ESC European Society of Cardiology

Europace (2022) **24**, 1276–1283
https://doi.org/10.1093/europace/euac039

CLINICAL RESEARCH
Pacing and cardiac resynchronization therapy

The MADIT-ICD benefit score helps to select implantable cardioverter-defibrillator candidates in cardiac resynchronization therapy

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Received 30 November 2021; editorial decision 23 February 2022; accepted after revision 5 March 2022; online publish-ahead-of-print 30 March 2022

See the editorial comment for this article 'How can we assess the risk for sudden cardiac death to decide for primary prophylactic implantable cardioverter-defibrillator in patients with heart failure in 2022?', by Jens Cosedis Nielsen and Nikolaos Dagres, https://doi.org/10.1093/europace/euac061.

Aims The aim of this study is to evaluate whether the MADIT-ICD benefit score can predict who benefits most from the addition of implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy (CRT) in real-world patients with heart failure with reduced ejection fraction (HFrEF) and to compare this with selection according to a multidisciplinary expert centre approach.

Methods and results Consecutive HFrEF patients who received a CRT for a guideline indication at a tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium) between October 2008 and September 2016, were retrospectively evaluated. The MADIT-ICD benefit groups (low, intermediate, and high) were compared with the current multidisciplinary expert centre approach. Endpoints were (i) sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and (ii) non-arrhythmic mortality. Of the 475 included patients, 165 (34.7%) were in the lowest, 220 (46.3%) in the intermediate, and 90 (19.0%) in the highest benefit group. After a median follow-up of 34 months, VT/VF occurred in 3 (1.8%) patients in the lowest, 9 (4.1%) in the intermediate, and 13 (14.4%) in the highest benefit group ($P < 0.001$). Vice versa, non-arrhythmic death occurred in 32 (19.4%) in the lowest, 32 (14.6%) in the intermediate, and 3 (3.3%) in the highest benefit group ($P = 0.002$). The predictive power for ICD benefit was comparable between expert multidisciplinary judgement and the MADIT-ICD benefit score: Uno's C-statistic 0.69 vs. 0.69 ($P = 0.936$) for VT/VF and 0.62 vs. 0.60 ($P = 0.790$) for non-arrhythmic mortality.

Conclusion The MADIT-ICD benefit score can identify who benefits most from CRT-D and is comparable with multidisciplinary judgement in a CRT expert centre.

Keywords Heart failure • Implantable cardioverter-defibrillator • Cardiac resynchronization therapy • Patient selection • MADIT-ICD benefit score

Introduction

Despite multiple trials indicating the benefit of implantable cardioverter-defibrillators (ICD) in primary prevention in heart failure (HF), the therapy is still underutilized.[1] A major issue in this context remains adequate patient selection. While ICDs have been shown to reduce mortality in patients with a left ventricular ejection fraction (LVEF) <35%,[2,3] only a minority will eventually need ICD therapy as there is also the competing risk for non-sudden cardiac death.[4] Furthermore, the role of ICDs in non-ischaemic

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What's new?

- The MADIT-ICD benefit score is a simple clinical risk score categorizing heart failure patients in highest, intermediate, and lowest benefit of implantable-cardioverter therapy.
- In cardiac resynchronization therapy (CRT) candidates, the MADIT-ICD benefit score identifies patients at greatest risk for ventricular arrhythmias and lowest risk for non-arrhythmic mortality, and thus with the highest benefit of CRT-defibrillator (CRT-D).
- Patients in the intermediate and lowest MADIT-ICD benefit group categories, have a similar outcome with low risk for ventricular arrhythmias and high risk for non-arrhythmic mortality. These patients might therefore better be suited for CRT-pacemaker (CRT-P).
- The MADIT-ICD benefit score performs similarly well in identifying patients with highest benefit of CRT-D vs. CRT-P as a multidisciplinary approach in a tertiary expert centre.

cardiomyopathy remains subject of debate. In the recent Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure (DANISH) trial, ICDs failed to reduce all-cause mortality.[5] Although ICDs reduced sudden cardiac death, most patients died because of other reasons. To help in better patient selection, a new clinical classification tool, the MADIT-ICD benefit score was developed and recently published.[6] This simple risk score stratifies patients in subgroups with low, intermediate, and high benefit of ICD implantation, using a weighed risk assessment score of both ventricular tachycardia (VT) and fibrillation (VF) risk vs. non-arrhythmogenic mortality risk based upon clinical variables. In other words, the benefit of the ICD is determined by balancing the risk of sudden cardiac death vs. the risk of non-sudden cardiac death. A very specific population in whom risk assessment is of additional importance are patients with an indication for cardiac resynchronization therapy (CRT). As CRT itself can further reduce arrhythmogenic mortality risk,[7] it is often challenging to select the right patients for CRT-D. Whether the MADIT-ICD benefit score can help in deciding between CRT-P and CRT-D is unclear. Therefore, this study investigates the performance of the MADIT-ICD benefit score in identifying patients with highest benefit of the addition of an ICD to CRT and compares it with current selection for ICD in a tertiary care centre in a real-world CRT population.

Methods

Study population

Consecutive patients with HF with reduced ejection fraction (HFrEF) who received a CRT for a guideline indication in a tertiary CRT expert centre (Ziekenhuis Oost-Limburg, Genk, Belgium) between October 2008 and September 2016, were retrospectively evaluated. Patients with a secondary prevention indication for ICD implantation were excluded. The choice between a CRT-P and CRT-D was multidisciplinary discussed prior to implantation, but final decision was left at the treating physician's discretion. Factors influencing choice have been published previously[8] and include clinical characteristics, electrocardiographic features, presence or absence of scar on cardiac magnetic resonance (CMR), genetic mutations, and presence or absence of non-sustained VT on a pre-implant Holter monitor (Supplementary material online, *Table S1*). After implantation, all patients were included in a multidisciplinary CRT care program, consisting of device optimization, patient education, HF therapy uptitration, loop diuretic downtitration, rehabilitation, and telemonitoring, which has been described previously.[8–10] Patient follow-up was scheduled 6 weeks and 6 months after implantation. Thereafter, patients were seen every 9–12 months if clinically stable. All patients were followed via telemonitoring, and alerts were checked every working day. The current study is in compliance with the Declaration of Helsinki. The study was approved by the local ethical committee.

Baseline characteristics and follow-up

Baseline data consisting of demographics, functional status, medical therapy, laboratory measurements, electrocardiogram, and echocardiography were retrospectively collected from the patient's electronic medical record. A prospective database, containing the interrogations of all devices both performed at the outpatient clinic and sent by telemonitoring, was available and used for the analysis.

MADIT-ICD benefit score

For each patient, the pre-implantation MADIT-ICD benefit category was determined.[6] In brief, the MADIT-ICD benefit score is composed of both a VT/VF risk score and a non-arrhythmic mortality score. The VT/VF score ranges from 0 to 13 points with a score ≥7 indicating a high risk to die from ventricular arrhythmias. The non-arrhythmic mortality risk score ranges from −1 to 10 with a score ≥3 indicating a high risk to die from non-arrhythmic causes. According to these scores, patients can be categorized as having lowest (low VT/VF score and high non-arrhythmic mortality), highest (high VT/VF score and low non-arrhythmic mortality score), or intermediate (both scores high or low) benefit of ICD implantation. In addition, the individual score ranging from 0 (lowest benefit) to 100 (highest benefit) was calculated for every patient. An online tool is available at https://is.gd/madit.

Endpoints

The occurrence of life-threatening ventricular arrhythmias was defined as either the occurrence of sustained VT not requiring therapy (>30 s) or appropriate therapy for VT and VF. In addition, ventricular arrhythmias were only collected as an endpoint if the rate was (i) ≥200 b.p.m. or (ii) <200 b.p.m. with signs of haemodynamic instability (hypotension, syncope, or near syncope). The stored intracardiac electrograms (EGM) were reviewed by a device specialist to confirm the ventricular arrhythmia, the appropriateness of therapy and final adjudication of the endpoint. In addition, non-arrhythmic mortality was collected using the electronic health records, which are linked to the national Belgian population register. Arrhythmic death was defined as (i) death caused by a shockable rhythm, witnessed during monitoring or at time of first medical contact or (ii) an unexpected death during sleep. For patients with undocumented cause of death, a thorough telephone interview with the primary care physician and relatives was performed to define the cause of death. Sudden unexpected death or sudden death with a witnessed ICD shock was categorized as arrhythmic death. Non-arrhythmic mortality was defined as death without any VT/VF and without fulfilling criteria for arrhythmic death. Patients who died because of end-stage HF, but developed VT/VF as terminal mode of death, were considered as having non-arrhythmic mortality.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation if normally distributed or median (25th–75th percentile) if otherwise. Categorical variables are displayed as number (percentage). Normality was checked using histograms, QQ-plots and Shapiro–Wilk testing. Baseline characteristics were compared for the highest, intermediate, and lowest MADIT-ICD benefit categories using one-way analysis of variance, Kruskal–Wallis, and χ^2 test as appropriate. The occurrence of ventricular arrhythmia and non-arrhythmic mortality were compared across the three groups in a time-to-first-event analysis with the long-rank test. The incremental risk of each category was assessed using a univariate Cox regression model and hazard ratios (HRs) with the lowest benefit group as the reference. Thereafter, the additional benefit of factors known to modify sudden cardiac death risk but not included in the MADIT-ICD score and baseline differences not explained by the MADIT-ICD score were explored in a multivariable Cox model. Next, the analysis was repeated to compare the endpoints in patients who received CRT-D vs. CRT-P. Again, a univariate Cox regression model was used with CRT-P as the reference. This model was considered as current practice and compared with the MADIT-ICD benefit model using Uno's C-statistic.[11] Finally, a sensitivity analysis was performed with an alternative definition of non-arrhythmic mortality: any death without fulfilling criteria for arrhythmic death, including patients who experienced a prior VT/VF. All tests were two-tailed and significance was defined as $P < 0.05$. Statistics were performed with Stata 12.0 (Statacorp, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Between October 2008 and September 2016, 475 patients received a CRT and met inclusion criteria for the analysis. Of these, 165 (34.7%) qualified for the lowest benefit group, 220 (46.3%) for the intermediate benefit group and 90 (19.0%) for the highest benefit group of ICD implantation according to the MADIT-ICD benefit score. The baseline characteristics of the study population are displayed in *Table 1*. The different components of the scores can be retrieved in Supplementary material online, *Table S2*. Patients in the highest benefit group had larger LV volumes, a higher haemoglobin and better renal function. In addition, they received more angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) and less loop diuretics. As a consequence of being components of score calculation, age, sex, body mass index, myocardial infarction, diabetes, and atrial fibrillation differed across the three groups. A CRT-D was implanted in 42 (25.4%) patients of the lowest benefit group, 103 (46.8%) of the intermediate benefit group, and 61 (67.8%) of the highest benefit group. Of note, the majority had a non-ischaemic cardiomyopathy across all groups. Baseline differences between CRT-D and CRT-P recipients are shown in Supplementary material online, *Table S3*.

Ventricular tachycardia/ventricular fibrillation risk

After a median follow-up of 34 (24–48) months, 25 (5.3%) patients had a VT/VF and 62 (13.1%) patients died from a non-arrhythmic cause (*Table 2*). VT/VF occurred in 3 (1.8%) patients in the lowest benefit group, 9 (4.1%) patients in the intermediate benefit group, and 13 (14.4%) patients in the highest benefit group (log-rank $P < 0.001$). The cumulative incidence of VT/VF is shown in *Figure 1*. With the lowest benefit group serving as a reference, those in the highest benefit group had a HR of 7.62 [95% confidence interval (CI) 2.2–26.75; $P = 0.001$] for VT/VF, while the HR was not significantly increased to 2.06 (95% CI 0.56–7.68; $P = 0.277$) in patients in the intermediate benefit group. The individual MADIT-ICD benefit score corresponded to an HR of 1.04 (1.02–1.07; $P < 0.001$) for VT/VF for every 1 point score increase.

The only univariable factor associated with a lower VT/VF risk besides the highest MADIT-ICD benefit group was the presence of a left bundle branch block (LBBB), which remained an independent negative predictor (HR 0.41; 95% CI 0.17–0.95; $P = 0.037$) in multivariable analysis (*Table 3*).

Non-arrhythmic mortality

In the lowest benefit group, 30 (18.2%) patients died from non-arrhythmic causes, compared with 31 (14.1%) patients in the intermediate benefit group and 1 (1.1%) in the highest benefit group (log-rank $P = 0.008$) (*Figure 2*). The HR for non-arrhythmic mortality was 0.06 (95% CI 0.01–0.42; $P = 0.005$) in patients in the highest benefit group, while there was no significant difference in risk in the intermediate benefit group (HR 0.81; 95% CI 0.49–1.35; $P = 0.420$) compared with those in the lowest benefit group. Every 1 point increase in the individual MADIT-ICD benefit score was associated with an HR of 0.99 (95% CI 0.97–0.99; $P = 0.009$) for non-arrhythmic death.

Other univariable factors associated with non-arrhythmic mortality were GFR, ACE-I/ARB use, and MRA use. In multivariable analysis, only MRA use remained independently negatively associated with non-arrhythmic mortality (HR 0.53; 95% CI 0.32–0.90; $P = 0.018$) in addition to the highest MADIT-ICD benefit group.

Comparison of the MADIT-ICD score with a multidisciplinary expert centre approach

During follow-up, 4 (1.5%) patients with a CRT-P and 21 (10.2%) patients with a CRT-D had a VT/VF (log-rank $P < 0.001$) (*Figure 1*). Patients who were selected for CRT-D had an increased HR of 7.15 (95% CI 2.45–20.8; $P < 0.001$) for VT/VF compared with those who received a CRT-P. Non-arrhythmic death occurred in 49 (18.2%) CRT-P recipients and in 18 (8.7%) CRT-D recipients (log-rank $P = 0.005$) (*Figure 2*). The HR for non-arrhythmic mortality was 0.47 (95% CI 0.27–0.81; $P = 0.006$) in CRT-D patients compared with CRT-P patients. Crude event rates are depicted in *Table 4*. Of note, four patients who received a CRT-P had a VT/VF of whom none was in the highest benefit group (Supplementary material online, *Table S4*). Of those, two died because of VT/VF and the other two received an upgrade to CRT-D. All 13 patients who were in the highest benefit group and experienced a VT/VF had received a CRT-D according to our multidisciplinary approach.

The MADIT-ICD benefit model had a UNO's C-statistic of 0.69 for predicting VT/VF while current clinical practice had a comparable C-statistic of 0.69 ($P = 0.936$). For predicting non-arrhythmic mortality, the MADIT-ICD benefit model had a C-statistic of 0.60, while current practice had a C-statistic of 0.62 ($P = 0.790$). These findings were similar when all non-arrhythmic deaths were included in a sensitivity analysis, including those that had a prior VT/VF (Supplementary material online, *Figure S1*).

Table I Baseline characteristics according to MADIT-ICD benefit category

MADIT-ICD benefit category	Lowest *N* = 165	Intermediate *N* = 220	Highest *N* = 90	*P*-value
MADIT-ICD benefit score	19 (15–22)	51 (44–55)	79 (76–83)	
Demographics				
Age (years)	79 ± 7	73 ± 10	64 ± 10	**<0.001**
Sex (male)	78 (47.3%)	148 (67.3%)	80 (88.9%)	**<0.001**
BMI (kg/m^2)	25.8 ± 5.2	26.9 ± 4.7	27.9 ± 3.6	**0.003**
Comorbidities				
Myocardial infarction	18 (10.9%)	56 (25.5%)	25 (27.8%)	**<0.001**
Arterial hypertension	139 (84.2%)	180 (81.8%)	73 (81.1%)	0.764
Dyslipidaemia	121 (73.3%)	154 (70.0%)	55 (61.1%)	0.125
Diabetes	61 (37.0%)	59 (26.8%)	9 (10.0%)	**<0.001**
Atrial fibrillation	74 (44.9%)	81 (36.8%)	21 (23.3%)	**<0.001**
COPD	29 (17.6%)	30 (13.6%)	12 (13.3%)	0.502
Stroke	16 (9.7%)	13 (5.9%)	6 (6.7%)	0.357
Heart failure characteristics				
Ischaemic aetiology	65 (39.4%)	83 (37.7%)	37 (41.1%)	0.848
Duration (months)	11 (2–73)	8 (2–64)	10 (3–64)	0.653
NYHA class				0.226
II	47 (28.5%)	65 (29.6%)	34 (37.8%)	
III	109 (66.1%)	138 (62.7%)	54 (60.0%)	
IV	7 (4.24%)	9 (4.09%)	0	
Clinical examination				
Heart rate (b.p.m.)	71 ± 17	70 ± 16	70 ± 17	0.942
Systolic blood pressure (mmHg)	126 ± 17	122 ± 15	117 ± 12	**<0.001**
Diastolic blood pressure (mmHg)	72 ± 11	71 ± 12	69 ± 10	0.128
Electrocardiogram				
QRS duration (ms)	155 ± 24	153 ± 28	155 ± 31	0.664
LBBB	140 (85.4%)	173 (78.6%)	73 (81.1%)	0.244
Echocardiography				
LVEF (%)	26 ± 6	27 ± 5	27 ± 6	**0.024**
LVEDV (mL)	173 ± 68	180 ± 63	202 ± 85	**0.007**
LVESV (mL)	129 ± 54	131 ± 52	148 ± 70	**0.013**
Laboratory analysis				
Haemoglobin (g/dL)	13.0 ± 1.7	13.3 ± 1.5	14.0 ± 1.4	**<0.001**
Creatinine (mg/dL)	1.17 (0.94–1.59)	1.16 (0.94–1.60)	1.08 (0.89–1.25)	0.064
GFR (mL/min)	54 (39–71)	60 (43–76)	71 (59–85)	**<0.001**
Therapy				
ACE-I/ARB	141 (85.5%)	183 (83.2%)	86 (95.6%)	**0.015**
Beta blocker	135 (81.8%)	188 (85.5%)	80 (88.9%)	0.304
MRA	108 (65.5%)	143 (65.0%)	66 (73.3%)	0.335
Loop diuretics	93 (56.4%)	101 (45.9%)	35 (38.9%)	**0.018**
Digoxin	25 (15.1%)	29 (13.2%)	12 (13.3%)	0.846
Nitrates	17 (10.3%)	21 (9.6%)	3 (3.3%)	0.134
Hydralazine	12 (7.3%)	17 (7.7%)	4 (4.4%)	0.574
Amiodarone	32 (19.4%)	35 (15.9%)	9 (10.0%)	0.148
Antiplatelets	86 (52.1%)	111 (50.5%)	53 (58.9%)	0.397
Anticoagulation	63 (38.2%)	70 (31.8%)	29 (32.2%)	0.392
CRT				**<0.001**
Pacemaker	123 (74.6%)	117 (53.2%)	29 (32.2%)	
Defibrillator	42 (25.4%)	103 (46.8%)	61 (67.8%)	
Prior non-sustained VT	12 (7.2%)	45 (20.5%)	45 (50.0%)	**<0.001**

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; ICD, internal cardiac defibrillator; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; VT, ventricular tachycardia.
P-value in bold is < 0.05.

Table 2 Crude event rate according to MADIT-ICD benefit group

MADIT-ICD benefit category	Lowest N = 165	Intermediate N = 220	Highest N = 90	P-value
VT/VF				
Overall	3 (1.8%)	9 (4.1%)	13 (14.4%)	**<0.001**
1 year	1 (0.6%)	3 (1.4%)	6 (6.7%)	**0.003**
2 years	2 (1.2%)	4 (1.8%)	8 (8.9%)	**0.001**
3 years	2 (1.2%)	7 (3.2%)	10 (11.1%)	**<0.001**
Non-arrhythmic mortality				
Overall	30 (18.2%)	31 (14.1%)	1 (1.1%)	**<0.001**
1 year	8 (4.6%)	12 (5.5%)	0	0.083
2 years	15 (9.1%)	17 (7.7%)	1 (1.1%)	**0.047**
3 years	22 (13.3%)	23 (10.5%)	1 (1.1%)	**0.006**

VF, ventricular fibrillation; VT, ventricular tachycardia.
P-value in bold is < 0.05.

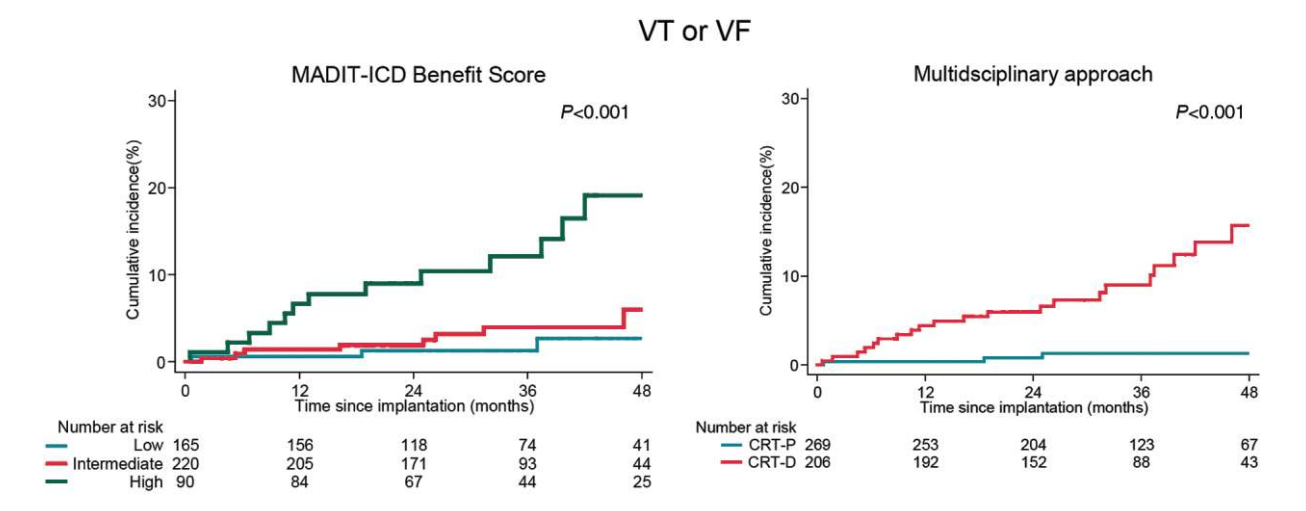

Figure 1 Cumulative incidence of VT or VF according to MADIT-ICD benefit category and multidisciplinary approach. VF, ventricular fibrillation; VT, ventricular tachycardia.

Discussion

In real-world HFrEF patients with a guideline CRT indication (i) the MADIT-ICD benefit score identified patients at highest risk for life-threatening arrhythmias and lowest risk for non-arrhythmic mortality, potentially benefitting most from CRT-D vs. CRT-P; (ii) in addition to the MADIT-ICD benefit score, the presence of LBBB was independently associated with lower incidence of life-threatening arrhythmias after CRT, while the use of MRAs was independently associated with lower incidence of non-arrhythmic mortality; and (iii) the MADIT-ICD benefit score performed equally well in identifying patients with highest benefit from CRT-D vs. CRT-P as the current multidisciplinary approach in a tertiary care expert centre.

This study is the first to test the performance of the MADIT-ICD benefit score in a real-world population. The recently published MADIT-ICD benefit score was initially derived from a pooled population from different Multicenter Automatic Defibrillator Implantation Trials (MADIT)[2,12,13] and subsequently validated in an independent cohort of the Ranolazine in High-Risk Patients With Implanted Cardioverter-Defibrillators (RAID) trial.[6,14] However, trial patients often represent a highly-selected group, which does not always reflect a real-world population encountered in daily clinical practice.[15] Indeed, the patients in our study were on average 8 years older, more symptomatic (majority in NYHA class III) and had more atrial arrhythmias (14% vs. 37%) than those in the pooled MADIT cohort. As such, our study population is more comparable to unselected patients as seen in routine practice. In addition, we specifically investigated the score in a CRT population, while only 40% of the pooled MADIT cohort received a CRT.

As intended by the MADIT-ICD benefit score, the patients in the highest MADIT-ICD benefit group had indeed the highest risk for VT/VF and the lowest risk for non-arrhythmic mortality. In addition, the risk for VT/VF was higher in that group than that of non-arrhythmic mortality. In contrast, there was little difference in both

Table 3 Univariable and multivariable predictors of VT/VF and non-arrhythmic mortality

	Univariable			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
VT/VF						
MADIT-ICD benefit category						
Lowest	Ref			Ref		
Intermediate	2.29	0.62–8.46	0.214	2.06	0.56–7.68	0.277
Highest	7.62	2.17–26.75	**0.002**	7.43	2.12–26.08	**0.002**
LBBB	0.41	0.18–0.96	**0.041**	0.41	0.17–0.95	**0.037**
QRS >150 ms	0.67	0.61–1.48	0.326			
GFR (mL/min)	1.00	0.8–1.01	0.762			
ACE-I/ARB use	0.65	0.24–1.69	0364			
Beta blocker use	0.92	0.31–2.70	0.885			
MRA use	1.09	0.47–2.54	0.836			
Non-arrhythmic mortality						
MADIT-ICD benefit category						
Lowest	Ref			Ref		
Intermediate	0.81	0.49–1.35	0.420	0.85	0.51–1.42	0.541
Highest	0.05	0.01–0.42	**0.005**	0.07	0.01–0.54	**0.010**
LBBB	0.91	0.46–1.80	0.792			
QRS >150 ms	0.64	0.39–1.07	0.088			
GFR (mL/min)	0.99	0.98–0.99	**0.023**	0.99	0.98–1.00	0.128
ACE-I/ARB use	0.53	0.29–0.97	**0.038**	0.78	0.42–1.45	0.439
Beta blocker use	0.94	0.48–1.86	0.879			
MRA use	0.50	0.31–0.83	**0.007**	0.54	0.32–0.90	**0.018**

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.
P-value in bold is < 0.05.

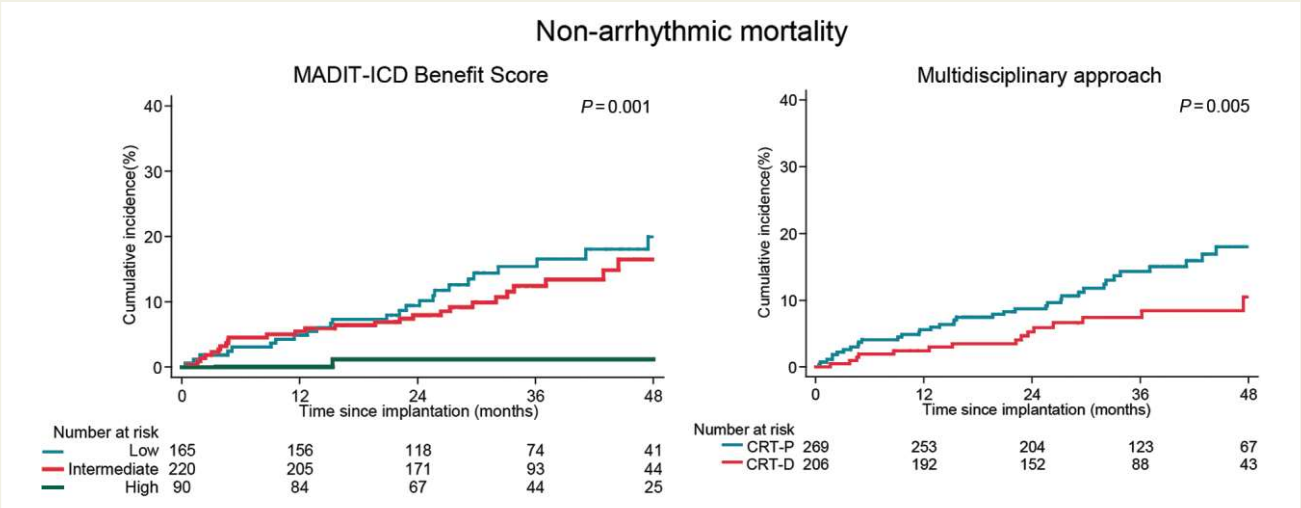

Figure 2 Cumulative incidence of non-arrhythmic mortality according to MADIT-ICD benefit category and multidisciplinary approach.

risks between the intermediate and low benefit groups and the risk for non-arrhythmic mortality was much higher than that of VT/VF in both groups. Therefore, patients in the highest MADIT-ICD benefit group would be good candidates for CRT-D, while a CRT-P might be preferred in patients in the intermediate and lowest benefit groups. Of note, the overall VT/VF event rate in our cohort was somewhat lower than predicted from the MADIT Benefit score. This is in contrast to a large French real-life registry of CRT recipients

Table 4 Crude event rate according to CRT-P vs. CRT-D

	CRT-P N = 269	CRT-D N = 206	P-value
VT/VF			
Overall	4 (1.5%)	21 (10.2%)	**<0.001**
1 year	1 (0.4%)	9 (4.4%)	**0.003**
2 years	2 (0.7%)	12 (5.8%)	**0.001**
3 years	3 (1.1%)	16 (7.8%)	**<0.001**
Non-arrhythmic mortality			
Overall	47 (17.5%)	15 (7.3%)	**<0.001**
1 year	15 (5.6%)	5 (2.4%)	0.090
2 years	23 (8.6%)	10 (4.9%)	0.116
3 years	33 (12.3%)	13 (6.3%)	**0.030**

CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; VF, ventricular fibrillation; VT, ventricular tachycardia.
P-value in bold is < 0.05.

(CeRtiTuDe) which reported an incidence of sudden cardiac death of 0.75–1.18% per year.[16] Patients with the highest benefit still had a 8.9% 3-year risk for VT/VF in our population, while the MADIT score predicted VT/VF risk of 17–23% at 3 years. This difference might relate to the known anti-arrhythmic effects of CRT[7,17] and differences in baseline characteristics between the studied populations. Approximately 60% of patients had a non-ischaemic cardiomyopathy in contrast to the MADIT trials that included none or only a minority of non-ischaemic patients. As overall VT/VF risk is lower in non-ischaemic cardiomyopathy,[8] this might at least partially explain the difference between the observed and predicted event rate. The risk for sudden cardiac death has also declined over the past 20 years in CRT recipients[18] and ICD patients in general.[19] This decline is probably linked to improvements in medical therapy, increased use of revascularization and changes in device recipients. Patients became older, baseline LVEF increased and beta blocker use increased over time.[18] This was also apparent in the MADIT trials with increased use of beta blockers in the consequent trials.[2,12,13] However, CRT also leads to an unanswered paradox. As CRT reduces the need for ICD, it improves survival and reduces the rate of death due to HF, thereby exposing patients to an increased duration of life in which sudden cardiac death can occur.[20] As such, it is important to recognize that in patients with low risk for non-sudden cardiac death, the addition of ICD is still warranted, especially in the high-risk groups. Of note, in an individual patient data network meta-analysis of 13 randomized trials, CRT-D was more effective in reducing all-cause mortality with a reduction of around 30% compared with CRT-P or ICD alone, indicating the additive value of combining a CRT and ICD. However, this analysis did not specifically address patients with a guideline indication for CRT, but included all trials in patients with HFrEF.[21] The ongoing Re-evaluation of Optimal Re-synchronisation Therapy in Patients With Chronic Heart Failure (RESEST-CRT) study is investigating whether CRT-P is non-inferior to CRT-D with respect to all-cause mortality in patients without previous life-threatening arrhythmias (NCT03494933) and will provide more contemporary evidence.

In addition to the MADIT-ICD benefit groups, LBBB was independently associated with a decreased risk for VT/VF. This finding is in concordance with previous studies indicating that LBBB patients have more reverse remodelling and reduction in ventricular arrhythmias with CRT.[17,22,23] Further, MRA use was independently associated with a reduced incidence of non-arrhythmic mortality. MRAs are a well-established pillar of current HFrEF therapy as they reduce cardiovascular mortality and HF hospitalizations.[24] In addition, as almost 90% of patients already took ACE-I/ARBs and beta blockers at the time of implant, the absence of risk modulation in multivariable analysis for these drugs is probably due to insufficient statistical power. Of note, CRT also enables uptitration of neurohumoral blockers.[25]

When comparing the MADIT-ICD benefit score with our current multidisciplinary approach, both performed equally well in predicting VT/VF and non-arrhythmic mortality. However, they did not completely identify the same patients as not all patients in the highest risk group received a CRT-D. Vice versa, some patients in the intermediate and lowest benefit group also received a CRT-D. The MADIT-ICD benefit score has the advantage to use simple clinical characteristics and could therefore easily be implemented in different maybe less experienced health care settings. Our multidisciplinary approach not only uses most of the same clinical characteristics and electrographic features but also integrates information data from CMR and genetic counselling in an expert discussion to decide between CRT-P and CRT-D. Therefore, the MADIT-ICD benefit score might be especially interesting to help decision making in settings where this multidisciplinary approach is not feasible.

Limitations

First, this is a retrospective analysis, which is inherently prone to missing data and confounding. However, the simple clinical variables, necessary to calculate the MADIT-ICD benefit score were available so all patients could be included. Second, we only included patients with a primary prevention indication for ICD, so this study does not apply to patients with a secondary prevention indication. Third, we not only included patients with VT ≥200 b.p.m. but also included all sustained VTs <200 b.p.m. with signs of haemodynamic compromise. This could lead to an overestimation of ventricular arrhythmias that are considered as life-threatening. Nevertheless, the overall VT/VF rate was lower than predicted by the MADIT-ICD benefit score. Finally, follow-up was relatively short and VT/VF can accumulate over lifetime.

Conclusion

In patients with a guideline indication for both a CRT and ICD in primary prevention, assessing benefit of ICD using the MADIT-ICD benefit score, allows for better patient selection. Although it does not perform better than multidisciplinary expert assessment, it can help guide decisions in less experienced centres.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

J.D., E.M., H.G., S.D., and W.M. are researchers for the Limburg Clinical Research Center (LCRC) UHasselt-ZOL-Jessa and

supported by the foundation Limburg Sterk Merk (LSM), Province of Limburg, Flemish Government, Hasselt University, Ziekenhuis Oost-Limburg, and Jessa Hospital. H.G. was also supported as predoctoral strategic basic research fellow by the Fund for Scientific Research Flanders (FWO 1S83221N).

Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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