

# CHA<sub>2</sub>DS<sub>2</sub>-VASc Score and the Risk of Ventricular Tachyarrhythmic Events and Mortality in MADIT-CRT

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**Background**—We hypothesized that multiple cardiovascular comorbidities, incorporated in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, may be useful in the assessment of ventricular tachyarrhythmias (VTAs) and mortality risk in heart failure (HF) patients.

**Methods and Results**—We evaluated the association between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (dichotomized as high at the upper quartile [ $\geq 5$ ] and further assessed as a continuous measure) and the risk of VTA and death among 1804 patients enrolled in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). A high CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $n=464$ ; 26%) was inversely associated with the risk of any VTA (hazard ratio [HR]: 0.64;  $P=0.001$ ), fast VTA  $>200$  beats/min (HR: 0.51;  $P<0.001$ ), and appropriate implantable cardioverter-defibrillator shocks (HR: 0.60;  $P<0.001$ ). In contrast, a high score was directly correlated with mortality risk (HR: 1.92;  $P<0.001$ ) and the risk of HF or death (HR: 1.60;  $P<0.001$ ). Consistently, each 1-U increment in CHA<sub>2</sub>DS<sub>2</sub>-VASc was associated with a significant 13% ( $P=0.003$ ) reduction in VTA risk but a corresponding 33% ( $P<0.001$ ) increase in mortality risk. Patients with a high CHA<sub>2</sub>DS<sub>2</sub>-VASc score and left bundle-branch block derived a pronounced 53% ( $P<0.001$ ) reduction in the risk of HF or death with cardiac resynchronization therapy with defibrillator versus implantable cardioverter-defibrillator-only therapy.

**Conclusions**—Our findings suggest that a high CHA<sub>2</sub>DS<sub>2</sub>-VASc score can be used to identify patients with mild HF who have low VTA risk and high morbidity or mortality risk and may derive a pronounced clinical benefit from cardiac resynchronization therapy without a defibrillator. These data suggest a possible role for the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in device selection among candidates for biventricular pacing. (*J Am Heart Assoc.* 2020;9:e014353. DOI: 10.1161/JAHA.119.014353.)

**Key Words:** CHA<sub>2</sub>DS<sub>2</sub>-VASc • mortality • ventricular tachycardia

**M**ADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) was a randomized multicenter trial that evaluated patients with low left ventricular ejection fraction (LVEF), wide QRS, and mild heart failure (HF) symptoms who were receiving either cardiac resynchronization therapy with defibrillator (CRT-D) or implantable cardioverter-defibrillator (ICD) alone.<sup>1</sup> The study showed pronounced short- and long-term benefits

with CRT-D in study patients with left bundle-branch block (LBBB).<sup>1</sup> However, selection of patients for ICD or CRTD remains challenging even after 3 decades of research. Participants included in the study had various comorbid conditions typical of an HF population. CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive HF, hypertension, age  $\geq 75$  years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], and vascular disease, age 65–74 years, and sex category [female]) is a well-validated risk stratification score for predicting stroke in patients with atrial fibrillation (AF).<sup>2</sup> Many individual risk factors included in this score are also risk factors for all-cause mortality, morbidity, and arrhythmia. This score was also found to predict mortality,<sup>3</sup> AF,<sup>4</sup> and HF events.<sup>5</sup> Because data are limited on the yield of the score as a marker for ventricular tachyarrhythmia (VTA), morbidity, and mortality in mild HF patients who receive implantable device therapy, we sought to evaluate the usefulness of a widely used simple risk score for predicting (1) VTA events, (2) mortality and morbidity events, and (3) the benefit of CRT-D versus ICD only in LBBB patients enrolled in the trial.

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## Clinical Perspective

### What Is New?

- Patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of >5 are at high risk of mortality and heart failure events but have fewer ventricular arrhythmias and implantable cardioverter-defibrillator shock events.
- Patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of >5 and left bundle-branch block derived a pronounced reduction in the risk of heart failure or death with cardiac resynchronization therapy with defibrillator versus defibrillator-only therapy.

### What Are the Clinical Implications?

- These findings suggest that a high CHA<sub>2</sub>DS<sub>2</sub>-VASc score can be used to identify patients with low arrhythmic risk and high morbidity or mortality risk who may derive a pronounced clinical benefit from cardiac resynchronization therapy without a defibrillator.

## Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

MADIT-CRT was approved by the institutional review board at each of the participating centers.<sup>1</sup> All patients provided written informed consent.

## Study Patients

This study population comprised patients who were enrolled in MADIT-CRT.<sup>1</sup> The study design and primary results of MADIT-CRT have been published elsewhere. In brief, the study included 1820 patients with HF, LVEF ≤30%, and prolonged intraventricular conduction with QRS ≥130 ms. Patients with ischemic cardiomyopathy were eligible for inclusion if they had New York Heart Association (NYHA) class I or II symptoms; patients with nonischemic cardiomyopathy were eligible if they had NYHA class II symptoms. Study patients were randomized in a 3:2 ratio to receive either CRT-D or ICD only, and they were stratified according to disease etiology (ischemic versus nonischemic cardiomyopathy). Important exclusions included reversible causes of nonischemic cardiomyopathy (eg, myocarditis), an existing indication for CRT, NYHA class III or IV in the 90 days preceding enrollment, pacemaker in situ, or myocardial infarction or coronary revascularization (coronary artery bypass grafting surgery or percutaneous coronary intervention) in the 90 days preceding enrollment. Data on CHA<sub>2</sub>DS<sub>2</sub>-VASc score components were available for 1804 patients (99%) who were enrolled in the trial and comprised this study sample.

## Follow-Up

The MADIT-CRT study started December 22, 2004, and was ended at the recommendation of the data and safety monitoring board on June 22, 2009. However, additional data collection on HF events, mortality, and arrhythmia end points were collected through December 31, 2009. Data on VTAs were collected via device interrogation and evaluated by an independent committee blinded to the treatment assignment and clinical characteristics of the patients.

## Device Programming and Interrogation

Commercially available transvenous devices (Boston Scientific) were used in the trial. Standard techniques to implant the CRT-D and ICD-only devices were used. Device testing and programming were performed as reported previously.<sup>6</sup> Devices were programmed to monitor plus therapy, with a protocol recommendation to a setting of the ventricular tachycardia (VT) zone at 180 beats/min and the ventricular fibrillation (VF) zone at 250 beats/min. Sensitivity was programmed according to physician discretion. Detection was 2.5 seconds for the VT zone and 1.0 second for the VF zone. The protocol recommended programming first therapy for the VT zone to burst-type antitachycardia pacing with 8 pulses at 88% of the measured cycle length and a 10-ms decrement between bursts, then shock therapy; second therapy was shock at the defibrillation threshold plus at least 10 J (if possible). The remaining therapies included maximal energy shocks. The ICDs were interrogated quarterly, after which ICD shocks and disks were sent to the core laboratory for categorization and final evaluation of detected arrhythmias. An arrhythmia episode was defined as any type of therapy rendered, including antitachycardia pacing and shock.

## Definitions and End Points

In the primary analysis, CHA<sub>2</sub>DS<sub>2</sub>-VASc was dichotomized at the approximate upper quartile (≥5 [defined as high] versus <5). In a secondary analysis, CHA<sub>2</sub>DS<sub>2</sub>-VASc was also assessed as a continuous measure, by 1-U increments.

The primary outcome measure of this study was any VTA event (VT or VF) detected by the implantable device and adjudicated by the study committee. Secondary outcome measures were (1) fast VTA (defined as >200 beats/min), (2) appropriate defibrillator therapies, (3) all-cause mortality, (4) the composite end point of HF or death, and (5) atrial arrhythmias and inappropriate device therapies.

## Statistical Analysis

Baseline characteristics according to comorbidity group were compared using the  $\chi^2$  test for categorical variables and the

nonparametric Kruskal–Wallis test for continuous variables. The cumulative probabilities of the primary outcome of any VT/VF and each secondary outcome by CHA<sub>2</sub>DS<sub>2</sub>-VAsC, and subsequently further stratified by treatment group, were determined with the Kaplan–Meier methodology and comparisons by means of the log-rank test. Multivariable Cox proportional hazards regression was used to estimate the relationship of CHA<sub>2</sub>DS<sub>2</sub>-VAsC on the various end points. Covariates in the multivariable model added to the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score were identified using the best subsets variable-reduction technique and with the stipulation that they also needed to be significant at <0.05. Final additional covariates included renal function, LBBB, antiarrhythmic medication, race, smoking, LVEF, and ischemic heart disease. To further validate the consistency of the association of the overall CHA<sub>2</sub>DS<sub>2</sub>-VAsC score (rather than a single component as the main contributor) with the main outcome measures, we carried out a sensitivity analyses in which one component of the score was taken out for each model at a time. All statistical tests were 2-sided, and *P*<0.05 was considered statistically significant. Statistical tests were not adjusted for multiplicity. The analyses were performed with SAS software (v9.3; SAS Institute).

## Results

### Patient Characteristics

The CHA<sub>2</sub>DS<sub>2</sub>-VAsC score distribution for the study population is shown in Figure 1 and was normal with a mean of 3.5±1.4. Baseline characteristics between patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC ≥5 and <5 are outlined in Table 1. There were no statistically significant differences in terms of assignment between CRT-D and ICD. The groups were similar regarding LVEF changes with treatment assignment, presence of LBBB at baseline, history of ventricular arrhythmias, and antiarrhythmic medications. As expected, patients with a CHA<sub>2</sub>DS<sub>2</sub>-VAsC score ≥5 were older, with a higher frequency of female sex, diabetes mellitus, ischemic heart disease, cerebral vascular events, and hypertension. In addition, these patients had higher serum creatinine levels, were less likely to be on β-blockers, and had relatively narrower QRS durations.

### CHA<sub>2</sub>DS<sub>2</sub>-VAsC and the Risk of VTA Events

Kaplan–Meier survival analysis showed that the rate of the primary outcome measure of any VTA at 4 years of follow-up was significantly lower among patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores ≥5 (20%) compared with the 4 lower CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores (28–31%; *P*=0.005 for the overall difference during follow-up among the 4 groups [Figure 2A]). Similarly, patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores ≥5 experienced a significantly lower rate of fast VTA events at 4 years of follow-up (11%)

compared with the 4 lower CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores (18–22%; *P*=0.002 for the overall difference during follow-up among the 5 groups [Figure 2A]).

Consistent with the univariate Kaplan–Meier findings, multivariate Cox proportional hazards regression analysis showed that a high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was inversely correlated with VTA risk (Table 2). Compared with those patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores <5, those with high scores (≥5) had a significantly lower risk of any VTA (36%; *P*=0.001) and corresponding 49% (*P*<0.001) and 40% (*P*<0.001) reductions in the risk of fast VTA and appropriate ICD therapies, respectively (Table 2).

Assessing CHA<sub>2</sub>DS<sub>2</sub>-VAsC score as a continuous measure showed that each 1-U increment in the score was associated with a corresponding 13% reduction of any VTA risk (*P*=0.003) and a 12% reduction of fast VTA risk (*P*<0.001).

Notably, high CHA<sub>2</sub>DS<sub>2</sub>-VAsC was not independently associated with the risk of atrial arrhythmias (HR: 1.01 [95% CI, 0.63–1.61]; *P*=0.97) and inappropriate device therapies (HR: 0.83 [95% CI, 0.60–1.15]; *P*=0.27; Table 3).

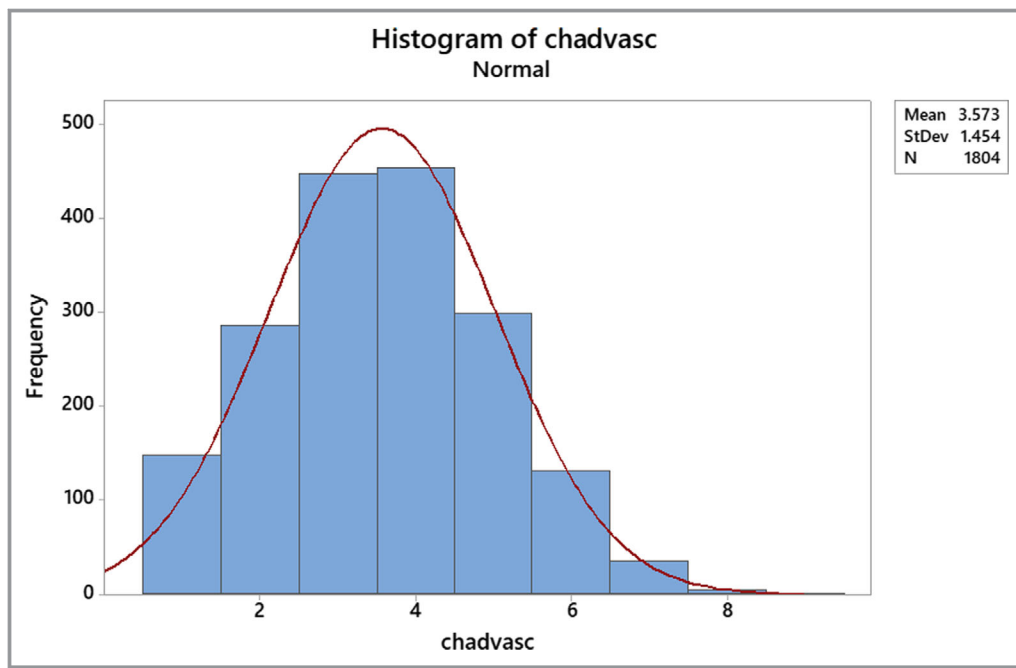
### CHA<sub>2</sub>DS<sub>2</sub>-VAsC and the Risk of All-Cause Mortality and HF Events

In contrast to the inverse relation with VTA risk, a high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was directly correlated with mortality and morbidity risk. Kaplan–Meier survival analysis showed that at 4 years of follow-up, the rate of all-cause mortality was significantly higher among patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores ≥5 (18%) and declined with lower CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores (7–14%; *P*<0.001 for the overall difference during follow-up among the 5 groups [Figure 3A]). Similarly, the rate of the composite end point of HF or death was also significantly higher among patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores ≥5 compared with the lower 4 groups (Figure 3B).

These findings persisted after multivariate adjustment (Table 3), demonstrating that CHA<sub>2</sub>DS<sub>2</sub>-VAsC score ≥5 was associated with a pronounced 92% (*P*<0.001) increase in the risk of all-cause mortality and with a 60% increased risk of HF or death (*P*<0.001) compared with patients with CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores <5. Assessing CHA<sub>2</sub>DS<sub>2</sub>-VAsC score as a continuous measure showed that each 1-U increment in the score was associated with a corresponding 33% increase in the risk of all-cause mortality (*P*<0.001) and a 29% increase in the risk of the composite end point of HF or death (*P*<0.001).

### Effect of CRT-D Versus ICD on HF or Death in LBBB Patients by CHA<sub>2</sub>DS<sub>2</sub>-VAsC

In MADIT-CRT the benefit of CRT was limited to patients with LBBB. Accordingly, we evaluated the benefit of CRT-D versus ICD-only therapy by CHA<sub>2</sub>DS<sub>2</sub>-VAsC score among study patients with LBBB. Kaplan–Meier survival analysis showed that among



**Figure 1.** Distribution of CHA<sub>2</sub>DS<sub>2</sub>-VASC scores in a multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy patients (MADIT-CRT [Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy]).

LBBB patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 5$ , treatment with CRT-D was associated with significantly lower rates of HF or death compared with ICD-only therapy (Figure 4A). Multivariate analysis consistently showed that among patients with a high score (CHA<sub>2</sub>DS<sub>2</sub>-VASC  $\geq 5$ ), CRT-D therapy was associated with a pronounced 53% reduction in the risk of HF or death compared with ICD-only therapy (HR: 0.47 [95% CI, 0.32–0.69];  $P < 0.001$ ).

### Sensitivity analysis

The inverse association between CHA<sub>2</sub>DS<sub>2</sub>-VASC (assessed as a continuous measure) and the risk of VTA remained consistent in a series of sensitivity analyses in which one component of the score was taken out for each model at a time. Furthermore, the direct correlation between CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 5$  and mortality remained consistent in a similar sensitivity analysis (all  $P < 0.001$  for 1-U change in CHA<sub>2</sub>DS<sub>2</sub>-VASC and the risk of VTA or death in all models). These findings suggest that the overall score is the main factor affecting outcomes rather than a single component within the score. Furthermore, the association between CHA<sub>2</sub>DS<sub>2</sub>-VASC score and the outcome measures remained consistent when assessed within the ICD and CRT-D groups separately (data not shown).

### Discussion

To our knowledge, this study is the first to assess the association between the cardiovascular comorbidities

incorporated into the CHA<sub>2</sub>DS<sub>2</sub>-VASC score and the risk of VTA among HF patients who received implantable device therapy. We showed that there is an inverse relation between CHA<sub>2</sub>DS<sub>2</sub>-VASC and the risk of VTA, including all VTA events detected by the device, fast VTAs, and appropriate ICD therapies, and that the life benefit of ICD therapy is lower among patients with a high CHA<sub>2</sub>DS<sub>2</sub>-VASC score. In contrast, there is a direct correlation between CHA<sub>2</sub>DS<sub>2</sub>-VASC and the risk of all-cause mortality and the risk of HF hospitalizations or death. We also showed that CRT is associated with a pronounced benefit in LBBB patients with a high CHA<sub>2</sub>DS<sub>2</sub>-VASC score, demonstrating a significant 53% reduction in the risk of HF events or death in this population. These findings suggest that the CHA<sub>2</sub>DS<sub>2</sub>-VASC score can be used to identify HF patients with lower arrhythmic risk and higher mortality and morbidity risk who will derive enhanced benefit from CRT but possibly a less benefit from an ICD.

### CHA<sub>2</sub>DS<sub>2</sub>-VASC Score: Morbidity, Mortality, and Ventricular Arrhythmic Risk

Surprisingly, CHA<sub>2</sub>DS<sub>2</sub>-VASC was found to have an inverse correlation to VT/VF. The higher the CHA<sub>2</sub>DS<sub>2</sub>-VASC score, the lower the number of VTA events. Likewise, CHA<sub>2</sub>DS<sub>2</sub>-VASC score negatively predicted ICD shocks. Nevertheless, and as expected, high CHA<sub>2</sub>DS<sub>2</sub>-VASC score did predict HF and mortality.

**Table 1.** Baseline Characteristics of Patients With CHA<sub>2</sub>DS<sub>2</sub>-VAsC Scores  $\geq 5$  and  $<5$ 

Clinical Characteristics	CHA <sub>2</sub> DS <sub>2</sub> -VAsC $<5$ (n=1333)	CHA <sub>2</sub> DS <sub>2</sub> -VAsC $\geq 5$ (n=471)	P Value
Age, y	61.3 $\pm$ 10.2	72.9 $\pm$ 7.1	$<0.001$
Female sex	290 (22)	160 (34)	$<0.001$
CRT-D	794 (60)	285 (61)	0.719
Ischemic heart disease	612 (46)	377 (80)	$<0.001$
LBBB	945 (71)	326 (69)	0.465
Prior congestive HF admissions	495 (38)	174 (38)	0.979
Cerebrovascular accident	19 (1)	97 (21)	$<0.001$
Diabetes mellitus	275 (21)	273 (58)	$<0.001$
Hypertension	712 (53)	429 (91)	$<0.001$
Past atrial arrhythmias	142 (11)	64 (14)	0.075
Past ventricular arrhythmias	97 (7)	29 (6)	0.415
Amiodarone	101 (8)	27 (6)	0.180
$\beta$ -Blocker	1254 (94)	427 (91)	0.011
Sotalol	4 (0)	1 (0)	1.000
QRS, ms	158.9 $\pm$ 20.2	155.7 $\pm$ 18.3	0.004
Body mass index	29.0 $\pm$ 5.4	28.0 $\pm$ 5.0	$<0.001$
Blood urea nitrogen	20.8 $\pm$ 8.4	23.7 $\pm$ 9.9	$<0.001$
Creatinine	1.14 $\pm$ 0.36	1.24 $\pm$ 0.38	$<0.001$
Glomerular filtration rate	71.9 $\pm$ 20.3	61.8 $\pm$ 18.8	$<0.001$
LVEF	28.9 $\pm$ 3.5	29.3 $\pm$ 3.2	0.053
LVEDV, mL/m <sup>2</sup>	254.1 $\pm$ 63.9	231.5 $\pm$ 51.6	$<0.001$
LVESV, mL/m <sup>2</sup>	181.7 $\pm$ 51.7	164.4 $\pm$ 41.3	$<0.001$

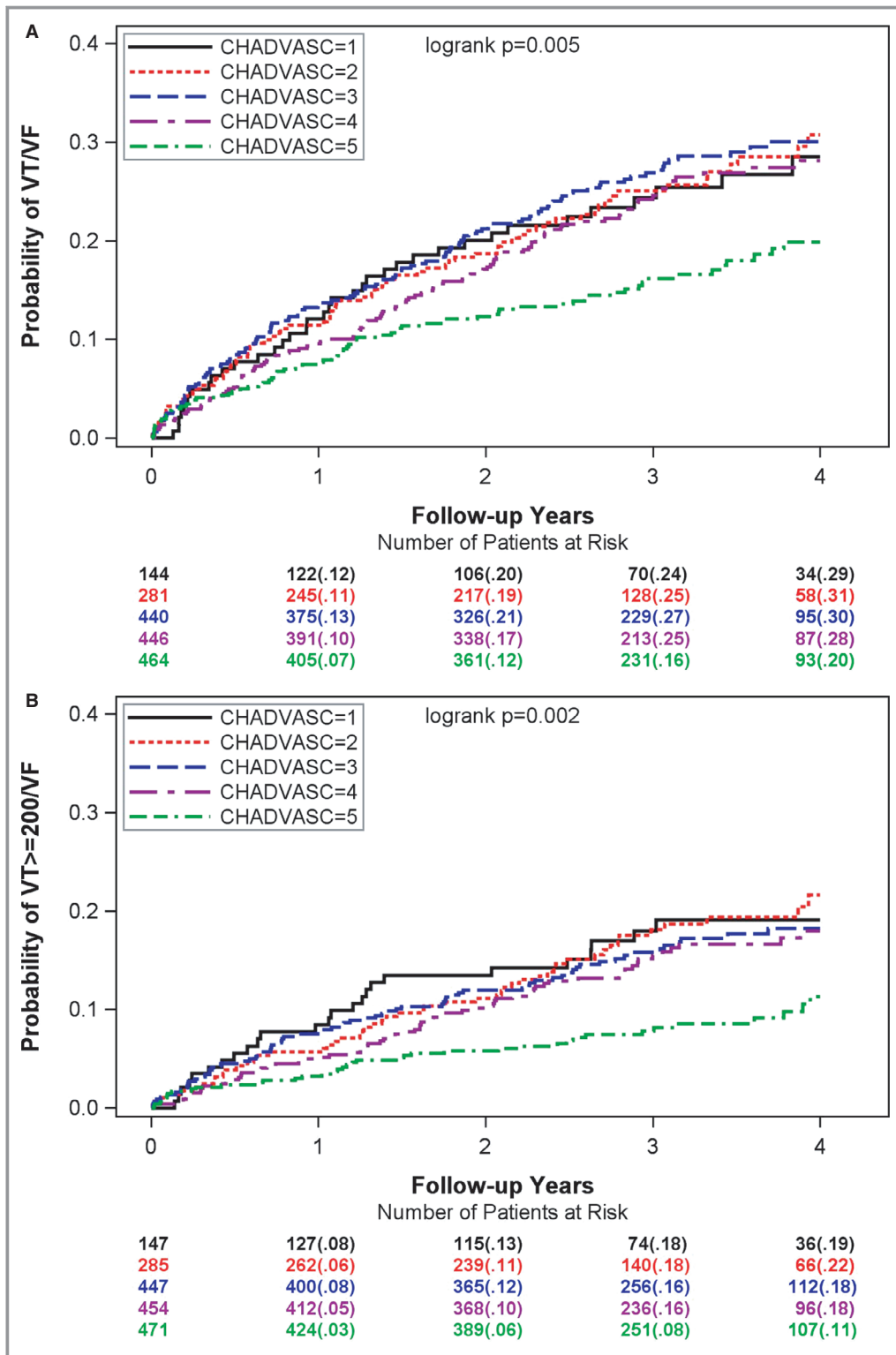
Data shown as mean $\pm$ SD or n (%). CRT-D indicates cardiac resynchronization therapy with defibrillator; HF, heart failure; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

Similar to other reports, CHA<sub>2</sub>DS<sub>2</sub>-VAsC was found to be predictive of mortality in a selected study cohort of patients with obstructive coronary artery disease, in patients with AF<sup>4</sup> and HF.<sup>5</sup> Our study showed that CHA<sub>2</sub>DS<sub>2</sub>-VAsC predicted mortality in a specified population of patients with low ejection fraction and mild HF symptoms—a different type of patients from the above-mentioned studies. HF patients often have multiple comorbid conditions. A previous study regarding MADIT-CRT patients found that there was no interaction between burden of comorbidity and reduction in death or nonfatal HF events associated with CRT-D compared with ICD.<sup>7</sup> However, in that study, patients were divided by categories based on comorbidity burden, with 0, 1, 2, and  $\geq 3$  comorbidities. Our study differs by method of risk assessment. The strength of CHA<sub>2</sub>DS<sub>2</sub>-VAsC is that it combines various cardiovascular comorbidities for the score. In our study, this score was found to reliably predict mortality and, even more, serve as a competing risk factor for other life-threatening events such as VTA. Of note, in our study, CHA<sub>2</sub>DS<sub>2</sub>-VAsC did not

predict AF. This is in contrast to previous studies in which CHA<sub>2</sub>DS<sub>2</sub>-VAsC was found to predict new-onset AF.<sup>4</sup> This difference could be attributed to the fact that our patient cohort consisted of sicker patients. In fact, it might be that CHA<sub>2</sub>DS<sub>2</sub>-VAsC predicts AF in healthier patients with longer life span.

### CHA<sub>2</sub>DS<sub>2</sub>-VAsC Score and the Benefit of CRT

The MADIT-CRT study showed pronounced short- and long-term benefits of the CRT-D in study patients with LBBB.<sup>1</sup> Our study showed that the results were consistent for patients with high CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores (Figure 4A) and low CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores (Figure 4B). However, our data suggest that patients with a low CHA<sub>2</sub>DS<sub>2</sub>-VAsC score benefit from both the CRT and the defibrillator components because the former reduces the risk of HF progression and mortality and the latter reduces the risk of arrhythmic mortality. In contrast, patients with a high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score appear to derive a pronounced reduction in the risk of HF events and



**Figure 2.** Cumulative probability of ventricular tachyarrhythmia events. **A**, Ventricular tachycardia/ventricular fibrillation (VT/VF). **B**, VT/VF >200. CHADSVASC indicates CHA<sub>2</sub>DS<sub>2</sub>-VASC score.

mortality from CRT but have a lower risk of arrhythmic mortality and thus may derive less benefit from the defibrillator component.

Selecting patients who could benefit from ICD remains challenging. ICDs have been shown to increase survival in patients with severe left ventricular dysfunction.<sup>1,8</sup> However,

**Table 2.** Multivariate Models: Association of CHA<sub>2</sub>DS<sub>2</sub>-VASc Score ≥5 Versus <5 With VTA Events

End Point	HR	95% CI	P Value
Any VT/VF	0.64	0.49–0.84	0.001
VT/VF >200 beats/min	0.51	0.36–0.74	<0.001
Appropriate ICD therapy	0.60	0.45–0.79	<0.001

Models adjusted for renal function, left bundle-branch block, antiarrhythmic medication, race, smoking, left ventricular ejection fraction, and ischemic heart disease. HR indicates hazard ratio; ICD, implantable cardioverter-defibrillator; VTA, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

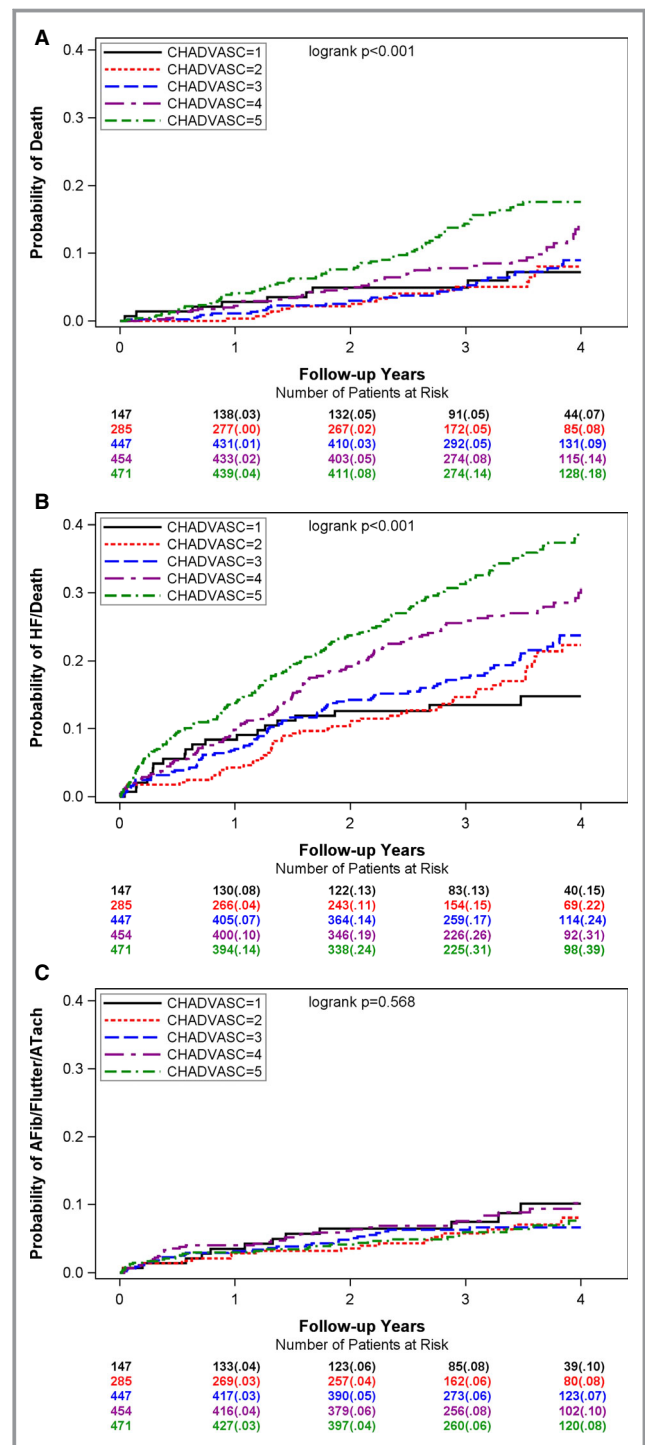
there are conflicting data regarding benefit of ICD in patients with more advanced HF, owing to the competing risk of death from causes other than sudden cardiac death. Therefore, improved risk-stratification tools are required to guide patient selection.

The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) showed no benefit of ICD over placebo in patients at NYHA class III, whereas there was a significant reduction in mortality in patients at NYHA class II.<sup>8</sup> Similarly, a subanalysis of the MUSTT (Multicenter Unsustained Tachycardia Trial) demonstrated a progressive increase in all-cause mortality with increased HF severity.<sup>9</sup> Nevertheless, the risk of arrhythmic death or cardiac arrest was not independently associated with NYHA functional class. All of the above-mentioned studies raise the concern that the benefit of ICDs may have an inverse correlation with the severity of HF. An additional limitation of the current patient-selection process is the use of the NYHA classification system. On one hand, the NYHA class itself has large variability; on the other hand, it usually changes with time in a specific patient. In contrast, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is a well-known validated score that is used on a daily basis for assessment of stroke risk in patients with AF.<sup>10</sup> Our findings suggest that CHA<sub>2</sub>DS<sub>2</sub>-VASc can also be useful in predicting those patients who will derive less benefit from ICDs because of the high rate of HF and mortality leading to low rates of arrhythmic events. These

**Table 3.** Multivariate Models: Association of CHA<sub>2</sub>DS<sub>2</sub>-VASc Score ≥5 Versus <5 With Non-VTA Events

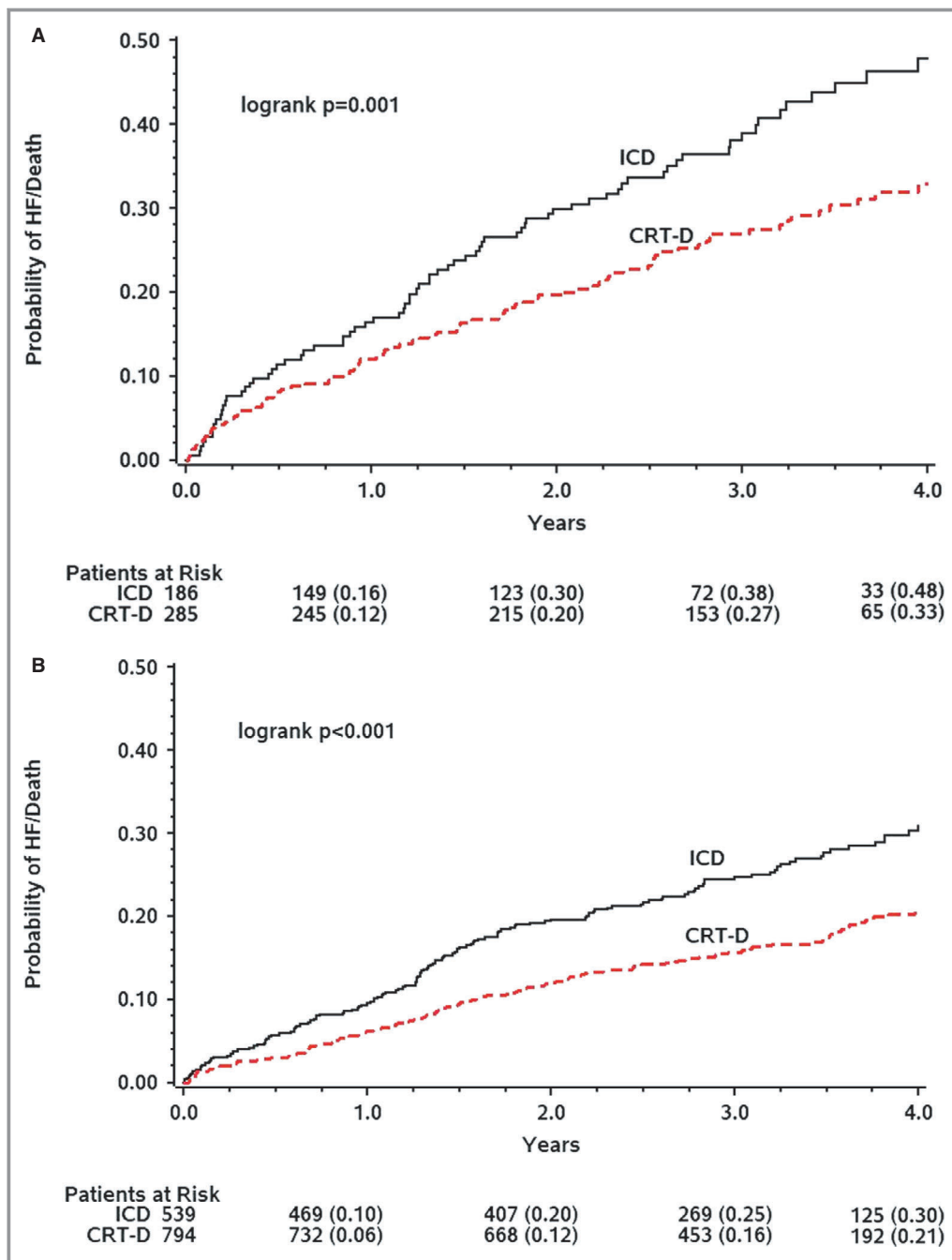
End Point	HR	95% CI	P Value
Atrial arrhythmia	1.01	0.63–1.61	0.97
Inappropriate ICD therapy	0.83	0.60–1.15	0.27
Death	1.92	1.38–2.67	<0.001
HF or death	1.60	1.29–1.99	<0.001

Models adjusted for renal function, left bundle-branch block, antiarrhythmic medication, race, smoking, left ventricular ejection fraction, and ischemic heart disease. HF indicates heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; VTA, ventricular tachyarrhythmia.



**Figure 3.** Cumulative probability of non-ventricular tachyarrhythmia events. **A**, Mortality. **B**, Heart failure (HF) or death. **C**, Atrial arrhythmias. CHADVASc indicates CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

findings suggest competing risk factors leading to death from nonarrhythmic causes in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥5, resulting in fewer VT/VF events, which translates to lower rates of appropriate ICD therapies. Accordingly, patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥5 and



**Figure 4.** Cumulative probability of heart failure (HF) or death events in cardiac resynchronization therapy with defibrillator (CRT-D) or implantable cardioverter-defibrillator (ICD). **A**, CHA<sub>2</sub>DS<sub>2</sub>-VAsc score  $\geq 5$  group. **B**, CHA<sub>2</sub>DS<sub>2</sub>-VAsc score  $< 5$  group.

LBBB were found to benefit more from CRT-D than ICD. In fact, our results are consistent in showing no benefit of ICD in this selected population but rather benefit from CRT.

Furthermore, a recent long-term outcome study in 1775 CRT recipients demonstrated that progressive HF death still represented the most frequent cause of death in patients surviving the first 5 years after CRT implant. In contrast, sudden cardiac death represented a low proportion of late

mortality regardless the presence of a defibrillator.<sup>11</sup> These findings also suggest that CRT without a defibrillator should be considered in selected patients with a wide QRS with a lower risk of arrhythmic mortality in whom the benefit of biventricular pacing for the prevention of HF mortality predominates.<sup>11</sup> These observations should lead to a hypothesis-generating study comparing CRT with pacemaker versus CRT-D in this patient population.



## Limitations

This study is a retrospective analysis of a prospective randomized controlled clinical trial. Data on the occurrence of VT/VF were derived from adjudicated device interrogations. Thus, lower rate episodes (ie, below the VT zone, which was mostly set to  $\geq 170$  beats/min) were not identified or included in this analysis. The number of AF events was also relatively low and may not be sufficient for analysis. Furthermore, this analysis period was relatively short, with half of patients followed up to 3 years and only a minority to 4 years; however, we assume that this trend will not change over time.

It should be noted that the present findings regarding the possible attenuated benefit of ICD in patients with high CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores are related to asymptomatic or mildly symptomatic left ventricular dysfunction; there are no current data regarding the risk among patients with more advanced HF symptoms. It should also be noted that despite the fact that the rate of life-threatening arrhythmic events ( $>200$  beats/min) was nearly 50% lower in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VAsC score  $\geq 5$ , it was still nonnegligible (2–3% per year). However, after accounting for the competing risk of death in this population, our data suggest that a high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score may be a marker of increased HF mortality versus arrhythmic mortality in candidates for CRT. The benefit of ICD in this subpopulation of patients with mild HF, low LVEF, and high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score should be further validated in prospective studies.

## Conclusions

In this study, we showed that patients with a CHA<sub>2</sub>DS<sub>2</sub>-VAsC score  $\geq 5$  have high mortality rates and few VT/VF events. Furthermore, these patients benefit more from CRT-D than ICD, leading to the postulation that these patients should be considered for CRT with pacemaker rather than CRT-D in cases of LBBB or no ICD at all in cases of non-LBBB. These findings may be used for improved device selection in this population.

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