Published in final edited form as:

Am J Cardiol. 2015 June 1; 115(11): 1539–1544. doi:10.1016/j.amjcard.2015.02.056.

Prevalence and Outcomes of Patients Receiving Implantable Cardioverter-Defibrillators for Primary Prevention Not Based on Guidelines

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Abstract

Implantable cardioverter-defibrillator (ICD) implantation outside practice guidelines remains contentious, particularly during the mandated waiting periods in patients with recent cardiac events. We assessed the prevalence and outcomes of noneguideline-based (NGB) ICD implantations in a tertiary academic medical center, with a specific focus on adjudication of arrhythmia events. All patients who underwent initial primary prevention ICD implantation at our institution from 2004 to 2012 were categorized as having received guideline-based (GB) or NGB implants and were retrospectively assessed for first episode of appropriate ICD therapy and total mortality. Of 807 patients, 137 (17.0%) received NGB implants. During a median follow-up of 2.9 years, patients with NGB implants had similar times to first appropriate ICD therapy (median time to event 1.94 vs 2.17 years in patients with GB implants, $p = 0.20$). After multivariable analysis, patients with NGB implants remained at higher risk for death (hazard ratio 1.54, 95% confidence interval 1.1 to 2.2, $p = 0.03$) but not appropriate ICD therapy (hazard ratio 0.83, 95% confidence interval 0.5 to 1.3, $p = 0.51$). Furthermore, only 1 of 125 patients who underwent implant within the 40-day waiting period after myocardial infarction or 3-month waiting period after revascularization or cardiomyopathy diagnosis received an appropriate therapy within this period. In conclusion, few patients received NGB ICD implants in our academic medical center. Although these patients have similar long-term risk of receiving appropriate ICD therapy compared with patients with GB implants, this risk is very low during the waiting periods mandated by clinical practice guidelines. These results suggest that there is little need to rush into implanting ICDs during these waiting periods.

Current practice guidelines for primary prevention implantable cardioverter-defibrillator (ICD) implantation mandate a 40-day period after a myocardial infarction (MI) before ICD

implantation, recommend against ICD implantation for patients with New York Heart Association (NYHA) class IV symptoms, and emphasize that ICDs have not been shown to improve survival when implanted within 3 months of myocardial revascularization. The guidelines also state that ICD therapy should be considered in patients with a recent cardiomyopathy diagnosis only after their response to optimal medical therapy for 3 months has been assessed.^{1–3} For a variety of reasons, however, ICDs may be implanted in patients who do not meet guideline-based (GB) criteria. A retrospective cohort study of cases submitted to the National Cardiovascular Data Registry-ICD Registry found that 22.5% of patients did not meet evidence-based criteria.⁴ This study was controversial in part because of the possibility that some variables in the ICD Registry may not have been recorded accurately.⁵ Furthermore, no information was available regarding long-term rates of appropriate ICD therapy or overall mortality. We undertook the present study to assess the prevalence of non–guideline-based (NGB) ICD implants at an academic medical center using prespecified criteria, leveraging full access to patients' medical records and associated clinical decision making. In addition, we compared rates of appropriate ICD therapy and survival between patients with NGB and GB implants, with particular emphasis on the rates of appropriate ICD therapy during the waiting periods mandated by the clinical guidelines.

Methods

All patients who underwent ICD implantation for primary prevention of sudden cardiac death at Beth Israel Deaconess Medical Center from January 1, 2004, to December 31, 2012, were included in this retrospective analysis. Patients were considered to have undergone primary prevention ICD implants if they had no history of cardiac arrest, spontaneous sustained ventricular tachycardia (VT), or syncope compatible with a ventricular arrhythmia with a subsequent electrophysiology study demonstrating inducible sustained VT. Patients with hypertrophic cardiomyopathy, cardiac sarcoidosis, arrhythmogenic right ventricular cardiomyopathy, long QT and Brugada syndromes, and other channelopathies were excluded from this analysis. Patients were also excluded if it was impossible or difficult to determine whether the implant was GB using our prespecified criteria or if there was insufficient information to estimate >3 of the clinical variables discussed subsequently. Patients were followed through December 31, 2013. Outcome data were extracted from the medical records by investigators blinded to the indication for the device.

Clinical variables were identified from medical records, including review of primary data (e.g., electrocardiograms, echocardiograms, and device electrograms) when available. The primary independent variable was NGB versus GB ICD implantation. Patients were classified as having an NGB ICD if their initial ICD was implanted within 40 days of the MI that resulted in their reduced left ventricular ejection fraction (LVEF), within 3 months of either percutaneous coronary intervention or coronary artery bypass graft surgery (revascularization) or within 3 months of cardiomyopathy diagnosis. Patients were also classified as having an NGB ICD if they had NYHA class IV symptoms and did not undergo concurrent cardiac (CRT) at the time of initial implant. For the multivariable analysis, patients who met >1 NGB criteria were included in only 1 NGB category using the hierarchy specified earlier (e.g., a patient with NYHA class IV heart failure with no CRT whose ICD was implanted within 40 days of MI would be categorized as a patient whose

ICD was implanted within 40 days of MI). Cases were adjudicated through chart review involving an internal medicine resident (MKT or RG) and an electro-physiology fellow (YCL). An attending electrophysiologist (AEB) was consulted in approximately 150 cases when further review was required.

The primary outcome variable was time to appropriate ICD therapy, which was defined as antitachycardia pacing or shock therapy for VT or ventricular fibrillation. We defined inappropriate therapy as intervention delivered for atrial tachyarrhythmias (including atrial fibrillation, atrial flutter, atrial tachycardia, and sinus tachycardia) or therapy delivered in response to extraneous potentials generated by other cardiac or extracardiac electromagnetic signals. For all ICDs, we recorded programming parameters, especially to ensure that there was no significant difference in detection times. Analysis of stored ICD electrograms was performed using previously published methods⁶ by an electrophysiology fellow (YCL) and an attending electrophysiologist (AEB) blinded to the identity of the patient being studied. The secondary outcome variable was death from any cause, determined by the medical record and social security death index. A censor date corresponding to the most recent ICD interrogation or last known follow-up was recorded for all patients who did not receive appropriate ICD therapy in the study period.

Continuous variables were expressed as mean and SD, and categorical variables were expressed as absolute and relative frequencies. Discrepancies in baseline characteristics were evaluated for statistical significance using analysis of variance or the chi-square test. To determine the risk of appropriate ICD therapy and mortality in the NGB categories, time-to-event analysis was performed using the Kaplan-Meier method. Multivariate analysis included the prognostic variables described earlier in a Cox proportional hazards regression model. The Fine and Gray approach was used for competing risk analysis. We performed separate survival analyses for appropriate ICD therapy and for total mortality using STATA IC/13 software (STATA Corporation, College Station, Texas). The study protocol was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center.

Results

The 806 patients in the study were selected and classified as shown in Figure 1. Patients with NGB ICDs underwent ICD implantation an average of 12, 45, and 42 days after MI, revascularization, or cardiomyopathy diagnosis, respectively. Of the NGB implants, 10 of 137 patients (7.3%) needed a permanent pacemaker, and because of this, it was decided to implant an ICD, rather than just a pacemaker.

Compared with patients whose implants were GB, those with NGB implants were more likely to have coronary artery disease (CAD), higher NYHA class, lower LVEF, shorter QRS duration, and tobacco use and were less likely to be taking antiarrhythmic medications or to have undergone concurrent CRT (Table 1). Other clinical variables were not significantly different between the 2 cohorts.

We compared ICD programming parameters in patients with GB and NGB implants. The number of tachycardia zones, cut-off values for VT detection, and number of intervals to

detect (Medtronic, Minneapolis, MN and St. Jude Medical Devices, St. Paul, MN) or detection times (Boston Scientific Devices, Marlborough, MA) were similar in both groups.

During a median follow-up of 2.9 years, 16.6% of all patients (134 of 807) received appropriate ICD therapy and 22.0% (177 of 807) died. Compared with patients with GB implants, patients with NGB implants had similar times to first appropriate ICD therapy (median time to event 1.94 vs 2.17 years, $p = 0.20$) but significantly shorter survival (median time to death 2.57 vs 3.03 years, adjusted $p = 0.015$; Table 2). After adjustment for initial LVEF, CAD, atrial fibrillation/flutter, cardiomyopathy type, NYHA class, antiarrhythmic drug use, and QRS duration, patients with NGB implants had similar risk of appropriate ICD therapy (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.5 to 1.3, $p = 0.51$, Figure 2) but significantly higher mortality (HR 1.54, 95% CI 1.1 to 2.2, $p = 0.03$, Figure 2). We also performed a competing risk analysis and found no significant differences in the risk of receiving appropriate ICD therapy between the 2 groups, when accounting for competing risk of death (subdistribution HR for NGB implants 0.75; 95% CI 0.5 to 1.2; $p = \text{NS}$). Appropriate ICD therapy was not associated with total mortality risk.

We then assessed the rates and time course of appropriate ICD therapy and mortality in the individual categories of NGB implants. With the exception of the higher mortality in patients with NYHA class IV with no CRT, our study was underpowered to assess the association of the individual categories with either outcome over the course of the follow-up period (Table 3). However, the absolute rate of appropriate ICD therapy was low (only 1 of 125 patients) in the 40-day period after MI or 3-month period after revascularization or cardiomyopathy diagnosis: 1 patient experienced appropriate ICD therapy 62 days after cardiomyopathy diagnosis. No patients experienced inappropriate ICD therapy during the waiting periods. Rates of total mortality were similarly low during the waiting periods: 1 patient died 16 days after percutaneous coronary intervention and 1 patient died 50 days after cardiomyopathy diagnosis.

Discussion

We found that 17% of primary prevention ICD implants at a tertiary care medical center where all implanting physicians are board-certified electrophysiologists and where each implant is critiqued before the procedure were NGB. This figure is similar to the rate of NGB implants (22.5%) in the National Cardiovascular Data Registry-ICD Registry.⁴ In most instances, when the ICD implant was “too early,” the implanting or referring physician did not explicitly justify the timing of implant. In situations in which premature timing of implant was acknowledged, the premature implant was usually justified for 1 of 2 reasons: either the patient required a pacemaker within this time frame ($n = 10$) or an ICD implant was preferred immediately for patients who had what was felt to be an usually high risk of ventricular arrhythmias (e.g., a patient with fast nonsustained VT soon after MI; $n = 18$). There were also a few situations in which the implanting electrophysiologist justified the premature implant based on the clinical rationale that the LVEF was not likely to recover with additional waiting time ($n = 3$). Clinical decision making did not seem to reflect the difference between patients shown not to benefit from ICDs (the post-MI NGB category) and patients whose benefit from ICDs remains unclear (the other NGB categories).

Our assessment of arrhythmias detected by ICD demonstrated a low rate (<1%) of both appropriate and inappropriate ICD therapy during the “waiting periods” associated with guideline-directed care after MI, revascularization, and cardiomyopathy diagnosis. These results are consistent with those of Pouleur et al,⁷ who found that the percentage of sudden deaths after an acute MI attributed to arrhythmia was higher than nonarrhythmic death⁸ only after the 3-month period post-MI had elapsed. In the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial survival curves did not diverge until approximately 9 months of follow-up,⁹ questioning the benefit of ICDs early after diagnosis of heart failure.¹⁰ Similarly, of 373 patients with nonischemic cardiomyopathy and LVEF <40% for <6 months, the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC-2) investigators identified 6 patients with sudden death, at a mean time to event of 420 days—far beyond the initial 3 months.¹¹ Our results support a low rate of ventricular arrhythmias in the waiting periods mandated by the clinical guidelines.

Of note, a study evaluating the use of the wearable cardioverter-defibrillator in 8,453 patients during mandated waiting periods after MI or revascularization found that 1.6% of patients received appropriate ICD shocks, 75% of which occurred in the first month.¹² This rate is slightly higher than the 0.8% rate of appropriate ICD therapy during the waiting periods in patients with NGB implants in our study. It is possible that because some patients with NGB implants had other reasons for early implantation (e.g., concurrent pacemaker therapy), the NGB group was less likely to experience VT or ventricular fibrillation than patients selected for wearable defibrillators, who were all deemed high risk for ventricular arrhythmias. However, it is difficult to compare our population with those patients selected for wearable defibrillators because information regarding co-morbidities, medical therapy, and specific reasons why these patients were chosen for wearable defibrillators was unknown.

Our data also show a difference in mortality between GB and NGB groups, with the NGB group demonstrating a significantly higher risk of death (HR 1.54) during a median follow-up of 2.9 years, after adjustment for covariates that affect mortality. This observation suggests that physicians are good at identifying patients at high mortality risk. However, clinical markers (that may be used by physicians to predict mortality) have no utility in predicting specific risk for arrhythmias. The higher mortality in the NGB implants may also be because of competing nonarrhythmic mortality rates in the patients in the NYHA class IV category and reinforces the futility of ICD implant in patients with end-stage heart failure. Additionally, certain subpopulations of patients after MI and after revascularization have higher nonarrhythmic mortality rates with early ICD implantation. A Defibrillation in Acute Myocardial Infarction trial¹³ sub-study found that a reduction in sudden death in ICD patients with recent (6 to 40 days) MI was completely offset by increased nonarrhythmic deaths because of recurrent ischemia and/or heart failure, leading to 40% mortality at 2 years.¹⁴ Furthermore, our patients classified as NGB had lower LVEF at the time of implant (Table 1), a variable associated with a relatively higher risk nonarrhythmic mortality. Because many of these “early implant” patients had persistent LV systolic dysfunction after the waiting periods,^{15,16} mortality remained higher over the course of the follow-up period. Future studies are needed to determine to what extent mortality rates in these “early implant” patients depend on future recovery of ventricular function. Patients with eventual

recovery of ventricular function may still have other unmeasured co-morbidities that may still portend higher mortality rates in the long term.

Because only 137 patients underwent NGB ICD implantations, our study was not powered to detect the individual contributions of each category. Patients may have had episodes of appropriate ICD therapy noted on device interrogations in other hospitals or clinics that were not documented in our medical records. However, our detailed review of each medical record—which included documentation from outside providers—minimized this possibility. The relatively short detection times programmed in some ICDs may have also led to identification of ICD therapy for arrhythmias that would have terminated spontaneously. It should also be noted that we included patients whose initial implants occurred before the publication of SCD-HeFT. Despite this, NGB implants occurred in an even distribution during the follow-up timing.

Acknowledgment

The authors express their appreciation to Mark E. Josephson, MD, for his review and thoughtful suggestions. Author contributions: Each of the authors has made substantive contributions to the report as follows: concept/design: YCL, MKT, and AEB; data analysis/ interpretation: all authors; drafting of the report or revising it critically: YCL, MKT, DBK, MAR, and AEB; final approval of the report: all authors; and statistics: YCL and MAR.

Dr. Buxton has research grants supported by Medtronic, Inc., Minneapolis, MN, and Biosense-Webster, Diamond Bar, CA. Dr. Kramer is the Lois Green Scholar at the Hebrew Senior Life Institute for Aging Research and is supported by a Paul B. Beeson Career Development Award in Aging Research (K23AG045963).

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Figure 1.

Derivation of patients included in the study cohort. The average number of days reported in the first 3 NGB categories represents the average time from the initial event (MI, revascularization, or heart failure diagnosis) to ICD implantation. CHF = congestive heart failure.

Figure 2.

(A) Kaplan-Meier curves for appropriate ICD therapy for all patients. Freedom from appropriate ICD therapy in patients with GB versus NGB implants is shown ($p = 0.40$ by the log-rank test). (B) Kaplan-Meier curves for total mortality for all patients. Freedom from total mortality in patients with GB versus NGB implants is shown ($p = 0.03$ by the log-rank test).

Table 1

Clinical characteristics of patients with implantable cardioverter-defibrillators implanted for primary prevention; n (%)

	Guideline-based	Non-guideline-based	p
Total	669 (82.9%)	137 (17.0%)	
Men	523 (78.2%)	108 (78.8%)	0.87
Age (mean±SD) (years)	65.8±12.1	65.5±13.1	0.84
Ischemic cardiomyopathy	350 (52.2%)	86 (62.8%)	0.04
Non-ischemic cardiomyopathy	260 (38.8%)	37 (27.0%)	0.03
Coronary artery disease	436 (65.2%)	104 (76.5%)	0.01
History of myocardial infarction	369 (55.2%)	86 (62.8%)	0.10
History of PCI	236 (35.3%)	84 (62.8%)	0.001
History of CABG	217 (32.4%)	51 (37.5%)	0.25
History of congestive heart failure	497 (74.3%)	113 (82.5%)	0.04
Cardiac resynchronization therapy	201 (30.0%)	22 (16.1%)	0.01
NYHA class I	177 (26.5%)	30 (21.9%)	0.04
NYHA class II	191 (28.6%)	39 (28.5%)	0.70
NYHA class III	280 (41.9%)	41 (29.9%)	0.03
LVEF (mean±SD)	26.2±9.2	23.8±8.5	0.005
Body mass index (mean±SD)	28.8±6.3	28.9±6.8	0.88
Diabetes	236 (36.2%)	55 (40.7%)	0.32
Hypertension	515 (77.3%)	106 (78.5%)	0.76
History of atrial fibrillation or flutter	235 (35.3%)	44 (32.4%)	0.51
Tobacco use (ever)	344 (52.7%)	82 (62.1%)	0.04
Tobacco use (current)	54 (8.8%)	25 (10.2%)	0.02
Peripheral vascular disease	87 (13.1%)	20 (14.6%)	0.63
Glomerular filtration rate (mean±SD)	82.0±39.7	84.6±37.5	0.50
Blood urea nitrogen (mean±SD)	26.6±15.2	25.8±12.7	0.62
Beta-blocker use	556 (83.1%)	113 (83.1%)	1.00
ACEi or ARB use	526 (78.6%)	103 (75.2%)	0.38
Aldosterone antagonist	149 (22.3%)	24 (17.5%)	0.22
Antiarrhythmic drug use	81 (12.1%)	7 (5.2%)	0.02
QRS duration (ms, mean±SD)	132.7±31.9	125.8±30.7	0.02
Echocardiogram LVDD (cm, mean±SD)	6.0±0.9	6.1±0.8	0.33
Echocardiogram LVH	138 (25.0%)	19 (16.7%)	0.10
Electrophysiology study	207 (30.9%)	48 (35.0%)	0.17
Inducible monomorphic VT	91 (44.0% [*])	21 (43.8% [*])	0.70

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; LVDD = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; VT = ventricular tachycardia.

* Denotes percentage of all patients who underwent an EP study.

Table 2

Implantable cardioverter-defibrillator therapy and mortality in all patients

Variable	All implants (N=806)	Guideline-based implants (N=669)	Non-guideline-based implants (N=137)
Appropriate ICD therapy	134 (16.6%)	115 (17.2%)	19 (13.9%)
Median time-to-first appropriate ICD therapy (years)	2.12	2.17	1.94
Inappropriate ICD therapy	50 (6.2%)	47 (7.0%)	3 (2.2%)
Death (# of patients)	177 (22.0%)	135 (20.2% [*])	42 (30.7% [*])
Median time-to-death (years)	2.92	3.03 [*]	2.57 [*]

* p <0.009 unadjusted; p <0.02 adjusted for initial LVEF, CAD, AF/flutter, cardiomyopathy type, NYHA class, antiarrhythmic drug use, QRS duration.

Table 3

Rates of implantable cardioverter-defibrillator therapy and total mortality in individual non-guidelines-based categories. Time-to-event analyses were compared with those of guidelines-based patients.

	MI within 40 days	PCI or CABG within 3 months	CHF diagnosed within 3 months	NYHA class IV (no CRT)
Total # of patients	23	61	41	12
Appropriate ICD therapy	2 (8.7%)	11 (18.0%)	5 (12.2%)	1 (8.3%)
Median time-to-first appropriate ICD therapy (years)	1.43	2.01	2.06	1.78
Inappropriate ICD therapy	0	1 (1.6%)	2 (4.9%)	1 (8.3%)
Death	6 (26.1%)	23 (37.7%)	5 (12.2%)	8 (66.7%)
Median time-to-death (years)	1.56	2.95	2.54	0.90 [*]

* p = 0.005 unadjusted; p = 0.02 adjusted for initial LVEF, CAD, AF/flutter, cardiomyopathy type, NYHA class, antiarrhythmic drug use, QRS duration.