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Primary Prevention Implantable Cardioverter-Defibrillators and Survival in Older Women

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ABSTRACT

OBJECTIVES The purpose of this study was to assess the benefit of primary prevention implantable cardioverter defibrillators (ICDs) in women.

BACKGROUND Clinical trials of primary prevention ICDs enrolled a limited number of women.

METHODS Using a propensity score method, we matched 490 women ≥65 years of age who received an ICD during a hospitalization for heart failure in the National Cardiovascular Data Registry ICD Registry from January 1, 2006, through December 31, 2007, to 490 ICD-eligible women without an ICD hospitalized for heart failure in the Get With The Guidelines for Heart Failure database from January 1, 2006, through December 31, 2009. The primary endpoint was all-cause mortality obtained from the Medicare Claims Database. An identical analysis was conducted in men.

RESULTS Median follow-up for patients with an ICD was 4.6 years versus 3.2 years for patients with no ICD. Compared with women with no ICD, those with an ICD were younger and less frequently white. In the matched cohorts, the survival of women with an ICD was significantly longer than that of women without an ICD (adjusted hazard ratio: 0.79, 95% confidence interval: 0.66 to 0.95; $p = 0.013$). Similarly, men with an ICD had longer survival than men without an ICD (adjusted hazard ratio: 0.73, 95% confidence interval: 0.65 to 0.83; $p < 0.0001$). There was no interaction between sex and the presence of an ICD with respect to survival ($p = 0.44$).

CONCLUSIONS Among older women with left ventricular dysfunction, a primary prevention ICD was associated with a significant survival benefit that was nearly identical to that seen in men. These findings support the use of primary prevention ICDs in eligible patients regardless of sex. (J Am Coll Cardiol HF 2015;3:159–67) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

CI = confidence interval

CMS = Centers for Medicare and Medicaid Services

CRT = cardiac resynchronization therapy

GWTG = Get With The Guidelines

HF = heart failure

HR = hazard ratio

HRS = Heart Rhythm Society

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

NCDR = National Cardiovascular Data Registry

Randomized clinical trials demonstrating a benefit of primary prevention implantable cardioverter-defibrillators (ICDs) comprised only 10% to 30% women (1–4). This lack of trial information, in part, led some to question whether primary prevention ICDs are beneficial in women; however, ICD recommendations in practice guidelines make no distinction between women and men (5,6). Studies have subsequently demonstrated substantially lower use of primary prevention ICDs in women seen in clinical practice (7,8). This disparity is likely multifactorial and may be in part caused by the lack of definitive data on the survival benefit of ICDs in women. Indeed, various retrospective and post-hoc analyses of existing trial data have produced conflicting results (9–14).

A Canadian registry-based study of a combined primary and secondary prevention ICD population demonstrated a wide sex differential in referrals for ICD but similar survival rates among men and women with an ICD (15). In addition, a recent single-center study matched men and women with ICDs by propensity score and found that mortality benefit was similar (16). Other comparisons of the mortality benefit associated with ICDs between men and women have reached similar conclusions (17,18). However, to date, there has been no large multicenter analysis comparing survival in eligible women with and without a primary prevention ICD. Although ideally one would conduct an adequately powered randomized clinical trial to address this specific question, such a trial is highly unlikely because of the associated cost and ethical challenges.

Therefore, this analysis of women in the National Cardiovascular Data Registry (NCDR) and American Heart Association (AHA) Get With The Guidelines-Heart Failure (GWTG-HF) database was conducted to examine the survival difference between women with a primary prevention ICD and eligible women with no ICD. Indeed, one of the primary goals of the NCDR is to determine whether the randomized controlled trial findings can be applied to subpopulations of interest, including women (19).

METHODS

DATA SOURCES. Data for this investigation were acquired from 3 sources: the NCDR ICD Registry, the GWTG-HF database, and the Centers for Medicare & Medicaid Services (CMS). The NCDR ICD Registry and the GWTG-HF database have been described previously (7,20,21). The ICD Registry was launched in 2005 by the American College of Cardiology and the Heart Rhythm Society to meet a CMS mandate that requires submission of data on all Medicare beneficiaries receiving a primary prevention ICD, but a large majority of participating hospitals submit data on all ICD implants. Data are submitted to the ICD Registry via a secure website and then undergo rigorous electronic quality checks. Formal auditing demonstrates that data within the NCDR accurately represent data from medical charts (22). In the most recently available audit data, the raw accuracy of data abstraction for the ICD Registry was 91.2%.

The GWTG program began in 2000 as a voluntary data collection and hospital-based quality improvement initiative. The HF module originated in March 2005 (23). Data quality is monitored via automated checks and site visits to ensure completeness and accuracy; only fully participating hospital sites are used in the analyses. Formal auditing of sample records showed a very high data quality against medical record sources (24). Quintiles Inc. (Durham, North Carolina) serves as the data collection (through their Patient Management Tool [PMT]) and coordination center for the AHA/American Stroke Association GWTG programs. The Duke Clinical Research Institute (Durham, NC) serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. Data include demographic and clinical characteristics, comorbidities, previous therapies and interventions, contraindications to evidence-based therapies, and in-hospital outcomes. Data on ICD therapy include whether an ICD was present on admission, was implanted during the index hospitalization, or was planned after hospital discharge; contraindications to ICD therapy; and any reason documented by a physician for not implanting an ICD during the index hospitalization. Patients enrolled in the GWTG-HF

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program have previously been shown to be representative of the Medicare population (25).

Medicare data include inpatient and outpatient claims and the corresponding denominator files for 2005 through 2011. We linked the registry data to Medicare claims data using a validated method that uses combinations of indirect identifiers (26).

STUDY POPULATION. The ICD group (from the Registry) consisted of all women who received a primary prevention ICD during a hospitalization for HF from January 1, 2006, through December 31, 2007, who were ≥65 years of age and whose primary insurance was Medicare (n = 3,195). We excluded records of patients with no documented left ventricular ejection fraction (LVEF) (n = 23) and patients with a contraindication to an ICD (n = 1,245), including recent onset of HF, recent myocardial infarction or coronary artery bypass grafting, or class IV HF symptoms. We further excluded patients with an LVEF >35% (n = 50) and patients who received a secondary prevention ICD (i.e., implanted for ventricular fibrillation, spontaneous sustained ventricular tachycardia, or inducible sustained ventricular tachycardia on electrophysiological testing; n = 79), an ICD with cardiac resynchronization therapy (CRT) (n = 1,129), or device replacements (n = 22). After these exclusions, 647 records remained from the ICD Registry group.

The initial group without ICDs (from GWTG-HF) included women in the GWTG-HF database hospitalized for HF from January 1, 2005 through December 31, 2009, who did not receive an ICD and were ≥65 years of age and whose primary insurance was Medicare (n = 26,273). Patients who received an ICD at any point during the time period containing the ICD implants used in this analysis (2006 to 2007) and who were recorded in the Registry were counted in the group with ICDs rather than GWTG-HF (n = 6). We excluded from the analysis records of patients who had new-onset HF (n = 2,450); patients with no documented LVEF (n = 4,603) or whose LVEF was >35% (n = 14,484); patients who left against medical advice (n = 17); patients transferred to another acute care facility (n = 119); and patients discharged to hospice, a skilled nursing facility, or a rehabilitation center (n = 1,611). We also excluded records of patients with a contraindication or other reason documented by a physician for not receiving an ICD, including recent onset of HF, recent myocardial infarction or coronary artery bypass grafting, class IV HF symptoms, and no reasonable expectation of survival for at least 1 year (n = 519). After these exclusions, 2,920 records remained for analysis from the GWTG-HF group.

After the above exclusions, qualifying records were then matched with enrollment files and inpatient claims from the CMS data to identify unique patients as described above. These files included information on all fee-for-service Medicare beneficiaries 65 years of age or older who were hospitalized for a diagnosis of HF (International Classification of Diseases-Ninth Revision-Clinical Modification 428.x, 402.x1, 404.x1, and 404.x3). Patient data in the registries were merged with Medicare Part A inpatient claims, with matching by admission and discharge dates, date of birth, sex, and hospital. Of the 3,567 hospitalizations of patients ≥65 years of age, we matched 3,386 to fee-for-service Medicare claims. Only the first hospitalization for each patient among matching records was selected; for patients who appeared in both registries, the ICD Registry record was retained. As a result, our analysis included 3,171 unique Medicare patients, 496 in the ICD Registry, and 2,675 in GWTG-HF.

The same process was used to obtain a study sample of men. The initial group of men from the Registry included all men who received a primary prevention ICD during a hospitalization for HF from January 1, 2006, through December 31, 2007, who were at least 65 years of age and whose primary insurance was Medicare (n = 7,129). Exclusions were applied in the same manner as for women (n = 1,373). The initial group of men from GWTG-HF included men hospitalized for HF from January 2, 2005, through December 31, 2009, who did not receive an ICD and were at least 65 years of age and whose primary insurance was Medicare (n = 18,976). After exclusions as above, 3,856 records remained for men. After matching, 4,527 unique male patients remained, including 1,064 from the Registry and 3,463 from GWTG-HF.

OUTCOMES. All-cause mortality was the primary outcome. Medicare claims data through December 31, 2011, were used to determine vital status. Patients with no record of death in the claims data were considered alive as of December 31, 2011, or the date on which the patient was no longer enrolled in Part A and Part B fee-for-service Medicare, whichever came first.

STATISTICAL ANALYSIS. We compared baseline characteristics of women with and without ICDs using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Summary statistics are reported as percentages for categorical variables and as medians and 25th and 75th percentiles for continuous variables. Any variables with missing values in ≥15% of patients in either group were excluded from further consideration in

TABLE 1 Baseline Characteristics for Women in the ICD Registry and GWTG-HF Registry

Baseline Characteristic	All Women Qualifying for Analysis				1:1 Matched Women			
	GWTG-HF (n = 2,675)	Registry (n = 496)	% Standardized Difference	p Value	GWTG-HF (n = 490)	Registry (n = 490)	% Standardized Difference	p Value
Age, yrs	80 (73, 85)	75 (71, 80)	55	<0.0001	75 (71, 80)	75 (71, 80)	0	0.93
White race	76% (2,010)	70% (346)	15	0.0020	72% (346)	70% (342)	5	0.46
LVEF, %	28 (20, 32)	25 (20, 30)	49	<0.0001	25 (20, 30)	25 (20, 30)	4	0.52
Ischemic heart disease	64% (1,721)	61% (303)	7	0.17	64% (312)	61% (301)	5	0.47
Prior atrial arrhythmia	31% (823)	39% (192)	17	0.0006	38% (185)	38% (187)	1	0.90
Systolic BP, mm Hg	138 (120, 156)	130 (112, 147)	32	<0.0001	131 (116, 148)	130 (113, 147)	3	0.54
Diabetes	40% (1,082)	48% (239)	16	0.0014	46% (227)	48% (236)	4	0.56
Hypertension	74% (1,982)	85% (422)	28	<0.0001	85% (418)	85% (416)	1	0.86
ACE inhibitor or ARB	73% (1,947)	72% (355)	1	0.83	74% (361)	73% (353)	2	0.75
Beta blocker	84% (2,245)	87% (427)	9	0.082	87% (426)	87% (421)	0	0.95
Calcium channel blocker	18% (417)	8% (38)	31	<0.0001	7% (31)	8% (38)	1	0.85
Digoxin	32% (752)	33% (162)	2	0.73	32% (136)	33% (160)	2	0.77
Diuretic	84% (2,031)	83% (406)	3	0.58	84% (371)	83% (401)	4	0.50
Statin	33% (864)	54% (267)	44	<0.0001	54% (258)	54% (261)	0	0.99

Values are median (25th, 75th percentiles) and are compared with Wilcoxon rank sum tests or % (n) and are compared with Pearson chi-square tests. The standardized difference is the absolute difference in means (or proportions) divided by the average standard deviation.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; GWTG-HF = Get With The Guidelines for Heart Failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

the analysis. The standardized difference between groups for each variable was defined as the absolute value of the difference in group means or proportions, divided by the average standard deviation and expressed as a percentage.

Baseline characteristics of patients with and without ICDs were expected to be quite different; this was confirmed with preliminary examination of the data. Therefore, a matching process was planned and employed using the Rosenbaum and Rubin method to derive a set of patients without ICDs similar to the sample of patients with ICDs (the smaller group) (27). After accounting for missing values, propensity models were built for men and women using baseline characteristics deemed to be potentially clinically significant, then patients with ICDs were matched 1:1 to patients without ICDs (Online Appendix).

A Cox proportional hazards model was used to evaluate the association of the presence of an ICD with the risk of all-cause mortality among the matched patients. The model included all women and men, a term for sex, and a term for the interaction between sex and presence of an ICD. The model also contained as covariates all baseline variables used in the matching model, to control for any residual confounding, and was stratified by quartile of propensity score. A robust sandwich variance estimator was used in the Cox models to account for correlation among patients at the same hospital. The proportional hazards assumption for the ICD term was assessed and determined to have been met. Risk relationships are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) within the subgroups of women and men, derived from the Cox model. The interaction term tests whether these 2 HRs are different. Mortality rates at 1 and 3 years are presented both as unadjusted Kaplan-Meier estimates and as adjusted rates derived from the Cox model. Differences were declared to be statistically significant at $p < 0.05$, and all statistical tests were 2-sided. For all analyses, SAS version 9.2 (SAS Institute) was used.

RESULTS

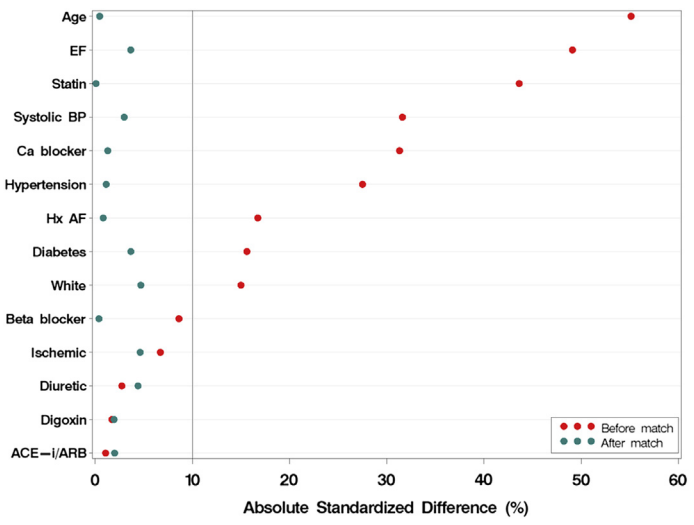
BASELINE CHARACTERISTICS. The baseline characteristics of patients from the ICD Registry and GWTG-HF database (patients without an ICD) before matching are shown in **Table 1**. Compared with women in the group with ICDs, women in the group without ICDs were older and more frequently white. Diabetes, hypertension, and atrial arrhythmias were less common in the group without ICDs before matching. The patients with ICDs had a lower LVEF and a lower systolic blood pressure. Rates of medical therapy with calcium channel blockers and statins also differed between groups.

Baseline characteristics in men for a similar analysis were different before matching (Online Table). Men without ICDs were older and more frequently white; they had different prevalences of diabetes and hypertension. Rates of medical therapy with calcium

channel blockers, diuretic agents, and statins also differed between the 2 groups.

After matching, the group characteristics became similar for women and men. Baseline characteristics in the matched groups are shown in **Table 1** and Online Table, respectively. The <10% absolute standardized difference in all included variables indicates that our matching was similarly effective for men and women (**Figure 1**, Online Table). On average, matched women were 75 years of age, and most were white. Mean LVEF was 25%, and the cause of HF was ischemic in two-thirds of the patients. Most patients were undergoing guideline-recommended medical therapy for HF, including beta-blockers (87% vs. 87%) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (74% vs. 73%). The proportions of patients in each group with diabetes, hypertension, and/or history of atrial arrhythmia were not different. A similar analysis of baseline characteristics in men before and after matching was performed (Online Table). At a significance level of 0.05, no measured variable was significantly different between groups for men or women. The c-index was 0.78 for the propensity model in both men and women.

FIGURE 1 Standardized Differences in Baseline Characteristics of Women Before and After Matching



Before propensity score matching, the groups of women with and without an implantable cardioverter-defibrillator differed by more than 10% on 9 variables. After matching, these groups became more similar, with less than a 10% standardized difference on all included variables. (Only variables used in propensity model and matching are included. Values imputed for the purpose of the matching process are omitted.) ACE-i/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BP = blood pressure; Ca blocker = calcium channel blocker; EF = ejection fraction; Hx AF = history of atrial fibrillation.

MORTALITY. During a median follow-up of 4.6 years, 286 matched women with ICDs died, and during a median follow-up of 3.1 years, 273 matched women without ICDs died (**Table 2**). For men with ICDs, during a median follow-up of 4.4 years, 582 matched men died, and 601 matched men without ICDs died during a median follow-up of 3 years (**Table 2**). As **Table 2** and **Figures 2 and 3** demonstrate, the mortality difference between the 2 groups of women was evident early, with adjusted mortality at 1 year of 21.7% in the patients with ICDs and 28.3% in the patients without ICDs, and this difference was maintained throughout the course of follow-up, with adjusted mortality at 3 years of 44.3% in the group with ICDs and 54.5% in the group without ICDs (**Figures 2 and 3**). Overall, the hazard of mortality in women with an ICD was significantly lower than that of matched patients without an ICD (HR: 0.79, 95% CI: 0.66 to 0.95; $p = 0.013$). Likewise, men with an ICD (in the ICD Registry) had a significantly lower risk of death than matched men with no ICD (in the GWTG database; HR: 0.73, 95% CI: 0.65 to 0.83; $p < 0.0001$) (**Table 2**). A test for interaction suggested no interaction of sex with the presence of an ICD in relation to mortality risk ($p = 0.44$).

Outcomes were examined by age tertile (**Table 3**). Tertile cutoffs were slightly different for men and women, reflecting a small shift in women from patients in their late 60s to patients in their 70s. We further tested for a 3-way interaction between sex, age (by tertile), and the presence of an ICD in relation to mortality risk. This showed no interaction ($p = 0.55$).

DISCUSSION

In this analysis, we found that among older women with depressed LVEF hospitalized for HF, implantation of a guideline-supported primary prevention ICD was associated with a significant survival advantage, similar in magnitude to that seen in men. The adjusted HR for mortality in the group with ICDs compared with the group without ICDs in our study was 0.79 for women and 0.73 for men. These adjusted HRs are consistent with results observed in randomized clinical trials that support the use of primary prevention ICDs in HF patients (1,4). Unlike what was observed in those clinical trials, in our study, the survival curves for women with an ICD versus women with no ICD separated early, likely because of the higher event rates in our population (1,2). Indeed, the mortality rates in follow-up of both groups in this analysis were higher than those seen in

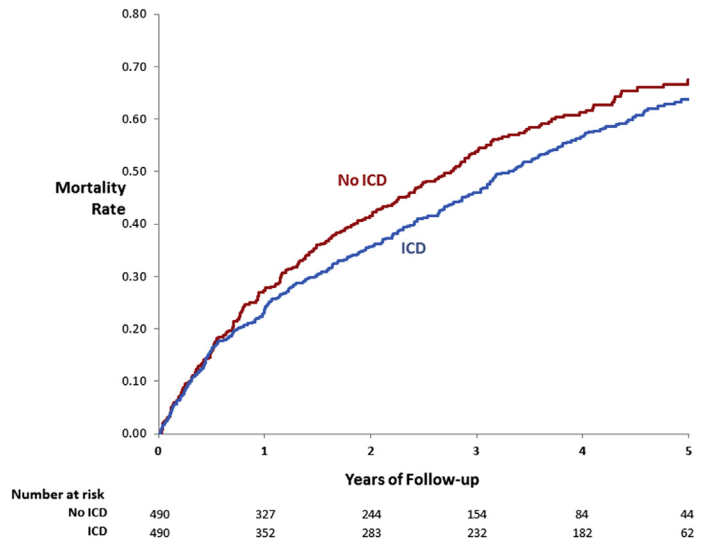
TABLE 2 Results of Mortality Analyses of ICD Use in Eligible Women and Men

	Women		Men	
	ICD (Registry)	No ICD (GWTG-HF)	ICD (Registry)	No ICD (GWTG-HF)
N	490	490	983	983
Follow-up duration among survivors, yrs				
Median	4.6	3.1	4.4	3.0
25th, 75th percentiles	4.0, 5.1	2.0, 4.3	2.5, 5.0	2.1, 4.1
Minimum, maximum	0.027, 5.8	0.014, 6.9	0.014, 6.0	0.030, 6.6
Total deaths	286	273	582	601
Mortality rate (95% CI) at 1 yr	23.7% (20.1-27.8)	27.4% (23.6-31.6)	22.8% (20.3-25.6)	30.1% (27.3-33.1)
Mortality rate (95% CI) at 3 yrs	46.0% (41.5-50.7)	53.8% (49.1-58.6)	47.0% (43.8-50.3)	56.9% (53.6-60.2)
Mortality rate (95% CI) at 3 yrs among 1-yr survivors	29.2% (24.7-34.4)	36.4% (31.1-42.3)	31.3% (28.0-35.0)	38.3% (34.5-42.5)
Adjusted mortality rate at 1 yr	21.7% (21.2-22.2)	28.3% (27.7-28.8)	23.5% (23.2-23.9)	30.5% (30.1-31.0)
Adjusted mortality rate at 3 yrs	44.3% (43.5-45.1)	54.5% (53.7-55.3)	47.3% (46.7-47.9)	57.7% (57.1-58.3)
Adjusted HR (95% CI) for ICD vs. no ICD	0.79 (0.66-0.95)		0.73 (0.65-0.83)	
p Value for HR	0.013		<0.0001	
p Value for interaction of sex with ICD	0.44			

CI = confidence interval; GWTG-HF = Get With The Guidelines for Heart Failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator.

randomized clinical trials. There are several potential explanations for this finding. All patients in this analysis were necessarily identified on the basis of an HF hospitalization, a well-established marker of poor health with a related increase in mortality in Medicare beneficiaries (28). In addition, the cohorts in our analysis were, on average, more than 10 years older than those studied in randomized clinical trials. This is why we looked for an interaction between age, sex, and ICD, which was not significant. This high p value supports the conclusion that if an interaction exists between age and the presence of an ICD in relation to mortality risk, it is consistent across sexes.

FIGURE 2 Unadjusted Kaplan-Meier Estimates of Mortality for Women With and Without an ICD



The unadjusted cumulative risk of death in women with an implantable cardioverter-defibrillator (ICD) was less than that of women without an ICD. This difference was evident at 1 year and persisted throughout the course of follow-up.

The age distribution in our analysis accurately reflects clinical practice. A report of the NCDR ICD Registry from 2010 and 2011 revealed that the average age of ICD recipients was 67.3 ± 13 years (including adult and pediatric patients). When examined by age decile, the largest group was those 70 to 79 years of age, who constituted 30.2% of all those who received implants (29). Moreover, patients undergoing primary prevention ICD implantation in clinical practice are known to have a higher burden of comorbidities than their counterparts in randomized controlled trials, especially when performed in the setting of an unplanned hospitalization (30,31). Therefore, the baseline mortality risk in our analysis was relatively high compared with that observed in randomized clinical trials, and the appropriateness of ICD implantation must be carefully considered on an individual basis.

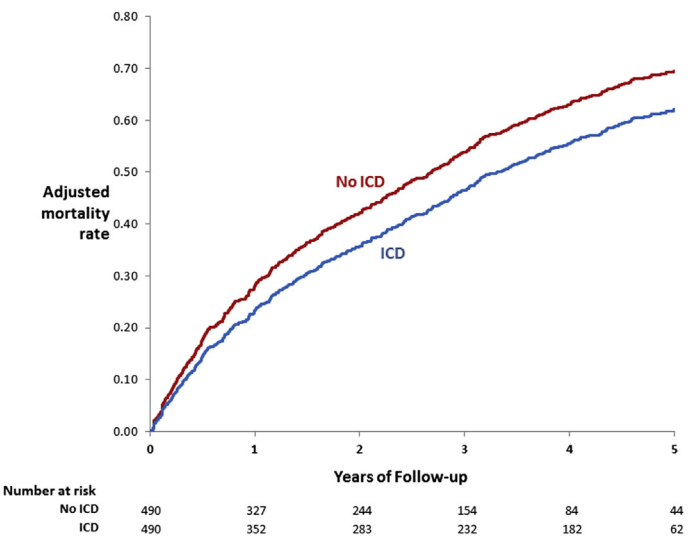
Retrospective examination of the subgroup of women enrolled in randomized clinical trials of primary prevention ICDs has not shown a mortality benefit. A 2009 meta-analysis that pooled data from 5 studies with a total of 934 women concluded that women derived no mortality benefit from primary prevention ICDs (10). A second meta-analysis of primary prevention ICD trials came to a similar conclusion; although the hazard of death was lower in

women with ICDs, the result was not statistically significant (13). However, subsequent retrospective studies and subgroup analyses have contradicted this finding (17,18). Although this controversy may have contributed to lower rates of ICD implantation in women relative to men in clinical practice (32), higher LVEF and older age in women than men with HF are more likely reasons for this difference. Indeed, the benefit of primary prevention ICDs in women has generally been assumed, and there has been insufficient equipoise to justify a clinical trial that randomizes women to an ICD versus no ICD. In the absence of such a trial, comparative effectiveness research such as ours could help inform clinical decision making.

Clinical trials are frequently underpowered to establish an effect in women. Ideally, the use of ICDs in women for primary prevention in HF would be supported by rigorously collected data from randomized clinical trials. However, randomized clinical trials establishing the benefit of primary prevention ICDs have enrolled insufficient women to establish benefit for this subgroup. Reasons for this insufficiency are likely multifactorial, including the fact that women are more likely to decline enrollment in clinical trials, and in the case of HF, women are less likely than their male counterparts to have reduced LVEF.

STUDY LIMITATIONS. One potential limitation of our analysis is residual confounding by variables not captured in our analysis. For example, we could not adjust for hospital setting because of the small overlap between GWTG-HF and NCDR-ICD participating hospitals. Additionally, New York Heart Association functional class was not available for this analysis. Despite the dynamic and subjective nature of this variable, it may be a potential confounder. All variables that were available in both datasets that may be surrogates for HF severity were included: LVEF, systolic blood pressure, and prior atrial arrhythmias (Table 1). The source of data for the non-ICD population was hospitals that participated voluntarily in the GWTG-HF for quality improvement. As such, patients who qualified for a primary prevention ICD but did not receive one may have had a comorbid condition not captured in our analysis that made them both at higher risk for mortality and less appropriate for ICD implantation. Also, we excluded patients who received a CRT device. Primary prevention ICD trials were conducted at a time before CRT was widely implemented, so some patients who would now be eligible for CRT were included in those trials. Their exclusion from our analysis may result in some selection bias for healthier patients with fewer competing mortality risks. Additionally, we relied on a propensity score approach to match groups, which resulted in the exclusion of variables with excessive missing values (e.g., blood urea nitrogen and creatinine) and patients who were too dissimilar to match, which may have excluded certain patients with higher burden of disease (e.g., persons who did not survive to receive an ICD). Because this analysis was limited to a Medicare population hospitalized for HF, there is reduced generalizability of our findings, especially to younger patients and those in different care settings. Thus, our findings may not apply to all women seen in clinical practice. Our analysis was based on data collection from the ICD Registry and the GWTG-HF database, as well as Medicare coding data. Inaccuracies in data entry or Medicare coding could influence our results. Finally, this study could

FIGURE 3 Adjusted Mortality Rates for Women With and Without an ICD



After multivariable adjustment for baseline characteristics listed in Table 1, the cumulative risk of death in women with an implantable cardioverter-defibrillator (ICD) was less than that of women without an ICD. At 1 year, mortality was 21.7% in the women with an ICD and 28.3% in the women without an ICD. At 3 years, adjusted mortality was 44.3% in the women with an ICD and 54.5% in the women without an ICD.

TABLE 3 Age Tertiles by Sex

Women		Men	
Tertile Range (yrs)	N	Tertile Range (yrs)	N
65-72	344	65-71	679
73-78	306	72-78	657
79-92	330	79-99	630

not analyze nonfatal complications of ICD device implantation, inappropriate shocks, quality of life, health status, and other outcomes that may be important in the evaluation of the use of ICD therapy.

CONCLUSIONS

In this propensity-score matched analysis of eligible older women, those who underwent implantation of a primary prevention ICD during hospitalization for HF had a significantly longer survival than those who did not receive an ICD. This survival benefit appeared within the first year and continued throughout follow-up. The survival of women with an ICD closely matched that of men who received this device. Ideally, the benefits of primary prevention ICDs in women would be confirmed with a randomized clinical trial, but until such time, these data support the existing ACC/AHA/HRS guideline recommendation for ICD use among all eligible patients regardless of sex.

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REFERENCES

1. Bardy GH, Lee KL, Mark DB, et al., for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure [published correction appears in N Engl J Med 2005;352:2146]. N Engl J Med 2005;352:225–37.

2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G, for the Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease [published correction appears in N Engl J Med 2000;342:1300]. N Engl J Med 1999;341:1882–90.

3. Kadish A, Dyer A, Daubert JP, et al., for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.

4. Moss AJ, Zareba W, Hall WJ, et al., for the Multicenter Automatic Defibrillator Implantation Trail II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.

5. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons [published corrections appear in J Am Coll Cardiol 2009;53:1473 and J Am Coll Cardiol 2009;53:147]. J Am Coll Cardiol 2008;51:e1–62.

6. Redberg RF. Disparities in use of implantable cardioverter-defibrillators: moving beyond process measures to outcomes data. JAMA 2007;298:1564–6.

7. Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF, Schulman KA. Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death. JAMA 2007;298:1517–24.

8. Hernandez AF, Fonarow GC, Liang L, et al. Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure. JAMA 2007;298:1525–32.

9. Albert CM, Quigg R, Saba S, et al., for the DEFINITE Investigators. Sex differences in outcome after implantable cardioverter defibrillator implantation in nonischemic cardiomyopathy. Am Heart J 2008;156:367–72.

10. Ghanbari H, Dalloul G, Hasan R, et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:1500–6.

11. Henyan NN, White CM, Gillespie EL, Smith K, Coleman CI, Kluger J. The impact of gender on survival amongst patients with implantable cardioverter defibrillators for primary prevention against sudden cardiac death. J Intern Med 2006;260:467–73.

12. Russo AM, Poole JE, Mark DB, et al. Primary prevention with defibrillator therapy in women: results from the Sudden Cardiac Death in Heart Failure Trial. J Cardiovasc Electrophysiol 2008;19:720–4.

13. Santangeli P, Pelargonio G, Dello Russo A, et al. Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis. Heart Rhythm 2010;7:876–82.

14. Zareba W, Moss AJ, Jackson Hall W, et al., MADIT II Investigators. Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. J Cardiovasc Electrophysiol 2005;16:1265–70.

15. MacFadden DR, Crystal E, Krahn AD, et al. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. Ann Intern Med 2012;156:195–203.

16. Bhavnani SP, Pavuluri V, Coleman CI, et al. The gender-paradox among patients with implantable cardioverter-defibrillators: a propensity-matched study. Pacing Clin Electrophysiol 2013;36:878–84.

17. Chen HA, Hsia HH, Vagelos R, Fowler M, Wang P, Al-Ahmad A. The effect of gender on mortality or appropriate shock in patients with nonischemic cardiomyopathy who have implantable cardioverter-defibrillators. Pacing Clin Electrophysiol 2007;30:390–4.

18. Hernandez AF, Fonarow GC, Hammill BG, et al. Clinical effectiveness of implantable cardioverter-defibrillators among Medicare beneficiaries with heart failure. Circ Heart Fail 2010;3:7–13.

19. Hammill SC, Stevenson LW, Kadish AH, et al. Review of the registry's first year, data collected, and future plans. Heart Rhythm 2007;4:1260–3.

20. National Cardiovascular Data Registry. Available at: https://www.ncdr.com/webncdr/home/. Accessed November 8, 2014.

21. Al-Khatib SM, Hellkamp A, Curtis J, et al. Non-evidence-based ICD implantations in the United States. JAMA 2011;305:43–9.

22. Messenger JC, Ho KK, Young CH, et al., NCDR Science and Quality Oversight Committee Data Quality Workgroup. The National Cardiovascular Data Registry (NCDR) Data Quality Brief: the NCDR Data Quality Program in 2012. J Am Coll Cardiol 2012;60:1484–8.

23. Fonarow GC, Abraham WT, Albert NM, et al. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. Am Heart J 2004;148:43–51.

24. Gheorghiade M, Abraham WT, Albert NM, et al., OPTIMIZE-HR Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296:2217–26.

25. Curtis LH, Greiner MA, Hammill BG, et al. Representativeness of a national heart failure quality-of-care registry: comparison of

OPTIMIZE-HF and non-OPTIMIZE-HF Medicare patients. Circ Cardiovasc Qual Outcomes 2009;2:377–84.

26. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. Am Heart J 2009;157:995–1000.

27. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33–8.

28. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA 2011;306:1669–78.

29. Kremers MS, Hammill SC, Berul CI, et al. The National ICD Registry Report: version 2.1 including leads and pediatrics for years 2010 and 2011. Heart Rhythm 2013;10:e59–65.

30. Al-Khatib SM, Hellkamp A, Bardy GH, et al. Survival of patients receiving a primary prevention implantable cardioverter-defibrillator in clinical practice vs clinical trials. JAMA 2013;309:55–62.

31. Stewart GC, Chen C-Y, Stevenson LW, et al. Outcomes among Medicare beneficiaries are optimized when primary ICD implant occurs during an elective rather than unplanned hospitalization (abstr). Circulation 2013;128:A11117.

32. Al-Khatib SM, Hellkamp AS, Hernandez AF, et al. Trends in use of implantable cardioverter-defibrillator therapy among patients hospitalized for heart failure: have the previously observed sex and racial disparities changed over time? Circulation 2012;125:1094–101.

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APPENDIX For an expanded Methods section and a supplemental table, please see the online version of this article.