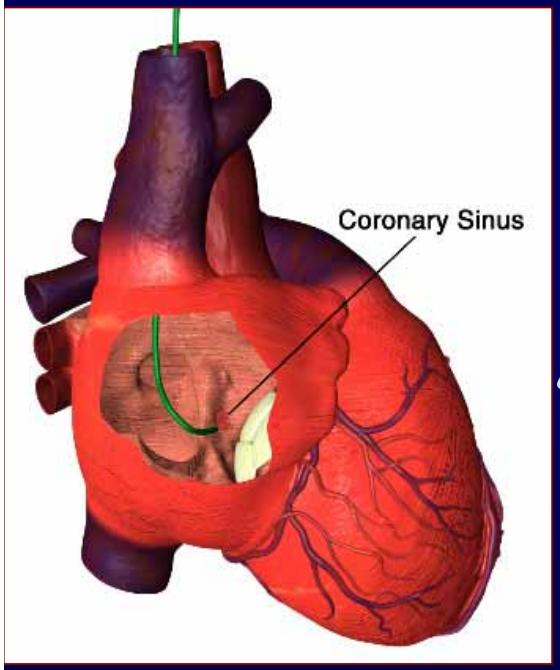
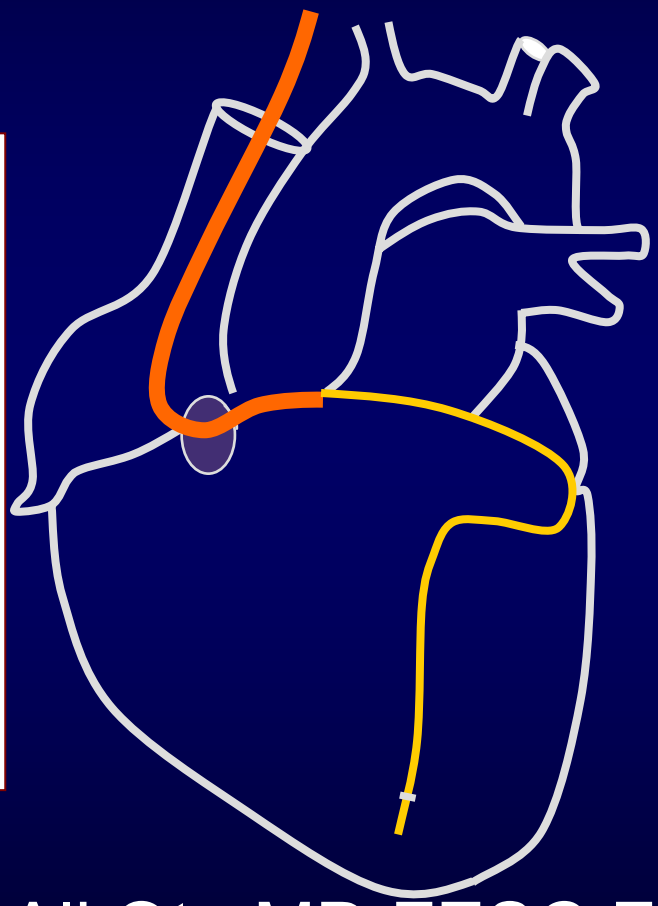
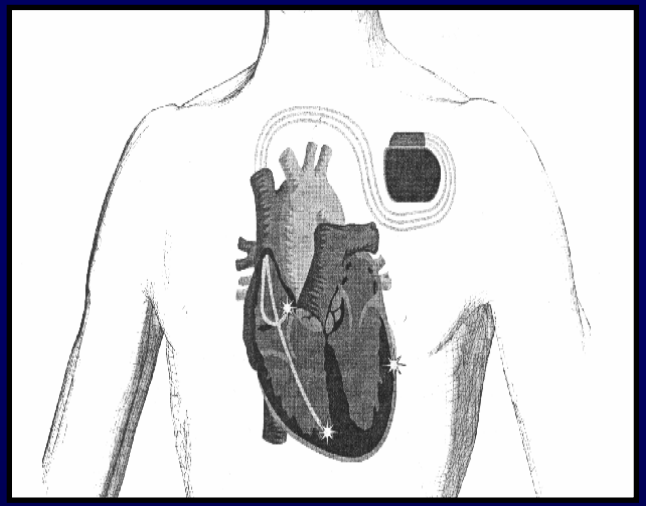
CARDIAC RESYNCHRONISATION THERAPY IN HEART FAILURE



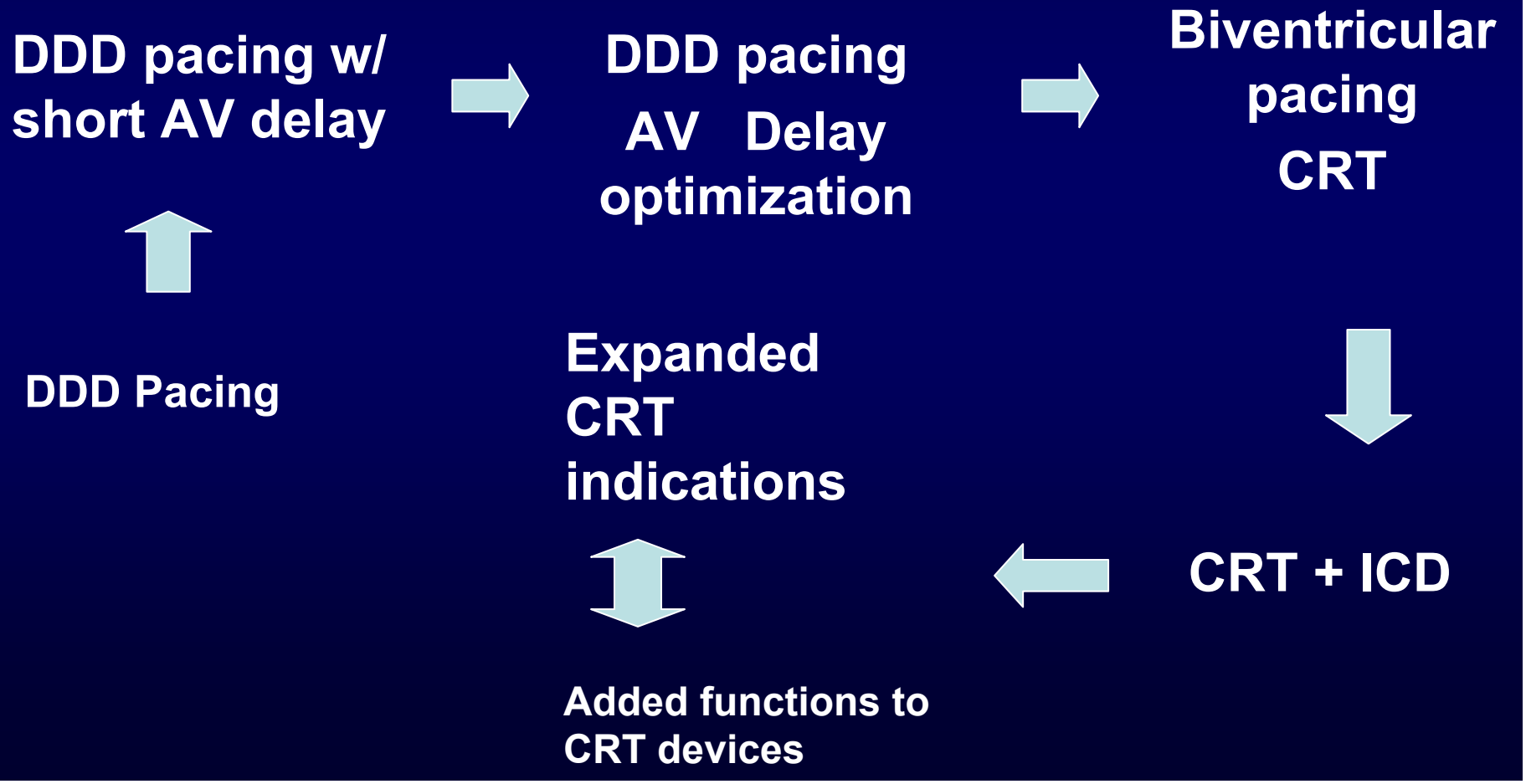




Prof. Ali Oto,MD,FESC,FACC

Hacettepe University,Ankara,Turkey

Pacing for heart failure

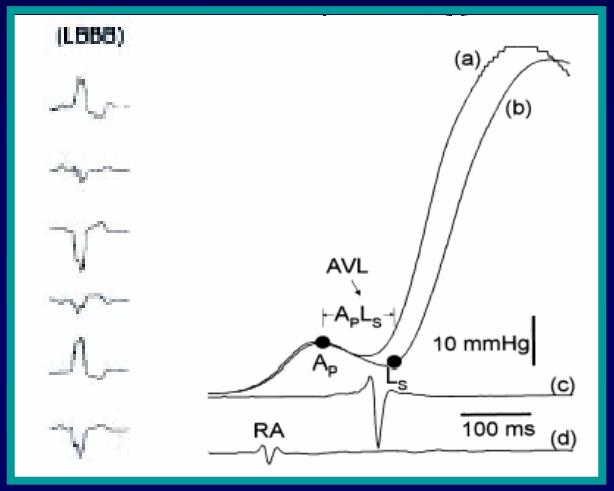


WHAT IS CARDIAC DYSSYNCHRONY ?

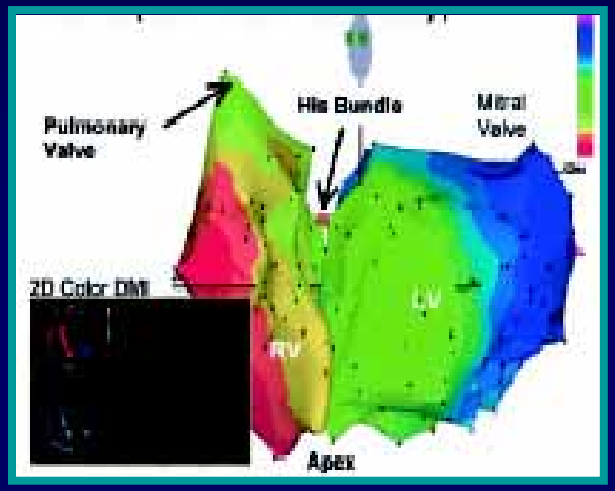
- Cardiac dyssynchrony means that the heart's contraction is not occuring in its usual orderly sequence
- The three components of dyssynchrony that may impair cardiac efficiency
    1. Atrio-ventricular dyssynchrony
    2. Interventricular dyssynchrony
    3. Intraventricular dyssynchrony

Electromechanical Delay in End Stage Heart Failure Patients With Conduction Delay

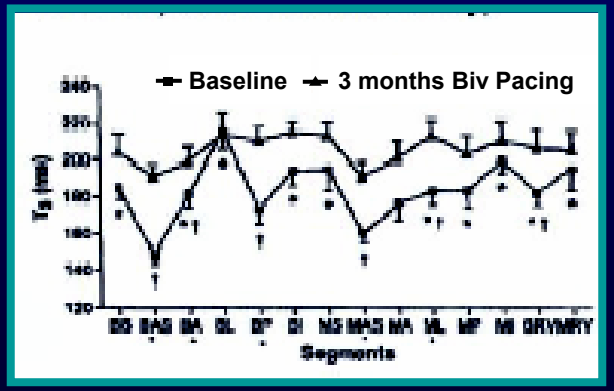
AV DELAY



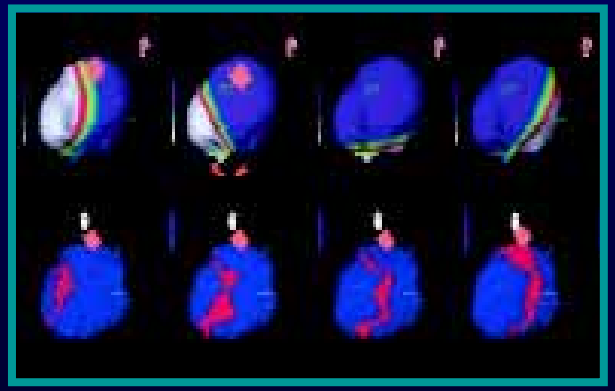
INTERVENTRICULAR DELAY



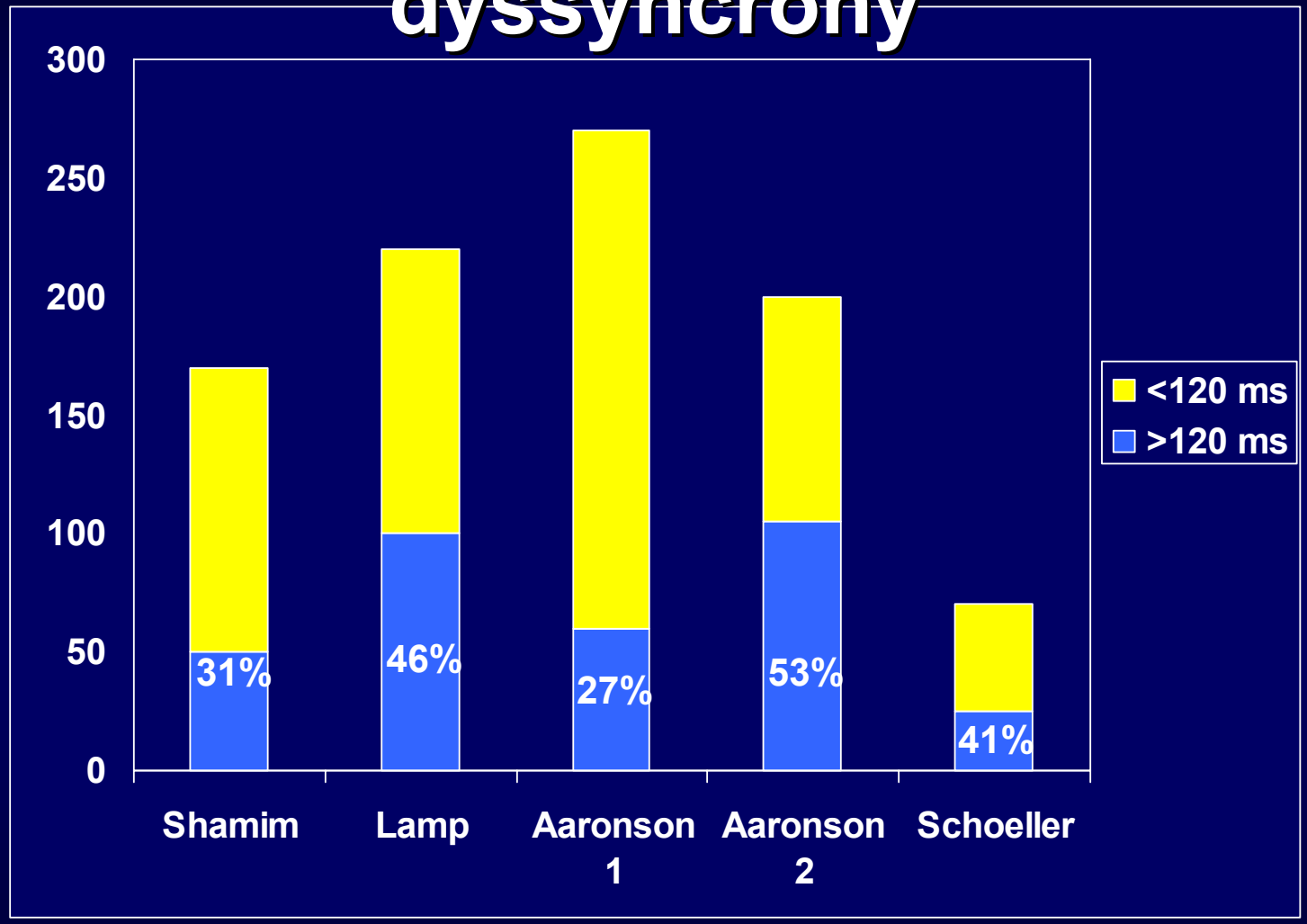
INTRAVENTRICULAR DELAY



INTRAMURAL DELAY



The prevalence of ventricular dyssyncrony



Shamim et all, Eur H J 19 Abs 926, 1998 Lamp et all, PACE 2:II-975, 1998
Aaronson et all, Circ 95: 2660-7, 1997 1, derivation sample; 2, validation sample
Schoeller et all, AJC 71: 720-26, 1993

NEGATIVE HEMODYNAMIC EFFECTS OF LEFT VENTRICULAR ACTIVATION DELAY: Concept of dyssynchrony

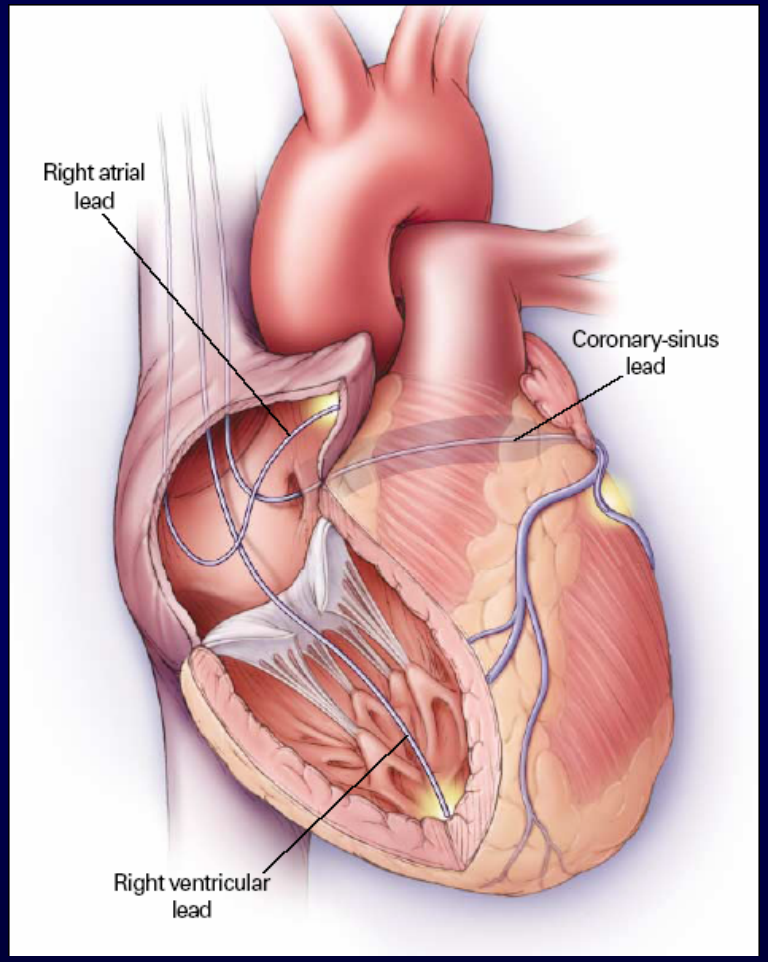
- Altered LV contration and relaxation intervals (↑ PEP, ↑ IVRT)
- Shortening of diastolic filling time
- Reduced systolic function (Global&Regional EF)
- Induction or worsenining of mitral regurgitation

CRT:ACUTE HEMODYNAMIIC EFFECTS

- Increase in cardiac index
- Increase in differential arterial pressure
- Increase in systolic arterial pressure and in left ventricular dp/dt max
- Increase in biventricular EF
- Decrease in systemic vascular resistance
- Decrease in pulmonary capillary pressure
- Decrease in amplitude of V wave in MR

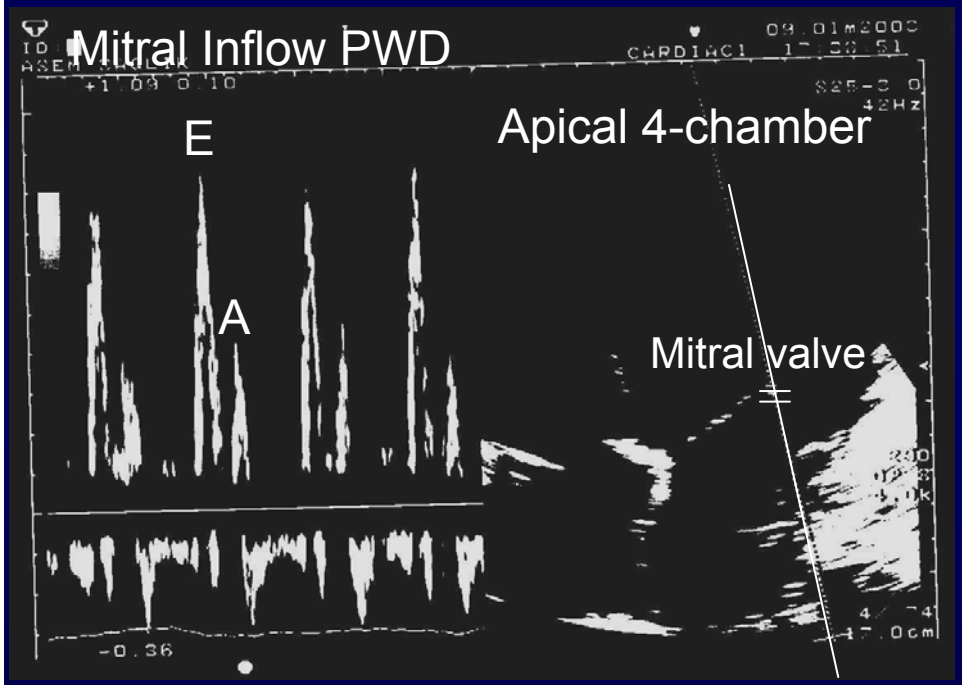
IMPROVED HEMODYNAMICS BY CRT IN CHF PATIENTS

- Optimization of AV contraction sequence
- Resynchronization of right and left ventricular contraction sequence
- Prolongation of diastolic filling time
- Septal motion resynchronization
- Reduction of severity or duration of mitral regurgitation



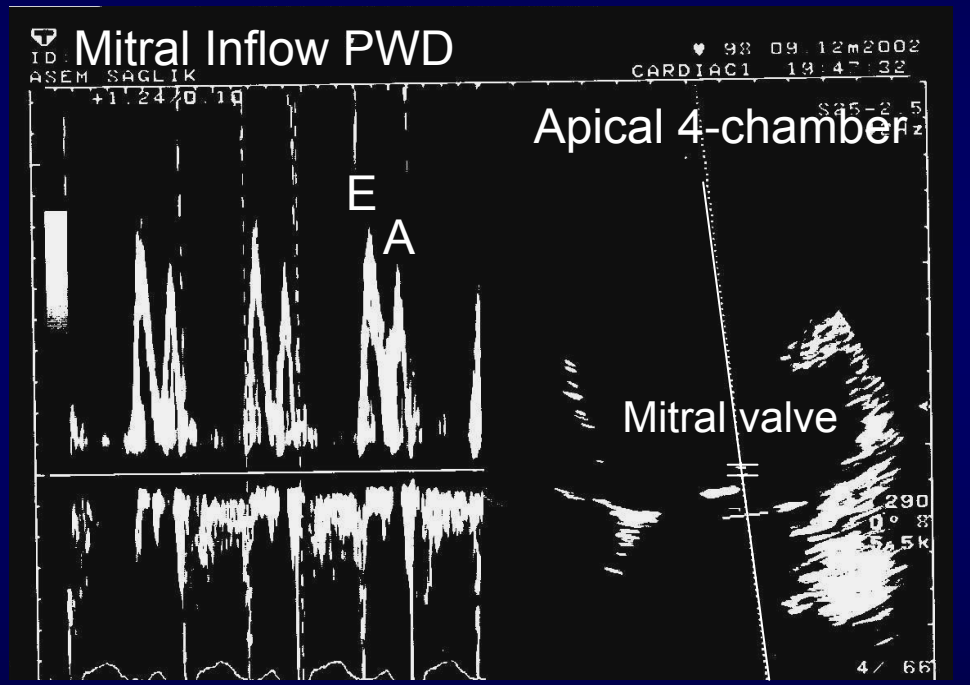
Improvement In Atrioventricular Synchrony

Before AVD Adjustment



E/A = 2.09
Diastolic filling time = 359ms

After AVD Adjustment



E/A = 1.3
Diastolic filling time = 450ms

Improvement in Interventricular Synchrony

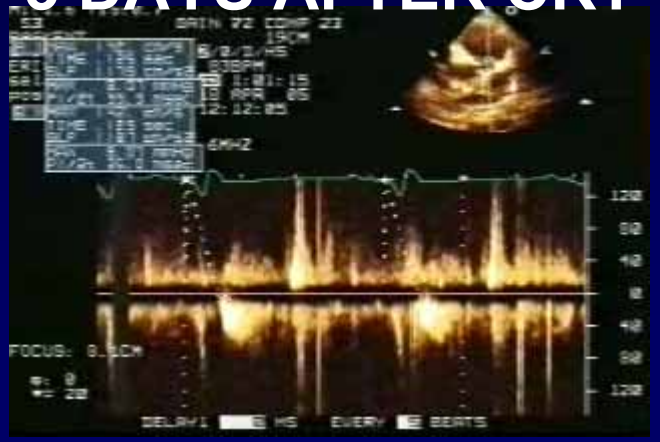
BEFORE CRT

QRS P = 70

QRS Ao = 180ms

DELAY: 180 - 70ms = 110ms

3 DAYS AFTER CRT



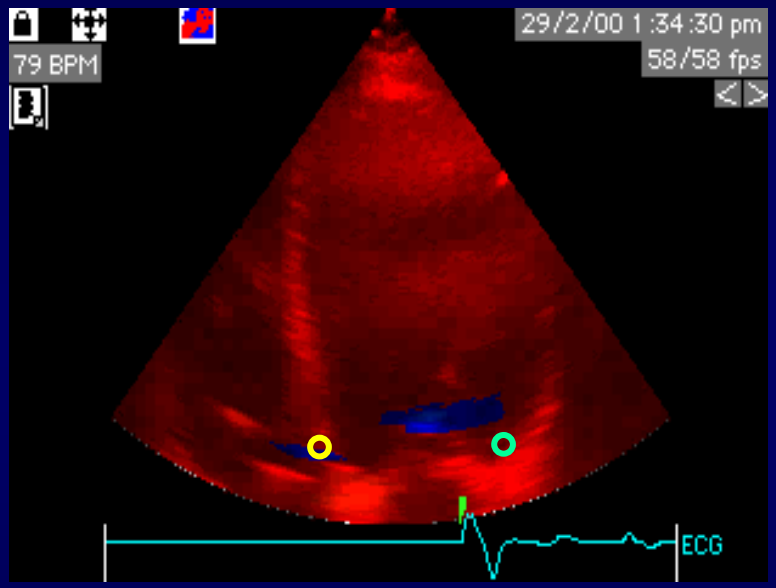
QRS P = 115 ms

QRS Ao = 124ms

DELAY: 124 - 115ms = 9ms

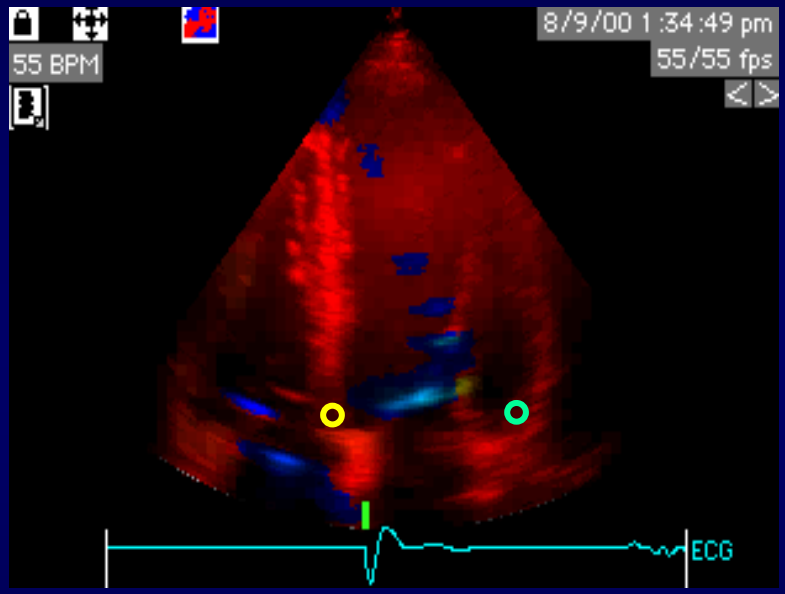
Improvement in Intraventricular Synchrony

Baseline

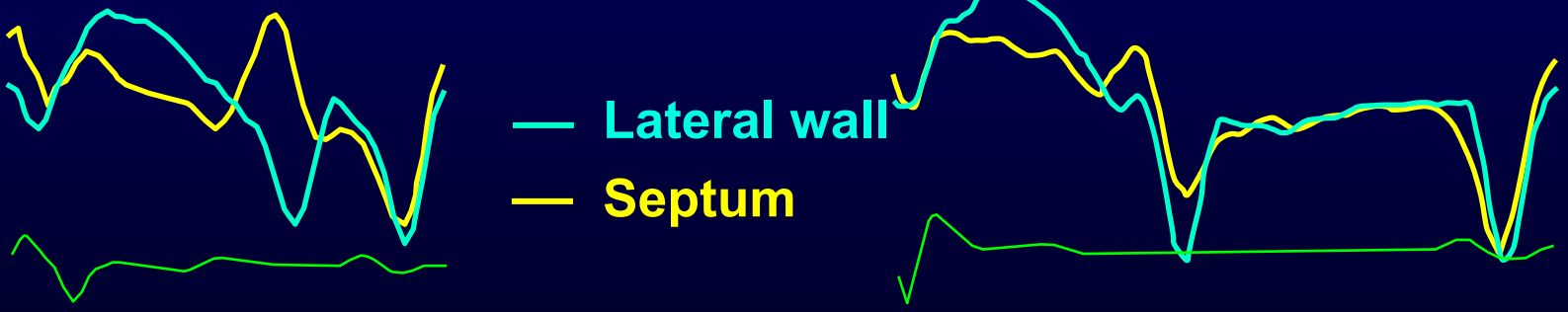


Synchrony r = 0.40

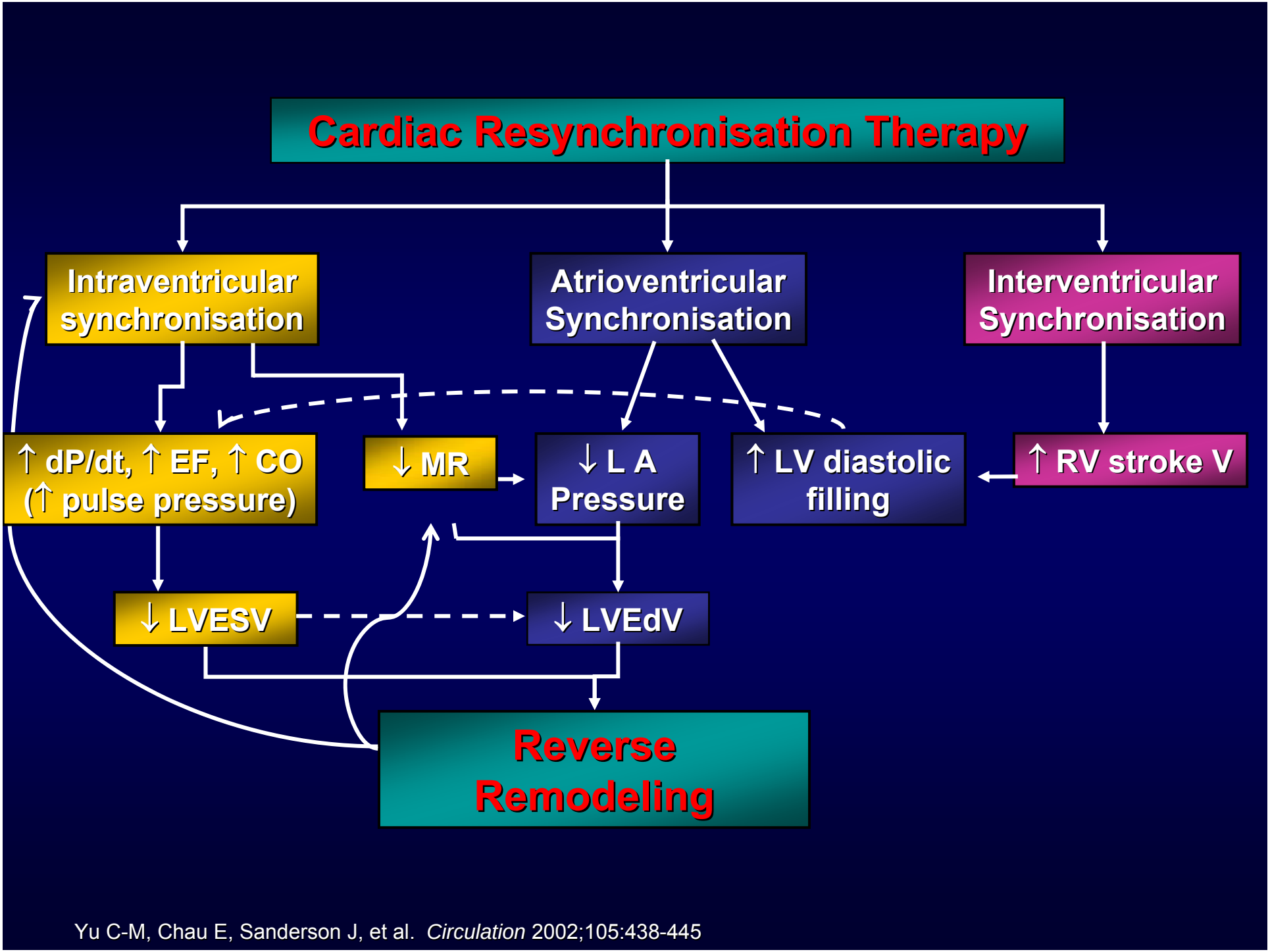
6 months BiV Pacing



Synchrony r = 0.87



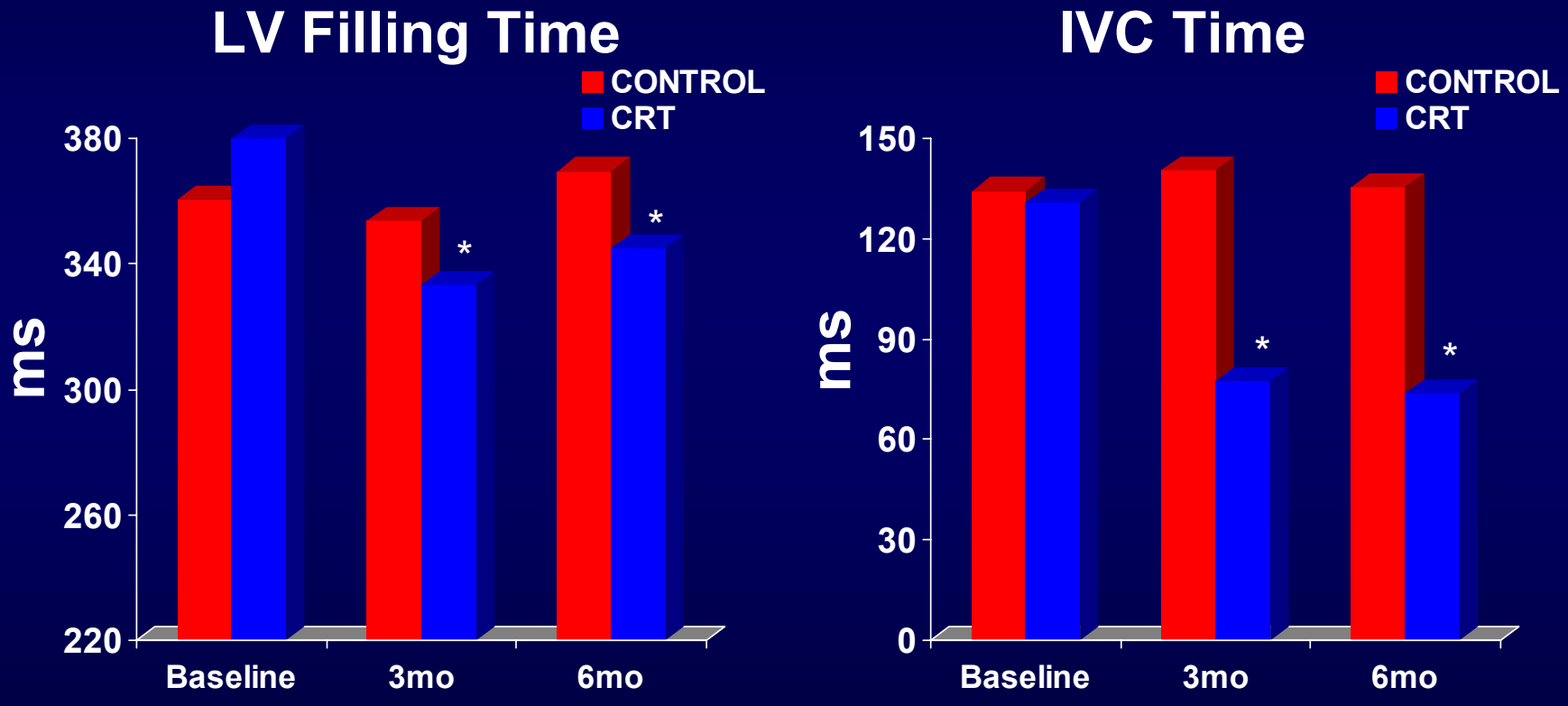
This slide summarizes these improvements showing tissue Doppler cine-loops with a corresponding mitral annular time velocity curves from baseline and 6 months.
A dyssynchronous rocking motion of the mitral annulus was seen at baseline.
This improved at 6 months, showing a more synchronous motion of the mitral annulus.
In addition, you can see an improvement in global LV function.



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

Evidence of LV Resynchronization by Spectral Doppler

MIRACLE Study



*:p<0.05

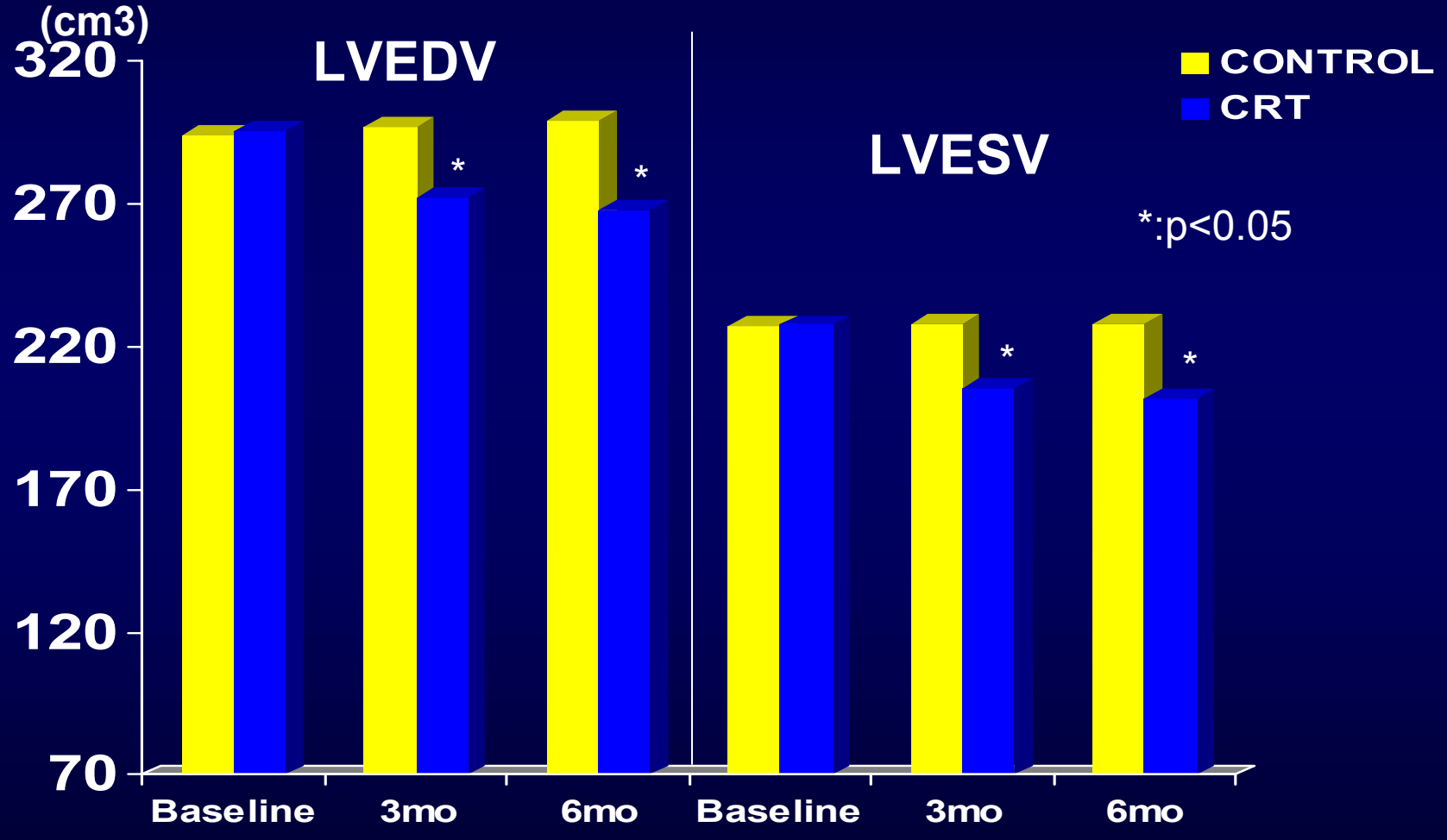
Sutton et al Circulation 2003;107:1985

Echocardiographic Evidence of LV Reverse Remodeling in Responders to CRT

- End diastolic diameter
- End diastolic volume
- End systolic diameter
- End systolic volume
- Ejection fraction
- Sphericity

LV Reverse Remodeling by CRT

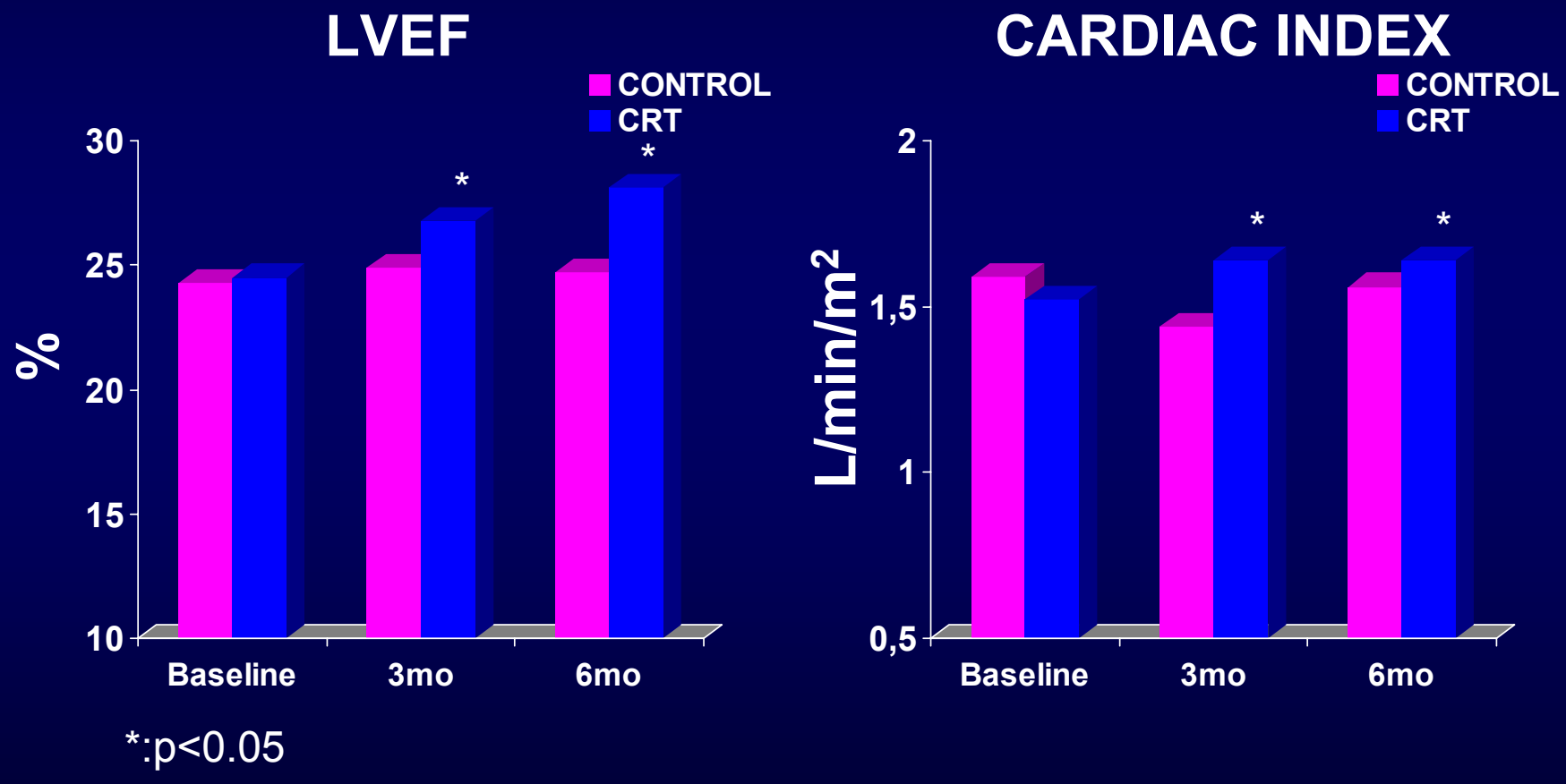
MIRACLE Study



Sutton et al Circulation 2003;107:1985

LV Reverse Remodeling by CRT

MIRACLE Study

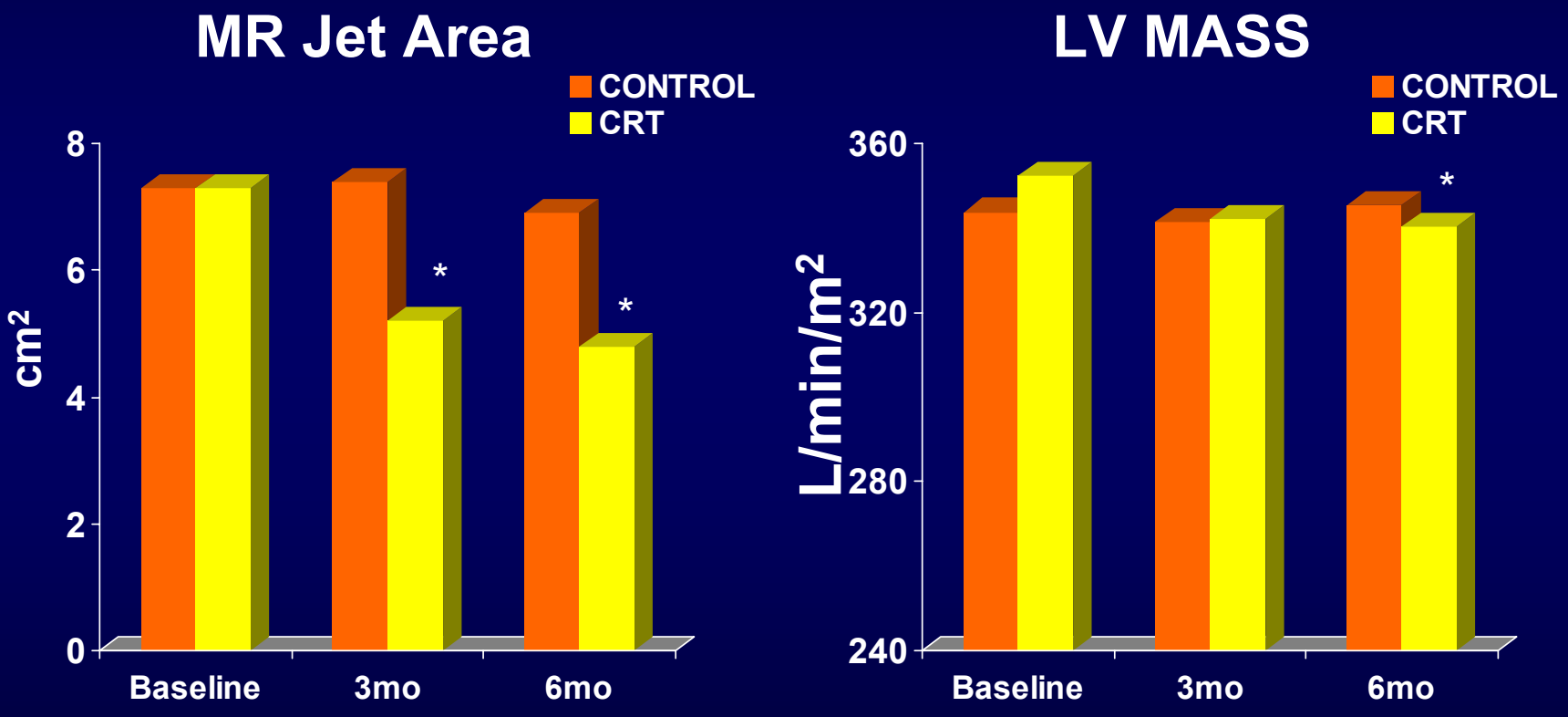


*:p<0.05

Sutton et al Circulation 2003;107:1985

LV Reverse Remodeling by CRT

MIRACLE Study



*:p<0.05

Sutton et al Circulation 2003;107:1985

CARE HF
Mechanistic Outcomes

At 18 months, compared to the control group, patients randomized to CRT had:

- Shorter Interventricular Mechanical delay $P < 0.0001$
- Higher LVEF (by about 7%) $P < 0.0001$
- Less mitral regurgitation $P = 0.003$
- Lower ventricular volumes $P < 0.0001$
- Higher systolic blood pressure $P < 0.0001$
- Lower NT-pro-BNP $P < 0.0016$

JGF Cleland et al., N Engl J Med 2005;352: 1539-1549

The biological hypothesis behind the study was also proven. With CRT, both at 3 and 18 months there was powerful evidence that resynchronisation had occurred, LV function had improved, mitral regurgitation was less severe, ventricular volumes were reduced, blood pressure had increased and NT-BNP had fallen.

Resynchronizaton and Reduction in Mitral Regurgitation

- *AV delay optimization*

  Reduction in presystolic MR

- *Septal to free wall resynchronization*

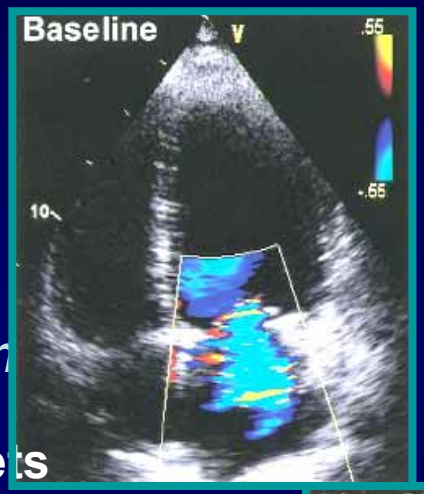
  Improved coaptation of the valve leaflets

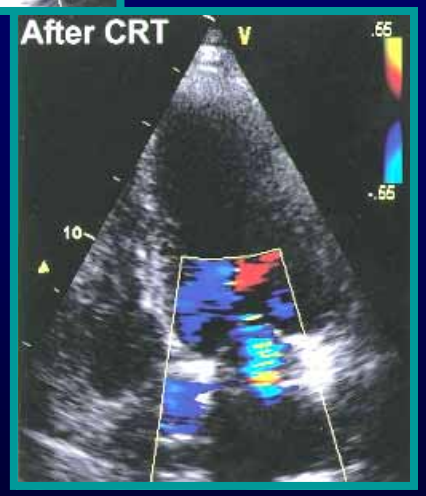
- *LV reverse remodeling*

  Decreased LV end systolic volume

- *Acute decrease in mitral regurgitation*

  Raise in mitral valve closing force by LV $+dP/dt_{max}$





Reduction in Mitral Regurgitation by a Raise in LV +dP/dt $_{max}$

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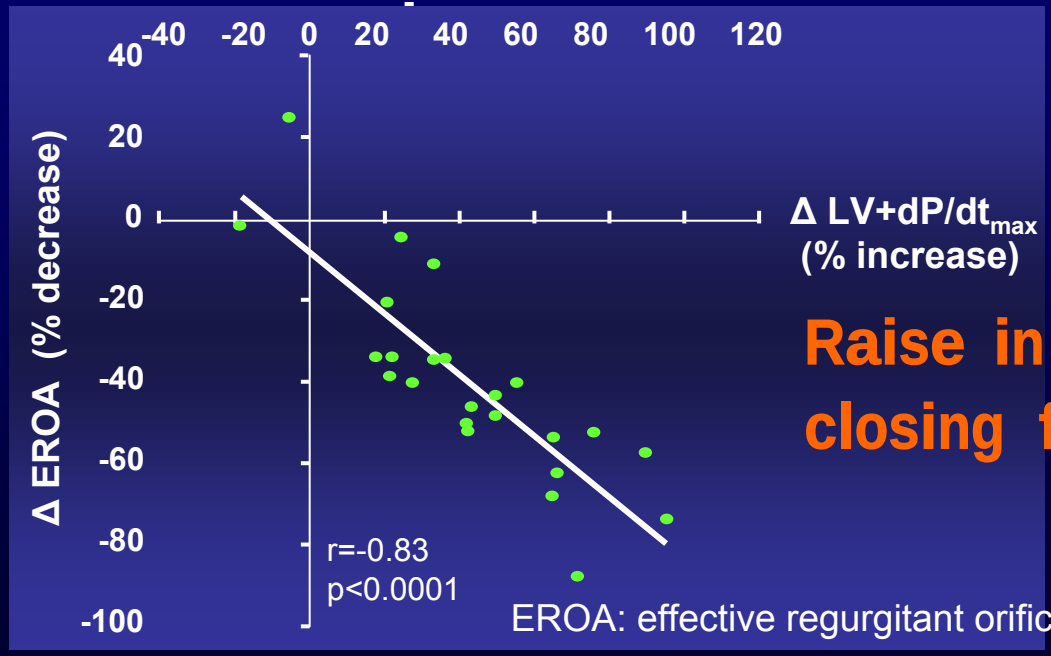
Acute Effects of Cardiac Resynchronization Therapy on Functional Mitral Regurgitation in Advanced Systolic Heart Failure

Ole A. Breithardt, MD,* Anil M. Sinha, MD,* Ehud Schwammenthal, MD, FESC,† Nadim Bidaoui, BSc,* Kai U. Markus, MD,* Andreas Franke, MD,* Christoph Stellbrink, MD, FESC*

Aachen, Germany; and Tel Hashomer, Israel

OBJECTIVES We studied the acute effects of cardiac resynchronization therapy (CRT) on functional mitral



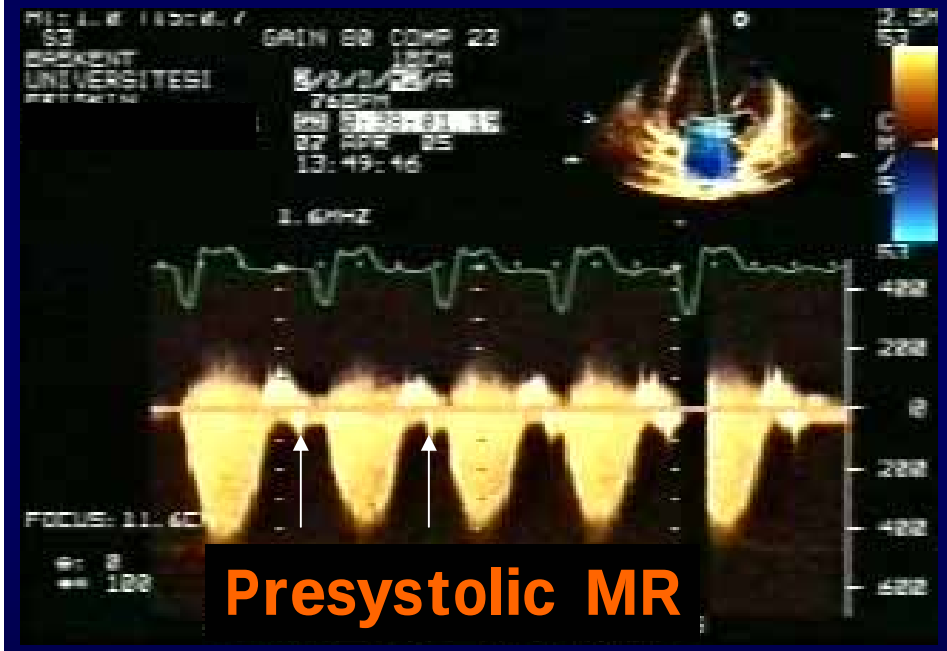
Raise in mitral valve closing force

EROA: effective regurgitant orifice area

Geometric changes alter the balance between tethering and closing forces and impede effective mitral valve closure. The accelerated rise transmitral pressure during isovolumic contraction phase effectively counteracts the increased tethering forces that impair midsystolic mitral leaflet tenting area.CRT increase LV contraction efficacy thereby generates effective transmitral closing force

Reduction in Mitral Regurgitation by AV Delay Optimization

BEFORE CRT



3 DAYS AFTER CRT

No presystolic MR,
Decreased MR time,
Decreased MR

Reduction in Mitral Regurgitation by Coordinated Timing of Mechanical Activation of Papillary Muscles

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doi:10.1016/j.jacc.2004.07.036

Echocardiography and Resynchronization

A Mechanism for Immediate Reduction in Mitral Regurgitation After Cardiac Resynchronization Therapy

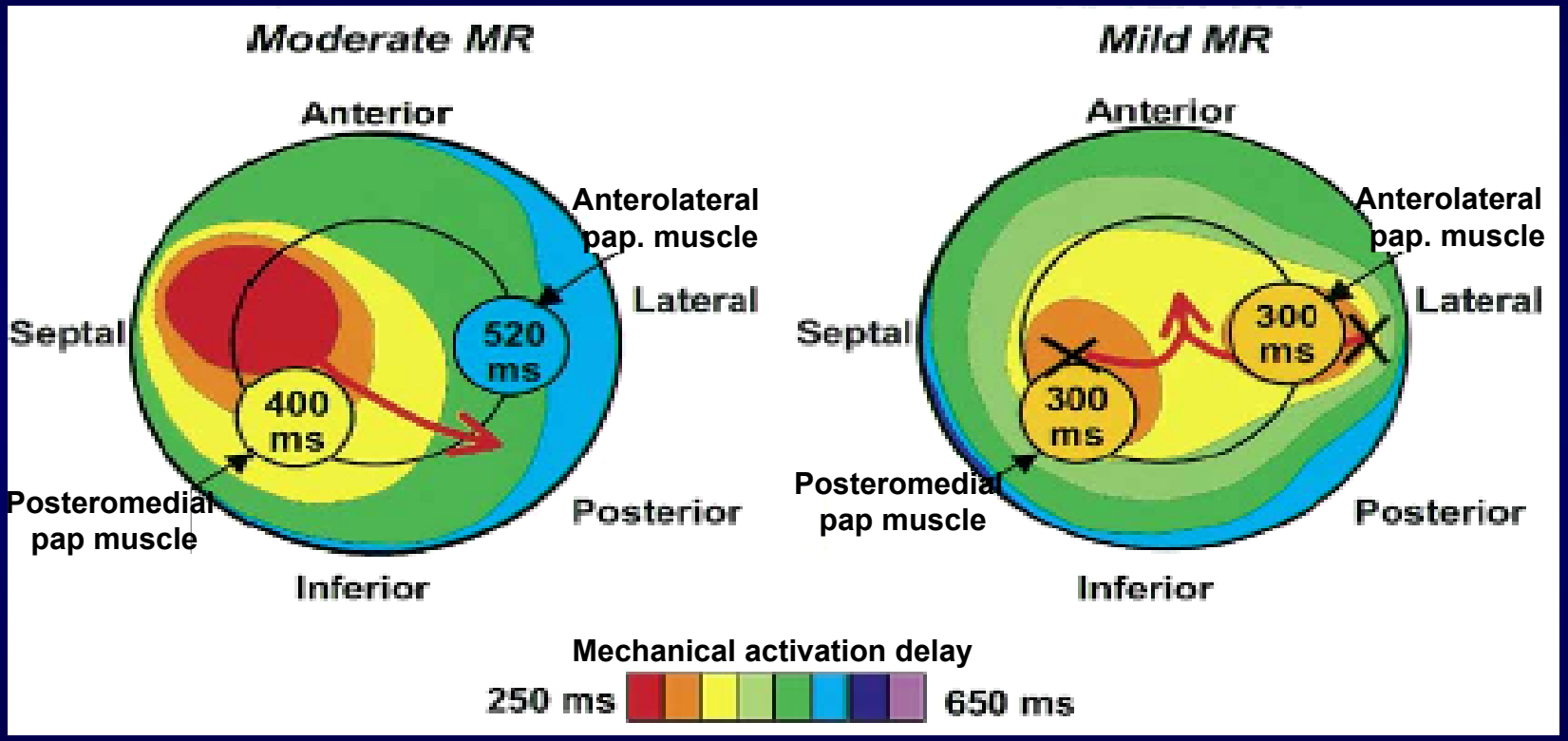
Insights From Mechanical Activation Strain Mapping

Hideaki Kanzaki, MD, Raveen Bazaz, MD, David Schwartzman, MD, FACC, Kaoru Dohi, MD, L. Elif Sade, MD, John Gorcsan III, MD, FACC

Pittsburgh, Pennsylvania

Improved coaptation of the valve leaflets

Mechanical Activation Maps in Bull's Eye Projection

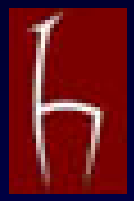


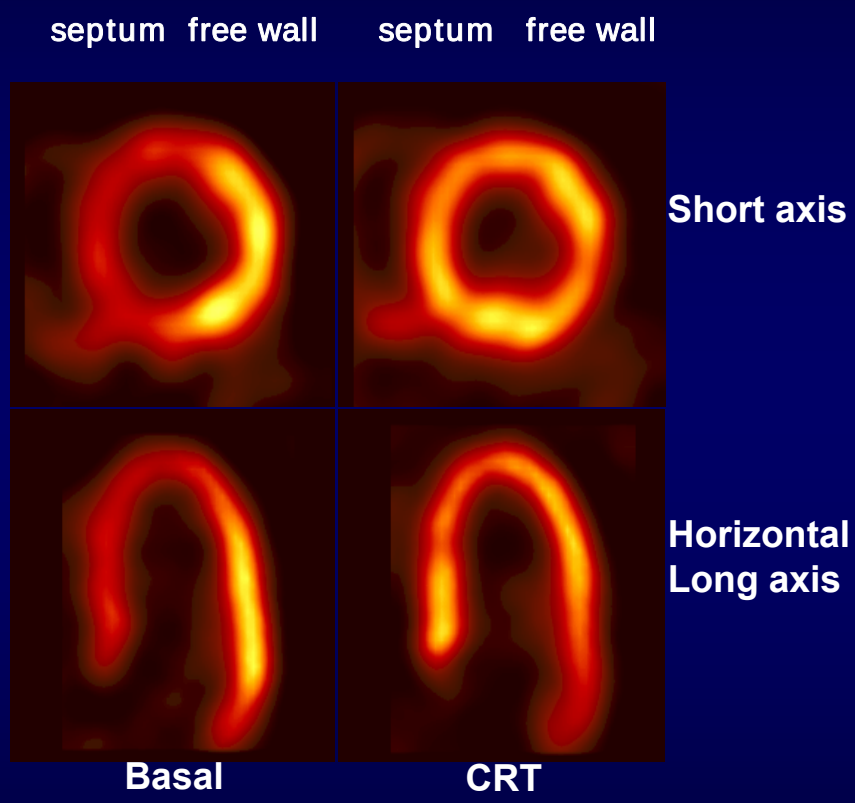
Time delay between papillary muscle insertion sites

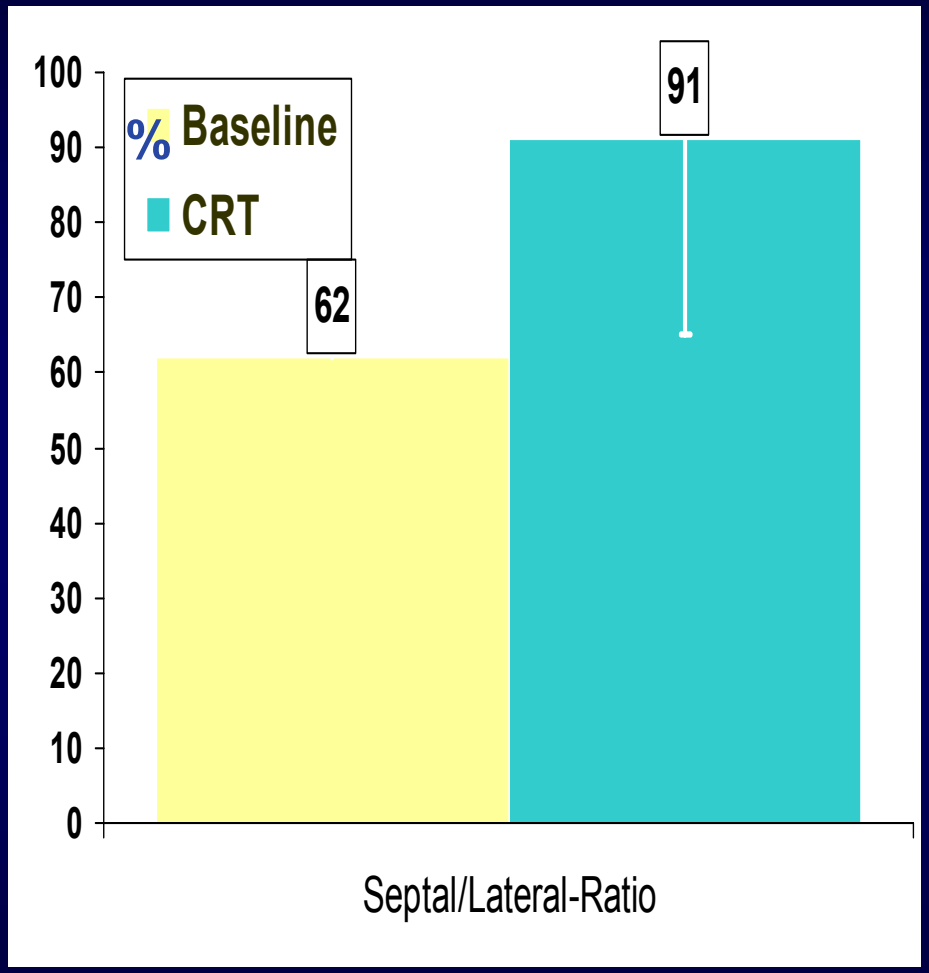
LBBB: 106±74ms AFTER CRT: 39±43ms Normal: 12±8ms

Kanzaki H et al. JACC 2004; 44:1619

CRT improves myocardial metabolism

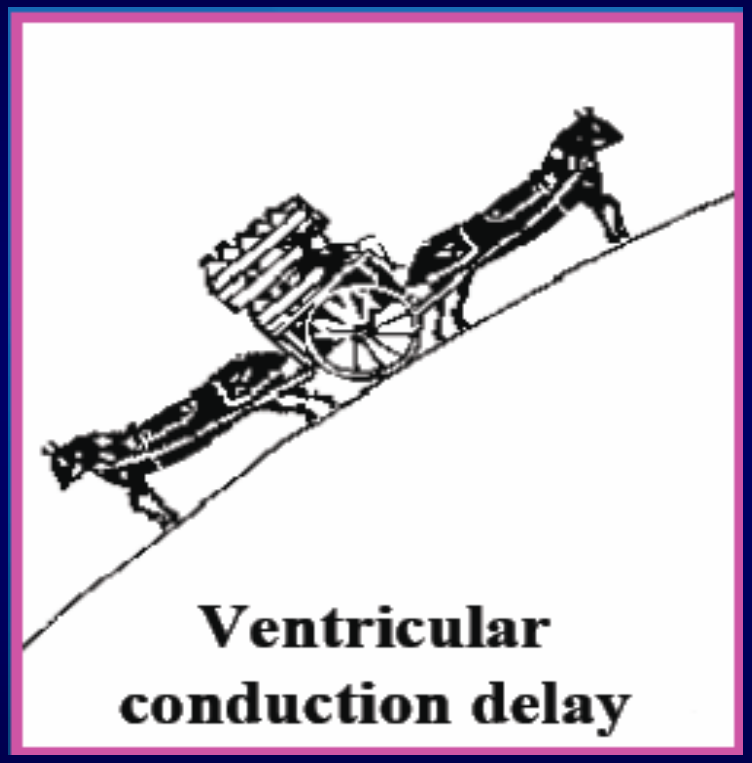


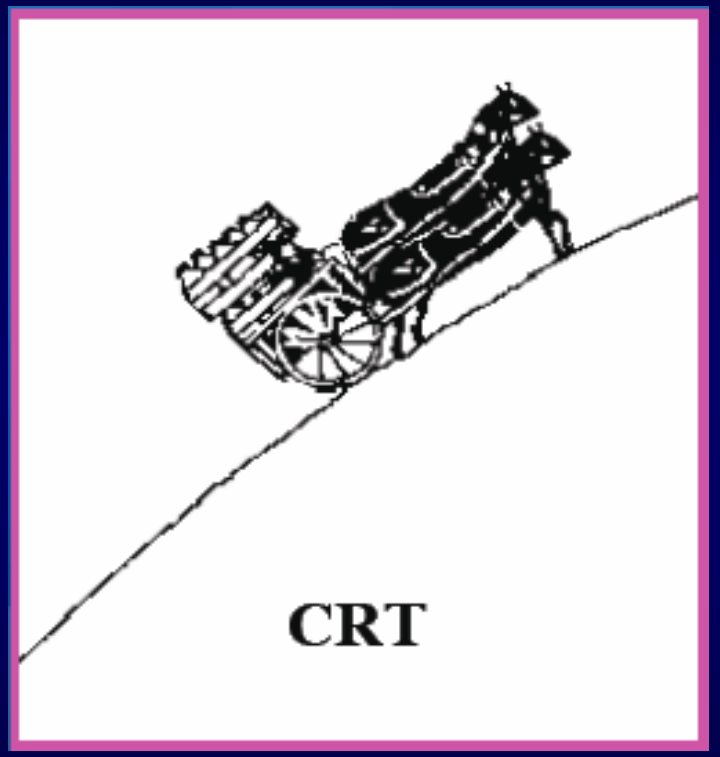




Nowak et al., JACC 2003

LV ENERGETICS BY CRT

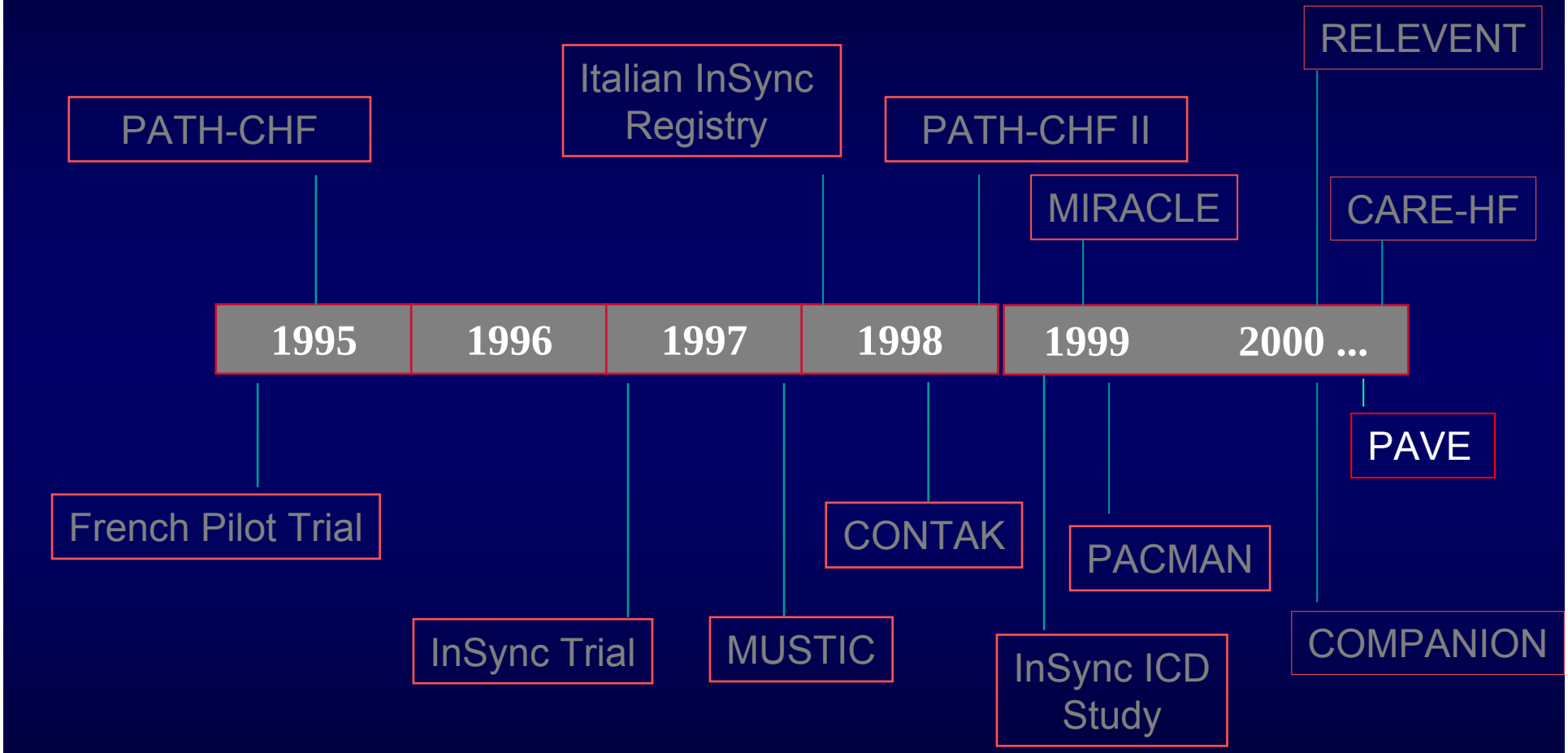




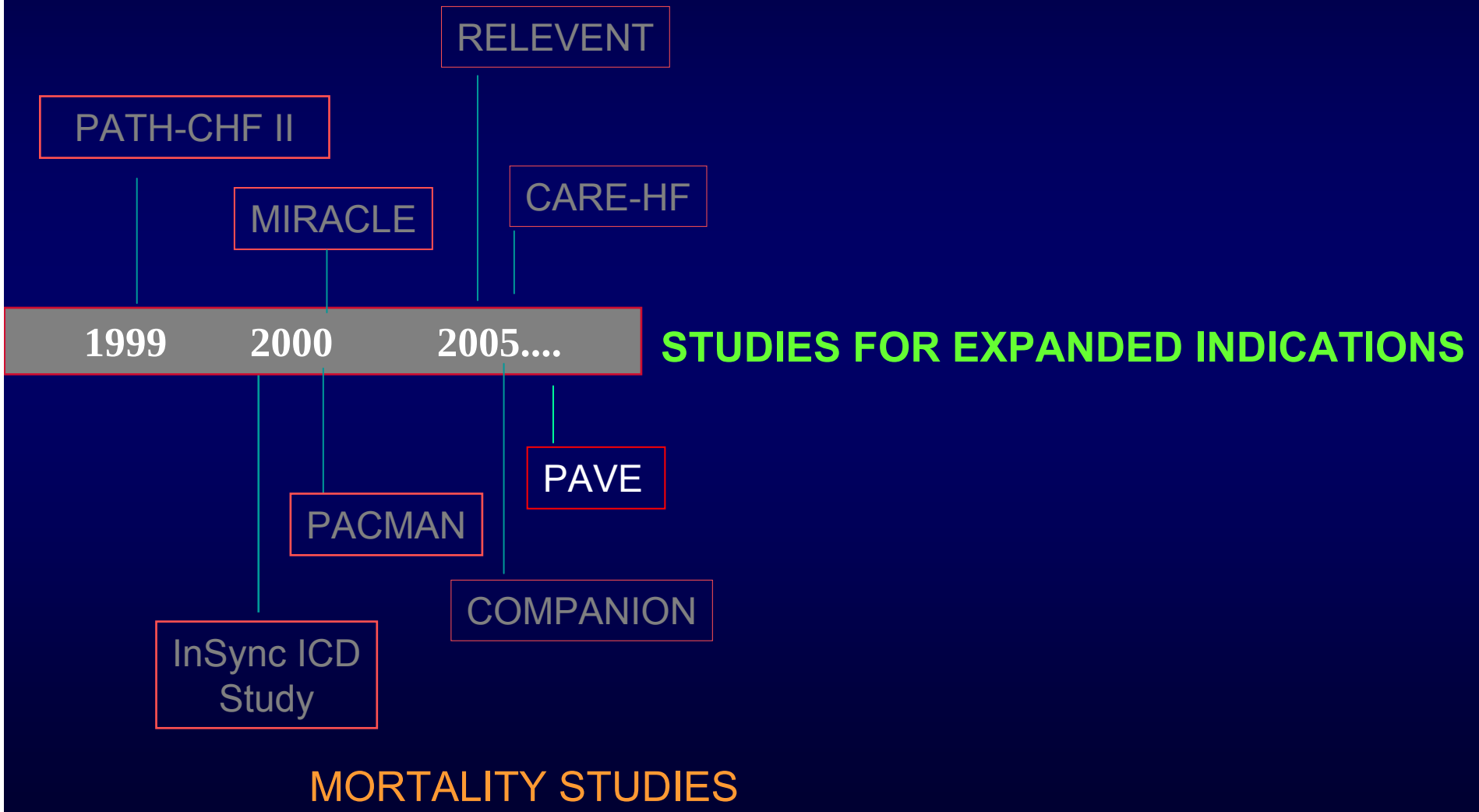
CRT increases efficacy of LV

at low energy cost

Evolution of CRT TRIALS



Evolution of CRT TRIALS



CRT IMPORTANT CLINICAL TRIALS

Completed

- French Pilot
- InSync
- In Sync III
- MUSTIC
- CONTAC-CD
- InSync ICD
- MIRA CLE
- PAVE
- **COMPANION**
- **CARE-HF**

Ongoing

- **PACMAN**
- **BIOPACE**
- **BELIEVE**
- **BLOCK- HF**
- **PROSPECT**
- **MADIT CRT**
- **REVERSE**
- **RELEVENT**

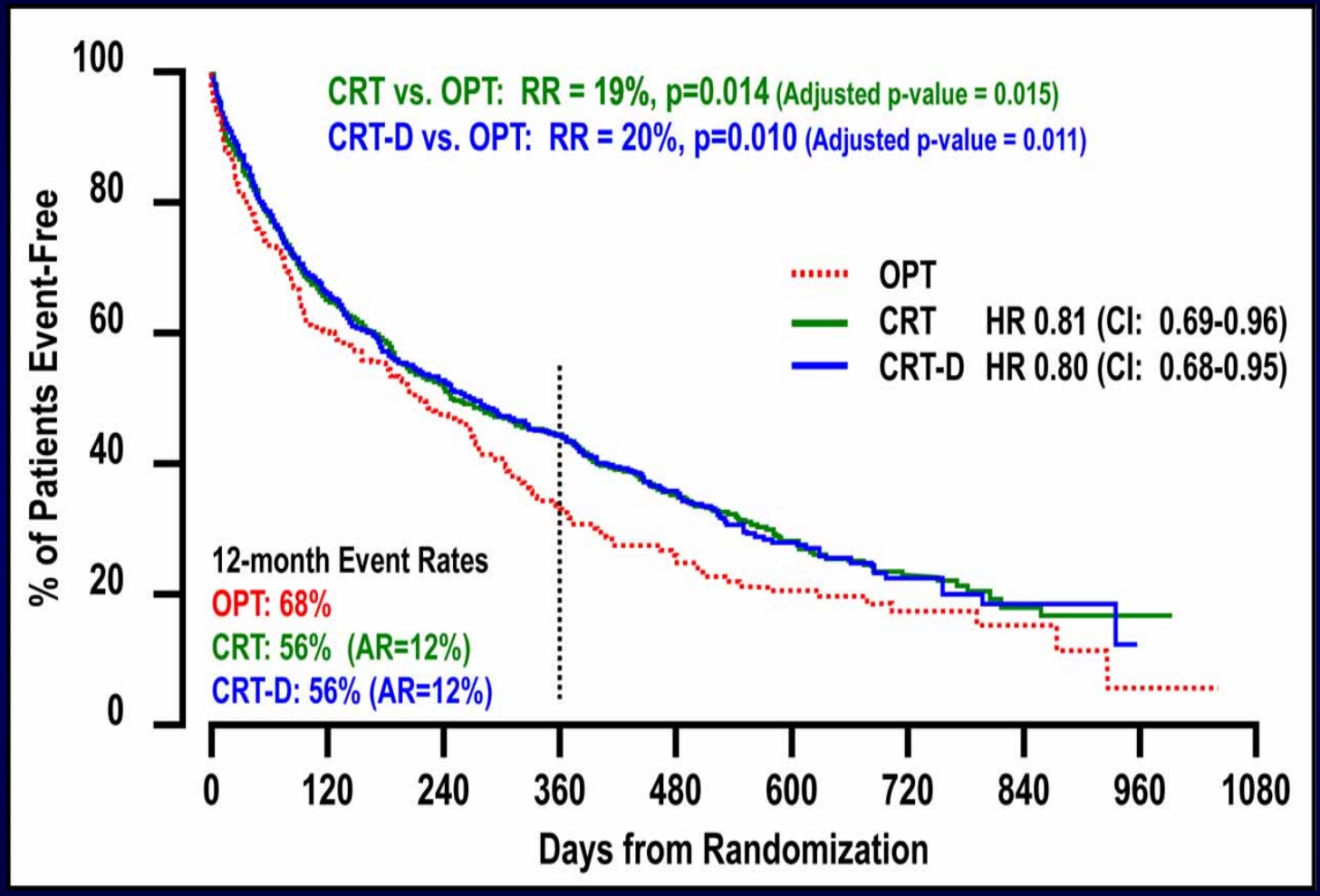
Functional Benefits of CRT

- ↑ 6 - minute walking distance
- ↑ Health related QOL score
- ↑ Peak oxygen consumption
- ↓ Hospitalizations for decompensated heart failure
- ↓ NYHA functional class

AHA Science AdvisoryCirculation 2005;111:2146-50

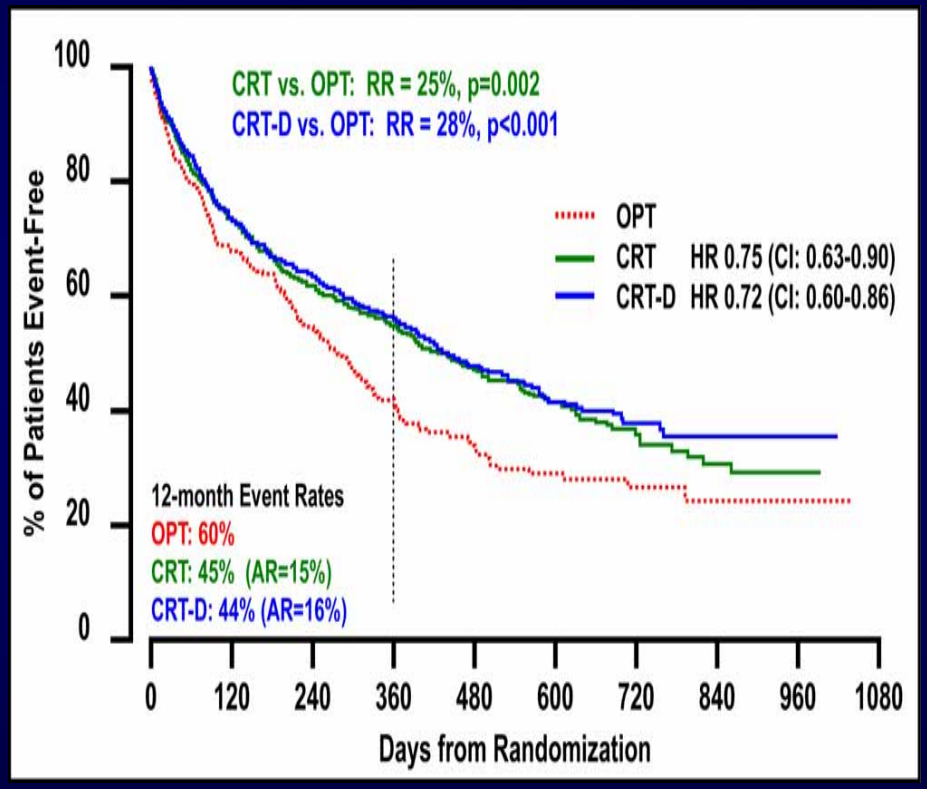
COMPANION: *Primary Endpoint*

Time to first all cause mortality or all cause hospitalization

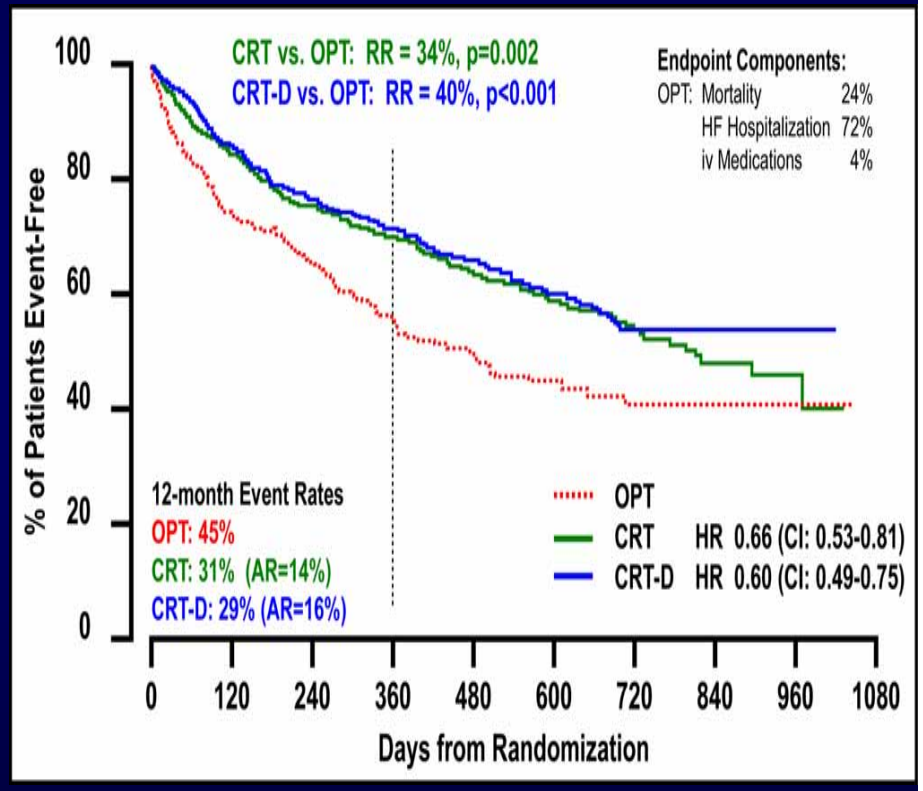


COMPANION

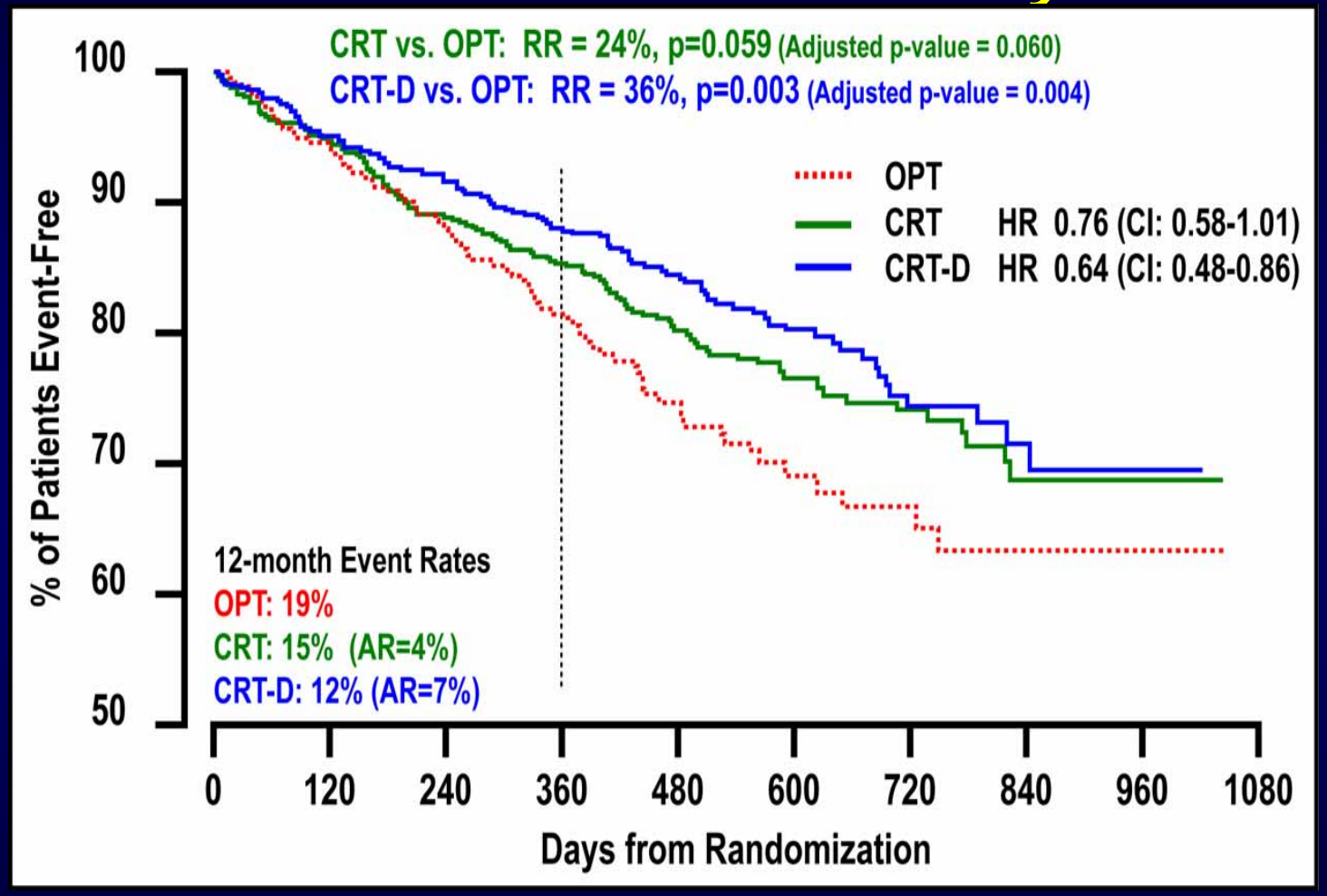
Death or CV Hospitalization



Death or HF Hospitalization



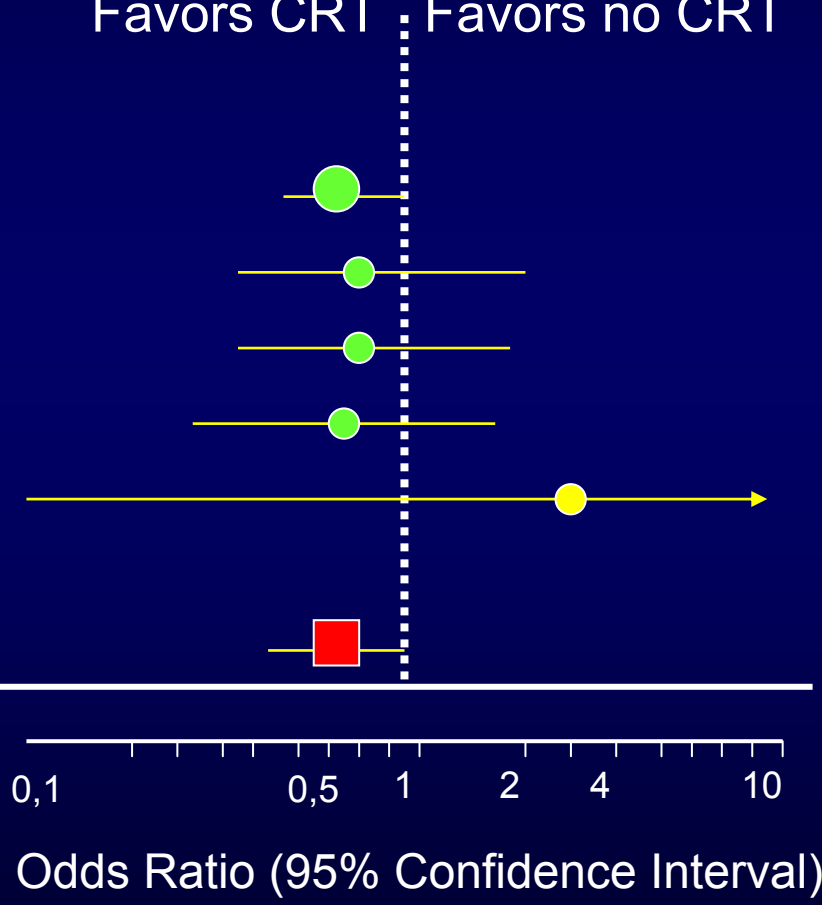
COMPANION: *Secondary Endpoint of All-Cause Mortality*



Meta-Analysis of CRT Trials

All cause mortality

Study	CRT	No CRT
	sayı	Sayı
COMPANION	617	308
CONTAK CD	245	245
InSync ICD	272	282
MIRACLE	263	269
MUSTIC	29	29
Total	1426	1133



Int J Cardiol 2004;93:101-103

- ***Need for a mortality trial***
  to test the effect of CRT alone on mortality
  in pts with chronic heart failure

CARE-HF STUDY

The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure

John G.F. Cleland, M.D., Jean-Claude Daubert, M.D.,
Erland Erdmann, M.D., Nick Freemantle, Ph.D., Daniel Gras, M.D.,
Lukas Kappenberger, M.D., and Luigi Tavazzi, M.D.,
for the Cardiac Resynchronization – Heart Failure (CARE-HF) Study Investigators*

Von Martin Borggrefe

JGF Cleland et al., N Engl J Med 2005;352: 1539-1549

CARE-HF :Main Inclusion & Exclusion Criteria

- Heart failure for at least 6 weeks requiring loop diuretics
- Currently in NYHA class III/IV
- A high standard of pharmacological therapy
- LV systolic dysfunction and dilation
  - EF ≤35%; EDD ≥30mm/height in metres
- QRS ≥120 ms
  - Dyssynchrony confirmed by echo if QRS 120-149 ms
    - Aortic pre-ejection delay >140 ms
    - Interventricular mechanical delay >40 ms
    - Delayed activation of postero-lateral LV wall
- Patients with AF or requiring pacing excluded

This slide shows the main inclusion/exclusion criteria. A full list of these criteria has been published (J.G.F. Cleland, J.C. Daubert, E. Erdmann et al. The CARE-HF study [CArdiac REsynchronisation in Heart Failure] study: rationale, design and end-points. Eur J Heart Fail 2001;3:481-9).

Patients with NYHA III/IV heart failure were selected because these patients have a heavy burden of symptoms and a high morbidity and mortality. Therefore, if intervention was effective in improving well-being and prognosis it should be obvious in this group of patients. Also, patients with few symptoms and a relatively good prognosis may have been unwilling to have a device implanted. Congestive signs and symptoms requiring control with diuretics is a bad prognostic sign. The higher the dose required the worse the prognosis. Requiring patients to be on loop diuretics excluded patients with few symptoms and a good prognosis.

A 6 week rather than 12 week duration of persistent symptoms was required because the prognosis of this group of patients is poor. Shortening the period of symptoms meant that more high-risk patients would be enrolled and any benefit might be observed sooner. A low LVEF is a marker of a poor prognosis and cardiac dyssynchrony occurs predominantly in patients with severe LVSD and LV dilatation.

The following trials of pharmacological therapy guided recommendations for pharmacological therapy (CONSENSUS and SOLVD for ACE inhibitors, US Carvedilol trial, MERIT and CIBIS-II for beta-blockers and RALES for Spironolactone). The following trials were reported only AFTER recruitment had started (COPERNICUS, COMET, CHARM and EPHESUS). Patients were therefore required to be on ACE inhibitors and beta-blockers and Spironolactone was strongly recommended for more severe patients. Investigators were encouraged to review medications frequently during the study to maintain and increase appropriate pharmacological therapy.

The MUSTIC trial (a positive trial) used a QRS cut-off $\geq$150msec, MIRACLE (a positive trial) a cut-off of $\geq$130msec and CONTAK (a neutral trial) used a cut-off of $\geq$120msec. The prevalence of cardiac dyssynchrony increases as QRS becomes longer as noted previously. Accordingly, patients with QRS $\geq$150msec did not require additional validation of dyssynchrony but patients with a QRS 120-149msec required additional echocardiographic evidence as shown on the slide.

Patients with AF were excluded as there was little evidence of benefit with CRT in this group of patients when CARE-HF was designed. Also, these patients could not benefit from atrio-ventricular resynchronisation.

Primary & Principal Secondary Endpoints

Primary composite endpoint

- All-cause mortality or unplanned hospitalisations for a major CVS event (time to first event analysis)

Principal secondary endpoint

- All-cause mortality

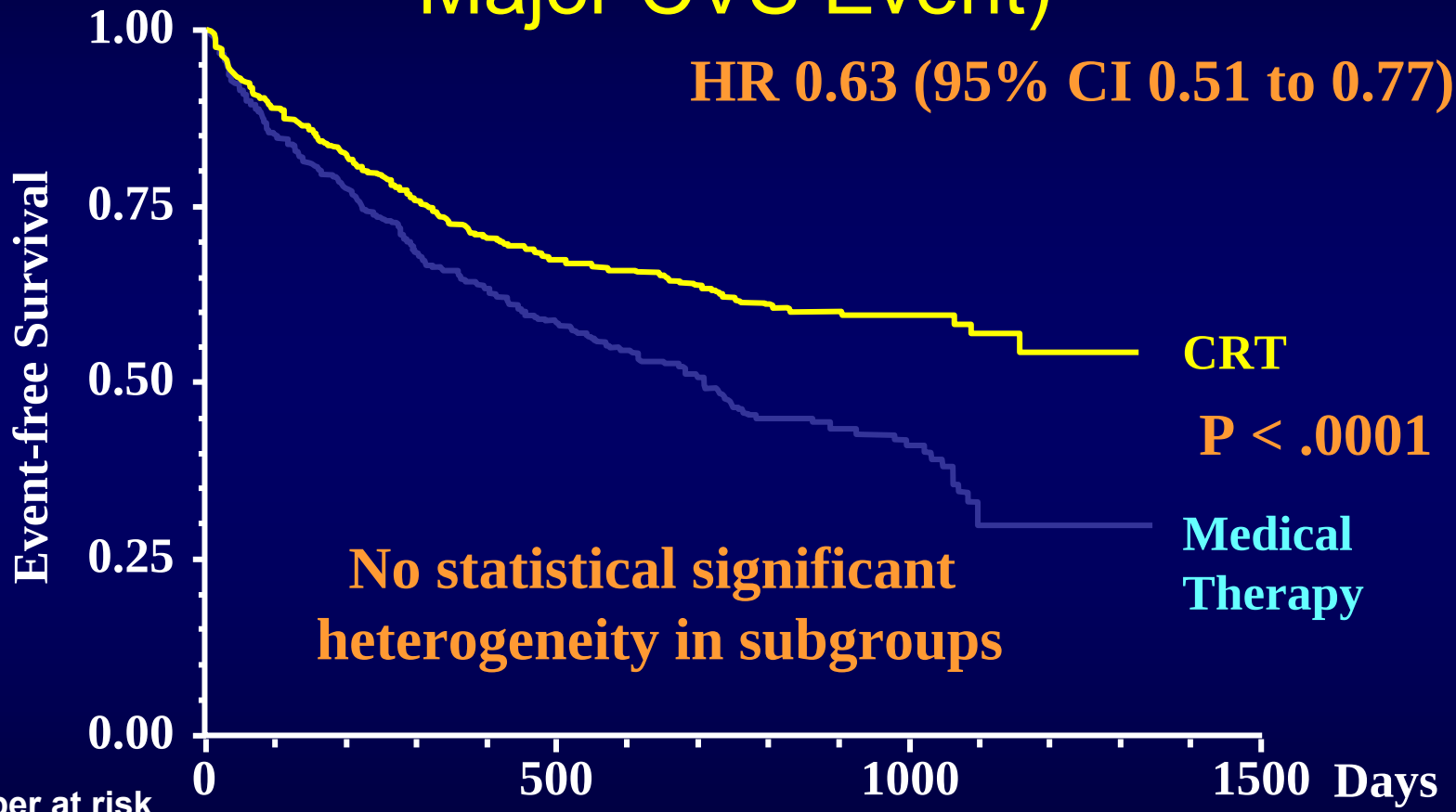
Device implantation is a substantial procedure for patients to undergo and therefore the events that the device can prevent should be of sufficient severity to warrant device therapy. It was considered that the major effect of CRT would be to improve LV function and symptoms leading to a reduction in hospitalisations for heart failure. It was thought possible that CRT could reduce arrhythmias and possibly other CVS events. Moreover, many patients are hospitalised for a combination of arrhythmias, ischaemic events and heart failure and it becomes difficult to classify patients accurately. However, improved LV function, a reduction in worsening heart failure and in other major CVS events would also be expected to reduce mortality.

Accordingly, the primary endpoint of the study was all-cause mortality or an unplanned (i.e. emergency) admission to hospital for a major CVS event. Emergency heart transplants were counted as deaths (and would have been part of the composite primary endpoint anyway). Elective heart transplants were censored 7 days after transplant, as deaths after this time are more likely to reflect complications of the transplant than the patients pre-operative state. Patients randomised to device implantation were admitted to hospital for the procedure and during this time cannot be admitted for another CVS problem (since they are already in hospital). This could have biased the trial **in favour of the device**. Therefore, only death and not hospitalisation could count towards the primary endpoint in the first 10 days because most patients randomised to a device would spend a few days in hospital for the procedure during this period. Planned admissions were defined as ones where there was at least 24 hours between the decision to admit and admission. All others were considered unplanned. Two expert cardiologists, **blinded to randomisation**, independently adjudicated all admissions (unless they were definitely planned) and decided whether the admission was cardiovascular or non-cardiovascular. Cardiovascular hospitalisations were then classified as admission for symptoms without a major event (e.g.:- chest pain without evidence of myocardial infarction, palpitations without syncope or evidence of arrhythmia), admission for ‘minor’ cardiovascular events (e.g.:- transient ischaemic attack, new onset well tolerated atrial fibrillation) or ‘major’ cardiovascular events (e.g.:- myocardial infarction, stroke, pulmonary oedema).

All-cause mortality was the principal secondary endpoint. It is the most robust outcome measure in an unblinded study.

Primary Endpoint

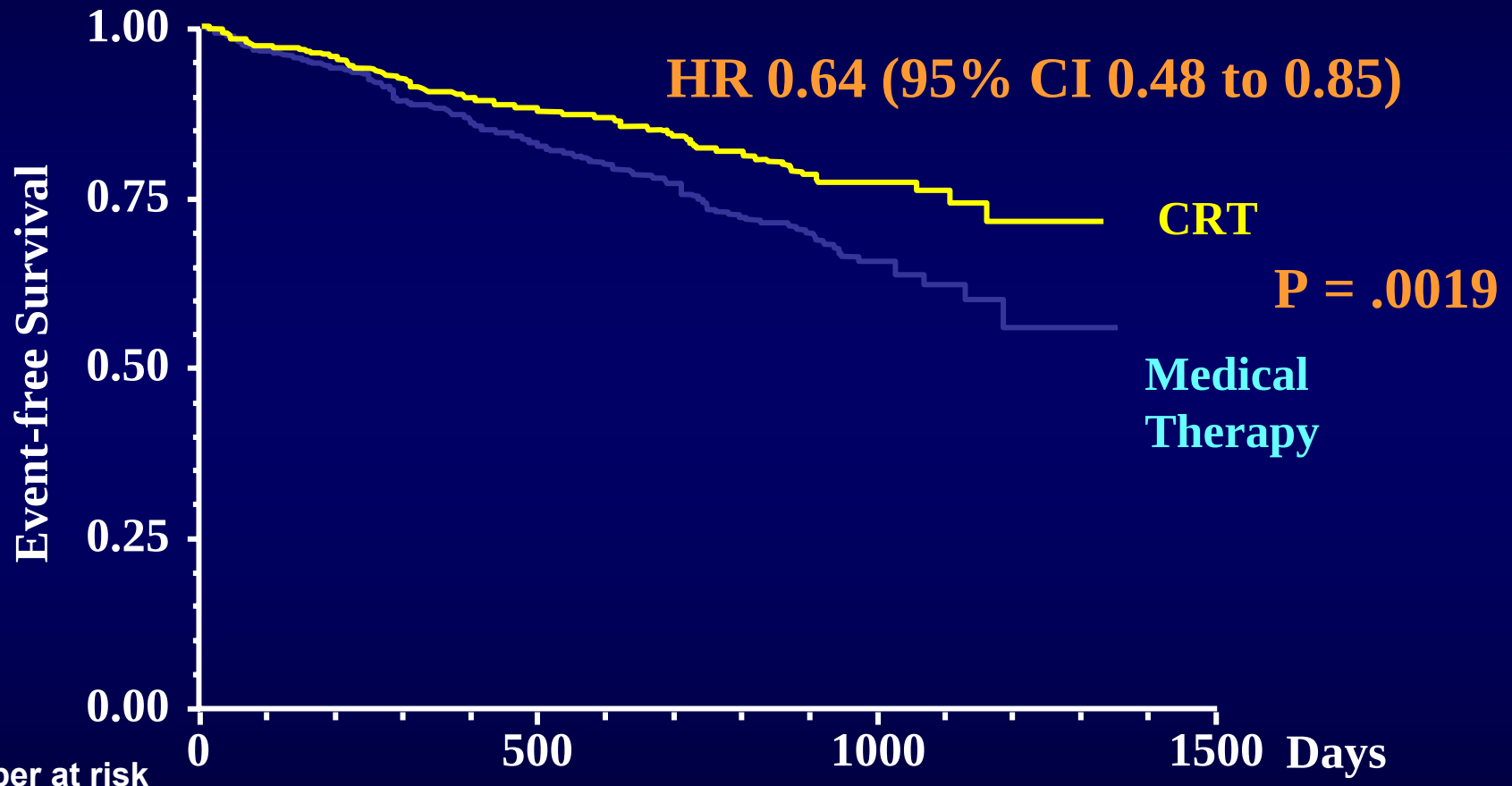
(All-cause Mortality or Unplanned Hosp. for Major CVS Event)



Number at risk						
CRT	409	323	273	166	68	7
Medical Therapy	404	292	232	118	48	3

There was no heterogeneity in effect in any of the pre-specified subgroups. In particular, benefit was observed in older patients, women, patients with ischaemic heart disease, in patients above and below median LVEF and in patients receiving or not receiving beta-blockers and Spironolactone (there were too few patients not receiving an ACE inhibitor or ARB and therefore this analysis was not included in the statistical analysis plan).

All-Cause Mortality



Number at risk						
CRT	409	376	351	213	89	8
Medical Therapy	404	365	321	192	71	5

There was a striking reduction in mortality in the CRT group. The absolute difference between control and CRT was 10%. Again, there was no early hazard and the curves begin to separate within the first 6 months of randomisation. A reduction in both sudden deaths and deaths due to worsening heart failure was observed. There were only 29 sudden deaths out of 82 in the CRT group.

The benefits of CRT are in addition to those of the above pharmacological therapy. The absolute difference in mortality at 2 years was 7.1%. This compares to 5.2% with Enalapril in the SOLVD-treatment study and is similar to the estimated two-year mortality difference between placebo and Bisoprolol in the CIBIS-II study or the 8.8% difference between placebo and Carvedilol in COPERNICUS (which using the method of trial duration used in our study had a duration of about 15 months).

The hazard ratio of the effect of CRT in CARE-HF (0.64; 95% confidence interval 0.48 to 0.85; p=0.0019) was similar to that of CRT-D compared to control in the COMPANION trial (0.64, 95% confidence interval, 0.48 to 0.86; P=0.003) . The absolute estimated difference at 2 years in the COMPANION study between CRT-D and control was about 8% with CRT and CRT-D having similar effects in that study.

CRT-Established benefits

- Improvement in global synchronization (Hemodynamically)
- Organized ventricular activation sequence (EF)
- Improvent in cardiac efficiency (peak VO2)
- Symptomatic improvement (QOL)
- Improved exercise tolerance (NYHA)
- Decreased sympathetic activity and myocarial energy consumption
- **IMPROVED SURVIVAL**

Characteristics of patients in whom CRT is strongly supported by randomized trials

- **Sinus rhythm**
- **LVES<0.35**
- **Ischemic or non-ischemic cardiomyopathy**
- **QRS complex duration>120 msc**
- **NYHA functional class III or IV**
- **Maximal pharmacological therapy for heart failure**

AHA Science Advisory . Circulation 2005;111:2146-50

ESC-GUIDELINES FOR DIAGNOSIS AND TREATMENT OF CHRONIC HEART FAILURE(Update 2005)

Resynchronization therapy using biventricular pacing can be considered

in patients with reduced EF and ventricular dyssynchrony (QRS width>120 ms) and who remain symptomatic (NYHA III and IV) despite optimal medical therapy

to improve symptoms (Class I ,Level of evidence A)

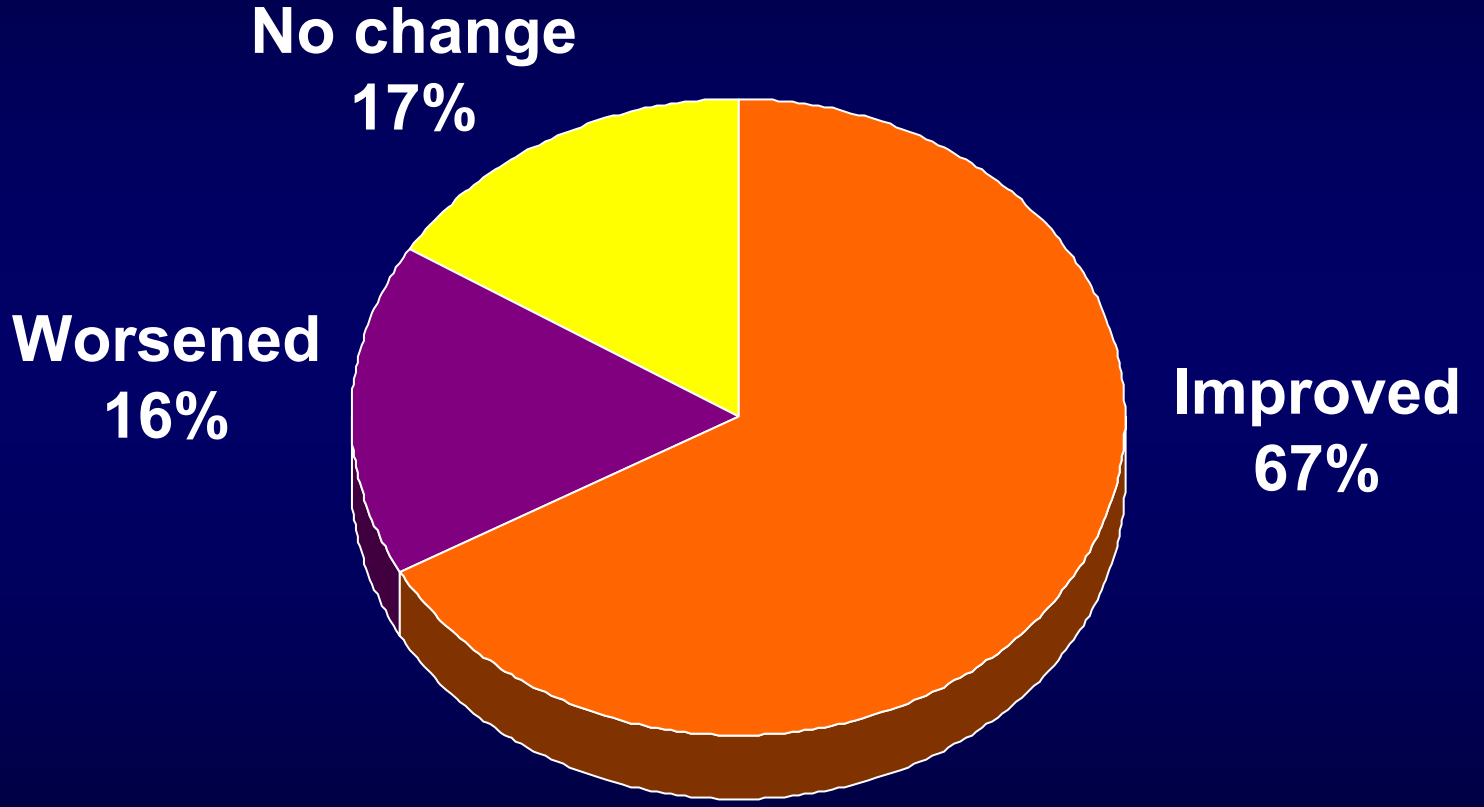
hospitalizations (Class I,level of evidence A)

mortality (Class I, Level of evidence B)

Eur Heart J 2005;26:1115-40

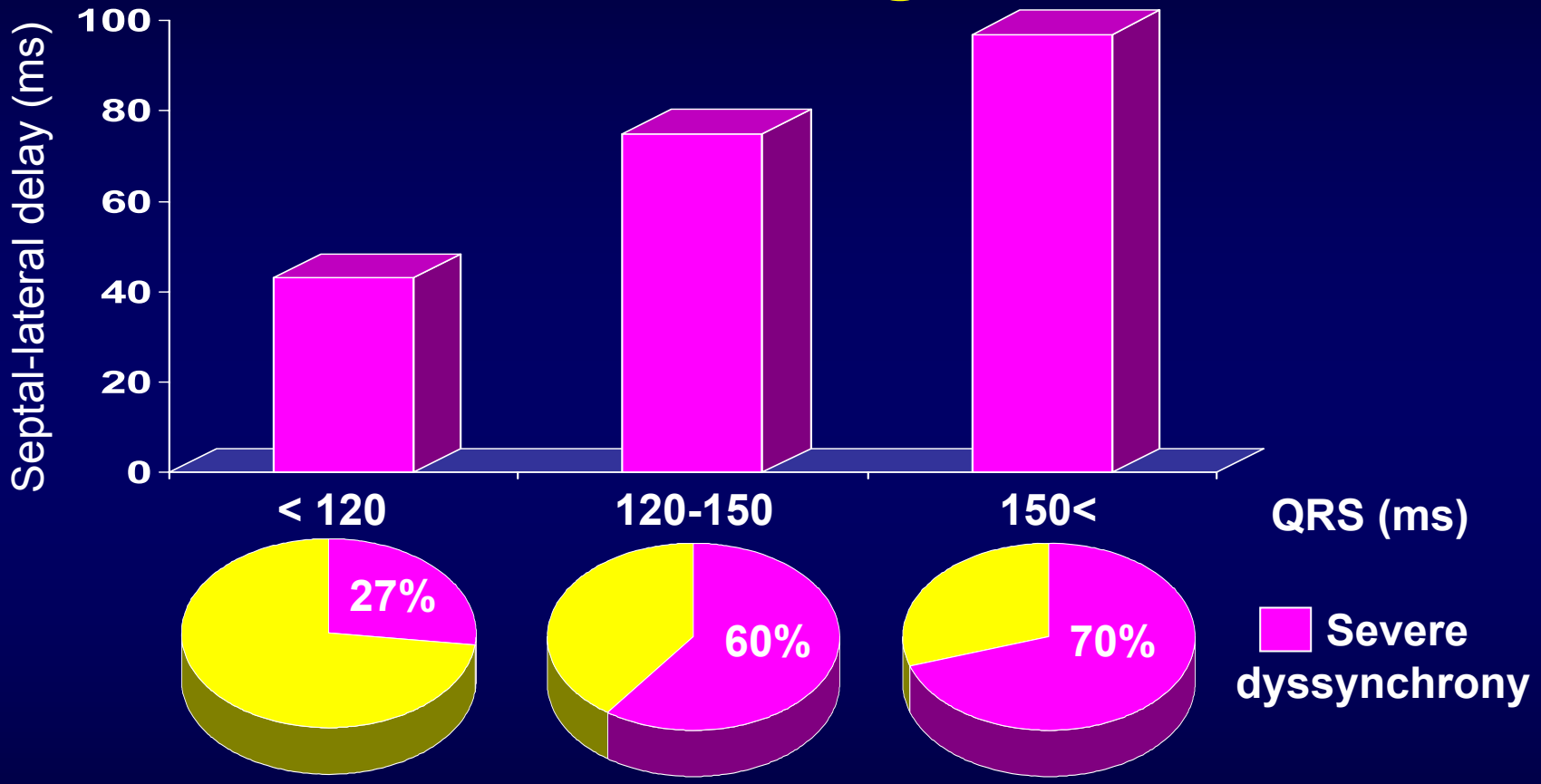
CRT in End Stage Heart Failure

MIRACLE Study



High number of non-responders !

QRS Duration and LV Dyssynchrony in End-Stage HF



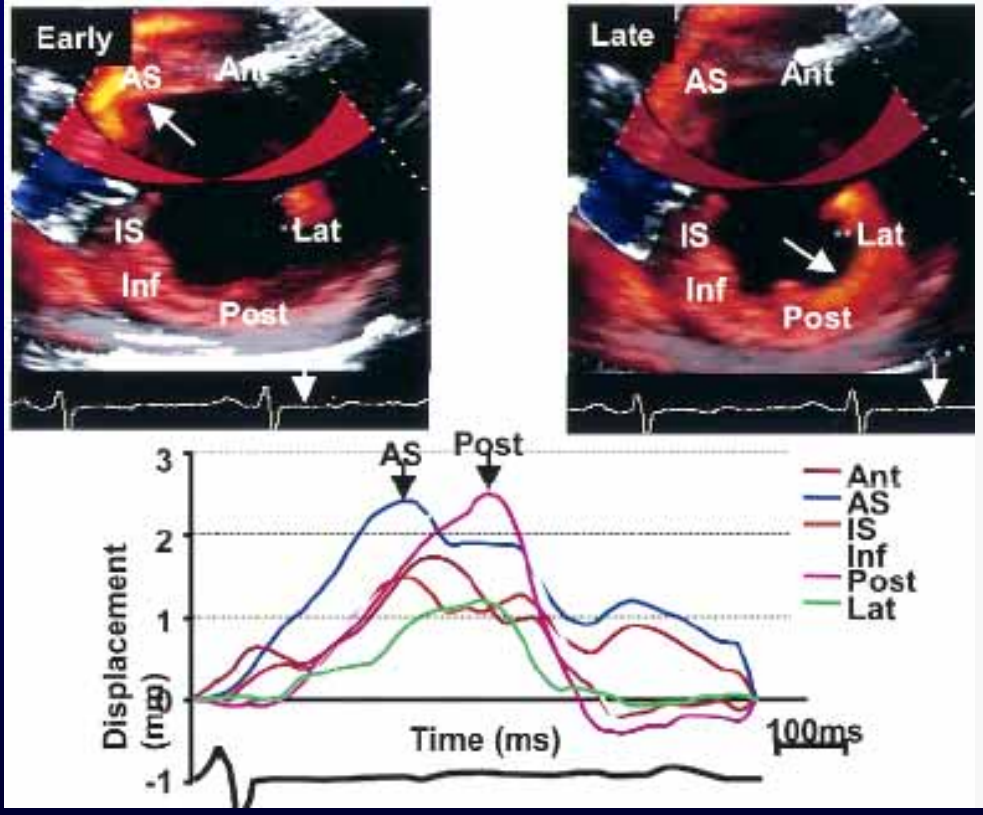
Some heterogeneity between electrical and mechanical dyssynchrony !

Blecker et al J Cardiovasc Electrophysiol 2004;15:544

LV Dyssynchrony in Patietns with Narrow QRS

Quantification of Radial Mechanical Dyssynchrony in Patients With Left Bundle Branch Block and Idiopathic Dilated Cardiomyopathy Without Conduction Delay by Tissue Displacement Imaging

L. Elif Sade, MD, Hideaki Kanzaki, MD, Donald Severyn, MS, Kaoru Dohi, MD, and John Gorcsan III, MD



ing from 25 to 180 ms) (Figure 3).

As a group, patients with IDC without electrical conduction delay had diminished and delayed regional wall displacement compared with normal controls (Table 2 and Figure 5). Significant delays were noted in all segments except for the septum. Two anteroseptal peaks were observed in most patients (83%), with S2 occurring 164 ± 64 ms after aortic valve closure. Evaluation of individual patients revealed heterogeneous patterns of regional dyssynchrony.

[redacted] with anteroseptal to posterior wall displacement delays of 169 ± 56 ms ($p < 0.001$ vs normal) (Figures 5 to 7).

...

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Long-Term Effectiveness of Cardiac Resynchronization Therapy in Patients With Refractory Heart Failure and "Narrow" QRS

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Viterbo and Albano Laziale, Italy

OBJECTIVES The aim of the study was to evaluate the effectiveness of cardiac resynchronization therapy (CRT) in patients with refractory heart failure (HF) and incomplete left bundle branch block

ms; PM: 451.7 ± 62.7 ms; p = 0.139), or as regards the other major clinical and functional parameters, therefore highlighting a substantial homogeneity of the subgroups.

Pacing therapy was effective in the significant reduction of IVD and Q-LW in the entire patient population. The QRS duration does not alter the impact of CRT on the IVD. In fact, IVD significantly improved in all groups after CRT with no statistically significant difference between the groups. Moreover, whereas a significant reduction in the Q-LW interval was observed after CRT only in group 1, the difference between groups 1 and 2 was not statistically significant.

A regression analysis of the asynchrony patterns and the echocardiographic outcome in both groups showed a sig-

DISCUSSION

The major finding of our paper is that [redacted]. This amelioration is comparable to that obtained in patients who are currently selected by means of current indications for CRT (QRS duration >120 to 150 ms) (1–5).

Current study rationale. To date, CRT has been reserved for patients with refractory HF and a consistent prolongation of the QRS (>120 to 150 ms), as suggested by previous studies (1–5). This assumption is based on epidemiologic

“The degree of

intraventricular dyssynchrony

evaluated by tissue Doppler imaging and not the baseline QRS duration, is predictive of the effectiveness of CRT.”

New imaging modalities to identify the candidates for CRT

- Standard 2D and spectral Doppler

  Global EF, dimensions, volumes, mass, transvalvular flows

- Tissue Doppler Imaging

  Regional systolic and diastolic function

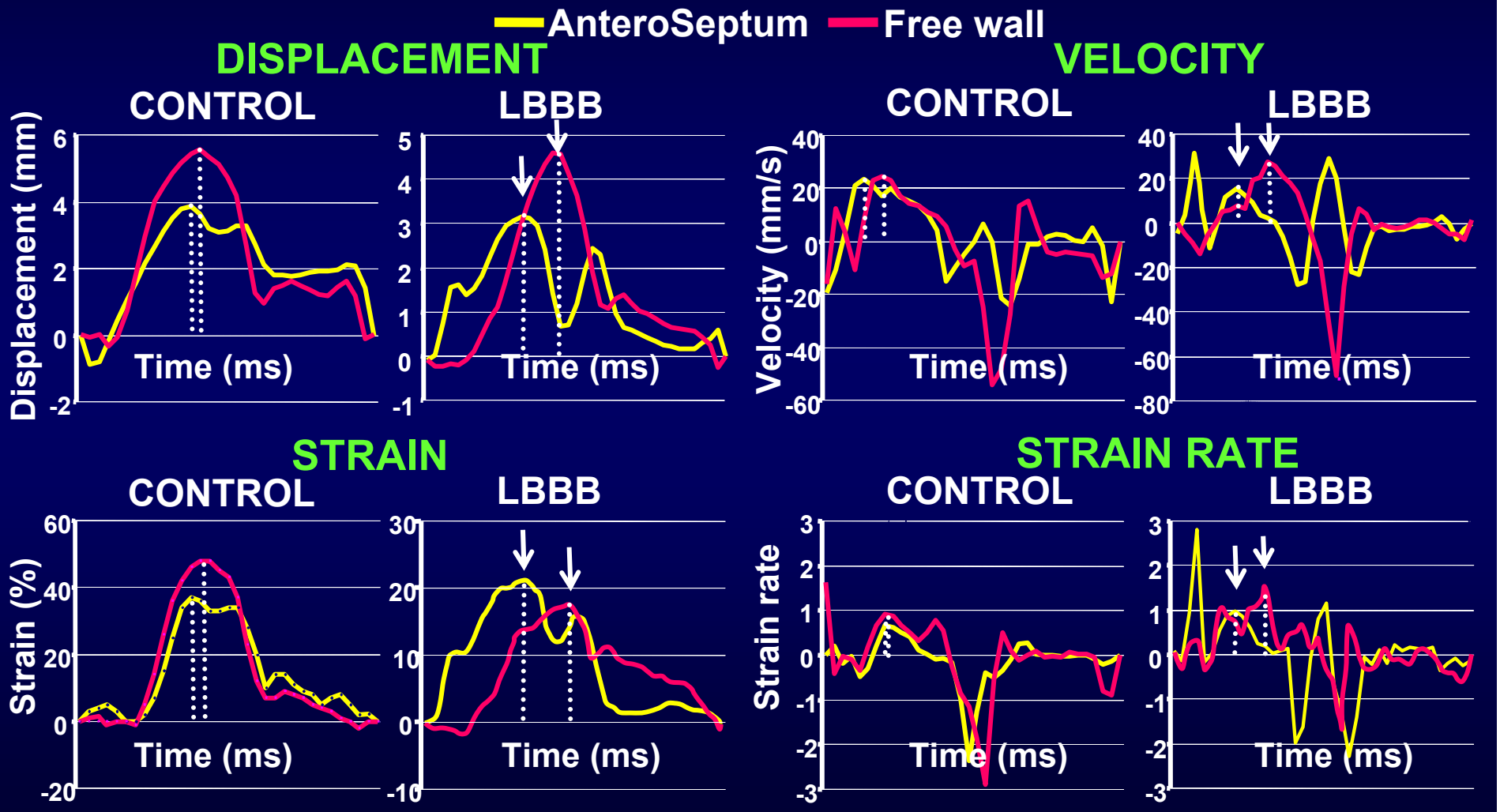
  Regional timing of mechanical events

- 3D echocardiography
- MRI

Echocardiography is a *Must* for the Success of CRT

- Evaluates the mechanical effects of CRT
- Helps predicting responders and non-responders – *evaluation of mechanical dyssynchrony*
- Helps avoiding site of delay- site of pacing mismatch - *optimal lead positioning*

Quantification of Septal To Free Wall Delay in LBBB by Different Tissue Doppler Imaging Modalities

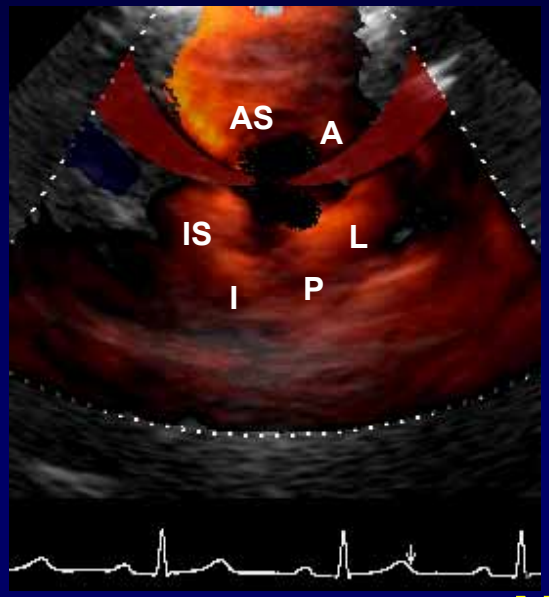


Sade LE Eur J Echocardiography 2003;4:S67

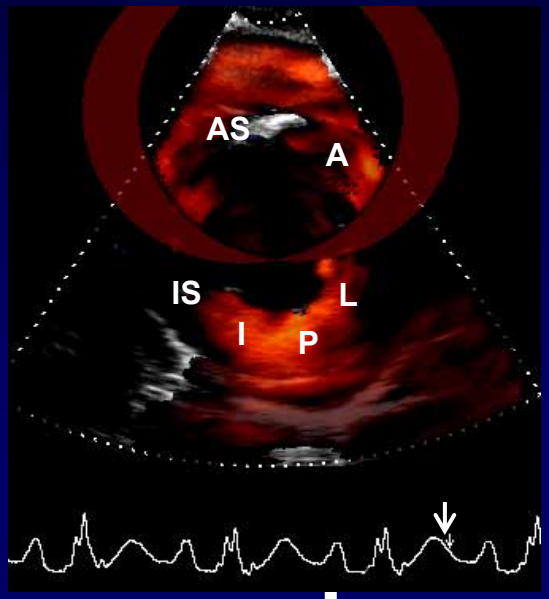
LV mechanical dyssynchrony in LBBB can also be identified by using angle corrected tissue velocity, strain and strain rate.

Quantification of Regional Dysynchrony

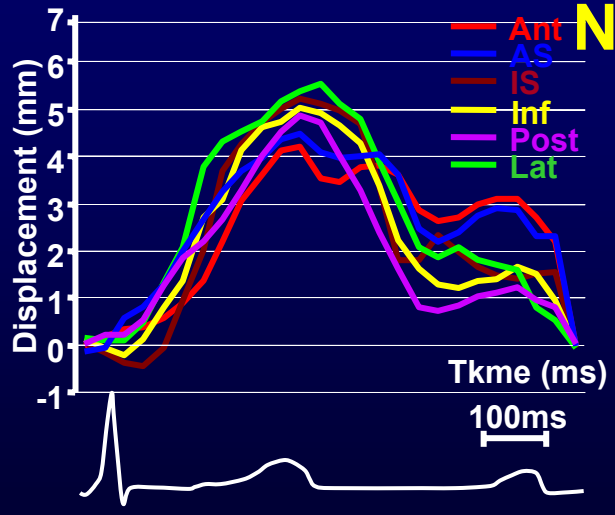
Angle-corrected Tissue Displacement Imaging



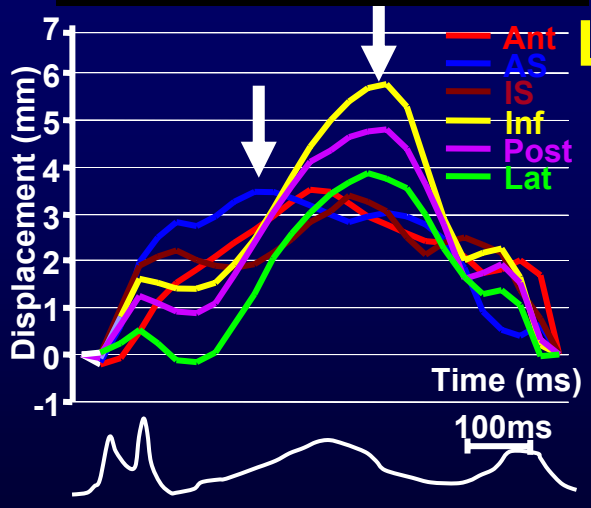
Short axis 6-segment model



NORMAL



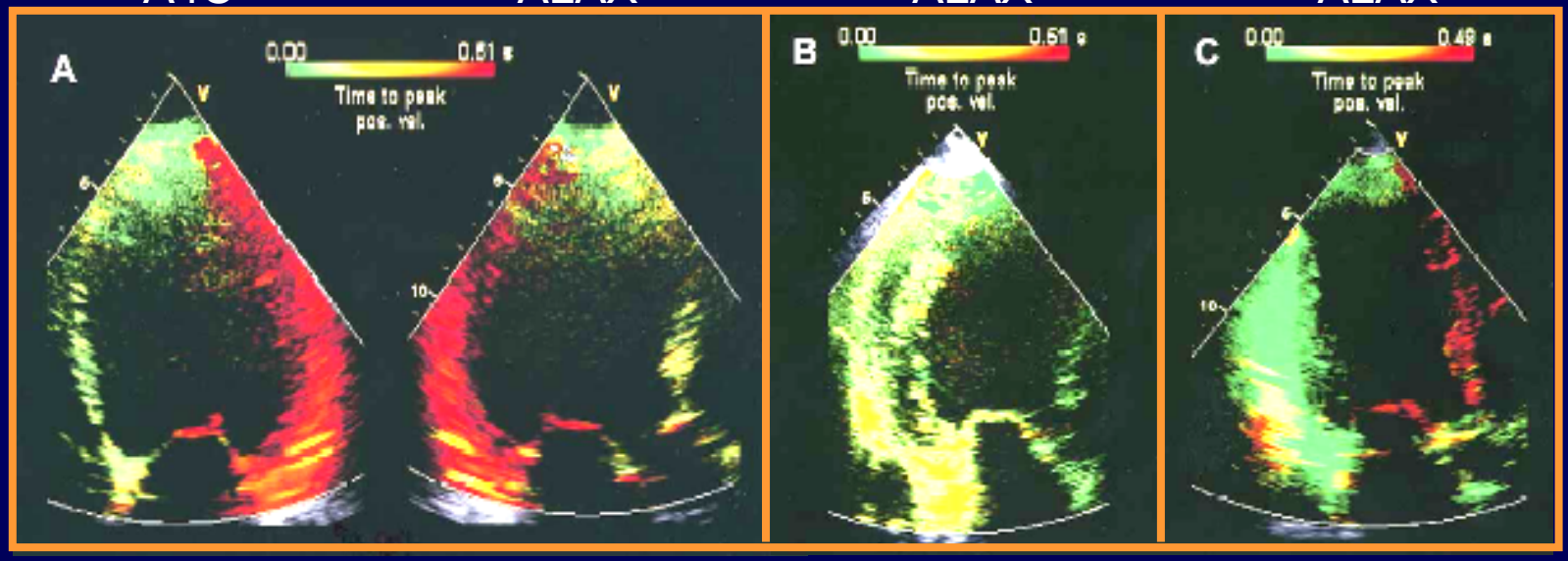
LBBB



Sade LE Am J Cardiol 2004; 94:514

Tissue Synchronization Imaging (TSI)

Time to peak velocity delay



Significant delay in the posterior and lateral walls

Responder

No delay

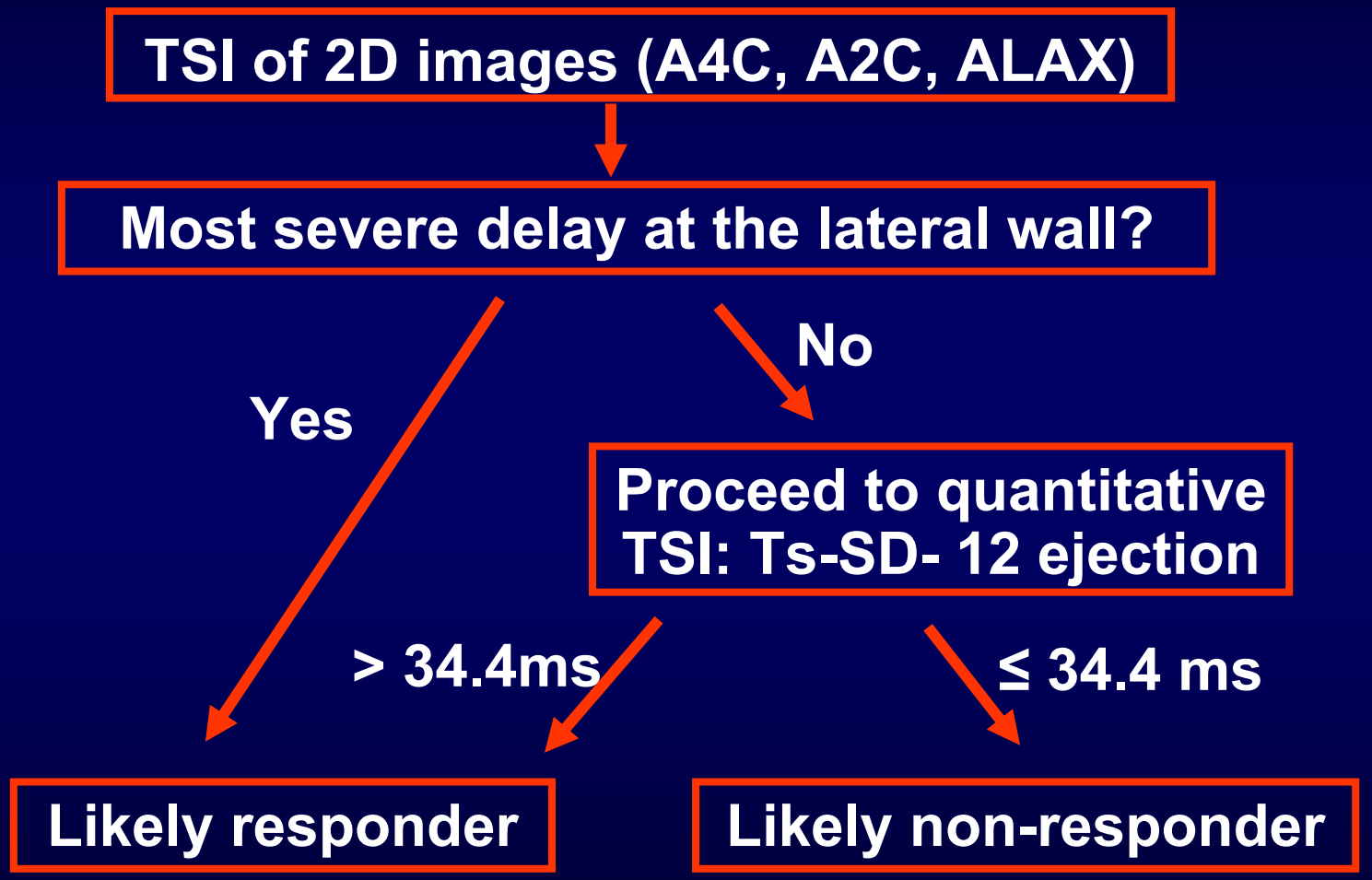
Non - responder

Reversed delay in the anterior septum

Non - responder

Gorcsan J et al. Am J Cardiol 2004;93:1178

Algorhytm to Predict Responders to CRT by TSI



Yu CM et al. JACC 2005; 45:677

Cut-off Values of Systolic Dyssynchrony Measured by TSI

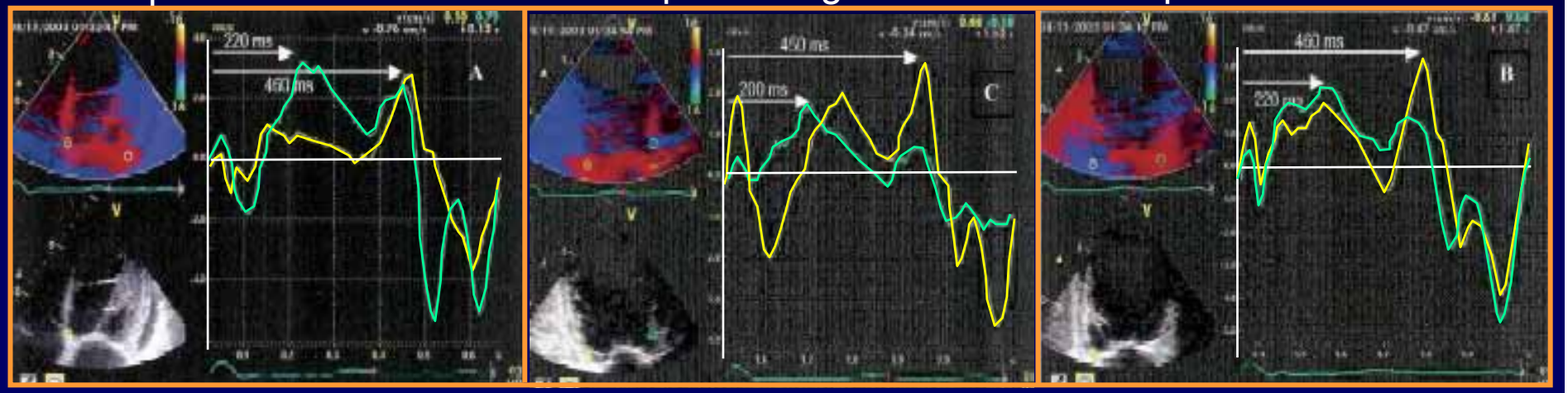
	Cut-off (ms)	Sensitivity (%)	Specificity (%)
Ts-SD-12 ejec	**34.4**	**87**	**81**
Ts-SD-6 ejec	34.5	70	92
Ts-12 ejec	**105**	**83**	**85**
Ts-6 ejec	78	73	77
Ts-SD-12 PSS	70	70	46
Ts-SD-6 PSS	40	87	61
Ts-12 PSS	250	70	50
Ts-6 PSS	102	87	61

Yu CM et al. JACC 2005; 45:677

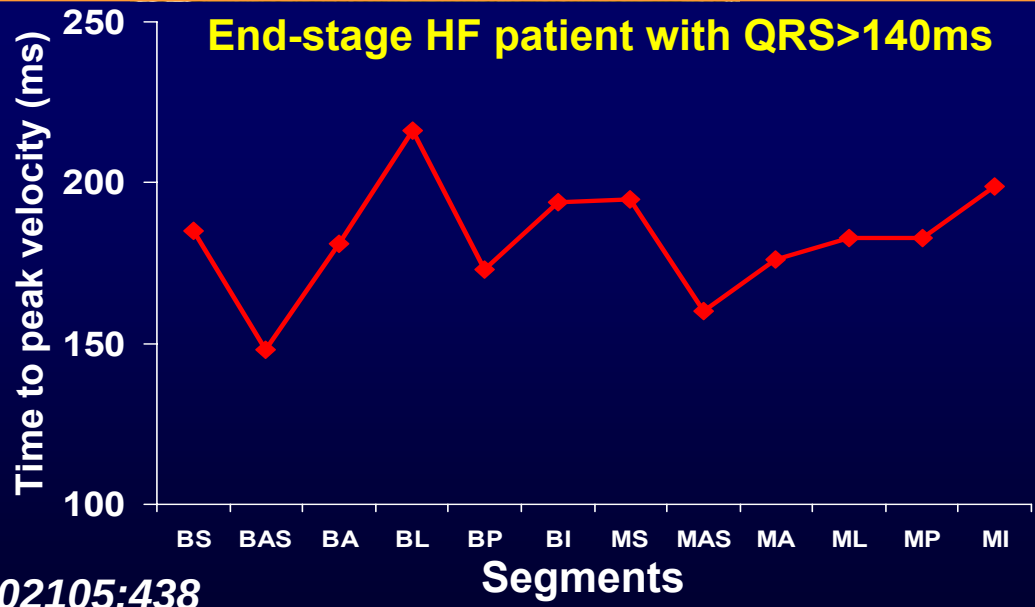
Quantification of Regional Dyssynchrony

Tissue Velocity Imaging

Apical 4 Chamber | Apical Long Axis | Apical 2 Chamber



Longitudinal 12-segment model

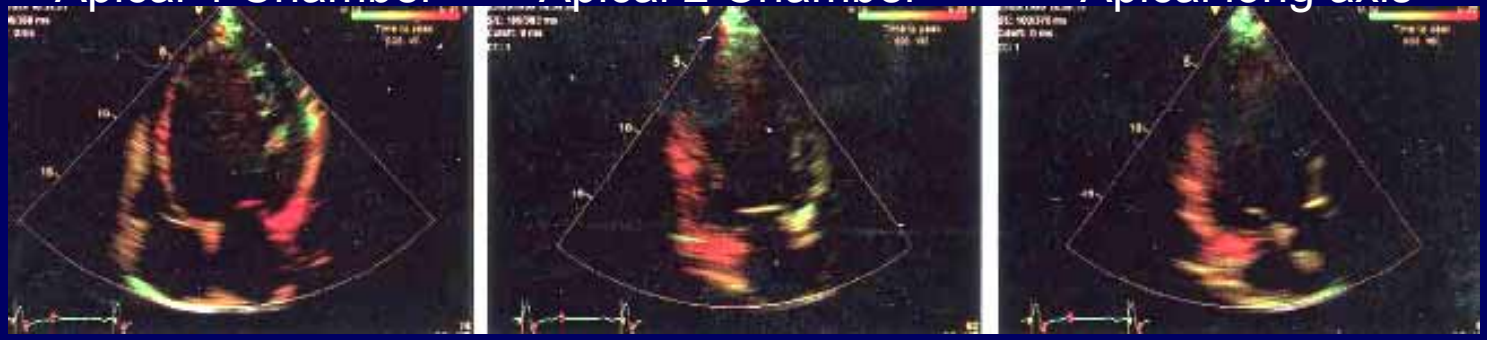
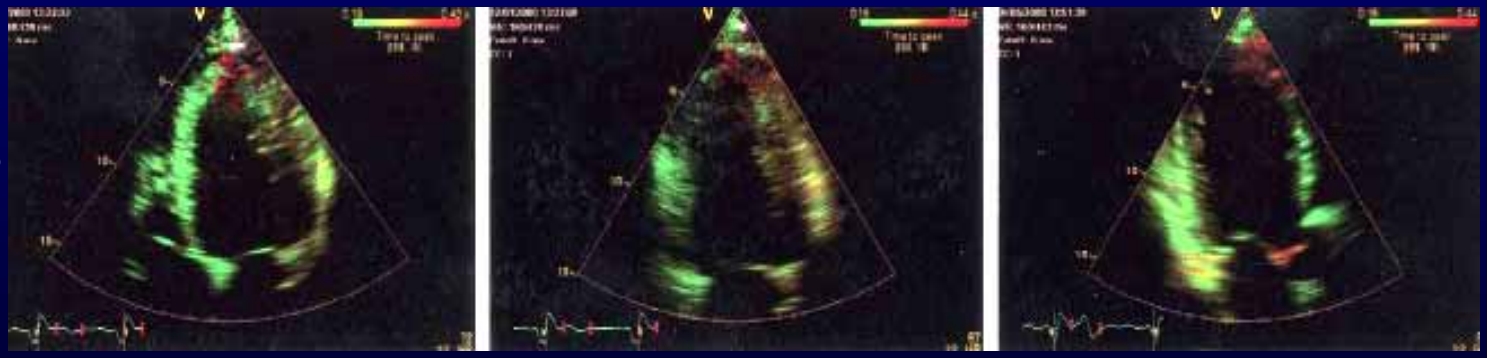


Yu CM et al Circulation 2002105:438

Tissue Synchronization Imaging (TSI)

Color coded display of time to peak velocity

Green: 20-150ms Normal timing
Yellow-orange: 150-300ms Moderate delay
Red: 300-500ms Severe delay

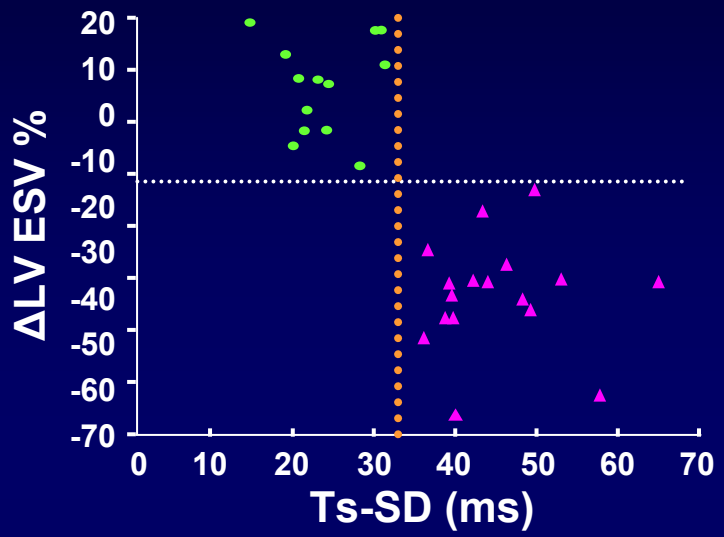
	Apical 4 Chamber	Apical 2 Chamber	Apical long axis
Baseline			
CRT for 3 months			

Yu CM JACC 2005; 45:677

Tissue sync imaging is a parametric imaging tool derived from 2D TDI images. It automatically calculates and color-codes the time to peak tissue velocity (Ts) in every position in the image with reference to the QRS onset. The TSI algorithm detects positive velocity peaks within a specified time interval, and the color coding ranges from green to yellow, orange to red within this interval. Herein, a TSI example set up to measure the time to peak myocardial systolic velocity at ejection. This patient had sever delay over the basal to mid-lateral wall and the whole septal wall, severe delay over the whole inf wall and moderate to severe delay over the posterior wall. 3 mo after crt a dramatic improvement of these delays was noticed with some residual delay over the lateral and inf walls.

Echocardiographic Dyssynchrony Index

Dyssynchrony index (Ts-SD) (ms)=
Standard deviation of segmental time to peak myocardial systolic contraction



Cut-off: Ts-SD >32.6ms

Predictive Value of Ts-SD For Reverse Remodeling

QRS	Sen	Spes	PPV	NPV
>120	94	83	88	90
120-150	100	78	88	90
>150	83	86	83	86

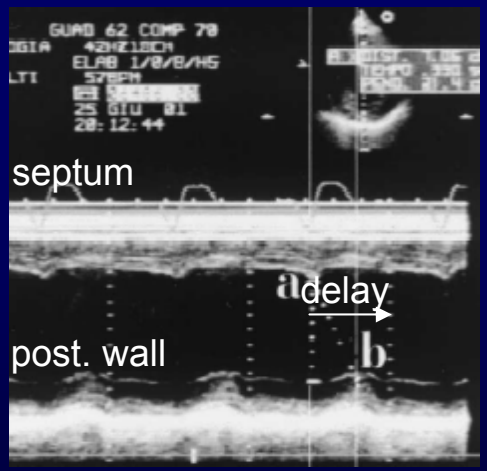
Yu CM Am J Cardiol 2002; 91:684
Yu CM J Cardiovasc Electrophysiol 2004 15:1058

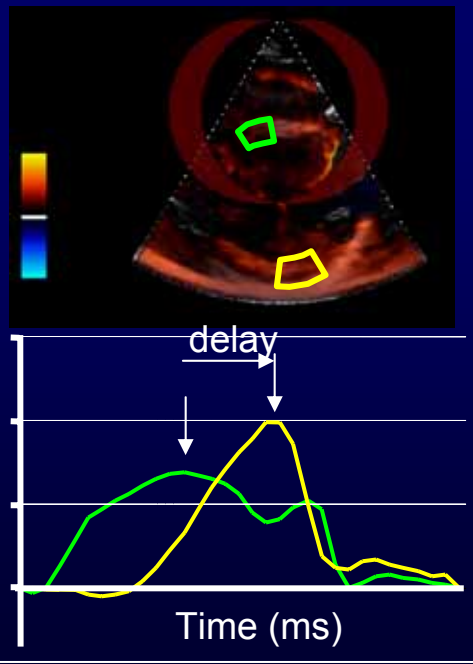
Echocardiographic Dyssynchrony Index

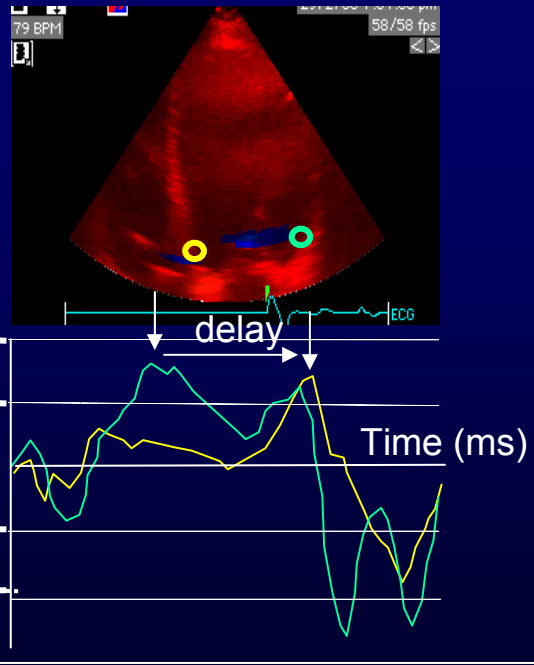
- Yu Index (Ts-SD)
- **Septal to free wall delay**

Yu CM J Cardiovasc Electrophysiol 2004 15:1058

Parasternal M-mode	Parasternal Short Axis	Apical views
Septum-Posterior Wall time to peak wall motion	Septum-Posterior Wall time to peak strain/displacement delay	Opposing wall time to peak velocity delay
Cut-off ≥ 130ms		Cut-off ≥ 60ms

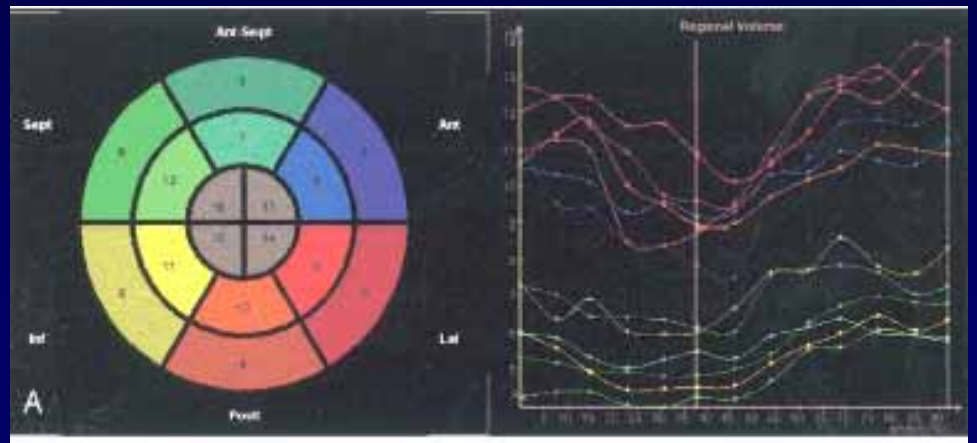






Regional Dyssynchrony by 3D Volumetric Curves

CRT OFF

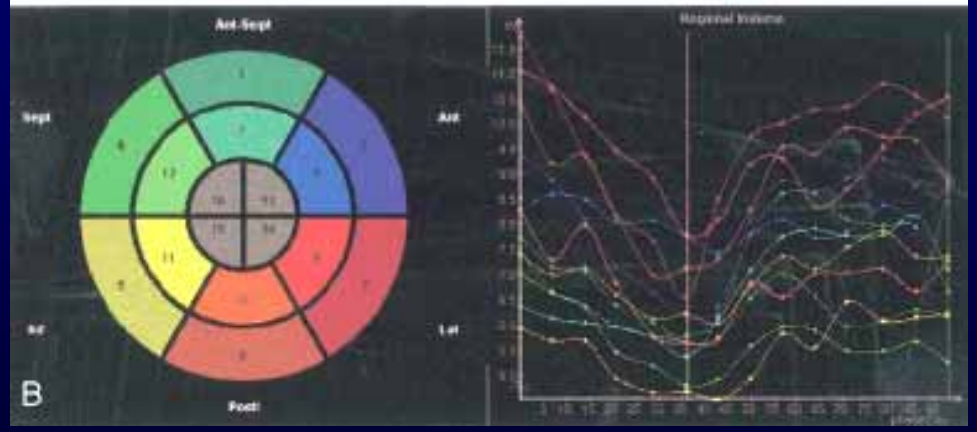


Tmsv 12 SD = 52 ms

Tmsv 12 dif = 136 ms

Tmsv: time to minimum systolic volume

CRT ON



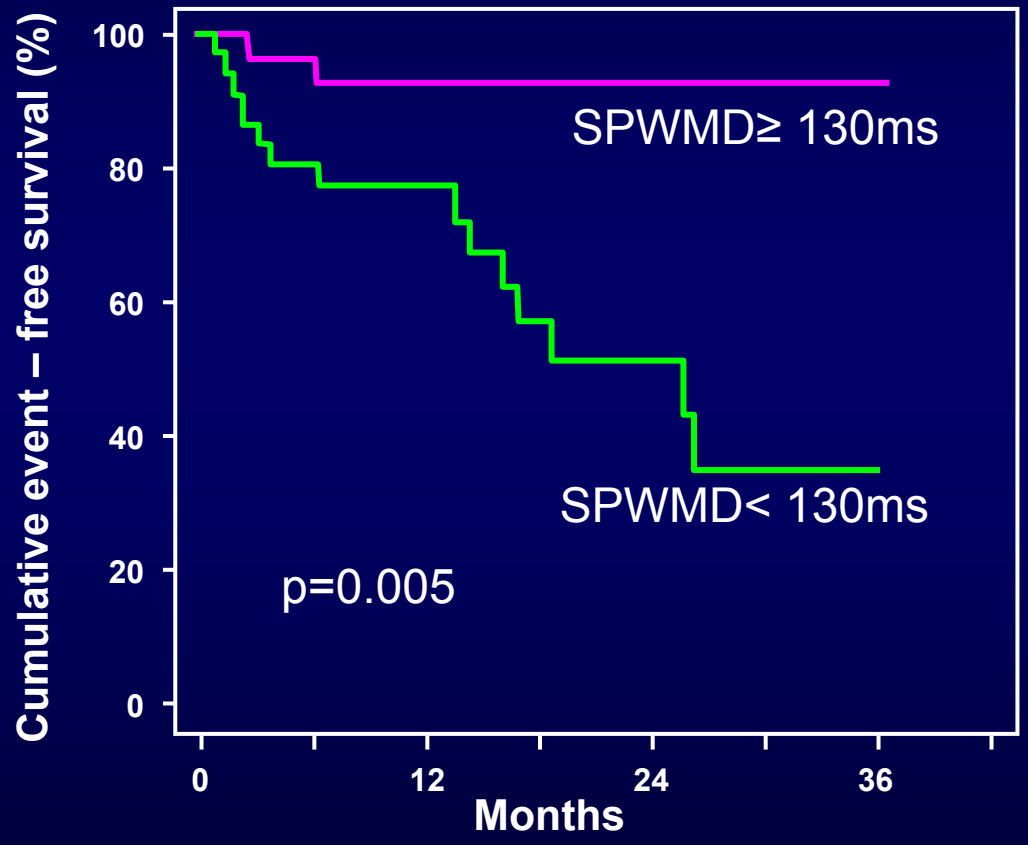
Tmsv 12 SD = 23 ms

Tmsv 12 dif = 77 ms

Zhang Q et al, AJC 2005; 95: 126

Upper panel: Regional voulmtric curves of 6 basal and mid segments in a study patient showing asynchronous LV contraction in CRT off mode: Scattered timings to minimal regional volume, with a Tmsv 12 SD=52 ms and Tmsv 12 dif 136 ms
Lower panel:

Pre-Implantation Mechanical Dyssynchrony is Predictive for Event Free Survival



SPWMD : septum-posterior wall motion delay

Pitzalis V et al JACC 2005; 45:65

RISKS AND COMPLICATIONS OF CRT

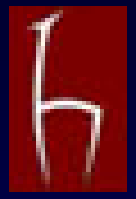
- Bleeding 1 %
- Infection 1 %
- Hematoma 1 %
- Pnemothorax 1 %
- Pericardial effusion 1 %
  w/wo tamponade
- MI/Stroke/death 1/500
- Coronary sinus
  dissection/perforation 1 %
- LV lead dislodgement 5 %

AHA Science Advisory Circulation 2005;111:2146-50

Long-term retention of CRT

- CRT is interrupted in 36 % of pts after successful implantation of a CRT device
- Most common causes of interruption of CRT are development of AT's (18 %) and loss of LV capture (10 %)
- CRT can be reinstituted in majority of patients and only 5 % of pts permanently lose CRT
- Long-term retention of CRT in 2.5 yrs is 83 % (Intention to treat)

JACC 2004;44:72-7



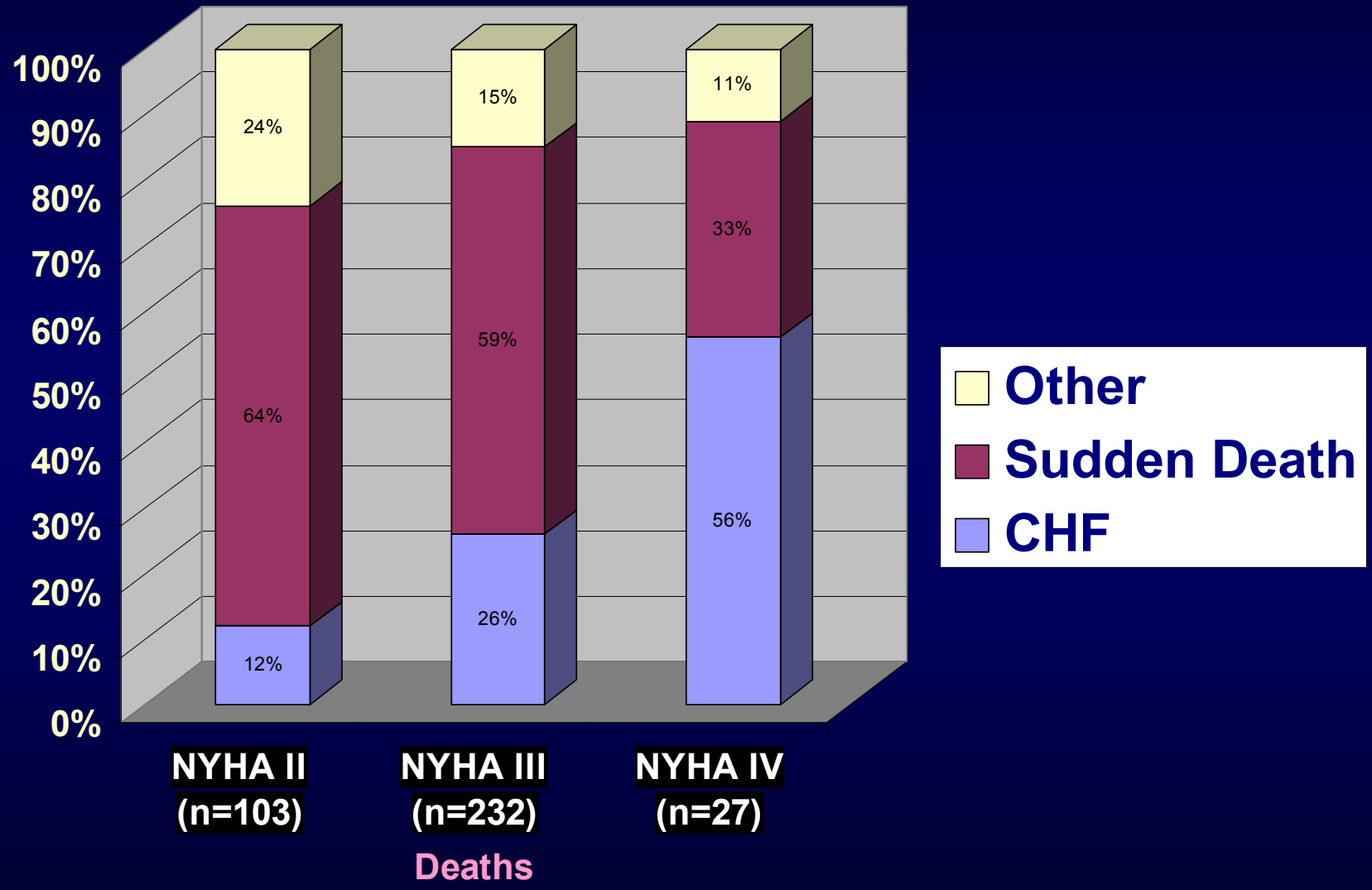
UNCERTAINTIES ABOUT CRT

1. Does CRT improve outcomes of all patients w advanced CHF regardless of their QRS width or NYHA Class?
2. Does CRT improve outcomes of patients w chr A Fib or RBBB ?
3. Is definition of rehospitalization in the clinical trials of CRT adequate?
4. Under what circumstances does CRT provide benefit in patients who would not derive a survival benefit from ICD?

Expert Panel Report Am Heart J 2005;149:1020

AHA Science Advisory Circulation 2005;111:2146-50

Major Causes of Death in CHF

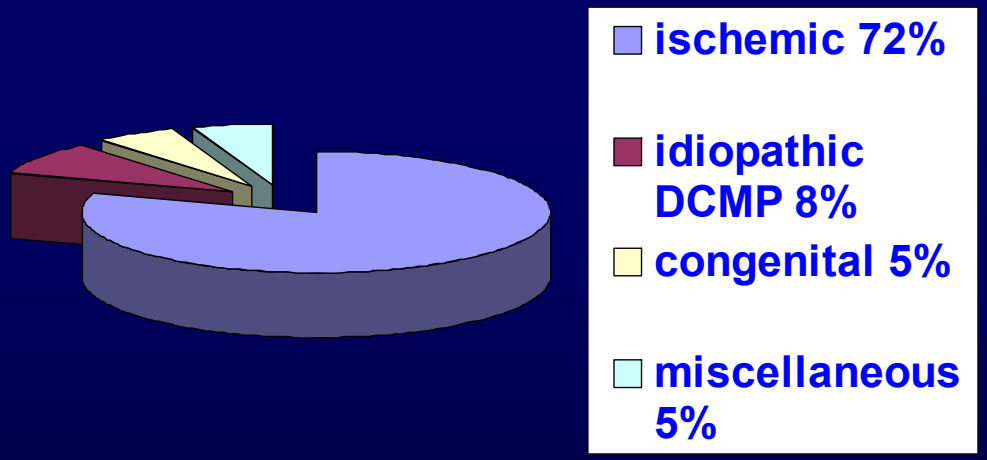


Am J Cardiol 2003;91(Suppl):62F-73F

- Does every patient who needs CRT also needs ICD?
- Does every patient who needs an ICD also needs CRT?

ELIGIBILITY FOR CRT IN PATIENTS WITH AN ICD

Etiology of Cardiac Disease in 79/390 (Appr 20 %) ICD Patients Eligible For CRT



Eur J Heart Failure 2003;5:315-17

COMPANION and CARE-HF
Eligibility criteria

COMPANION

- NYHA III or IV
- SR, QRS ≥120 ms, PR >150 ms
- LVEF ≤35 %
- LVEDD ≥60 mm

CARE-HF

- NYHA class III or IV
- QRS ≥ 120 msec
- LV EF ≤ 35%
- LVEDD ≥ 30 mm (indexed to height)

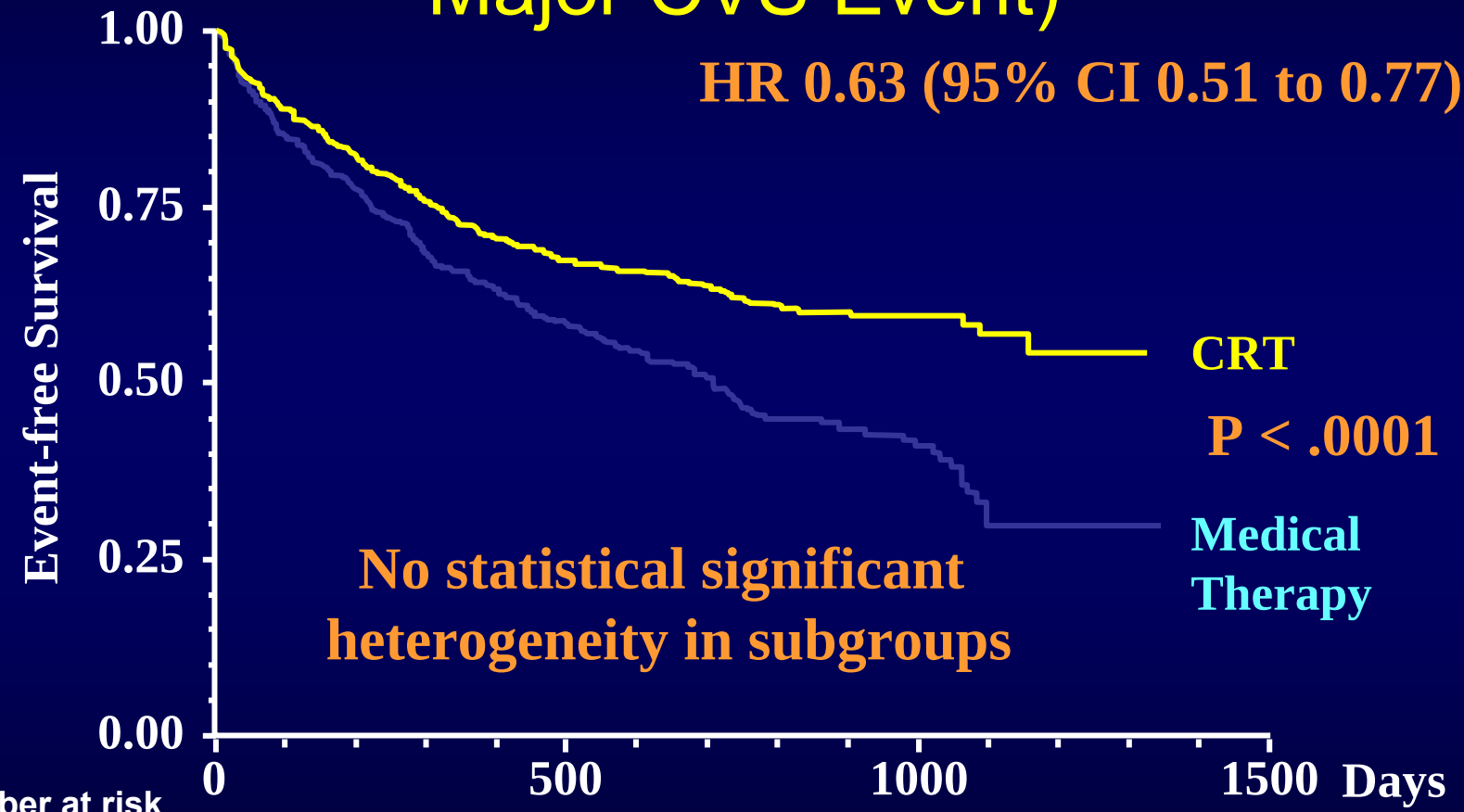
Bristow et al., NEJM 2004; 350: 2140-50

JGF Cleland et al., NEJM 2005;352: 1539-49

CARE- HF

Primary Endpoint

(All-cause Mortality or Unplanned Hosp. for Major CVS Event)

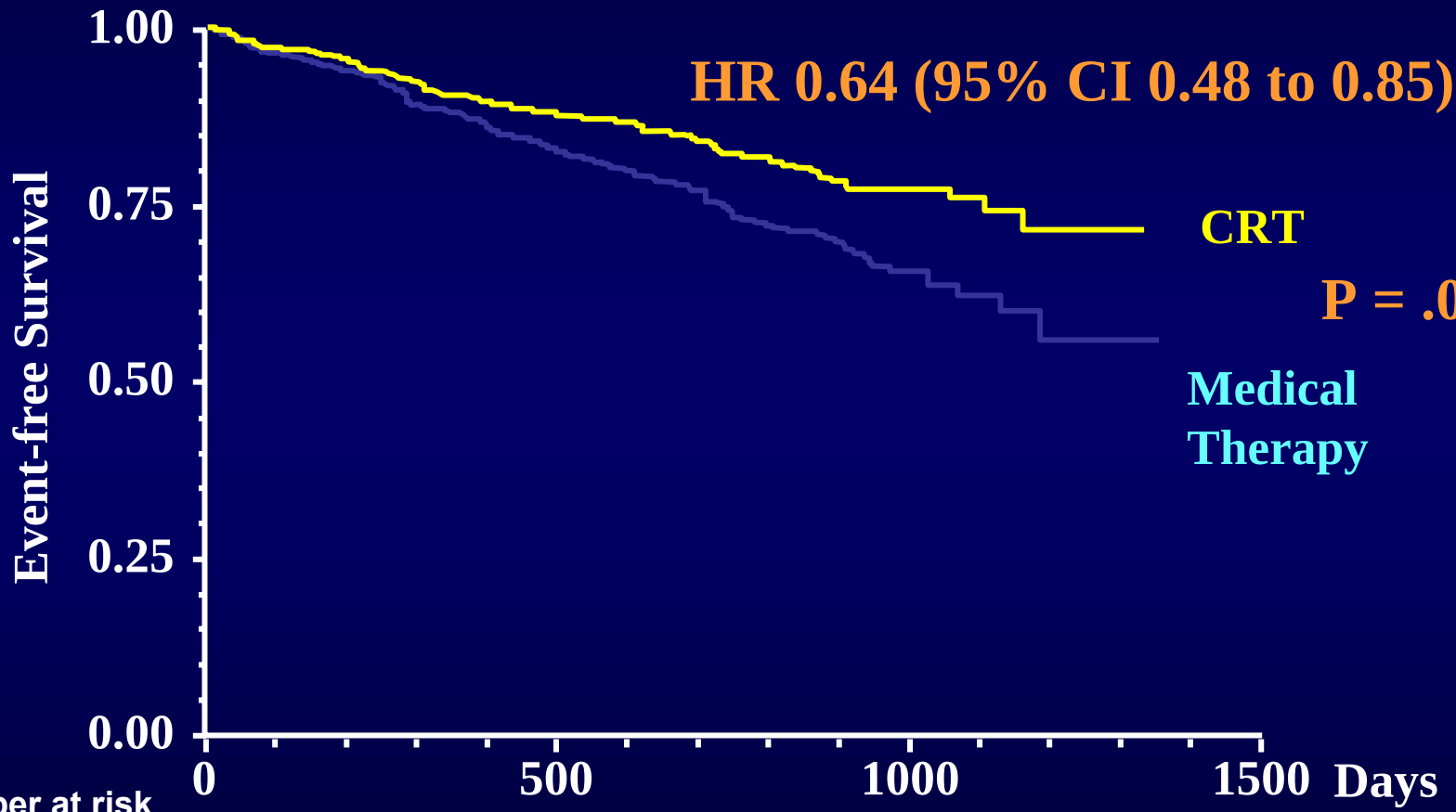


Number at risk						
CRT	409	323	273	166	68	7
Medical Therapy	404	292	232	118	48	3

There was no heterogeneity in effect in any of the pre-specified subgroups. In particular, benefit was observed in older patients, women, patients with ischaemic heart disease, in patients above and below median LVEF and in patients receiving or not receiving beta-blockers and Spironolactone (there were too few patients not receiving an ACE inhibitor or ARB and therefore this analysis was not included in the statistical analysis plan).

CARE-HF

All-Cause Mortality



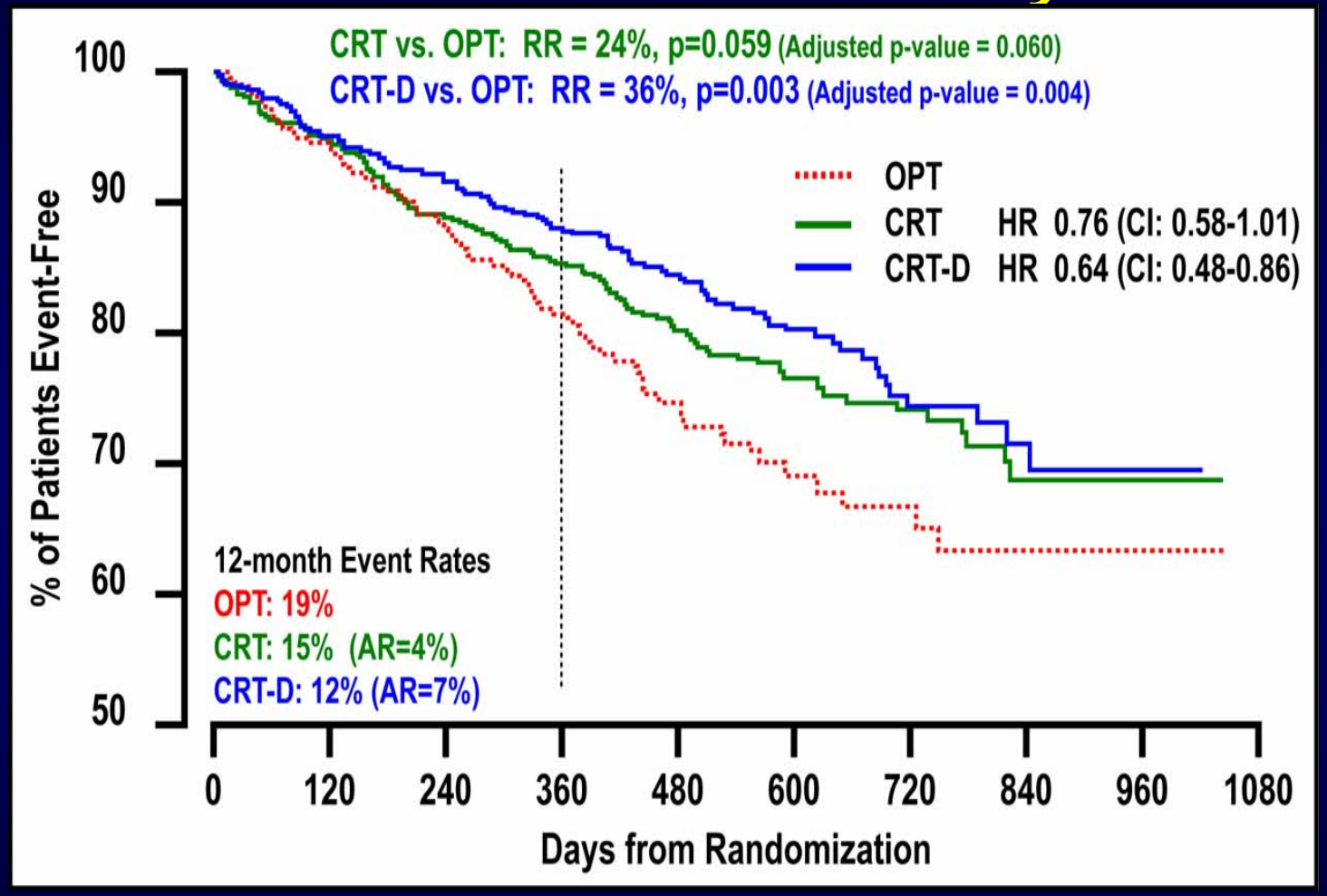
Number at risk						
CRT	409	376	351	213	89	8
Medical Therapy	404	365	321	192	71	5

There was a striking reduction in mortality in the CRT group. The absolute difference between control and CRT was 10%. Again, there was no early hazard and the curves begin to separate within the first 6 months of randomisation. A reduction in both sudden deaths and deaths due to worsening heart failure was observed. There were only 29 sudden deaths out of 82 in the CRT group.

The benefits of CRT are in addition to those of the above pharmacological therapy. The absolute difference in mortality at 2 years was 7.1%. This compares to 5.2% with Enalapril in the SOLVD-treatment study and is similar to the estimated two-year mortality difference between placebo and Bisoprolol in the CIBIS-II study or the 8.8% difference between placebo and Carvedilol in COPERNICUS (which using the method of trial duration used in our study had a duration of about 15 months).

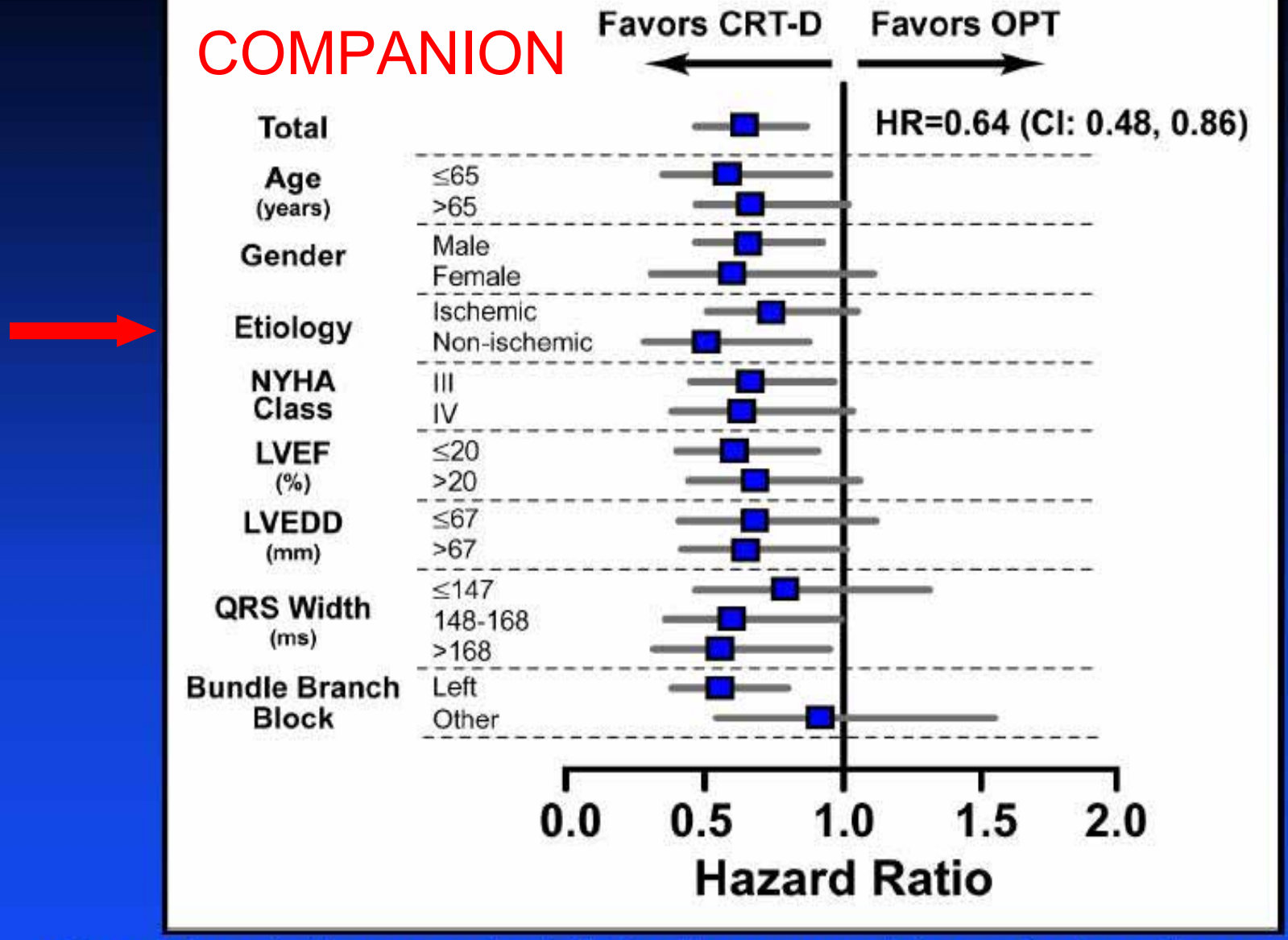
The hazard ratio of the effect of CRT in CARE-HF (0.64; 95% confidence interval 0.48 to 0.85; p=0.0019) was similar to that of CRT-D compared to control in the COMPANION trial (0.64, 95% confidence interval, 0.48 to 0.86; P=0.003) . The absolute estimated difference at 2 years in the COMPANION study between CRT-D and control was about 8% with CRT and CRT-D having similar effects in that study.

COMPANION: *Secondary Endpoint of All-Cause Mortality*



Bristow et al., N Engl J Med 2004; 350: 214050

Subgroup Hazard Ratios (univariate) Mortality



NOTE: The study was not statistically powered to evaluate subgroups

Bristow et al., N Engl J Med 2004; 350: 214050

COMPANION

- CRT alone was associated with a trend (p = .06) for reduction (by 24%) in mortality
- The addition of an ICD to CRT enhanced the mortality reduction by an additional ~ 50% (from 24% to 36%) which was significant (p = .003)
- The CRT-D mortality benefit appeared higher in non-ischemic pts than in ischemic pts
- No difference in morbidity between CRT alone vs CRT-D

Bristow et al., N Engl J Med 2004; 350: 2140-50

ESC HEART FAILURE GUIDELINES-Recommendations for CRT-D

CLASS II a (Level of evidence B)

Implantation of an ICD in combination w biventricular pacing can be considered in patients who remain symptomatic w severe heart failure NYHA Class III-IV w LVEF >35 % and QRS>120ms to improve morbidity and mortality)

The selection criteria

The limited FU

Increased morbidity associated w ICD implantation

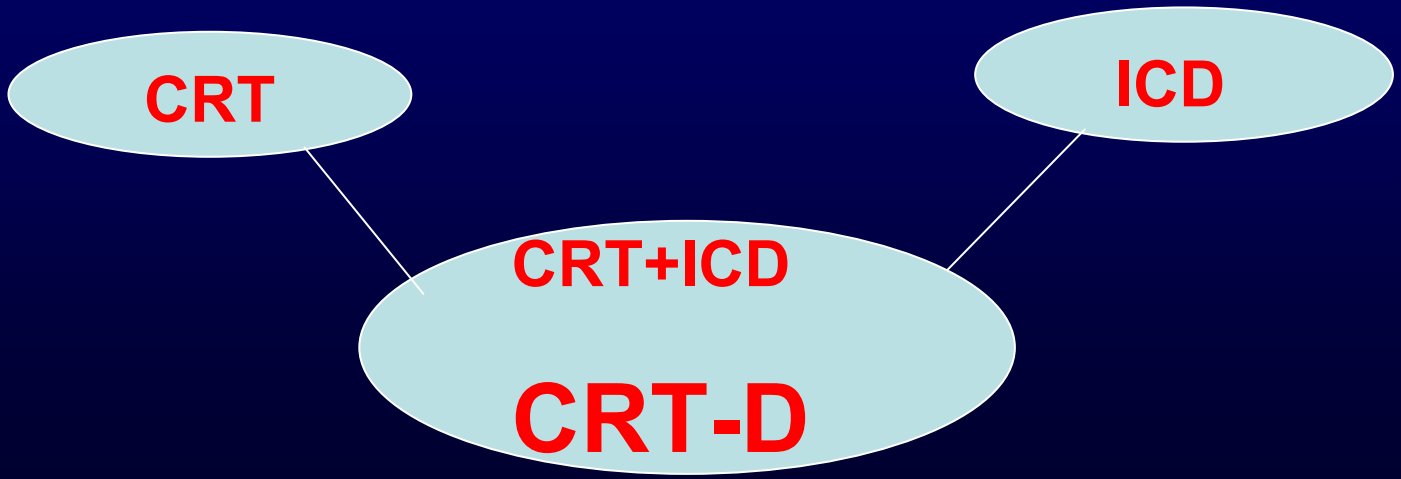
Low cost-effectiveness prevent to extend the findings into general population w CHF

Eur Heart J 2005;26:1115

Optimal pharmachologic therapy

PROGRESSION OF HF
(PUMP FAILURE)

SCD



Pacing for heart failure

DDD Pacing

DDD pacing w/ short AV delay

DDD pacing AV Delay optimization

Biventricular pacing CRT

CRT + ICD

Expanded CRT indications

Added functions to CRT devices

FUTURE

CRT-D&Gene Based therapy

CONCLUSIONS

- CRT REDUCES MORBIDITY AND MORTALITY IN ADVANCED HEART FAILURE
- **MORE DATA IS NEEDED FOR CERTAIN PATIENT GROUPS (MILDLY SYMPTOMATIC, Pts w AF,N QRS)**
- The answer to the question 'Does every patient with CRT needs ICD ?' is not clear yet.