Left Ventricular Longitudinal Function Predicts Life-Threatening Ventricular Arrhythmia and Death in Adults With Repaired Tetralogy of Fallot

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Background—Sudden cardiac death and life-threatening ventricular arrhythmia remain a concern in adult patients with repaired tetralogy of Fallot. Longitudinal left ventricular (LV) function is sensitive in detecting early myocardial damage and may have prognostic implications in this setting.

Methods and Results—We included 413 tetralogy of Fallot patients (age, 36±13 years; QRS duration, 148±27 milliseconds; LV ejection fraction, 55±10%). A composite end point of sudden cardiac death/life-threatening ventricular arrhythmia (sustained ventricular tachycardia, resuscitated sudden cardiac death, or appropriate implantable cardioverter-defibrillator discharge) was used. During a median follow-up of 2.9 years, 5 patients died suddenly, 9 had documented sustained ventricular tachycardia, and another 5 had appropriate implantable cardioverter-defibrillator shocks. On univariate Cox analysis, QRS duration (hazard ratio [HR], 1.02 per 1 ms; P=0.046), right atrial area (HR, 1.05 per 1 cm²; P=0.02), right ventricular fractional area change (HR, 0.94 per 1%; P=0.02), right ventricular outflow tract diameter (HR, 1.08 per 1 mm; P=0.01), mitral annular plane systolic excursion (HR, 0.84 per 1 mm; P=0.03), and LV global longitudinal 2-dimensional strain (HR, 0.87 per 1%; P=0.03) were related to the combined end point. On bivariable analysis, mitral annular plane systolic excursion and LV global longitudinal 2-dimensional strain were related to outcome independently of QRS duration (P=0.002 and P=0.01, respectively). In addition, a combination of echocardiographic variables, including right atrial area, right ventricular fractional area change, and LV global longitudinal 2-dimensional strain or mitral annular plane systolic excursion, was also found to be significantly related to outcome (P<0.001; c statistic, 0.70).

Conclusions—LV longitudinal dysfunction was associated with greater risk of sudden cardiac death/life-threatening ventricular arrhythmias. In combination with echocardiographic right heart variables, also available from routine echocardiography, these measures provide important outcome information and should be considered a useful adjunct to established markers such as QRS duration in the estimation of prognosis in this challenging population. (Circulation. 2012;125:2440-2446.)

Key Words: adult ■ death, sudden, cardiac ■ echocardiography ■ heart diseases ■ prognosis ■ risk assessment ■ Tetralogy of Fallot

Tetralogy of Fallot (ToF) represents the most common cyanotic heart defect at birth, accounting for ≈10% of all congenital cardiac defects.1 Early surgical repair has dramatically improved the outcome of ToF, but serious late complications remain of concern. Pulmonary regurgitation is common in this population and may lead to right ventricular (RV) dilatation, RV dysfunction, exercise intolerance, and eventually life-threatening arrhythmia (LTA) and sudden cardiac death (SCD).2-7 Timely pulmonary valve replacement may avoid irreversible RV damage with its deleterious consequences. Nonetheless, SCD is not entirely preventable by this approach.8 Accurate risk stratification and the development of appropriate algorithms for the selection of patients who may benefit from an implantable cardioverter-defibrillator (ICD) would be crucial in this context. Previous studies have focused on the predictive value of surgical history, ECG...
variables, inducible arrhythmia, exercise intolerance, and RV burden of myocardial fibrosis. More recently, left ventricular (LV) systolic dysfunction and diastolic dysfunction have been reported to carry prognostic information in this setting. Although LV impairment is not uncommon in ToF patients, few patients present with more than mildly reduced LV ejection fraction. Therefore, more sensitive measures of early LV dysfunction may be required. Recent studies in various cardiovascular conditions have consistently demonstrated that variables of LV longitudinal function are more sensitive in detecting early myocardial damage than ejection fraction. Traditionally, longitudinal LV systolic function has been assessed by measuring mitral annular plane systolic excursion (MAPSE). Tissue Doppler echocardiography has also been used to assess longitudinal myocardial velocities at the mitral annular level. More recently, speckle tracking echocardiography has emerged as a promising tool for assessing myocardial performance. Unlike MAPSE, speckle tracking-derived strain and strain rate measurements can be performed at different positions within the myocardium, thus allowing the measurement of local myocardial function. Furthermore, unlike myocardial tissue Doppler velocities, 2-dimensional (2D) speckle tracking strain measurements are not angle dependent and are not affected by tethering effects. We have previously demonstrated that despite the presence of normal LV ejection fraction, 2D peak longitudinal strain is frequently reduced in ToF patients. The purpose of the present study was to assess the prognostic value of longitudinal LV function and its incremental value to established predictors of outcome in a large cohort of ToF patients.

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Methods

All patients with repaired ToF followed up at the Adult Congenital Heart Disease Program, Royal Brompton Hospital (London, UK) and at the Adult Congenital and Valvular Heart Disease Center at the University of Münster (Münster, Germany) who had undergone transthoracic echocardiography between February 2004 and October 2010 with adequate digitally stored images available were included. For those patients who had >1 examination during this period, only the first was used.

Echocardiography

A comprehensive echocardiographic study including M-mode, 2D, and Doppler echocardiography was performed. For offline assessment of peak global longitudinal 2D LV strain (LV-LS) and RV strain, a commercially available software package (2D Cardiac Performance Analysis Software, TomTec, Unterschleissheim, Germany) was used. LV-LS and longitudinal 2D RV strain were defined as the peak negative value on the strain curve during the entire cardiac cycle. Biventricular long-axis function on M-mode echocardiography (MAPSE and tricuspid annular plane systolic excursion) was measured as described previously. Chamber dimensions, LV ejection fraction, and RV fractional area change were measured according to current recommendations.

For assessment of LV diastolic function, left atrial pressure was estimated according to the algorithm recommended by the American Society of Echocardiography and European Society of Echocardiography based on mitral inflow E- and A-wave peak velocities, E-wave deceleration time, early mitral annular velocities (e’), and left atrial volume index. Patients were stratified into a group with normal or elevated left atrial pressure. Because the E/e’ ratio has been reported to relate to the LV end-diastolic pressure, this parameter was also tested as a continuous variable in the statistical analysis.

Clinical Variables and Study Protocol

New York Heart Association functional class and QRS duration at the time of the echocardiographic investigations and demographic variables were collected from medical records. Follow-up time started at the time of echocardiography. The end point of the study was a composite of SCD or LTA. LTA was defined as documented sustained ventricular tachycardia, resuscitated nearly missed SCD, or appropriate ICD discharge. Routine ICD follow-up protocols were reviewed for all ICD patients to ensure that ICD therapies were appropriate. Patients who underwent pulmonary valve replacement during the study period (n=85) were censored at the time of operation because surgery alters ventricular volumes and function and may affect outcome. The study was approved by the local ethics committee.

Statistics

Values are presented as mean and SD or median and interquartile range (25th and 75th percentile), depending on variable distribution. Categorical variables are presented as frequencies and percentages. Comparisons between subgroups were performed by the unpaired t test, Mann-Whitney U test, or χ² test. The relationship between demographic, clinical, or echocardiographic variables and outcome was investigated by univariable and bivariable Cox proportional hazard analyses. In addition, the prognostic value of models incorporating different combinations of variables of LV longitudinal function and right heart variables was explored. Concordance probabilities (C indexes, indexex conceptually similar to area under the curve on receiver-operating characteristic curve analysis) were calculated for the Cox models using a resampling validation algorithm based on the rms R package. For all analyses, a 2-tailed value of P<0.05 was used as the criterion for statistical significance. R version 2.12.2 was used for all analyses.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Overall, 413 patients with repaired ToF and appropriate echocardiographic recordings were included. The mean age was 36±13 years, and 211 patients (51%) were male. Additional demographic and clinical information is presented in Table 1.

During a median follow-up period of 2.9 years (interquartile range, 1.4–4.4 years), 19 patients reached the predefined end point of SCD or LTA: 5 patients died suddenly, 9 patients had documented sustained ventricular tachycardia or required resuscitation for nearly missed SCD (and subsequently underwent ICD implantation for secondary prevention), and 5 patients had appropriate ICD shocks delivered by an ICD implanted before initial echocardiography. The annual probability of SCD/LTA was 2.4%. The incidence of SCD was 0.5%/y.

Prognostic Value of Demographic Variables, Clinical Markers, and Surgical History

Age and sex were not significantly related to the primary end point of SCD or LTA. In contrast, a New York Heart Association functional class >1, a longer QRS duration, and a history of >1 previous cardiac surgery with extracorporeal circulation were significantly associated with SCD/LTA on Cox proportional hazard analysis as shown in Table 2.
LV Variables
None of the variables of LV diastolic function were significantly related to the study end point (Table 2). On univariable Cox proportional hazard analysis, however, MAPSE and LV-LS were significantly related to the risk of SCD/LTA (Table 2 and the Figure). In contrast, LV ejection fraction was not significantly associated (P = 0.06) with SCD/LTA (Table 2). In addition, bivariable Cox proportional hazard analysis confirmed that both LV-LS and MAPSE were associated with SCD/LTA independently of LV ejection fraction (with LV ejection fraction not maintained in the model).

Right Heart Variables
Right atrial area was significantly related to the risk of SCD/LTA (Table 2). This association was independent of the presence of a restrictive RV physiology on bivariable analysis (hazard ratio, 1.04; 95% confidence interval, 1.004–1.085; P = 0.03 for right atrial area). In addition, RV end-diastolic area measured from an apical 4-chamber view, RV outflow tract diameter, and RV fractional area change were related to SCD/LTA (Table 2), whereas tricuspid annular plane systolic excursion and RV 2D systolic strain were not.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Patients (n=413)</th>
<th>Patients Without SCD or LTA (n=394)</th>
<th>Patients With SCD or LTA (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>35.9 (13.4)</td>
<td>35.9 (13.4)</td>
<td>35.8 (14.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>211 (51)</td>
<td>199 (51)</td>
<td>12 (62.5)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.6 (17.2)</td>
<td>72.2 (17.6)</td>
<td>67.3 (11.6)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.8 (11.4)</td>
<td>168.8 (11.6)</td>
<td>170.4 (9.5)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.83 (0.25)</td>
<td>1.83 (0.25)</td>
<td>1.80 (0.19)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.0 (5.2)</td>
<td>25.1 (5.3)</td>
<td>23.3 (2.7)</td>
</tr>
</tbody>
</table>

Clinical status and history
NYHA FC I/II/III/IV, %  52/38/9/1  54/38/8/0  17/65/18/0
Palpitations, n (%)  107 (26)  95 (24)  12 (63)
Angina, n (%)  17 (4)  16 (4)  1 (5)
Antiarrhythmics, n (%)  63 (15)  55 (14)  9 (47)
Cardiac surgeries, n (IQR)  1.40±0.6 (1.0–2.0)  1.4±0.6 (1.0–2.0)  1.8±0.7 (1.0–2.0)
Age at corrective surgery (IQR), y  8.2±10.0 (2.0–9.4)  8.1±9.9 (2.0–9.4)  8.6±9.2 (1.8–10.3)

Echocardiographic and ECG variables
Moderate to severe TR, n (%)  17 (4.1)  15 (3.8)  2 (10.5)
Moderate to severe PR, n (%)  210 (51)  201 (51)  9 (47)
Right atrial area, cm²  22.3 (8.2)  22.1 (8.2)  26.8 (7.8)
RV end-diastolic area, cm²  31.4 (8.9)  31.0 (8.8)  38.4 (9.1)
RVOT diastolic diameter, mm  34.6 (7.5)  34.5 (7.5)  38.3 (6.3)
RV fractional area change, %  38.3 (9.5)  38.9 (9)  33.7 (12.3)
TAPSE, mm  15.6 (3.7)  15.7 (3.7)  14 (3.6)
LV ejection fraction, %  55.3 (10.3)  55.8 (9.9)  50.4 (10.3)
MAPSE, mm  14.1 (3.3)  14.2 (3.3)  12.4 (3.8)
LV longitudinal 2D strain, %  15.4 (4.7)  15.8 (4)  13.5 (4.8)
QRS duration, ms  148 (27)  147.7 (27.2)  160.4 (17.7)

Incremental Prognostic Value of Variables of Longitudinal LV Function
To assess the incremental prognostic value of measures of LV longitudinal function compared with known risk factors such as QRS duration and RV function, bivariable Cox analyses with calculation of concordance indices (c statistic) were performed. Both MAPSE and LV-LS were significantly associated with a higher risk of SCD/LTA independently of QRS-duration on bivariable analysis (P = 0.002 and P = 0.01 for MAPSE and LV-LS, respectively). Furthermore, including MAPSE or LV-LS in addition to QRS duration in the model improved the c index from 0.65 for QRS duration alone to 0.78 and 0.71 for a model including QRS duration and MAPSE or LV-LS, respectively. A similar picture emerged for RV fractional area change; MAPSE was significantly associated with a higher risk of SCD/LTA independently of RV fractional area change on bivariable analysis (P = 0.02). Furthermore, including MAPSE or LV-LS in addition to RV fractional area change in the model improved the c index from 0.65 for RV fractional area change alone to 0.68 and 0.76 for a model including RV fractional area change and MAPSE or LV-LS, respectively.
Combined Prognostic Value of Echocardiographic Variables

Echocardiographic measures significantly associated with the risk of SCD/LTA on univariable Cox analysis were assessed to estimate the combined prognostic value of echocardiographic variables. The full model included a parameter of LV systolic function (either MAPSE or LV-LS), a parameter of RV inflow and apical size (RV end-diastolic area), a measure of RV outflow tract size (RV outflow tract diastolic diameter), a measure of RV function (RV fractional area change), and a parameter of right atrial enlargement (right atrial area).

In addition, simplified models were constructed that contained only a subset of these variables. Because LV ejection fraction was not significant on univariable Cox analysis, this measure was not included in any of these models. Incorporating previously published limits of normal values, we used the following cutoff values: LV-LS <12 mm, right atrial area >20 cm², and RV fractional area change <32%; hazard ratio per unit, 2.74; 95% confidence interval, 1.58–4.19; P=0.0001; combination of LV-LS <15%, right atrial area >20 cm², and RV fractional area change <32%; hazard ratio per unit, 2.74; 95% confidence interval, 1.75–4.30; P<0.0001).

Discussion

The results of the present study demonstrate for the first time that LV longitudinal dysfunction is associated with SCD and LTA in patients with repaired ToF. Measures of LV longitudinal function are readily available from routine transthoracic echocardiographic assessments with conventional echocardiography systems and have incremental prognostic value when considering RV variables or established predictors of outcome such as QRS duration in this challenging population. A combination of echocardiographic variables, including right atrial area and RV fractional area change, as well as LV-LS or MAPSE, may therefore be useful in risk stratifying ToF patients.

The reasons for impaired LV function in ToF are poorly understood. It has been suggested that myocardial ischemia before corrective surgery may account in part for late LV dysfunction. In fact, Hausdorf et al have reported that the severity of preoperative hypoxemia affected late systolic function. In addition, shared myocardial fibers between the LV and RV and the adverse impact of septal shift have been suggested to account for LV dysfunction in this setting. LV dysfunction in ToF patients is rarely of the severity encountered in patients with acquired heart failure. However, previous studies have linked low LV ejection fraction in this setting to poor outcome. We have recently demonstrated that LV ejection fraction may lack sensitivity in detecting early myocardial damage in ToF patients. The present study was therefore performed to test the hypothesis that variables of LV longitudinal function (especially LV-LS)
are significant predictors of SCD/LTA and superior to LV ejection fraction. On univariable Cox proportional hazard analysis, LV-LS and MAPSE were significantly associated with a higher risk of SCD/LTA, whereas LV ejection fraction was not. Somewhat surprisingly, MAPSE, a simpler measure of LV longitudinal function measured on conventional M-mode, was as helpful as LV-LS in assessing prognosis. In contrast to a previous study using invasive measurements of LV end-diastolic pressure,10 we could not confirm an association between LV diastolic dysfunction, as derived echocardiographically, and outcome. This could be explained by the inherent limitations of estimating end-diastolic pressure from an echocardiographic assessment.24 This finding, however, may have important clinical implications because cardiac catheterization merely for risk stratification is not justified in this setting, and the results of our study show that extrapolating from echocardiographic measures of diastolic function on prognosis should be avoided. The present study also demonstrates the prognostic value of right atrial enlargement, impaired RV function, and RV dilatation in this cohort.

Assessment of RV volumes and RV function based on conventional volumetric variables such as ejection fraction remains challenging on echocardiography because of the complicated geometry of the RV and limited acoustic windows in many patients.32–34 Although LV function and dimensions can be assessed accurately on transthoracic echocardiography, these measurements remain the province of cardiac magnetic resonance imaging (MRI) with its advantages of a wide field of view, lack of anatomic plane restriction, and superior reproducibility.35 However, there is no unrestricted access to this technique, and MRI studies are currently not possible in the growing population of ToF patients with ICDs. Echocardiography will therefore remain the workhorse in the routine assessment of ToF patients. Not surprisingly, measures of RV size and function were found to be related to outcome in this study. Interestingly, however, tricuspid annular plane systolic excursion was unrelated to the end point of SCD/LTA. Measures of RV longitudinal function are theoretically appealing for assessing RV systolic function because anatomic studies have demonstrated that the deeper RV muscle fibers are arranged predominantly in a longitudinal fashion from the tricuspid valve annulus to the apex.36 and RV stroke volume grossly depends on longitudinal shortening.37 Thus, reduced tricuspid annular plane systolic excursion, closely reflecting RV free wall dysfunction, should precede circumferential RV impairment. One possible interpretation for the failure of tricuspid annular plane systolic excursion to reflect prognosis could be its high sensitivity. In the setting of a chronically volume overloaded, enlarged, and impaired RV, a too-sensitive parameter will provide little information on outcome. In contrast, sensitive measures of LV longitudinal function may be better suited to detect subtle changes/impairment in LV function.

Although rare overall, SCD remains a particular concern for this young patient population and is not well predicted. Risk stratification remains challenging and has been discussed in detail elsewhere.9 The annual incidence of death in adult ToF patients varies with age but is generally believed to be ~0.5%/y.38-39 This concurs with the incidence of SCD in the present study. Another clinically relevant and objective outcome measure is the annual incidence of SCD or documented ventricular tachycardia.8 The annual incidence of SCD/LTA in the present study was 2.4%, which is similar to the rate reported by Harrild et al (2.9%).9

Khairy et al9,10 have previously proposed a risk score based on clinical history, QRS duration, the results of electrophysiological studies, and invasive assessment of LV end-diastolic pressures. However, neither invasive pressure measurements nor electrophysiological studies can be performed routinely for risk assessment in patients after ToF repair. Thus, the results of the present study suggesting that measures obtained from a routine transthoracic echocardiographic study can also be used to risk stratify ToF patients may have particular clinical relevance. Because of the lack of invasive pressure and electrophysiological data in the majority of patients, the present study was unable to compare the performance of the score published by Khairy et al with our echocardiographic score directly. Nevertheless, the results of this study suggest that echocardiographic measures should be incorporated into future comprehensive score systems. In an editorial on the seminal article identifying QRS prolongation as major risk factor of SCD in 1995, Bricker40 estimated that ~1700 ToF patients with a follow-up time of 10 years would be required to attain sufficient statistical power to construct a meaningful multivariable statistical model to predict such events. Not surprisingly, even 1½ decades later, no such comprehensive model exists. Until sufficient statistical power can be achieved as part of even larger multicenter studies, no strong recommendations are possible, and clinicians will have to rely on their training and experience, supplemented by the results of various studies, rather than on an algorithmic approach. We believe that the findings of the present study should be helpful to clinicians for estimating the risk of LTA or SCD and may represent a useful adjunct or alternative to the score system provided by Khairy and colleagues.9,10

Study Limitations
This study was performed at tertiary care centers for adult congenital heart disease. Therefore, we cannot exclude the possibility that the patients in the study could be a biased sample, favoring those with more symptoms and advanced disease. Furthermore, this study focused on longitudinal biventricular function using speckle tracking analysis. Analysis of radial, circumferential, and torsional deformation may have provided additional prognostic information. However, global 2-D LV-LS was chosen because it can be calculated semiautomatically from speckle tracking analysis and offers good intraobserver and interobserver variability.41,42 In addition, it has been demonstrated to be useful in predicting outcome in heart failure patients.43 Although virtually all patients without a contraindication underwent cardiac MRI scans during the follow-up period, MRI measures were available in only ~50% of the patients within 6 months of the echocardiographic investigations, thus considerably reducing the event rate and statistical power in this subgroup. We therefore did not provide estimates of the prognostic value of MRI variables. Further MRI studies are required to provide such information. As a result of inadequate acoustic windows...
and the inability to clearly delineate the entire right heart on an apical 4-chamber view, RV fractional area change could not be determined in 16% and right atrial area was unavailable in 7% of patients. This may represent a limitation of the method described, especially if retrospective data are to be used to estimate prognosis on the basis of the echocardiographic score provided.

Low annual event rates are a major drawback of studies attempting to improve risk stratification in ToF patients. Even in the present study including the sizable number of 413 patients with 1144 patients-years of follow-up, only 5 SCDs occurred and 19 patients had a combined end point of SCD/LTA. Therefore, estimates of prognosis are associated with considerable uncertainty, and even very abnormal values of LV longitudinal function/high predictive scores may not be isolated warrant implantation of an ICD for primary prevention of SCD. This study was designed to test the hypothesis that LV-LS and MAPSE are superior to LV ejection fraction in predicting outcome in ToF patients. Beyond the results of these hypothesis-driven analyses, we also present the results of exploratory analyses of the association between (mainly right heart) echocardiographic or clinical variables and outcome. We cannot exclude the possibility that the type I error might be increased for these additional comparisons, and clinicians should take this limitation into account when applying the results of this study in practice. Larger studies with a higher number of events are required to validate the results of the present analysis and especially to confirm the value of combinations of echocardiographic variables in predicting LTA/SCD in this setting.

Conclusions
LV longitudinal dysfunction is associated with a higher risk of SCD/LTA in contemporary ToF patients. In combination with echocardiographic measures of right atrial size, RV function and dimensions, LV-LS, and MAPSE identify a subgroup of ToF patients at increased risk of SCD/LTA. Because all these variables are readily available from routine transthoracic echocardiographic assessment, they should be considered a useful adjunct to established markers such as QRS duration in the assessment of prognosis in this challenging population.

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Disclosures
None.

References
Sudden cardiac death and life-threatening ventricular arrhythmia are a major concern in adults after repair of tetralogy of Fallot. Accurate risk stratification of patients who may benefit from implantable cardioverter-defibrillators would be crucial in this context. Previous studies have focused on the predictive value of surgical history, ECG parameters, inducible arrhythmia, exercise intolerance, and burden of myocardial fibrosis. More recently, left ventricular (LV) systolic dysfunction and diastolic dysfunction have been reported to carry prognostic information. Recent studies, however, suggest that longitudinal LV function, measured by speckle tracking echocardiography, is more sensitive in detecting early myocardial damage compared with LV ejection fraction. We assessed the relation between measures of LV longitudinal systolic function on speckle tracking (global LV strain) and on M-mode echocardiography (mitral annular plane systolic excursion) and outcome (sustained ventricular tachycardia, resuscitated sudden cardiac death, or appropriate implantable cardioverter-defibrillator discharge) in 413 tetralogy of Fallot patients (median follow-up, 2.9 years). On univariable Cox analysis, mitral annular plane systolic excursion and global LV strain were significantly related to the combined end point, whereas LV ejection fraction and echocardiographic estimates of LV diastolic dysfunction were not. An echocardiographic model was constructed using global LV strain or mitral annular plane systolic excursion, right ventricular fractional area change, and right atrial area, identifying tetralogy of Fallot patients with a higher risk of sudden cardiac death and life-threatening ventricular arrhythmias. The results of this study suggest that longitudinal measures of LV systolic function outperform LV ejection fraction in providing information on outcome and should be considered a useful adjunct to established markers such as QRS duration in the estimation of prognosis in this challenging population.
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