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**Device Therapies among Patients Receiving Primary Prevention Implantable Cardioverter  
Defibrillators in the Cardiovascular Research Network**

**Running title:** *Greenlee et al.; Device Therapies from Primary Prevention ICDs*

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**Journal Subject Terms:** Quality and Outcomes; Arrhythmias; Catheter Ablation and Implantable Cardioverter-Defibrillator

**Abstract**

**Background** - Primary prevention implantable cardioverter defibrillators (ICDs) reduce mortality in selected patients with left ventricular systolic dysfunction by delivering therapies (anti-tachycardia pacing or shocks) to terminate potentially lethal arrhythmias; inappropriate therapies also occur. We assessed device therapies among adults receiving primary prevention ICDs in seven healthcare systems.

**Methods and Results** - We linked medical record data, adjudicated device therapies, and the National Cardiovascular Data Registry ICD Registry. Survival analysis evaluated therapy probability and predictors following ICD implant 2006-2009, with attention to Centers for Medicare and Medicaid Services (CMS) Coverage with Evidence Development (CED) subgroups: left ventricular ejection fraction 31-35%; non-ischemic cardiomyopathy <9 months duration; New York Heart Association class IV heart failure with cardiac resynchronization therapy defibrillator (CRT-D). Among 2540 patients, 35% were <65 years old, 26% were women, 59% were white. During 27 (median) months, 738 (29%) received  $\geq 1$  therapy. Three-year therapy risk was 36% (appropriate 24%, inappropriate 12%). Appropriate therapy was more common in men (adjusted hazard ratio 1.84, 95% confidence interval 1.43-2.35). Inappropriate therapy was more common in atrial fibrillation patients (2.20, 1.68-2.87), but less common among patients  $\geq 65$  years (0.72, 0.54-0.95 vs. younger) and in recent implants, e.g., in 2009 (0.66, 0.46-0.95 vs. 2006). In CMS CED analysis, inappropriate therapy was less common with CRT-D (0.55, 0.36-0.84 vs. single chamber); therapy risk did not otherwise differ for CMS CED subgroups.

**Conclusions** - In this community cohort of primary prevention ICD patients, therapy delivery varied across demographic and clinical characteristics, but did not differ meaningfully for CMS CED subgroups.

**Key words:** Inappropriate shock, implantable cardioverter-defibrillator; outcomes research; arrhythmia; sudden cardiac death

## **Clinical Perspective**

### **What Is New?**

- In this large observational cohort study of community practice patients receiving an implantable cardioverter defibrillator for primary prevention of sudden cardiac death, the occurrence of device therapies was generally lower than reported in efficacy trials (3-year cumulative probability of first device therapy was 36% for therapies of any type, 24% for shocks), and we have found that the occurrence of both appropriate and inappropriate device therapies was similar for patient subgroups identified for further study by the Centers for Medicare and Medicaid Services, when compared to their counterparts, even after accounting for differences in baseline device programming.

### **What Are the Clinical Implications?**

- Based on a large and broadly representative population of patients from several U.S. health systems, this study offers useful prognostic information to providers and patients on the likelihood of appropriate and inappropriate device therapies occurring following implantable cardioverter defibrillator placement for primary prevention, across a range of demographic, clinical, and device characteristics.

In clinical trials of selected patients with left ventricular systolic dysfunction, implantable cardioverter defibrillators (ICDs) reduce risk of death as a primary prevention strategy (1-3). These devices detect and terminate life-threatening ventricular tachyarrhythmias with device-delivered therapies (anti-tachycardia pacing [ATP] and/or high-voltage shocks). However, inappropriate device therapies can also be delivered in response to non-lethal tachyarrhythmias or as a result of device malfunction. Inappropriate ICD therapies are associated with subsequent morbidity, mortality, worsening health status, and cost (4-6). A greater understanding of the incidence and predictors of device therapies, both appropriate and inappropriate, following

primary prevention ICD implantation is needed to optimize clinical decision-making and to inform health policy (7).

In practice, the use of primary prevention ICDs has expanded beyond the selected participants in clinical trials, with almost 200,000 devices implanted annually in the US (8). Because patients receiving care in the community differ from those enrolled in trials, outcomes of ICD therapy in clinical practice may also vary (8-10). When expanding Medicare coverage for ICDs in 2005, CMS issued a 'Coverage with Evidence Development' (CED) decision that established a national registry of patients receiving primary prevention ICDs to address knowledge gaps in patient selection and clinical decision making (11). Three patient subgroups required further study: those with left ventricular ejection fraction 31-35%; non-ischemic dilated cardiomyopathy (NIDCM) of <9 months duration; and New York Heart Association (NYHA) class IV heart failure symptoms with a cardiac resynchronization therapy defibrillator (CRT-D) (12). Within the framework of the Longitudinal Study of Implantable Cardioverter Defibrillators (LS-ICD) (13), we aimed to describe the occurrence of appropriate and inappropriate device-delivered therapies in contemporary practice, and to identify device therapy predictors, with particular attention to CMS CED subgroups.

## **Methods**

### *Setting and Study Population*

The LS-ICD is a retrospective study of primary prevention ICDs within 7 geographically distributed, community-based healthcare systems participating in the Cardiovascular Research Network (13-14). We identified all adults receiving an ICD for primary prevention between January 1, 2006 and December 31, 2009, excluding patients if they had a left ventricular ejection fraction >35%, had previously received an ICD, or if follow-up data were not available. The study was approved by institutional review boards at participating sites, with waiver of informed consent due to the observational nature of the study.

### *Data Sources*

The LS-ICD links baseline patient and device characteristics from the National Cardiovascular Data Registry (NCDR) ICD Registry (8), additional baseline and longitudinal clinical data (diagnoses, procedures, laboratory test results, medications) from the electronic health records of participating sites (14-15), and a novel repository of device-delivered therapies ascertained through manual record review by trained local abstractors coupled with remote device monitoring data sources when used, and centralized clinical adjudication (13). While study materials have been made available in a supplemental appendix to a previous publication (13), study data for this analysis are not directly available to other researchers for purposes of reproducing the results or replicating the procedure.

### *Outcomes*

Patients were observed for up to 3 years after ICD placement for device interrogations and the occurrence of device therapies, with those receiving ICDs in 2009 followed for up to 2 years. Of more than 28,000 device interrogations, 60% were from ambulatory clinic visits, 33% from remote monitoring sources, and 6% from hospital sources. For those patients with 10 or more therapy episodes (n=61), adjudication was limited to the first 10, and a maximum of 3 therapies were collected from any 24-hour period to limit potential influence of ventricular tachycardia 'storm' (16). Device therapies were reviewed by two members of a central clinical panel [HV, PS, JH, RGM] in order to confirm the episode, type of therapy, and therapy appropriateness based on device interrogation reports and intra-cardiac electrograms. Therapies were classified as appropriate (in response to a potentially malignant ventricular tachyarrhythmia), or inappropriate (due to other causes, including supraventricular arrhythmias, or problems with device sensing or function) (13). Review relied on local provider interpretation as documented in clinical notes in absence of device documentation (28% of episodes). Therapy appropriateness was deemed uncertain when sources were inadequate or unavailable (15% of episodes). Device therapies were classified as ATP alone or as a therapy resulting in shock (either ATP followed by shock or shock alone). Discrepancies between reviewers were resolved by consensus, with additional review by expert electrophysiology adjudicators [SH, AK, PV] for unresolved discrepancies and quality assurance.

### *Patient characteristics*

Patient characteristics included: age, sex, race/ethnicity, year of implant, device type, left ventricular ejection fraction, etiology (ischemic/non-ischemic) and duration of cardiomyopathy, NYHA functional class, cardiovascular and other comorbidities (previous coronary artery bypass graft, previous percutaneous coronary intervention, lung disease, diabetes mellitus, hypertension, atrial fibrillation, QRS duration and left bundle branch block morphology, non-sustained ventricular tachycardia), select lab values (blood urea nitrogen and serum creatinine), and medications prescribed at discharge following ICD implant, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aspirin, beta blockers, digoxin, and statins. Special attention was given to patient subgroups designated for further evaluation by CMS in their 2005 CED decision for primary prevention ICDs. Baseline device settings, including arrhythmia detection enhancements (on/off) and lowest programmed rate threshold for delivery of tachyarrhythmia therapy (<180, 180-199 and >200 beats per minute), were available in 74% of patients.

#### *Statistical Analysis*

All analyses were conducted using SAS (SAS 9.3, SAS Institute, Inc., Cary, NC). We first estimated crude incidence density rates of total device-delivered therapies. Kaplan Meier curves were generated for time to first device-delivered therapy, stratified by therapy appropriateness, both overall and within the pre-defined CMS CED subgroups. For each subject, follow-up time accrued from date of implant until the event of interest or censoring at the earliest of the following: end of the observation period, date of last device interrogation, date of death, date of device deactivation/explantation.

Cox regression assessed correlates of time to first appropriate therapy and time to first inappropriate therapy. All candidate variables associated with the outcome with a univariate  $P < 0.20$  and the CMS subgroup variables were included in final models, along with study site as a random effect to account for clustering. Proportional hazard assumptions were evaluated by modeling covariate-by-time interactions, and potential collinearity among covariates was evaluated using condition indices and variance decomposition proportions (17). For the few variables with negligible missing values (<0.4% of records), simple imputation employed the mode. For the two variables with greater missing proportions, cardiomyopathy etiology/duration

(1.1%), and QRS duration and morphology (9.0%), missing values were assigned a separate category (18).

### *Sensitivity Analyses*

We explored potential bias from outcome misclassification due to therapies with uncertain appropriateness, employing probabilistic bias analysis with record-level replacement (19). In a second sensitivity analysis, we explored secular changes in baseline device programming over the course of the study, and evaluated the potential influence of incorporating device setting information on the observed outcomes of our primary analysis.

## **Results**

### *Baseline characteristics*

Among 2669 initial patients, we excluded 129 who had either a previous ICD placement, a left ventricular ejection fraction >35%, or a lack of follow-up care in the implanting health system, leaving a final analysis set of 2540 study subjects (**Figure 1**). The proportion of total study subjects ascertained from each of the seven study sites ranged from 5% to 30%. Twenty-six percent of the study group were women, 35% were <65 years, and 59% were non-Hispanic white (**Table 1**). A prior history of clinical heart failure (96.3%) and hypertension (73.1%) were common. With respect to subgroups identified in the CMS CED criteria, 358 (14.1%) patients had a left ventricular ejection fraction of 31-35%, 183 (7.2%) had NIDCM <9 months duration, and 31 (1.2%) patients had NYHA Class IV heart failure symptoms and CRT-D. Due to the small number in this last group, NYHA Class and device type were considered separately. Most patients in the study cohort had NYHA Class II (47.2%) or Class III (39.5%) symptoms, and there was balanced representation of device type (single chamber 35.6%, dual chamber 31.9%, and CRT-D 32.4%).

### *Device Therapy rates*

During a median follow-up of 27-months, 29.1% of patients experienced at least one episode that resulted in delivery of a device therapy (20% had  $\geq 1$  appropriate therapy, 11% had  $\geq 1$  inappropriate therapy). Upon review of the 2455 therapy episodes received by these subjects,

55% were classified as appropriate, 30% as inappropriate, and 15% were deemed unclassifiable based upon the clinical information available (**Figure 1**). Approximately 43% of treated episodes resulted in a shock. Of 738 patients receiving device therapies, 38% had one, 31% had 2-3, 23% had 4-9, and 8% had 10 or more therapy episodes. Patient characteristics and corresponding therapy incidence rates are shown in **Table 1**.

The cumulative probability of a first device therapy of any type at 3 years was 36% (24% appropriate, 12% inappropriate, **Figure 2**). The 3-year cumulative probability of a first therapy resulting in shock was 24% overall (14% appropriate, 9% inappropriate). At 1 year, the probabilities of an appropriate shock (6.1%) and an inappropriate shock (5.0%) were not significantly different,  $p=0.06$ ). The only notable difference in cumulative probability of first device therapy across CMS CED characteristics, in unadjusted analysis, was that patients with NIDCM <9 months duration were more likely to receive an *inappropriate* therapy (18%) compared to patients with NIDCM >9 months duration (13%), NIDCM of unknown duration (12%), and ischemic etiology (11%,  $p=0.05$ , **Figure 3**). The cumulative probability of first *appropriate* therapy did not differ by ischemic vs. non-ischemic etiologies nor other CMS CED characteristics.

#### *Device Therapy Predictors*

In multivariable modeling, men were nearly twice as likely as women to receive an appropriate therapy (adjusted hazard ratio [HR] 1.84 [1.43-2.35]), as were patients with a history of non-sustained ventricular tachycardia (HR 1.73 [1.37-2.20], **Table 2**). The rate of appropriate therapy was lower among those of Hispanic ethnicity (HR 0.68 [0.49-0.94]) compared with non-Hispanic whites. Adjusted rates of appropriate therapy were not significantly different among the CMS CED patient subgroups compared to their respective referents.

Patients with atrial fibrillation were more than twice as likely to receive inappropriate therapies (HR 2.20 [1.68-2.87]). The rate of inappropriate therapy was lower for patients  $\geq 65$  years compared with younger patients (HR 0.72 [0.54-0.95]) and for those receiving an ICD in 2009 compared to 2006 (HR 0.66 [0.46-0.95]). Compared with patients receiving single-chamber devices, the adjusted rate of inappropriate therapy was lower for patients receiving CRT-D (HR



0.55 [0.36-0.84]). Otherwise, adjusted rates of inappropriate therapy were similar for CMS CED subgroups and their referents, including for patients with NIDCM <9 months duration compared to longer NIDCM durations or ischemic etiologies.

### *Sensitivity analysis outcomes*

In our first sensitivity analysis, we determined that the estimated cumulative probability of appropriate therapies at 3 years could have been 2-6 percentage points higher (i.e., 26%-30% rather than 24%) if the appropriateness of all therapies in the cohort had been classifiable. Similarly, for inappropriate shocks, the cumulative probability could have been as high as 13% rather than the 9% estimated from the classified therapies. However, the simulation results also show that the correction size was consistent across levels of study covariates, indicating that the observed measures of association were stable despite inability to classify some of the therapies.

In the second sensitivity analysis, among the subset with partial device setting data available, the proportion with a VT rate threshold of >200 bpm at implant increased from 6% in 2006 to 18% in 2009. Similarly, the proportion of subjects with arrhythmia detection enhancement programmed to 'on' at baseline increased over the study accrual period from 2% to 30%. In adjusted analyses, patients with a VT rate threshold of >200 beats per minute had a significantly lower rate of inappropriate therapy (HR 0.51 [0.26-1.00]) compared to patients with a baseline VT rate threshold of <180 beats per minute, whereas the rate of appropriate therapy was statistically similar between the groups (HR 0.67 [0.39-1.14], **Table 3**). While baseline arrhythmia detection enhancement programmed to 'on' was associated with a small increased rate of appropriate therapies (of any type) (HR 1.50 [1.06-2.14]), further exploration by therapy type shows that this was not the case for device shocks, with the rate of appropriate shocks lower among those with baseline arrhythmia detection enhancement programming compared to those without (0.72, 0.53-1.00,  $p=0.047$ ). Notably, adjustment for device settings did not change the observed associations of other significant covariate predictors of appropriate or inappropriate therapies (**Table 3**).

## **Discussion**

In this community-based cohort of patients with left ventricular systolic dysfunction who received an ICD for primary prevention, nearly one-third received at least one device therapy over median follow-up of almost 2.5 years. Rates of therapy varied by age, sex, race/ethnicity, and across cardiovascular characteristics; rates of inappropriate therapies declined for implants after 2006. Notably, device therapy rates did not significantly differ for subgroups of interest to CMS in their 2005 coverage expansion (12) and were consistent after accounting for differences in device programming. Results from this “real world” population help address evidence gaps for primary prevention ICD use outside of clinical trials (8,20).

### *Device Therapy Rates*

Rates of device-delivered therapy in this cohort were lower than reported among participants in the randomized clinical trials that established efficacy of ICDs for primary prevention (5,21-22). For example, the 3-year cumulative therapy rate was lower than reported in MADIT II, both for appropriate therapies (34% vs. 24%) (21) and for inappropriate therapies (18% vs. 12%) (22). Several factors may explain this. First, demographic and clinical profiles of this community cohort differ from trial participants (13). Second, rates of evidence-based medical therapies in this cohort were higher than those reported in trials (13).

Third, with nearly a decade between the conduct of landmark efficacy trials and our study period, improvements in device technologies and refined programming strategies likely contributed to lower risks of therapy in our observational cohort. Programming strategies, including higher ventricular tachycardia rate thresholds, longer detection delays, advanced detection algorithms, and optimized discriminators have been shown to reduce the risk of both inappropriate device therapies as well as the risk of appropriate (but unnecessary) device therapies (those that would have terminated spontaneously) (23). While our study period preceded the publication of MADIT-RIT, DECREASE, ADVANCE III, PROVIDE and other recent studies with results supportive of such programming strategies (23-27), it coincides with the reporting of earlier trials including EMPIRIC and PREPARE (28-29) which demonstrated the promise of strategic or standardized device programming. Given the changes we observed in baseline device programming over time, it appears that some strategy refinement was occurring naturally in community practice during the time of our study. Thus, compared with the original

efficacy trial subjects, we believe the lower rates of therapy observed in this more contemporary and diverse cohort of patients are relevant in providing more accurate prognostic information for patients undergoing primary prevention ICD implantation.

Directly comparing device therapy rates across published observational cohort studies is challenging because of variable populations, differential follow up time, and in some cases, restriction of outcomes to shocks alone. Nevertheless, therapy rates in our cohort are comparable to those reported in recent observational studies in Canada, Europe, and the US (30-33). In the Omni study, for example, 25% received an appropriate therapy over a mean of 39 months compared to 20% over 27 months in the LS-ICD (33). Advantages of the observations from the LS-ICD include the large, diverse study population and rigorous clinical adjudication process.

#### *Device Therapy Predictors*

Higher rates of appropriate ICD therapies were observed in men and in non-Hispanic whites compared to Hispanic patients, while higher rates of inappropriate therapies were noted in younger patients. Higher rates of therapy in men have been reported from clinical trials (34) and other observational studies (30,32,35-36). The mechanisms for this are unclear, but men may be more likely to develop malignant ventricular arrhythmias compared with women, which may also explain greater ICD efficacy observed in men in some studies (37). The relation between younger age and inappropriate therapies has been reported in some (38-39) but not in other (22) studies, and may result from more robust atrioventricular conduction of supraventricular arrhythmias among younger patients. The considerably lower risk of appropriate therapy among Hispanic patients is novel and warrants further investigation, especially given reports of similar survival associated with ICD therapy in Hispanic and non-Hispanic white patients (40).

Patients with a history of non-sustained ventricular tachycardia were at increased risk for appropriate device therapies, consistent with prior reports that this rhythm is a risk marker in patients with structural heart disease (41). Atrial fibrillation, a risk factor for inappropriate therapies in previous studies (22,38-39), was associated with a more than twofold higher risk for inappropriate therapy during follow-up. An understanding of the magnitude of this risk, as well

as the impact of evidence-based therapies (e.g., AV nodal blockers) on this risk, will be informative to patients with atrial fibrillation considering ICD therapy.

#### *CMS Coverage with Evidence Development subgroups*

Device therapies among the subgroups defined in the CMS CED decision have not been well characterized despite importance to policy- and clinical decision-makers (12). A key finding of our study is that therapy rates were not significantly different for patients within these subgroups compared with the broader population of ICD patients, with the exception of those receiving CRT-D, who had significantly lower risk of inappropriate therapy compared with single chamber devices. An interesting result in unadjusted analysis, that the cumulative incidence of inappropriate therapy was somewhat higher for patients with NIDCM <9 months duration compared to longer durations of NIDCM or ischemic etiologies, was not borne out in adjusted results. Our findings among these key CMS CED subgroups are consistent with results from the OMNI study (33), which addressed similar questions but was limited to remote monitoring patients, a single device manufacturer, and a much higher proportion of CRT-D devices.

We recognize that the occurrence of an appropriate device therapy is not equivalent to the provision of device benefit (i.e., a device therapy that prevents an arrhythmic death that would have otherwise resulted if the therapy were not delivered). Some malignant ventricular arrhythmias that prompt delivery of an appropriate therapy may have otherwise terminated spontaneously, rendering an appropriate therapy as unnecessary. However, we also know that the two concepts are correlated, and the results can help distinguish characteristics of those who may be benefitting, those who receive inappropriate therapies that are definitely not providing benefit, and those who are not receiving therapies at all.

#### *Limitations*

Certain factors should be considered in interpreting the results of this study. A rigorous process for central adjudication of therapy events is a particular strength of this study. All therapy events were reviewed independently by at least 2 members of the clinical review panel, with any discrepancies resolved through consensus discussion. Cases selected at random for quality assurance review by an external panel of electrophysiology experts showed high agreement on

therapy appropriateness from the central reviewers and the external panel (Kappa = 0.87). Despite this, some therapy events could not be designated as appropriate or inappropriate due to insufficient or inconclusive records. However, in sensitivity analyses, the potential impact of this appeared to be modest, and primarily limited to the magnitude of observed therapy rates and not to the association of therapy predictors. Second, in this observational study, we cannot fully exclude the possibility of residual confounding despite inclusion of a wide range of measured characteristics.

Finally, information on device settings was not available for all patients, and longitudinal changes in device programming for individual patients were not considered. However, in a sizable subset of subjects, we did observe secular trends in baseline settings over the accrual period of our study. Further, the associations of baseline device settings with therapy delivery in this observational cohort are compatible with results of trials assessing the impact of device programming strategies, including in a sensitivity analysis a reduction in the rate of inappropriate therapies with a VT rate threshold >200 bpm, and less appropriate shocks with arrhythmia detection enhancement set to 'on', possibly reflecting reduction of 'appropriate but unnecessary' shocks (i.e, those delivered for ventricular tachycardia that would otherwise have resolved spontaneously). Further, adjusting for baseline device settings did not substantially alter the results or conclusions regarding the associations of other potential predictor covariates in our primary analysis. This suggests that factors other than device programming are responsible for observed relationships, and that consequently, our results provide relevant insights for current clinical practice. To our knowledge, the LS-ICD is the only observational study of the rates and general predictors of all device therapies that has ascertained device programming data and explored its relation to the study outcomes.

### *Conclusion*

The LS-ICD provides estimates of the incidence and correlates of appropriate and inappropriate device therapies in adults receiving primary prevention ICDs in contemporary clinical practice. Rates of therapies in this cohort were lower than reported from clinical trials and varied by certain patient and device characteristics, providing clinicians and patients with useful prognostic data for the growing population of patients treated with ICDs for the primary prevention of

sudden cardiac death. Inappropriate therapies were less common in more recent implants, which is compatible with recognized improvements over time in device programming. The results also offer policy stakeholders confidence in the coverage expansion decisions originally made based on the select populations of randomized clinical trials.

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**Table 1. Baseline Characteristics and Incidence (Rate Per 100 Person Years) of Device-Delivered Therapies (Any Type, Any Appropriateness)**

Characteristics	Number		Mean (Std)	Person Years (PY)	All Device Therapies			
	of Subjects N=2540	Percent*			Number of Therapies N=2455	Incidence		95% CI
						Per 100 PY		
Sex								
	Female	653	25.7	1435	464	32.3	29.5	35.4
	Male	1887	74.3	4050	1991	49.2	47.1	51.4
Age at Implant in years			66.7 (11.5)					
	≥65	1646	64.8	3629	1493	41.1	39.1	43.3
	<65	894	35.2	1855	962	51.9	48.7	55.2
Race/Ethnicity								
	White	1510	59.4	3346	1483	44.3	42.1	46.6
	Black	431	17.0	866	526	60.8	55.8	66.2
	Hispanic	317	12.5	667	225	33.7	29.6	38.4
	Other	282	11.1	605	221	36.5	32.0	41.7
Year of Implant								
	2006	630	24.8	1509	672	44.5	41.3	48.0
	2007	588	23.1	1368	662	48.4	44.9	52.2
	2008	583	23.0	1399	521	37.2	34.2	40.6
	2009	739	29.1	1209	600	49.6	45.8	53.8
Ejection Fraction %								
	≤30	2182	85.9	4701	2096	44.6	42.7	46.5
	31-35	358	14.1	783	359	45.8	41.3	50.8
New York Heart Association Class								
	I	279	11.0	638	273	42.8	38.0	48.2
	II	1200	47.2	2664	1233	46.3	43.8	48.9
	III	1004	39.5	2087	912	43.7	41.0	46.6
	IV	52	2.0	87	37	42.4	30.7	58.5
Device Type								
	Single Chamber	905	35.6	1955	869	44.4	41.6	47.5
	Dual Chamber	811	31.9	1717	888	51.7	48.4	55.2
	Biventricular	824	32.4	1812	698	38.5	35.8	41.5
Left Ventricular Systolic Dysfunction Etiology								
	Ischemic	1593	62.7	3414	1500	43.9	41.8	46.2
	NIDCM, within 9 months	183	7.2	410	177	43.2	37.3	50.1
	NIDCM, greater than 9 months	737	29.0	1600	762	47.6	44.4	51.1
	NIDCM, timing not known	27	1.1	61	16	26.2	16.0	42.7
Congestive Heart Failure								

	No	94	3.7	232	100	43.1	35.5	52.5
	Yes	2446	96.3	5253	2355	44.8	43.1	46.7
Previous Coronary Artery Bypass Graft								
	No	1754	69.1	3781	1751	46.3	44.2	48.5
	Yes	784	30.9	1700	704	41.4	38.5	44.6
Previous Percutaneous Coronary Intervention								
	No	1767	69.6	3819	1811	47.4	45.3	49.7
	Yes	772	30.4	1663	644	38.7	35.9	41.8
Chronic Lung Disease								
	No	2044	80.5	4458	1938	43.5	41.6	45.5
	Yes	495	19.5	1023	516	50.4	46.3	55.0
Diabetes								
	No	1480	58.3	3279	1456	44.4	42.2	46.7
	Yes	1058	41.7	2199	998	45.4	42.7	48.4
Hypertension								
	No	678	26.7	1515	623	41.1	38.0	44.5
	Yes	1858	73.1	3960	1829	46.2	44.1	48.4
Atrial Fibrillation/Atrial Flutter								
	No	1741	68.5	3797	1404	37.0	35.1	39.0
	Yes	794	31.3	1674	1040	62.1	58.5	66.0
QRS Duration/Morphology								
	< 120 msec	1036	40.8	2252	1248	55.4	52.4	58.6
	≥ 120 msec without LBBB	621	24.4	1300	582	44.8	41.3	48.6
	≥120 msec with LBBB	654	25.7	1499	524	35.0	32.1	38.1
	Not fully documented	229	9.0	433	101	23.3	19.2	28.3
Non-Sustained Ventricular Tachycardia								
	No	2191	86.3	4789	1884	39.3	37.6	41.2
	Yes	345	13.6	684	561	82.0	75.5	89.1
Blood Urea Nitrogen Level in mg/dl								
	≥26	870	34.3	1732	788	45.5	42.4	48.8
	18-25	865	34.1	1944	765	39.3	36.7	42.2
	1-17	801	31.5	1796	897	49.9	46.8	53.3
Creatinine Level in mg/dl								
	≥1.4	865	34.1	1719	795	46.3	43.2	49.6
	1.1-1.3	799	31.5	1781	800	44.9	41.9	48.2
	0-1.0	871	34.3	1971	855	43.4	40.6	46.4
ACE Inhibitor or ARB								
	No	357	14.1	714	382	53.5	48.4	59.2
	Yes	2176	85.7	4763	2071	43.5	41.7	45.4
Aspirin								
	No	828	32.6	1784	829	46.5	43.4	49.8
	Yes	1704	67.1	3688	1624	44.0	42.0	46.2
Beta Blocker								
	No	211	8.3	469	246	52.5	46.3	59.5
	Yes	2322	91.4	5005	2207	44.1	42.3	46.0

Coumadin	No	1724	67.9	3766	1516	40.3	38.3	42.3
	Yes	807	31.8	1706	937	54.9	51.5	58.6
Digoxin	No	1776	69.9	3822	1603	41.9	39.9	44.1
	Yes	755	29.7	1649	850	51.5	48.2	55.1
Statin	No	574	22.6	1238	699	56.5	52.5	60.8
	Yes	1959	77.1	4236	1754	41.4	39.5	43.4

\*Percents may not sum to 100% because of rounding/missing values

Std - Standard Deviation

NIDCM - Non-Ischemic Dilated Cardiomyopathy

msec - millisecond

LBBB- Left Bundle Branch Block

mg - milligrams

dL - deciliter

ACE - Angiotensin Converting Enzyme

ARB - Angiotensin II Receptor Blocker

**Table 2. Associations of Baseline Characteristics with Time to First Appropriate and Time to First Inappropriate Device-Delivered Therapy**

Characteristics	Appropriate Therapy*			Inappropriate Therapy*		
	Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits	
Sex (Male vs Female)						
Male	1.84	1.43	2.35	1.30	0.94	1.80
Age at Implant in years ( $\geq 65$ vs $< 65$ )						
$\geq 65$	0.89	0.72	1.11	0.72	0.54	0.95
Race/Ethnicity (ref: White)						
Black	1.24	0.94	1.63	NA		
Hispanic	0.68	0.49	0.94	NA		
Other	0.88	0.64	1.20	NA		
Year of Implant (ref: 2006)						
2007	NA			0.75	0.53	1.07
2008	NA			0.76	0.53	1.10
2009	NA			0.66	0.46	0.95
Ejection Fraction % (31-35 vs $\leq 30$ )						
31-35	0.98	0.75	1.27	1.00	0.70	1.44
New York Heart Association Class (ref: I)						
II	1.25	0.91	1.70	1.22	0.73	2.04



	III	1.32	0.93	1.88	1.65	0.95	2.84
	IV	1.59	0.79	3.19	2.14	0.82	5.59
Device Type (ref: Single Chamber)							
	Dual Chamber	0.97	0.75	1.25	1.04	0.75	1.44
	Biventricular	0.96	0.70	1.32	0.55	0.36	0.84
Left Ventricular Systolic Dysfunction							
Etiology (ref: Ischemic)							
	NIDCM, within 9 months	1.02	0.70	1.48	1.38	0.88	2.18
	NIDCM, greater than 9 months	1.16	0.91	1.48	1.12	0.79	1.59
	NIDCM, timing not known	0.80	0.29	2.18	1.06	0.33	3.44
Congestive Heart Failure (Yes vs No)							
	Yes	NA			1.33	0.52	3.37
Previous Coronary Artery Bypass Graft (Yes vs No)							
	Yes	NA			0.82	0.58	1.15
Previous Percutaneous Coronary Intervention (Yes vs No)							
	Yes	0.74	0.59	0.93	NA		
Diabetes (Yes vs No)							
	Yes	1.20	0.99	1.45	NA		
Atrial Fibrillation/Atrial Flutter (Yes vs No)							
	Yes	1.12	0.92	1.37	2.20	1.68	2.87
QRS Duration/Morphology (ref: <120 msec)							
	≥ 120 msec without LBBB	0.87	0.68	1.12	0.71	0.37	1.38
	≥ 120 msec with LBBB	0.79	0.60	1.05	0.61	0.42	0.90
	Not fully documented	0.46	0.24	0.87	1.01	0.70	1.46
Non-Sustained Ventricular Tachycardia (Yes vs No)							
	Yes	1.73	1.37	2.20	1.27	0.90	1.80
Blood Urea Nitrogen Level in mg/dl (ref: ≥ 26)							
	18-25	0.85	0.68	1.07	1.29	0.93	1.79
	1-17	1.12	0.89	1.42	1.46	1.04	2.04
ACE Inhibitor or ARB (Yes vs No)							
	Yes	NA			0.78	0.56	1.11
Digoxin (Yes vs No)							
	Yes	1.17	0.96	1.43	NA		
Statin (Yes vs No)							
	Yes	NA			0.83	0.61	1.13

\*Models control for Study Site as a random effect

ref. - Referent Group

NA - Not Applicable to that model as variable was dropped at the screening stage

NIDCM - Non-Ischemic Dilated Cardiomyopathy

msec - millisecond  
 LBBB- Left Bundle Branch Block  
 mg - milligrams  
 dl - deciliter  
 ACE - Angiotensin Converting Enzyme  
 ARB - Angiotensin II Receptor Blocker

**Table 3. Associations of Selected Baseline Characteristics with Time to First Appropriate and Time to First Inappropriate Device-Delivered Therapy, Sensitivity Analysis in Subset with Baseline Device Settings (N=1889)**

	Appropriate Therapy*			
	Final Model Rerun in Device Settings Subset		Final Model, including Device Setting Variables in Device Settings Subset	
	Hazard Ratio	95% Confidence Limits	Hazard Ratio	95% Confidence Limits
Sex (Male vs Female)				
Male	1.81	1.34 2.45	1.83	1.35 2.47
Race/Ethnicity (ref: White)				
Black	1.27	0.92 1.76	1.29	0.93 1.78
Hispanic	0.78	0.54 1.13	0.78	0.54 1.14
Other	1.07	0.73 1.57	1.08	0.73 1.58
Previous Percutaneous Coronary Intervention (Yes vs No)				
Yes	0.71	0.53 0.96	0.72	0.53 0.98
Non Sustained Ventricular Tachycardia (Yes vs No)				
Yes	2.03	1.52 2.71	2.04	1.53 2.73
Ventricular Tachycardia Rate Threshold Setting in beats per minute (ref: < 180)				
180-199	NA	NA	0.74	0.54 1.01
200+	NA	NA	0.67	0.39 1.14
Enhanced Detection Setting (Yes vs No)				
Yes	NA	NA	1.50	1.06 2.14
	Inappropriate Therapy†			
	Final Model Rerun in Device Settings Subset		Final Model, including Device Settings, in Device Settings Subset	
	Hazard Ratio	95% Confidence Limits	Hazard Ratio	95% Confidence Limits
Age at Implant in years (≥ 65 vs <65)				
≥65	0.62	0.44 0.88	0.60	0.43 0.85
Year of Implant (ref: 2006)				
2007	0.71	0.45 1.13	0.74	0.46 1.17
2008	0.64	0.40 1.02	0.65	0.40 1.06

2009	0.68	0.44 1.07	0.66	0.40 1.06
Device Type (ref: Single Chamber)				
Dual Chamber	1.46	1.00 2.13	1.29	0.87 1.92
Biventricular	0.60	0.35 1.03	0.55	0.32 0.94
Atrial Fibrillation (Yes vs No)				
Yes	2.29	1.65 3.18	2.25	1.62 3.13
QRS Duration/Morphology (ref: <120 msec)				
≥120 msec without LBBB	0.74	0.47 1.15	0.75	0.48 1.17
≥120 msec with LBBB	0.97	0.61 1.54	0.99	0.62 1.57
Not fully documented	0.93	0.48 1.82	1.26	0.59 2.72
Blood Urea Nitrogen Level in mg/dl (ref: ≥ 26)				
18-25	1.10	0.73 1.45	1.09	0.72 1.64
1-17	1.40	0.94 2.09	1.37	0.92 2.04
Ventricular Tachycardia Rate Threshold Setting in beats per minute (ref: < 180)				
180-199	NA	NA	0.75	0.50 1.11
200+	NA	NA	0.51	0.26 1.00
Enhanced Detection Setting (Yes vs No)				
Yes	NA	NA	1.17	0.69 2.00

\*In addition to variables shown, final model covariates also included age at implant, ejection fraction, New York Heart Association class, device type, left ventricular systolic dysfunction etiology, diabetes, atrial fibrillation, QRS duration/morphology, blood urea nitrogen level, digoxin, plus Study Site as a random effect

†In addition to variables shown, final model covariates also included sex, ejection fraction, New York Heart Association class, left ventricular systolic dysfunction etiology, congestive heart failure, previous coronary artery bypass graft, non-sustained ventricular tachycardia, Angiotensin Converting Enzyme inhibitor/Angiotensin II Receptor Blocker, statins plus Study Site as a random effect

ref. – Referent Group

NA – Not Applicable to that model

msec - millisecond

LBBB- Left Bundle Branch Block

## Figure Legends:

**Figure 1.** Application of exclusion criteria to reach final study cohort (n=2540 total subjects), with display of the distribution of type and appropriateness of device-delivered therapies (n=2455 therapies) among the 738 (29%) subjects who received any device-delivered therapy. Abbreviations: ICD – implantable cardioverter defibrillator; ATP – anti-tachycardia pacing.

**Figure 2.** Unadjusted Kaplan-Meier estimates for occurrence of first device-delivered therapy, by therapy type, with estimated cumulative probability of first therapy (%) at 1, 2, and 3 years, for (A) therapy of any appropriateness, (B) appropriate therapy, and (C) inappropriate therapy. Abbreviation: No. – number.

**Figure 3.** Unadjusted Kaplan-Meier estimates for occurrence of first device-delivered therapy, by baseline clinical strata and therapy appropriateness, with estimated cumulative probability of first therapy (%) at 1, 2, and 3 years, for (A) LVSD etiology – appropriate therapy, (B) LVSD etiology – inappropriate therapy, (C) NYHA class – appropriate therapy, (D) NYHA class – inappropriate therapy, (E) ejection fraction – appropriate therapy, and (F) ejection fraction – inappropriate therapy. Abbreviations: LVSD – left ventricular systolic dysfunction; NIDCM – non-ischemic dilated cardiomyopathy; NYHA – New York Heart Association; EF – ejection fraction; No. – number; gt – greater than; mo – months.