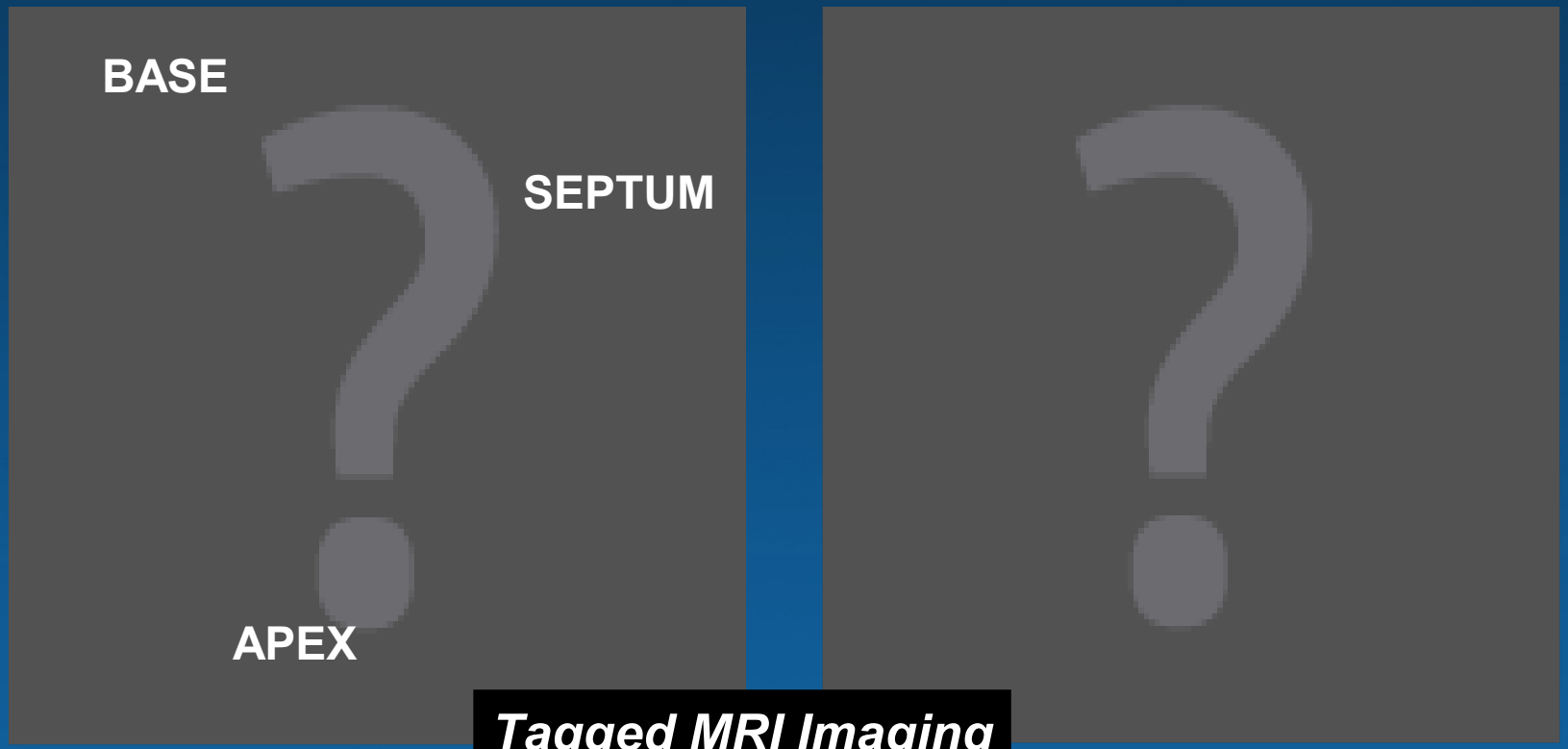


Shrier http://www.mmip.mcgill.ca/unit2/shrier/lect34electrocardiogram.htm

Normal vs Abnormal Contraction

Mechanical Dyssynchrony with IVCD

Normal **Dilated Cardiomyopathy**



Tagged MRI Imaging

Curry C. Circulation 2000;101:e2

Dysynchrony - Consequences

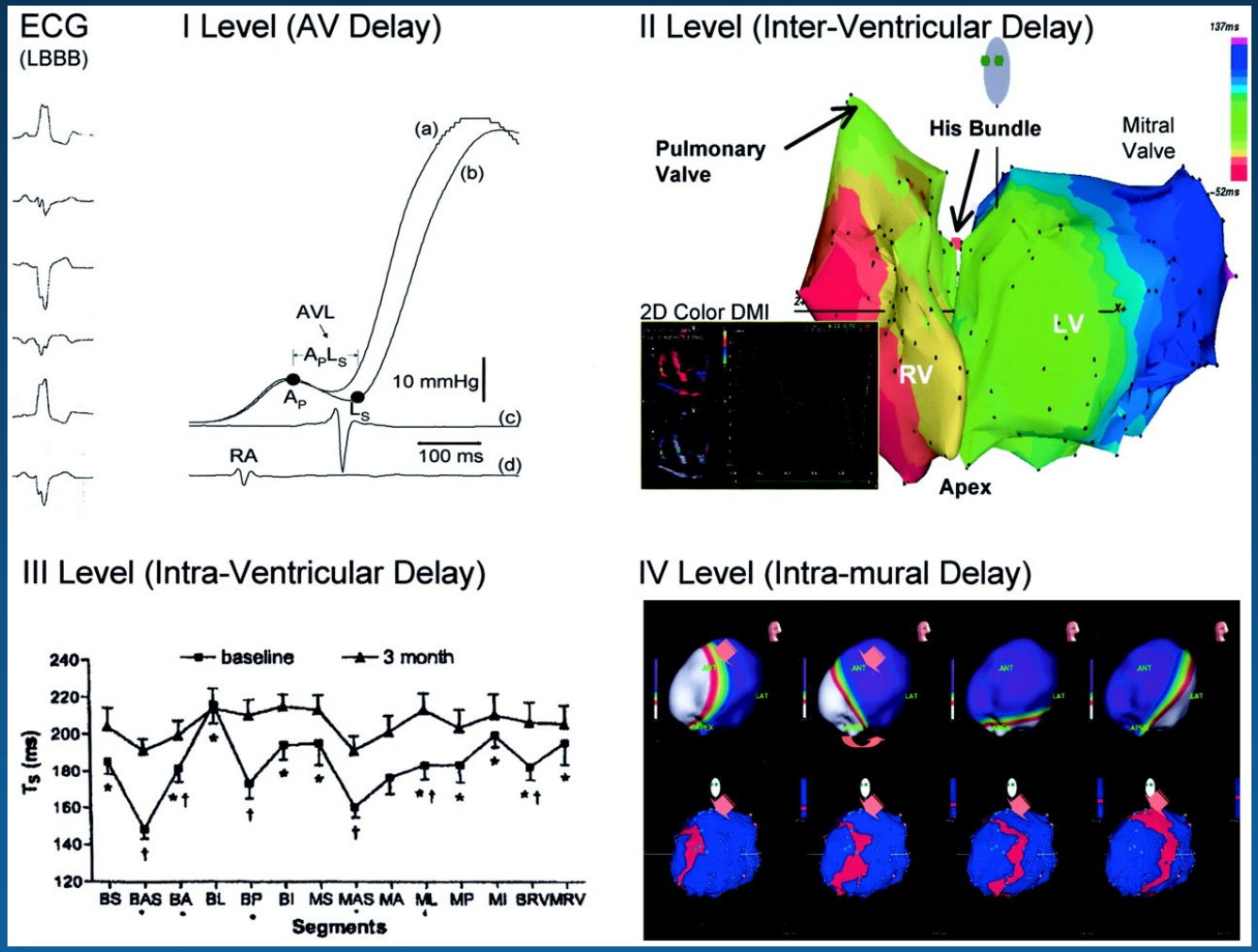
- Abnormal septal motion[1]
- Reduced dP/dt[3,4]
- Reduced pulse pressure[4]
- Lower ejection fraction[4]
- Reduced diastolic filling [1,2,4]
- Mitral regurgitation[1,2,4]

1 Grines CL, Bashore TM, Boudoulas H, et al. *Circulation* 1989;79:845-853.

2 Xiao, HB, Lee CH, Gibson DG. *Br Heart J* 1991;66:443-447.

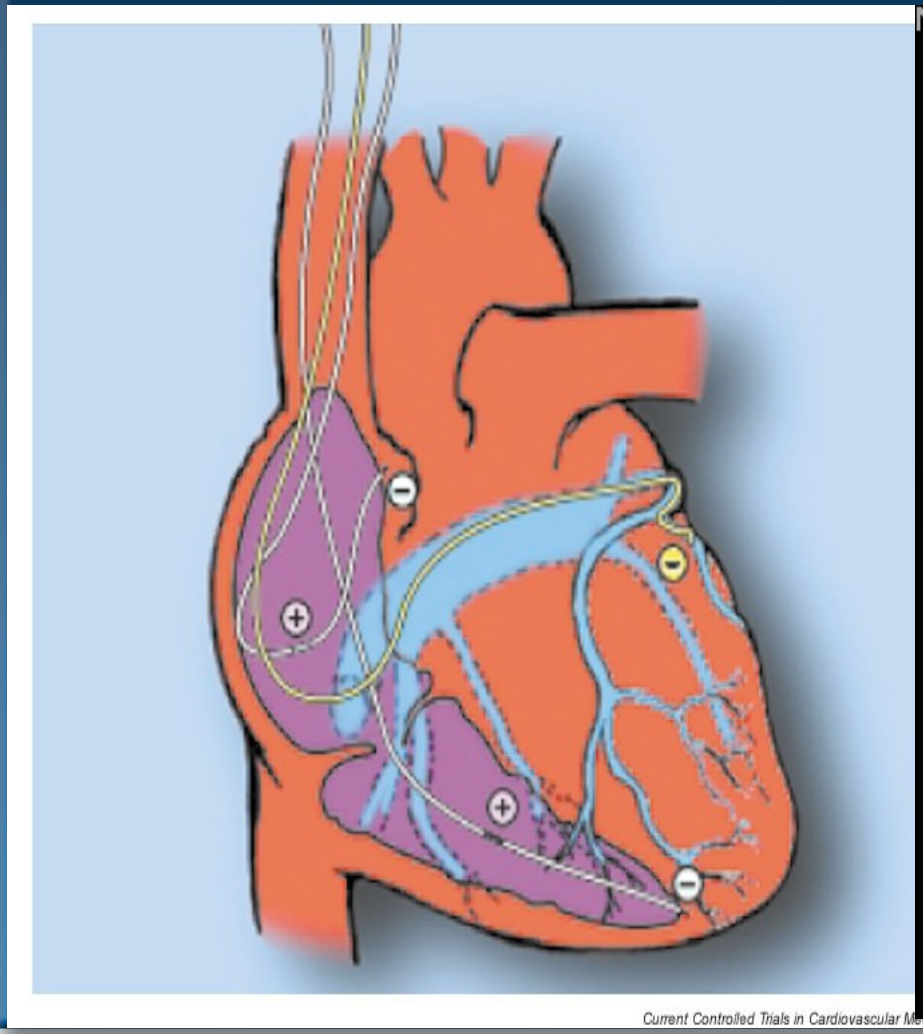
3 Xiao HB, Brecker SJD, Gibson DG. *Br Heart J* 1992;68:403-407.

Dysynchrony Has Many Levels

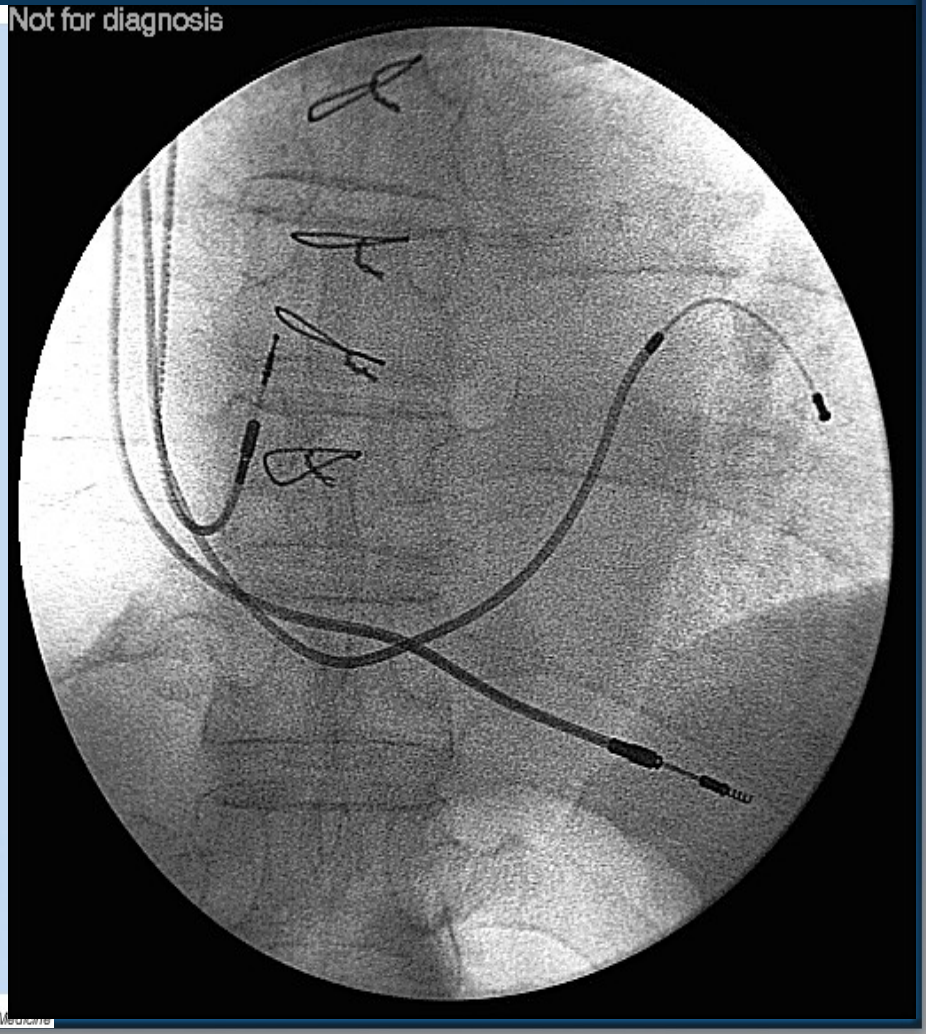


Auricchio Circulation. 2004;109:300-30

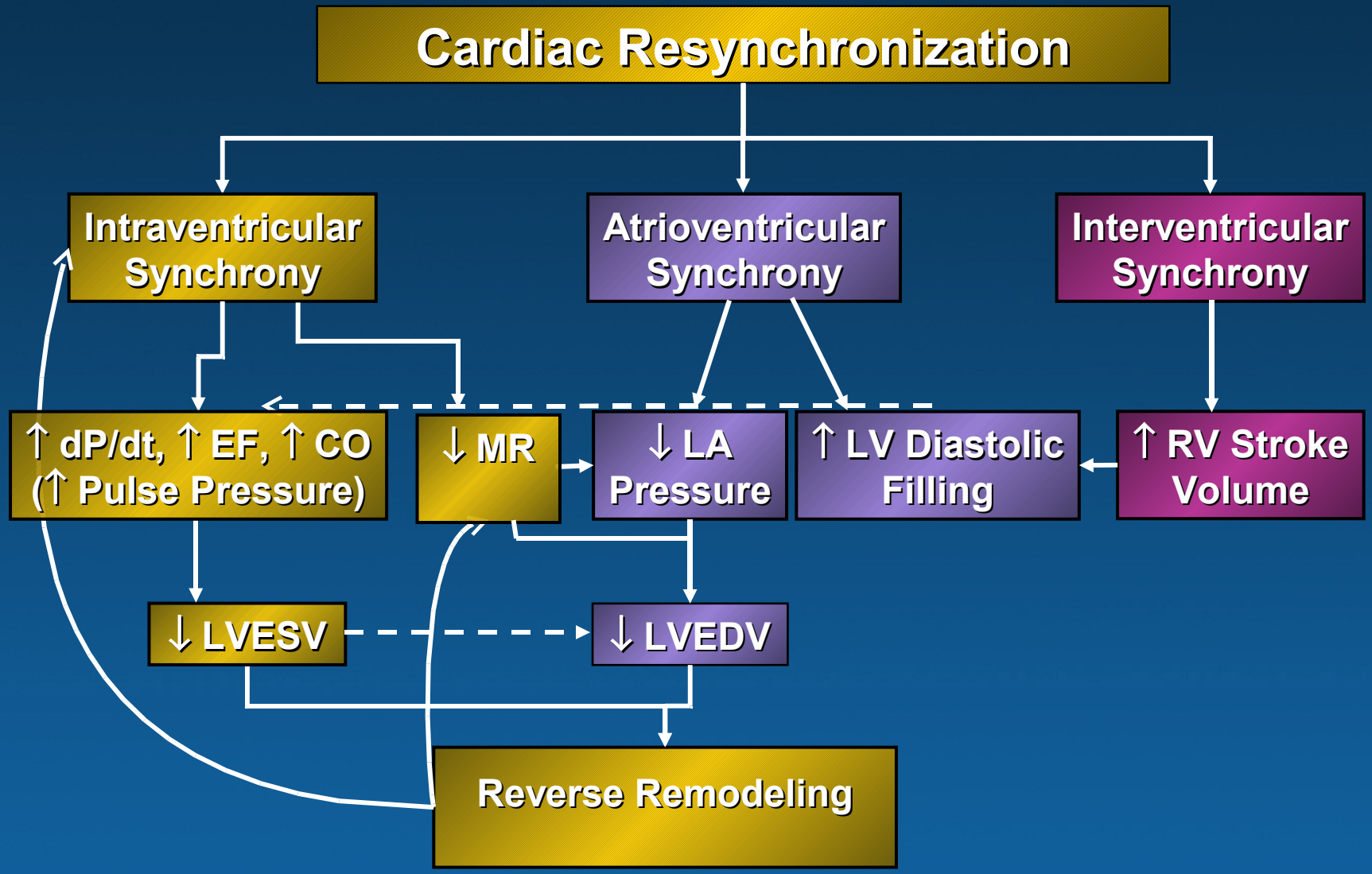
Biventricular pacemaker leads



Current Controlled Trials in Cardiovascular Medicine



Cardiac Resynchronization: Proposed Mechanisms



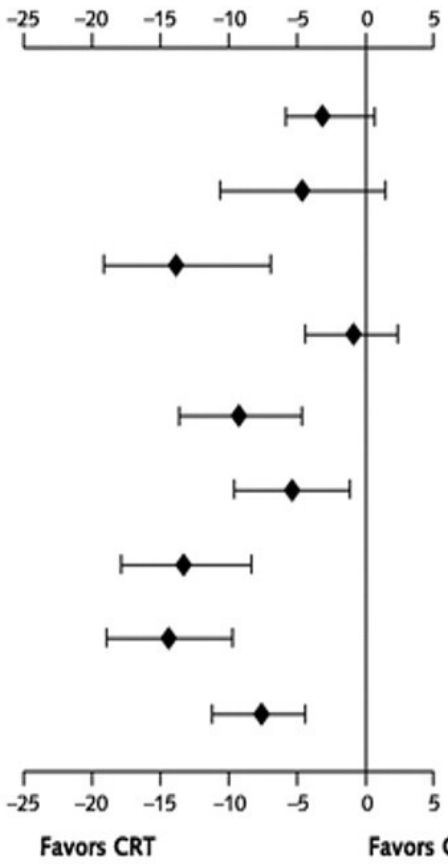
Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445

CRT Background

- CRT has been shown to be consistently associated with:
  - Reductions in LV size and volume
  - Increased Stroke Volume
  - Increased Ejection Fraction
  - Reduced Mitral Regurgitation
  - Improved exercise capacity
  - Improved QOL and functional capacity
- Effects of CRT on hospitalisation and mortality remain uncertain

Quality of Life and CRT

Study, Year (Reference)	Quality of Life: CRT Group Patients, *n*	CRT Group Mean MLWHF Score ± SD	Control Group Patients, *n*	Control Group Mean MLWHF Score ± SD	Weighted Mean Difference in MLWHF Score (95% CI)
PATH-CHF, 2002 (19)	41	25.2 ± 10.6	41	28.1 ± 11.2	–2.9 (–6.4 to 0.6)
MUSTIC-AF, 2002 (18)	39	–9.9 ± 21.3	39	–5.5 ± 21.7	–4.4 (–11.2 to 2.4)
MUSTIC-SR, 2001 (12)	45	–17.4 ± 21.6	45	–3.8 ± 22.4	–13.6 (–20 to –7.2)
CONTAK-CD, 2003 (15)	234	–5.2 ± 19.8	225	–4.5 ± 20.2	–0.7 (–4.4 to 3)
MIRACLE, 2002 (13)	213	–18 ± 28.6	193	–9 ± 22.9	–9 (–14 to –4)
MIRACLE-ICD, 2003 (14)	162	–18.3 ± 23.2	153	–13.1 ± 22.7	–5.2 (–10.3 to –0.1)
COMPANION, 2004 (21)	459	–25 ± –26	104	–12 ± 23	–13 (–18 to –8)
COMPANION-CD, 2004 (21)	479	–26 ± 28	103	–12 ± 23	–14 (–19.1 to –8.9)
Overall					–7.6 (–11.5 to –3.8)

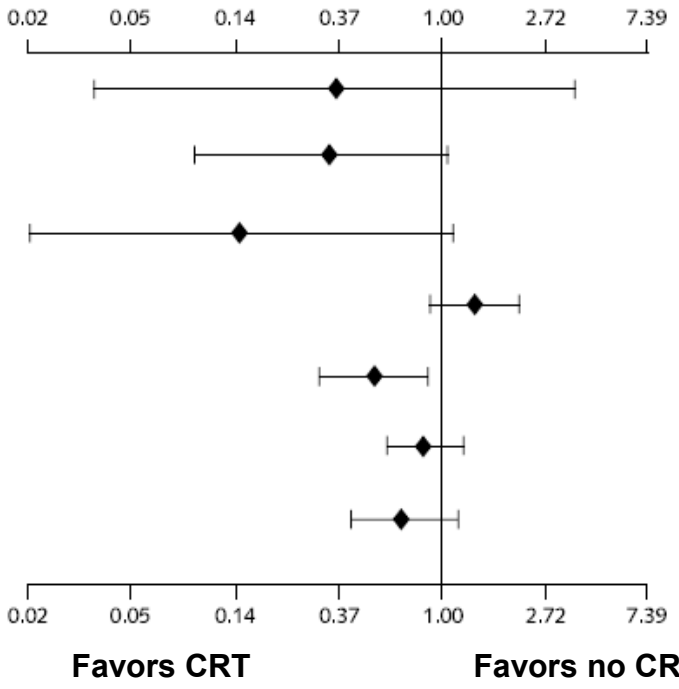


Favors CRT Favors no CRT

McAlister FA. Ann Intern Med 2004;141:381-390

CHF Hospitalizations with CRT

Study, Year (Reference)	Heart Failure Hospitalizations: CRT Group, *n/n*	Control Group, *n/n*	RR (95% CI)
MUSTIC-AF, 2002 (18)	1/25	2/18	0.36 (0.04–3.67)
MUSTIC-SR, 2002 (12)	3/29	9/29	0.33 (0.1–1.11)
RD-CHF, 2003 (22)	1/22	7/22	0.14 (0.02–1.07)
CONTAK-CD, 2003 (15)	32/245	39/245	1.39 (0.91–2.11)
MIRACLE, 2002 (13)	18/228	34/225	0.52 (0.3–0.9)
MIRACLE-ICD, 2003 (14)	47/272	58/282	0.84 (0.59–1.19)
Overall			0.68 (0.41–1.12)

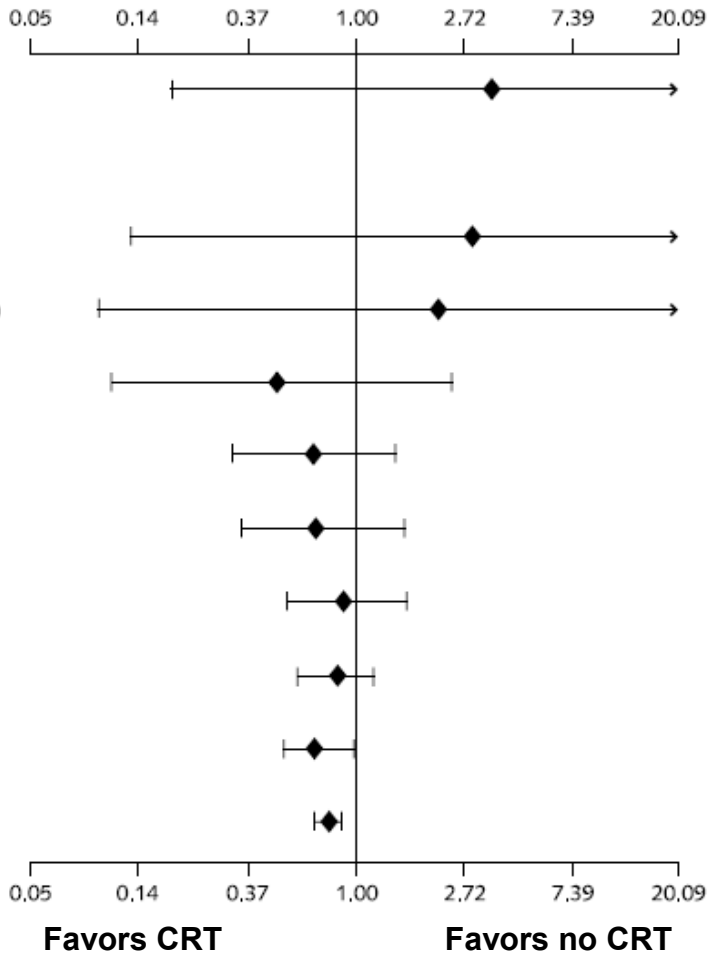


McAlister FA. Ann Intern Med 2004;141:381-390

Does CRT Prevent Death?

All Cause Mortality and CRT

Study, Year (Reference)	All-Cause Mortality		
	CRT Group, *n/n*	Control Group, *n/n*	RR (95% CI)
PATH-CHF, 2002 (19)	2/24	0/17	3.6 (0.18–70.54)
Garrigue et al., 2002 (20)	0/6	0/7	Excluded
MUSTIC-SR, 2001 (12)	1/29	0/29	3 (0.13–70.74)
MUSTIC-AF, 2002 (18)	1/25	0/18	2.19 (0.09–50.93)
RD-CHF, 2003 (22)	2/22	4/22	0.5 (0.1–2.45)
CONTAK-CD, 2003 (15)	11/245	16/245	0.69 (0.33–1.45)
MIRACLE, 2002 (13)	12/228	16/225	0.74 (0.36–1.53)
MIRACLE-ICD, 2003 (14)	24/272	27/282	0.92 (0.55–1.56)
COMPANION, 2004 (21)	131/617	39/154	0.84 (0.61–1.14)
COMPANION-CD, 2004 (21)	105/595	38/154	0.72 (0.52–0.99)
Overall			0.79 (0.66–0.96)



McAlister FA. Ann Intern Med 2004;141:381-39

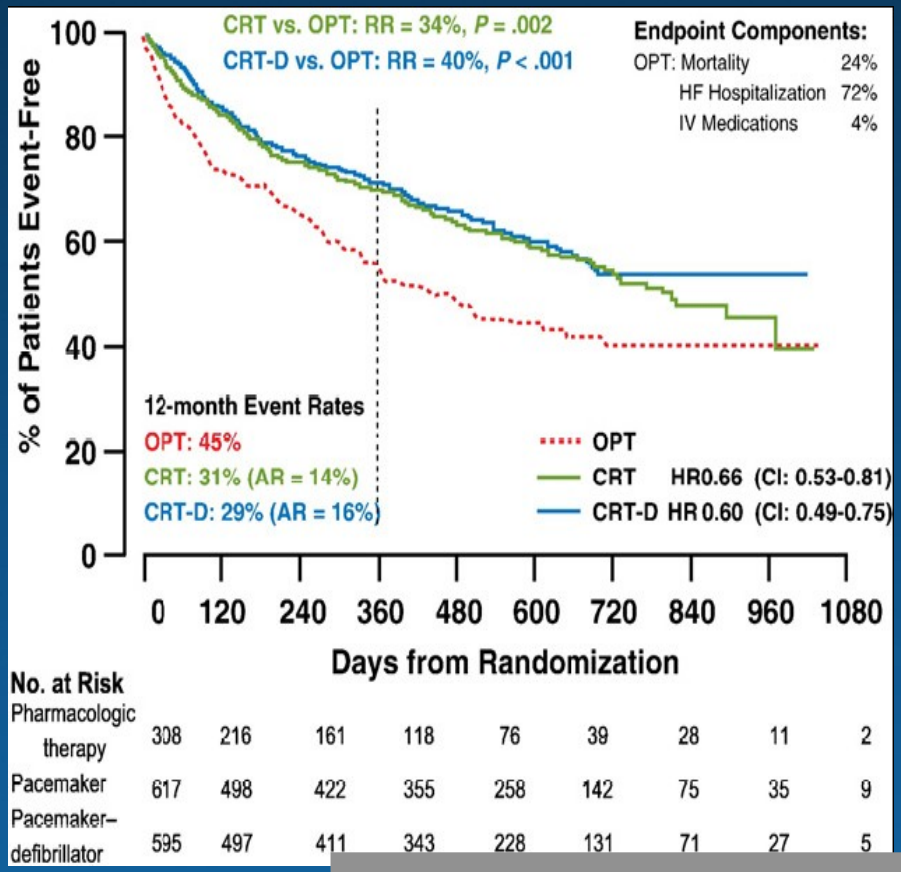
The COMPANION Trial

- 1520 patients* enrolled at 30 centers
- NYHA FC III/IV, LVEF ≤0.35, QRS ≥120 ms
- Optimal medical therapy vs. CRTp vs. CRTd with optimal medical therapy

**stopped early by DSMB; 2200 planne*

COMPANION: 1^0 Endpoint

Death, Hospitalization or Outpatient Medication

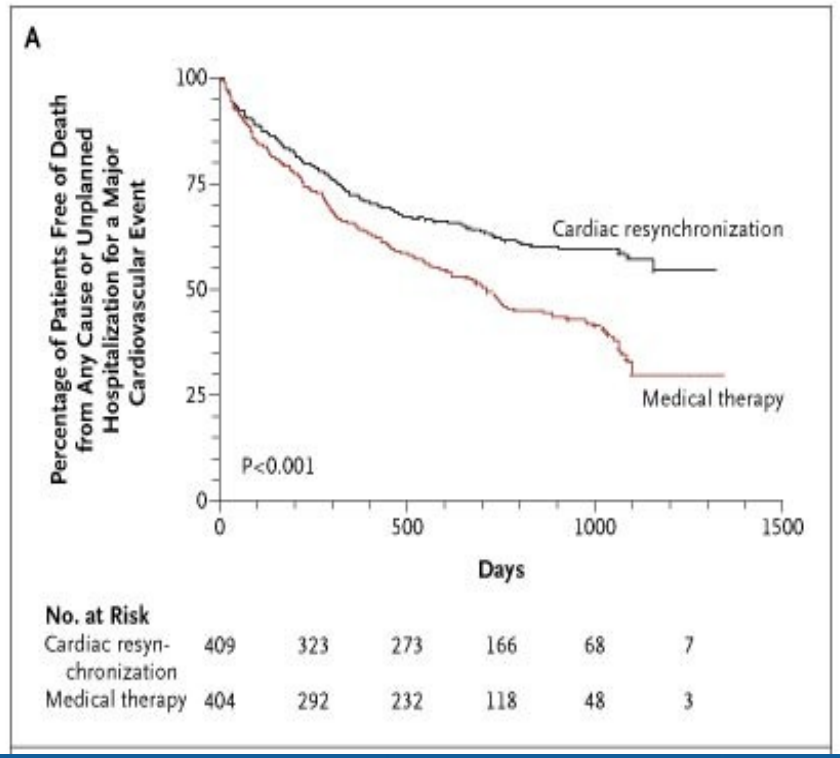


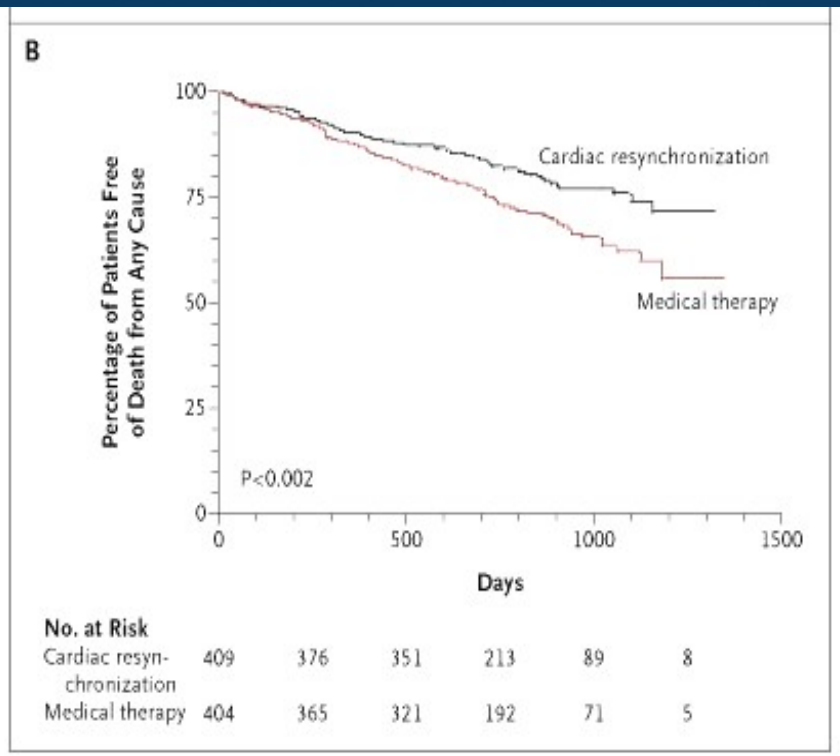
Bristow M N Engl J Med 2004;350:2140-2150

CARE – HF Study

Maybe CRTp is all that is needed

36% reduction in all-cause mortality,
10% absolute risk reduction





Cleland JGF N Engl J Med 2005;352:1539-1549

Current Status of ICD and CRT Therapy in Heart Failure

- 2 major CRT trials showed mortality reduction and reduction in hospitalizations:
  - CARE- HF: CRT without defibrillator (CRT-P)
  - COMPANION: CRT alone and CRT-D

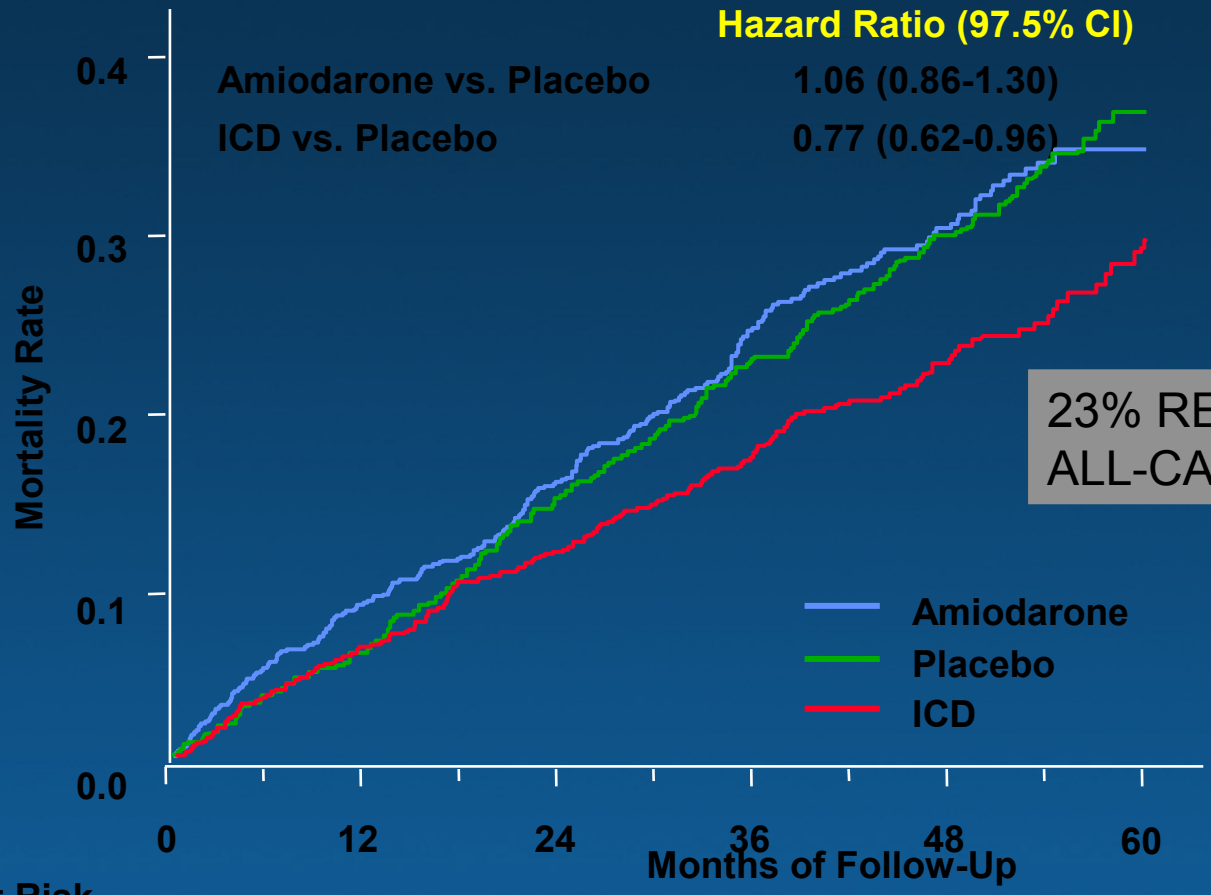
→ Class I recommendation for CRT

- The main challenge is to identify appropriate pts and implement appropriate therapy

Current Status of ICD and CRT Therapy in Heart Failure

- ICD and CRT for selected pts now is standard of care added to optimal medical therapy (OMT).
- ICD trials:
  - MADIT-II: post MI/LV dx (EF <30%) – reduction in all-cause mortality.
  - SCD-HEFT: Ischemic and non-ischemic class II/III HF, EF ≤35% despite OMT – reduction in all-cause mortality.
- CLASS I RECOMMENDATION FOR THESE PTS IN

SCD-HeFT
Mortality Rate Overall Results

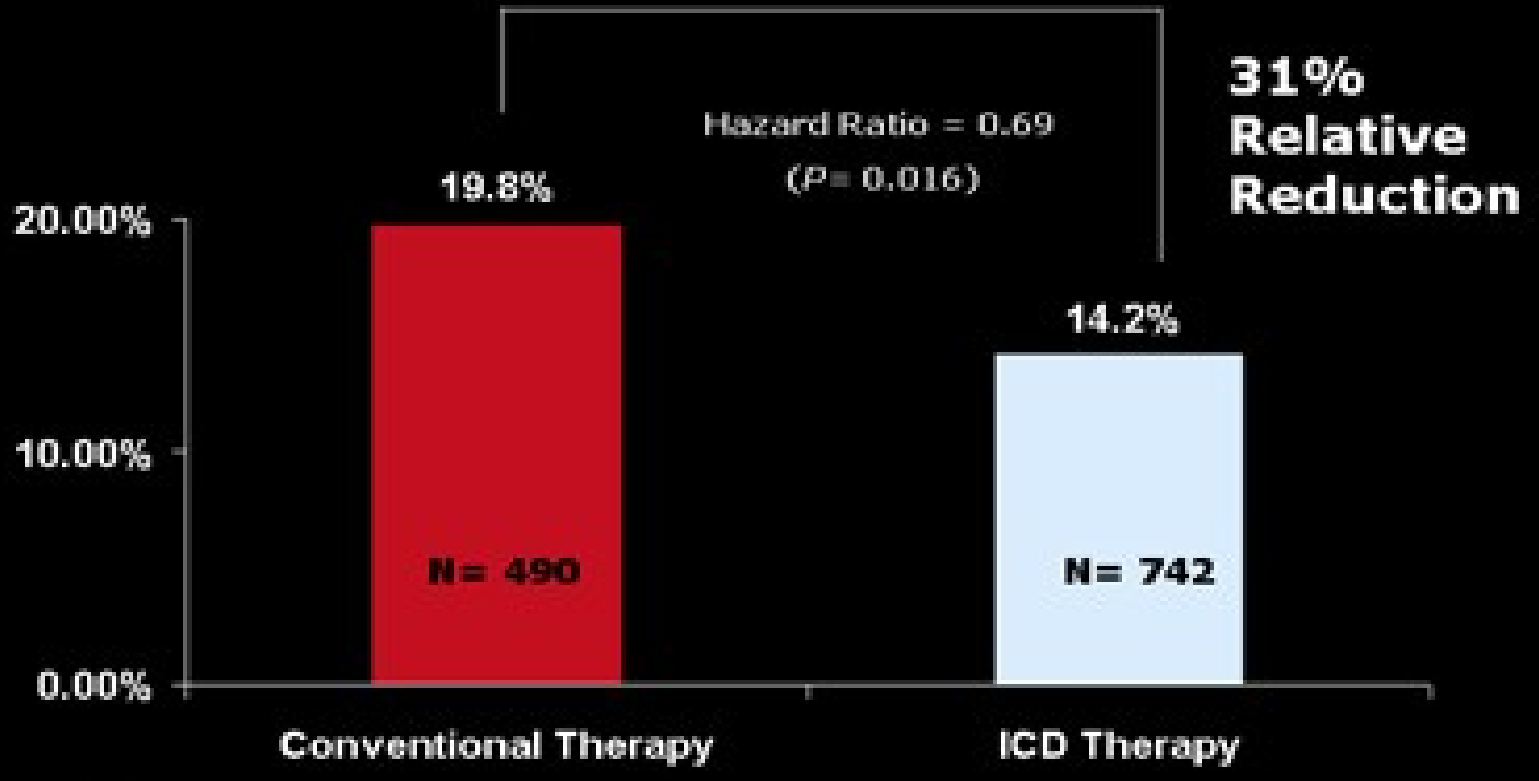


23% REDUCTION IN ALL-CAUSE MORTALITY

No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD	829	778	733	501	304	103

Bardy GH. *N Engl J Med.* 2005;352:225-237.

MADIT II: Multicenter Automatic Defibrillator Implantation Trial II

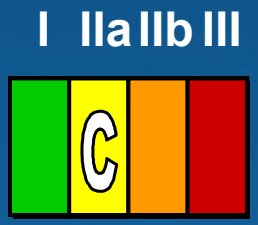


Moss AJ. *N Engl J Med.* 2002;346:877-883

Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

For patients who have left ventricular ejection fraction (LVEF) less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, cardiac resynchronization therapy (CRT) with or without an ICD is indicated for the treatment of New York Heart Association (NYHA) functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.

For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.



For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

For patients with LVEF less than or equal to 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered.

CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing.

CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

3. Cardiac Resynchronisation Therapy (CRT) in Patients with Heart Failure

Recommendations for the use of cardiac resynchronization therapy by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an ICD (CRT-D) in HF patients.

Heart failure patients who remain symptomatic in NYHA Class IIHV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), left ventricular dilatation*, normal sinus rhythm and wide QRS complex (≥ 120 ms)

- Class I - Level of evidence A for CRT-P to reduce morbidity and mortality.
- CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year, Class I - Level of evidence B.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m², LV end diastolic diameter > 30 mm/m (height).

3. Cardiac Resynchronisation Therapy (CRT) in Patients with Heart Failure

Recommendations for the use of biventricular pacing in HF patients with a concomitant indication for permanent pacing.

Heart failure patients with NYHA Class III-IV symptoms, low ejection fraction (LVEF ≤ 35%), left ventricular dilatation* and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker).

- Class IIa - Level of evidence C

Recommendations for the use of an ICD combined with biventricular pacemaker (CRT-D) in HF patients with an indication for an ICD.

Heart failure patients with a Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), left ventricular dilatation*, wide QRS complex (≥ 120ms).

- Class I - Level of evidence B.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m², LV end diastolic diameter > 30 mm/m (height).

3. Cardiac Resynchronisation Therapy (CRT) in Patients with Heart Failure

Recommendations for the use of biventricular pacing in HF patients with permanent atrial fibrillation.

Heart failure patients who remain symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), LV dilatation*, permanent atrial fibrillation and indication for AV junction ablation.

- Class IIa - Level of evidence C.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m², LV end diastolic diameter > 30 mm/m (height).

Possible Risks for Implantable Devices

- Vascular complications
- Long-term risk of infections
- Leads may break/fracture
- Recalls

BUT:

Significant benefits –evaluate patients carefully

Devices are very reliable and improving constantly

The Importance of Patient Selection

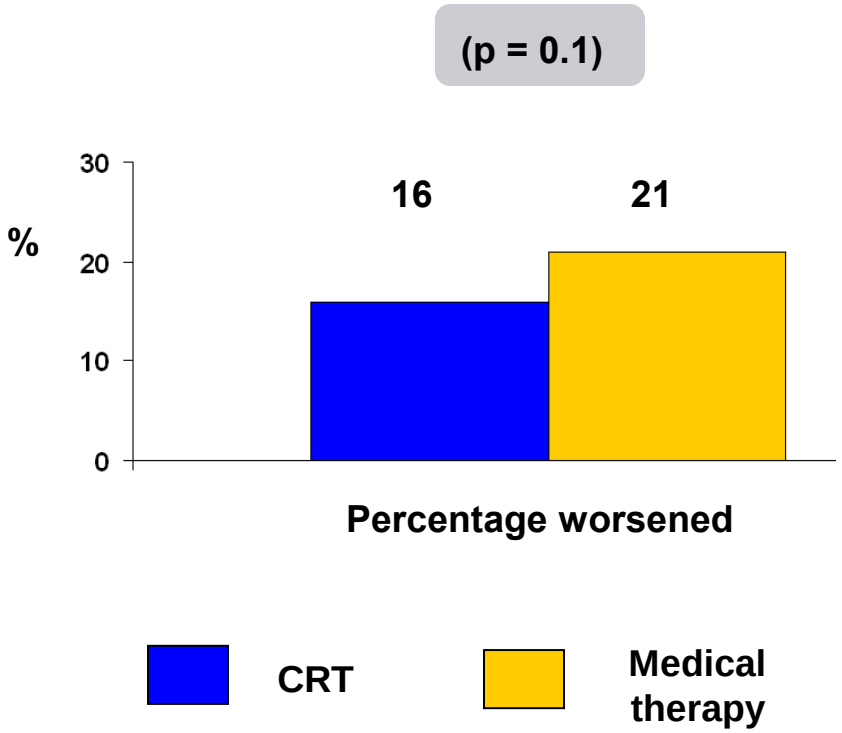
- Maintain relationship with EP/patient and family
- Need to understand:
  - Why treatment is indicated
  - What are the downsides
  - Will continue with medical therapy
  - Possibility of inappropriate shocks

IMPROVE HF: Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting

- 167 outpatient cardiology practices surveyed in the USA
- 15 381 pts with HF, previous MI/LV Dx
- Results for utilization of device therapy in eligible patients:
  - ICD/CRT-D 51%
  - CRT – 39%
- Median 27% of pts received all HF therapies for which they were potentially eligible on the basis of chart documentation.
- Use of guideline-recommended therapies by practices varied widely
- Need to translate outcomes of RC[redacted]
clinical practice

REVERSE *(SPONSORED BY MEDTRONIC)*

Trial design: Patients with LV dysfunction (NYHA class I-II) and wide QRS were randomized to cardiac resynchronization therapy (CRT) (n = 419) or optimal medical therapy (n = 191).



Results

- Patients worsened: 16% with CRT vs. 21% with optimal medical therapy (p = 0.1)
- LV end-systolic volume index: decreased 18.4 ml/m^2 vs. 1.3 ml/m^2 (p < 0.0001), respectively
- Risk of heart failure hospitalization reduced with CRT (p = 0.03)

Conclusions

- CRT for mild heart failure does not reduce the percentage of patients that clinically worsen
- CRT improves LV end-systolic volume index and reduces the risk of hospitalization compared with optimal medical therapy

Presented Dr. Cecilia Linde at SCAI-ACC i2 Summit/ACC 2008

MADIT-CRT: Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy

- N=1820
- EF < 30%. Class I or II HF
- Randomized to CRT_D (60%) or ICD-only (40%)
- OMT
- Combined end-point of all-cause mortality/HF events when compared with ICD-only therapy
- Ongoing study

The Resynchronization Therapy in Normal QRS (RethinQ) Study
Beshai et al., NEJM, 2007

Study Sponsored by St. Jude Medical

Inclusion and Exclusion Criteria

Inclusion Criteria

- NYHA class III HF
- LVEF ≤ 35%
- Evidence of mechanical dyssynchrony
- QRS duration < 130ms

Exclusion Criteria

- NYHA class I, II, or IV
- Permanent Atrial Fibrillation
- Recent MI, unstable angina or cardiac revascularization
- Prior cardiac resynchronization therapy

Conclusion

- CRT did not improve Peak VO_2 during exercise in patients with NYHA Class **III** heart failure, QRS duration <130ms, EF ≤ 35% and mechanical dyssynchrony as specified in this trial.
- While there was a statistically significant improvement of NYHA class, a secondary endpoint, there was no improvement in quality-of-life, 6-minute walking test, or echocardiographic measures of reverse LV remodeling
- A subgroup of patients with QRS duration between **120 ms and 130 ms demonstrated an improvement from CRT,** however patients with QRS duration **< 120 ms** did not demonstrate improvement
- The subgroup of patients stratified on the basis of cardiomyopathy etiology did not demonstrate an improvement in peak VO2.

Post-Implant Follow-Up

- Management outside EP office:
  - Cardiologists with HF training
  - Need for more practitioners as number of patients with devices grows

Optimisation of Device

  - Important clinical data is recorded by device to evaluate patient progress
  - Optimisation of AV, VV delays in CRT devices

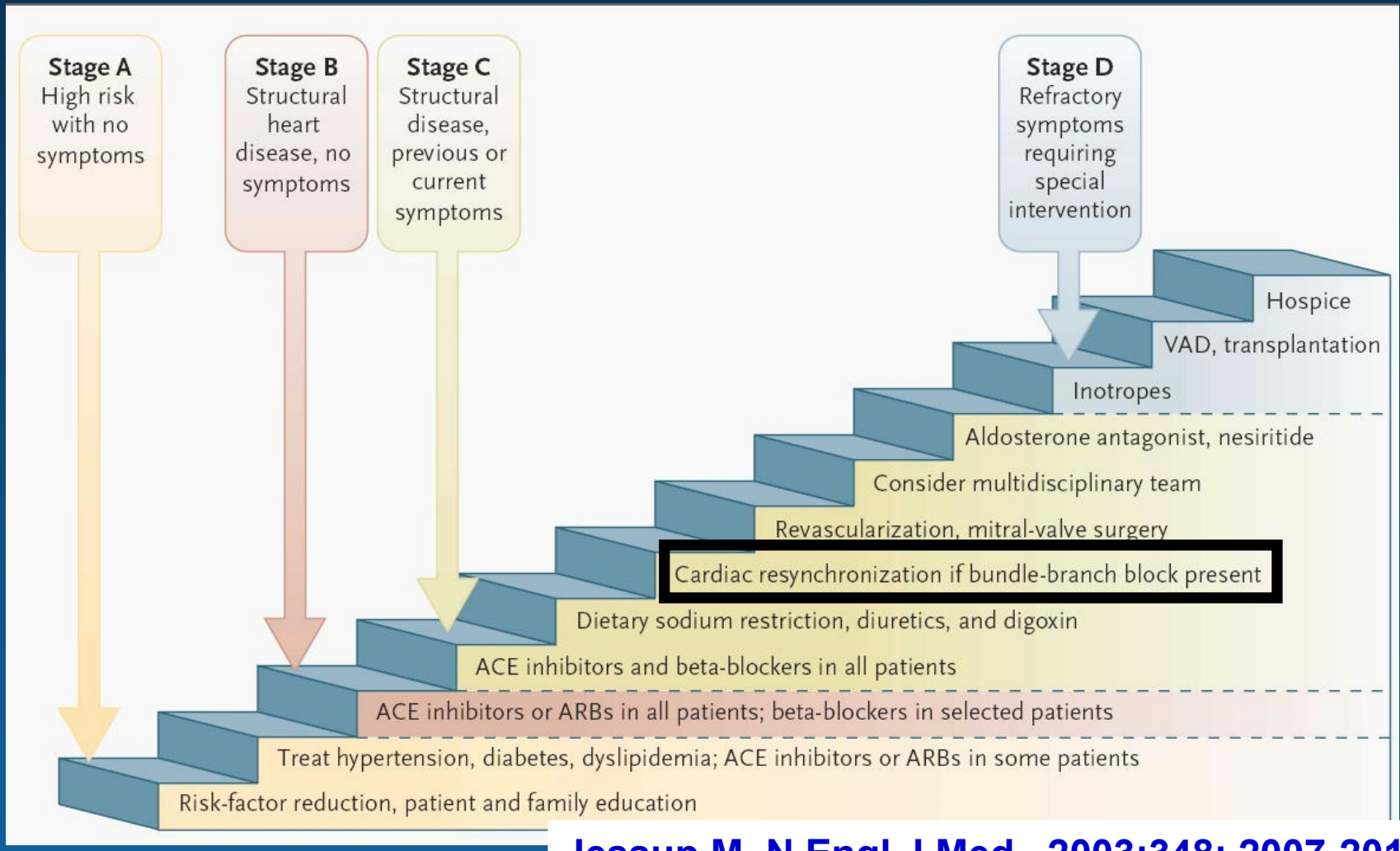
CRT Therapy – The Future

- Possible new indications
- Better optimization techniques (echo, etc.)
- Better programming (VV, AV algorithms)
- Better therapy (multiple activation sites)
- Auto-optimization
- More sophisticated monitoring

Conclusion

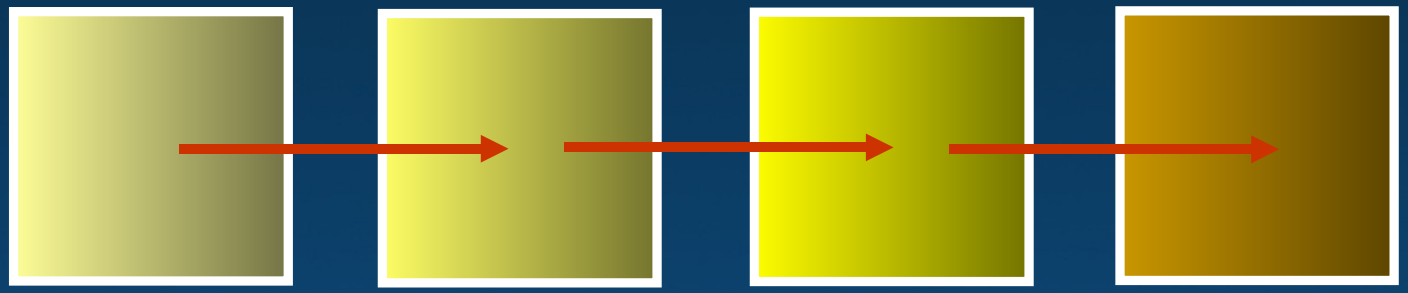
- CRT benefits many but not all patients with severe heart failure, low left ventricular ejection fractions and wide QRS complexes

Stages of Therapy



Jessup M. N Engl J Med. 2003:348;.2007-2018

Pharmacologic and Device Therapy Across the Continuum



AIRE/SAVE (ramipril/captopril)	SOLVD Treatment (enalapril)	CONSENSUS (enalapril)
CAPRICORN (carvedilol)	US Carvedilol/MERIT (carvedilol/metoprolol)	COPERNICUS (carvedilol)
EPHESUS (eplerenone)	CHARM/Val-HeFT (candesartan/valsartan)	RALES (spironolactone)

MADIT, MUSTT (ICD)

SCD-HeFT, MADIT-II (ICD)

MIRACLE, COMPANION, MUSTIC (CRT +/- ICD) CARE-HF