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Use of Guideline-Directed Medications for Heart Failure Before Cardioverter-Defibrillator Implantation

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ABSTRACT

BACKGROUND Guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) is recommended before primary prevention implantable cardioverter-defibrillator (ICD) placement. Adherence to this recommendation and associated outcomes are unknown.

OBJECTIVES This study examined the use of GDMT (≥1 prescription filled for both a renin-angiotensin inhibitor [RAI] and a heart failure–approved beta-blocker [HFBB]) within 90 days before primary prevention ICD placement in patients with HFrEF.

METHODS Data from the National Cardiovascular Data Registry ICD Registry were merged with a 40% random sample of Medicare administrative data. Prescription fills for recipients of primary prevention ICD between 2007 and 2011 were examined, analyzing GDMT overall and for each U.S. hospital referral region. We identified characteristics associated with GDMT and the association with 1-year mortality.

RESULTS Among 19,733 patients with HFrEF and primary prevention ICD, 61.1% filled any GDMT before implantation. Across hospital referral regions, GDMT was applied in 51% to 71%. The strongest predictors of any GDMT included absence of chronic renal disease or nonsustained ventricular tachycardia, low-income prescription benefits subsidy, and less recent left ventricular ejection fraction evaluation. Patients receiving GDMT versus those without had a lower 1-year mortality rate after ICD implantation (11.1% vs. 16.2%), even after adjustment for comorbidities, left ventricular ejection fraction, and functional heart failure class.

CONCLUSIONS Rates of GDMT for HFrEF before primary prevention ICD implantation were low, and failure to achieve GDMT was associated with significantly decreased 1-year survival. (J Am Coll Cardiol 2016;67:1062–9)

The benefit of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) is well established, but no study, to our knowledge, has examined GDMT use in the critical period before implantable cardioverter-defibrillator (ICD) placement for primary prevention of ventricular arrhythmias (1,2). Professional society guidelines recommend treating patients

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with GDMT for HFrEF before ICD implantation based on its beneficial effect on HFrEF in general (3–5). Furthermore, primary prevention ICD trials have expected patients to receive appropriate medical therapy before ICD placement. Adherence to GDMT before implantation has the potential to improve survival and may improve left ventricular ejection fraction (LVEF) enough that an ICD is no longer indicated (6,7).

To better understand GDMT use before ICD receipt in the United States, data from the National Cardiovascular Data Registry (NCDR) ICD Registry were linked with Medicare administrative data, and prescription fill patterns in the months before ICD implantation among this older population were examined. We hypothesized that treatment with GDMT would be low, revealing an opportunity to improve pharmacotherapy at a critical time for these patients. Predictors of GDMT were examined, as well as 1-year mortality among patients who did or did not receive GDMT in the 3 months before ICD receipt.

METHODS

STUDY POPULATION. Patients in the NCDR ICD registry from 2007 to 2011 were identified who also appeared in a 40% Medicare random sample denominator file (Master Beneficiary Summary File) and were enrolled in fee-for-service Medicare Parts A (inpatient insurance), B (outpatient insurance), and D (prescription insurance) at the time of ICD receipt. Patients were included in our study cohort if they met the following criteria based on ICD registry data: diagnosed with heart failure, most recent LVEF was ≤40%, ICD indication was primary prevention, and they had no previous ICD implants. Using the Medicare administrative data, patients were excluded if they were: aged <65 years; living outside the United States; and without continuous fee-for-service Parts A, B, and D enrollment for 6 months before ICD, with no Part D prescription fill record in the 6 months before ICD, and without continuous enrollment in fee-for-service Parts A and B in the 12 months after the implantation date or until death (Online Table 1).

OUTCOMES. GDMT was defined as ≥1 prescription fill for both a heart failure-approved beta-blocker (HFBB) (carvedilol, metoprolol, or bisoprolol) and any renin-angiotensin inhibitor (RAI) (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) in the 90 days before ICD implantation (Online Table 2). As a conservative assumption, both short- and long-acting formulations of beta-blockers were included. The 90-day search time before ICD implantation was selected to reflect the minimum recommendation of the Heart Failure Society of America in 2006 and the 2010 Comprehensive Heart Failure Practice Guideline, which suggests a GDMT trial period of 3 to 6 months before primary prevention ICD placement (4). Selected medications were identified from the Medicare Part D Prescription Drug Event file, which records pharmacy dispensing events.

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GDMT was measured in 2 ways. First, we identified patients with ≥1 fill of both an RAI and an HFBB in a 90-day pre-implantation period, a measure of the receipt of any GDMT. Second, we assessed receipt of an adequate supply of GDMT, defined as a medication possession ratio of at least 80% of days covered by GDMT in a 90-day pre-implantation period (i.e., 72 of 90 days). This goal was achieved by assessing GDMT fills in the 120-day pre-ICD period to permit supply carryover into the 90-day pre-ICD period. Each of the 90 pre-implantation days were classified as covered or not covered by using the fill date and the days' supply variables. We assumed dispensed medication supply was not used during inpatient stays (e.g., acute care hospitalization or rehabilitation). The Medicare denominator file was used to measure death within 1 year after ICD implantation.

COVARIATES. Patient characteristics were identified from the ICD registry and Medicare data. The Medicare denominator file was used to identify race and ethnicity, categorized as black, Hispanic, or other (8). Low-income status was based on receipt of the Medicare Part D low-income subsidy dichotomized, a proxy measure of income ≤150% of the federal poverty level. The following comorbidities, diagnosed on 1 inpatient or 2 outpatient Medicare claims in the 6 months before ICD implantation, were also ascertained: cerebrovascular disease, chronic obstructive lung disease, including tobacco use, chronic renal disease, dementia, and diabetes. The number of hospital admissions and admission length in the 6 months before ICD receipt were determined from the Medicare Part A claims. Residential zip code was used to assign each patient to a Dartmouth Atlas of Health Care hospital referral region (HRR), which represents regional health care markets for tertiary medical care (9). ICD registry covariates included: ischemic heart disease, nonischemic dilated cardiomyopathy, past nonsustained ventricular tachycardia, duration of heart failure, New York Heart Association functional class, LVEF, and time since last LVEF measurement.

ABBREVIATIONS AND ACRONYMS

GDMT = guideline-directed medical therapy

HFBB = heart failure–approved beta-blocker

HFrEF = heart failure with reduced ejection fraction

HRR = health referral region

ICD = implanted cardioverter defibrillator

LVEF = left ventricular ejection fraction

NCDR = National Cardiovascular Data Registry

RAI = renin-angiotensin inhibitor

STATISTICAL MODELS. Descriptive statistics were used to assess characteristics of the cohort overall and across subgroups defined according to pre-ICD implantation GDMT use. Relative risk coefficients were estimated by using a Poisson model in which GDMT receipt was a function of demographic characteristics, comorbidities, and heart failure severity. In addition, Poisson regression was used to model the association between receipt of both any GDMT or adequate pre-implantation GDMT and 1-year mortality adjusted for patient characteristics and heart failure severity. Our final models revealed no evidence of overdispersion. For regional measures of GDMT, the age-, sex-, and race-adjusted proportion of patients in the 133 regions with ≥50 total primary prevention ICD recipients in our study sample were calculated. The Committee for the Protection of Human Subjects at Dartmouth College approved this study.

RESULTS

The random 40% Medicare sample included 172,877 subjects in the ICD registry; of these, 78,655 met our inclusion criteria. Exclusions due to requiring continuous Medicare enrollment, age >65 years, and restriction to the contiguous United States decreased the cohort from 78,655 to 20,188. Requiring that 1 of any kind of prescription (not just GDMT) had been filled in the previous 6 months further reduced the cohort from 20,173 to 19,773 (Online Table 1). **Table 1** displays the patient characteristics overall and according to receipt of GDMT. Mean age was 74.9 ± 6.2 years, and 35.4% were female. Based on ICD registry data, 74.4% of patients had ischemic heart disease and 62.0% had nonischemic dilated cardiomyopathy; both conditions were reported for some patients. Symptom severity was moderate, with most patients reported to have NYHA functional class II or III symptoms. LVEF was 20% to 30% for 70.6% of patients and <20% for 12.4% of patients. Heart failure was diagnosed >9 months before implantation for 70.6% of patients; the most recent evaluation of LVEF was within 1 month of implantation for 49.0% of patients. Patients were hospitalized a mean of 1.9 ± 1.4 times in the 6 months before ICD implantation.

Overall, 12,073 (61.1%) patients received any GDMT in the 90 days before ICD receipt while 5,590 (28.3%) received an adequate supply (80% coverage of the 90 days before implantation) of both an HFBB and a RAI (**Table 2**). The proportion of patients receiving GDMT was consistent from year to year (Online Table 3). Data on age, sex, race/ethnicity, poverty, and comorbidities were similar among those receiving GDMT and those not receiving GDMT. At least 1 HFBB or RAI prescription was filled by three-quarters of patients, but slightly less than one-half were dispensed a supply sufficient to cover at least 80% of those 90 days. A sensitivity analysis examining the use of any beta-blocker (HFBB or not) found only slightly higher rates compared with HFBB. The mean number of days covered for HFBB and RAI were 69 and 70, respectively, with a bimodal distribution in which patients had either a high or low number of days covered. Mean days covered according to subgroup is shown in Online Table 4.

The strongest predictors of filling any GDMT prescription included absence of chronic renal disease, absence of past nonsustained ventricular tachycardia, receipt of a low-income prescription benefits subsidy, and the most recent LVEF evaluation >1 month before implantation. **Table 3** presents Poisson regression results for factors associated with GDMT receipt. LVEF, NYHA functional class, race, diabetes, dementia, and timing of symptom onset were not significantly associated with receipt of GDMT.

Death within 1 year of implantation occurred less frequently for patients receiving any pre-implantation GDMT compared with those receiving none (11.1% vs. 16.2%, respectively). In models adjusting for individual characteristics, comorbidities, and heart failure severity, patients who filled any GDMT remained significantly less likely to die within 1 year (adjusted relative risk: 0.80; 95% confidence interval: 0.73 to 0.87) (Online Table 5). Death within 1 year after implantation was also less common for patients with adequate, i.e., 80% medication possession ratio, GDMT (9.4% vs. 14.6%; adjusted relative risk: 0.80; 95% confidence interval: 0.72 to 0.89).

We examined geographic variation in the proportion of patients not achieving GDMT across 133 U.S. health referral regions (HRRs) with >50 ICDs implanted within our study sample (**Central Illustration**). The proportion of patients who filled any GDMT ranged from 44% to 76% (51% to 71% for the 5th to 95th percentile). The proportion of patients with an adequate supply was much lower, ranging from 16% to 49% (5th to 95th percentile: 19% to 38%) (**Figure 1**).

DISCUSSION

Among Medicare beneficiaries with at least moderate HFrEF, 61% of patients filled ≥1 prescription for GDMT in the 90 days before receiving a primary prevention ICD but only one-half that many received a supply adequate to cover 80% of those days. In this

TABLE 1 Demographic and Clinical Characteristics of Patients Categorized According to GDMT Before Implantation

	Total (N = 19,773)	No GDMT Prescriptions Filled (n = 7,770, 38.9%)	Any GDMT Prescription Filled (n = 12,073, 61.1%)	At least 80% of Days Covered by GDMT (n = 5,590, 28.3%)
Age, yrs	74.9 ± 6.2	75.5 ± 6.3	74.5 ± 6.2	74.6 ± 6.1
Black race	1,941 (9.8)	689 (9.0)	1,252 (10.4)	503 (9.0)
Hispanic ethnicity	1,359 (6.9)	477 (6.2)	882 (7.3)	347 (6.2)
Female	6,989 (35.4)	2,477 (32.2)	4,512 (37.4)	2,139 (38.3)
Medicare prescription low-income subsidy	6,696 (33.9)	2,376 (30.9)	4,320 (35.8)	1,949 (34.9)
Hospital admissions in 6 months before implantation	1.94 (1.38)	1.88 (1.36)	1.98 (1.4)	1.70 (1.1)
Year of implantation				
2007	2,382 (12.1)	991 (12.9)	1,391 (11.5)	611 (10.9)
2008	4,601 (23.3)	1,787 (23.2)	2,814 (23.3)	1,321 (23.6)
2009	4,634 (23.4)	1,760 (22.9)	2,874 (23.8)	1,271 (22.7)
2010	4,281 (21.7)	1,674 (21.7)	2,607 (21.6)	1,211 (21.7)
2011	3,875 (19.6)	1,488 (19.3)	2,387 (19.8)	1,176 (21.0)
Comorbidities from medicare claims				
Cerebrovascular disease	4,690 (23.7)	1,910 (25.8)	2,780 (23.0)	1,153 (20.6)
Chronic pulmonary disease	9,016 (45.6)	3,647 (47.4)	5,369 (44.5)	2,293 (41.0)
Chronic renal disease	6,193 (31.3)	2,713 (35.2)	3,480 (28.8)	1,413 (25.3)
Dementia	508 (2.6)	228 (3.0)	280 (2.3)	98 (1.8)
Diabetes	10,010 (50.6)	3,894 (50.6)	6,116 (50.7)	2,755 (49.3)
Clinical data from ICD registry				
Ischemic heart disease	14,689 (74.4)	5,897 (76.7)	8,792 (73.0)	4,039 (72.4)
Nonischemic dilated cardiomyopathy	12,238 (62.0)	4,336 (56.4)	7,902 (65.6)	3,744 (67.1)
Prior nonsustained ventricular tachycardia	4,553 (23.1)	2,093 (27.2)	2,460 (20.4)	1,017 (18.2)
New York Heart Association functional class				
I	537 (2.72)	188 (2.5)	349 (2.9)	180 (3.2)
II	5,796 (29.4)	2,131 (27.8)	3,665 (30.4)	1,835 (32.9)
III	12,519 (63.5)	4,963 (64.7)	7,556 (62.8)	3,375 (60.6)
IV	857 (4.4)	388 (5.1)	469 (3.9)	183 (3.3)
Duration of diagnosed heart failure before implantation				
<3 months	2,684 (13.6)	1,229 (16.0)	1,455 (12.1)	547 (9.8)
3–9 months	3,104 (15.8)	1,111 (14.5)	1,993 (16.6)	937 (16.8)
>9 months	13,917 (70.6)	5,341 (69.5)	8,576 (71.3)	4,083 (73.3)
Left ventricular systolic function				
LVEF	25.58 (6.6)	25.69 (6.7)	25.52 (6.5)	25.93 (6.3)
EF <20%	2,432 (12.4)	967 (12.7)	1,465 (12.3)	577 (10.4)
EF 20%–25%	8,345 (42.6)	3,153 (41.4)	5,192 (43.4)	2,383 (43.0)
EF 26%–30%	5,476 (28.0)	2,125 (27.9)	3,351 (28.0)	1,621 (29.3)
EF 31%–35%	2,872 (14.7)	1,161 (15.3)	1,711 (14.3)	863 (15.6)
EF 36%–40%	449 (2.3)	207 (2.7)	242 (2.0)	98 (1.8)
Timing of most recent LVEF measurement before implantation				
<1 month	9,552 (49.0)	4,186 (55.2)	5,366 (45.0)	2,331 (42.2)
1 month to <3 months	5,409 (28.0)	1,805 (23.8)	3,604 (30.2)	1,655 (30.0)
3 months to <6 months	2,236 (11.5)	728 (9.6)	1,508 (12.7)	774 (14.0)
>6 months	2,318 (11.9)	871 (11.5)	1,447 (12.1)	760 (13.8)

Values are n (%) or mean ± SD. Guideline-directed medical therapy (GDMT) was defined as filling a prescription for carvedilol, metoprolol, or bisoprolol and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the 90-day preimplantation period. Low-income subsidy is a dichotomous indicator of poverty equal to <150% of the federal poverty level and based on the Medicare Part D low-income subsidy qualification variable, dichotomized.

EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

cohort of older Americans fully insured by Medicare, we also observed broad regional variation in the proportion of patients receiving adequate GDMT before ICD receipt, ranging from 16% to 49% across HRRs. These disparities in the use of heart failure pharmacotherapy suggest opportunities to improve the selection and care of patients receiving primary prevention ICDs (10).

TABLE 2 Prescription Fill Rates for GDMT During 90 Days Before ICD Implantation

	Any GDMT Prescription Filled	At least 80% of Days Covered by GDMT
ACE inhibitor or ARB	74.3	46.3
HFBB	77.1	47.0
Any beta-blocker	80.7	52.8
ACE inhibitor or ARB plus HFBB	61.1	28.3
ACE inhibitor or ARB plus any beta-blocker	63.7	32.0

Values are %.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HFBB = heart failure-approved beta-blocker; other abbreviations as in Table 1.

Our findings showed that the ICD recipients with the shortest duration of heart failure and most recently evaluated LVEF were least likely to receive an adequate trial of medical therapy. This association between use of GDMT and both the timing of heart failure diagnosis and the timing of the measurement of LVEF was independent of comorbidities and heart failure severity, suggesting nonclinical factors may play a role in preventing adequate trials of heart failure pharmacotherapy. For example, receipt of a low-income prescription benefit subsidy available to Medicare beneficiaries with income <150% of the federal poverty level significantly increased the likelihood of filling prescriptions for GDMT.

TABLE 3 Poisson Regression Results: Patient Characteristics Significantly Associated With Filling ≥1 Prescription for GDMT in the 90 Days Before Implantation

	RR	95% CI	p Value
Age	0.99	0.99–0.99	<0.001
Female	1.06	1.02–1.10	0.003
Low-income subsidy	1.07	1.03–1.12	0.001
COPD/tobacco	0.95	0.91–0.98	0.004
Chronic renal disease	0.89	0.85–0.93	<0.001
No. of hospital admissions	1.03	1.02–1.04	<0.001
Duration of CHF <3 months	0.91	0.85–0.96	0.001
Nonischemic dilated cardiomyopathy	1.07	1.01–1.14	0.03
Nonsustained ventricular tachycardia	0.90	0.86–0.94	<0.001
Most recent LVEF >1 to <3 months	1.16	1.11–1.21	<0.001
Most recent LVEF >3 to <6 months	1.16	1.09–1.23	<0.001
Most recent LVEF >6 months	1.09	1.02–1.15	0.01

GDMT was defined as filling ≥1 prescription for carvedilol, metoprolol, or bisoprolol and an ACE inhibitor or ARB in the 90-day pre-implantation period. Model covariates also included black race, Hispanic ethnicity, cerebrovascular disease, dementia, diabetes, timing of heart failure symptom onset 3 to 6 months, ischemic heart disease, New York Heart Association functional class, and LVEF at most recent assessment. Timing of the most recent LVEF assessment was compared with assessment <1 month before implantation. Duration of congestive heart failure (CHF) <3 months was compared with duration >9 months.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; RR = relative risk; other abbreviations as in Tables 1 and 2.

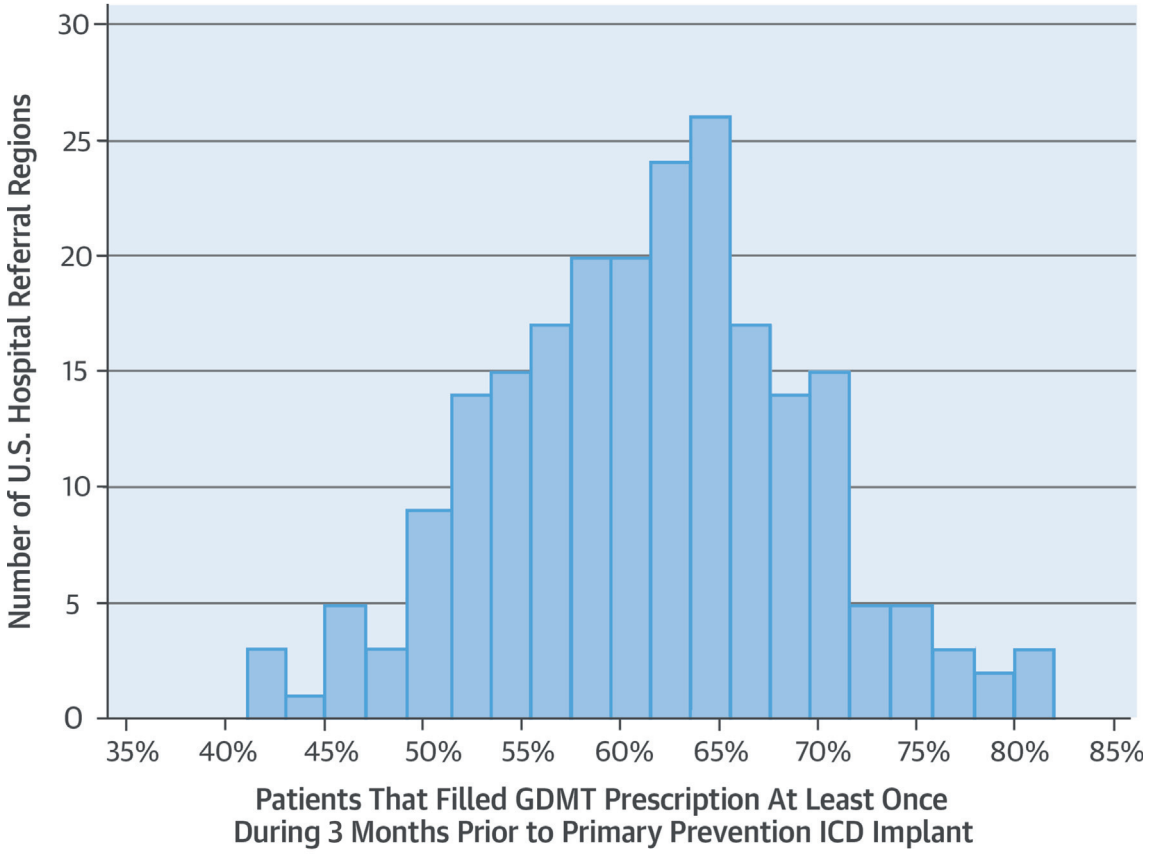
Why would a physician not prescribe a trial of GDMT before ICD implantation? A history of nonsustained ventricular tachycardia and chronic renal disease were associated with a lower likelihood of filling GDMT prescriptions in our study. The use of electrophysiology testing, severe symptoms during nonsustained ventricular tachycardia, persistent hypotension, or chronic kidney disease may lead a physician to forgo treatment with GDMT for the recommended 3 to 6 months before ICD implantation. However, these clinical scenarios are unlikely to explain the wide regional variation in GDMT use observed in our study. For example, prescriptions for adequate GDMT were filled by only 24% to 29% of ICD recipients in Los Angeles, Houston, and Atlanta, the 3 busiest HRRs in our study sample.

The identification of high-risk subpopulations such as those not receiving pre-implantation GDMT is clinically important given the potential survival benefit of heart failure pharmacotherapy for patients with HFrEF in general and the potential to improve selection of patients for primary prevention ICD therapy (10). Current recommendations for selecting ICD candidates rely on the clinical characteristics most likely to improve with adequate GDMT before implantation, including NYHA functional class and LVEF. In the future, physicians should consider documenting medication prescription fills as evidence of a trial of appropriate GDMT in addition to clinical criteria.

SCD-HeFT (the Sudden Cardiac Death in Heart Failure Trial), the largest randomized clinical trial of primary prevention ICD therapy, enrolled patients receiving GDMT for at least 4 weeks. A recent study found no difference in GDMT prescription rates at discharge after ICD implantation, and no difference in survival overall, between patients enrolled in SCD-HeFT and propensity score-matched patients enrolled in the NCDR ICD registry (11,12). Although substantial differences exist between our patient populations and those in randomized clinical trials of primary prevention ICD (notably our inclusion of patients with chronic renal disease), the death rate among patients without any pre-implantation GDMT at 1 year in our study was twice as high as both the ICD and comparator arms of the SCD-HeFT trial (16.2% in our study vs. 8.8% and 7.7% in SCD-HeFT, respectively).

Previous studies have examined gaps in the delivery of GDMT. Miller et al. (13) found that 25.7% of medication-eligible patients failed to receive prescriptions for optimal medical therapy at the time of discharge after ICD implantation. This low rate of prescribing is particularly concerning because the

CENTRAL ILLUSTRATION **Regional Variation in the Proportion of Patients Receiving Guideline-Directed Medical Therapy for HFrEF Prior to Primary Prevention ICD**

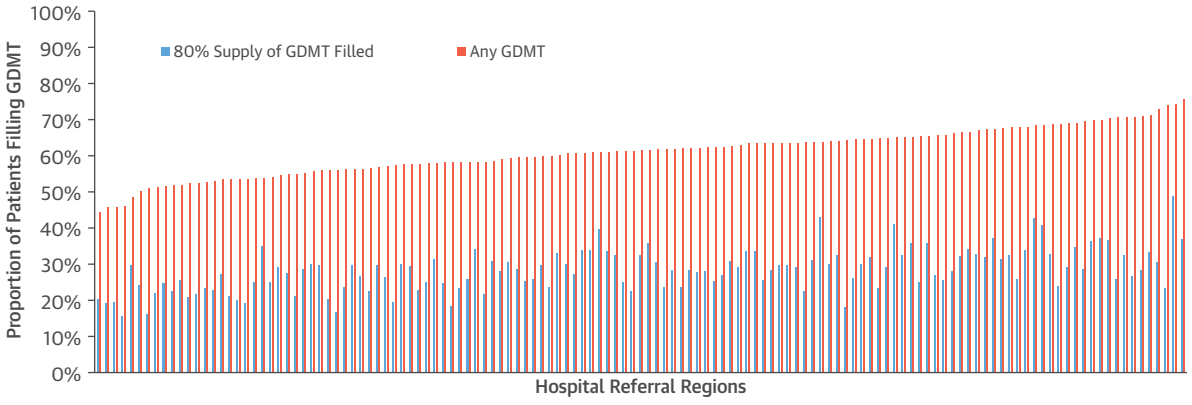


Number of Medicare Beneficiaries	19,773
Number of Hospital Referral Regions Included*	221
Filled heart failure beta blocker at least once	77.1%
Filled ACEi or ARB at least once	74.3%
Filled GDMT (HF Beta Blocker Plus ACEi/ARB)	61.1%
No GDMT Filled	38.9%
GDMT 80% Medication Possession Ratio	28.3%

Roth, G.A. et al. J Am Coll Cardiol. 2016; 67(9):1062–9.

Data from a 40% random sample of Medicare administrative data, 2007 to 2011, and the National Cardiovascular Data Registry Implanted Cardioverter Defibrillator Registry. Restricted to regions with at least 15 device implants. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; GDMT = guideline-directed medical therapy, defined as at least 1 heart failure-approved beta blocker and at least 1 angiotensin-converting enzyme inhibitor or angiotensin receptor blocker prescription filled during the 120 days prior to device implant; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator. *Including regions with at least 15 device implants.

FIGURE 1 Use of GDMT for Heart Failure Before ICD Implantation for 133 HRRs



Proportion of patients with heart failure with reduced ejection fraction receiving guideline-directed medical therapy (GDMT) before implantation of a primary prevention implantable cardioverter-defibrillator (ICD) for 133 hospital referral regions (HRR) in the United States. Included were HRRs in which >50 ICDs were implanted during study sample years 2007 through 2011.

registry variables explicitly included contraindications to GDMT after implantation, something we cannot replicate with the claims data used in our study. Only 1 other study has examined the role of medication use before ICD implantation. Using prescription claims data, Hauptman et al. (14) found that, in a large managed care organization between the years 2003 and 2006, the median number of days covered by any HFBB during the 90 days before ICD implantation was 46. This finding compares with a median of 81 days and a mean of 69 days in our study for HFBB. Notably, the cohort for their study was younger (mean age 60 years) and healthier, with lower rates of diabetes and lung disease, and was not nationally representative. The increase in the prescribing of HFBB from the mid-2000s to the more recent cohort in our study is consistent with national trends and reflects successful diffusion of this important therapy. For example, a cohort of patients receiving primary prevention ICDs at 14 academic hospitals between 2006 and 2009 had discharge prescription rates as high as 91% for HFBB (15).

Adherence to medical therapy is often difficult for physicians performing implantations to ascertain in routine clinical practice. Increased access to electronic health records linked to pharmacy databases may provide opportunities for physicians to better identify patients not filling prescriptions for GDMT. Information about outpatient medication prescription use and careful medication reconciliation by a patient's managing cardiologist should be a vital component of the clinical evaluation of patients with HFrEF before referral for primary prevention ICD therapy.

STUDY LIMITATIONS. Our study was a retrospective data analysis and therefore subject to the limitations common to this research. The association between GDMT before ICD implantation and 1-year survival should not be assumed causal. Indeed, patients who do not fill prescriptions are known to be different from those who do fill prescriptions; these differences are not always well accounted for by using traditional risk adjustment (16). The survival benefit associated with GDMT receipt before ICD implantation may represent the effect of other characteristics correlated with filling prescriptions. Confounding due to these factors could lead to an overestimation of the magnitude of benefit from GDMT. However, given our use of detailed clinical characteristics (including NYHA functional class and LVEF), it is unlikely that this survival benefit is biased by differences in heart failure severity.

Our study used pharmacy fill records to assess prescription receipt. It is unknown if low rates of GDMT are due to inadequate prescribing by physicians or barriers to patients' filling prescriptions. We cannot know whether managing physicians were aware of their patients' adherence rates. Similarly, no data were available on contraindications to GDMT for the study population. However, medication contraindications are not a likely explanation of the observed geographic variation between HRR.

Finally, we defined GDMT as treatment for 90 days before ICD receipt; however, alternate definitions

could be considered and might produce different results. A formal evaluation of clinical benefit rather than an arbitrary amount of time may be the best determinant of an adequate GDMT trial before ICD.

CONCLUSIONS

Rates of GDMT for HFrEF before implantation of primary prevention ICDs were low in this Medicare population, and failure to achieve GDMT were associated with significantly decreased survival within the first year after ICD implantation. There was significant regional variation in the delivery of GDMT during this critical time before ICD implantation. An adequate trial of GDMT before ICD implantation should be part of routine clinical practice. Better delivery of GDMT may improve clinical outcomes and decrease the need for ICD therapy among those patients whose heart failure responds to medical therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: When not contraindicated, patients with HFrEF should receive GDMT before implantation of an ICD for the primary prevention of ventricular arrhythmic death.

TRANSLATIONAL OUTLOOK: Further studies are needed to understand the interaction between pharmaceutical and device therapies, particularly for elderly patients with HFrEF.

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APPENDIX For supplemental tables, please see the online version of this article.