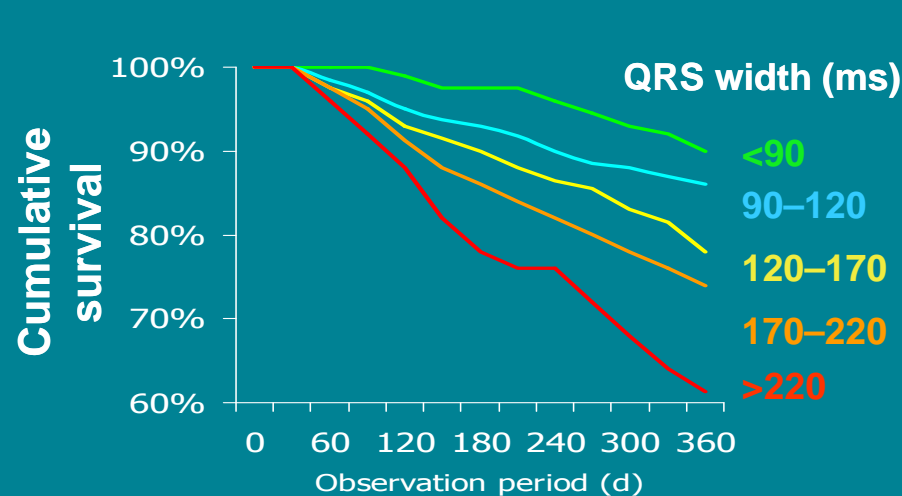


# HOW TO SELECT CRT PATIENTS? CURRENT AND EMERGING CRITERIA

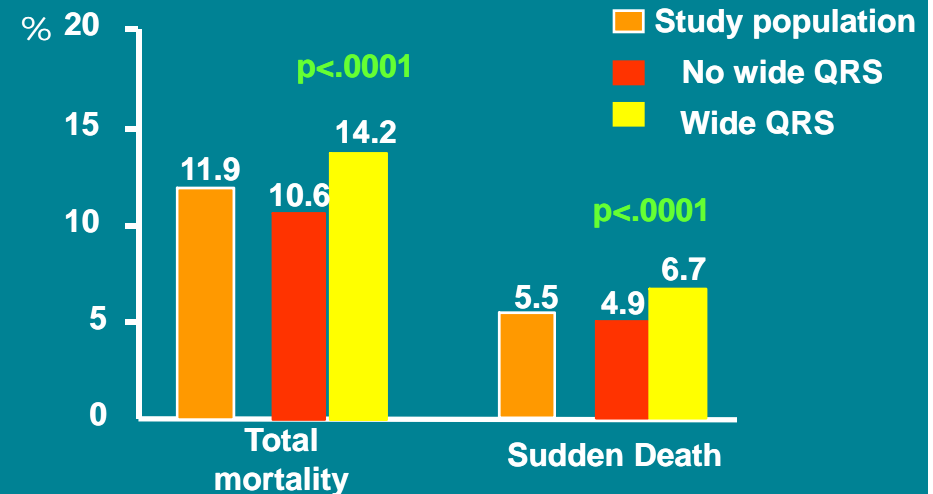
Dr. Maurizio Gasparini  
Chief of Electrophysiology and Pacing Unit  
IRCCS, Istituto Clinico Humanitas, Rozzano-Milano, Italy

## Principles of pacing in HF

- ✓ Cardiac resynchronization therapy (CRT) is a non-pharmacological approach to treat drug-refractory advanced heart failure (HF);
- ✓ Wide QRS, mainly left bundle-branch block (LBBB), in HF is an independent predictor of adverse prognosis:



[Gottipaty, JACC 1999; 33(2):145A]



[Baldasseroni et al., Am Heart J 2002;143:398-405]

- ✓ Right ventricular pacing induces LBBB-like activation → may have deleterious long-term effects on LV function

[Wilkoff et al, JAMA 2002; Sweeney et al, Circulation 2003].

## Principles of pacing in HF

- ✓ The correction of the electromechanical disorder present in refractory HF achieved using cardiac pacing is termed **"cardiac resynchronization therapy"** (CRT);
- ✓ CRT:
  - Should be delivered through biventricular (Auricchio et al, Circulation 1999) or left ventricular (LV) stimulation (Gasparini et al, Am Heart J 2006) mode as these pacing modes confer the greatest hemodynamic benefit;
  - Requires that the LV electrode be positioned preferably in a lateral or postero-lateral position;
  - Requires atrio-ventricular interval optimization;
  - May require ventricle-ventricular interval optimization.

## Randomized Trials on CRT

✓ Randomized clinical CRT trials enrolled patients according to the following inclusion criteria:

- NYHA class III-IV on optimized medical therapy;
- Left ventricular ejection fraction  $\leq 35\%$ ;
- Dilated left ventricle;
- Wide QRS:
  - MUSTIC  $\rightarrow \geq 150$  ms
  - MIRACLE  $\rightarrow \geq 130$  ms
  - CARE-HF  $\rightarrow > 150$  ms and between 120-150 with dyssynch criteria
  - COMPANION  $\rightarrow \geq 120$  ms

✓ Earlier trials focused on the effects of CRT on functional status (6 MWT, NYHA, QOL, and peak O<sub>2</sub>);

✓ More recent trials have focused on morbidity and mortality.

## Randomized Trials on CRT (functional status)

<b>Trials</b>	<b>Pt n.</b>	<b>Design</b>	<b>Primary (PEP) &amp; Secondary (SEP) Endpoints</b>	<b>MAIN RESULTS</b>
<b>MUSTIC SR</b> (Cazeau et al, NEJM 2001)	<b>58</b>	<b>Crossover</b>	<b><u>PEP:</u> 6MWT</b> <b><u>SEP:</u> NYHA, QOL, peak VO<sub>2</sub>, LV volumes, MR, Hosps, Total mortality</b>	<b>CRT improved all</b>
<b>PATH-CHF</b> (Auricchio et al, JACC 2002)	<b>41</b>	<b>Crossover</b>	<b><u>PEP:</u> 6MWT, Peak VO<sub>2</sub></b> <b><u>SEP:</u> NYHA, QOL, Hosps</b>	<b>Improved all with biventricular or left ventricular pacing</b>
<b>MIRACLE</b> (Abraham et al., NEJM 2002)	<b>453</b>	<b>Parallel arms</b>	<b><u>PEP:</u> 6MWT, NYHA, QOL</b> <b><u>SEP:</u> Peak VO<sub>2</sub>, LVEF, LVEDD, MR, clinical composite response</b>	<b>Improved all in CRT arm</b>
<b>MIRACLE ICD</b> (Young et al., JAMA 2003)	<b>555</b>	<b>Parallel arms</b>	<b><u>PEP:</u> 6MWT, NYHA, QOL</b> <b><u>SEP:</u> Peak VO<sub>2</sub>, LVEF, LV volumes, MR, clinical composite response</b>	<b>After CRT NYHA class and QOL improved</b>

[Adapted from Bax JJ et al, JACC 2005]

→ randomized controlled studies demonstrated improved 6MWT distance, NYHA functional class, and QOL score after CRT.

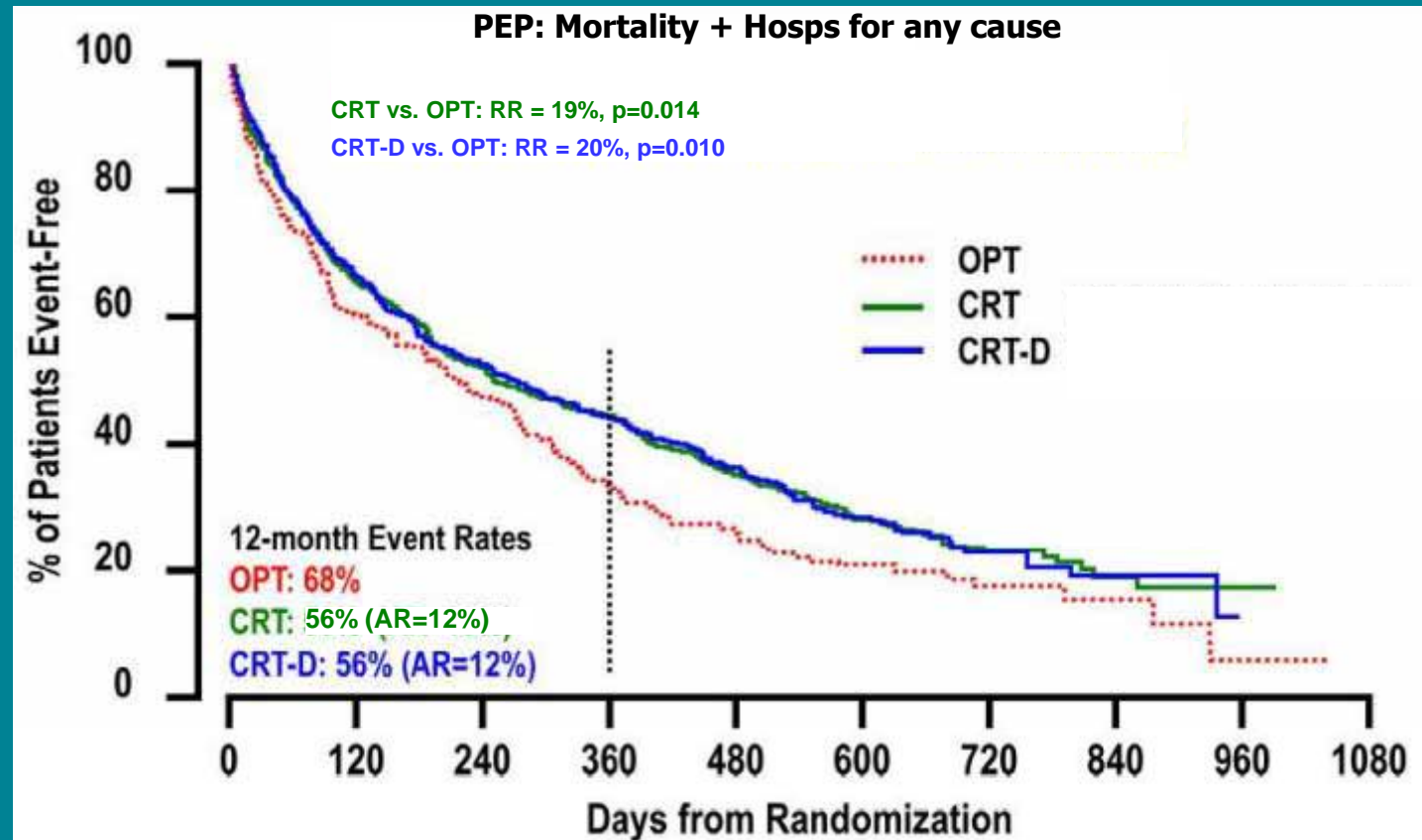


## Randomized Trials on CRT (morbidity & mortality)

### COMPANION- 1520 pts randomized to 3 treatment arms

[Bristow et al. *N Engl J Med.* 2005; 350 (21): 2140-2150]

→ CRT on its own (CRT) or with ICD back-up (CRT-D) reduced the composite end-point of all-cause mortality or hospitalization.

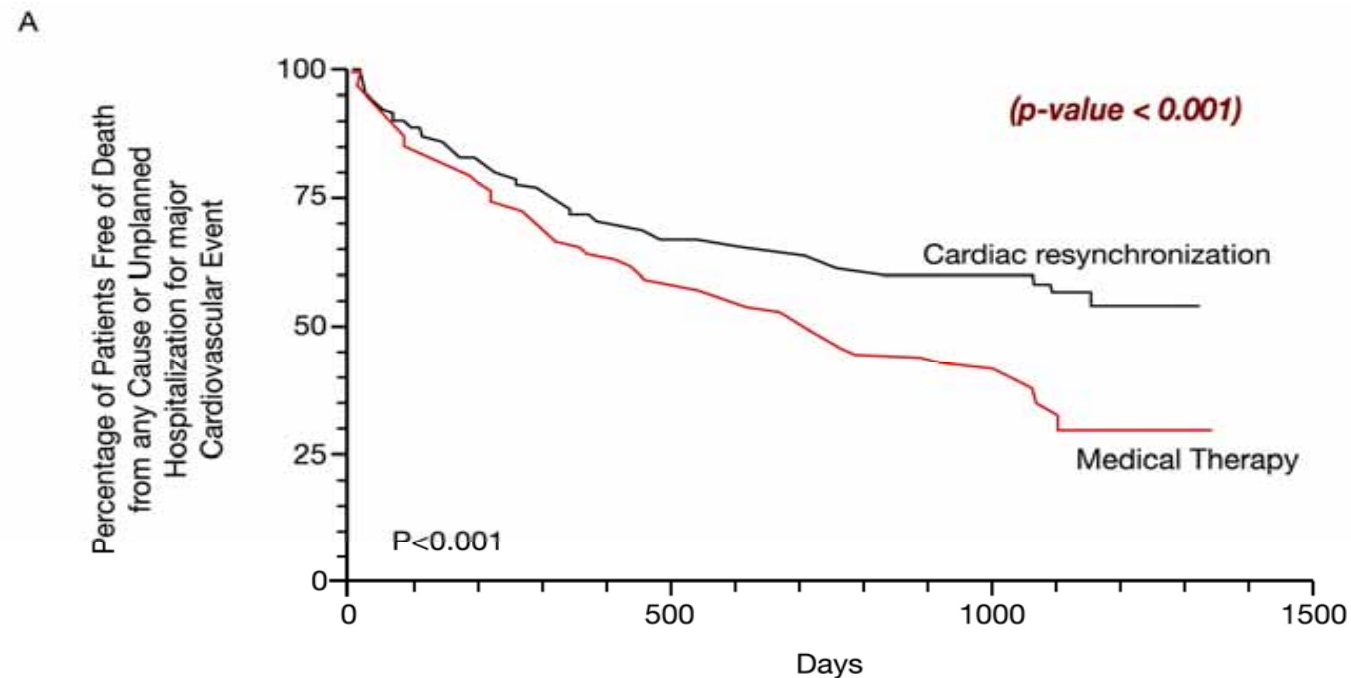


# Randomized Trials on CRT (morbidity & mortality)

## CARE-HF- 814 pts randomized to CRT or OPT

[Cleland J. G.F. et al. *N Engl J Med.* 2005;352: 1539-1549]

→ CRT reduced all-cause mortality and morbidity



### No. at Risk

Cardiac resynchronization	409	323	273	166	68	7
Medical therapy	404	292	232	118	48	3

ESC Guideline for Pacing and CRT (Sept '07)

NYHA class III-IV  
(OPT)

Sinus rhythm

CRT-D

QRS  $\geq$  120 msec

LV dilatation  
(LVEDD > 55 mm)

LVEF  $\leq$  35%

Class I-B

## ESC Guideline for Pacing and CRT (Sept '07)

NYHA class III-IV  
(OPT)  
QRS  $\geq$  120 msec

**CRT-D**

Sinus rhythm  
LV dilatation  
(LVEDD  $>$  55 mm)  
LVEF  $\leq$  35%

+

Pre-existing ICD indication

Class I-B

ESC Guideline for Pacing and CRT (Sept '07)

NYHA class III-IV  
(OPT)

Atrial fibrillation

CRT

QRS  $\geq$  120 msec

LV dilatation  
(LVEDD > 55 mm)

LVEF  $\leq$  35%

**CRT in permanent AF:**

AF patients: 20-25% pts implanted [Auricchio et al, AJC 2007]

Management problems  $\rightarrow$  reduce effective CRT delivery

AF patients have been excluded from CRT RCTs

No indications on how to adequately manage CRT in AF

# ESC Guideline for Pacing and CRT (Sept '07)

STUDY	Pt n.	Selection criteria	F.U. months	DESIGN & AIM	MAIN RESULTS
MUSTIC AF (JACC 2002)	64	NYHA III QRS $\geq$ 150 ms EF < 35%	12	Comparative longitudinal: BVP SR vs AF	Both AF & SR improved: 6MWT; pVO <sub>2</sub> ; QOL; NYHA class; EF; MR
Leon et al. (JACC 2002)	88	NYHA III-IV EF < 35%	> 6	Longitudinal observational; baseline	BVP in AF improves: NYHA class; EF; QOL
Leclet et al. (EHJ 2002)	100	NYHA III-IV EF < 35%	12	Comparative: BVP in SR vs AF	Both AF & SR improved: 6MWT; QOL
Puggioni et al. (JACC 2003)	100	NYHA III-IV EF < 35%	12	Comparative: BVP in SR vs AF	Both AF & SR improved: 6MWT; QOL
Molhoek et al. (Am J Cardiol 2004)	60	NYHA III-IV EF < 35% QRS > 120 ms	up to 24	Comparative: BVP in SR vs AF	Both AF & SR improved: 6MWT; QOL; NYHA. Similar survival;
Gasparini et al. (JACC 2006)	673	NYHA $\geq$ II-IV EF < 35% QRS $\geq$ 120 ms	25	Comparative: AF AVJ abl vs AF no abl	AF AVJ abl improve for functional status & global LV function

CRT may be adequately delivered only if the interference of intrinsic rhythm is minimized...

ESC Guideline for Pacing and CRT (Sept '07)

NYHA class III-IV  
(OPT)

Atrial Fibrillation

CRT

QRS  $\geq$  120 msec

LV dilatation  
(LVEDD > 55 mm)

LVEF  $\leq$  35%

Class IIa-C



Combined with  
AV node ablation

## Issues in patient selection for CRT- limits of “wide QRS”

✓ **QRS width *may not* be the ideal criterion for identifying CRT responders !**

**1) wide QRS duration criteria range in CRT trials:  
120 to 150ms**

**2) “narrow QRS” pts may present LV dyssynchrony [Bleeker et al, 2004]**

**3) 30% pts with “wide QRS” are non-responders**

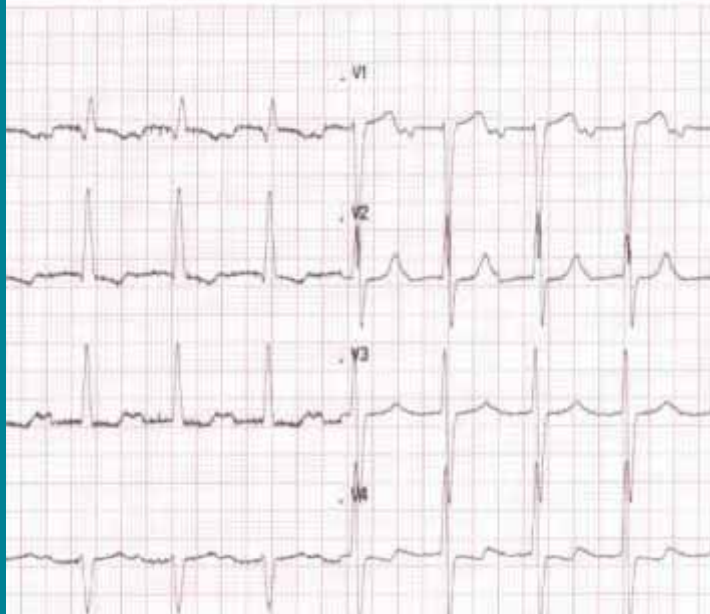
**4) poor correlation between QRS width and intra-ventricular dyssynchrony [Yu et al, 2002]**

**5) QRS width may oscillate up to 30 msec in HF pts [Aranda et al, 2002]**

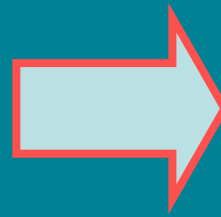
# Issues in patient selection for CRT- limits of "wide QRS"

3-May-2007 15:23:47

Freq Vent: 83 BPM  
Int PR: 305 ms  
Dur QRS: 125 ms  
QT/QTc: 416/456 ms  
Assi P-R-T: 154 79 195

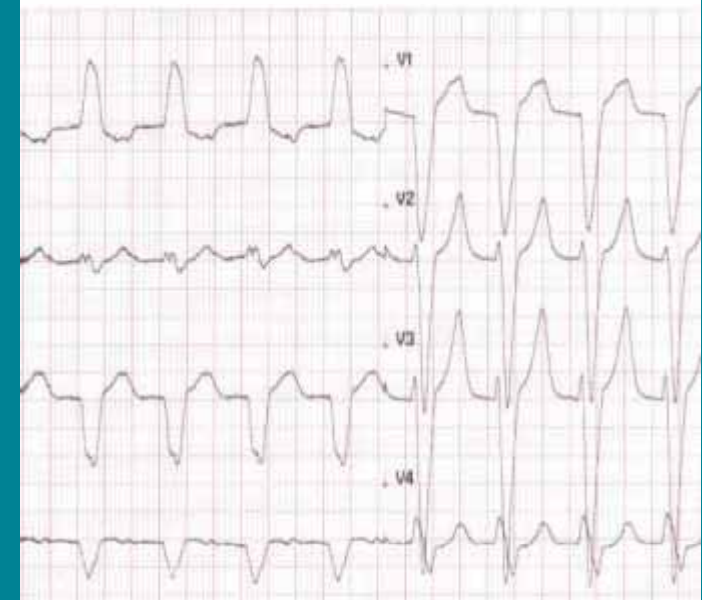


Rate-dependent  
LBBB



14-May-2007 7:56:58

Freq Vent: 99 BPM  
Int PR: 0 ms  
Dur QRS: 190 ms  
QT/QTc: 455/511 ms  
Assi P-R-T: 999 -33 126



How should we consider this patient?  
"Narrow" or "wide" QRS?

## Issues in patient selection for CRT- beyond QRS duration

✓ **Emerging concepts to improve patient selection and to predict CRT response:**

- **LV dyssynchrony** assessment;
- **myocardial viability** assessment;
- **conventional echocardiographic** measures .

# Issues in patient selection for CRT- beyond QRS duration

## Inter-ventricular dyssynchrony

Rouleau et al. (*PACE* 2001)

(Q-Ao)-(q-Pulm) and (Q-Mit)-(Q-tri) → IMD  
[standard pulsed Doppler, Doppler tissue imaging]

Ghio et al (*Eur Heart J.* 2004)

(Q-Ao)-(q-Pulm) → IVMD

## Intra-ventricular dyssynchrony

Pitzalis et al. (*JACC* 2002)

SPWM delay (M-mode, > or = 130 msec)

Sogaard et al. (*JACC* 2002)

delayed longitudinal contraction (TDI)

Breithardt (*JACC* 2002)

septal and lateral wall motion phase angle differences

Yu et al. (*Am J Cardiol* 2003)

time-to-peak systolic contraction [TDI]

Breithardt (*JACC* 2003)

peak lateral- peak septal wall strains

Bax et al. (*JACC* 2004)

Septal/lateral wall delay [TVI, > or = 65 msec]

Penicka et al. (*JACC* 2002)

LV + LV-RV asynchrony [TDI, sum > or = 100 msec]

Gorcsan et al. (*Am J Cardiol* 2004)

time-to-peak velocities of lat/sep walls [TSI]

Yu et al. (*Circulation* 2004)

SD of Ts time to peak myocardial velocity [TDI]

Bordachar et al. (*JACC* 2004)

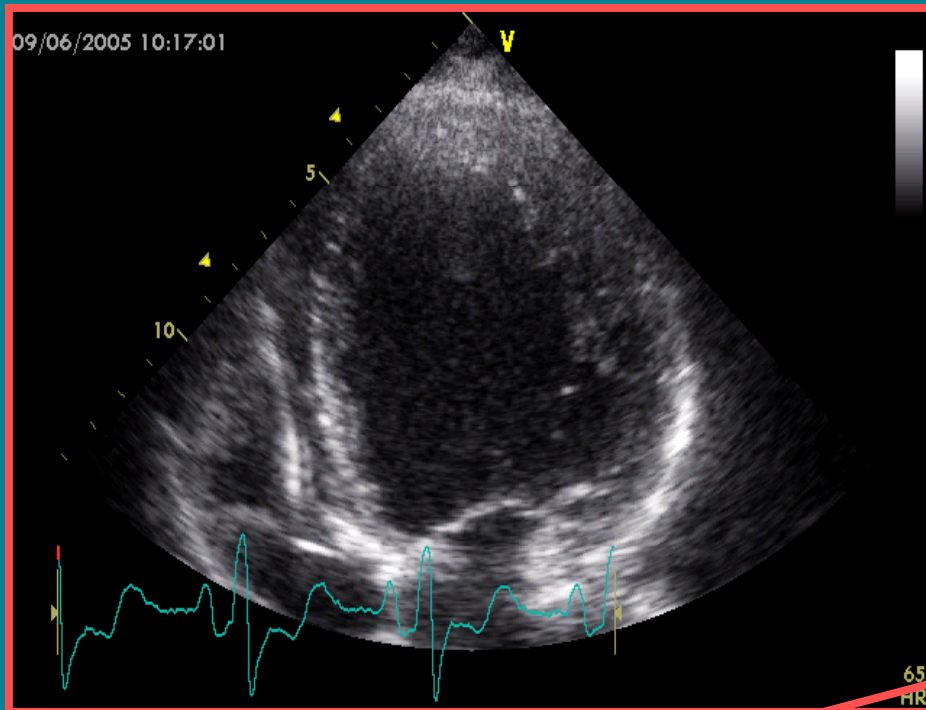
intra-LV delay peak, intr-LV delay onset [TDI]

Suffoletto et al. (*Circulation* 2006)

radial strain from BW echo

# Issues in patient selection for CRT- beyond QRS duration

## Viabile myocardium



## Non-viable myocardium



**Important SCAR BURDEN → unlikely to benefit from CRT**

## Issues in patient selection for CRT- Viability studies

STUDY	Pt n.	Method used	F.U. months	DESIGN & AIM	MAIN RESULTS
White et al. JACC 2006	28	DE-MRI	3	- scar burden and response	Scar < 15% assessed by DE-MRI accurately predicts response
Adelstein et al. Am H J 2006	50	PET 201 T1, myocardial perfusion imaging	11	- scar burden predicts poor response	high scar burden, greater scar burden around the LV tip: little or no response
Bleeker et al. Circ 2006	40	Contrast-enhanced MRI	6	- relation: posterolateral transmural scar and response	Pts with scar burden: - no remodeling - no resynchrony
Ypenburg, Bleeker et al. Eur Heart J 2007	50	Gated SPECT	6	- relation between response to CRT and extent of viable myocardium	> scar burden → ↓ CRT response

## Issues in patient selection for CRT- beyond QRS duration

Conventional echocardiographic measures may predict unfavourable response after CRT:

- EF extremely low (< 15-18%);
- EDV > 250 ml [Gasparini et al, AHA 2003];
- End-diastolic wall thickness (EDWT) < 6 mm  
[Cwajg et al, JACC 2000]



Moderate as opposed to severe LV dilatation and dysfunction may influence CRT response favourably...

[Auricchio et al, JACC 2002, Gasparini et al, PACE 2007]

## Issues in patient selection for CRT- beyond QRS duration

✓ ... Moving beyond QRS duration to select patients:

- **LV dyssynchrony:** many (maybe too many) echo dyssynchrony criteria → PROSPECT trial [Yu et al, Am Heart J 2005] designed to define the predictive value of dyssynchrony criteria;
- **Myocardial viability:** data derived from small studies using different methodics which, such as MRI, are expensive, not reproducible, and may not be tolerated (claustrophobia)

**In the meantime,  
QRS duration ( $\geq 120$  msec) continues  
to be cardinal for patient selection...**

## CONCLUSIONS

### ✓ ESC Recommendations for CRT (Sept '07) :

- CLASS I**
- **CRT-P:** HF patients in NYHA class III-IV in spite of optimal medical therapy, LVEF $\leq$  35%, LVEDD $\geq$  55 mm, normal sinus rhythm, and wide QRS ( $\geq$  120 ms) (Level A)
  - **CRT-D:** HF patients in NYHA class III-IV in spite of optimal medical therapy, LVEF $\leq$  35%, LVEDD $\geq$  55 mm, normal sinus rhythm, and wide QRS ( $\geq$  120 ms) (Level B)
  - **CRT-D:** HF patients with **ICD indication** in NYHA class III-IV in spite of optimal medical therapy, LVEF $\leq$  35%, LVEDD $\geq$  55 mm, normal sinus rhythm, and wide QRS ( $\geq$  120 ms) (Level B)
- CLASS IIa**
- **CRT-P/D:** HF patients with **atrial fibrillation** in NYHA class III-IV in spite of optimal medical therapy, LVEF $\leq$  35%, LVEDD $\geq$  55 mm, wide QRS ( $\geq$  120 ms), and concomitant AV node ablation (Level C) .