



# Cardiac Resynchronisation Therapy:

Who needs a device?

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Conflicts of interest: none



# Chronic heart failure (CHF)

- Syndrome:
  - Exercise intolerance (breathlessness and fatigue)
  - Cardiac dysfunction (most often left ventricular systolic dysfunction)
- Other features
  - High mortality (10-15% p.a.)
  - Frequent hospital readmissions (10-15%p.a.)
  - Impaired quality of life

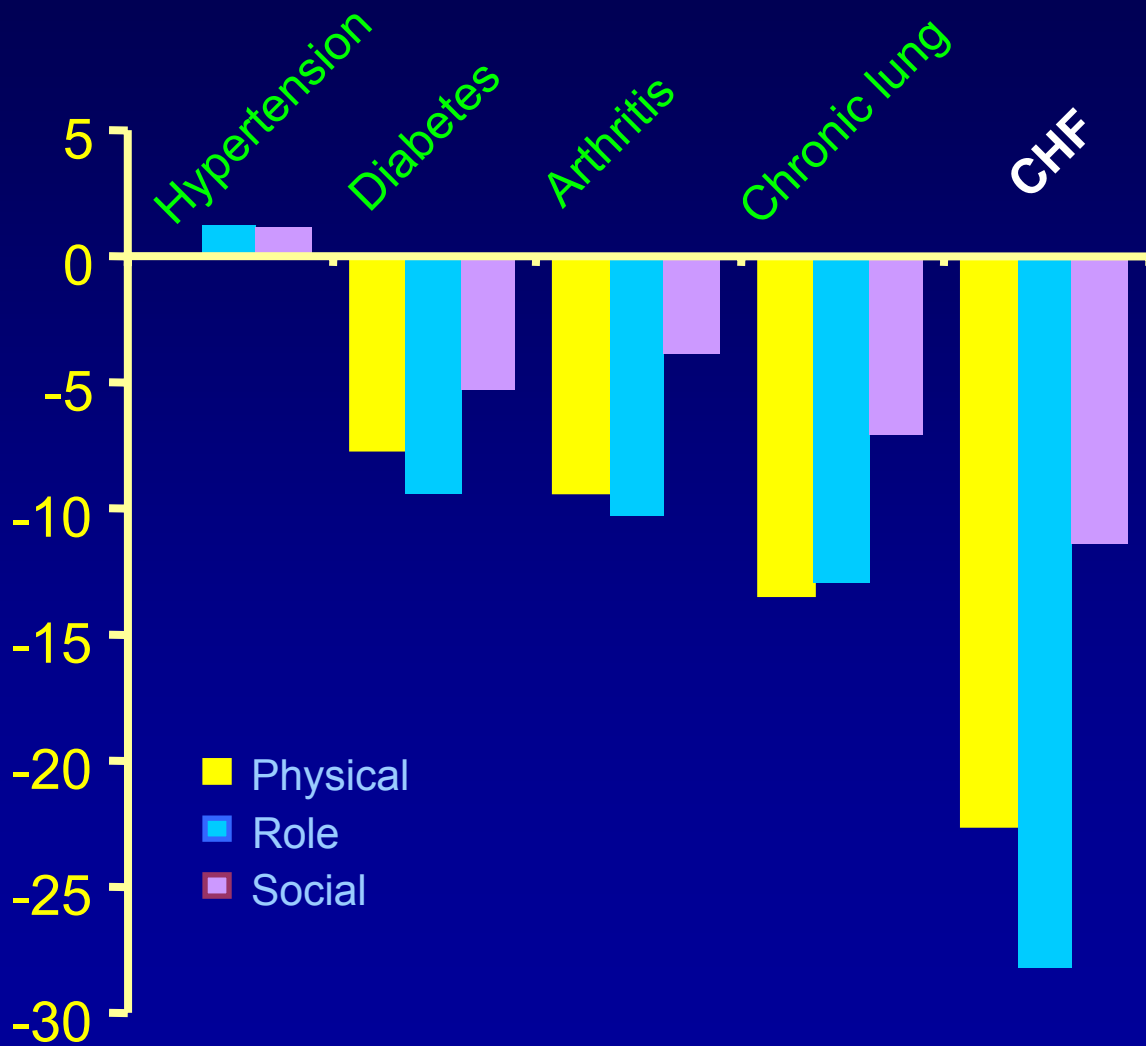


# CHF prevalence and mortality

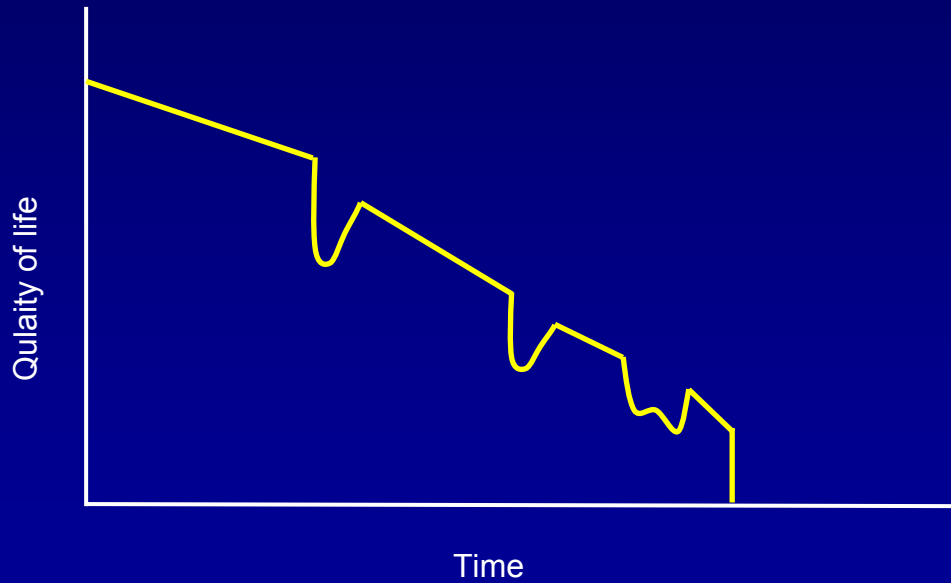
	Number (/100,000)	Chance of surviving for 5 years
Prostate cancer	120	71%
Breast cancer	116	79%
Lung cancer	64	7%
Bowel cancer	60	55%
Cervical cancer	9	65%
Heart failure	130	40%



# Disability in chronic heart failure



# Natural history





# CHF recognised treatments

- Diuretics
- ACE inhibitors
- Beta-blockers
- Spironolactone
- Cardiac resynchronisation therapy (CRT)



# Reductions in mortality

- Absolute one year mortality in control arm
  - 1987 Consensus (enalapril) 44%
  - 1999 RALES (spironolactone) 33%
  - 1999 Dig trial (digitalis) 18%
  - 2002 CIBIS II (bisoprolol) 13%
  - 2003 CHARM (AIIA) 13%
  - 2005 CARE-HF (CRT) 10%

...in study patients

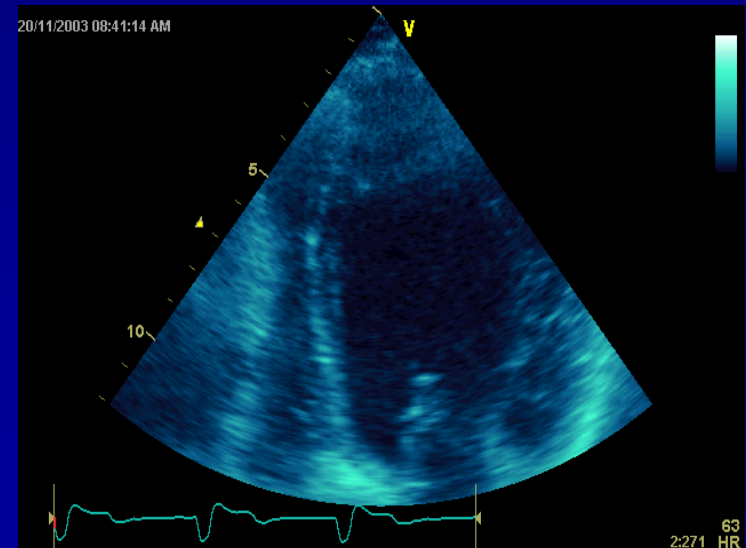
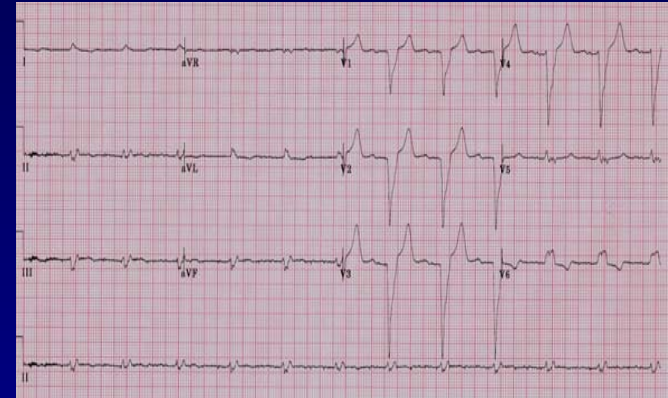
# Rose tinted spectacles

- EVEREST (Europe) – unselected admissions with HF
  - 50% readmission the first year
  - 25% mortality year
  - Higher chance of dying following CHF admission than ACS admission
  - But much less info and investment



# CHF with conduction delay

- QRS > 120ms seen in 30% with LVSD
- QRS duration inversely related to LVEF
- QRS lengthens as CHF worsens
- Incidence of MR also increases with QRS (20% if >120ms, 8% if QRS<120ms)
- Death rate increases with QRS (<120ms; 20% and >160ms; 58% at 36 months)





# What do the early studies tell us?

Trial	Number of patients	Design	Blinding	Follow-up	Entry criteria		Symptoms	Hospitalisation	Mortality (number of patients)	
					NYHA (LVEF)	QRS (mean value)			Control	Resynch.
MUSTIC <sup>24</sup>	59 implanted 48 completers	X-over	Single	3 months in each arm	III (<35%)	>150 ms (176 ms)	Improved	Reduced	1	2
MUSTIC-AF <sup>24,26</sup>	54 implanted 37 completers	X-over	Single	3 months in each arm	III (<35%)	>200 ms	Improved	No effect	0	1
MIRACLE <sup>25</sup>	453	Parallel	Double	6 months	III-IV (≤35%)	≥130 ms (166 ms)	Improved	Reduced	16	12
CONTAK-CD <sup>27</sup>	490	Parallel	Double	4.5 months	II-IV (≤35%)	≥120 ms (158 ms)	Improved	No effect	14	11
MIRACLE-ICD <sup>22,28</sup>	374	Parallel	Double	6 months	III-IV (≤35%)	≥130 ms	Improved	Reduced	15	14
PATH-CHF II <sup>23</sup>	89 implanted 65 completers	X-over	Double	3 months	II-III (≤30%)	≥120 ms	Increased exercise time	NA	NA	NA
Total <sup>b</sup>	1467	NA	NA	NA	NA	NA	NA	NA	46	40

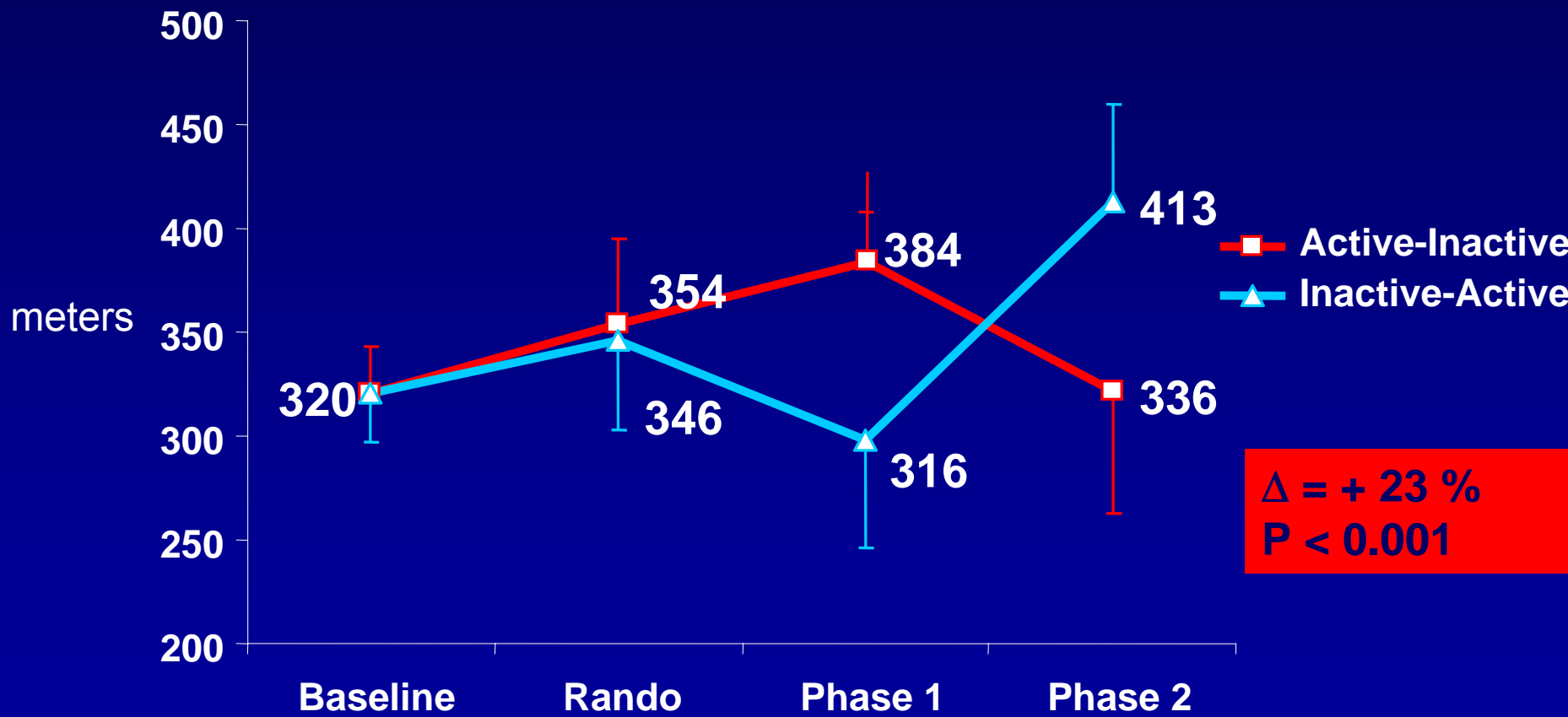
Parallel=patients randomised and followed-up in two parallel arms; X-over=patients randomised and crossed-over after the end of the first treatment period; NA=not available; MUSTIC=multisite stimulation in cardiomyopathy; MUSTIC-AF=multisite stimulation in cardiomyopathy in patients with atrial fibrillation; MIRACLE=multi-centre InSync randomised clinical evaluation; CONTAK-CD=CONTAK-CD programme; MIRACLE-ICD=multi-centre InSync randomised clinical evaluation in patients requiring an ICD; PATH-CF=pacing therapies in congestive heart failure II.

<sup>a</sup>Based on preliminary reports.

<sup>b</sup>Total includes only patients who completed cross-over studies.



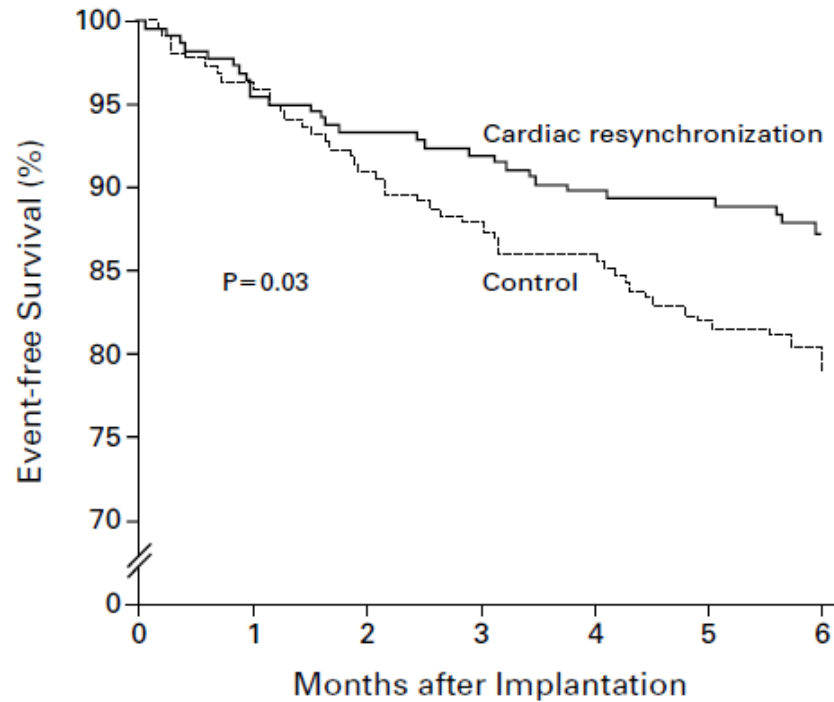
# MUSTIC study



$\Delta = + 23 \%$   
 $P < 0.001$



# INSYNC – CRT-P



No. AT RISK

Control	225	214	204	197	191	179	70
Cardiac resynchronization	228	218	213	209	204	201	99



# Benefits of CRT alone (CRT-P)

- Symptom reduction
- Increased exercise tolerance (MIRACL, MUSTIC, PATH-CHF, InSYNC)
- Reduced hospital admission
- Improved haemodynamics and LV function
  - (Vigor-CHF)
- Improved renal function



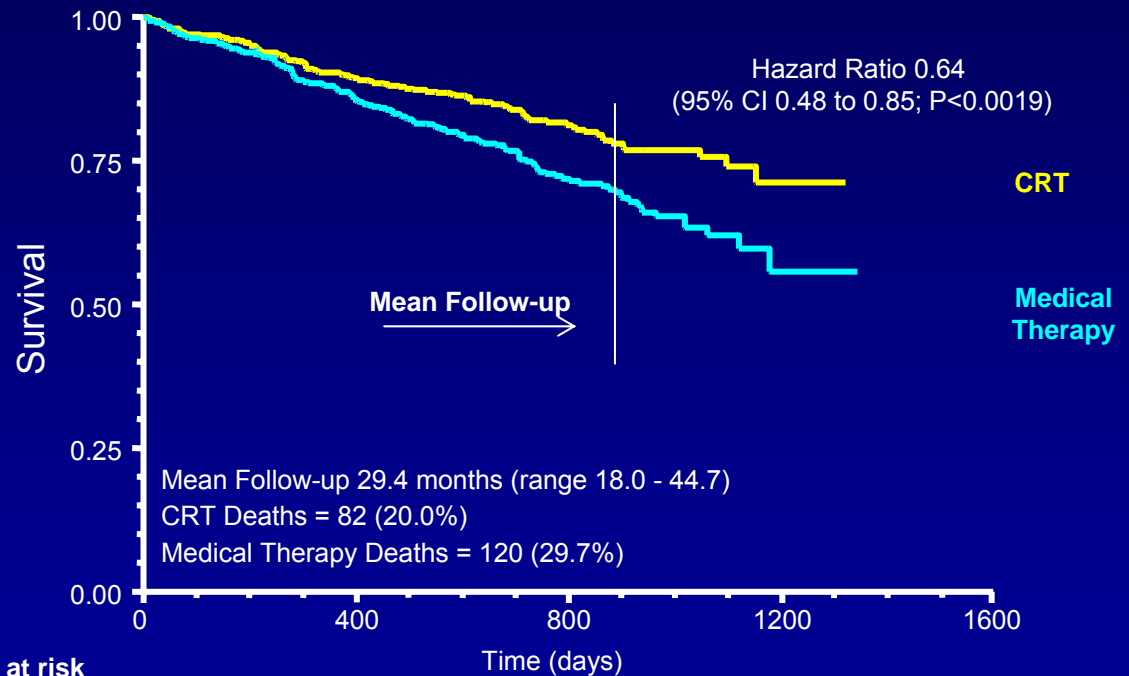
# Later studies - mortality data





# CARE-HF

- QRS >150ms (or 120ms with simple dyssynchrony)
- EF < 35%
- NYHA class III / IV



	Number at risk					
	0	400	800	1200	1600	
CRT	409	376	351	213	89	8
Medical therapy	404	365	321	192	71	5



# Benefits of CRT alone (CRT-P)

- Symptom reduction
  - Increased exercise tolerance (MIRACL, MUSTIC, PATH-CHF, InSYNC)
- Reduced hospital admission
- Improves haemodynamics and LV function
  - (Vigor-CHF)
- Improved renal function
- Mortality reduction
  - Reduced pump failure death (and sudden death)(CARE-HF)



# Current NICE indications for CRT

- Currently *or previously* New York Heart Association class III–IV symptoms
- Sinus rhythm:
  - **either** with QRS duration of 150ms or greater
  - **or** with a QRS duration of 120–149 ms *and* mechanical dyssynchrony
- Left ventricular ejection fraction of  $\leq 35\%$
- Receiving optimal pharmacological therapy



# Holes in our knowledge

- Previously outstanding issues:
  - NYHA status / symptoms / ‘severity’
  - Narrow QRS
  - Atrial fibrillation
  - Elderly
  - Co-morbidities
  - RV paced patients (upgrades)
  - Currently hospitalised patients
  - Mechanical dyssynchrony



# Current NICE indications for CRT

- Symptoms
- QRS duration
- Mechanical dyssynchrony
- Sinus rhythm
- Left ventricular ejection fraction
- Pharmacological therapy



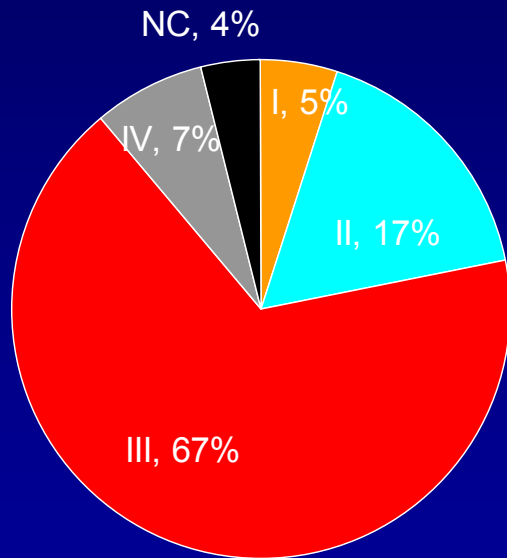
# Symptoms to guide CRT

- Which symptoms matter: fatigue v breathlessness?
- Are symptoms reproducible?
- Are symptoms reliable?
- Do they change?
- What about responders to medical therapy following an exacerbation?
- Do other CHF treatments depend upon symptoms?
- Are patients in class IV already too sick?

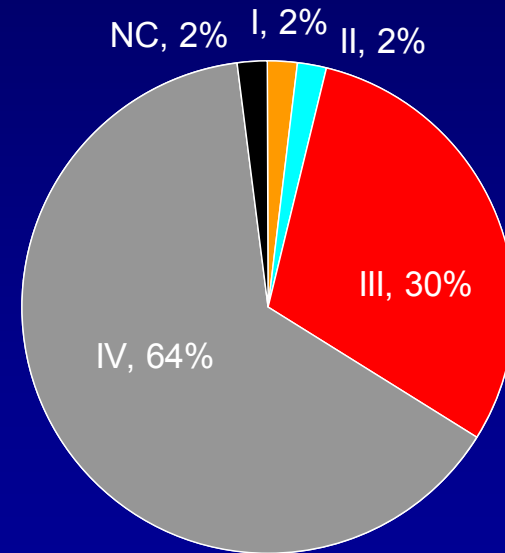


# CARE-HF NYHA class

Investigator-assigned NYHA III (n=763)

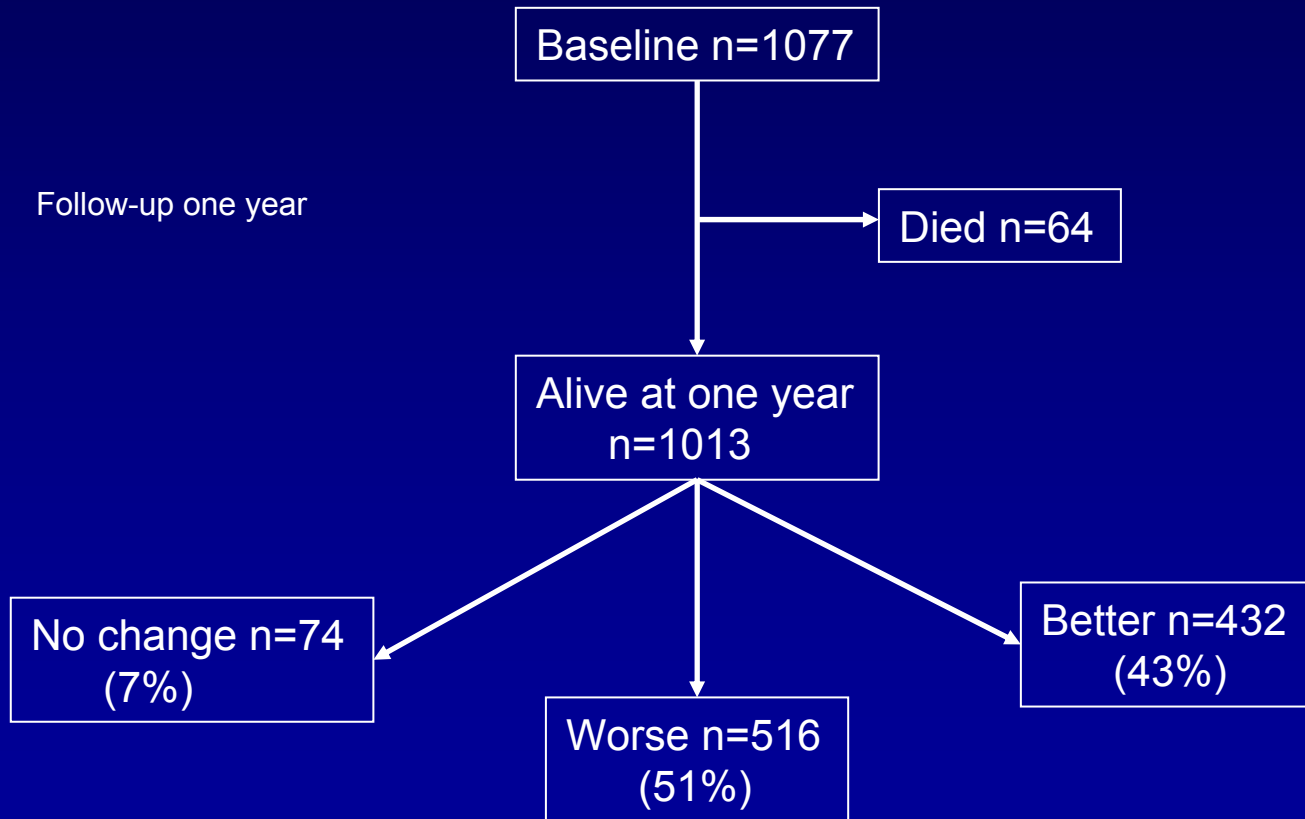


Investigator-assigned NYHA IV (n=50)



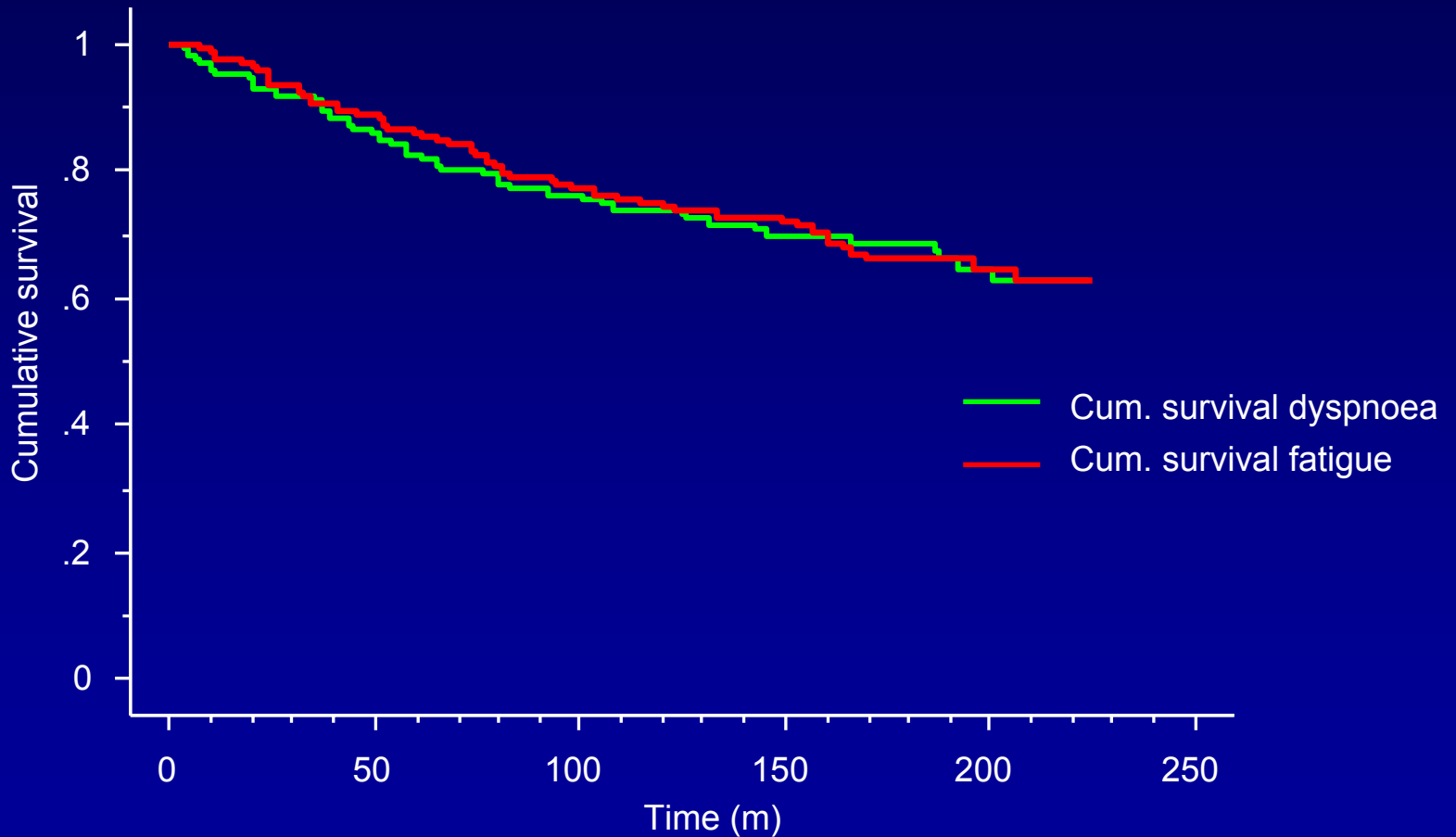


# What happens to patients' symptoms?



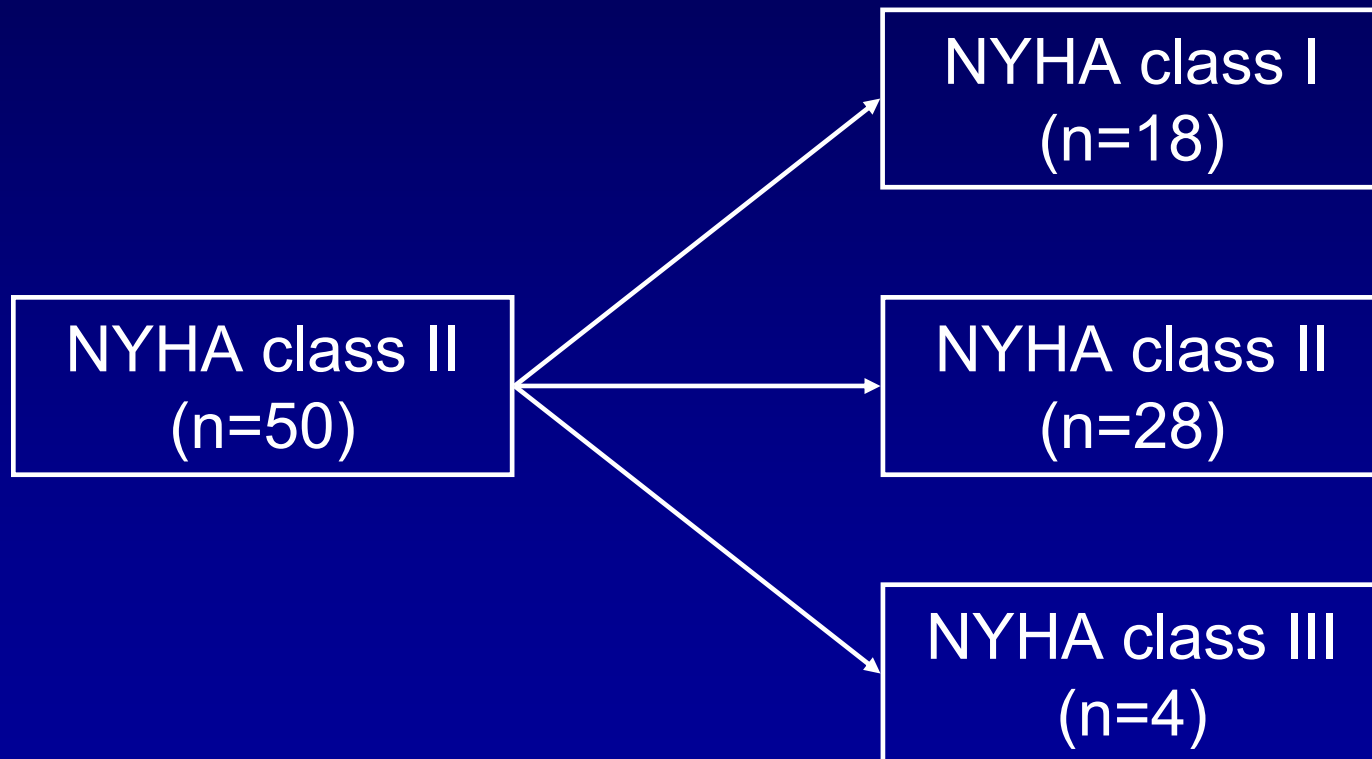


# Severity not nature is a predictor of outcome





# CRT for 'mild' CHF



EF 25%(7) with QRS 160ms, optimal medical management, follow-up 6 months



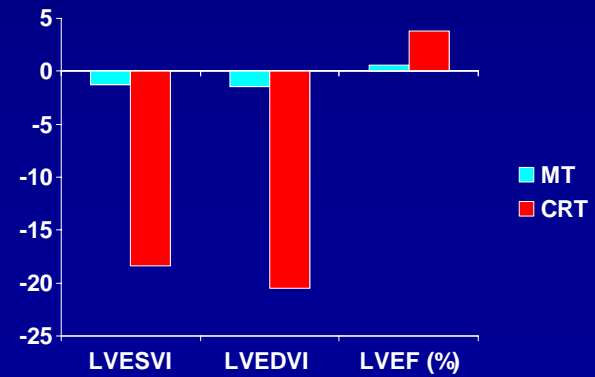
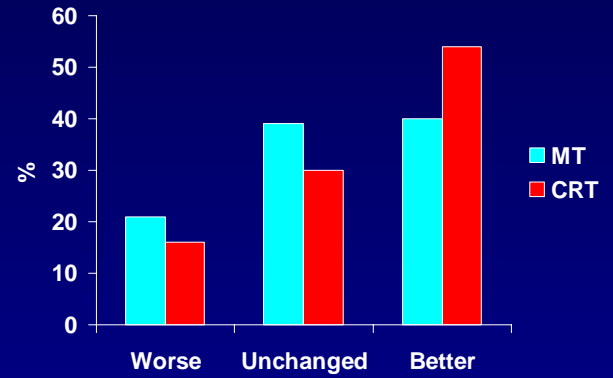
# REVERSE

- Does CRT decrease 'disease progression' in patients with mild/asymptomatic heart failure and ventricular systolic dysfunction?
- NYHA class I or II (incl. medical responders)
- QRS > 120 ms
- LVEF  $\leq$  40%, LVEDD > 55mm
- Enrolled patients:
  - 642 implant attempts (621 successful implants)
  - EF 26%, LVEDD 70mm, QRS 154ms
  - 55% IHD, 95% BB, 97% ACEi, 78% diuretics
  - 191 – CRT on; 419 – CRT off – blinded for 12 months (Europe 24 months)



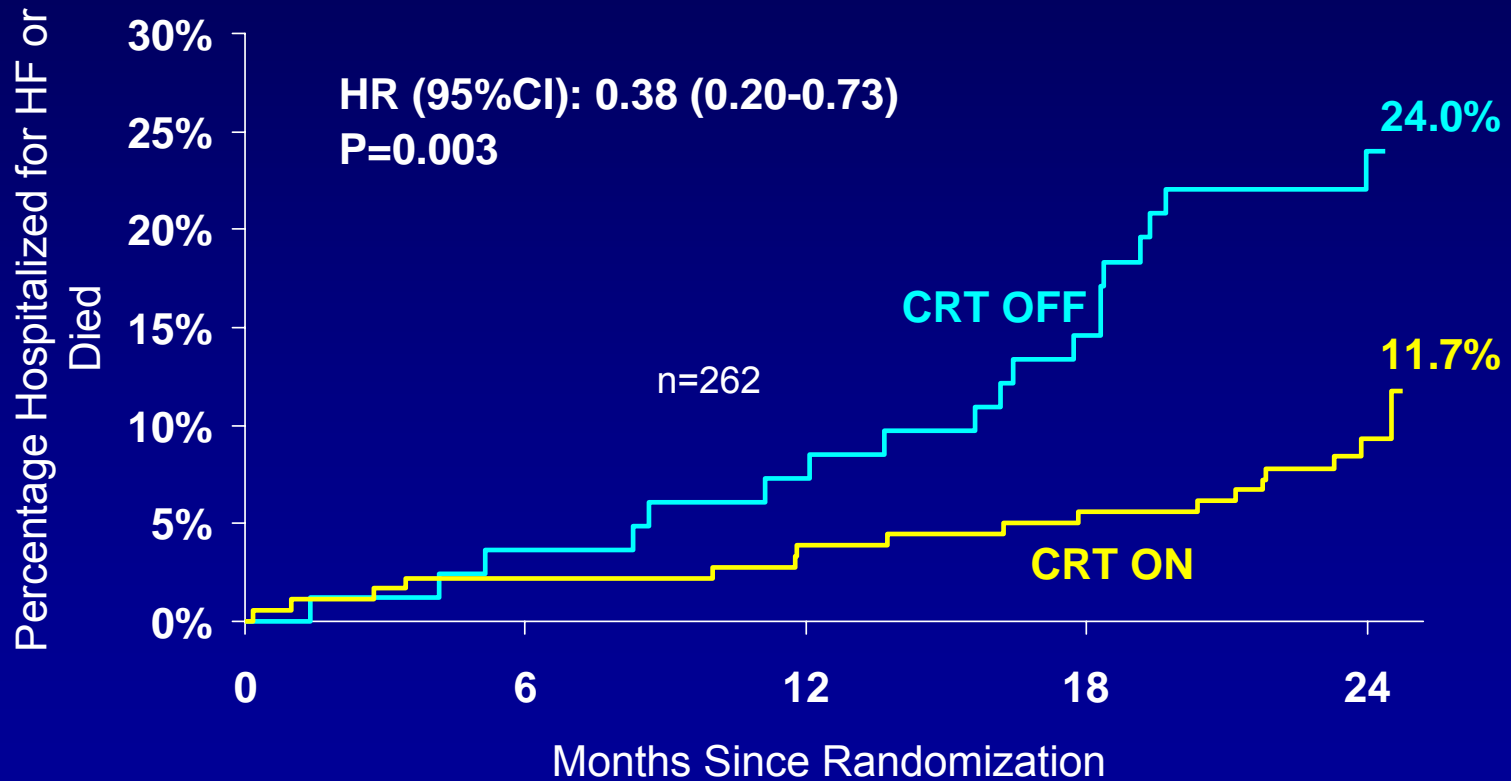
# REVERSE

- 1° endpoint (clinical features)





# REVERSE - European cohort



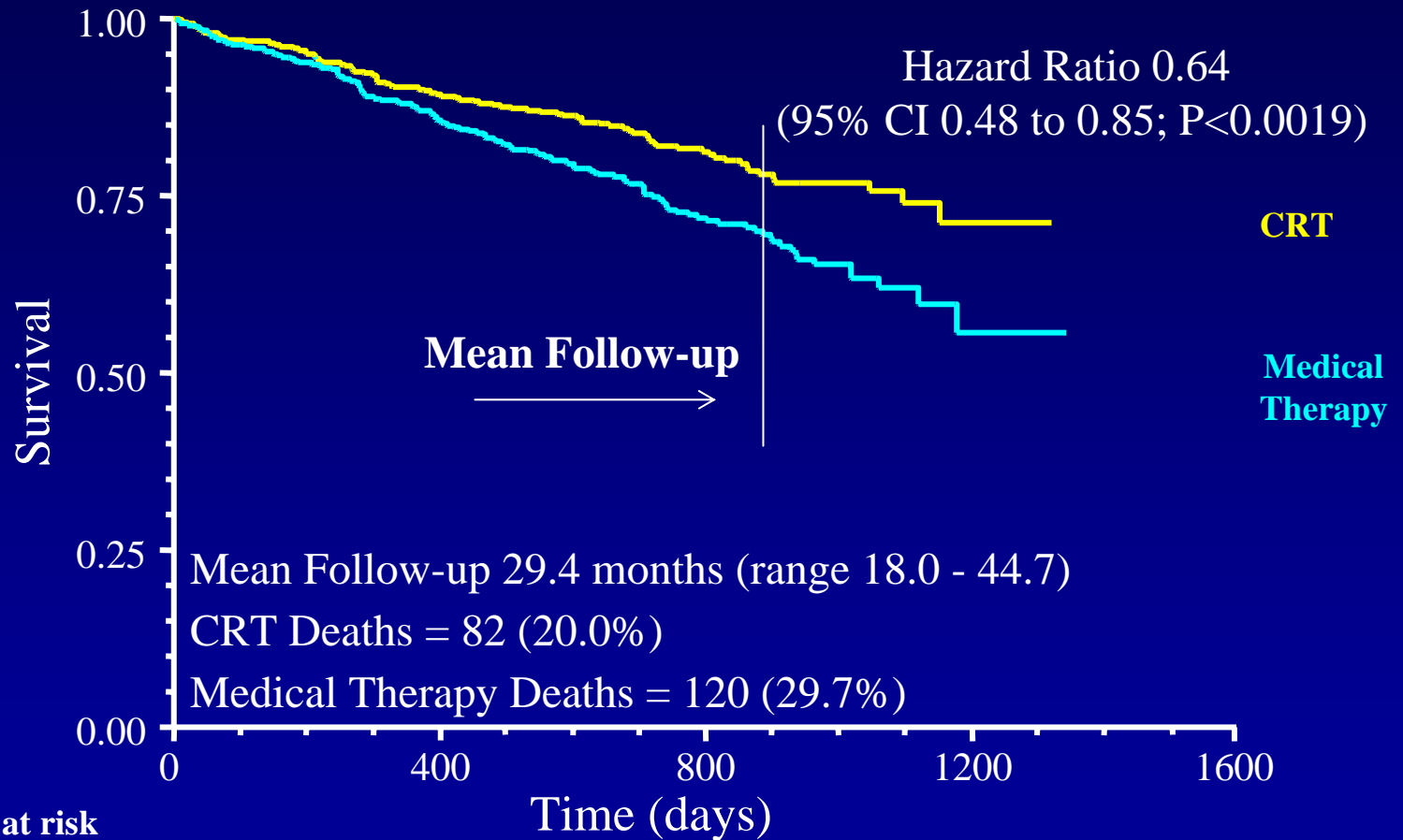
NYHA class I; n=44 – no significant different in terms of composite clinical score, or improvement in LV function but not sign



# CARE-HF Main Study

## Effect of CRT on All-Cause Mortality

(Emergency heart transplant included in definition)



Number at risk

CRT	409	376	351	213	89	8
Medical therapy	404	365	321	192	71	5



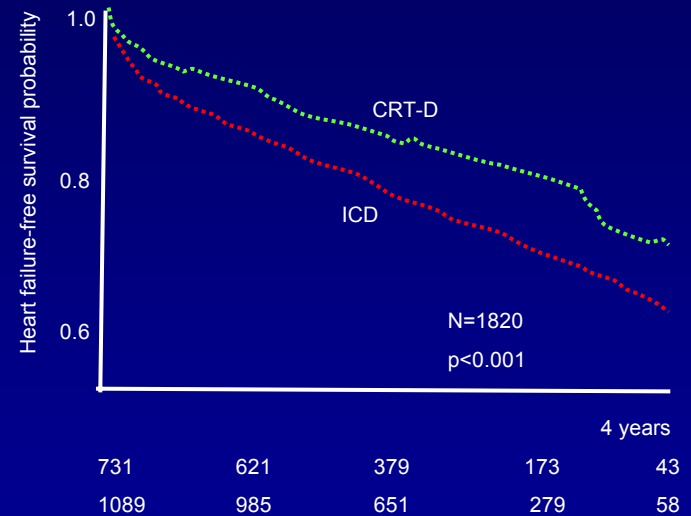
# MADIT-CRT

- Does 'early' CRT improve outcomes?
  - ICD v CRT-D
  - EF < 30%,
  - QRS > 130ms
  - Class I or II
  - DCM or IHD
- 1820 patients, followed 4.5 years



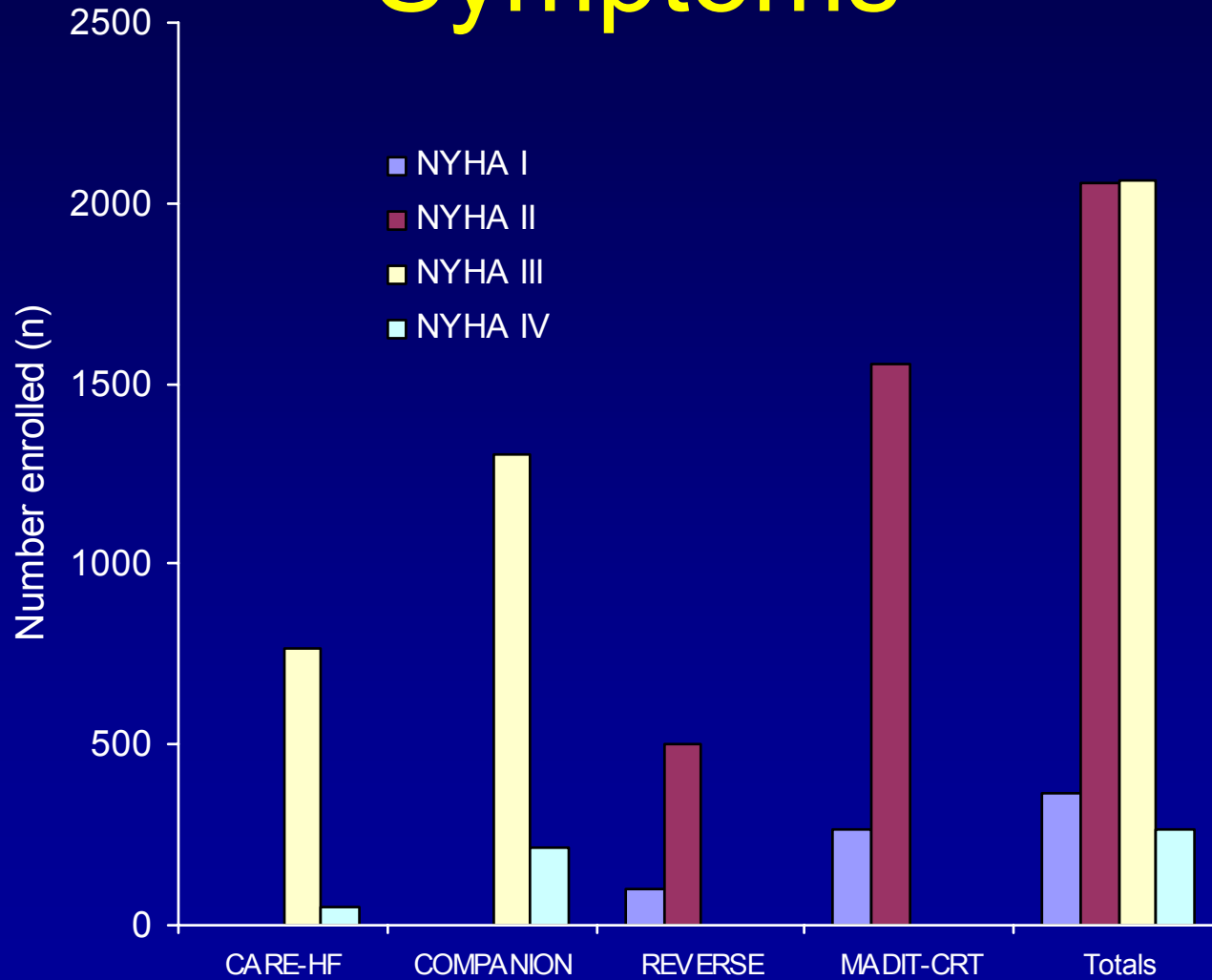
# MADIT-CRT

- All-cause mortality + heart failure:
  - 25.3 v 17.2% (HR 0.66;  $p < 0.001$ ) (31%)
- HF events:
  - 22.6 to 13.9% (HR 0.59;  $p < 0.001$ ) (41%)
- Death:
  - 7.3 to 6.8% (HR 1.00)  $p = 0.99$
  - Annual death rate 2.5%
- Heterogeneity
  - $>150\text{ms}$  v  $<150\text{ms}$
  - women 63% reduction in HF events
  - not for EF ( $>/<25\%$ )





# Symptoms





# Heart failure 'severity'

- CARE-HF study:
  - Relative reduction in mortality greater in those with modestly elevated BNP
  - Change in symptoms not a useful guide to prognostic benefits of CRT
  - Change in LV function (at 6/12) unrelated to change in outcome
- REVERSE and MADIT-CRT:
  - Reduction in mortality greater and earlier than in CARE-HF
- Class II and class I patients might be gaining years quickly and the class III and class IV gaining months slowly
- Symptoms probably not a good way to select patients for CRT



# Current NICE indications for CRT

- Symptoms
- QRS duration
- Mechanical dyssynchrony
- Sinus rhythm
- Left ventricular ejection fraction
- Pharmacological therapy



# QRS duration

- COMPANION <147ms (ns)
- CARE-HF <160ms (CI 0.54-1.02)
- MADIT-CRT - <150ms no benefit (645 patients)
- REVERSE – <152 no benefit (120 v 142)
- Dyssynchrony studies?



# PROSPECT

- 426 patients – 69% clinical improvement  
(76% for DCM and 64% for IHD)
- Clinical benefit in 76% non-ischaemic and  
64% ischaemic
- LVESV in 63% non-ischaemic, and 50%  
ischaemic patients



# PROSPECT

- None of the current echo measures of dyssynchrony better than QRS in predicting ‘responders’:
  - Ts sept-lat >65ms,
  - LPEI
  - IVMD (>40ms)
  - SPMWD (>130ms)
  - Left ventricular filling time/RR
- 7 echo variables (some could only be assessed in 50%) were no better than QRS



# What about $<120\text{ms}$ ?

- No RCT yet
- ECHO-CRT  $<130\text{ms}$  (ongoing)



# Current NICE indications for CRT

- Symptoms
- QRS duration
- Mechanical dyssynchrony
- Sinus rhythm
- Left ventricular ejection fraction
- Pharmacological therapy



# Atrial fibrillation

- MUSTIC-AF – slow VR response
- CARE-HF – no difference in relative reduction in mortality
- SPARE (Am J Cardiol 2008)
  - AF v SR in CRT recipients 470 patients incl 126 with AF
  - No difference in change in QoL, 6MWT, LV remodeling
  - AF worse outcome
- Meta-analysis (JACC 2008)
  - 1164 patients, baseline and one year (SRv AF)
  - NYHA class improved similarly
  - 6MWT less improvement in AF patients
  - Echo greater improvement in AF patients



# Holes in our knowledge

- Previously outstanding issues:
  - NYHA status / symptoms / ‘severity’
  - Narrow QRS
  - Mechanical dyssynchrony
  - Atrial fibrillation
  - Elderly
  - Co-morbidities
  - Currently hospitalised patients
  - RV paced patients (upgrades)



# Old people

- Companion 

	<70	>70
– ACM/hospitalisation	HR 0.81	0.81
– QoL improvement	-15	-20
– NYHA %improved	20	22
- Elderly patients (>80years) have similar benefit on LV function, volumes and hosp from CRT (*Am Heart J* 2008)



# Co-morbidities

- Renal dysfunction
- Anaemia



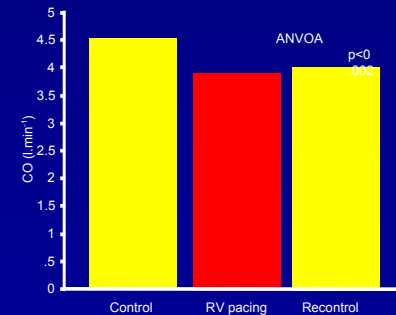
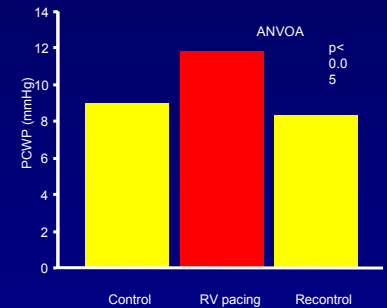
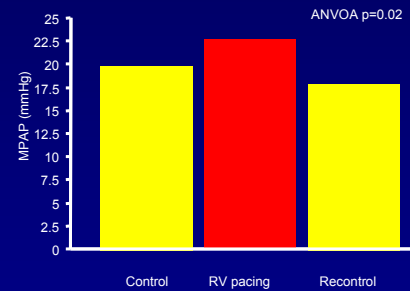
# Hospitalised patients

- Few data
- Some data for cardiogenic shock



# RV pacing in CHF patients

- regional ischaemia
- adverse LV remodelling,
- LV dilatation,
- assymetrical hypertrophy
- myocardial fibrosis,
- fat deposition,
- mitochondrial morphological changes
- cardiac sympathetic activation (and increased tissue catecholamine levels)





# CHF patients upgraded to CRT

	Non-paced patients (n=39)		Previously paced patients (n=32)	
	Pre	Post	Pre	Post
LVEF (%)	20 (1)	27 (2) <sup>***</sup>	20 (2)	30 (3) <sup>***</sup>
LVEDV (ml)	249 (14)	240 (12)	232 (15)	212 (16) <sup>*</sup>
LVEDD (mm)	70 (2)	71 (2)	70 (2)	71 (2)
RVP (mmHg)	36 (2)	29 (2) <sup>**</sup>	33 (2)	31 (2)
Aortic-pulmonary delay (ms)	56 (5)	25 (4) <sup>***</sup>	57 (8)	27 (7) <sup>**</sup>
SPWMD (ms)	235 (16)	22(19) <sup>***</sup>	180 (19)	48 (21) <sup>***</sup>
Lateral wall-septal mitral annulus delay TDi (4ch) (ms)	76 (12)	12 (8) <sup>**</sup>	101 (12)	10 (9) <sup>***</sup>
Lateral mitral – tricuspid annulus delay TDi (4ch) (ms)	77 (11)	33 (12) <sup>*</sup>	97 (11)	26 (12) <sup>**</sup>

Values are means (SE).

LVEF, Ejection fraction by Simpson's calculation; LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end systolic volume; LA, left atrial diameter; \* p<0.05, \*\* p<0.005, \*\*\* p<0.0001 from baseline.



# 'Upgrade' to CRT - conclusions

- In class III and IV
  - No difference in baseline dyssynchrony between groups
  - No difference in baseline medical therapy
  - No difference in reductions in frusemide dose, dyssynchrony and improvements in symptoms and LV function between groups
- No RCT
- No data on class I or II

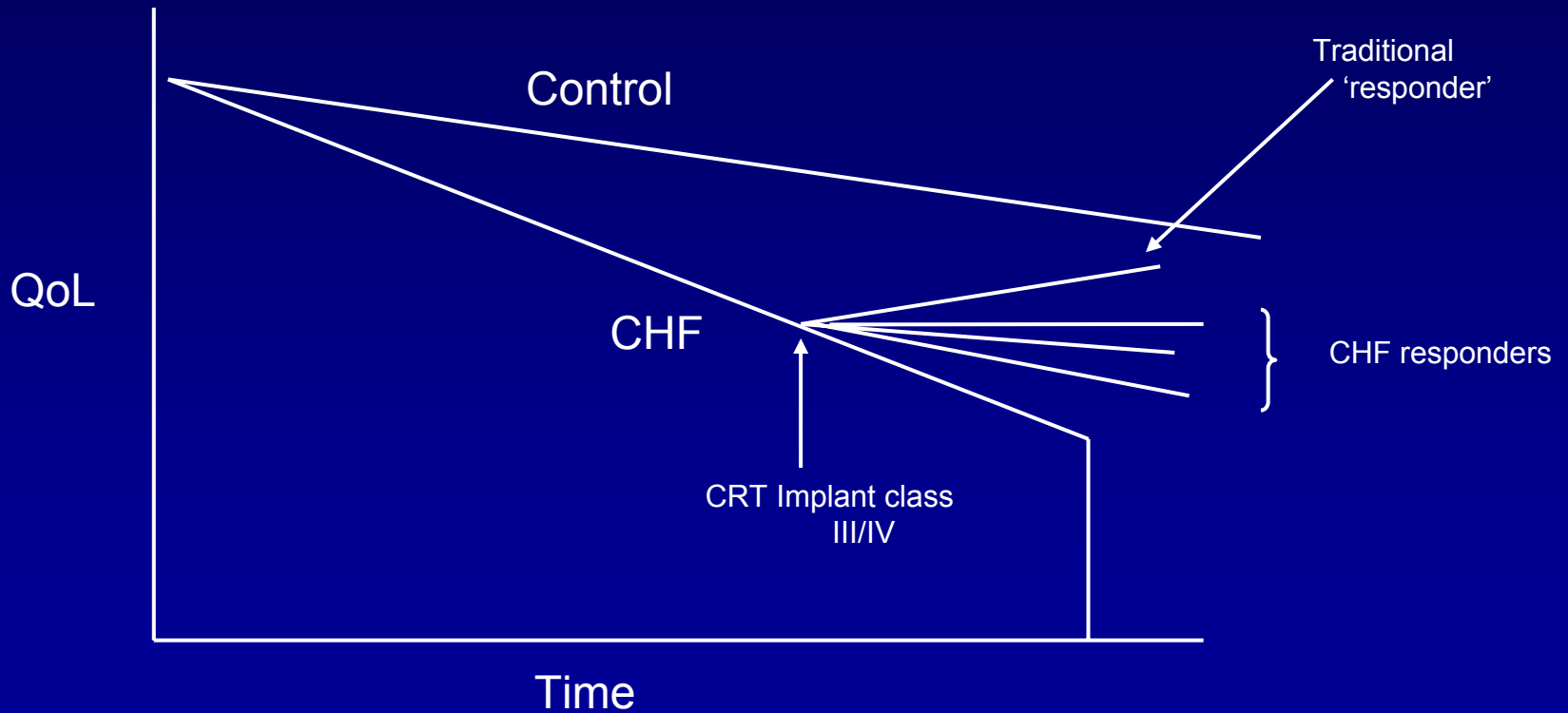


# Myths in CRT exposed

- Selection for CRT is difficult
- Failure to improve LV function = failure to benefit
- CRT implantation is complex and high risk
- IHD do less well
- RBBB is not suitable
- CRT pacemakers just work on symptoms and not on survival – for that you need a defibrillator
- High non-responder rate
- Patients have to be '*really sick*' to benefit
- AF is a contraindication
- Patients responding to medical therapy don't need it
- Old people do less well
- 'Upgrades' from standard pacemakers are high risk and low benefit
- CRT is expensive



# What is a 'responder'?





# 2009 status

- Proven

- QRS >150ms
- NYHA class II, III and IV
- LVEF <35%
- DCM and IHD

- Unclear

- QRS <120ms
- NYHA class I
- LVEF 35-50%

- Atrial fibrillation
- Pacemaker patients



# Future indications for CRT

- Current or previous symptoms of heart failure
- QRS duration of  $>120\text{ms}$
- Left ventricular ejection fraction of  $\leq 35\%$
- Receiving optimal pharmacological therapy (as tolerated)



# Enrollment criteria

- MIRACLE (<35% and 6MWT<450m, 130ms, class III or IV)
  - QoL and 6MWT
- MIRACLE-ICD (130ms, NYHA III or IV, EF<35%),
  - QoL, NYHA, 6MWT (6/12 follow-up )
- MUSTIC (QRS 150ms, class III, <35%, EF>60mm
  - QoL and 6MWT
- MUSTIC-AF (slow VR needing pacing, EF<35%, 6MWT<450m QRS >200ms when paced)
  - 6MWT and pVo<sub>2</sub>
- PATH-CHF (120ms, class III or IV)
  - 6MWT, pVo<sub>2</sub>, haemodynamics
- InSYNC (150ms, class III or IV, <35%)
  - 6MWT, QoL NYHA
- (VIGOR-CHF (class III or IV, QRS >120ms)