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Relative Wall Thickness and the Risk for Ventricular Tachyarrhythmias in Patients With Left Ventricular Dysfunction

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ABSTRACT

BACKGROUND Relative wall thickness (RWT), defined as 2 times posterior wall thickness divided by the left ventricular (LV) diastolic diameter, is a measure of LV geometry and may be a marker for adverse events in patients with LV dysfunction.

OBJECTIVES The aim of this study was to investigate the relationship between RWT and the risk for ventricular tachyarrhythmia (VA) in patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study.

METHODS The study population comprised 1,260 patients with mild heart failure and left bundle branch block.

RESULTS In a multivariable model, RWT was the most powerful echocardiographic measure for estimating the risk of VAs compared with commonly used echocardiographic variables. Patients with low RWT (<0.24) had 83% ($p < 0.001$) increased risk for VA and 68% ($p < 0.001$) increase in VA risk or death (VA/death) compared with patients with higher RWT values. Each 0.01-unit decrease in RWT was associated with 12% ($p < 0.001$) and 10% ($p < 0.001$) increases in the risk of VA and VA/death, respectively. Treatment with cardiac resynchronization therapy with defibrillator (CRT-D; CRT with implantable cardioverter-defibrillator) was associated with a greater increase in RWT compared with implantable cardioverter-defibrillator at 12 months ($4.6 \pm 6.8\%$ vs. $1.5 \pm 2.7\%$; $p < 0.001$), and every 10% increase in RWT in CRT-D patients was associated with 34% ($p = 0.027$) and 36% ($p = 0.009$) reductions in the risk of subsequent VA and VA/death, respectively.

CONCLUSIONS In patients with mild heart failure and left bundle branch block, decreased RWT was associated with an increase in the risk of VA and VA/death. CRT-D therapy was associated with a favorable increase in RWT and reduction in risk of VA and VA/death. (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2016;67:303–12)

Reduced left ventricular ejection fraction (LVEF) and the presence of myocardial scar are associated with higher risk of ventricular arrhythmia (VA) and sudden cardiac death (1). The implantable cardioverter-defibrillator (ICD) is an established therapy for reducing mortality associated with VA (1,2). Cardiac resynchronization therapy with defibrillator (CRT-D) compared with ICD was shown

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ABBREVIATIONS AND ACRONYMS

CRT-D = cardiac resynchronization therapy with defibrillator

HF = heart failure

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

LVEDD = left ventricular end-diastolic diameter

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

PWT = posterior wall thickness

RWT = relative wall thickness

SWT = septal wall thickness

VA = ventricular tachyarrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

to reduce VA incidence, most likely through a mechanism of reverse remodeling in patients with prolonged QRS duration and left bundle branch block (LBBB) morphology (3-6).

Remodeling patterns of the LV can be assessed by echocardiographic measurement of relative wall thickness (RWT) and broadly categorized as normal or adverse remodeling, either eccentric or concentric. Previous studies have shown that concentric remodeling (high RWT) is associated with increased morbidity and mortality in hypertensive patients with hypertrophic cardiomyopathy (7-9). However, data regarding the relation between the magnitude of eccentric hypertrophy (low RWT) and the risk of VA in patients with dilated cardiomyopathy are scarce.

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The present study was carried out in 1,260 patients with mild heart failure (HF) and LBBB enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study. We aimed to investigate: 1) the predictive value of RWT for the risk of VA compared with other commonly used echocardiographic variables; 2) the relationship between LV morphology and the risk of VA by measuring RWT; and 3) the remodeling effect of CRT-D on RWT.

METHODS

The study population comprised 1,260 patients enrolled in the MADIT-CRT trial with LBBB at baseline electrocardiogram (70% of the original 1,820 patients). The design and results of the MADIT-CRT study have been reported previously (3,10). Briefly, patients who had ischemic cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or nonischemic cardiomyopathy (NYHA functional class II), LVEF ≤30%, normal sinus rhythm, and QRS duration ≥130 ms, were randomized to receive CRT-D or ICD therapy in a 3:2 ratio.

Device interrogation and programming were performed as previously reported (10). All devices were programmed to monitor and deliver therapy, antitachycardia pacing, and/or shock therapy. All devices were interrogated 1 month after enrollment and thereafter every 3 months; arrhythmia episodes were adjudicated by an independent core laboratory for pre-defined categories of appropriate or inappropriate therapy. A VA episode was defined when device-rendered therapy including antitachycardia pacing or shock was appropriately delivered. Ventricular tachycardia (VT) was defined as an episode with ventricular rates between 180 and 250 beats/min; ventricular fibrillation (VF) was defined as an episode with ventricular rates >250 beats/min. Fast VT was defined as an episode with ventricular rates ≥200 beats/min or VF.

Echocardiograms were obtained according to a study-specific protocol at baseline, which was before device implantation, and at 1 year. Echocardiography recordings were analyzed offline by a single technician in an independent core laboratory. Echocardiography investigators analyzing the images were blinded to treatment assignment and clinical outcome. Reproducibility of the primary measures was assessed by the primary observer reanalyzing 101 random studies.

LV volumes were measured with the Simpson disk method in the apical 4- and 2-chamber views, and LVEF was calculated according to the established

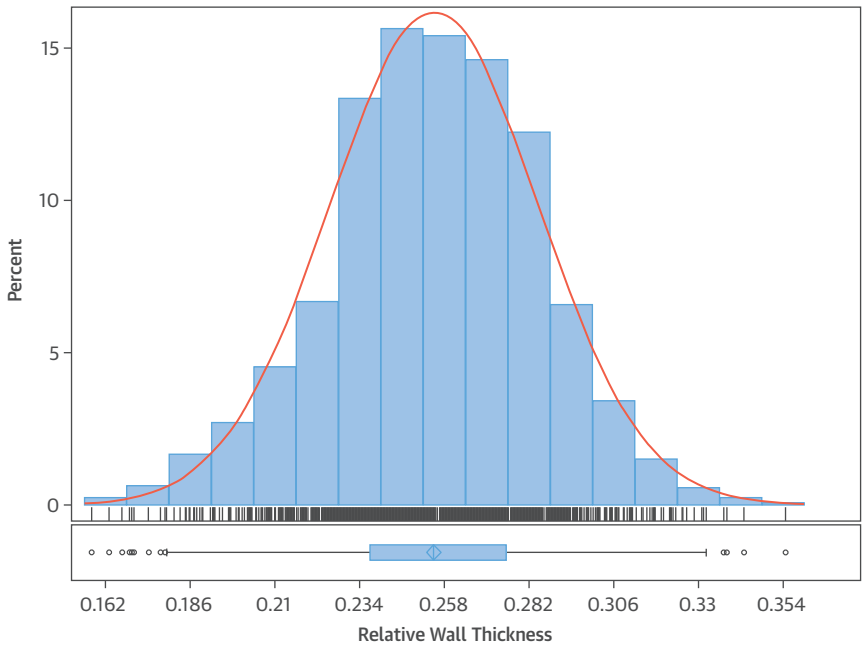
TABLE 1 Patient Characteristics

	Low RWT (<0.24) (n = 414)	High RWT (≥0.24) (n = 846)
Age at enrollment, yrs	61.2 ± 11.0	65.7 ± 10.5*
Female	22	35*
CRT-D assigned therapy	58	61
Ischemic cardiomyopathy	43	45
Diabetes	30	30
Hypertension	57	66*
Smoking	14	9*
Prior atrial arrhythmia	10	12
Prior ventricular arrhythmia	9	5*
Prior HF hospitalization	40	38
Prior CABG	23	22
Antiarrhythmic treatment	8	6
ACE inhibitor or ARB	97	96
Aspirin	58	63
Beta-blocker	95	93
Diuretic	71	67
Statin	61	65
QRS duration, ms	168.0 ± 21.3	160.6 ± 17.7*
Heart rate, beats/min	69.1 ± 11.0	67.9 ± 10.9*
BMI, kg/m^2	29.0 ± 5.2	28.3 ± 5.1*
Creatinine, mg/dl	1.15 ± 0.31	1.13 ± 0.32
BNP, pg/ml	147.5 ± 185.2	100.9 ± 128.4*
SBP, mm Hg	118.5 ± 16.6	124.8 ± 17.0*
LVEF, %	26.8 ± 3.4	29.7 ± 3.1*
LVEDV indexed by BSA, ml/m^2	147.3 ± 35.3	115.6 ± 20.1*
LVESV indexed by BSA, ml/m^2	108.3 ± 28.8	81.5 ± 15.7*
LAV indexed by BSA, ml/m^2	52.4 ± 10.8	44.5 ± 8.6*

Values are mean ± SD or %. *p < 0.05.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BSA = body surface area; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; HF = heart failure; LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RWT = relative wall thickness; SBP = systolic blood pressure.

FIGURE 1 RWT Distribution



Relative wall thickness (RWT) was normally distributed among 1,260 study patients (0.26 ± 0.03).

American Society of Echocardiography protocols (11). Linear measures were obtained either directly from 2-dimensional echocardiograms or from 2-dimensional-directed M-mode echocardiograms, using whichever was of better quality. Septal wall thickness (SWT) and posterior wall thickness (PWT) were assessed using linear measurements in parasternal long-axis view images as previously suggested. RWT was calculated as 2 times PWT divided by the LV diastolic diameter (11). A second method of measuring RWT (the sum of SWT and PWT divided by LV diastolic diameter) was also used to examine the consistency of the results (12).

The coefficients of variation for SWT and PWT were 9.6% and 10.3%, respectively. Patients were dichotomized between the lowest RWT tertile (<0.24) and the upper 2 tertiles (≥0.24), as pre-specified in this substudy.

The primary endpoint was the combined endpoint of VT or VF. Secondary endpoints included the following separate endpoints: VT, VF, fast VT (≥200 beats/min or VF), and the combined endpoint of VT, VF, and death.

STATISTICAL ANALYSIS. Baseline clinical characteristics were compared between RWT subgroups using the chi-square or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Categorical data are presented as frequency and percentage and continuous variables as mean ± SD or median and corresponding interquartile range.

The cumulative probability of VA or mortality by RWT subgroups was graphically displayed according to the method of Kaplan and Meier, with comparison of groups by the log-rank test. Multivariable Cox proportional hazards regression analysis was used to assess the association of RWT with reducing the risk

TABLE 2 Risk of VT/VF* by Model

Models†	HR†	95% CI	p Value	AIC†
Baseline†				3,441.66
RWT, per 0.01-U decrement	1.12	1.07–1.17	<0.001	3,420.12
LVEDV indexed by BSA, per 10 ml/m^2	1.09	1.05–1.12	<0.001	3,425.21
LVESV indexed by BSA, per 10 ml/m^2	1.10	1.06–1.15	<0.001	3,425.87
LVEF, %, per unit percentage	0.96	0.93–0.99	0.021	3,438.42
LAV indexed by BSA, per 10 ml/m^2	1.23	1.10–1.38	<0.001	3,431.03
LV mass indexed by BSA, per 10 g/m^2	1.05	0.99–1.12	0.125	3,441.38
LV mass/LVEDV ratio, per 0.01-U decrement	1.25	1.13–1.38	<0.001	3,424.38

*258 events. †Findings regarding risk associated with each echocardiographic parameter were obtained from separate models, each adjusted for the following covariates: treatment arm, female sex, glomerular filtration rate, previous myocardial infarction, New York Heart Association class, QRS duration ≥150 ms, SBP, previous ventricular arrhythmia (VA), and age at enrollment.

AIC = Akaike Information Criterion; HR = hazard ratio; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

TABLE 3 Comparison of Predictive Value of Different Variables for VT/VF*

Models†	Wald p Value	HR	95% CI	Log Likelihood Ratio	Chi-Square Difference‡	Likelihood Ratio Test p Value
Baseline				3,423.66		
Models with LVEDV						
LVEDV indexed by BSA, per 10 ml/m^2	<0.001	1.09	1.05–1.12	3,405.21	18.46	<0.001
LVEDV indexed by BSA, per 10 ml/m^2	0.096	1.04	0.99–1.09	3,397.41	26.26	<0.001
RWT, per 0.01-U decrement	0.005	1.08	1.02–1.15			0.005
Models with LVESV						
LVESV indexed by BSA, per 10 ml/m^2	<0.001	1.10	1.06–1.15	3,405.87	17.80	<0.001
LVESV indexed by BSA, per 10 ml/m^2	0.134	1.05	0.99–1.11	3,397.93	25.73	<0.001
RWT, per 0.01-U decrement	0.005	1.09	1.03–1.15			0.005
Models with LVEF						
LVEF, %, per unit percentage	0.021	0.96	0.93–0.99	3,418.42	5.24	0.022
LVEF, %, per unit percentage	0.979	1.00	0.96–1.04	3,400.11	23.55	<0.001
RWT, per 0.01-U decrement	<0.001	1.12	1.06–1.17			<0.001
Models with LAV						
LAV indexed by BSA, per 10 ml/m^2	<0.001	1.23	1.10–1.38	3,411.03	12.63	<0.001
LAV indexed by BSA, per 10 ml/m^2	0.153	1.10	0.97–1.25	3,398.11	25.55	<0.001
RWT, per 0.01-U decrement	<0.001	1.10	1.04–1.15			<0.001
Models with LV mass						
LV mass indexed by BSA, per 10 g/m^2	0.125	1.05	0.99–1.12	3,421.38	2.29	0.130
LV mass indexed by BSA, per 10 g/m^2	0.43	1.03	0.96–1.09	3,399.50	24.16	<0.001
RWT, per 0.01-U decrement	<0.001	1.11	1.06–1.16			<0.001

*Values added to the baseline multivariate model alone and together with RWT. †Findings regarding risk associated with each echocardiographic parameter were obtained from separate models, each adjusted for the following covariates: treatment arm, female sex, glomerular filtration rate, previous myocardial infarction, New York Heart Association functional class, QRS duration ≥150 ms, SBP, previous VA, and age at enrollment. ‡The chi-square difference was calculated by deducting the chi-square of each model from the chi-square of the baseline model (83.30).

Abbreviations as in Tables 1 and 2.

of VT/VF, VT, VF, fast VT, and the combined endpoint of VT/VF/death.

Covariates included in the multivariate models were identified using a best subset procedure for the VT/VF endpoint, choosing among a wide variety of available baseline measures with the additional stipulation that they needed to be statistically significant with an individual p value <0.05 for inclusion. Thus, all models were adjusted for CRT-D therapy, female sex, glomerular filtration rate, previous myocardial infarction, NYHA functional class, QRS duration ≥150 ms, systolic blood pressure, previous VA, and age at enrollment.

TABLE 4 Risk of VT and Death by Model*

Models†	HR†	95% CI	p Value	AIC
VT/VF				
RWT, per 0.01-U decrement	1.12	1.07–1.17	<0.001	3,420.12
LVEDD, per cm increase	1.59	1.28–1.96	<0.001	3,426.92
LVPWT, per mm decrease	1.32	1.10–1.60	0.003	3,435.03
LVSWT, per mm decrease	1.32	1.11–1.57	0.002	3,433.68
VT/VF/death				
RWT, per 0.01-U decrement	1.10	1.05–1.14	<0.001	4,401.72
LVEDD, per cm increase	1.58	1.30–1.91	<0.001	4,402.24
LVPWT, per mm decrease	1.20	1.02–1.42	0.027	4,417.60
LVSWT, per mm decrease	1.19	1.02–1.39	0.024	4,417.37

*332 events. †Findings regarding risk associated with each echocardiographic parameter were obtained from separate models, each adjusted for the following covariates: treatment arm, female sex, glomerular filtration rate, previous myocardial infarction, New York Heart Association class, QRS duration ≥150 ms, SBP, previous VA, and age at enrollment.

LVEDD = left ventricular end-diastolic diameter; LVPWT = left ventricular posterior wall thickness; LVSWT = left ventricular septal wall thickness; other abbreviations as in Tables 1 and 2.

For comparison of the predictive value of RWT with other commonly used echocardiographic variables in a multivariable model setting, the Akaike information criterion (AIC) was used as a measure of model fit, due to the comparisons necessary among nonnested models. Separate multivariable models were estimated for each echocardiographic parameter, and the AIC values were compared. The components of RWT, left ventricular end-diastolic diameter (LVEDD) and LVPWT, were also compared using AIC values with the same multivariable adjustment. Finally, both the continuous and dichotomized (at the first tertile) RWT values were fit into multivariable models for a variety of VA outcomes.

Additionally, we analyzed the incremental increase to the predictive value of the model when RWT was entered into a multivariate model in conjunction with each echocardiographic variable in a pairwise fashion.

This was done by comparing the fit of the multivariate model with an echocardiographic variable with the model after adding RWT. Because these models were nested, we used a likelihood ratio test for the overall fit of the model, whereas the Wald test was used to assess the significance of the hazard ratio (HR) for RWT. In a separate analysis, the relationship between RWT percent changes from baseline to follow-up and the risk of the primary and secondary endpoints subsequent to the 1-year echocardiogram (landmark-type analysis) was assessed using Cox proportional hazards regression, again with the same multivariable adjustments.

All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant. Analyses were carried out with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

The baseline clinical characteristics of 1,260 study patients dichotomized into low (<0.24, lowest tertile) and high RWT (≥0.24) are shown in **Table 1**. (Further separation into 3 tertiles is shown in Online Table 1).

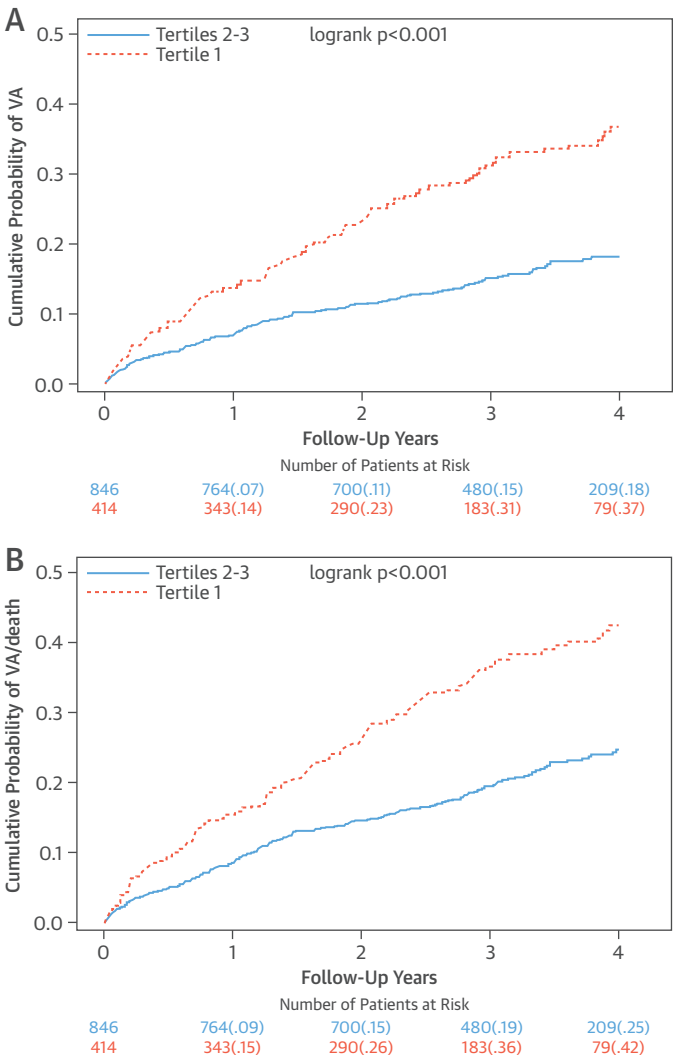
Patients with low RWT were younger than patients with high RWT but had a higher frequency of clinical characteristics associated with more advanced HF, such as lower LVEF, larger cardiac volumes, wider baseline QRS duration, higher B-type natriuretic peptide (BNP) levels, and a greater incidence of previous VA >3 months prior to enrollment. The high RWT subgroup had a greater proportion of women and a lower proportion of smokers.

RELATIONSHIP BETWEEN RWT AND VA. RWT was normally distributed among study patients (0.26 ± 0.03) (**Figure 1**). We compared the risk associated with several echocardiographic parameters (including left ventricular end-diastolic volume [LVEDV], LV end-systolic volume, left atrial volume, LVEF, LV mass, and LV mass/LVEDV ratio) by constructing separate multivariate models for the endpoint of VA that included each echocardiographic parameter at a time. (The baseline multivariate model is shown in Online Table 2.)

The comparison of the model fit was assessed using the AIC (**Table 2**, further detailed comparison in Online Table 3). The model that included RWT as an echocardiographic measure had the best fit (lowest AIC value), thereby suggesting that RWT is the best echocardiographic variable in predicting the risk of VA compared with other commonly used echocardiographic parameters.

In a second analysis, we compared the incremental increase to the predictive value of each model when RWT was entered into a multivariate model with each echocardiographic variable in a pairwise fashion (compared with the baseline model of each echocardiographic variable). The comparison of the model fit was assessed using the likelihood ratio test, whereas the Wald test was used to assess the significance of the HR for RWT (**Table 3**). Accordingly, RWT was a significant and superior predictor even when combined with other echocardiographic variables and added significantly to the predictive capacity of all of the models (lower log likelihood ratio).

FIGURE 2 Event Probability by RWT



Patients with low relative wall thickness (RWT) (<0.24 [lower tertile]) **(orange)** had a significantly higher risk for **(A)** ventricular arrhythmia (VA) and **(B)** VA or death compared with patients with high RWT (≥0.24 [2 upper tertiles]) **(blue)**. *The values in the parentheses are Kaplan-Meier event rates.

TABLE 5 Risk of VT by RWT*

Outcome (Number of Events)	Continuous			RWT <0.24 Versus RWT ≥0.24		
	HR†	95% CI	p Value	HR‡	95% CI	p Value
VT/VF (n = 258)	1.12	1.07–1.17	<0.001	1.83	1.42–2.37	<0.001
VT ≥200/VF (n = 161)	1.15	1.09–1.21	<.001	1.93	1.39–2.66	<0.001
VT/VF/death (n = 332)	1.10	1.05–1.14	<0.001	1.68	1.37–2.10	<0.001
VT (n = 221)	1.11	1.06–1.17	<0.001	1.91	1.45–2.52	<0.001
VF (n = 73)	1.08	1.00–1.17	0.065	1.61	0.99–2.60	0.054

*Adjusted for CRT-D therapy, female sex, glomerular filtration rate, previous myocardial infarction, New York Heart Association class, QRS duration ≥150 ms, SBP, previous VA, and age at enrollment. †HR per 0.01-unit decrement of RWT. ‡HR for the lowest RWT tertile <0.24 versus upper 2 tertiles ≥0.24.

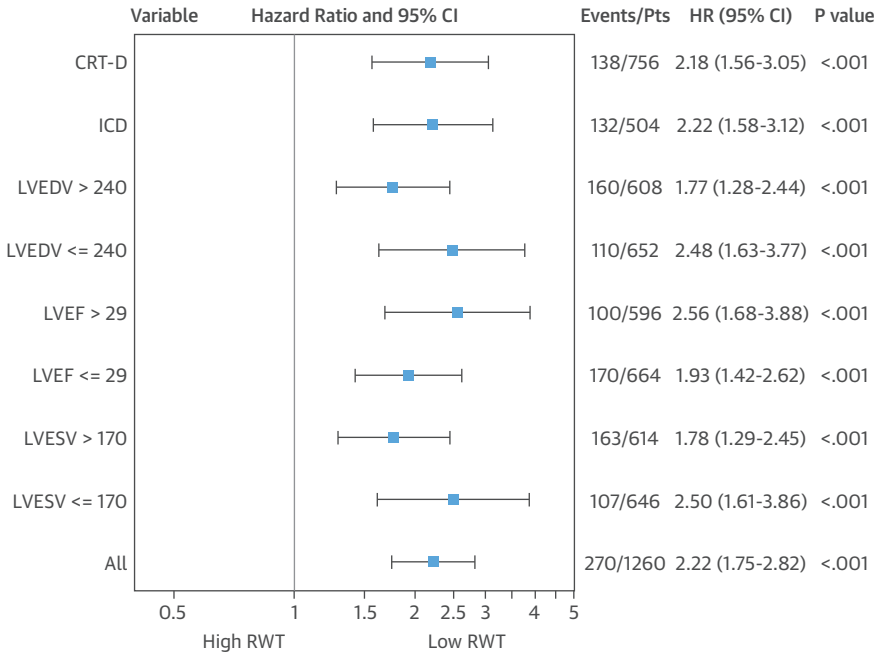
Abbreviations as in Tables 1 and 2.

The 2 components of RWT, LVEDD and LVPWT, were significant independent predictors of VT/VF and VT/VF/death. LVEDD was a better predictor versus LVPWT (lower AIC); however, these relationships existed in an opposite manner: whereas wider LVEDD was related to increased hazard, lower LVPWT was harmful (Table 4). Importantly, the model with RWT had a better fit compared with its 2 components and with the LV mass/LVEDV ratio (Tables 2 and 4).

Patients with low RWT (<0.24 [lower tertile] vs. ≥0.24 [2 upper tertiles]) had a significantly higher risk for VA and VA/death events (Figures 2A and 2B). Consistent with these findings, multivariable analysis demonstrated that lower RWT as either categorical or continuous (i.e., every 0.01-U decrease in RWT) variable was significantly related to higher risk of the entire spectrum of VA and combined outcome of VA or death (Table 5). These findings were consistently significant, even after further adjustments to baseline differences (BNP, body mass index, and smoking), and in all pre-specified subgroups (Figure 3). Results were also consistent when an alternative formula was used for measuring RWT (SWT + PWT divided by LVEDD); each 0.01-U decrease in RWT was associated with a respective 11% (HR: 0.89; 95% CI: 0.86 to 0.93; $p < 0.001$) and 9% (HR: 0.91; 95% CI: 0.88 to 0.95; $p < 0.001$) increase in the risk of VA and VA/death, respectively.

THE EFFECT OF CRT-D ON RWT. CRT-D therapy was associated with a greater increase in RWT compared with ICD therapy at 12 months (4.6 ± 6.8% vs. 1.5 ± 2.7%; $p < 0.001$). Among all study patients, Kaplan-Meier survival analysis (Figure 4) showed that the cumulative probability of a first occurrence of VT/VF 3 years after assessment of echocardiographic

FIGURE 3 Multivariable Analysis of VA Risk by RWT

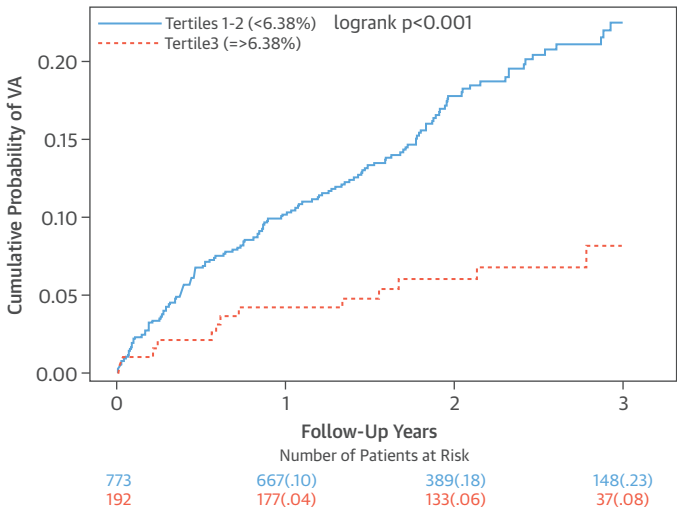


The risk for ventricular arrhythmia (VA) was consistently and significantly higher with low relative wall thickness (RWT) in the pre-specified echocardiographic and treatment arm subgroups (each $p < 0.001$). CRT-D = cardiac resynchronization therapy with defibrillator; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

response was significantly lower in those with increased RWT (greater than the upper tertile percent change in RWT) compared with those with lower changes in RWT at 12 months. Accordingly, in a multivariable model (**Table 6**), every 10% increase of RWT at 12 months with CRT-D was associated with 34% (p = 0.027) and 36% (p = 0.009) reductions in the rates of subsequent VA events and subsequent VA/death, respectively.

Baseline RWT was a significant predictor of VT/VF in both the ischemic and nonischemic subgroups. The HR for the ischemic subgroup was 1.11 (95% CI: 1.04 to 1.19; p = 0.001) and for the nonischemic subgroup was 1.12 (95% CI: 1.06 to 1.18; p < 0.0001; p for interaction = 0.937). The same finding was evident when the change of RWT at 12 months was assessed; hence, RWT increase at 12 months was associated with risk reduction for VT/VF in both subgroups (p for interaction = 0.478).

FIGURE 4 One-Year VA Risk by Change in RWT



Patients who had a higher relative wall thickness (RWT) increase after 12 months with cardiac resynchronization therapy **(red)** had lower risk for ventricular arrhythmia (VA) versus those with lower changes in RWT **(blue)**. The values in the parentheses are Kaplan-Meier event rates.

DISCUSSION

The present study provided several important novel findings regarding the prognostic importance of LV geometry and its relation to VA in patients with mild HF (LVEF ≤30%) and LBBB configuration: 1) RWT was the best echocardiographic predictor for VA events compared with commonly used echocardiographic measurements; 2) RWT was inversely related to the risk of VA in patients with eccentric hypertrophy; and 3) increased RWT after 1 year of CRT-D treatment was related to lower risk for VA in patients with eccentric hypertrophy (**Central Illustration**). These findings were consistent among all pre-specified patient subgroups and when an alternative RWT formula was used (including the dimensions of the posterior wall and the interventricular septum).

The relation between LV geometry and clinical outcome was originally assessed in healthy controls participating in the Framingham Heart Study. The development of concentric hypertrophy was shown to carry the worst prognosis, followed by eccentric hypertrophy, concentric remodeling, and normal morphology; these groupings were defined by distinct cutoffs related to relative LV mass and relative wall thickness (13). Several studies (8,14,15) described the same relation between the remodeling morphologies and cardiac morbidity and mortality, primarily in patients with hypertension.

There is a paucity of data, however, on the relation between LV geometry, in particular eccentric hypertrophy, and VA. St. John Sutton et al. (16) showed that in patients with ischemic cardiomyopathy, larger end-diastolic and end-systolic volumes were associated with increased incidence of VT and premature ventricular complexes; however, in a multivariable model, LVEF was a stronger predictor for this outcome. Draper et al. (17) demonstrated that in patients with a reduced LVEF (≤45%) and ICD therapy, eccentric hypertrophy was associated with a higher risk for VT/VF compared with normal and concentric remodeling. Yet, those investigators did not report the effect of different RWT values within the eccentric hypertrophy group nor was there a CRT-D therapy group.

In the present study, almost all of the patients had eccentric hypertrophy (RWT <0.32), and only a few had normal geometry (0.32 < RWT <0.42), as one would expect in the case of severe systolic HF leading

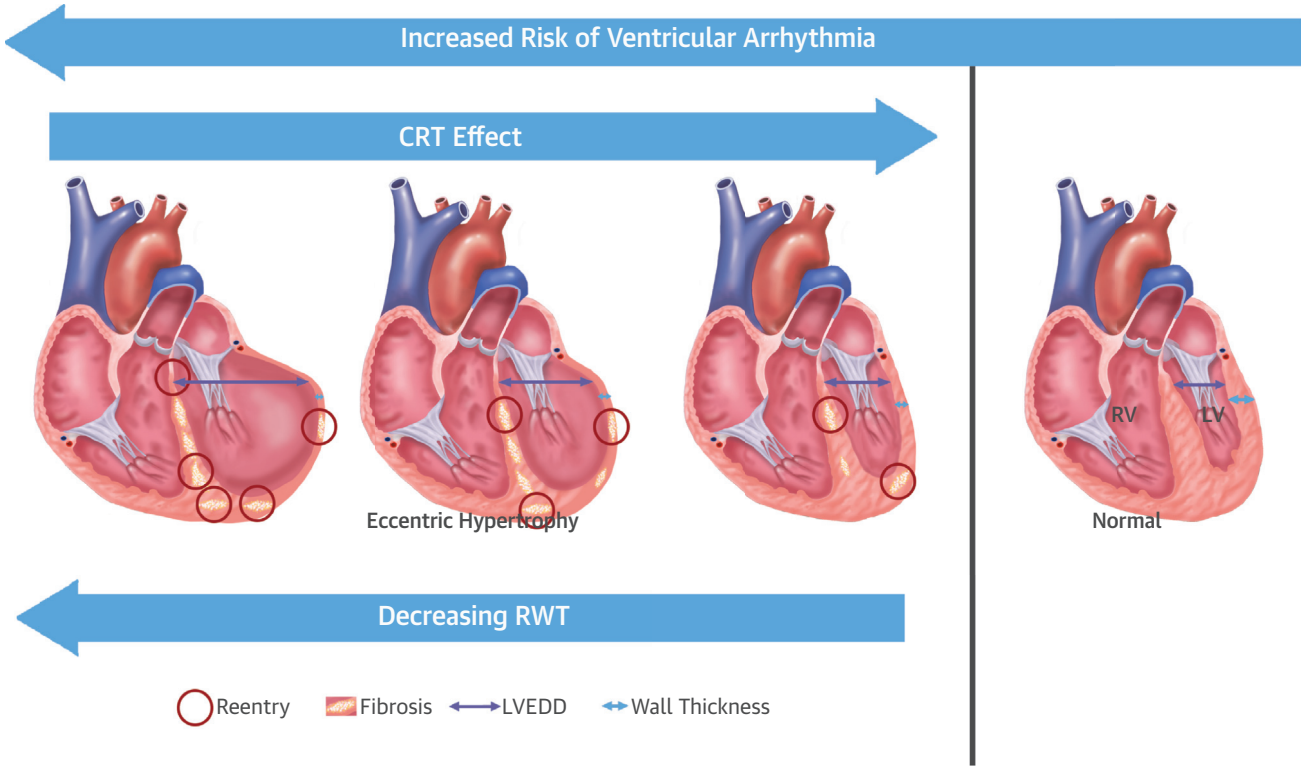
TABLE 6 RWT Change During 12 Months and Risk of Subsequent VAs

Outcome (Number of Events)	HR*	95% CI	p Value
VT/VF (n = 153)	0.66	0.45-0.95	0.027
VT ≥200/VF (n = 95)	0.68	0.41-1.14	0.141
VT/VF/death (n = 194)	0.64	0.46-0.89	0.009
VT (n = 133)	0.68	0.46-1.00	0.052
VF (n = 39)	0.51	0.23-1.16	0.108

*HR per 10% increase in RWT at 12 months compared with baseline. Adjusted for CRT-D therapy, female sex, glomerular filtration rate, previous myocardial infarction, New York Heart Association functional class, QRS duration ≥150 ms, SBP, previous VA, and age at enrollment.

Abbreviations as in **Tables 1 and 2**.

CENTRAL ILLUSTRATION **Relative Wall Thickness and Risk of Ventricular Arrhythmias**



Biton, Y. et al. J Am Coll Cardiol. 2016; 67(3):303–12.

Remodeling of the left ventricle (LV) can be determined by echocardiographic measurement of relative wall thickness (RWT); as RWT decreases (leading to eccentric hypertrophy) and left ventricular end-diastolic diameter (LVEDD) increases, the risk of ventricular arrhythmias rises. In patients with heart failure, the remodeling process induces fibrosis and scar formation that serves as a substrate for reentry circuits. Treatment with cardiac resynchronization therapy (CRT) helps reverse these effects. RV = right ventricle.

to dilated cardiomyopathy (18). Therefore, we were able to further support previous observations and provide incremental data demonstrating that in patients with mild HF, with either ischemic or non-ischemic cardiomyopathy, the magnitude of RWT (a measure of baseline eccentric hypertrophy) rather than just the categorization of LV geometry itself, could predict the risk for VA and mortality. We showed an inverse relationship between RWT and VA risk: the lower the RWT measured, the higher the risk for VA. This conclusion is also supported by our observation that among patients treated with CRT-D, a pronounced increase in RWT after 1 year (i.e., the heart becomes less "eccentric" and more normal in configuration) was associated with a significant reduction in the risk for VA or death.

Several mechanisms could potentially explain our findings. The remodeling process of the diseased heart is characterized by the replacement of necrotized myocytes with fibroblasts, which in turn increase collagen formation throughout the heart (19,20). This process induces fibrosis and scar formation that can potentially cause even healthy myocytes to undergo apoptosis; this paradigm is known to serve as a substrate for reentry circuits, early after-depolarizations, and the formation of VA, especially in patients with enlarged ventricles with slowed impulse propagation velocities over fibrotic tissue (21,22). Additional evidence shows that fibrosis enhances the ability of oxidative stress to induce spontaneous VF (23). Previous clinical trials showed a correlation between the degree of fibrosis, as measured by cardiac magnetic resonance imaging, and the risk of VA (24,25). The risk for VA also was associated with the degree of adverse remodeling, as measured by LVEDV in other trials (26). RWT is directly correlated with wall thickness and inversely correlated with LVEDV. Thus, among patients with

eccentric hypertrophy, the magnitude of RWT can mirror the extent of LV fibrosis and scarring on one hand and the extent of the remodeling process on the other hand. In the current study, both of these measures (wall thickness as a measure of wall fibrosis and diastolic diameter as a measure of remodeling) were independently associated with the risk of VA. Importantly, RWT had a higher predictive capacity compared with its own components. Thus, patients with very low RWT have larger LV volumes and thinner fibrotic walls, pre-disposing the patients to VA.

STUDY LIMITATIONS. First, this was a retrospective, nonrandomized post-hoc study. Although multivariate analysis showed higher risk of VA for patients with low RWT, after adjustment for many confounders, this was not a prospective trial and so possible unmeasured confounders may have biased the results; therefore, our results should be interpreted as hypothesis generating. Second, we only included patients with LBBB morphology because CRT-D benefit was shown to be limited to this subgroup; thus, we excluded approximately one-third of the original study patients. It should be noted that LBBB was not a pre-specified variable in the MADIT-CRT study. Lastly, the goal of our research was to show the incremental value of RWT compared with other echocardiographic variables and not necessarily to comprehensively develop the best model for the prediction of VT/VF.

Further studies, preferably randomized controlled clinical trials, are needed to corroborate our findings, provide better understanding of the relationship between RWT and VA, and more clearly define the evolution of RWT in patients with CRT therapy.

CONCLUSIONS

Defining the baseline degree of eccentric hypertrophy using RWT measurement can be useful for prediction of VA in patients with impaired LVEF and mild HF. Furthermore, among patients implanted with a CRT-D device, the magnitude of RWT increase attributed to CRT-D can predict VA risk as well.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: RWT is inversely related to the risk of VT in patients with systolic HF and LBBB.

TRANSLATIONAL OUTLOOK: Prospective clinical studies are necessary to confirm the therapeutic implications of RWT in patients with eccentric hypertrophy with regard to pharmacological treatment, ICD programming, and cardiac resynchronization.

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APPENDIX For supplemental tables, please see the online version of this article.