The Benefit of Prophylactic Implantable Cardioverter Defibrillator Implantation in Asymptomatic Heart Failure Patients With a Reduced Ejection Fraction

Anne-Lotte C.J. van der Lingen, MD[a], Stefan A.J. Timmer, MD, PhD[a], Laurens J.H. Allaart, BS[a], Mischa T. Rijnierse, MD, PhD[a], Peter M. van de Ven, PhD[b], Albert C. van Rossum, MD, PhD[a], Michiel J.B. Kemme, MD, PhD[a], Vokko P. van Halm, MD, PhD[a], and Cornelis P. Allaart, MD, PhD[a,*]

Recommendations for prophylactic implantable cardioverter defibrillator (ICD) implantation in asymptomatic heart failure patients with a reduced left ventricular ejection fraction (LVEF) differ between guidelines. Evidence on the risk of appropriate device therapy (ADT) and death in New York Heart Association (NYHA) class I patients is scarce. Aim of this study is to evaluate ADT and mortality in NYHA-I primary prevention ICD patients with a LVEF ≤35%. A retrospective cohort was studied, including 572 patients with LVEF ≤35% who received a prophylactic ICD with or without resynchronization therapy (CRT-D). To evaluate the incidence of ADT and mortality, NYHA-I was compared with NYHA-II-III using Cox regression analysis. During a follow-up of 4.1 ± 2.4 years, 33% of the NYHA-I patients received ADT compared with 20% of the NYHA-II-III patients (hazard ratio 1.5, 95% confidence interval 1.04 to 2.31, p = 0.03). No differences in mortality were observed (hazard ratio 0.70, 95% confidence interval 0.49 to 1.07, p = 0.10). Additional analyses showed no difference in time to ADT excluding CRT patients (ICD-NYHA-I patients vs ICD-NYHA-II-III patients, p = 0.17) and comparing ischemic and nonischemic cardiomyopathy NYHA-I patients (p = 0.13). Multivariable Cox regression analyses showed that NYHA class was the strongest independent predictor of ADT. In conclusion, primary prevention NYHA-I ICD patients showed a higher incidence of ADT compared with NYHA-II-III ICD patients. These results strongly suggest that primary prevention NYHA-I patients with a LVEF ≤35% are likely to benefit from ICD therapy and should not be excluded from a potentially life-saving therapy. **(Am J Cardiol 2019;124:560−566)**

Prophylactic implantable cardioverter defibrillator (ICD) implantation is recommended in heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class II-III, currently advocated in the ESC, AHA/ACC/HRS, and NICE guidelines for sudden cardiac death (SCD).[1−3] However, discrepancy exists between guidelines concerning asymptomatic HF patients. The NICE guidelines recommend prophylactic ICD implantation in NYHA-I patients,[2] whereas ESC guidelines advise against it, and the AHA/ACC/HRS guidelines differentiate between patients with ischemic cardiomyopathy (CMP) and nonischemic CMP.[1,3] Apparently, the pivotal primary prevention ICD randomized controlled trials (RCTs) which served as the basis for the ICD guidelines do not unambiguously translate to guidelines for clinical practice.[4−7] The majority of these trials have been conducted almost 2 decades ago. Since then, advancements in medical therapy have led to a decrease in risks of mortality and SCD in HF patients, questioning the validity of the study data in this era. The present study set out to evaluate the occurrence of appropriate device therapy (ADT) and death in a contemporary NYHA-I patient cohort with systolic HF who received an ICD for primary prevention of SCD.

Methods

The study was designed as a retrospective cohort study. Patients who received a prophylactic ICD from January 2009 to December 2016 were included. The Local Ethics Committee approved data collection and management of this study. All patients received an ICD for primary prevention with or without resynchronization therapy (CRT-D) according to the pre-2015 ESC guidelines, thus including NYHA-I patients.[8] Exclusion criteria were (1) patients with a hypertrophic CMP, arrhythmogenic right ventricular CMP, systemic infiltrative cardiac disease (amyloidosis, systemic sclerosis) or channelopathy; (2) unknown NYHA class or NYHA-IV at time of implantation; and (3) lost to follow-up immediately after device implantation. The following baseline characteristics before device implantation were collected: demographics, medical history, medication, NYHA class assessment, electrocardiographic data, cardiac function assessed by cardiovascular magnetic resonance

[a]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Cardiology, Amsterdam, the Netherlands; and [b]Department of Epidemiology and Biostatistics, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands. Manuscript received March 7, 2019; revised manuscript received and accepted May 16, 2019.

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*Corresponding author: Tel: +31 20 44445043; fax: +31 20 4443395.
E-mail address: cp.allaart@amsterdamumc.nl (C.P. Allaart).

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imaging, echocardiography (Simpsons biplane LVEF) or nuclear imaging (LVEF measured in resting conditions), and laboratory results. NYHA class (I-IV) was determined before device implantation by a clinician or a nurse practitioner specialized in HF, according to ESC guidelines.[9] Patients described as NYHA class I-II, were classified as NYHA-II patients, and patients described as NYHA class II-III, were classified as NYHA-III patients.

The primary end point was defined as occurrence of first ADT. The secondary end point was all-cause mortality. Deaths were identified using the National Health and Social Care Information Service to ensure none were missed. ADT was defined as antitachycardia pacing or shock for ventricular tachyarrhythmia (VTA). VTA was defined as sustained ventricular tachycardia or ventricular fibrillation. ICD programming for detection and treatment of VTA was typically guided by the results of the painFREE Rx-II (2004) and MADIT-RIT study (2012).[10,11] Clinical follow-up was obtained with intervals of 6 months, and event transmissions of patient devices connected to home monitoring. In case of ADT, each episode was reviewed by specialized cardiac device technicians and electrophysiologists. Date and type of the VTA leading to ADT was recorded, as well as the cumulative number of ADT.

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Q-Q plots were used to determine if continuous data were normally distributed. Dichotomous and categorical data were expressed as frequencies and percentages. The chi-square test or Fischer's exact test was used for dichotomous variables. Continuous variables were compared using the independent-samples *t* test if normally distributed or the Mann-Whitney test otherwise. Ordinal data were compared using the Mann-Whitney test. A logistic regression analysis was used to test the difference of ADT within 1 year of device implantation, stratified by year of implantation. Survival curves were obtained with a Kaplan-Meier curve, compared using a log-rank test. Hazard ratios (HR) and 95% confidence intervals (95% CI) were obtained using Cox regression. For comparison of time to ADT, patients without ADT were censored at end of follow-up or time of death. For comparison of overall-survival, patients still alive at end of follow-up were censored at end of follow-up. The following variables were tested as potential confounders or effect modifier: gender, age, β-blocker use, and LVEF. A covariate was considered a confounder if the regression coefficient of the determinant changed with >10%. Effect modification was tested by including interaction terms and was considered as effect modifier if the interaction term was statistically significant ($p < 0.05$). Univariable Cox regression analyses were performed for clinical and imaging variables that may be associated with ADT. Next, for the multivariate analysis, NYHA class was entered as a dichotomous variable (NYHA-I vs NYHA-II-III) after variables with a $p < 0.10$ in univariable analysis were added to the model. Nonsignificant variables were subsequently removed from the multivariable model using a backward elimination procedure. Two-sided p values <0.05 were regarded as significant. All statistical analyses were performed using SPSS software package (version 22.0; IBM Corporation, Armonk, New York).

Results

From 2009 to 2016, a total of 1,098 patients were eligible for ICD implantation. Figure 1 provides a flow diagram of patient selection. A total of 572 patients were included after applying inclusion and exclusion criteria. Baseline characteristics are described in Table 1. At baseline, 106 (19%) patients were in NYHA-I, 277 (48%) were in NYHA-II, and 189 (33%) patients were in NYHA-III.

During a mean follow-up of 4.1 ± 2.4 years, 127 (22%) patients received ADT (incidence rate of 6% per person-year) and 175 (31%) patients died during follow-up. Twenty percent of NYHA II-III patients received ADT compared with 33% of NYHA-I patients. No difference was found in the cumulative number of ADT per patient between NYHA-I and NYHA II-III patients, median of 1.0 (IQR 1 to 3) versus median of 1.0 (IQR 1 to 2), respectively ($p = 0.66$). Ventricular tachycardia was the leading cause of ADT in both NYHA subgroups; ventricular fibrillation occurred in 21% of the NYHA-I patients and in 27% of the NYHA II-III patients ($p = 0.89$). Gender was identified as confounder for ADT and NYHA class and was added to the Cox regression models. As shown in Figure 2, time to receiving ADT was shorter in NYHA-I patients compared with NYHA II-III patients ($p = 0.03$). Since the advised optimal medical treatment and the programmed device detection times have changed over time, occurrence of ADT within 1 year of device implantation was examined, stratified by implantation year (Table 2). Table 2 illustrates that there was no difference in the percentage of ADT within the first year of implantation ($p = 0.83$). No difference was found in mortality between NYHA-I and NYHA II-III patients, 26% versus 32% ($p = 0.10$, Figure 2).

Kaplan-Meier curves, stratified by NYHA class and CMP etiology, are presented in Figure 3, and show that

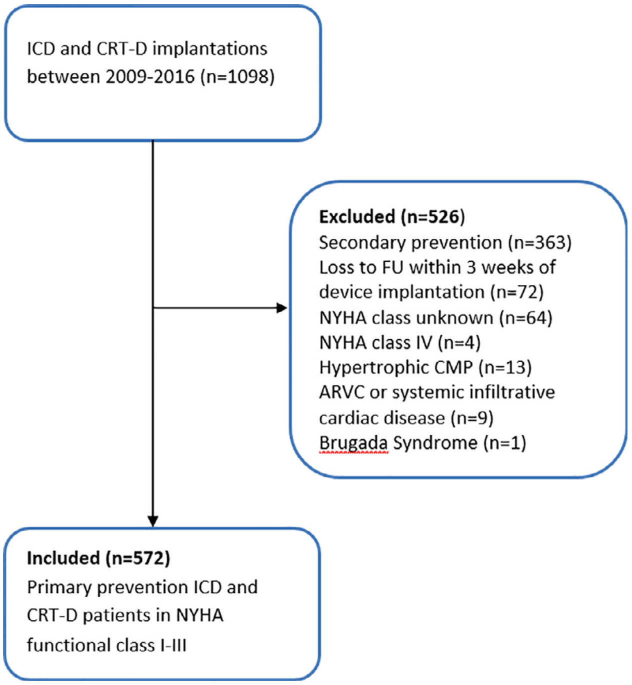

Figure 1. Consort diagram of the study inclusion process.

Table 1
Baseline characteristics

Characteristics	Total (n = 572)	New York Heart Association Class		p Value
		I (n = 106)	II-III (n = 466)	
Age (years)	67 ± 9	67 ± 9	68 ± 10	0.42
Men	420 (73%)	94 (89%)	326 (70%)	<0.01
Ischemic cardiomyopathy	323 (57%)	66 (62%)	257 (55%)	0.18
Diabetes mellitus	149 (26%)	22 (21%)	127 (27%)	0.17
Chronic Atrial fibrillation	84 (15%)	10 (9%)	74 (16%)	0.09
QRS duration (msec)	126 (70−182)	112 (72−157)	130 (75−185)	<0.01*
NT-proBNP (ng/L)†	1079 (74−3191)	819 (165−1955)	1340 (74−3911)	<0.01*
Creatinine (μmol/L)	92 (55−129)	89 (61−116)	90 (54−133)	0.23*
Left ventricular ejection fraction − %	26 ± 7	27 ± 7	26 ± 7	0.31
Late gadolinium enhancement‡	225 (39%)	56 (86%)	169 (78%)	0.15
Resynchronization therapy	247 (43%)	6 (6%)	241 (52%)	<0.01
Medications				
ACE-inhibitors/Angiotensin-II-receptor blockers	475 (83%)	90 (85%)	385 (83%)	0.57
Beta-blockers	468 (82%)	84 (79%)	384 (82%)	0.45
Diuretics	382 (67%)	58 (55%)	324 (70%)	<0.01
Aldosterone inhibitor	211 (37%)	31 (30%)	179 (38%)	0.11
Amiodarone	35 (6%)	4 (4%)	31 (7%)	0.26

* Tested using the Mann-Whitney *U* test.
† Based on n = 201.
‡ Based on n = 282.

NYHA-I patients receive more ADT compared to NYHA II-III patients, regardless of CMP etiology (p = 0.03). Forty percent of nonischemic NYHA-I patients and 29% of ischemic NYHA-I patients experienced ADT (p = 0.13). To evaluate risk of ADT and mortality stratified by NYHA class and device type, the study population was subdivided in ICD patients (n = 325) and CRT-D patients (n = 247). Overall, 26% of the ICD patients received ADT compared with 17% of the CRT-D patients, and time to ADT was shorter in the former group (p = 0.02). ICD patients displayed a lower mortality rate compared with CRT-D patients (27% vs 35%) and CRT-D patients showed a shorter time to death (p = 0.03, Figure 3). As shown in Figure 3, no difference was observed in time to ADT in the ICD-NYHA-I group compared with the ICD-NYHA-II-III group (33% vs 23%, HR 1.36, p = 0.17). There was no difference in time to all-cause mortality between the ICD-NYHA-I and ICD-NYHA-II-III patients (p = 0.28, Figure 3).

Table 3 summarizes the univariable and multivariable analyses of clinical and imaging parameters for association with time to ADT. Parameters that were associated with time to ADT were gender (HR 1.68 for men vs women); use of angiotensin converting enzyme inhibitors (ACE) or angiotensin-II-receptor blockers (ARB; HR 0.62 for using ACE/ARB vs not-using ACE/ARB); NYHA class (HR 1.68 of NYHA-I vs NYHA-II-III); and type of device (HR 1.51 for ICD vs CRT-D). Multivariable analyses using backwards selection showed that besides NYHA class and gender, no other variables were associated with time to ADT.

Discussion

This study demonstrates that NYHA-I HF patients with reduced LVEF frequently receive ADT. In addition, ADT was observed in both ischemic and nonischemic CMP NYHA-I patients. These results imply that NYHA-I HF patients are likely to benefit from prophylactic ICD implantation, and that this is irrespective of CMP etiology.

To date, there are no dedicated defibrillator RCTs available studying the benefit of prophylactic ICD implantation in NYHA-I patients. The NYHA-I subgroup is included only in the earliest trials,[4−6,12,13] whereas more recent ICD studies exclusively included symptomatic HF patients.[7,14] Nonetheless, trials including NYHA-I patients suggest that asymptomatic HF patients convey a subgroup with substantial risk of SCD.[5,12,13] The MADIT-II population consisted of roughly one-third NYHA-I patients, and showed survival benefit associated with prophylactic ICD implantation to be similar for the NYHA-I and NYHA-II-III patients,[5] with sustained survival benefit 8 years after enrollment.[15,16] Reports focusing on the benefit of prophylactic ICD implantation in different NYHA subgroups based on the incidence of ADT have reported conflicting results.[17,18] A subanalysis of the MADIT-II showed that NYHA-I had a lower probability of ADT compared with NYHA-II-III patients (p = 0.012). However, overall-survival in the NYHA-I and NYHA-II group was comparable, indicating similar benefit from ICD therapy between subgroups.[17] In contrast, Provindência et al performed a study in 847 ICD patients and found a similar occurrence of ADT across the 3 NYHA classes.[18]

Surprisingly, the present study observed more ADT in NYHA-I as compared with NYHA-II-III. It can be hypothesized that patients who are without limitation of physical activity (i.e., NYHA class I) are physically more active, thereby exposing themselves to a greater risk of exercised-induced VTA.[19,20] Our findings are in line with a subanalysis of the DANISH Trial indicating that younger patients and patients with a lower NT-proBNP have an increased benefit of ICD implantation,[14] further supporting the hypothesis of a higher risk of exercised-induced VTA in younger and more active patients. An alternative

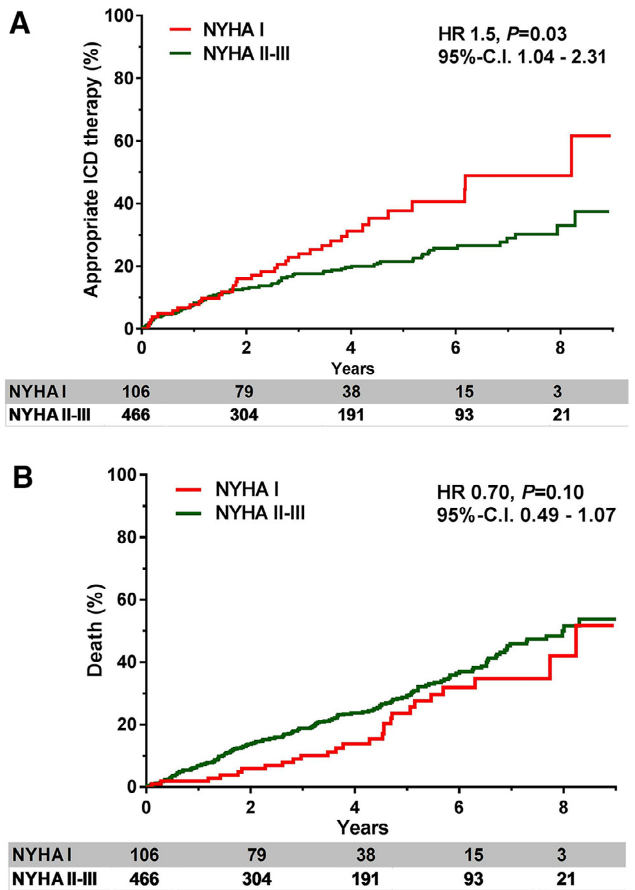

Figure 2. (**A**) Kaplan-Meier curve depicting differences in appropriate device therapy in NYHA-I patients compared to NYHA-II-III patients. Unadjustedvalues for time to ADT between NYHA-I and NYHA-II-III patients: HR 1.6, 95% CI 1.14 to 2.49, p = 0.009. (**B**) Kaplan-Meier curve depicting differences in all-cause mortality differences between the NYHA-I and NYHA-II-III patients. Unadjusted value for time to death between NYHA-I and NYHA-II-III patients: HR 0.72, 95% CI 0.48 to 1.10, p = 0.12. Differences in risk of appropriate device therapy and all-cause mortality were assessed using adjusted Cox proportional hazards models. Adjustment performed for gender.

Table 2
Appropriate device therapy stratified by year of implantation

Year of implantation	ADT (%) within one year of implantation*	ADT NYHA class I	ADT NYHA class II-III
2009	9/90 (10%)	1/13 (8%)	8/77 (10%)
2010	9/84 (11%)	2/7 (29%)	7/77 (9%)
2011	3/74 (4%)	0/21 (0%)	3/53 (6%)
2012	6/84 (7%)	3/18 (17%)	3/66 (5%)
2013	5/69 (7%)	0/16 (0%)	5/53 (9%)
2014	6/63 (10%)	0/18 (0%)	6/45 (13%)
2015	4/56 (7%)	2/10 (20%)	2/46 (4%)
2016	3/52 (6%)	0/3 (0%)	3/49 (6%)

ADT = appropriate device therapy; NYHA = New York Heart Association.

* No difference in percentage of appropriate device therapy within 1 year of implantation was observed (Unadjusted p value = 0.83). Adjusted p value ADT within 1 year of implantation, adjusted for gender, use of β-blocking therapy and ACE inhibitors/AT II blockers (p = 0.85).

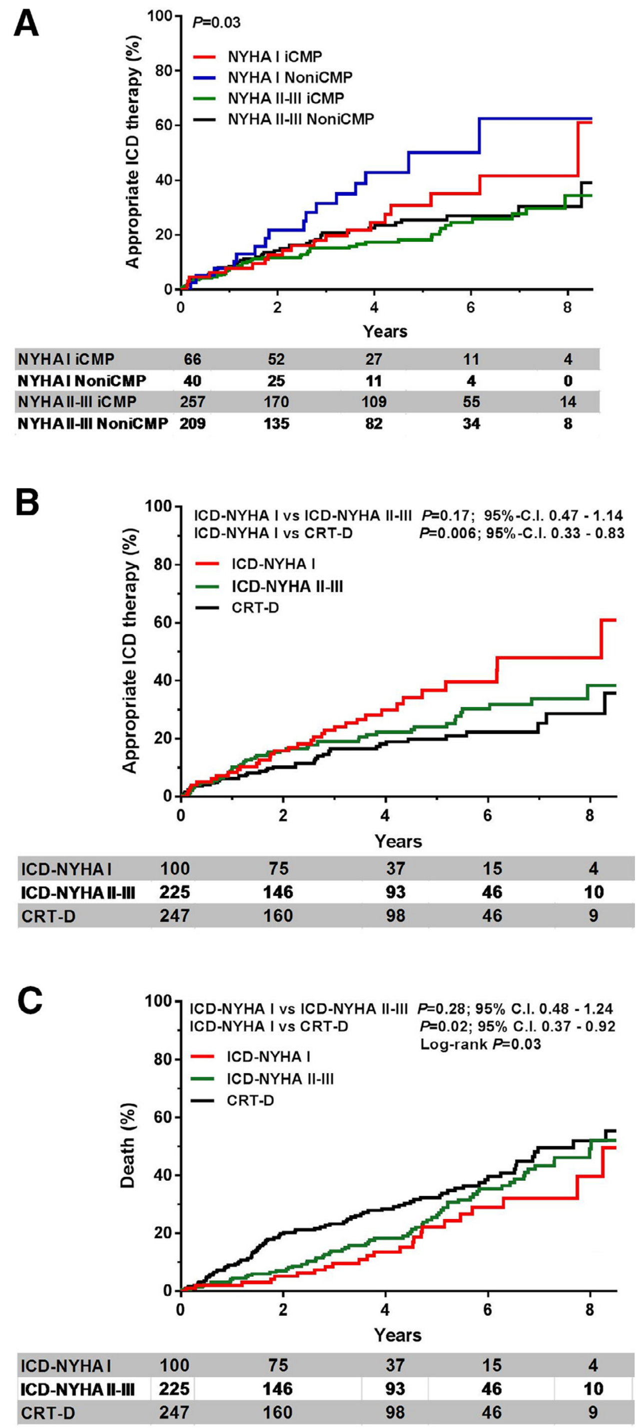

Figure 3. Kaplan-Meier curve depicting differences in (**A**) appropriate device therapy in NYHA-I patients and NYHA-II-III patients, stratified for cardiomyopathy etiology. The differences in risk of appropriate device therapy between the subgroups were assessed using the log-rank test. (**B**) Difference in appropriate device therapy and (**C**) mortality between ICD-NYHA-I patients (n = 100), ICD-NYHA-II-III patients (n = 225) and CRT-D patients (n = 247). Differences in risk of appropriate device therapy between the subgroups were assessed using adjusted Cox proportional hazards models. Adjustment performed for gender.

Table 3
Univariable and multivariable backwards stepwise Cox regression analysis of clinical and imaging parameters for predicting appropriate device therapy

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Men	1.68 (1.08−2.64)	0.02	1.56 (0.99−2.45)	0.06
Age (years)	0.99 (0.97−1.01)	0.38		
Ischemic cardiomyopathy	0.80 (0.57−1.14)	0.21		
Chronic atrial fibrillation	0.72 (0.46−1.14)	0.16		
New York Heart Association class	1.68 (1.14−2.48)	0.009	1.55 (1.04−2.31)	0.03
Diabetes mellitus	1.03 (0.68−1.55)	0.91		
Left ventricular ejection fraction (%)	0.99 (0.96−1.02)	0.52		
Late gadolinium enhancement	0.77 (0.39−1.52)	0.46		
ICD without resynchronization therapy	1.51 (1.05−2.20)	0.03	-	-
NT-proBNP (per ng/L)	1.04 (0.80−1.34)	0.77		
Creatinine (μmol/L)	1.09 (0.92−1.28)	0.31		
Potassium (mmol/L)	1.07 (0.73−1.56)	0.75		
Hemoglobin (mmol/L)	1.15 (0.86−1.53)	0.34		
Beta-blocking therapy	1.21 (0.79−1.87)	0.37		
ACE-inhibitor/Angiotensin II receptor blocker	0.62 (0.36−1.07)	0.09	-	-
Amiodarone	0.53 (0.20−1.44)	0.21		

explanation for the higher incidence of ADT in NYHA-I patients could be that the results are influenced by multiple types of bias, such as healthy candidate bias, referral bias, and survivor bias. In daily clinical practice, patients are referred for ICD implantation based on multiple clinical parameters, such as frailty and overall prognosis. Severity of HF is associated with age, co-morbidities, and lower social status,[21,22] and it is possible that patients with severe HF are more often refused for prophylactic ICD therapy. This may influence the comparison of the benefit of ICD therapy in asymptomatic and symptomatic HF patients.

Our results show no difference in all-cause mortality among the 3 different NYHA classes, in line with RCTs including NYHA-I patients which do not suggest a lower mortality reduction in asymptomatic patients compared with symptomatic patients.[5,12,13] The current data reveal a higher mortality and a lower rate of ADT in CRT-D patients, as compared with patients who received an ICD only. These results also seem to be consistent with other studies, showing a higher mortality rate and lower annual incidence of ADT in CRT-D patients compared with ICD patients.[23] This might be explained by CRT causing positive remodeling of the left ventricle. The increase in LVEF may alter the substrate for VTA and reduce the risk of SCD.[24,25]

Our results suggest that NYHA-I patients with nonischemic CMP have a similar risk of developing VTA as compared with patients with ischemic CMP. Prophylactic ICD implantation in ischemic CMP has been studied extensively, and survival benefit in this subgroup is undisputable.[4−6] Contrary, there is less agreement on the effectiveness of prophylactic ICD implantation in nonischemic CMP. SCD-HeFT showed that NYHA-II patients benefit from ICD therapy, regardless of CMP etiology.[7] In contrast, the DANISH and DEFINITE enrolled only nonischemic CMP patients and observed a nonsignificant reduction in all-cause mortality, although a significant reduction of SCD was found.[12,14] However, the DEFINITE data must be interpreted with caution because of the relatively small sample size of the different NYHA subgroups and the relatively low number of deaths.[12] Moreover, data for the risk of SCD in the NYHA-I nonischemic patients compared with the symptomatic nonischemic patients in the DEFINITE is lacking. It is often suggested that an increase in HF severity is associated with a higher risk of death due to pump failure and a lower risk of SCD.[18,26] It is therefore possible that the nonischemic NYHA-I patients benefit significantly from ICD therapy, because they are less likely to die from other causes.

As stated before, the European, British, and American guidelines differ in recommendations for primary prevention ICD therapy in asymptomatic HF patients.[1−3] With the differences in recommendations, the eligibility of NYHA-I patients for prophylactic ICD implantation remains ambiguous and at the physicians' discretion. Obviously, selecting patients for ICD implantation must be done carefully and the decision should not solely be based on NYHA class. Nevertheless, the current data, in line with previous studies, imply that asymptomatic HF patients with LVEF ≤35% are at substantial risk of developing VTA and it therefore seems only reasonable that prophylactic ICD implantation should be considered. Nonetheless, future RCTs focusing on prophylactic ICD implantation in asymptomatic HF patients seem to be essential to evaluate if ICD therapy reduces mortality in the modern era.

Several limitations should be acknowledged. First, this is a retrospective cohort study. As only patients of which the NYHA class was assessed before implantation were included in the study, this may have introduced selection bias. Second, over the past years ICD arrhythmia detection algorithms have altered, such as longer detection times and changes in zone settings. This might influence the incidence of ADT in our historic cohort. However, Table 2 shows no difference in incidence of ADT within 1 year of implantation, suggesting that the influence of different device settings is limited. Third, previous studies have shown that ADT is not equal to life-saving therapy.[11,27] It is therefore possible that we overemphasize the value of an ICD in HF patients.

In conclusion, NYHA class I HF patients with a LVEF ≤35% frequently receive ADT for VTA, regardless of

CMP etiology. Our study suggests that NYHA-I HF patients with a reduced LVEF are at substantial risk for VTA and that this subgroup of patients should be considered for prophylactic ICD implantation.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.026.

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