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Added Value of 3- Versus 2-Dimensional Echocardiography Left Ventricular Ejection Fraction to Predict Arrhythmic Risk in Patients With Left Ventricular Dysfunction

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ABSTRACT

OBJECTIVES The study sought to evaluate the potential clinical impact of using 3-dimensional echocardiography (3DE) to measure left ventricular ejection fraction (LVEF) in patients considered for implantable cardioverter-defibrillator (ICD) implantation and to assess the predictive value of 3DE LVEF for arrhythmic events.

BACKGROUND ICD therapy is currently recommended to prevent sudden cardiac death in patients with symptomatic heart failure and LVEF ≤35%, and in asymptomatic patients with ischemic heart disease and LVEF ≤30%. Two-dimensional echocardiography (2DE) is currently used to calculate LVEF. However, 3DE has been reported to be more reproducible and accurate than 2DE to measure LVEF.

METHODS The study prospectively enrolled 172 patients with LV dysfunction (71% ischemic). Both 2DE and 3DE LVEF were obtained during the same study. The outcome was the occurrence of major arrhythmic events (sudden cardiac death, aborted cardiac arrest, appropriate ICD therapy).

RESULTS After a median follow up of 56 (range 18 to 65) months, major arrhythmic events occurred in 30% of the patients. Compared with 2DE, 3DE changed the assignment above or below the LVEF thresholds for ICD implantation in 20% of patients, most of them having 2DE LVEFs within ± 10% from threshold. By cause-specific hazard model, 3DE LVEF was the only independent predictor of the occurrence of major arrhythmic events.

CONCLUSIONS LVEF by 3DE was an independent predictor of major arrhythmic events and improved arrhythmic risk prediction in patients with LV dysfunction. When compared with 2DE LVEF, 3DE measurement of LVEF may change the decision to implant an ICD in a sizable number of patients. (J Am Coll Cardiol Img 2018;■:■-■)
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Current guidelines recommend the use of implantable cardioverter-defibrillators (ICDs) for primary prevention in patients with symptomatic heart failure and left ventricular ejection fraction (LVEF) ≤35%, and in asymptomatic patients with ischemic heart disease and LVEF ≤30%, to reduce the risk of sudden cardiac death (SCD) and all-cause mortality (1,2). However,

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ABBREVIATIONS AND ACRONYMS

2DE = 2-dimensional echocardiography

3DE = 3-dimensional echocardiography

CI = confidence interval

CMR = cardiac magnetic resonance

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

SCD = sudden cardiac death

the optimal imaging modality to assess LVEF remains to be determined (2,3).

In the era of multimodality imaging and increasing costs of health care, this issue becomes highly relevant, as LVEF measurements by different imaging modalities are not interchangeable and different imaging modalities have different costs and availability (4). Two-dimensional echocardiography (2DE) is the most frequently used imaging modality to assess LVEF, but it has been shown to have substantial intra- and interobserver variability and suboptimal accuracy and repeatability (5). Over the last decade, 3-dimensional echocardiography (3DE) has become increasingly implemented in clinical practice. 3DE provides a more accurate LVEF quantitation, as it avoids geometric assumptions and left ventricular (LV) foreshortening, has better reproducibility (including test-retest evaluations), and has incremental value to predict adverse outcomes in comparison with conventional 2DE (5–8).

However, the role of 3DE to improve arrhythmic risk prediction in patients with LV dysfunction has not been yet assessed. Accordingly, we sought to evaluate the potential clinical impact of using 3DE to measure LVEF in patients considered for ICD implantation and to assess the predictive value of 3DE LVEF for arrhythmic events in patients with ischemic and nonischemic LV dysfunction.

METHODS

STUDY POPULATION. We prospectively enrolled patients with ischemic or nonischemic LV dysfunction (LVEF<50%) and New York Heart Association (NYHA) functional class I to III, referred for an echocardiographic study to qualify them for an ICD implantation from October 2011 to July 2013. Ischemic cause of LV dysfunction was defined as stenosis >50% of the left main coronary artery or >70% of 1 or more major coronary arteries at angiography, previous myocardial infarction, or coronary revascularization. Patients without an ischemic cause were classified as having nonischemic LV dysfunction. Exclusion criteria at enrolment were unwillingness to be part of the study, history of unexplained syncope, aborted SCD or documented sustained ventricular tachycardia, insufficient acoustic window to allow the quantitation of 2DE LVEF without the infusion of contrast agents (i.e., more than 2 LV segments not adequately visualized), atrial fibrillation during the exam, myocardial infarction in the 40 days or revascularization in the 90 days preceding the enrollment, and more than moderate stenosis or regurgitation of any valve. Minimum follow up time after enrollment was 12 months.

Patients were seen in a dedicated outpatient clinic at regular intervals of 6 months, and a structured interview protocol was used to collect clinical data. Major arrhythmic events were defined as sustained ventricular tachycardia with hemodynamic impairment (hypotension, chest pain, altered mental status), SCD, aborted cardiac arrest, and appropriate ICD therapy (antitachycardia pacing or shock). SCD was defined as an unexpected nontraumatic death occurring within 1 h of symptom onset or, if unwitnessed, the patients should have been seen well and alive in the last 24 h (9). Telephonic interviews, electronic medical record review of regular outpatient visits and hospital admission, and the Italian National Registry of Mortality Consultations were used to assign events. Patients in whom there was no information available about readmission or cause of death were excluded from the analysis.

ECHOCARDIOGRAPHIC EXAMINATION. Echocardiographic images were acquired by experienced echocardiographers using a commercially available Vivid E9 machine (GE Vingmed Ultrasound AS, Horten, Norway) equipped with M5S and 4V probes for 2DE and 3DE acquisitions, respectively. All patients were examined using grayscale second-harmonic 2DE imaging. Image contrast, frequency, depth, and sector size were adjusted for adequate frame rate and optimal LV border visualization. Dataset acquisition for 3DE images was performed using second-harmonic imaging from the apical approach. During acquisition, we used the multislice display to ensure that the entire LV cavity was included in the dataset. Four to 6 consecutive electrocardiography-gated subvolumes were acquired during breath holding to generate full-volume datasets with a minimum volume rate of 20 vps (10). Datasets were stored digitally in raw-data format and exported to a separate workstation. The treating physician was unaware of the 3DE LVEF and, consequently, this parameter did not influence the clinical management of patients. The study complied with the declaration of Helsinki and was approved by the University of Padua Ethics Committee (protocol # 3311/AO/14). Signed informed consent was collected at enrolment.

IMAGE ANALYSIS. Calculation of 2D volumes and LVEF was performed using the biplane disk summation algorithm (modified Simpson's rule) (6). Manual tracing of the endocardial border was performed at both end-diastole and end-systole, paying attention

to include LV wall trabeculations and papillary muscles within the cavity.

Measurements of 3DE LV volumes and LVEF were performed using a commercially available software package (4D AutoLVQ, GE Vingmed Ultrasound, Horten, Norway) previously validated against cardiac magnetic resonance (11). Briefly, initialization of LV endocardial border tracing was manually performed by identifying 2 points on the 4-chamber view image at end-diastole and at end-systole (1 point in the middle of the mitral annulus and a second point at the LV apex). Manual editing of the semi-automatically generated endocardial contours was routinely applied to include the LV outflow tract, as well as papillary muscles and trabeculae within the LV cavity (11,12).

STATISTICAL ANALYSIS. Statistical analysis was performed with SPSS version 20 (IBM Corporation, Armonk, New York) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) software packages. Continuous variables were summarized as mean ± SD or as median (interquartile range), as appropriate. Categorical variables were expressed as percentage. Differences between groups were explored using Student's *t* test for normally distributed variables and Mann-Whitney *U* tests otherwise. Chi-square tests were used to compare categorical variables. We assessed the proportion of patients who would have been reclassified using 3DE instead of 2DE above and below LVEF ≤35% (in patients with NYHA functional class II to III) and LVEF ≤30% (in patients with ischemic heart disease and NYHA functional class I symptoms) (1,2). A categorical net reclassification improvement index for time to event model was computed to evaluate the extent of improvement obtained by the introduction of 2DE LVEF or 3DE LVEF to a model which took into account the etiology (ischemic vs. nonischemic) of LV dysfunction and NYHA functional class. To identify the ranges in which 3DE may have a greater impact to change the decision to implant an ICD, we used the same thresholds supported by both American and European guidelines and patients were further divided into 4 LVEF groups.

Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were calculated to evaluate the accuracy of both 2DE and 3DE to identify patients with arrhythmic events. In addition, receiver-operating characteristic analysis was performed to estimate the most accurate cutoff value to predict the occurrence of major arrhythmias for both 2DE and 3DE LVEF. A multivariable cause-specific hazard model was computed to identify the predictors of major arrhythmic events including significant variables at the univariate analysis, except for the ischemic etiology of LV dysfunction, which was forced in the model.

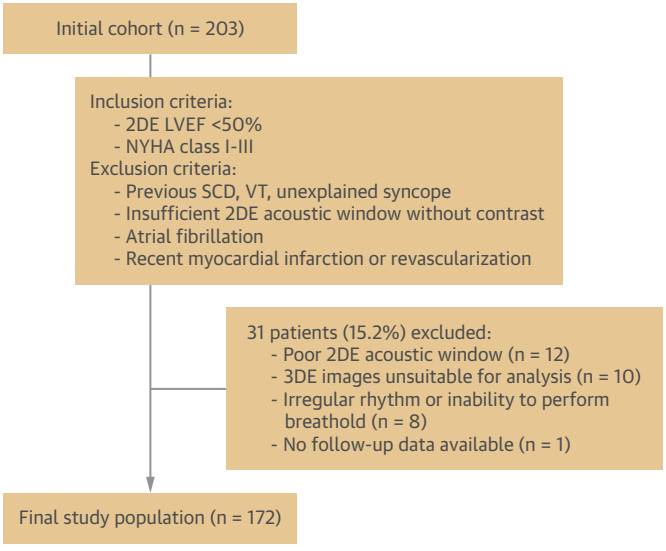
The linearity assumption of continuous variables in the models was tested by refitting the model allowing the effect of a continuous variable is nonlinear using natural cubic splines with 3 degrees of freedom. To test if the effect of a continuous variable is nonlinear in the log hazard scale, we fit the model under the null hypothesis that assumes and linear effect and we compare the 2 models using the likelihood ratio test. Linearity of continuous variables was assumed if the 2 models did not differ statistically. Variance of inflation factor was used to assess any multicollinearity among the variables to include into the model. Only variables with variance of inflation factor values <5 were included into the model. The proportional hazards assumption for the Cox regression model was checked applying proportional hazards tests and diagnostics based on weighted residuals. A p value >0.05 indicated no violation of the proportionality assumption. Kaplan-Meier curves were generated to illustrate the prognostic value of both 2DE and 3DE LVEF using American College of Cardiology/American Heart Association guidelines recommended value, which corresponds to a LVEF ≤35% in patients with NYHA functional class II to III symptoms or a LVEF ≤30% in patients with ischemic heart disease and no symptoms, NYHA functional class I (1).

RESULTS

From an initial cohort of 203 patients, we excluded 12 patients with poor 2DE acoustic window, 10 patients with 3DE datasets unsuitable for quantitative analysis despite an acceptable 2DE acoustic window, and 8 patients because of irregular rhythms or inability to perform breath holding preventing the acquisition of multibeat full-volume 3D datasets of the LV. Finally, data regarding the cause of death were available in all except 1 patient, who was excluded from the analysis (**Figure 1**).

Thus, we included in our final study cohort 172 patients in whom LVEF could be measured with both 2DE and 3DE, and follow-up data were available. The quality of 3D datasets was judged subjectively, considering the signal-to-noise ratio, the degree of blood-tissue contrast, and the completeness of LV wall visualization: image quality was excellent in 33%, good in 47%, and fair in 20% of enrolled patients. **Table 1** shows baseline demographic and clinical characteristics of the whole study cohort, and of

FIGURE 1 Study Enrollment Flow Chart



Detailed graphical description of patient enrollment. 2DE = 2-dimensional echocardiography; 3DE = 3-dimensional echocardiography; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia.

the subgroups with and without major arrhythmic events. Patients who experienced major arrhythmic events had worse NYHA functional class ($p < 0.001$), more frequently received antiarrhythmic therapy ($p = 0.047$), had larger 2DE and 3DE LV volumes ($p < 0.001$), had lower 2DE and 3DE LVEF ($p < 0.001$), and had higher mortality (hazard ratio [HR]: 4.5; 95% confidence interval [CI]: 2.02 to 10.30; $p < 0.001$).

POTENTIAL IMPACT OF 3DE LVEF ON ICD PATIENT SELECTION. Sixty-nine (40%) patients underwent ICD implantation for primary prevention of SCD using conventional 2DE LVEF criteria. Using 3DE LVEF, 34 patients (20% of the overall population) would have been reclassified. Twenty-seven patients with 2DE LVEF above the thresholds for ICD implantation recommended by American College of Cardiology/American Heart Association guidelines would have qualified for ICD implantation if 3DE LVEF had been used. Conversely, 7 patients who received an ICD based on 2DE LVEF were found to have a 3DE LVEF above the threshold recommended by the American College of Cardiology/American Heart Association guidelines. Most of the patients reclassified using 3DE LVEF (20 of 34 patients, 58%) had ischemic heart disease and LV wall motion abnormalities. Patients with a 2DE LVEF within 10% difference from guidelines threshold had the highest likelihood to be reallocated when LVEF was measured by 3DE (Figure 2).

In our study population, 3DE LVEF had a larger area under the curve than 2DE LVEF did, for both 30% and 35% cutoffs recommended by guidelines. Moreover, 3DE LVEF had substantially higher sensitivity and slightly higher specificity to identify patients who experienced major arrhythmic events during follow-up, compared with 2DE LVEF (Tables 2 and 3).

IMPACT OF 3DE LVEF ON ARRHYTHMIC RISK STRATIFICATION. During a median follow-up of 56 (range 18 to 65) months, major arrhythmic events occurred in 52 (30%) patients: 31 episodes of sustained ventricular tachycardia treated with appropriate device therapy, 9 aborted sudden cardiac arrests, and 12 cases of SCD.

Reallocation of patients to ICD indication using 3DE LVEF, and the arrhythmic event rate of patients with and without an indication for an ICD, according to LVEF measured with 2DE and 3DE echocardiography, are shown in Figure 3. 3DE identified 27 patients (25% of the patients with 2DE LVEF above the guideline threshold) at increased risk of major arrhythmic events (HR: 2.2; 95% CI: 1.2 to 4.0; $p = 0.011$). The net reclassification improvement for adding 3DE LVEF to a model taking into account the etiology (ischemic vs. nonischemic) of LV dysfunction and NYHA functional class was 0.59 (bootstrap 95% CI: 0.22 to 0.77). The net reclassification improvement for including the 2DE LVEF in the same model was 0.30 (bootstrap 95% CI: -0.01 to 0.52). These data also support the value of 3DE LVEF to better stratify the arrhythmic risk in our patients.

At multivariable cause-specific hazard analysis, 3DE LVEF was an independent predictor of major arrhythmic events (Table 4). 3DE LVEF predictive value was particularly strong, with a 31% decrease of the risk of major arrhythmic events per each 5% increase in LVEF.

Age (HR: 1.030; 95% CI: 1.008 to 1.050 per year; $p = 0.007$) and 3DE LVEF (HR: 0.69; 95% CI: 0.52 to 0.96 per 5% increase; $p = 0.02$) remained the only significant predictors of the occurrence of major arrhythmic events also when we took into account the competing risk of dying before reaching the endpoint.

By Kaplan Meier analysis, both 3DE LVEF below guideline recommended threshold ($\chi^2 = 37$; $p < 0.001$) and 2DE LVEF below guideline recommended threshold ($\chi^2 = 19$; $p < 0.001$) were useful to identify patients at increased risk of arrhythmic events (Figure 4).

DISCUSSION

The present study provides new evidence supporting the use of 3DE LVEF to stratify the arrhythmic risk in patients with LV dysfunction. Our main findings can be summarized as follows: 1) 3DE LVEF has the potential to redefine the indication for ICD implantation in a sizable number of patients, particularly, in those with 2DE LVEF within 10% difference from the guideline recommended threshold values; and 2) LVEF values below threshold values recommended by current guidelines measured with 3DE are stronger predictors of major arrhythmic events than the same values calculated with 2DE.

Current guideline recommendations for ICD implantation for primary prevention of SCD (13) rely mainly on studies that used 2DE LVEF as the entry criteria (1,14-17). However, in previous ICD landmark clinical trials, different imaging modalities have been used to assess the LVEF (18). As the LVEF measurements using different imaging modalities are not necessarily similar, this adds to the complexity of patient selection for an ICD (19-21).

Calculation of LVEF with 2DE is limited by the fact that the functional contribution of only 12 (imaged in the apical 4- and 2-chamber apical views) of the 16 LV segments are taken into account, ignoring wall motion abnormalities occurring in the anterior septum and in the inferolateral LV walls. Moreover, LV volumes calculations are based on geometric assumptions about LV shape that are not necessarily met in patients with LV dysfunction (particularly in patients with ischemic heart disease) and frequently hampered by the foreshortening of the apical views during acquisition (Online Figure 1). This technical limitations, coupled with a reported 14% interobserver variability of LVEF calculations (22,23) may explain the uncertainties of the indications to ICD when decisions are made on the basis of 2DE LVEF (23).

A previous study enrolling 409 patients with ischemic and nonischemic dilated cardiomyopathy as potential candidates for ICD implantation found that the use of cardiac magnetic resonance (CMR) to measure LVEF provided incremental value over 2DE LVEF (24). In this study, a CMR LVEF ≤35% was a significant predictor of major arrhythmic events at multivariable analysis (HR: 2.17; 95% CI: 1.25 to 3.79; $p < 0.001$), whereas 2DE LVEF was not (HR: 1.22; 95% CI 0.79 to 1.88; $p = 0.35$) (24). However, the use of CMR to select patients for ICD implantation is limited by its high costs, specific contraindications, and limited availability.

TABLE 1 Baseline Clinical and Echocardiographic Parameters in the Overall Study Population, and in Patients With and Without Major Arrhythmic Events During Follow-Up

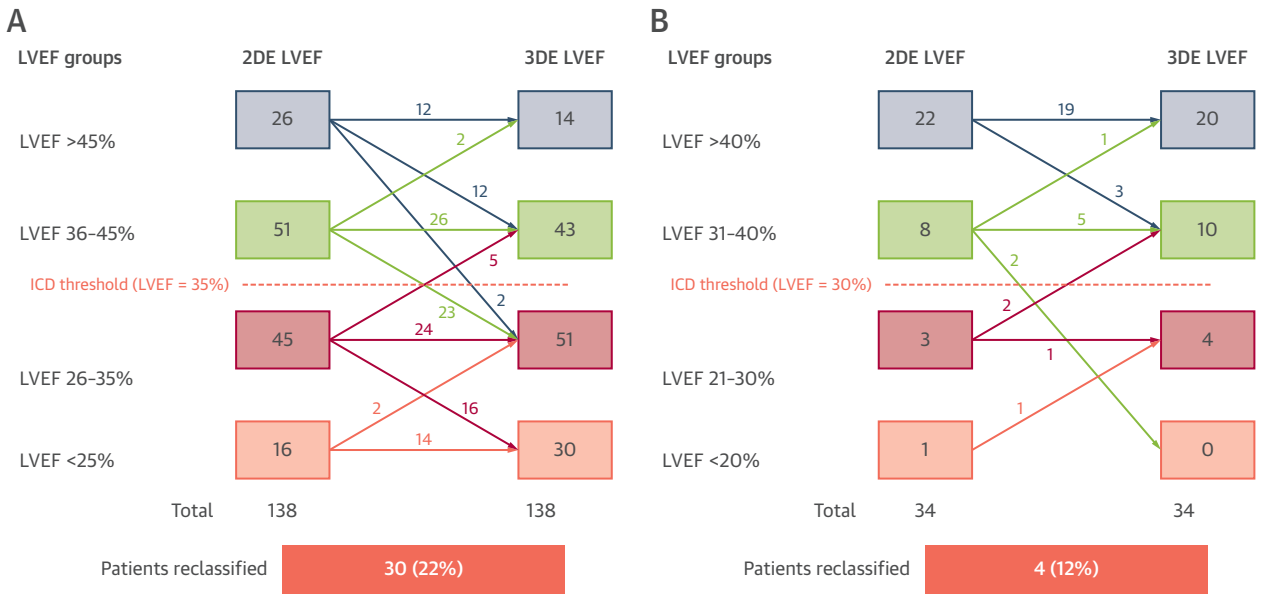
	All Patients (N = 172)	Patients With Arrhythmic Events (n = 52)	Patients Without Arrhythmic Events (n = 120)	p Value
Age, yrs	63 ± 16	64 ± 14	60 ± 15	0.26
Male	142 (83)	44 (85)	98 (82)	0.40
BMI, kg/m^2	26 ± 4	26 ± 4	26 ± 4	0.81
Ischemic	123 (71)	36 (70)	87 (72)	0.39
Previous atrial fibrillation	43 (25)	15 (29)	28 (23)	0.28
Hypertension	104 (60)	32 (62)	72 (60)	0.49
Diabetes	43 (30)	17 (33)	26 (22)	0.09
Chronic kidney insufficiency	12 (7)	7 (13)	5 (4)	0.035
GFR, ml/min/1.73 m^2	69 ± 25	60 ± 26	74 ± 23	0.001
Beta-blockers	134 (78)	40 (77)	94 (78)	0.45
ACE inhibitor	142 (83)	41 (79)	101 (84)	0.5
Antiarrhythmic	46 (27)	19 (37)	27 (23)	0.047
NYHA functional class	2.2 ± 0.8	2.5 ± 0.7	2.0 ± 0.8	<0.001
ICD	69 (40)	34 (65)	35 (23)	<0.001
CRT-D	17 (10)	5 (10)	12 (10)	0.59
Mortality	52 (30)	39 (75)	11 (9)	<0.001
2DE LVEDVi, ml/m^2	96 ± 31	113 ± 37	91 ± 27	<0.001
2DE LVESVi, ml/m^2	62 ± 29	79 ± 33	56 ± 25	<0.001
2DE LVEF, %	37 ± 9	31 ± 9	39 ± 9	<0.001
3DE LVEDVi, ml/m^2	107 ± 34	125 ± 37	100 ± 29	<0.001
3DE LVESVi, ml/m^2	72 ± 32	92 ± 33	64 ± 28	<0.001
3DE LVEF, %	35 ± 10	26 ± 6	38 ± 10	<0.001

Values are mean ± SD or n (%). The p values refer to chi-square or Student's *t* test.

2DE = 2-dimensional echocardiography; 3DE = 3-dimensional echocardiography; ACE = angiotensin-converting enzyme; CRT-D = cardiac resynchronization therapy defibrillator; GFR= glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index.

In the last decade, 3DE LVEF has been validated using CMR as a reference modality, and normative values for 3DE LV volumes and EF have been established (6,25). Compared with 2DE, 3DE is free of the issues related to the foreshortening of LV apical views, does not rely on any geometric assumptions about LV shape to measure LV volumes, and includes the functional contribution of all 17 LV myocardial segments into the calculation of LVEF (13). Moreover, 3DE LVEF has been reported to have higher accuracy, better reproducibility, and lower test-retest variability than 2DE LVEF (5,12,26). Accordingly, 3DE seems better suited than 2DE for accurate LVEF quantitation needed to select patients for ICD implantation, particularly in ischemic patients with abnormal LV geometry or extensive wall motion abnormalities (27). Although previous studies have shown that 3DE LV volumes and LVEF provide increasing predictive power to predict outcomes over their 2DE equivalents (7,8), to the best of our knowledge, no study has previously focused on the value of 3DE LVEF to select patients for ICD implantation.

FIGURE 2 Reclassification of Patients According to LVEF Using the American College of Cardiology/American Heart Association Guidelines Threshold Values Obtained by 2DE and 3DE



(A) Symptomatic patients and reclassification using an LVEF threshold ≤35%. **(B)** Asymptomatic patients with ischemic heart disease and reclassification using a LVEF threshold ≤30%. See Online Videos 1, 2, 3, and 4. ICD = implantable cardioverter-defibrillator; other abbreviations as in Figure 1.

The intraobserver standard measurement error of 3DE LVEF has been reported to be 1.7%, whereas the same parameter for 2DE LVEF was twice higher (3.3%) (5). This difference may be clinically relevant for patients undergoing echocardiography to be evaluated for ICD implantation. Theoretically, a patient with a 2DE LVEF of 37% and NYHA functional class II symptoms would not be considered for ICD implantation (1,2). However, if the same observer performed a second 2DE LVEF measurement, he or she would be likely to obtain a value in the range between 28% and 46%, either qualifying or disqualifying the patient for ICD implant. By using 3DE LVEF, the same hypothetical patient would have a 3DE LVEF ranging from 32% to 42%, which is significantly tighter than the one by 2DE LVEF. Accordingly, our study patients with a 2DE LVEF within 10% of guideline threshold were the ones who were more likely to be reclassified when LVEF was obtained by 3DE. Our findings are consistent with previous studies (24,28). Furthermore, our patients who were reclassified to LVEF ≤35% and NYHA functional class II to III symptoms or LVEF ≤30% and NYHA functional class I symptoms using 3DE LVEF had a higher risk of arrhythmic events. Patients with LVEF below the threshold value for ICD implantation by both 2DE and 3DE had a lower event rate (44%) than did patients reclassified by 3DE LVEF (53%). This finding could be explained by the higher number of patients with ischemic heart disease (wall motion abnormalities) among those reclassified with 3DE, highlighting the importance of taking into account the functional

TABLE 2 Sensitivity, Specificity, PPV and NPV, and LR of 2DE and 3DE LVEF Values to Identify Symptomatic Patients With Ischemic and Nonischemic Heart Disease Who Will Experience Major Arrhythmic Events

	Cutoff Value (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
2DE LVEF	≤35	0.63 ± 0.05	51	67	52	74	1.50	0.73
3DE LVEF	≤35	0.67 ± 0.04	80	68	50	86	2.58	0.28

Values are mean ± SD unless otherwise indicated.
AUC = area under the curve; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

TABLE 3 Sensitivity, Specificity, PPV and NPV, and LR of 2DE and 3DE LVEF to Identify Aysmptomatic Patients With Ischemic Heart Disease Who Will Experience Major Arrhythmic Events

	Cutoff Values (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
2DE LVEF	≤30	0.73 ± 0.04	33	91	25	93	3.6	0.84
3DE LVEF	≤30	0.87 ± 0.07	66	93	50	97	9.4	0.47

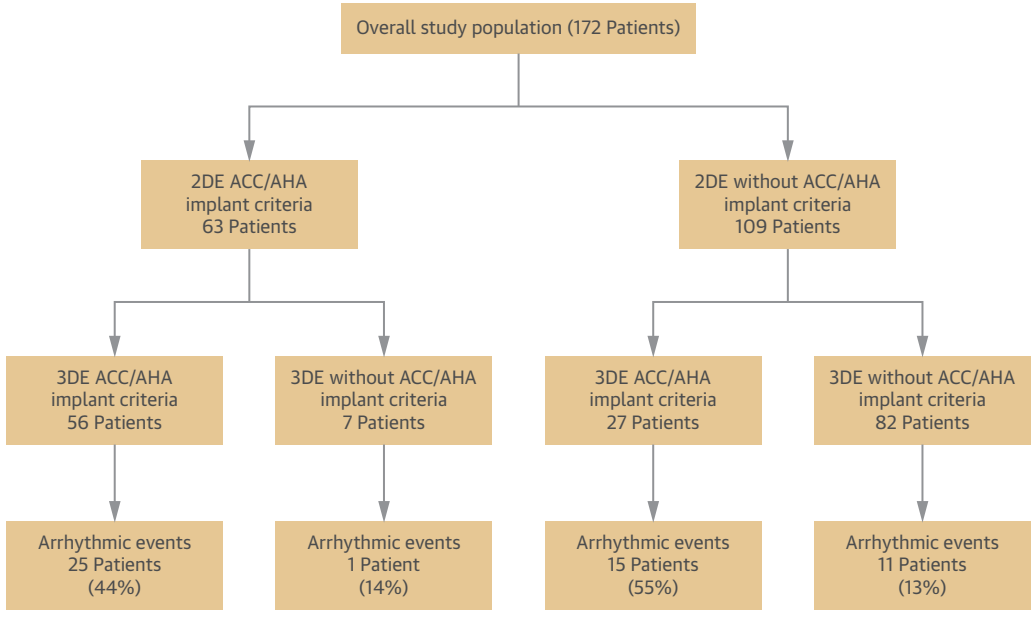
Values are mean ± SD unless otherwise indicated.
Abbreviations as in Table 1 and 2.

contribution of all LV myocardial segments to overall LVEF. A representative case of a patient with wall motion abnormalities in the anterior septum is shown in Online Figure 1 and Online Videos 1, 2, 3, and 4.

Therefore, the results of the present study provide novel evidence of the added value of 3DE to predict major arrhythmic events. Although both 2DE and 3DE LVEF were related to arrhythmic risk in our study population, 3DE LVEF improved significantly the arrhythmic risk stratification. This finding is important because a sizable number of SCD occur in patients with 2DE LVEF above the cutoff value recommended by current guidelines for ICD implantation (29,30). Particularly important is the substantially higher sensitivity of 3DE LVEF compared with 2DE LVEF, which might help identify patients at increased risk of arrhythmic events without compromising specificity. Consequently 3DE LVEF might help to identify patients misclassified using 2DE LVEF, which might account for over 20% of cases of SCD in the community (30). However, it is also true that, even using a more precise imaging modality, a substantial number of patients at risk of SCD would still have LVEF values above those which qualify for an ICD implantation, highlighting the importance of identifying additional imaging markers for increased arrhythmic risk independently from LVEF (31-34).

STUDY LIMITATIONS. The main limitation of the present study is its observational design. However, it would have been unethical denying ICD implantation to patients who met current guideline criteria because of the change in LVEF values measured with a relatively new technique, whose predictive value

FIGURE 3 Impact of 3DE LVEF Over 2DE LVEF to Assess Eligibility to ICD



Patients who met ICD implant criteria using 3DE LVEF had a higher prevalence of arrhythmic events. Abbreviations as in Figures 1 and 2.

TABLE 4 Predictors of Major Arrhythmic Events by Cause-Specific Hazard Model Analysis

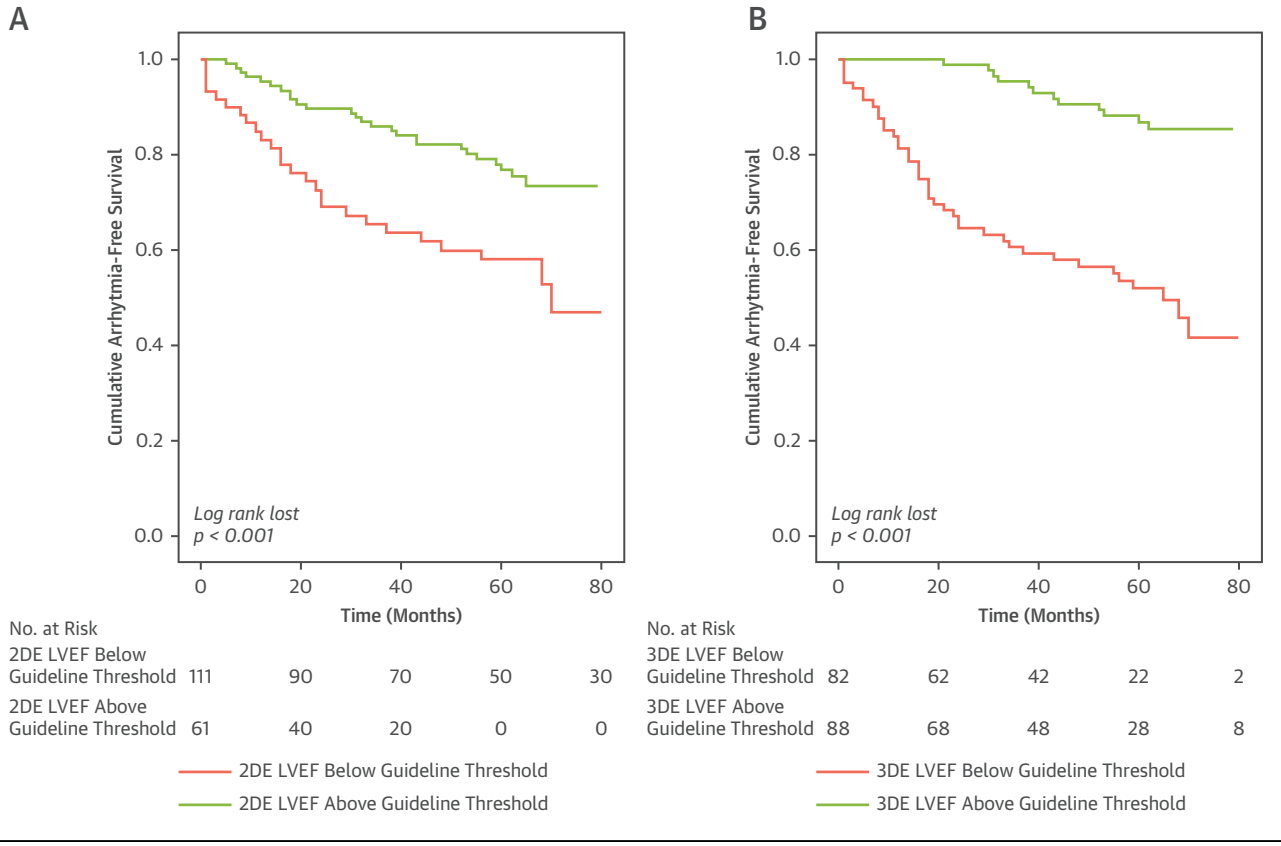
	Univariate HR (95% CI)	p Value	Multivariate HR (95% CI)	p Value
Age (per 5 yrs)	1.180 (1.070–1.320)	0.001	1.100 (0.980–1.230)	0.094
NYHA functional class	1.888 (1.410–2.520)	<0.001	1.380 (0.940–2.030)	0.099
GFR	0.810 (0.730–0.890)	<0.001	0.940 (0.830–1.070)	0.385
Ischemic etiology	1.420 (0.800–2.500)	0.227	1.120 (0.580–2.140)	0.732
2DE LVEF (<30% for NYHA functional class I and <35% for NYHA functional class >I)	0.280 (0.160–0.480)	<0.001		
3DE LVEF (<30% for NYHA functional class I and <35% for NYHA functional class >I)	0.130 (0.070–0.250)	<0.001	0.150 (0.070–0.310)	<0.001

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

has never been explored before. On the other hand, implanting patients with 2DE LVEF above guideline thresholds would have been inappropriate.

In the present study, we did not use contrast to enhance the visualization of the LV endocardial border in patients with poor 2DE acoustic window. First, recommended 2DE LVEF thresholds to implant ICD derive from studies which did not use contrast to calculate LVEF. Our aim was to compare the predictive value of 2DE and 3DE LVEF. Accordingly, we included only patients with good acoustic window. Moreover, the use of contrast agents would have added the complexities of having a third technique to test. Second, although echocardiographic contrast improves the visualization of segments difficult to evaluate, it does not overcome the basic limitations of

FIGURE 4 Arrhythmia-Free Outcomes in Patients Meeting ACC/AHA Guideline Criteria for an ICD Using LVEF Measured by 2DE and 3DE



Using Kaplan Meier curves we show both patients with both **(A)** 2DE and **(B)** 3DE LVEF above guideline implant threshold have higher free outcome survival. ACC = American College of Cardiology; AHA = American Heart Association; other abbreviations as in Figures 1 and 2.

2DE to calculate LVEF (e.g., view foreshortening, geometrical assumptions about LV shape, inclusion of a limited number of LV myocardial segments in the calculation).

The exclusion of patients with suboptimal 3D image quality limits the applicability of 3DE in this patient subset. However, in our study the feasibility for 3DE was 85%, similar to that previously reported in unselected patients (28). We have not included CMR as a reference method to validate LV volumes and LVEF obtained with 3DE. However, accuracy of 3DE to measure LV size and function has been addressed in previous studies (12,25,35), and our goal was to compare the prognostic power of 2DE and 3DE to predict arrhythmic events.

Because the use of echocardiographic contrast was not performed during 2DE examination in this study we cannot exclude that this technology might be of value for arrhythmic risk prediction. This issue should be addressed in future studies.

Finally, our study population had a high prevalence of ischemic heart disease with resting wall motion abnormalities, which may explain in part the superiority of 3DE over 2DE in LVEF measurements and risk stratification. However, 3DE LVEF remained a significant predictor of major arrhythmic events even after adjusting for ischemic heart disease.

CONCLUSIONS

Compared with 2DE, the use of 3DE LVEF has the potential to change the decision to implant an ICD in a sizable number of patients. Those patients with a 2DE LVEF within 10% difference from the implant threshold are more likely to benefit from LVEF quantitation by 3DE. 3DE LVEF is an independent predictor of major arrhythmic events. Patients with a 3DE LVEF <35% and NYHA functional class II to III symptoms or 3DE LVEF <30% are at increased risk for major arrhythmic events and may benefit from an ICD. The results of our study may represent the basis to design a specific trial to address the issue of which imaging modality provides the most cost-effective assessment of LVEF to select patients for ICD implantation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patient selection for an ICD requires determination of LVEF. The use of 3DE should be preferred, particularly in patients with ischemic heart disease and a 2D LVEF within 10% difference from the implant threshold. According to our data, using a 3D LVEF cutoff of 35% in symptomatic patients or a cutoff of 30% in ischemic asymptomatic patients for ICD patient selection may be appropriate.

TRANSLATIONAL OUTLOOK: Further trials should confirm the superiority and establish the optimal threshold of 3D LVEF for ICD patient selection.

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APPENDIX For a supplemental figure and videos, please see the online version of this paper.