Intraventricular Dyssynchrony Predicts Mortality and Morbidity After Cardiac Resynchronization Therapy

A Study Using Cardiovascular Magnetic Resonance Tissue Synchronization Imaging

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Objectives   We aimed to assess a novel measure of left ventricular (LV) dyssynchrony, a cardiovascular magnetic resonance-tissue synchronization index (CMR-TSI), in patients with heart failure (HF). A further aim was to determine whether CMR-TSI predicts mortality and major cardiovascular events (MCE) after cardiac resynchronization therapy (CRT).

Background   Cardiac dyssynchrony is a predictor of mortality in patients with HF. The unparalleled spatial resolution of CMR may render CMR-TSI a predictor of clinical benefit after CRT.

Methods   In substudy A, CMR-TSI was assessed in 66 patients with HF (age 60.8 ± 10.8 years, LV ejection fraction 23.9 ± 12.1% [mean ± SD]) and 20 age-matched control subjects. In substudy B, CMR-TSI was assessed in relation to clinical events in 77 patients with HF and with a QRS ≥120 ms undergoing CRT.

Results   In analysis A, CMR-TSI was higher in patients with HF and a QRS <120 ms (79.5 ± 31.2 ms, p = 0.0003) and in those with a QRS ≥120 ms (105.9 ± 55.8 ms, p < 0.0001) than in control subjects (21.2 ± 8.1 ms). In analysis B, a CMR-TSI ≥110 ms emerged as an independent predictor of the composite end points of death or unplanned hospitalization for MCE (hazard ratio [HR] 2.45; 95% confidence interval [CI] 1.51 to 4.34, p = 0.0002) or death from any cause or unplanned hospitalization for HF (HR 2.15; 95% CI 1.23 to 4.14, p = 0.0060) as well as death from any cause (HR: 2.6; 95% CI 1.29 to 6.73, p = 0.0061) and cardiovascular death (HR 3.82; 95% CI 1.63 to 16.5, p = 0.0007) over a mean follow-up of 764 days.

Conclusions   Myocardial dyssynchrony assessed by CMR-TSI is a powerful independent predictor of mortality and morbidity after CRT.   (J Am Coll Cardiol 2007;50:243–52) © 2007 by the American College of Cardiology Foundation

The benefits of cardiac resynchronization therapy (CRT) are well established. In the CARE-HF (Cardiac Resynchronization Heart Failure) study, CRT was associated with 36% reduction in all-cause mortality (1). It is well accepted, however, that the prognostic benefit of CRT in individual patients is difficult to predict from pre-implant assessments, such as echocardiography.

Studies using tissue Doppler imaging have shown that, in patients with heart failure (HF), intraventricular dyssynchrony is associated with a higher rate of cardiac decompensation (2). In patients with hypertrophic cardiomyopathy, intraventricular dyssynchrony is an independent predictor of sudden cardiac death (3). With regard to patients undergoing CRT, numerous studies have focused on echocardiographic predictors of reverse left ventricular (LV) remodeling and/or symptoms (4,5), but few have explored cardiac dyssynchrony in relation to mortality.

In the assessment of cardiac dyssynchrony, echocardiography is limited to imaging only a portion of the LV. In contrast, cardiovascular magnetic resonance (CMR) allows imaging of the entire heart. In this study, a novel technique for assessing cardiac dyssynchrony, CMR-tissue resynchronization imaging, was developed using short-axis views of the LV. Segmental radial wall motion data were used to construct tissue synchronization polar maps of the LV and to derive a global dyssynchrony measure, the tissue synchronization index (CMR-TSI). This study comprised 2 analyses: in the first, the CMR-TSI was assessed in healthy

subjects and in patients with HF; in the second, the CMR-TSI was assessed in relation to mortality as well as hospitalizations, LV remodeling, functional capacity, and quality of life in patients with HF undergoing CRT.

Methods

This study consisted of 2 substudies, both of which entailed quantification of LV volumes, LV ejection fraction (LVEF), and CMR-TSI.

Substudy 1. In this substudy, the measurements as described in the preceding text were studied in relation to QRS duration in 66 consecutive patients with HF in New York Heart Association (NYHA) functional class III or IV and with an LVEF <35%. The etiology was coronary heart disease in 53 patients and dilated cardiomyopathy in 13. These were compared with 20 age-matched, healthy control subjects with a QRS duration <120 ms.

Substudy 2. The aim of this substudy was to determine the ability of the CMR-TSI to predict cardiovascular death, death from any cause, major cardiovascular events (MCE), and HF admissions in 77 patients with HF and a QRS ≥120 ms undergoing CRT. This group included 42 patients from substudy 1.

Patients in substudy 2 also underwent a 6-min hall walk test (6), a quality-of-life assessment using Minnesota Living with Heart Failure questionnaire (7), and transthoracic echocardiography on the day before implantation, at 1, 3, and 6 months thereafter. Follow-up data on patients who died relates to the last available review before death.

Device therapy. All patients in substudy 2 underwent transvenous biventricular pacemaker implantation using standard techniques under local anesthesia. Patients were entered into the study only after a successful implantation and were followed-up in a dedicated CRT clinic. None of the patients in atrial fibrillation underwent atrioventricular node ablation. Patients in sinus rhythm (n = 68) underwent transmitral Doppler-directed optimization of atrioventricular delay (8) before discharge and at every scheduled visit thereafter. Backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an interventricular delay of 4 ms. For patients in chronic atrial fibrillation (n = 9), right ventricular and LV leads were implanted, and a Medtronic InSync III generator (model 8042, Medtronic, Minneapolis, Minnesota) was used, plugging the atrial port and programming the generator to a ventricular triggered mode. Generators used included the Medtronic InSync III

model 8040 8042 (n = 61), St. Jude Frontier (St. Jude Medical, St. Paul, Minnesota) (n = 2), Vitatron CRT 8000 (Vitatron B.V., Arnhem, the Netherlands) (n = 2), Biotronik Stratos (Biotronik GmbH, Berlin, Germany) (n = 8), and Guidant Contak Renewal TR2 (Guidant Corp., St. Paul, Minnesota) (n = 4).

CMR. Images were acquired on a 1.5-T (General Electric Signa, GE Healthcare Worldwide, Slough, United Kingdom) scanner using a phased-array cardiac coil during repeated 8-s breathholds. A short-axis stack of LV images was acquired using a steady-state in free precession sequence (repetition time 3.0 to 3.8 ms; excitation time 1.0 ms; image matrix 224 × 224; field of view 36 to 42 cm; flip angle 45°) in sequential 8-mm slices (2-mm interslice gap) from the atrioventricular ring to apex. Left ventricular volumes, ejection fraction, and mass (myocardial density = 1.05 g/cm^3) were quantified using manual planimetry of all short-axis steady state free precession cine images with MASS analysis software (Medis, Leiden, the Netherlands). Each slice in the short-axis stack (Fig. 1A) was divided into 100 cords, running clockwise from a first cord located at the junction between the inferior right ventricular free wall and the interventricular septum. Radial wall motion was quantified semiautomatically for all cords at up to 20 phases (time points) in each R-R interval. This yielded up to 16,000 raw data points per patient (100 cords for each of 8 slices imaged over 20 phases). Radial wall motion data were obtained for each of 6 segments (Fig. 1B) in each of, typically, 8 slices, for 20 phases (time points). The observer was blinded to all other clinical details of the patients, including the outcome measures.

TSI. The maximum radial wall motion value of a segmental radial wall motion time series was chosen to parameterize the peak radial wall motion for each segment for this analysis. The time-dependent segmental radial wall motion data (y) were fitted to an empirical sine wave function $y = a + b * \sin(t/RR + c)$. The sine wave function was chosen to account for the cyclic nature of myocardial motion and to specifically obtain the main cyclic radial wall motion component from the radial wall motion data. The mean segmental radial wall motion (a), the cyclic segmental radial wall motion amplitude (b), and the segmental phase shift of the maximum radial wall motion (c) were extracted from the fit. The CMR-TSI was finally calculated as the standard deviation (SD) of all segmental phase shift of the radial wall motion extracted from the fit.

Echocardiography. Standard 2-dimensional echocardiography was performed using System 5 (GE Healthcare Worldwide). Standard left parasternal long-axis and short-axis, and apical, 4-, 5-, and 2-chamber views were obtained. Digital images were transferred to a computer (EchoPAC, GE Healthcare Worldwide) for off-line analysis. Left ventricular volumes were assessed using planimetry of apical 4-chamber views and Simpson's equation. The LVEF was calculated as follows: (left ventricular end-diastolic volume
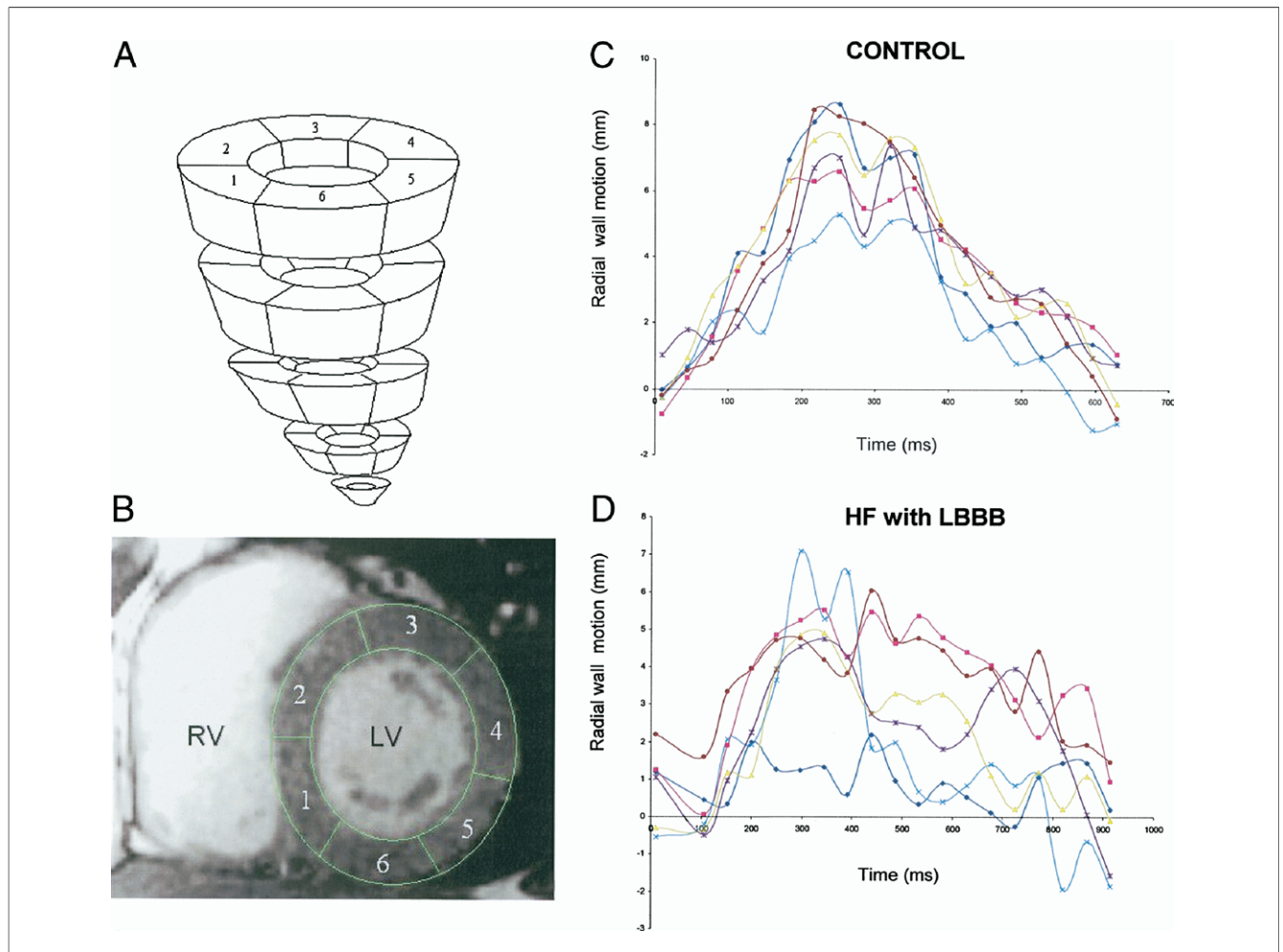
Figure 1 Myocardial Wall Motion in a Control Subject and in a Patient With Heart Failure

(A) Division of the left ventricular (LV) myocardium into slices and segments. (B) The junction between the interventricular septum and the right ventricular (RV) free wall delimits the beginning of segment 1 and the end of segment 6, counting clockwise. (C and D) Representative graph of radial wall motion of LV segments throughout the cardiac cycle in an LV basal slice in a control subject (C) and in a patient with heart failure (HF) and a left bundle branch block (LBBB) (D).

[LVEDV] − left ventricular end-systolic volume [LVESV])/ LVEDV × 100%.

Follow-up and end points. After pacemaker implantation, patients were followed up in a dedicated CRT clinic. As in the CARE-HF study (1), the clinical end points considered were the composite of death from any cause or an unplanned hospitalization for a MCE, which included cardiac transplantation. Hospitalizations for worsening HF, myocardial infarction, unstable angina, arrhythmia, stroke, pulmonary embolism, or upgrading to an implantable cardioverter-defibrillator were included in this end point. The first event was included in the analysis. The second end point considered was the composite of death from any cause and unplanned hospitalization with worsening HF. The third end point considered was mortality from any cause. The additional end point of cardiovascular mortality was also considered. Sudden cardiac death was defined as "a natural, unexpected death due to cardiac causes, heralded by an abrupt loss of consciousness within one hour of the onset

of acute symptoms" (9). Mortality data were collected through medical records and, where appropriate, from interviews with patients' caregivers. Information regarding clinical outcome was collected by an investigator who was blinded to the results of the CMR study.

Statistical analysis. Continuous variables are expressed as mean ± SD. Normality was tested using the Shapiro-Wilk test (the W-statistic). Variables that were not normally distributed were log-transformed before statistical analyses. Comparisons between normally distributed continuous variables were made using analysis of variance (ANOVA) with Scheffe's F procedure for multiple comparisons. Categorical variables were analyzed using chi-square tests and Fisher exact post-hoc test. Changes in variables from baseline to follow-up were analyzed using repeated measures ANOVA. Variables showing significant group differences at baseline were entered into Cox proportional hazards analyses.

Receiver-operating characteristic (ROC) curves were used to derive optimal cutoff points for CMR-TSI. For the
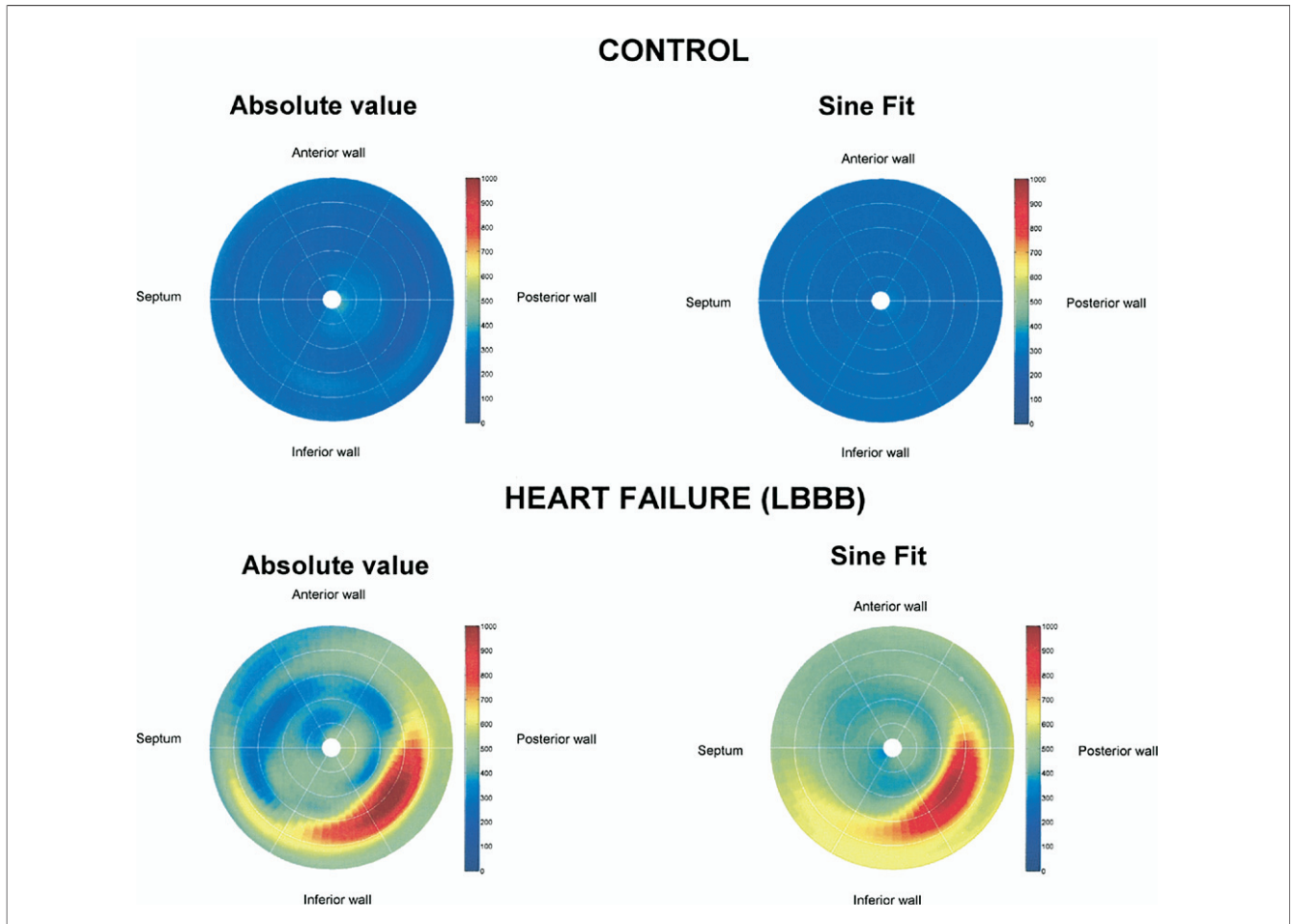
Figure 2   CMR-TSI Polar Color Maps in a Healthy Control Subject and in a Patient With Heart Failure and an LBBB

Note the late contraction of the inferoposterior wall in the patient with heart failure and a left bundle branch block (LBBB). CMR-TSI = cardiovascular magnetic resonance tissue synchronization index.

differentiation between control subjects and patients with HF in substudy 1, the value of CMR-TSI with the optimum sensitivity and specificity was 40 ms. For the differentiation between the groups at the highest risk of meeting the various end points in substudy 2, the value of CMR-TSI with the optimum sensitivity and specificity was 110 ms for all end points. The ability of CMR-TSI to discriminate between patients in the various risk categories at this cutoff value was assessed using Cox proportional hazards analyses and Kaplan-Meier survival curves. Differences in survival curves between the groups were assessed using the log-rank (Mantel-Cox) test. Statistical analyses were performed using Statview (Cary, North Carolina) and SPSS 13.0 (Chicago, Illinois). A 2-tailed p value of <0.05 was considered statistically significant.

Intraobserver variability of CMR-TSI was derived from manual planimetry of short-axis stacks from CMR of 10 randomly selected subjects. Studies were performed by the same observer on 2 occasions 11 months apart. Interobserver variability was derived from the same subjects, performed by 2 blinded observers. Both intra- and interobserver variabilities
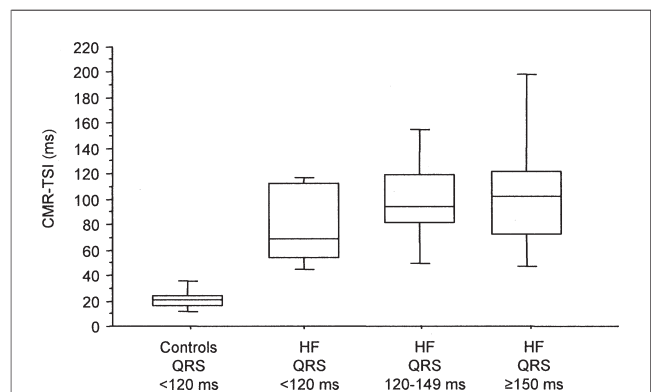
Figure 3   Intraventricular Dyssynchrony in Control Subjects and in Patients With HF

Box and whisker plot for CMR-TSI in 20 healthy control subjects with a QRS <120 ms and in 66 patients with heart failure, grouped according to QRS <120 ms, QRS 120 to 149 ms, and QRS ≥150 ms. The **5 horizontal lines** represent the 10th, 25th, 50th, 75th, and 90th percentiles, from **bottom to top**. CMR-TSI = cardiovascular magnetic resonance tissue synchronization index; HF = heart failure.

were calculated as the SD of the absolute differences between the 2 measurements divided by the mean of both measurements, and expressed as a percentage. Intraobserver and interobserver variability for CMR-TSI was 3.01% and 8.84%, respectively. Intraobserver and interobserver correlations were 0.99 and 0.98, respectively. In Bland Altman analyses, the intraobserver and interobserver agreements, expressed in terms of the mean difference ± 2 SD (upper and lower limits of agreement), were 1.16 (2.04 to 4.36) and 1.25 (−6.92 to 9.41), respectively.

Analysis of wall motion was performed using the R statistical language (10). The nonlinear least square fit function implemented by Bates and DebRoy into the "nls" packet of R was used for the sine fit (11).

Results

Substudy 1. Patients with HF (n = 66, age 60.8 ± 10.8 years) had an LVEF of 23.9 ± 12.1% and a QRS duration of 147.8 ± 25.0 ms. As shown in Figure 1C, the pattern of wall motion was relatively homogenous in healthy control subjects, but heterogenous in patients with HF. The heterogeneity of radial wall motion in patients with HF was also apparent in color polar maps of CMR-TSI (Fig. 2). The more homogenous distribution of color in the sine fit polar maps compared with the absolute value of the time-to-peak wall motion is a reflection of the smoothing effect of the sine fit.

The CMR-TSI was higher in patients with HF and a QRS <120 ms (79.5 ± 31.2 ms, p = 0.0003), in patients

Table 1	Baseline Clinical and Cardiovascular Magnetic Resonance Imaging Characteristics and Clinical End Points for Patients Undergoing Cardiac Resynchronization Therapy, Grouped According to Degree of Dyssynchrony			
	All	**CMR-TSI <110 ms**	**CMR-TSI ≥110 ms**	**p Value***
n	77	43	34	
Follow-up period, days†	764 (379)	763 (368)	765 (398)	NS
Age, yrs	67.3 ± 9.8	68.5 ± 10.2	66.4 ± 9.6	NS
Gender, male (%)	58 (75)	31 (72)	27 (79)	NS
Etiology, n (%)				
Coronary heart disease	58 (75)	28 (65)	30 (88)	0.0195
Dilated cardiomyopathy	19 (25)	15 (35)	4 (12)	0.0195
Systolic blood pressure, mm Hg	118.3 ± 20.0	119.3 ± 22.2	117.3 ± 18.8	NS
Diastolic blood pressure, mm Hg	70.1 ± 11.2	70.1 ± 11.6	70.1 ± 11.1	NS
Comorbidity				
Diabetes mellitus	9 (12)	3 (7)	6 (18)	NS
Hypertension	20 (26)	12 (28)	8 (24)	NS
CABG	20 (26)	9 (21)	11 (32)	NS
Valve replacement	1 (0.01)	0	1 (3)	NS
Medication, n (%)				
Loop diuretics	68 (88)	38 (88)	30 (88)	NS
ACE-I or ARB	70 (91)	39 (91)	31 (91)	NS
Beta-blockers	43 (56)	23 (53)	20 (59)	NS
Spironolactone	37 (48)	22 (51)	15 (44)	NS
Amiodarone	10 (13)	5 (12)	5 (15)	NS
ECG variables				
Sinus rhythm	68 (88)	37 (86)	31 (91)	NS
Atrial fibrillation	9 (12)	6 (14)	3 (9)	NS
QRS duration, ms	150.3 ± 25.1	145.1 ± 21.4	157.0 ± 28.0	0.0372
CMR variables				
LVEDV, cm^3	237.8 ± 93.4	203.8 ± 69.4	282.6 ± 102.9	0.0002
LVESV, cm^3	191.9 ± 92.2	158.0 ± 72.1	236.8 ± 97.6	0.0002
LVEF, %	22.6 ± 11.5	26.6 ± 13.0	17.2 ± 5.9	0.0004
CMR-TSI, ms	112.6 ± 53.2	78.4 ± 21.6	154.7 ± 50.3	<0.0001
Mode of death				
Pump failure	10	0	10	<0.0001
Sudden cardiac death	2	1	1	NS
End points				
Death from any cause or hospitalization for MCE	26 (34)	5 (12)	21 (62)	<0.0001
Death from any cause or hospitalization for HF	19 (25)	4 (9)	15 (44)	0.0004
Death from any cause	15 (19)	2 (5)	12 (35)	0.0004
Cardiovascular death	14 (18)	1 (2)	13 (38)	<0.0001

*Refers to differences between the cardiovascular magnetic resonance tissue synchronization index (CMR-TSI) <110 group and the CMR-TSI ≥110 ms group; †Refers to follow-up period for events. Continuous variables are expressed as mean ± SD.

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass grafting; ECG = electrocardiogram; HF = heart failure; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MCE = major adverse cardiac events.

with HF and a QRS between 120 and 149 ms (98.5 ± 36.2 ms, $p < 0.0001$), and in patients with HF and a QRS $\geq$150 ms (112.1 ± 68.7 ms, $p < 0.0001$) than in control subjects (21.2 ± 8.1 ms) (Fig. 3). At a cutoff of 40 ms, CMR-TSI achieved almost absolute discrimination between control subjects and patients with HF (area under ROC 0.99, sensitivity 94%, specificity of 100%, $p < 0.0001$), a reflection of the lack of overlap in CMR-TSI between the groups.

Substudy 2. As shown in Table 1, patients with a CMR-TSI $\geq$110 ms had a longer QRS duration ($p = 0.0372$), higher LVEDV and LVESV (both $p = 0.0002$), and a lower LVEF ($p = 0.0004$) than patients with a CMR-TSI <110 ms. In the 77 patients undergoing CRT, CMR-TSI at baseline correlated positively with LVEDV ($r = 0.46$), LVESV ($r = 0.49$), and negatively with LVEF ($r = -0.55$) (all $p < 0.0001$). There was a positive correlation between QRS duration and CMR-TSI ($r = 0.46$, $p < 0.0001$).

Over a mean follow-up of 764 days (range 85 to 1,602 days), patients with a CMR-TSI $\geq$110 ms were 5.2 times more likely to die from any cause or to be hospitalized for a MCE, 11 times more likely die from any cause or to be hospitalized for HF, 7 times more likely to die from any cause, and 19 times more likely to suffer a cardiovascular death than those with a CMR-TSI <110 ms.

Over a mean of 557 days (range 59 to 1,144 days) to the latest available clinical review, significant reductions in NYHA functional class as well as improvements in 6-min walk test distance and quality-of-life scores were observed in both the CMR-TSI <110 ms and the CMR-TSI $\geq$110 ms groups (Table 2). An increase in LVEF was observed in the CMR-TSI <110 ms group ($p < 0.01$), but not in the CMR-TSI $\geq$110 ms group. A reduction in LVESV was observed in the CMR-TSI <110 ms group, but this was not statistically significant ($p = 0.0986$).

As shown in Figure 4, the area under ROCs relating to the ability of CMR-TSI to discriminate between patients meeting the various end points ranged from 0.75 to 0.82. At

a cutoff of 110 ms, CMR-TSI predicted cardiovascular death with a sensitivity of 93% and a specificity of 67% ($p < 0.0001$). Kaplan-Meier survival curves showed that the rates of meeting the various end points were higher in the CMR-TSI $\geq$110 ms group than in the CMR-TSI <110 ms group (Fig. 5). In Cox proportional hazards analyses, CMR-TSI emerged as a strong predictor of all clinical end points, independent of LVEDV, LVESV, LVEF, and QRS duration (Table 3).

An additional analysis using QRS duration as a dichotomous variable, either between 120 ms and 149 ms (n = 31) or $\geq$150 ms (n = 46), no group differences emerged with respect to the composite of death from any cause or an unplanned hospitalization for an MCE (9 and 17 patients, respectively), the composite of death from any cause and unplanned hospitalization with worsening HF (8 and 11 patients, respectively), death from any cause (6 and 9 patients, respectively), or cardiovascular death (6 and 8 patients, respectively). When QRS duration as a dichotomized variable was entered into Cox proportional hazards analyses for each of the end points, it failed to reach statistical significance (data not shown).

Discussion

We have shown that, on the basis of CMR-TSI, a novel measure of LV dyssynchrony, almost all patients with HF have LV dyssynchrony. The most salient finding from this study is that in patients undergoing CRT, CMR-TSI predicts death from any cause, cardiovascular mortality, as well as the combined end points of death from any cause or hospitalizations for an MCE, and death from any cause or hospitalization from HF.

Dyssynchrony as a predictor of mortality and morbidity. Our finding that increasing LV dyssynchrony, quantified using the CMR-TSI, predicts survival and morbidity might be expected from our observation that LV dyssynchrony correlates positively with LV volumes, and nega-

Table 2	Clinical and Echocardiographic Variables During Follow-Up in Patients Undergoing Cardiac Resynchronization Therapy, Grouped According to Degree of Dyssynchrony at Baseline			

	CMR-TSI <110 ms (n = 43)		CMR-TSI $\geq$110 ms (n = 34)	
	Baseline	**Follow-Up**	**Baseline**	**Follow-Up**
NYHA functional class, n (%)				
I	0	12 (28)*	0	6 (18)*
II	0	21 (49)*	0	19 (56)*
III	29 (67)	8 (19)*	28 (82)	9 (26)*
IV	14 (33)	2 (5)*	6 (18)	0*
6-min walk test, m	273.6 ± 106.2	355.1 ± 122.2*	254.2 ± 99.8	326.1 ± 97.8†
Quality-of-life score	61.7 ± 18.1	28.2 ± 25.8*	47.1 ± 18.3	29.0 ± 21.0†
Echocardiography				
LVESV, cm³	150.7 ± 60.3	136.1 ± 58.1	170.0 ± 58.8	163.1 ± 49.2
LVEDV, cm³	197.3 ± 62.0	190.8 ± 60.5	221.8 ± 57.9	209.7 ± 53.4
LVEF, %	26.5 ± 12.0	31.8 ± 12.1‡	24.1 ± 10.3	24.4 ± 0.09

*$p < 0.0001$; †$p < 0.001$; ‡$p < 0.01$. p values refer to differences from baseline values within the group.
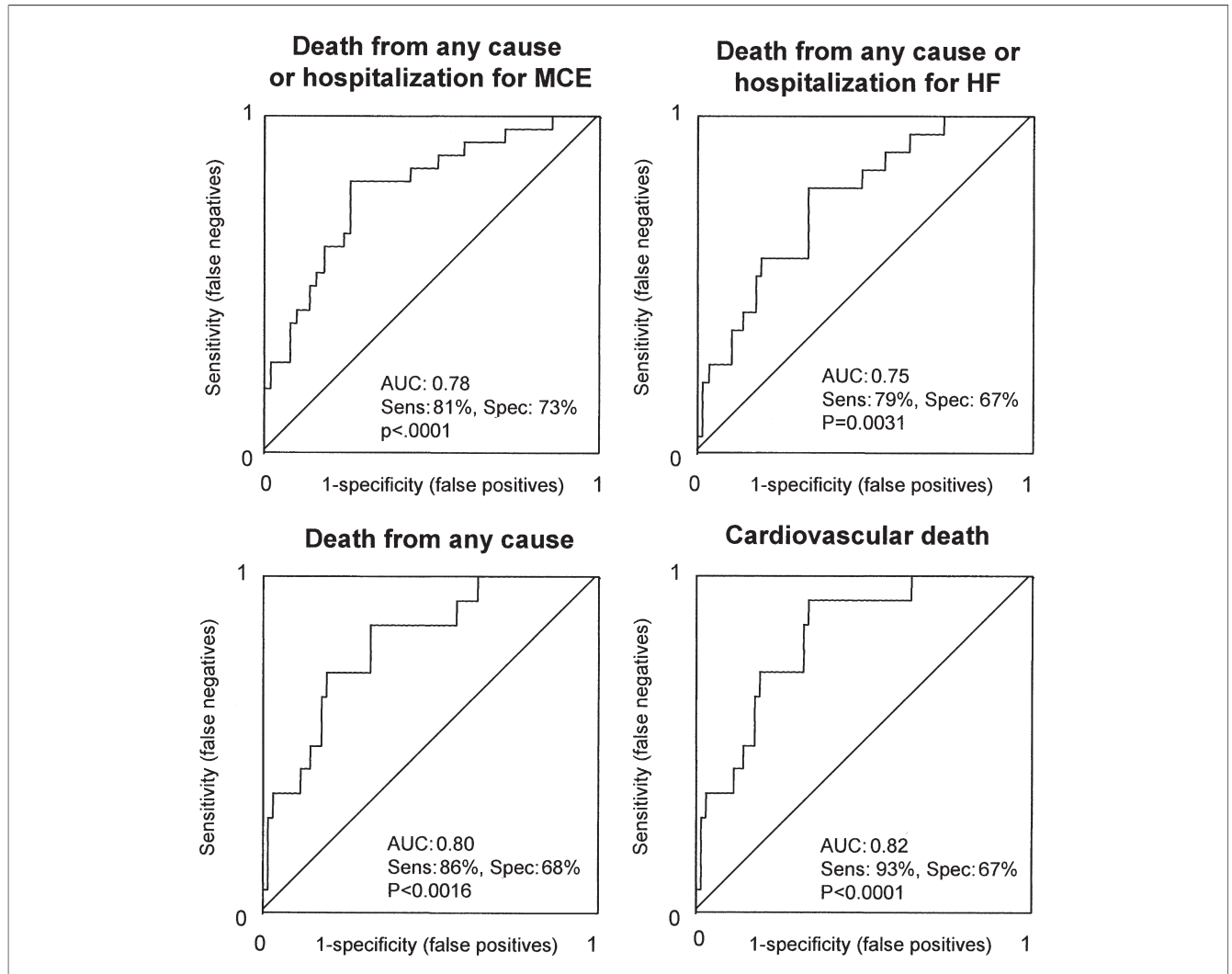NYHA = New York Heart Association; other abbreviations as in Table 1.

Figure 4   Receiver-Operating Characteristic Curves for CMR-TSI in Relation to Clinical End Points

AUC = area under the curve; MCE = major cardiovascular events; sens = sensitivity; spec = specificity; other abbreviations as in Figure 3.

tively with LVEF. It would appear, therefore, that dyssynchrony is a marker of poor cardiac function and the patients with the most dyssynchronous, dilated, and poorly functioning LVs are the least likely to respond to CRT, measured in terms of mortality and hospital readmissions. At a cutoff of 110 ms, CMR-TSI predicted cardiovascular death with a sensitivity of 93% and a specificity of 67% (p < 0.0001).

Numerous echocardiographic studies have shown that LV dyssynchrony is a predictor of improvement in LV function and reverse LV remodeling after CRT (12–14). Bax et al. (14), however, found that LV dyssynchrony correlated positively with reductions in LVESV after CRT, but up to a limit. Beyond a septal-to-posterior wall motion delay of 100 ms, CRT did not result in reductions in LVESV. In the present study, we have not observed evidence of LV remodeling after CRT. However, an improvement in LVEF was witnessed in the CMR-TSI <110 ms, but not in the CMR-TSI ≥110 ms group. This lack of improvement in LVEF was paralleled by a

marked increase in the risk of death or hospitalizations for both MCE and HF. A possible interpretation of this finding is that there is an upper limit of dyssynchrony beyond which CRT fails to confer a benefit.

Intuitively, patients who die or who are repeatedly hospitalized for HF after CRT would also be expected to be the symptomatic nonresponders. In the present study, patients with a CMR-TSI ≥110 ms were at higher risk of death and readmissions for MCE and HF than those with a CMR-TSI <110 ms, but improvements in NYHA functional class, 6-min walk test, and quality-of-life scores up to the last available follow-up were nevertheless significant. This is in keeping with the demonstration that clinical improvement after CRT is not necessarily a predictor of survival (15). It is also in keeping with the finding of a lack of correlation between clinical and echocardiographic changes after CRT (16).

Dyssynchrony in HF. Echocardiographic studies using tissue Doppler imaging have shown evidence of LV dyssyn-
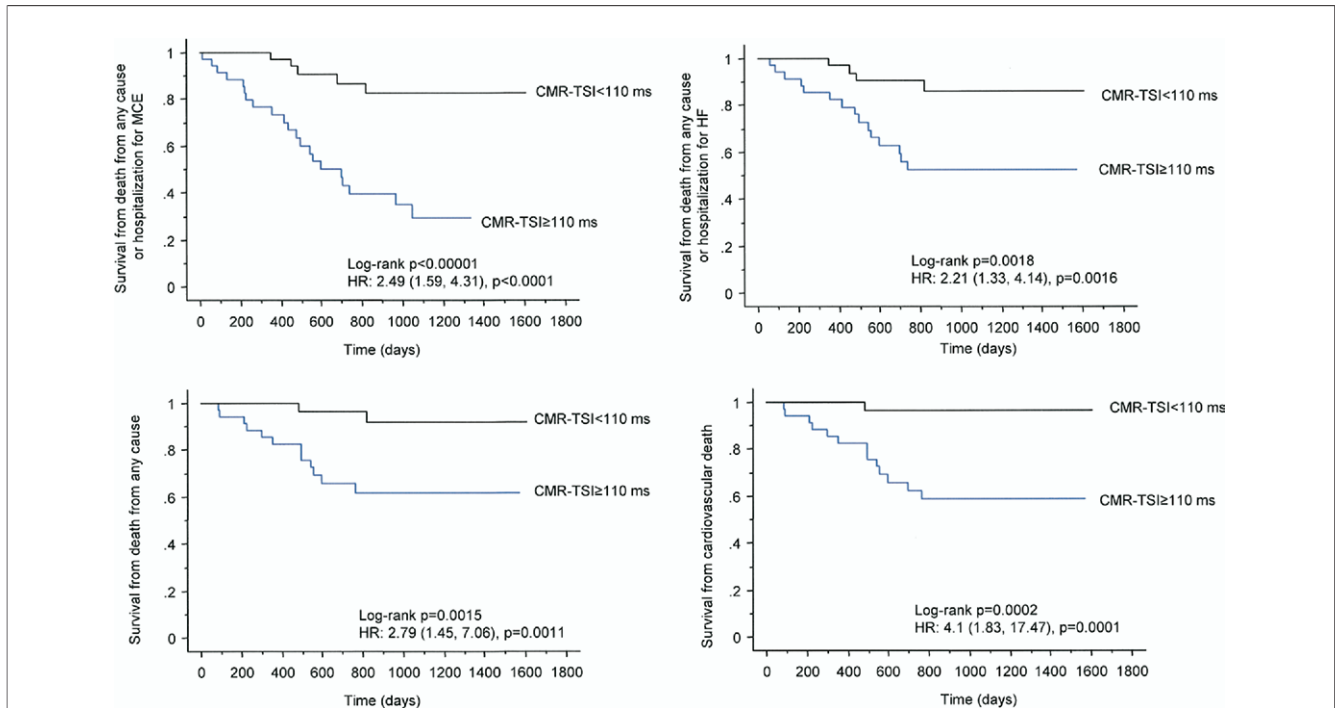
Figure 5   Kaplan-Meier Estimates of the Time to the Various Clinical End Points

Patients were stratified according to a pre-implant cardiovascular magnetic resonance tissue synchronization imaging score (CMR-TSI) <110 ms or CMR-TSI ≥110 ms. Results of univariate Cox proportional hazards analyses are expressed in terms of the hazard ratio (HR) and 95% confidence limits. HF = heart failure; MCE = major cardiovascular events.

chrony only in a proportion of patients with HF (17). Using the SD of the time to peak systolic velocity in a 12 myocardial segment model as a measure of dyssynchrony, Yu et al. (17) demonstrated systolic dyssynchrony in only 64% of patients with HF and a QRS duration ≥120 ms. In the present study, however, nearly all patients with HF had LV dyssynchrony, defined in terms of a CMR-TSIs ≥40 ms. It would appear, therefore, that, at least on the basis of CMR-TSI, HF is synonymous with LV dyssynchrony. This ability of CMR-TSI to almost totally discriminate between patients with HF and healthy control subjects is perhaps a reflection of the capacity of CMR to image the entire LV with superior spatial resolution.

Methods for assessing cardiac dyssynchrony using CMR are emerging. Myocardial tagging, for example, allows assessment of wall motion and strain in circumferential, radial, and longitudinal dimensions (18,19). Strain-coded CMR provides real-time quantitative strain measurement, which has the potential for rapid assessment of LV dyssynchrony (18). Helm et al. (20) have recently developed a method for assessing dyssynchrony using 3-dimensional tagged CMR. Velocity-encoded CMR has recently been shown to have an excellent agreement with tissue Doppler imaging (21). By comparison, our measure of dyssynchrony, CMR-TSI, is comparatively crude, insofar as it is based solely on radial motion. Notwithstanding, this relatively

simple measure provides powerful prognostic information in patients undergoing CRT.

QRS duration and mechanical dyssynchrony. Small mechanistic studies have shown that QRS duration correlated with LV dyssynchrony. Using a 12-segment model and tissue Doppler imaging, Yu et al. (17) failed to find a correlation between QRS duration and the LV dyssynchrony. We have, however, found that QRS duration does correlate strongly with CMR-TSI. This may be related to the high spatial resolution of CMR. Notwithstanding, QRS duration failed to emerge as a predictor of clinical outcome measures when entered into analysis as either a continuous or a dichotomous (between 120 and 149 ms or ≥150 ms) variable.

Clinical application. The interobserver and intraobserver variabilities for CMR-TSI of <9% compare favorably to other CMR measures of dyssynchrony, such as velocity-encoded CMR, for example, which is associated with interobserver and intraobserver variabilities of 10% (21). Intraobserver and interobserver correlations for CMR-TSI were 0.99 and 0.98, respectively. Bader et al. (2) observed intraobserver and interobserver correlations of 0.99 and 0.97, respectively, for an echocardiographic tissue Doppler measure of dyssynchrony in 10 patients with HF. The derivation of CMR-TSI is time-consuming, insofar as it involves manual tracing of endocardial borders and determination of peak wall motion for each myocardial segment.

Table 3	Univariate and Multivariate Cox Proportional Hazards Analyses of Clinical End Points in Relation to Cardiac Magnetic Resonance Variables	

	HR (95% CI)	p Value
Death from any cause or hospitalization for MCE		
Univariate		
CMR-TSI ≥110 ms	2.49 (1.59 to 4.31)	<0.0001
LVEDV	1.00 (1.00 to 1.01)	0.0621
LVESV	1.00 (1.00 to 1.01)	0.0459
LVEF	0.94 (0.91 to 0.99)	0.0115
QRS duration	1.00 (0.99 to 1.02)	NS
Multivariate		
1. CMR-TSI ≥110 ms	2.45 (1.51 to 4.34)	0.0002
LVEDV	1.00 (1.00 to 1.00)	NS
2. CMR-TSI ≥110 ms	2.43 (1.29 to 4.33)	0.0002
LVESV	1.00 (1.00 to 1.00)	NS
3. CMR-TSI ≥110 ms	2.28 (1.39 to 4.12)	0.0006
LVEF	0.98 (0.92 to 1.03)	NS
Death from any cause or hospitalization for HF		
Univariate		
CMR-TSI ≥110 ms	2.21 (1.33 to 4.14)	0.0016
LVEDV	1.00 (1.00 to 1.01)	NS
LVESV	1.00 (1.00 to 1.01)	NS
LVEF	0.93 (0.88 to 0.98)	0.0064
QRS duration	1.00 (0.98 to 1.02)	NS
Multivariate		
1. CMR-TSI ≥110 ms	2.15 (1.23 to 4.14)	0.0060
LVEDV	1.00 (1.00 to 1.01)	NS
2. CMR-TSI ≥110 ms	2.11 (1.20 to 4.07)	0.0083
LVESV	1.00 (1.00 to 1.01)	NS
3. CMR-TSI ≥110 ms	1.82 (1.07 to 3.52)	0.0266
LVEF	0.95 (0.88 to 1.01)	NS
Death from any cause		
Univariate		
CMR-TSI ≥110 ms	2.79 (1.45 to 7.06)	0.0011
LVEDV	1.00 (1.00 to 1.01)	NS
LVESV	1.00 (1.00 to 1.01)	NS
LVEF	0.93 (0.86 to 0.99)	0.0139
QRS duration	1.00 (0.98 to 1.02)	NS
Multivariate		
1. CMR-TSI ≥110 ms	2.60 (1.29 to 6.73)	0.0061
LVEDV	1.00 (1.00 to 1.01)	NS
2. CMR-TSI ≥110 ms	2.55 (1.26 to 6.62)	0.0077
LVESV	1.00 (1.00 to 1.01)	NS
3. CMR-TSI ≥110 ms	2.28 (1.16 to 5.90)	0.0143
LVEF	0.94 (0.86 to 1.02)	NS
Cardiovascular death		
Univariate		
CMR-TSI ≥110 ms	4.1 (1.83 to 17.47)	0.0001
LVEDV	1.00 (1.00 to 1.00)	0.0487
LVESV	1.00 (1.00 to 1.01)	0.0368
LVEF	0.93 (0.86 to 0.99)	0.0183
QRS duration	1.01 (0.99 to 1.03)	NS
Multivariate		
1. CMR-TSI ≥110 ms	3.82 (1.63 to 16.5)	0.0007
LVEDV	1.00 (0.99 to 1.01)	NS
2. CMR-TSI ≥110 ms	3.77 (1.61 to 16.3)	0.0009
LVESV	1.00 (0.99 to 1.01)	NS
3. CMR-TSI ≥110 ms	3.49 (1.50 to 15.2)	0.0014
LVEF	0.96 (0.87 to 1.05)	NS

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

The technique, however, does not involve specialized acquisition, as it employs the short-axis stacks of the LV normally acquired during a standard CMR LV function study.

Study limitations. One of the limitations of CMR relates to its safety in patients with pacemakers, which may preclude its use after implantation. Recent studies, however, have shown that CMR can be performed with safety in such patients (22,23). These concerns are likely to wane with emergence of CMR-compatible pacemakers. With respect to the quantification of CMR-TSI, impaired LV contraction is associated with less variation in wall motion during the cardiac cycle. Consequently, CMR-TSI may reflect higher noise, or dyskinesis, rather than true dyssynchrony. Our study of patients undergoing CRT is limited to patients with a QRS ≥120 ms. Our cutoff of 110 ms for CMR-TSI as a predictor of mortality and events can, therefore, only be applied to a similar population, and not to patients with a QRS <120 ms, in whom this cutoff is likely to be lower. A further limitation is the lack of scar imaging. As demonstrated by others (24–26), scar size as well as location are also powerful predictors of outcome after CRT and could, conceivably, be superior to CMR-TSI.

Conclusions

Using a novel CMR measure of LV dyssynchrony, CMR-TSI, we have shown that HF is synonymous with intraventricular dyssynchrony. Importantly, CMR-TSI is a powerful independent predictor of total mortality, cardiovascular mortality, and hospitalizations for MCE and for HF after CRT. This measure is, therefore, likely to be valuable in risk-stratifying patients with ischemic cardiomyopathy before CRT.

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