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Device Therapies Among Patients Receiving Primary Prevention Implantable Cardioverter-Defibrillators in the Cardiovascular Research Network

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ORIGINAL RESEARCH

Device Therapies Among Patients Receiving Primary Prevention Implantable Cardioverter-Defibrillators in the Cardiovascular Research Network

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***Background*—**Primary prevention implantable cardioverter-defibrillators (ICDs) reduce mortality in selected patients with left ventricular systolic dysfunction by delivering therapies (antitachycardia pacing or shocks) to terminate potentially lethal arrhythmias; inappropriate therapies also occur. We assessed device therapies among adults receiving primary prevention ICDs in 7 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 after ICD implant from 2006 to 2009, with attention to Centers for Medicare and Medicaid Services Coverage With Evidence Development subgroups: left ventricular ejection fraction, 31% to 35%; nonischemic cardiomyopathy <9 months' duration; and New York Heart Association class IV heart failure with cardiac resynchronization therapy defibrillator. Among 2540 patients, 35% were <65 years old, 26% were women, and 59% were white. During 27 (median) months, 738 (29%) received ≥1 therapy. Three-year therapy risk was 36% (appropriate, 24%; inappropriate, 12%). Appropriate therapy was more common in men (adjusted hazard ratio [HR], 1.84; 95% confidence interval [CI], 1.43–2.35). Inappropriate therapy was more common in patients with atrial fibrillation (adjusted HR, 2.20; 95% CI, 1.68–2.87), but less common among patients ≥65 years old versus younger (adjusted HR, 0.72; 95% CI, 0.54–0.95) and in recent implants (eg, in 2009 versus 2006; adjusted HR, 0.66; 95% CI, 0.46–0.95). In Centers for Medicare and Medicaid Services Coverage With Evidence Development analysis, inappropriate therapy was less common with cardiac resynchronization therapy defibrillator versus single chamber (adjusted HR, 0.55; 95% CI, 0.36–0.84); therapy risk did not otherwise differ for Centers for Medicare and Medicaid Services Coverage With Evidence Development subgroups.

***Conclusions*—**In this community cohort of primary prevention patients receiving ICD, therapy delivery varied across demographic and clinical characteristics, but did not differ meaningfully for Centers for Medicare and Medicaid Services Coverage With Evidence Development subgroups. **(*J Am Heart Assoc*. 2018;7:e008292. DOI: 10.1161/JAHA.117.008292.)**

Key Words: arrhythmia • implantable cardioverter-defibrillator • inappropriate shock • outcomes research • sudden cardiac death

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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 (antitachycardia pacing and/or high-voltage shocks). However,

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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 and 24% for shocks). 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 with their counterparts, even after accounting for differences in baseline device programming.

What Are the Clinical Implications?

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

inappropriate device therapies can also be delivered in response to nonlethal tachyarrhythmias or as a result of device malfunction. Inappropriate ICD therapies are associated with subsequent morbidity and mortality, worsening health status, and cost.[4–6] A greater understanding of the incidence and predictors of device therapies, both appropriate and inappropriate, after 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 United States.[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, the Centers for Medicare and Medicaid Services (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% to 35%; those with nonischemic dilated cardiomyopathy (NIDCM) of <9 months' duration; and those with New York Heart Association (NYHA) class IV heart failure symptoms with a cardiac resynchronization therapy defibrillator (CRT-D).[12] Within the framework of the LS-ICD (Longitudinal Study of Implantable Cardioverter Defibrillators),[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%, if they 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 because of the observational nature of the study.

Data Sources

The LS-ICD links baseline patient and device characteristics from the National Cardiovascular Data Registry ICD Registry,[8] additional baseline and longitudinal clinical data (diagnoses, procedures, laboratory test results, and medications) from the electronic health records of participating sites,[14,15] 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] Although 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 up for up to 2 years. Of >28 000 device interrogations, 60% were from ambulatory clinic visits, 33% were from remote monitoring sources, and 6% were from hospital sources. For those patients with ≥10 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 (VT) "storm."[16] Device therapies were reviewed by 2 members of a central clinical panel (H.V.,

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P.S., J.H., and R.G.M.) to confirm the episode, type of therapy, and therapy appropriateness on the basis of device interrogation reports and intracardiac electrograms. Therapies were classified as appropriate (in response to a potentially malignant ventricular tachyarrhythmia) or inappropriate (attributable 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 antitachycardia pacing alone or as a therapy resulting in shock (either antitachycardia pacing followed by shock or shock alone). Discrepancies between reviewers were resolved by consensus, with additional review by expert electrophysiology adjudicators (S.H., A.K., and P.V.) for unresolved discrepancies and quality assurance.

Patient Characteristics

Patient characteristics included the following: age, sex, race/ethnicity, year of implant, device type, left ventricular ejection fraction, cause (ischemic/nonischemic) 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, left bundle branch block morphological features, and nonsustained VT), select laboratory values (blood urea nitrogen and serum creatinine), and medications prescribed at discharge after ICD implant, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aspirin, β 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 [bpm]), were available in 74% of patients.

Statistical Analysis

All analyses were conducted using 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 predefined 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, or 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 indexes and variance decomposition proportions.[17] For the few variables with negligible missing values (<0.4% of records), simple imputation used the mode. For the 2 variables with greater missing proportions, cardiomyopathy cause/duration (1.1%) and QRS duration and morphological features (9.0%), missing values were assigned a separate category.[18]

Sensitivity Analyses

We explored potential bias from outcome misclassification because of therapies with uncertain appropriateness, using probabilistic bias analysis with record-level replacement.[19] In a second sensitivity analysis, we explored secular changes in baseline device programming during 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 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 7 study sites ranged from 5% to 30%. Of the study group, 26% were women, 35% were <65 years old, and 59% were non-Hispanic white (Table 1). Histories of clinical heart failure (96.3%) and hypertension (73.1%) were common. With respect to subgroups identified in the CMS CED criteria, 358 patients (14.1%) had a left ventricular ejection fraction of 31% to 35%, 183 patients (7.2%) had NIDCM <9 months' duration, and 31 patients (1.2%) had NYHA class IV heart failure symptoms and CRT-D. Because of 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%).

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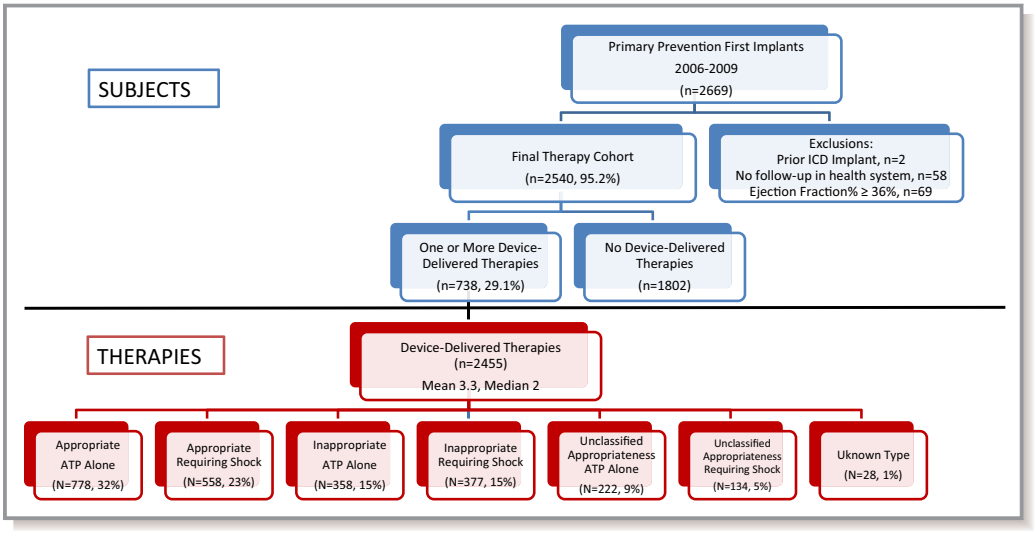

Figure 1. Application of exclusion criteria to reach final study cohort (n=2540 total subjects), with display of the distribution of type and appropriateness of device-delivered therapies (n=2455 therapies) among the 738 subjects (29%) who received any device-delivered therapy. ATP indicates antitachycardia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

Device Therapy Rates

During a median follow-up of 27 months, 29.1% of patients experienced at least 1 episode that resulted in delivery of a device therapy (20% had ≥1 appropriate therapy, and 11% had ≥1 inappropriate therapy). On review of the 2455 therapy episodes received by these subjects, 55% were classified as appropriate, 30% were classified as inappropriate, and 15% were deemed unclassifiable on the basis of the clinical information available (Figure 1). Approximately 43% of treated episodes resulted in a shock. Of 738 patients receiving device therapies, 38% had 1, 31% had 2 to 3, 23% had 4 to 9, and 8% had ≥10 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 and 12% inappropriate; Figure 2). The 3-year cumulative probability of a first therapy resulting in shock was 24% overall (14% appropriate and 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 with patients with NIDCM >9 months' duration (13%), NIDCM of unknown duration (12%), and ischemic cause (11%, P=0.05; Figure 3). The cumulative probability of first *appropriate* therapy did not differ by ischemic versus nonischemic causes 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; 95% confidence interval [CI], 1.43–2.35), as were patients with a history of nonsustained VT (HR, 1.73; 95% CI, 1.37–2.20; Table 2). The rate of appropriate therapy was lower among those of Hispanic ethnicity (HR, 0.68; 95% CI, 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 with their respective referents.

Patients with atrial fibrillation were more than twice as likely to receive inappropriate therapies (HR, 2.20; 95% CI, 1.68–2.87). The rate of inappropriate therapy was lower for patients ≥65 years old compared with younger patients (HR, 0.72; 95% CI, 0.54–0.95) and for those receiving an ICD in 2009 compared with 2006 (HR, 0.66; 95% CI, 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; 95% CI, 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 with longer NIDCM durations or ischemic causes.

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 to 6 percentage points higher (ie,

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

Characteristics	No. of Subjects (N=2540)	%*	Mean (SD)	Person-Years	All Device Therapies		
					No. of Therapies (N=2455)	Incidence	
						Per 100 Person-Years	95% CI
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, y			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 cause							
Ischemic	1593	62.7		3414	1500	43.9	41.8–46.2
NIDCM, within 9 mo	183	7.2		410	177	43.2	37.3–50.1
NIDCM, >9 mo	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

Continued

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Table 1. Continued

Characteristics	No. of Subjects (N=2540)	%*	Mean (SD)	Person-Years	All Device Therapies		
					No. of Therapies (N=2455)	Incidence	
						Per 100 Person-Years	95% CI
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 mellitus							
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/morphological features							
<120 ms	1036	40.8		2252	1248	55.4	52.4–58.6
≥120 ms without LBBB	621	24.4		1300	582	44.8	41.3–48.6
≥120 ms 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
Nonsustained 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, mg/dL			24.9 (13.7)				
≥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, mg/dL			1.4 (0.9)				
≥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

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Table 1. Continued

Characteristics	No. of Subjects (N=2540)	%*	Mean (SD)	Person-Years	All Device Therapies		
					No. of Therapies (N=2455)	Incidence	
						Per 100 Person-Years	95% CI
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
β 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

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; LBBB, left bundle branch block; and NIDCM, nonischemic dilated cardiomyopathy.
*Percentages may not sum to 100% because of rounding/missing values.

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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 bpm had a significantly lower rate of inappropriate therapy (HR, 0.51; 95% CI, 0.26–1.00) compared with patients with a baseline VT rate threshold of <180 bpm, whereas the rate of appropriate therapy was statistically similar between the groups (HR, 0.67; 95% CI, 0.39–1.14; Table 3). Although baseline arrhythmia detection enhancement programmed to on was associated with a small increased rate of appropriate therapies (of any type) (HR, 1.50; 95% CI, 1.06–2.14), further exploration by therapy type shows that this was not the case for device shocks. The rate of appropriate shocks was lower among those with baseline arrhythmia detection enhancement programming compared with those without (HR, 0.72; 95% CI, 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 1 device therapy over a median follow-up of almost 2.5 years. Rates of therapy varied by age, sex, and 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]

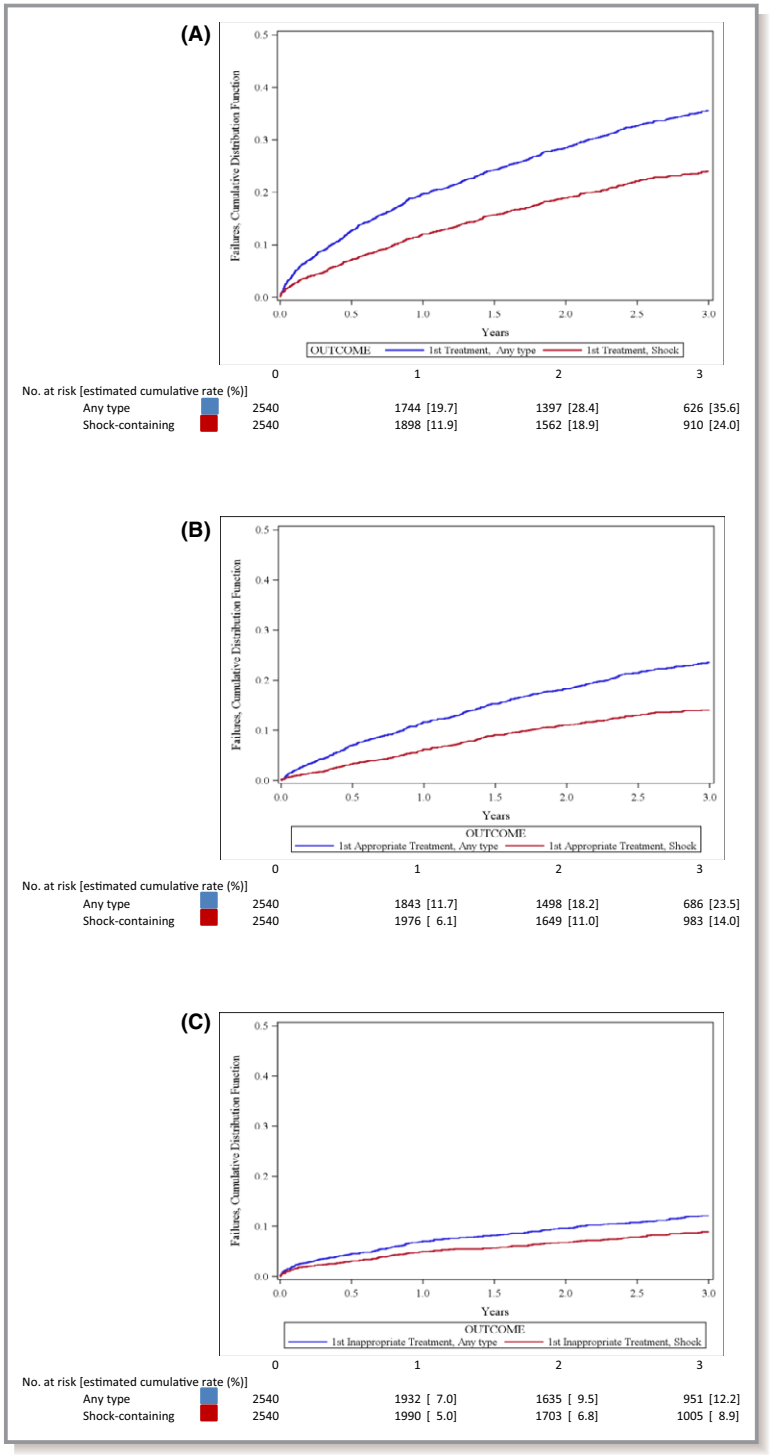

Figure 2. Unadjusted Kaplan-Meier estimates for occurrence of first device-delivered therapy, by therapy type, with estimated cumulative probability of first therapy (percentage) at 1, 2, and 3 years for therapy of any appropriateness (A), appropriate therapy (B), and inappropriate therapy (C).

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 (Multicenter Automatic Defibrillator Implantation Trial) II, for both appropriate

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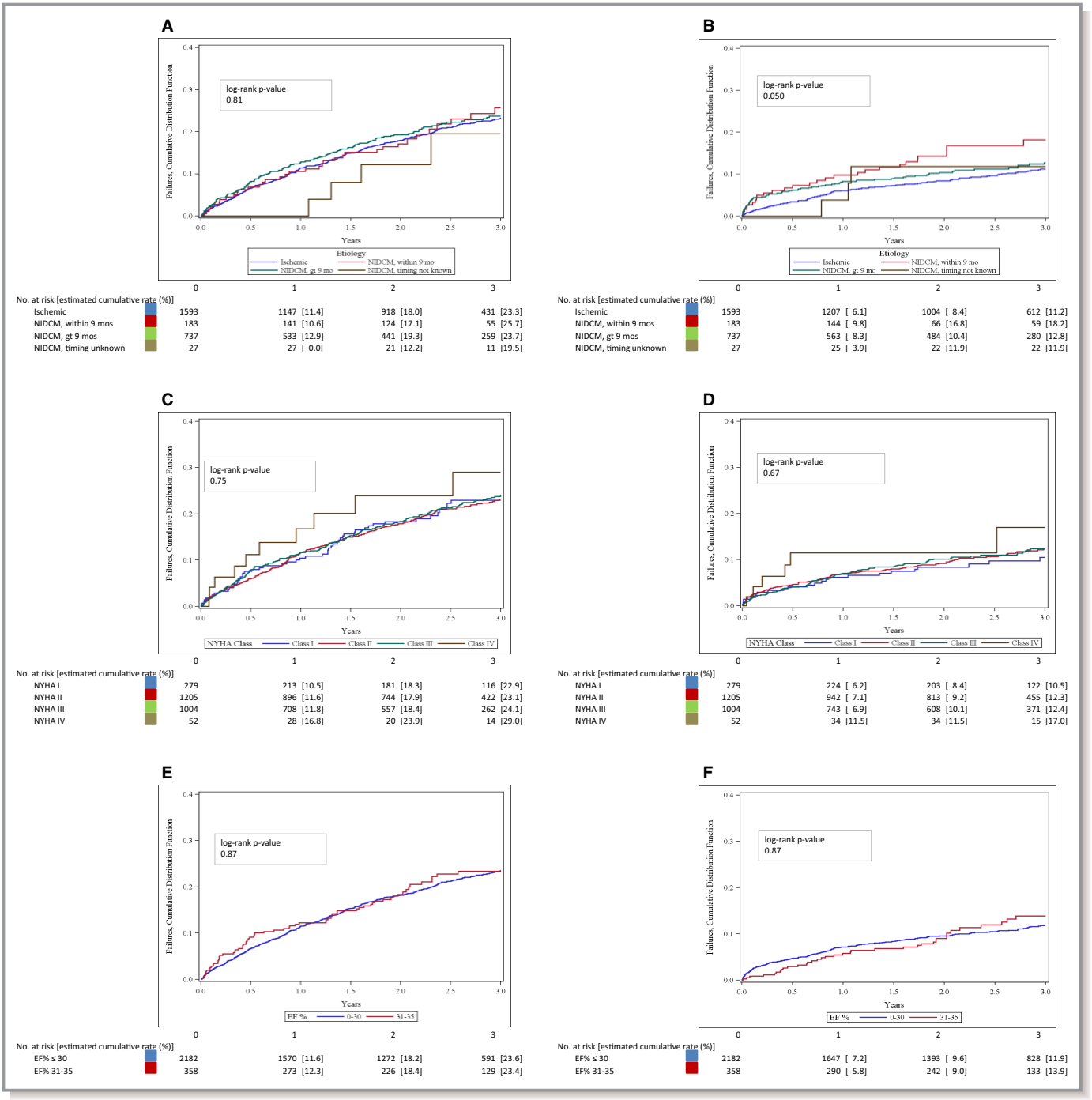

Figure 3. Unadjusted Kaplan-Meier estimates for occurrence of first device-delivered therapy, by baseline clinical strata and therapy appropriateness, with estimated cumulative probability of first therapy (percentage) at 1, 2, and 3 years for left ventricular systolic dysfunction (LVSD) cause (appropriate therapy; A), LVSD cause (inappropriate therapy; B), New York Heart Association (NYHA) class (appropriate therapy; C), NYHA class (inappropriate therapy; D), ejection fraction (EF; appropriate therapy; E), and ejection fraction (inappropriate therapy; F). NIDCM indicates nonischemic dilated cardiomyopathy.

therapies (34% versus 24%)[21] and inappropriate therapies (18% versus 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 VT rate thresholds, longer detection delays, advanced detection

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

Characteristics	Appropriate Therapy*		Inappropriate Therapy*	
	HR	95% CI	HR	95% CI
Sex (male vs female)				
	1.84	1.43–2.35	1.30	0.94–1.80
Age at implant (≥65 vs <65), y				
	0.89	0.72–1.11	0.72	0.54–0.95
Race/ethnicity (referent, 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 (referent, 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 ≤30), %				
	0.98	0.75–1.27	1.00	0.70–1.44
New York Heart Association class (referent, 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 (referent, 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 cause (referent, ischemic)				
NIDCM, within 9 mo	1.02	0.70–1.48	1.38	0.88–2.18
NIDCM, >9 mo	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)				
	NA		1.33	0.52–3.37
Previous coronary artery bypass graft (yes vs no)				
	NA		0.82	0.58–1.15
Previous percutaneous coronary intervention (yes vs no)				
	0.74	0.59–0.93	NA	
Diabetes mellitus (yes vs no)				
	1.20	0.99–1.45	NA	
Atrial fibrillation/atrial flutter (yes vs no)				
	1.12	0.92–1.37	2.20	1.68–2.87
QRS duration/morphological feature (referent, <120 ms)				
≥120 ms without LBBB	0.87	0.68–1.12	0.71	0.37–1.38
≥120 ms 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
Nonsustained ventricular tachycardia (yes vs no)				
	1.73	1.37–2.20	1.27	0.90–1.80
Blood urea nitrogen level, (referent, ≥26), mg/dL				
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)				
	NA		0.78	0.56–1.11
Digoxin (yes vs no)				
	1.17	0.96–1.43	NA	
Statin (yes vs no)				
	NA		0.83	0.61–1.13

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio; LBBB, left bundle branch block; NA, not applicable to that model because variable was dropped at the screening stage; and NIDCM, nonischemic dilated cardiomyopathy.
*Models control for study site as a random effect.

algorithms, and optimized discriminators, have been shown to reduce the risk of both inappropriate device therapies and the risk of appropriate (but unnecessary) device therapies (those that would have terminated spontaneously).[23] Although our study period preceded the publication of MADIT-RIT (Reduce Inappropriate Therapy), DECREASE (Reduction of Inappropriate ICD Therapies in Patients with Approved Indication for Primary Prevention of Sudden Cardiac Death), ADVANCE (Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients) III, PROVIDE (Programming Implantable Cardioverter Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock), and other recent studies, with results supportive of such programming strategies,[23–27] it coincides with the reporting of earlier trials, including EMPIRIC (Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter-Defibrillators) and PREPARE (Primary Prevention Parameters Evaluation),[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

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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)

Variable	Final Model Rerun in Device Settings Subset		Final Model, Including Device Setting Variables in Device Settings Subset	
	HR	95% CI	HR	95% CI
Appropriate therapy*				
Sex (male vs female)				
	1.81	1.34–2.45	1.83	1.35–2.47
Race/ethnicity (referent, 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)				
	0.71	0.53–0.96	0.72	0.53–0.98
Nonsustained ventricular tachycardia (yes vs no)				
	2.03	1.52–2.71	2.04	1.53–2.73
Ventricular tachycardia rate threshold setting, (referent, <180), beats per minute				
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)				
	NA	NA	1.50	1.06–2.14
Inappropriate therapy†				
Age at implant (≥65 vs <65), y				
	0.62	0.44–0.88	0.60	0.43–0.85
Year of implant (referent, 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 (referent, 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)				
	2.29	1.65–3.18	2.25	1.62–3.13
QRS duration/morphological features (referent, <120 ms)				
≥120 ms without LBBB	0.74	0.47–1.15	0.75	0.48–1.17
≥120 ms 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 (referent, ≥26), mg/dL				
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 (referent, <180), beats per minute				
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)				
	NA	NA	1.17	0.69–2.00

CI indicates confidence interval; HR, hazard ratio; LBBB, left bundle branch block; and NA, not applicable to that model.
*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 cause, diabetes mellitus, atrial fibrillation, QRS duration/morphological features, 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 cause, congestive heart failure, previous coronary artery bypass graft, nonsustained ventricular tachycardia, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, statins, plus study site as a random effect.

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 United States.[30–33] In the OMNI (Assessing Therapies in Medtronic Pacemaker, Defibrillator, and Cardiac Resynchronization Therapy Devices) study, for example, 25% received an appropriate therapy over a mean of 39 months compared with 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 with Hispanic patients, whereas 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,

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especially given reports of similar survival associated with ICD therapy in Hispanic and non-Hispanic white patients.[40]

Patients with a history of nonsustained VT 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 >2-fold 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 (eg, 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 patients receiving ICDs, with the exception of those receiving CRT-D, who had significantly lower risk of inappropriate therapy compared with those receiving 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 with longer durations of NIDCM or ischemic causes, 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 (ie, 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 2 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 (K=0.87). Despite this, some therapy events could not be designated as appropriate or inappropriate because of 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. Furthermore, 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. These include a reduction in the rate of inappropriate therapies with a VT rate threshold >200 bpm in a sensitivity analysis and less appropriate shocks with arrhythmia detection enhancement set to on, possibly reflecting reduction of "appropriate but unnecessary" shocks (ie, those delivered for VT that would otherwise have resolved spontaneously). Furthermore, adjusting for baseline device settings did not substantially alter the results or conclusions on 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 their 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

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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 on the basis of the select populations of randomized clinical trials.

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Disclosures

Masoudi has a contract with the American College of Cardiology for his role as the Chief Science Officer of the National Cardiovascular Data Registries. Go has received research funding through his institution from iRhythm Technologies. Gupta serves as local site principal investigator on multicenter clinical trials sponsored by St Jude Medical and Boston Scientific. Hayes has consulting contracts with Medtronic and Boston Scientific. McManus is supported through 1R01HL126911-01A1 and NSF Award #1522052, and has received consultation or research funding from Samsung Electronics, Philips Healthcare, FlexCon, Biotronik, Bristol Myers Squibb, Pfizer, Care Evolution; Inventor/Equity Stake: MobileSense Technologies, LLC (NIH SBIR R43 HL135961). Reynolds has had research funding from Amgen Inc, CSL Behring, and iRhythm. Schuger has had research funding from Boston Scientific, Biotronik, and St. Jude. The other authors have no relevant disclosures to report.

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