Cardiac resynchronization therapy (CRT) is an important therapy for patients with heart failure (HF) with reduced left ventricular (LV) ejection fraction (EF) and widened QRS that can improve symptoms and reduce the risk of death and hospitalizations.1 Response to CRT remains variable, and current guidelines most strongly support selecting patients by electrocardiographic (ECG) criteria of QRS duration ≥150 ms and left bundle branch block (LBBB).2 The benefit of CRT to patients with intermediate QRS duration (120–149 ms) or non-LBBB morphology is more unpredictable, and there is increased interest in predicting prognosis in these patients.4,5 Factors related to CRT response have included a complex interaction of myocardial substrate, timing of electromechanical regional activation, clinical characteristics, and implant-related factors such as LV lead position.6-9 Evidence has increased that echocardiographic measures of LV deformation by speckle-tracking global circumferential strain (GCS) and global longitudinal strain (GLS) can characterize the myocardial contractile function and scar, which can play major roles in CRT response.10 Therefore, the specific aims were: (1) to determine the prognostic value of baseline GLS and GCS with respect to long-term clinical outcomes after CRT; (2) to assess prognostic value of GLS and GCS in patient subgroups of ischemic cardiomyopathy versus nonischemic cardiomyopathy; and, finally, (3) to determine the additive prognostic value of GLS and GCS in patients with intermediate ECG criteria, where there is high interest in predicting CRT response.

Additive Prognostic Value of Echocardiographic Global Longitudinal and Global Circumferential Strain to Electrocardiographic Criteria in Patients With Heart Failure Undergoing Cardiac Resynchronization Therapy

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Background—Response to cardiac resynchronization therapy is most favorable in patients with heart failure with QRS duration ≥150 ms and left bundle branch block and less predictable in those with QRS width 120 to 149 ms or non–left bundle branch block.

Methods and Results—We studied 205 patients with heart failure referred for cardiac resynchronization therapy with QRS ≥120 ms and ejection fraction ≤35%. We tested the hypothesis that contractile function using speckle-tracking echocardiographic global circumferential strain (GCS) from 2 short-axis views and global longitudinal strain (GLS) from 3 apical views add prognostic value to electrocardiographic criteria. There were 112 patients (55%) with GLS >−9% and 136 patients (66%) with GCS >−9%. During 4 years, 81 patients reached the combined primary end point (death, circulatory support, or transplant) and 120 reached the secondary end point (heart failure hospitalization or death). Both GLS >−9% and GCS >−9% were associated with increased risk of unfavorable events as follows: for the primary end point (hazard ratio=2.91; 95% confidence interval, 1.88–4.49; P<0.001) and (hazard ratio=3.73; 95% confidence interval, 2.39–5.82; P<0.001) for the secondary end point (hazard ratio=2.10; 95% confidence interval, 1.45–3.05; P<0.001) and (hazard ratio=3.25; 95% confidence interval, 2.23–4.75; P<0.001). In a prespecified subgroup of 120 patients with QRS 120 to 149 ms or non–left bundle branch block, significant associations of baseline GLS and GCS and outcomes remained: P=0.014 and P=0.002 for the primary end point and P=0.049 and P=0.001 for the secondary end point. Global strain measures had additive prognostic value to routine clinical or electrocardiographic parameters (P<0.001).

Conclusions—Baseline GCS and GLS were significantly associated with long-term outcome after cardiac resynchronization therapy and had additive prognostic value to routine clinical and electrocardiographic selection criteria for cardiac resynchronization therapy. (Circ Cardiovasc Imaging. 2016;9:e004241. DOI: 10.1161/CIRCIMAGING.115.004241.)

Key Words: cardiac resynchronization therapy ▪ cardiomyopathy ▪ echocardiography ▪ heart failure ▪ hospitalization ▪ prognosis
Methods

Patient Population
This was a prospective longitudinal study design at a single center. All patients fulfilled current criteria for CRT implant with New York Heart Association (NYHA) class II to IV HF on optimal pharmacological therapy, QRS width ≥120 ms, and LVEF ≤35%. This study was approved by the Institutional Review Board of Biomedical Research, and all patients gave informed consent according to this study protocol. Patients with chronic right ventricular pacing or a failed CRT implant were excluded. The study population included 205 consecutive CRT patients with baseline echocardiography suitable for speckle-tracking analysis, which was 91% of the initial cohort. Ischemic pathogenesis was defined as ≥70% stenosis in ≥1 epicardial coronary vessel on angiography or history of myocardial infarction or revascularization. Baseline LBBB and right bundle branch block (RBBB) morphology were defined using standard criteria. Intraventricular conduction delay was defined as QRS duration ≥120 ms not meeting criteria for either LBBB or RBBB. Intermediate ECG criteria were QRS 120 to 149 ms, regardless of morphology or non-LBBB morphology (RBBB or intraventricular conduction delay). Patients with atrial fibrillation were not included. All patients had a biventricular pacing system implanted with a standard right atrial lead, a right ventricular apical lead, and LV lead positioned through the coronary sinus, targeting the lateral or posterolateral LV free wall. Patients were typically programmed to an atrioventricular interval of 120–130 ms with no ventricular–ventricular pacing offset. These patients did not routinely undergo formal atrioventricular or ventricular–ventricular optimization studies.

Echocardiography
All echocardiographic studies were performed with similar echocardiography systems (Vivid 7; GE Vingmed, Horten, Norway). Routine echocardiography included standard apical views, and basal and mid-LV short-axis views. Frame rates were 72±19 Hz for short-axis view and 60±20 Hz for apical views. LV volumes and EF were calculated with the modified biplane Simpson’s method. Speckle-tracking strain analysis was performed offline (EchoPAC BT11 or BT12, GE Vingmed). For GLS, regions of interest were applied to LV epicardium and endocardium in apical 4-chamber, apical 2-chamber, and apical long-axis views as previously described. GLS was calculated as an average from the 18 segmental strain values (Figure 1). For GCS calculations, regions of interest were applied to epicardial and endocardial borders from basal short-axis and mid-LV short-axis views. GCS was averaged from the 12 segmental peak strain values (Figure 2). Calculation of GCS is less standardized, with the use of different approaches by previous studies (average of 6–16 segments depending on the use of different levels of LV short-axis view). We also measured baseline septal to posterior wall peak-to-peak radial strain delay (±130 ms) as a measure of mechanical dyssynchrony, from mid-LV short-axis images as previously described. Although sensitive for timing, we did not assess global radial strain because of reported higher variability. We predefined a cutoff for GCS of −9% based on the previous report of prognosis of GLS in patients with HF and with reduced LVEF. Because our GCS using 12 segments from 2 short-axis views was novel, we prespecified the same −9% cutoff. GLS and GCS are reported as having negative values by convention; greater or lesser LV function is reflected by their absolute values.

Variability
Intraclass correlation coefficients were used to assess intra- and interobserver reproducibility. Fifteen patients were randomly selected for strain analysis using the same cine-loops for each view, including the selection or regions of interest, detection of peak segmental strain, and calculation of global longitudinal and circumferential strain. The intraclass correlation coefficients for GLS intraobserver agreement was 0.97 and for GLS interobserver agreement 0.92; intraclass correlation coefficients for GCS intraobserver agreement was 0.96 and for GCS interobserver agreement 0.92, in accordance with previous published data.

Clinical Outcomes
Two clinical outcomes were predefined to assess the cohort long-term prognosis. First, we analyzed the composite end point of death, LV assist device (LVAD) implant, or heart transplant during 4 years. These end points were combined because only patients with limited survival were selected to undergo rescue advanced HF therapy, such as LVAD or transplant. Second, we predefined the outcome of first HF hospitalization or death during the same 4-year period.

Statistical Analyses
All statistical analyses were performed using MedCalc software (version 12.3.0.0, Mariakerke, Belgium) and SPSS version 20.0 (IBM, Chicago, IL). Continuous variables were expressed as means±SD, tested for normal distribution with the Kolmogorov–Smirnov test, and compared with unpaired t test for independent variables. Categorical variables were expressed as frequency and percentages and compared with χ² test or Fisher’s exact test. Kaplan–Meier curves were used to plot freedom from the clinical end points. The cumulative events between groups were compared with log-rank test. Cox regression analysis was performed to identify long-term univariable associations; clinically and statistically significant variables were then introduced in a multivariable analysis of GLS and GCS as continuous variables using a forward stepwise method and exclusion of variables with P>0.1. Multicollinearity was assessed by the variance inflation factor with values above 4 considered to have probable collinearity and excluded from the model. We then constructed sequential Cox models and assessed the improvement in predictive value using the integrated discrimination index. Two-tailed P values <0.05 were considered significant.

Results

Baseline Characteristics
Of 264 consecutive patients referred for CRT, 6 (2%) had failed implant, 28 (11%) had baseline RV pacing, and 25 (9%) had inadequate image quality for speckle-tracking analysis. The final study cohort comprised 205 patients with a mean age of 65±11 years, LVEF of 24±6%, and QRS duration of 157±26 ms. Using a predefined cutoff of −9%, 112 (55%) had GLS >−9% and 136 (66%) had GCS >−9%. Regarding ECG subgroups, 85 patients (42%) had LBBB morphology with QRS duration ≥150 ms (class I indication), and 120 had intermediate ECG criteria: 43 (36%) with LBBB and QRS 120 to 149 ms, with wider QRS duration non-LBBB morphology (15 intraventricular conduction delay and 12 RBBB), both having class IIa indications, and 50 with intermediate QRS duration non-LBBB morphology (40 intraventricular conduction delay and 10 RBBB) corresponding to class Ib indications (Table 1). The intermediate ECG criteria group had, by definition, narrower QRS width than the wide LBBB group (P<0.001) and more prevalent ischemic disease (P=0.019). ECG criteria subgroups were balanced to all other baseline characteristics.

Association of Global Strain With CRT Response in All Patients
Regarding the first composite end point, there were 81 clinical end points reached (60 deaths, 8 LVADs, and 13 transplants) during the 4-year follow-up (median: 3.8 years). GLS using a cutoff of −9% versus ≤−9% was significantly associated with...
the combined outcome of death, LVAD, or transplant (unadjusted hazard ratio [HR]: 2.91; 95% CI, 1.88–4.49; P<0.001). GCS >−9% versus ≤−9% was also significantly associated with death, LVAD, or transplant (unadjusted HR: 3.73; 95% CI, 2.39–5.82; P<0.001; Figure 3). Regarding the second outcome, there were 74 HF hospitalizations and 36 deaths. The time to first event was included in the analysis; 32 patients with a HF hospitalization had subsequent death, LVAD, or transplant. GLS using a cutoff of >−9% versus ≤−9% was significantly associated with HF hospitalization or death (unadjusted HR: 2.10; 95% CI, 1.45–3.05; P<0.01). GCS >−9% versus ≤−9% was also significantly associated with this second outcome (unadjusted HR: 3.25; 95% CI, 2.23–4.75; P<0.001). Factors associated with death, LVAD, or transplant in univariable analysis were ischemic pathogenesis, creatinine, QRS duration, LBBB morphology, LV end-systolic volume, LVEF, septal to posterior wall peak-to-peak radial strain delay, GLS, and GCS. In a multivariable analysis, factors that remained significantly associated with death were baseline serum creatinine (P=0.001), LBBB (P=0.025), baseline LV end-systolic volume (P=0.021), and GCS (HR: 0.80; 95% CI, 0.72–0.89; P<0.001).

Of the 205 patients, 129 (63%) had ischemic cardiomyopathy and 76 had nonischemic cardiomyopathy. There were 59 (46%) deaths, LVADs, or transplants in the ischemic group, and 22 (29%) in the nonischemic group. Both GLS and GCS >−9% had significant associations with outcomes in patients with ischemic and nonischemic disease (Figure 4 and Table 3).

### Association of Global Strain With Long-Term Outcome in Patient Subgroup With QRS Width 120–149 ms or Non-LBBB Morphology

In the patient subgroup with LBBB and QRS duration ≥150 ms, end points of death, LVADs, or transplants during 4 years were reached in 23 (27%) patients compared with 58 (48%) patients with intermediate ECG criteria (QRS duration 120–149 ms and/or non-LBBB; P=0.003). Seventy-one of 120 patients (59%) with intermediate ECG criteria had GLS >−9% and 84 (70%) had GCS >−9%. There were 36
HF hospitalizations or deaths in the patients with LBBB ≥150 ms and 74 in the patients with intermediate ECG criteria (P=0.010). As anticipated, patients with intermediate ECG criteria had a less favorable outcome overall when compared with those with LBBB ≥150 ms: HR: 2.16; 95% CI, 1.39 to 3.34; P=0.001 for death, LVAD, and transplant; HR: 1.89; 95% CI, 1.30 to 2.75; P=0.001 for HF hospitalization or death. Importantly, intermediate ECG criteria patients with a baseline GLS or GCS strain <−9% had a much more favorable outcome, similar to the patients with QRS width ≥150 ms and LBBB. This result was similar for both end points (Figure 5 and Table 3). In a multivariable analysis of the patient subgroup with intermediate ECG criteria, GCS remained independently associated with outcome, even after adjusting for other baseline variables: HR: 0.86; 95% CI, 0.75 to 0.99; P=0.041.

Additive Prognostic Value of Global Strain to Clinical and Electrocardiographic Criteria
We used Cox proportional hazards models to show the incremental prognostic value of global strain compared with conventional parameters known to be associated with survival. The addition of GLS and GCS improved the outcome prediction compared with conventional clinical (age, male sex, and ischemic heart disease), electrocardiographic (QRS duration and LBBB morphology), or echocardiographic (baseline EF, baseline end-systolic volume, and radial delay) parameters in all the patients (P<0.001; integrated discrimination index=0.034). In the prespecified intermediate ECG criteria subgroup, the global strain parameters added prognostic value to the models (P=0.006; integrated discrimination index=0.017; Figure I in the Data Supplement).

Discussion
Our current study shows that baseline GLS and GCS added prognostic value to ECG selection criteria in a large series of patients with HF undergoing CRT. We showed that a predefined cutoff of −9% for both GLS and GCS was associated with long-term outcomes in terms of overall survival or combined end points of HF hospitalizations and death. Our findings confirm previous observations of global strain measures in HF patients overall10,19,20,24 and extend their prognostic utility in a novel way to patients undergoing CRT. GLS has become increasingly recognized for its prognostic value in addition to LVEF and has been shown to be prognostic in CRT patients.19 Our new approach of calculating GCS averaged from 2 basal views adds new support as a prognostic marker in CRT. This study also provides new mechanistic insight of GLS and GCS as markers of myocardial substrate in subgroups of patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy, where similar prognostic associations were observed. These observations imply that depressed
GLS or GCS from either scar or profoundly depressed contractility from nonischemic causes are both unfavorable for optimal CRT response. Importantly, our study also demonstrates in a new way that GLS and GCS are of independent and additive prognostic value to the subgroup of patients with intermediate ECG criteria (QRS 120–149 ms wide or non-LBBB) where the ECG criteria alone have been shown to be less predictive of CRT response.

**Global Strain and Myocardial Function**

Measures of cardiac deformation by GLS and GCS can provide valuable prognostic information beyond routine LVEF. LV chamber deformation is closely related to blood volume displacement, with GLS and GCS linearly related to LVEF. However, GLS and GCS can provide additional information in hypertrophic cardiomyopathy, amyloidosis, chemother-apy-induced cardiomyopathy, aortic stenosis, and mitral

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical and Echocardiographic Characteristics in the Total Sample and in Electrocardiographic Criteria Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Sample</strong> (N=205)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker, n (%)</td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
</tr>
<tr>
<td>GLS, %</td>
</tr>
<tr>
<td>GCS, %</td>
</tr>
</tbody>
</table>

Values shown as mean±SD or n (%). ACE indicates angiotensin-converting enzyme; GCS, global circumferential strain; GLS, global longitudinal strain; LBBB, left bundle branch block; LV, left ventricular; and NYHA, New York Heart Association.

*P* value for QRS duration and LBBB not shown because they were the factors used to design the subgroups.

**Figure 3.** Associations of global strain with clinical outcomes. Kaplan–Meier plots for global longitudinal strain (GLS; left) and global circumferential strain (GCS; right) and 4-y clinical outcomes after cardiac resynchronization therapy in all 205 patients. A cutoff of >−9% was significantly associated with an increased risk for the combined end point of death, left ventricular assist device (LVAD), and heart transplant (top), and for the combined end point of heart failure hospitalization or death (bottom). CI indicates confidence interval; and HR, hazard ratio.
Global strain measures may provide additional prognostic information as recently shown in the analysis from the Framingham Heart Study. In this study, LV mechanical function measured by longitudinal, circumferential, and radial strain was associated with long-term outcomes, even adjusting for cardiovascular risk factors. Specifically, circumferential strain was significantly related to incidental HF (HR per SD increment: 1.79; 95% CI, 1.35–2.37; \( P < 0.001 \)), as well as decreased strain measures were related to all-cause mortality (\( P < 0.008 \) for all). Although LV contraction in 3 dimensions is complex, GLS measures primarily the long-axis contraction performed by longitudinally oriented subendocardial and subepicardial fibers. GLS has been shown to be additive to LVEF in patients with preserved EF. GCS is thought to measure short-axis circular fiber shortening in the mid layer and can provide additional prognostic information. It is presently decreased strain measures were related to all-cause mortality (\( P < 0.008 \) for all). Although LV contraction in 3 dimensions is complex, GLS measures primarily the long-axis contraction performed by longitudinally oriented subendocardial and subepicardial fibers. GLS has been shown to be additive to LVEF in patients with preserved EF. GCS is thought to measure short-axis circular fiber shortening in the mid layer and can provide additional prognostic information. It is presently

\[
\text{GLS} = \frac{\text{GCS} \times \text{LVEF}}{100}
\]

### Table 2. Univariable and Multivariable Cox Regression Analysis for Associations With Long-Term Outcomes After Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Total Cohort (n=205)</th>
<th>Subgroup With QRS 120–149 ms or Non-LBBB (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI P</td>
<td>HR 95% CI P</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.00 0.98–1.02 0.675</td>
<td>...</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.39 0.82–2.33 0.222</td>
<td>...</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.76 1.08–2.87 0.024</td>
<td>...</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.53 1.19–1.96 0.001</td>
<td>1.64 1.22–2.22 0.001</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>0.99 0.98–0.99 0.011</td>
<td>...</td>
</tr>
<tr>
<td>LBBB</td>
<td>0.47 0.31–0.73 0.001</td>
<td>0.53 0.32–0.88 0.015</td>
</tr>
<tr>
<td>LV ESV, per 10 mL</td>
<td>1.04 1.01–1.07 0.004</td>
<td>1.05 1.00–1.10 0.024</td>
</tr>
<tr>
<td>LVEF, per 5%</td>
<td>0.74 0.60–0.92 0.006</td>
<td>...</td>
</tr>
<tr>
<td>Radial delay, per 10 ms</td>
<td>0.99 0.99–1.00 0.029</td>
<td>...</td>
</tr>
<tr>
<td>GLS, %</td>
<td>0.84 0.77–0.91 &lt;0.001</td>
<td>0.90 0.81–0.99 0.032</td>
</tr>
<tr>
<td>GCS, %</td>
<td>0.69 0.62–0.78 &lt;0.001</td>
<td>0.74 0.64–0.85 &lt;0.001</td>
</tr>
</tbody>
</table>

Outcomes were predefined as death, left ventricular assist device, or transplant during 4-y follow-up. GLS and GCS were assessed as continuous variables. CI indicates confidence interval; ESV, end-systolic volume; GCS, global circumferential strain; GLS, global longitudinal strain; HR, hazard ratio; LBBB, left bundle branch block; LV, left ventricular; and LVEF, left ventricular ejection fraction.

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**Figure 4.** Associations of global strain with clinical outcomes by disease subgroup. Kaplan–Meier plots of patients grouped by ischemic cardiomyopathy (top) and nonischemic cardiomyopathy (bottom) with associations of global longitudinal strain (GLS; left) and global circumferential strain (GCS, right) with outcomes during 4 y after cardiac resynchronization therapy. In all subgroups, a cutoff of >−9% was highly significantly associated with an increased risk for the combined end point of death, left ventricular assist device (LVAD), and heart transplant and for the combined end point of heart failure hospitalization or death. CI indicates confidence interval; and HR, hazard ratio.
unclear if GLS or GCS is superior and the precise mechanistic reason for GLS and GCS is to provide additional information to LVEF. It seems that GLS and GCS may further characterize the myocardial substrate that is not responsive to CRT by reflecting the myocardial scar burden in patients with ischemic cardiomyopathy and profound myocardial dysfunction in patients with nonischemic cardiomyopathy. Both GLS and GCS have been validated as having less variability than LVEF calculations. A meta-analysis by Kalam et al showed that the HR per SD change in GLS was associated with a reduction in mortality, 1.62 (95% CI, 1.13–2.33; P = 0.009) times greater than the HR per SD change in LVEF. GLS may also have a high sensitivity for detecting alterations of contractility in patients with normal or nearly normal LVEF, where alterations in longitudinal contraction may precede decreases in LVEF. GCS as a marker of contractility has been less studied, especially in patients with HF. Tanaka et al reported a mid-LV GCS value of ≥5.4% (in absolute value) to be predictive of LV reverse remodeling in patients with dilated cardiomyopathy treated with β-blocker therapy. In patients with ischemic cardiomyopathy, subendocardial longitudinal fibers are initially affected with progressive damage to mid-wall circumferential with transmural scar.

Global Strain and CRT Response
Response to CRT is influenced by multiple interacting factors, including the appropriate electromechanical substrate (electric

### Table 3. Associations of Global Strain With Clinical Outcomes in All Patients and Subgroups

<table>
<thead>
<tr>
<th>Events (N=205)</th>
<th>GCS &gt;−9%</th>
<th>GLS &gt;−9%</th>
<th>Events (N=205)</th>
<th>GCS &gt;−9%</th>
<th>GLS &gt;−9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, LVAD, or Transplant</td>
<td>GLS &gt;−9%</td>
<td>GCS &gt;−9%</td>
<td>Heart Failure Hospitalization or Death</td>
<td>GLS &gt;−9%</td>
<td>GCS &gt;−9%</td>
</tr>
<tr>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>All patients*</td>
<td>81</td>
<td>2.34</td>
<td>1.40–3.92</td>
<td>0.001</td>
<td>3.01</td>
</tr>
<tr>
<td>Ischemic heart disease†</td>
<td>59</td>
<td>1.77</td>
<td>0.95–3.29</td>
<td>0.073</td>
<td>2.77</td>
</tr>
<tr>
<td>Nonischemic heart disease‡</td>
<td>22</td>
<td>3.21</td>
<td>1.13–9.16</td>
<td>0.029</td>
<td>4.76</td>
</tr>
<tr>
<td>Intermediate ECG criteria§</td>
<td>58</td>
<td>2.47</td>
<td>1.43–4.28</td>
<td>0.001</td>
<td>3.42</td>
</tr>
<tr>
<td>Intermediate ECG criteria¶</td>
<td>58</td>
<td>1.93</td>
<td>1.04–3.57</td>
<td>0.037</td>
<td>2.56</td>
</tr>
</tbody>
</table>

Clinical outcomes during 4-y follow-up. Results are shown in all patients and in subgroups according to ischemic or nonischemic pathogenesis, and in intermediate ECG group (LBBB QRS 120–149 ms and/or non-LBBB). CI indicates confidence interval; ECG, electrocardiographic; GCS, global circumferential strain; GLS, global longitudinal strain; HR, hazard ratio; LBBB, left bundle branch block; and LVAD, left ventricular assist device.

*Adjusted for creatinine, LBBB, and LVESV.
†Adjusted for creatinine and LBBB.
‡Adjusted for creatinine.
§Adjusted for creatinine and LBBB.
¶Adjusted for ICM and creatinine.
‖Intermediate ECG criteria group with global strain >−9% compared with LBBB ≥150 ms patients.
#Intermediate ECG criteria group with global strain >−9% compared with intermediate ECG criteria group with global strain ≤−9%.

![Figure 5. Associations of global strain with clinical outcomes by electrocardiographic (ECG) subgroups. Kaplan-Meier plots of patients grouped by ECG criteria and global longitudinal strain (GLS; left) and global circumferential strain (GCS; right) and the combined end point of death, left ventricular assist device (LVAD), and heart transplant during 4 y after cardiac resynchronization therapy. Patients were grouped by QRS width ≥150 ms and left bundle branch block (LBBB) or intermediate (Inter) ECG criteria (QRS 120–149 ms or non-LBBB). Intermediate ECG criteria patients with better baseline ventricular function by strain imaging (GLS >−9%; left or GCS >−9%; right) had more favorable long-term prognosis, similar to those with QRS ≥150 ms and LBBB. CI indicates confidence interval; and HR, hazard ratio.](http://circimaging.ahajournals.org/download/figure5.png)
delay combined with mechanical dyssynchrony), global scar burden, LV lead position, and relationship to regional scar. \(^6,9,39\)

This study adds characterization of the myocardial substrate in terms of global deformation by GLS and GCS as a new prognostic feature for CRT response. Extent of fibrosis and the interstitial matrix quantified by late gadolinium enhancement using cardiac magnetic resonance imaging is associated with a worse prognosis, regardless of HF pathogenesis or baseline EF. \(^40\) D’Andrea et al \(^41\) demonstrated that GLS is inversely correlated with LV scar tissue assessed by cardiac magnetic resonance, which was associated with response to CRT. In a subgroup analysis from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), GLS with a similar cutoff to our present study of \(-8.7\%\), combined with moderate dyssynchrony (measured as SD of time-to-peak transverse strain), predicted a greater benefit from CRT. \(^35\) Similarly, Hasselberg et al \(^42\) showed the association of GLS \(> -8.3\%\) before CRT to fatal outcome (death, heart transplant, and LVAD) in 170 patients with HF after 2 years of follow-up, \(P <0.001\). In this population, \(48\%\) of whom had ischemic cardiomyopathy and \(90\%\) of whom had native or RV pacing–induced LBBB, GCS measured from 3 short-axis views showed no association with clinical outcome, despite circumferential function being the main contributor to CRT volumetric response. Mochizuki et al \(^43\) reported in 132 patients, including \(24\%\) with ischemic disease, that a GCS \(> 3.9\%\) (absolute value) along with radial dyssynchrony or GCS \(\geq 6.6\%\) and lack of radial dyssynchrony predicted fewer cardiovascular events during the 40-month follow-up. The results of our subgroup analysis extend support to GLS and GCS as playing a role in identifying patients with intermediate ECG criteria who may respond similarly to CRT as those with LBBB and QRS width \(\geq 150\) ms.

**Study Limitations**

This was not a randomized clinical trial, and there was no control group to compare results of CRT in an?intermediate criteria ECG group with medical therapy alone. There are multiple other factors which play a role in CRT response and were not evaluated in this study, such as site of latest activation and LV lead position. It would be of interest to have another imaging method to quantify scar, such as single-photon emission computed tomography or late gadolinium enhancement cardiac magnetic resonance. \(^6\)

Because GLS and GCS may be depressed from either scar or profound hypocontractility, scar quantification to compare to GLS and GCS in CRT patients is worthy of future study. Although image-guided LV lead positioning may play a role in improving CRT response as it was shown in both the Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET) study and in the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) trial, \(^43,44\) this study focused on providing prognostic information to patients with routine CRT because image-guided LV lead placement is rare in current clinical practice. \(^45\) As previously reported, the presence of dyssynchrony before CRT is associated with favorable clinical outcomes. \(^15\) Although baseline dyssynchrony measured by radial delay (radial strain–derived sepal to posterior wall delay) was evaluated in univariable and multivariable analyses, it was a limitation that follow-up assessment for resynchronization was not part of the current study. \(^7\) The presence of dyssynchrony after CRT has been associated with worse clinical outcome in wide QRS patients \(^8,47\) as well as narrow QRS. \(^48\)

A known limitation of speckle-tracking echocardiography is that it cannot be applied to all patients. \(^35,46\) However, we were able to obtain meaningful GLS and GCS results in \(> 90\%\) of consecutive patients. We acknowledge that a possible statistical limitation of this study is the potentially inflated type I error because of multiple testing. Another limitation is the lack of follow-up strain analysis in this cohort of patients.

**Conclusions**

Strain imaging has emerged as a powerful tool to quantify myocardial mechanics, including longitudinal and circumferential shortening. Characterization of the baseline LV myocardial substrate by GCS and GLS may be an important marker for subsequent CRT benefit. Importantly, GLS and, in particular, 12-segment GCS from basal and mid levels, may provide incremental prognostic value compared with existing measures such as LVEF, QRS duration, or LBBB morphology. Global strain measurements also show utility in patients with intermediate ECG criteria. Although GLS and GCS are potentially useful prognostic tools, future prospective study of their role in patient selection is required.

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**References**


Cardiac resynchronization therapy (CRT) may be of great benefit to patients with advanced heart failure; however, there are multiple factors that may influence the response to CRT, including adequate electrophysiological substrate, scar burden, and lead position. Current guidelines are based on electrocardiographic criteria of QRS duration and morphology, favoring patients with QRS duration ≥150 ms and left bundle branch morphology. However, nonresponder rate remains in one third of patients. Recent advances in echocardiography-based strain techniques allow us a greater understanding of the role of deformation parameters to quantify the pathophysiology and mechanisms of cardiac function. Our study showed that global longitudinal strain and global circumferential strain measured before CRT are strongly associated with important long-term clinical outcomes. Low global longitudinal strain or global circumferential strain (in absolute values) may be considered as markers of advanced myocardial dysfunction from scar or profound hypocontractility and are associated with a worse prognosis after CRT. Impaired baseline global longitudinal strain and global circumferential strain before CRT was associated with more heart failure hospitalizations and deaths, and greater need for ventricular assist device implants or heart transplantation. Interestingly, global longitudinal strain and global circumferential strain had similar prognostic value in both ischemic and nonischemic cardiomyopathy patients. Importantly, global strain parameters were associated with outcome in the group of patients with intermediate ECG criteria for CRT (QRS 120–149 ms or those with non–left bundle branch morphology). Future study of the potential role of myocardial deformation parameters, which seem additive to ECG criteria for patient selection for CRT is warranted.
Additive Prognostic Value of Echocardiographic Global Longitudinal and Global Circumferential Strain to Electrocardiographic Criteria in Patients With Heart Failure Undergoing Cardiac Resynchronization Therapy
Antonia Delgado-Montero, Bhupendar Tayal, Akiko Goda, Keiko Ryo, Josef J. Marek, Masataka Sugahara, Zhi Qi, Andrew D. Althouse, Samir Saba, David Schwartzman and John Gorcsan III

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Supplemental Material

Supplemental Figure. Incremental prognostic value of global strain.

Bar graphs of Chi-square analysis showing incremental prognostic value of global longitudinal strain (GLS) and global circumferential strain (GCS) to the combined end-point of death, left ventricular assist device or heart transplant, over conventional clinical and routine echocardiographic (ECHO) parameters. Clinical factors were age, male sex and ischemic heart disease. Electrocardiographic (ECG) parameters were QRS width and left bundle branch block (LBBB). ECHO parameters were left ventricular (LV) end-systolic volume, LV ejection fraction and radial strain septal to posterior wall delay.
Supplemental Figure

A  All: QRS Width ≥ 120 ms

- CLINICAL Age
- Male
- Ischemic
- ECG QRS duration
- LBBB
- ECHO LVESV
- LVEF
- Radial Delay
- STRAIN GLS
- GCS

n = 205

Chi-square

B  QRS 120-149 ms or Non-LBBB

- CLINICAL Age
- Male
- Ischemic
- ECG QRS duration
- LBBB
- ECHO LVESV
- LVEF
- Radial Delay
- STRAIN GLS
- GCS

n = 120

Chi-square

p < 0.001
p < 0.001
p = 0.001
p = 0.001
p = 0.001
p = 0.006
p = 0.091
p = 0.004
p = 0.570
p = 0.006