Arrhythmic burden among asymptomatic patients with ischemic cardiomyopathy and an implantable cardioverter-defibrillator

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BACKGROUND The clinical benefit of primary prevention implantable cardioverter-defibrillator (ICD) therapy in asymptomatic patients (New York Heart Association [NYHA] functional class I) with ischemic cardiomyopathy and left ventricular dysfunction is continually disputed.

OBJECTIVE The purpose of this study was to evaluate the incidence of ventricular arrhythmias, mortality rates, and appropriate device therapies by NYHA class in a prospective national ICD registry.

METHODS The study comprised 1670 consecutive patients with ischemic cardiomyopathy who were implanted with a primary prevention ICD and enrolled in the prospective national Israeli ICD Registry from 2010. The risk for clinical and arrhythmic events was assessed by NYHA class.

RESULTS Asymptomatic patients (NYHA I) composed 19% of the study cohort. Comparison according to NYHA class showed that the highest mortality rate was in the NYHA III–IV group vs NYHA I and NYHA II (10.5% vs 5.4% and 5.8%, respectively; log rank P = .003). Conversely, cumulative incidence of appropriate ICD therapies, corrected for death as a competing risk, were higher among patients with NYHA I (11% vs 7%; P = .021). In a multivariate model, NYHA I vs ≥II remained independently associated with a significant 2-fold risk for appropriate ICD therapy (hazard ratio 2.03; 95% confidence interval 1.28–3.24).

CONCLUSION Our findings indicate that patients with ischemic cardiomyopathy without heart failure symptoms have a higher risk of appropriate ICD therapy compared with symptomatic patients after adjustment for the competing risk of death, suggesting possible incremental benefit of primary ICD implantation in this population.

KEYWORDS Appropriate therapy; Competing risk; Defibrillator; Ischemic cardiomyopathy; Primary prevention

(Heart Rhythm 2019;16:813–819) © 2019 Published by Elsevier Inc. on behalf of Heart Rhythm Society.

Introduction

Selection of patients for implantation of a defibrillator for primary prevention of sudden cardiac death (SCD) remains challenging even after 3 decades of research. The characteristics, management, and survival of patients with significant left ventricular dysfunction have changed significantly since the publication of the first landmark studies that addressed this question.1,2 Recent reports have shown a possible decline in appropriate defibrillator discharges in contemporary cohorts,3 raising doubts about the cost-effectiveness of placement of implantable cardioverter-defibrillators (ICDs) in the patient profile defined by the current guidelines for primary prevention.4,5

Data regarding the efficacy of ICD for primary prevention in asymptomatic patients defined as New York Heart Association (NYHA) functional class I with ischemic cardiomyopathy (ICM) are limited and are derived mainly from a subgroup of MADIT (Multicenter Automatic Defibrillator Implantation Trial)–II patients,6 leading to the exclusion of this population from the recent European Heart Rhythm Association guidelines.7 However, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society guidelines still recommend implantation of an ICD in asymptomatic patients with advanced left ventricular dysfunction.8 However, clinical trials on primary ICD therapy were performed more than a decade ago and were not aimed at evaluating the risk of ICD therapy per NYHA functional class, thus accounting for possible differences in mortality risk after ICD implantation between asymptomatic

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1547-5271/8-see front matter © 2019 Published by Elsevier Inc. on behalf of Heart Rhythm Society.
and symptomatic patients. Accordingly, we sought to compare the risk of sustained ventricular tachyarrhythmias, after accounting for the competing risk for death, between ICM patients with and those without heart failure (HF) failure symptoms who were enrolled and prospectively followed-up in the Israeli ICD Registry.

### Methods

#### Study population

The Israeli ICD Registry is a national prospective cohort of all patients referred for implantation or replacement of an ICD or cardiac resynchronization therapy–defibrillator (CRT-D). The registry was initiated in July 2010 and incorporated all 21 centers in the country. The registry is approved by the local institutional review board of all participating centers, and enrolled subjects provided written informed consent. Prospective yearly follow-up of registry patients was initiated in July 2011. The present study population comprises patients who met the following inclusion criteria: (1) a diagnosis of ICM by the enrolling center (defined as a history of myocardial infarction or the presence of ischemic heart disease that was sufficiently significant to explain the left ventricular dysfunction by the treating cardiologist); (2) implantation of an ICD for primary prevention; and (3) left ventricular ejection fraction (LVEF) ≤ 35%.

#### Data collection

Data were prospectively collected from the index hospitalization at the time of initial ICD/CRT-D implantation by the local electrophysiologist at the implanting center using a standard electronic case report form. The registry includes demographic and clinical characteristics, indication for defibrillator, comorbidities, LVEF, hemoglobin concentration and serum creatinine level, previous treatments, device manufacturer, device type, and unique device identifier.

#### Follow-up and study endpoints

Data were collected at 6-month intervals and included information on NYHA functional status, therapies, and death. Information on all-cause mortality was obtained from the Israeli National Population Register. Devices were programmed at the discretion of the treating electrophysiology physician. ICD therapy was classified as appropriate or inappropriate by an experienced clinical electrophysiologist who reviewed the intracardiac electrograms at the recruiting centers.

This study’s coprimary endpoints included the separate occurrence of a first appropriate ICD therapy and all-cause mortality in a competing risk analysis. Secondary endpoints included any first appropriate device therapy (ie, antitachycardia pacing or shocks), inappropriate therapy, mode of death (categorized as cardiac vs noncardiac), and rates of hospitalization due to HF. Cardiac mortality was defined as death due to all cardiovascular reasons including worsening HF, acute coronary syndrome, arrhythmia-related mortality, ICD/CRT-D–related mortality, cerebrovascular accidents, or other cardiovascular events. Each case was adjudicated locally by the investigator (an electrophysiologist) at the recruiting site (22 hospitals with electrophysiology services). There was no central adjudication of this outcome. Finally, we calculated the total burden of recurrent appropriate device therapies per 100 person-years. The groups were compared using Poisson regression.

#### Statistical analysis

Baseline clinical characteristics were compared between patients with and those without HF symptoms implanted with a defibrillator. The χ² test was used for dichotomous variables, and the Student t test was used for continuous variables. Data are expressed as mean ± SD or frequency and percentage when appropriate. Cumulative event-free probability of all-cause mortality is graphically displayed by the Kaplan-Meier method, and outcome differences between patients with and those without HF symptoms, as well as according to NYHA functional class, were compared with a log-rank test.

To evaluate the risk of appropriate ICD, HF rehospitalization, and inappropriate therapy in symptomatic and asymptomatic patients, after accounting for possible differences in mortality risk between these populations, a competing risk analysis was carried out with appropriate therapy as the primary event of interest and all-cause mortality as the competing event. We used the Fine and Gray subdistribution hazard method to calculate unconditional risk of appropriate therapy based on cumulative hazard function, to control the chance of the patient dying before administration of appropriate therapy. We further analyzed the univariable association of all potential covariates in the study outcomes (appropriate therapy and HF hospitalization) using a Fine and Gray subdistribution hazard method. All variables significantly associated with the outcomes P < .01 were included in the multivariate models. The best subset method was used in order to select the model. The result of multivariable Fine and Gray competing risk analysis is presented in a forest plot. To further analyze multiple events of recurrent appropriate device therapy, we used Poisson regression model with log time as an offset variable to compare between 2 study groups. Results are presented as event rate per 100 person-years. This was calculated by dividing the total number of therapies in each group by the total follow-up duration and multiplying the result by 100.

Finally, to evaluate the potential bias of including patients implanted with CRT devices (all of whom were NYHA ≥ II), we performed a secondary analysis after excluding these patients. This analysis included all the stages described earlier. All analyses were performed by the Israeli Center for Cardiovascular Research (ICCR) using R software (R Foundation for Statistical Computing, Vienna, Austria).

### Results

The study population comprised 1670 patients with ICM, of whom 317 (19%) had no HF symptoms (NYHA I). The
The average age was 66 ± 10 years, the majority were male (90%), and most had a history of myocardial infarction (87%). Predictably, there were significant differences in the baseline clinical characteristics between patients with and those without HF symptoms (Table 1). Patients with NYHA ≥II were older and had a higher burden of comorbidities, including chronic lung disease, hypertension, and diabetes mellitus (P < .01 for all). Patients with NYHA ≥II also received more intense medical therapy, including angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics (P < .05 for all). However, there were no differences in the use of antiarrhythmic drugs (Table 1). The proportion of severe left ventricular dysfunction (LVEF <30%) and wide QRS complexes was higher in this group. Consistent with current guidelines, only patients with NYHA ≥II and QRS ≥120 ms received CRT-D devices (Table 1). Baseline characteristics by NYHA functional class is given in Supplementary Table 1.

### Risk of mortality by NYHA class

A total of 107 patients died during follow-up. The cumulative incidence of all-cause mortality at 30 months was higher among patients with advanced HF symptoms (NYHA III–IV) compared to asymptomatic patients (NYHA I) or those in NYHA functional class II (10.5% vs 5.4% and 5.8%, respectively; log rank P = .003) (Figure 1).

### Risk of arrhythmic events by HF status

During median follow-up of 30 months (interquartile range 25–30), a total of 116 patients experienced at least 1 appropriate therapy (antitachycardia pacing or shocks). To account for the conflicting trends in arrhythmic and mortality risk between asymptomatic and symptomatic patients, we performed a competing risk analysis, which evaluated the risk of appropriate ICD therapy by NYHA class, after adjusting for the competing risk of death between the 2 groups (Fine and Gray subdistribution hazard method). Based on this analysis, the cumulative risk of first appropriate therapy at 30-month follow-up was higher in patients without HF symptoms compared to symptomatic patients (11% vs 9%, respectively: P = .021) (Figure 2). The cumulative incidence of both mortality and appropriate device therapy for patients with and those without symptomatic HF is shown in Table 1.
Supplementary Figures 1B and 1A, respectively, demonstrating the different trends.

A multivariable analysis, correcting for death as a competing risk and other relevant covariates, yielded consistent results. NYHA I functional class was associated with an 88% increased risk for appropriate therapy (hazard ratio [HR] 1.88; 95% confidence interval [CI] 1.19–2.95; \( P = .006 \)) (Figure 3) compared to patients with NYHA II. No other covariates emerged as independent predictors of appropriate therapy in our analysis. Consistent with these findings, the total burden of recurrent appropriate therapies was also higher among asymptomatic compared with symptomatic patients (38.2 vs 27.9 therapies per 100 patient-years, respectively; \( P < .001 \)) (Table 2).

CRT devices, implanted only in patients with NYHA \( \geq II \) and QRS \( \geq 120 \) ms, were considered a possible source of bias. Therefore, in addition to including use of CRT as a potential confounder in all multivariate models, a secondary
sensitivity analysis of the same cohort excluding patients treated with cardiac resynchronization (n = 1065) was performed. As with the primary analysis, mortality rates were highest among patients in the NYHA III–IV groups (5.8%, 5.3%, and 10.7% for NYHA class I, II, and III–VI, respectively; \(P = .034\)), and asymptomatic patients had a higher cumulative incidence of appropriate therapy compared to HF patients (11% vs 0.07%; \(P = .021\)). Thus, NYHA I was independently associated with appropriate defibrillator therapy in a multivariate analysis after adjustment for death as a competing risk (HR 2.01; 95% CI 1.23–3.3).

Secondary endpoints
Predictably, rates of HF hospitalization at 30-month follow-up were lower in patients without HF symptoms at baseline even after controlling for death as a competing risk (6.1% vs 15.6%, respectively; \(P < .001\)). A multivariable analysis in which death was controlled as a competing risk showed that NYHA I was associated with a 50.8% reduction in the risk of HF hospitalization (HR 0.492; 95% CI 0.28–0.85; \(P = .011\)). Additional independent predictors of increased risk were diabetes mellitus and ejection fraction <30% (Supplementary Table 2). Conversely, asymptomatic patients had a higher rate of inappropriate therapies (5.2% vs 2.8% at 30-month follow-up, respectively; \(P = .031\)). NYHA I was still independently associated with inappropriate therapies in a similar multivariable analysis that controlled for death as a competing risk (HR 2.3; 96% CI 1.12–4.7). No other covariates emerged as independent predictors of this outcome (Supplementary Table 3).

Discussion
Our main findings based on this large contemporary, national prospective registry demonstrate that (1) survival rates at 30-month follow-up were similar in NYHA I and II patients and were significantly higher compared to NYHA III patients; (2) after controlling for mortality and multivariable adjustment, rates of both first appropriate defibrillator therapy and total appropriate defibrillator therapies were higher among NYHA I patients compared to symptomatic patients; (3) patients with HF symptoms at baseline were more likely to be hospitalized due to HF during follow-up; and (4) the risk of inappropriate therapy was higher among asymptomatic patients. Conjointly, our findings indicate that the arrhythmic risk of asymptomatic ICM patients with an implanted ICD for primary prevention is higher than in symptomatic patients, suggesting a possible incremental benefit of primary ICD therapy in ICM patients with NYHA class I symptoms.

ICDs have been shown to increase survival in patients with ICM and severe LV dysfunction. Yet, uncertainty remains regarding the subgroup of asymptomatic patients.
because data are limited.\textsuperscript{7} The only randomized controlled trial designed to evaluate the efficacy of ICDs for primary prevention that included such patients is the MADIT-II trial.\textsuperscript{6} A subgroup analysis conducted as part of the original publication found no differences in the survival benefit of defibrillators between patients at NYHA I and those with higher class. Furthermore, in a long-term follow-up of MADIT-II, patients with NYHA I experienced a significant 41\% reduction in the risk for death with ICD vs those with no ICD therapy.\textsuperscript{11} However, subsequent primary prevention randomized clinical trials excluded ICM patients with NYHA I,\textsuperscript{7} and accordingly clinical data regarding this population remain limited to the MADIT-II population, which was conducted more than a decade ago.

Although no other studies specifically focused on the benefit of ICDs in patients with ICM and NYHA I, several previous subanalyses have reported greater benefit in NYHA II patients than in those with a higher NYHA class. Notably, SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) showed no benefit of ICD over placebo in patients in NYHA III, whereas there was a significant reduction in mortality in patients with NYHA II.\textsuperscript{2} Although any conclusions derived from these data are limited by the fact that this study included 48\% of patients with non-ICM and that it was performed from 1997 to 2003, it definitely raises a concern that the benefit of ICDs may have an inverse correlation with the severity of HF. Of note, a subanalysis of MUSTT (Multicenter Unsustained Tachycardia Trial),\textsuperscript{12} which included only patients with ICM in NYHA functional class I–III, demonstrated a progressive increase in all-cause mortality, reflecting the increase in HF severity. However, the risk of arrhythmic death or cardiac arrest was not independently associated with NYHA functional class. This notion is further supported by the results of a recent meta-analysis that summarized the results of the major relevant randomized control trials, including MADIT, MADIT-II, COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure), DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation), and SCD-HeFT.\textsuperscript{14} The authors concluded that the relative efficacy of ICD therapy was greater in patients with baseline NYHA class II vs those with NYHA III–IV. Furthermore, a previous study based on an early cohort of the Israeli ICD Registry compared patients with NYHA I and II to those with NYHA ≥II and showed an increased mortality but lower rates on appropriate therapies in the latter group.\textsuperscript{15} Additionally, a recent study based on the DAI-PP (Défibrillateur Automatique Implantable-Prévention Primaire) study showed that both total and cardiovascular death increased with NYHA class, but the likelihood of appropriate ICD therapy was similar in patients with NYHA classes I–III.\textsuperscript{16} These data are consistent with our present findings, suggesting that a competing risk between arrhythmias and mortality by NYHA class results in an overall higher arrhythmic burden among patients with less advanced HF symptoms.

Clearly, the only possible benefit that may be derived from an ICD is delivery of appropriate treatment of a potentially lethal rapid ventricular tachyarrhythmia. Therefore, a defibrillator will be most beneficial in a person at high risk for such events. In contrast, among patients with more advanced HF symptoms, the risk of mortality due to HF may be higher. This may explain why ICDs are not as beneficial in patients with higher NYHA class. Of note, although many studies found a progressive increase in mortality risk in parallel to the increase in HF severity,\textsuperscript{17} the association with SCD or arrhythmic mortality is less well established. In fact, several studies have shown that the proportion of SCD decreases in patients with advanced HF compared to those with milder HF symptoms.\textsuperscript{18–20} Finally, we also found a trend toward an increase in inappropriate therapies in NYHA I patients, which may be secondary to a more preserved conduction system in this group, thus allowing for higher ventricular response to atrial tachyarrhythmia.

**Study limitations**

Our findings are based on a real-life contemporary prospective registry, and all analyses are limited by the observational and retrospective nature of our study. Furthermore, our data are derived from a national Israeli registry, and accordingly any generalization of our conclusions should be made with caution. The most important limitation of our cohort is the fact that all participants were implanted with a defibrillator. A true evaluation of the efficacy of defibrillator implantation in asymptomatic patients with ICM will require a randomized controlled study comparing optimal medical therapy with or without defibrillator implantation. However, it is unlikely that such a study will be carried out in the current climate, so this question may be answered indirectly.

The integrity of follow-up data was monitored by supervisors of the ICCR. Although the mortality data, ascertained from the Israeli National Population Registry, are robust, we had no access to the cause of death. Data on device therapies were reported by electrophysiology clinicians from the enrolling centers but were not adjudicated by an independent committee. Furthermore, information on untreated events was not obtained. Thus, rates of ventricular tachyarrhythmic events that were missed by programming (ie, device cutoff or delayed detection) could not be assessed. The ICD programming protocols used in each medical center were previously reported.\textsuperscript{3} These protocols varied slightly between the medical centers, but most implemented a high threshold (>180 bpm) for therapies and was generally used in all primary prevention patients similarly, irrespective of NYHA class. The calcifications of mode death was based on prespecified criteria but was researched at each site. This classification was not centrally adjudicated. Finally, we did not have access to biomarkers such as troponin or natriuretic peptides, which may have further improved risk stratification.

**Conclusion**

Our data indicate that after multivariable adjustment and controlling for the competing risk of death, over 30 months of follow-up the risk of receiving an appropriate ICD therapy
is higher among patients with ICM and class I HF compared to patients with higher degrees of NYHA. These findings do not support the recent exclusion of this population in the ESC guidelines.

**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.03.030.

**References**