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Comparative Effectiveness of Implantable Cardioverter Defibrillators for Primary Prevention in Women:

Zeitler et al: Primary Prevention ICDs in Women

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Abstract

Background—Clinical trials of implantable cardioverter defibrillators (ICDs) for primary prevention enrolled a limited number of women. We sought to examine clinical practice data to compare survival rates among women with heart failure (HF) with or without a primary prevention ICD.

Methods and Results—We linked data from 264 US hospitals included in the Get With The Guidelines for Heart Failure (GWTG-HF) registry with data from the Centers for Medicare and Medicaid Services (CMS). From these sources, we propensity score matched 430 women with HF who received a primary prevention ICD to 430 women who did not; we further adjusted using a Cox proportional hazards model. Median follow up was 3.4 and 3.0 years, respectively. For comparison, we matched 859 men receiving an ICD with 859 not; median follow-up was 3.9 vs 2.9 years. In the matched cohorts, an ICD was associated with similarly better survival in women (HR 0.78 95% CI 0.66-0.92 p=0.003) and men (HR 0.76 95% CI 0.67-0.87 p<0.001). There was no interaction between sex and presence of an ICD with respect to survival (p = 0.79).

Conclusions—Among patients with heart failure with reduced LVEF, a primary prevention ICD was associated with a significant survival advantage among women as well as among men. These findings support guideline-directed use of primary prevention ICDs in eligible patients.

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Keywords

comparative effectiveness; heart failure; implantable cardioverter defibrillator; morbidity/mortality; women

Randomized clinical trials established a survival benefit of primary prevention implantable cardioverter defibrillators (ICDs) in patients with heart failure (HF) and reduced ejection fraction. [1-3] However, these trials generally enrolled a majority of men and were underpowered to assess benefits in the smaller subset of women which represented 10-30% of enrolled subjects. Some experts have questioned whether primary prevention ICDs provide benefit to women and have raised substantial concerns regarding underrepresentation of women in clinical trials for devices. [4] Nonetheless, the results of these trials were assumed in national guidelines to apply to otherwise eligible patients regardless of sex. [5] Despite sex neutral guideline recommendations, the actual use of primary prevention ICDs is lower in women versus men[6], and one possible explanation for this may be concerns regarding the paucity of evidence supporting primary prevention ICDs in women.

Ethical challenges make it unlikely that there will ever be a trial of primary prevention ICDs in women. As such, two meta-analyses have been conducted to assess the impact of primary prevention ICDs on survival in women with benefit demonstrated in one [7], but not the other [8]. Results in other post-hoc and observational analyses of primary prevention ICDs in women have been mixed. [9, 10] However, conclusions from these studies were fundamentally limited due to study design leaving unanswered questions about the benefit of primary prevention ICDs in women. We previously compared survival of women with an ICD from the National Cardiovascular Data Registry (NCDR) ICD Registry to matched women without an ICD from Get With The Guidelines for Heart Failure (GWTG – HF), a voluntary hospital based improvement program. [11] We found that the presence of an ICD was associated with improved survival, and there was no evidence of an interaction between sex and the presence of an ICD with respect to survival. However, patients could not be matched based on hospital characteristics, and this may have confounded the analysis.

In this analysis we sought to compare survival between women hospitalized for HF and implanted with a primary prevention ICD with eligible women from similar hospital settings without an ICD implanted. We then compared this with similar matched analyses among men.

Methods

Data Sources

Data for this investigation were acquired from the GWTG-HF registry and the Centers for Medicare & Medicaid Services (CMS). The GWTG-HF registry has been described previously.[12] Briefly, it began in 2000 as a voluntary data collection and hospital-based quality improvement initiative. The HF module originated from the March 2005 Organized Program to Initiate Lifesaving Treatment of Patients Hospitalized with Heart Failure (OPTIMIZE-HF) study.[13] All participating institutions are required to comply with local

regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Outcome, A Quintiles Company (Cambridge, MA), is the data collection and coordination center for the American Heart Association/American Stroke Association Get With The Guidelines programs, and the Duke Clinical Research Institute (DCRI) (Durham, NC) serves as the data analysis center. The DCRI has an agreement to analyze the aggregate de-identified data for research purposes. Hospital characteristics as well as patient demographic and clinical characteristics including comorbidities, previous therapies and interventions, contraindications to evidence-based therapies, and in-hospital outcomes are collected prospectively. Data related to ICD therapy for each hospitalization include whether an ICD was present at admission, implanted during the hospitalization, or planned after hospital discharge; contraindications to ICD therapy, and any reason documented by a physician for not implanting or prescribing an ICD.

Medicare data include Part A inpatient claims and the corresponding denominator files for 2005 through 2012. We linked the registry data to Medicare claims data using a validated method that uses combinations of indirect identifiers and identifies patients 91% of the time. [14]

Study Population

Heart failure admissions in the GWTG-HF registry were merged with Medicare Part A inpatient claims, matching by admission and discharge dates, date of birth, sex, and hospital, using methodology previously described. [14] These linked data were available for admissions from January 1, 2005 through December 31, 2012.

For the present analysis, the initial group of interest included women in the GWTG-HF registry who were at least 65 years old, whose primary insurance was Medicare, and who were linked to CMS data as described above (n=58,742). We sequentially excluded from the analysis records of patients who died during hospital admission (n=2142); received comfort care only (n=2953); were not discharged to home (n=17,809); already had an ICD in place (n=1868); were missing an LVEF or medical history data (n=5398); had an LVEF >35% (n=20,821); or had a contraindication to ICD including recent onset of HF (i.e., HF diagnosis not predating the index admission), recent myocardial infarction (within 40 days) or coronary revascularization (percutaneous coronary intervention or CABG within 90 days), class IV HF symptoms, or no reasonable expectation of survival to one year (n=935); and those who received cardiac resynchronization therapy (CRT) (n=720) because , in these cases, the effect of CRT cannot be distinguished from that of the ICD. Records of subsequent hospitalizations were also excluded (n=716). After these exclusions, 3788 unique Medicare patients remained. Of these, 430 (11%) had an ICD implanted or prescribed during the index hospitalization, and this group made up the ICD population to which non-ICD patients were matched.

The same process was employed to obtain a study sample of men (n=48,478) which resulted in 5,273 unique Medicare patients; 863 of these had an ICD implanted or prescribed during the hospitalization.

Outcomes

All-cause mortality was the primary outcome of this analysis, determined from the Medicare denominator file through 12/31/2012. Patients with no record of death in the denominator file were considered alive as of 12/31/2012 or the date at which the patient was no longer enrolled in Part A & Part B fee-for-service Medicare, whichever came first.

Statistical Analysis

We compared the baseline characteristics of women with and without an ICD using the Pearson 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 25^{th} and 75^{th} percentiles for continuous variables. 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.

Significant differences between ICD and non-ICD patients were expected in this non-randomized sample, and a preliminary examination of the data confirmed this. We used the methods of Rosenbaum and Rubin to develop matched groups. [15] First, for continuous variables, we excluded non-ICD patients whose value was below the minimum or above the maximum for ICD patients. Second, missing data were imputed. Missing rates were generally quite low, but up to 15% of data on medications were missing. When a contraindication to the medication was noted, the value for that medication was set to 0; otherwise missing data were imputed by using a single Markov chain Monte Carlo (MCMC) imputation. Third, a propensity model was built using logistic regression in which the dependent (outcome) variable was an indicator of whether each patient belonged to the group with an ICD or without an ICD, and the independent (predictor) variables were baseline characteristics including age; race (white versus other); LVEF; systolic blood pressure (SBP); medical history including ischemic heart disease, prior atrial arrhythmia (including atrial fibrillation and/or atrial flutter), diabetes, hypertension, chronic renal insufficiency, depression, chronic obstructive pulmonary disease (COPD) or asthma, anemia, or prior CVA/TIA; medications at discharge including angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), beta blocker, calcium channel blocker, digoxin, diuretic, and statin; relevant laboratory values including hemoglobin, sodium, BNP, and creatinine from admission when available and otherwise from discharge; and hospital characteristics including geographic region, teaching hospital, number of beds, and whether the hospital performs advanced cardiac procedures. From the logistic regression model, an estimated propensity score (the probability – p—of being an ICD patient) and a corresponding logit for the propensity score ($\log_e[p/(1-p)]$) were calculated for each patient.

Fourth, for the matching process, a caliper width of 0.25*(standard deviation of the logit) was used. For a given patient with an ICD, all patients without an ICD were considered whose logit differed from the ICD patient's logit by less than the caliper width. Among these patients, the patient without an ICD with the shortest Mahalanobis distance from the ICD patient was selected as a match. Variables used in calculating the Mahalanobis distance were

all significant predictors from the propensity model. Each patient without an ICD was matched no more than once; there were no patients with an ICD left unmatched. These procedures were repeated to develop a subgroup of men.

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. Because the patient cohorts were matched, the unadjusted results are considered the primary results. A robust sandwich variance estimator was used 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. As a sensitivity analysis, to determine whether residual confounding affected the estimates, the model was repeated adjusting for all variables in the propensity model, and stratified by quartile of propensity score. Missing values of covariates were imputed using multiple imputation. Risk relationships are expressed as hazard ratios (HR) with 95% confidence intervals (CI) within the subgroups of women and men derived from each Cox model. Mortality rates at 1 and 3 years are presented as Kaplan-Meier estimates in the primary results and as predicted (adjusted) rates in the sensitivity results.

Differences were declared to be statistically significant at $p < .05$, and all statistical tests were 2-sided. For all analyses, SAS version 9.2 (SAS Institute, Cary NC) was used.

Preliminary examination of the primary outcome data demonstrated very early separation in survival curves between the groups of patients with and without an ICD. We explored whether excluding patients who died in the first 30 days after hospitalization would reduce this effect. A landmark model was performed beginning 30 days after discharge which resulted in omission of 29 ICD patients (2%) and all similar patients without an ICD (n=343, 4%). The samples were re-matched and the Cox model was recreated.

Results

Baseline Characteristics

The unmatched baseline characteristics of women from GWTG-HF with and without an ICD are shown in Table 1. A similar table for men is included in Appendix I. Compared with women with HF and no ICD, those with an ICD were younger and were more likely to have been admitted to a larger teaching hospital. The rates of comorbid conditions including ischemic heart disease, diabetes, hypertension, renal failure, depression, and history of stroke or TIA were similar between the 2 groups. After propensity score matching, the differences between groups were smaller (Table 2 and Figure 1) with an absolute standardized difference on all variables less than 10%. In this group, 64% of patients received an ICD during the index admission with the remaining patients (36%) being prescribed an ICD on discharge. Matching in the subgroup of men achieved absolute standardized differences on all variables no greater than 10% (Figure 1).

Mortality

The median follow up was 3.4 and 3.0 years respectively for the propensity matched groups of women with and without an ICD. The overall risk of mortality was significantly lower in women with an ICD compared with those without an ICD (HR 0.78 95% CI 0.66-0.92, p=0.003). This mortality difference appeared early and persisted throughout follow up with mortality at 3 years of 40.2% in the group with an ICD and 48.7% in the group without an ICD (Table 3, Figure 2A). A similar survival benefit was seen in the propensity matched group of men with an ICD compared to those without an ICD (HR 0.76 95% CI 0.067-0.087, p<0.001) (Table 3, Figure 2B). A test for interaction demonstrated that improved survival associated with implantation of an ICD did not depend on sex (p=0.79).

To further adjust for small remaining imbalances between groups, the primary propensity matched results were adjusted for the covariates listed in Table 2. In this propensity matched and adjusted model, the risk of mortality in women with an ICD compared with those without an ICD was nearly identical to the primary propensity matched results (HR 0.75 95% CI 0.63-0.90, p=0.002) (Table 3). This was also true in men (HR 0.76 95% CI 0.67-0.86, p<0.001) (Table 3).

In a 30-day landmark analysis we removed early deaths. Even after removing those with early mortality the propensity matched mortality HR was nearly identical to that observed in the primary analysis (0.80 for women and 0.81 for men (Table 3).

Finally, we conducted a survival analysis in women and men in which all patients with an ICD – including those with an ICD at the time of HF hospitalization – were included in the ICD group. While the survival benefits were attenuated modestly in both men and women, no interaction of ICD and sex was seen (Appendix II).

Discussion

Our study found that in both older women and men with HF and reduced LVEF, implantation or prescription of a primary prevention ICD on discharge was associated with improved survival. Relative to those not receiving an ICD, those receiving (or prescribed) an ICD had similarly improved survival in both women and men, with no significant sex-based interactions. These hazard ratios are similar to those seen overall in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (HR for mortality in ICD versus placebo groups = 0.77) which, among the landmark randomized clinical trials of primary prevention ICDs, most closely resembles the population studied here. [1]

Despite the survival benefits of primary prevention ICDs in HF patients demonstrated in randomized clinical trials, benefit in the subgroup of women from these trials has not been definitively proved. [7-9] This uncertainty regarding survival benefit may be one of several contributing factors to the lower rates of ICD referral and implantation in eligible women. [6, 16, 17] Indeed, in this cohort, only 11% of eligible women and 16% of eligible men received an ICD or a prescription for one at the time of HF hospitalization. These low rates are consistent with other investigations which found underutilization of ICDs. [18, 19] In the absence of an adequately powered analysis from a randomized clinical trial, we previously

compared survival of women with an ICD from the National Cardiovascular Data Registry (NCDR) ICD Registry to matched women without an ICD from GWTG–HF. [11] The survival benefit of a primary prevention ICD for women was similar to that seen in this analysis, but we were unable to match for certain patient and hospital characteristics resulting in possible confounding Moreover, the cohort size of women with a primary prevention ICD studied in this analysis (and our previous investigation) is greater than any examined in a randomized clinical trial.

In this analysis we matched women hospitalized for HF who were eligible for a primary prevention ICD and either received one (or were prescribed one on discharge) or did not receive one. Given the observational nature of these data, we used propensity score matching to create groups that were as similar as possible using a model that included variables representing demographic and clinical patient characteristics as well as characteristics of the hospital in which patients were treated for HF. Notably, hospital characteristics were very similar after matching (Table 2 and Figure 1) differing by no more than 2% on geographic region, teaching versus non-teaching, size, and availability of advanced cardiac procedures. This indicates that each woman with an ICD was generally compared with a woman without an ICD from a similar hospital; therefore, hospital site does not explain differences in survival.

Importantly, the survival curves in this analysis separated early (Figure 2). In part, this may be due to the high event rates observed in this population based on relatively older age and more comorbidities compared to clinical trial patients.[20] In addition, patients in this analysis were necessarily identified based on a HF hospitalization which has been associated with worse outcomes in Medicare patients[21, 22]. Indeed, when the benefits of a primary prevention ICD have been examined in the sickest subgroup of patients in clinical trials, a similar finding of early curve separation has been seen as in the case of New York Heart Association (NYHA) class III patients in SCD-HeFT and Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trials. [1, 2] However, to fully investigate early curves separation in this context, we performed a 30-day landmark analysis to examine the effect of early deaths on the survival curves (Table 3). Exclusion of patients who died early simply delayed the early separation of curves by 30 days. This suggests that the differences in survival were not explained by a lead time bias.

Investigation of the mortality benefit of a primary prevention ICD in women has been ongoing since the landmark clinical trials which did not answer this question definitively. Various retrospective, post hoc, registry-based, and/or meta-analytic studies have sought to answer this question and have arrived at varying results. [7-10] In light of this controversy, providers, professional societies, guideline committees, regulators, and others have assumed that, on average, the potential benefit of a primary prevention ICD in women outweighs the associated risks. Therefore, there is insufficient equipoise to justify a randomized controlled clinical trial, and in the absence of such a trial, analyses of non-randomized clinical cohorts such as this are important to inform clinical decision making.

While this analysis and others demonstrate a mortality benefit for women from a primary prevention ICD, this benefit must be weighed against potential risks. This is particularly

important for women because complication rates associated with primary prevention ICD implantation tend to be higher compared with men. [23] Future research is needed to identify ways to reduce complication rates in order to maximize the net benefit from primary prevention ICDs in women.

Limitations

The primary limitation of this analysis is that treatment assignment was not assigned randomly, and despite propensity matching and additional risk adjustment there remains the potential for residual measured and unmeasured confounding by variables not captured in the GWTG-HF registry, and a provider's assessment of a patient's overall fitness for ICD implantation includes consideration of many of these factors together. Those patients without an ICD implanted or prescribed may have been too sick to undergo the procedure such that mortality differences may be a reflection of underlying comorbidities. For example, NYHA class was not available for this analysis, nor were characteristics describing quality of life and patient and provider preferences, and these variables may have contributed to decisions surrounding ICD implantation as well as survival differences. This analysis was concerned with outcomes in patients who had an ICD implanted or prescribed during a HF hospitalization, but planned implantations cannot be confirmed. Most patients undergoing ICD implantation in the US do so during a hospital stay that is less than 24 hours[24], so data related to these implants are not available in the Medicare Part A claims to which we had access. We relied on a propensity score matching process to develop groups for comparison which necessarily excludes patients who are too dissimilar to match (e.g., those with a high burden of disease). Lastly, we limited our analysis to Medicare patients hospitalized at a hospital participating in GWTG-HF which is a voluntary quality improvement program. While this group has previously been demonstrated to be similar to the Medicare population as a whole [25-27], our results may not generalize to younger, healthier patients or those in alternative clinical settings.

Conclusion

In a propensity score matched analysis of Medicare patients with HF and reduced LVEF, we found both women and men implanted with a primary prevention ICD during or following a heart failure hospitalization had significantly longer survival compared with their counterparts who did not receive an ICD, and there were no significant sex-based interactions for the survival benefits associated with ICD placement. The associated survival benefit appeared early post hospitalization but was not sensitive to the exclusion of patients who died within a month of discharge, and this benefit was present throughout available follow up. These data support current guideline recommendations for the implantation of a primary prevention ICD in eligible women as well as men with heart failure and reduced LVEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspective

Clinical trials of implantable cardioverter defibrillators (ICDs) for primary prevention enrolled a limited number of women and were underpowered to assess benefits in this important subgroup. However, in light of the overall results of these landmark trials, the benefits of primary prevention ICDs have been assumed in national guidelines to apply to all eligible heart failure (HF) patients regardless of sex. Ethical limitations make it unlikely that there will ever be a randomized trial of primary prevention ICDs in women. As such, various post hoc, retrospective, and meta-analytic evaluations of the effect of ICDs on mortality in women have generated varying results. Therefore, in this analysis from the Get With The Guidelines for Heart Failure (GWTG-HF) Registry, women hospitalized for heart failure who had an ICD implanted or prescribed were matched to similar women without an implanted or prescribed ICD using a propensity score model. When survival was compared between these two groups, those women who had a primary prevention ICD implanted or prescribed had a significant survival advantage over women without an ICD. A parallel analysis of men from GWTG-HF demonstrated similar results. These findings support guideline-directed use of primary prevention ICDs in eligible patients regardless of sex.

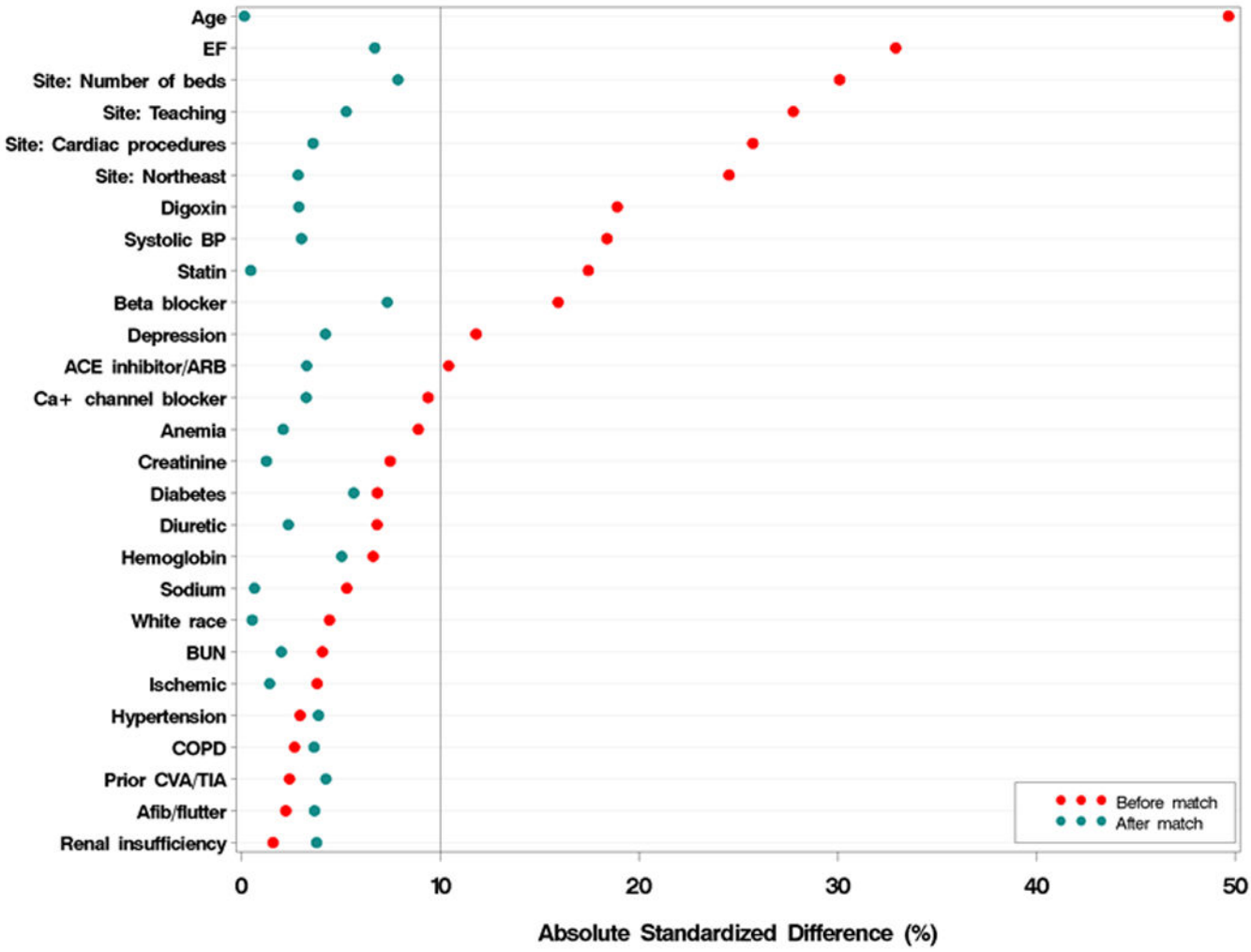
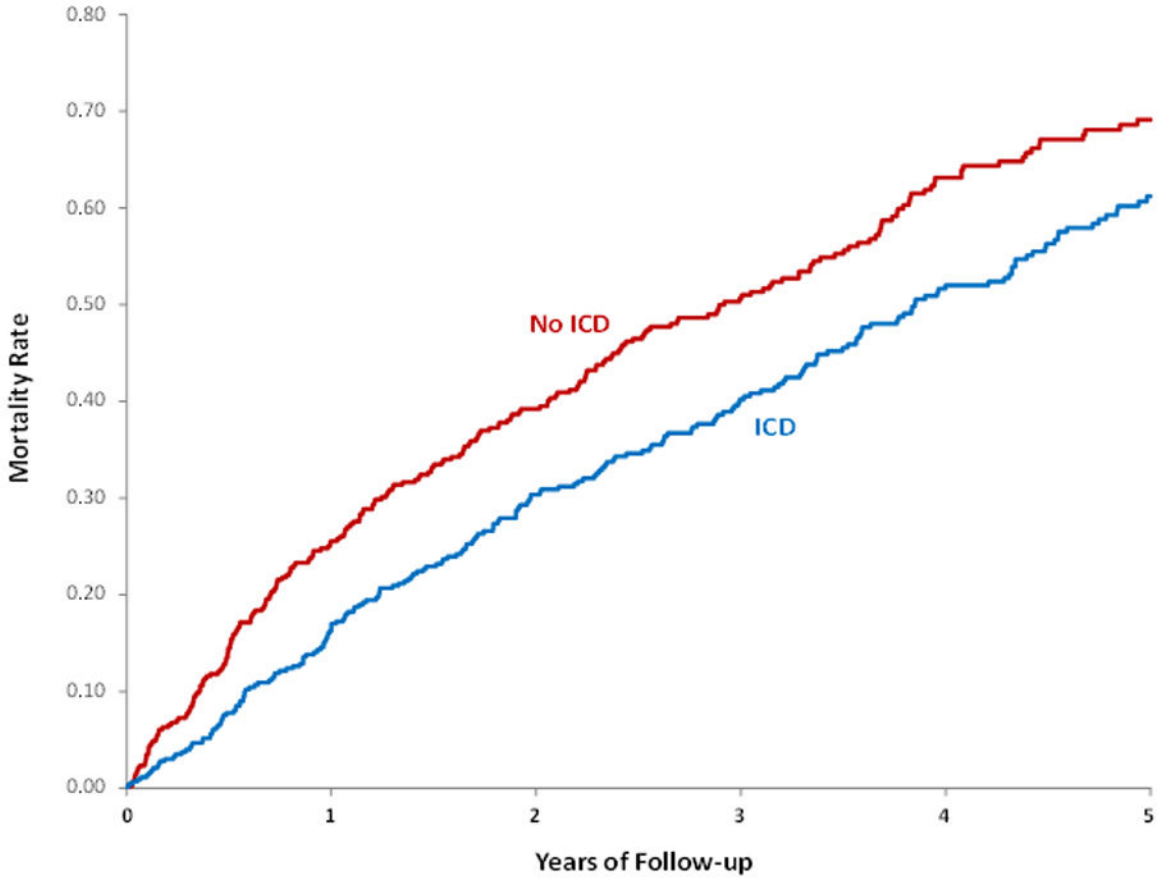


Figure 1. Standardized differences in baseline characteristics in women before and after matching



Number at risk						
No ICD	430	297	215	148	90	58
ICD	430	340	254	188	130	76

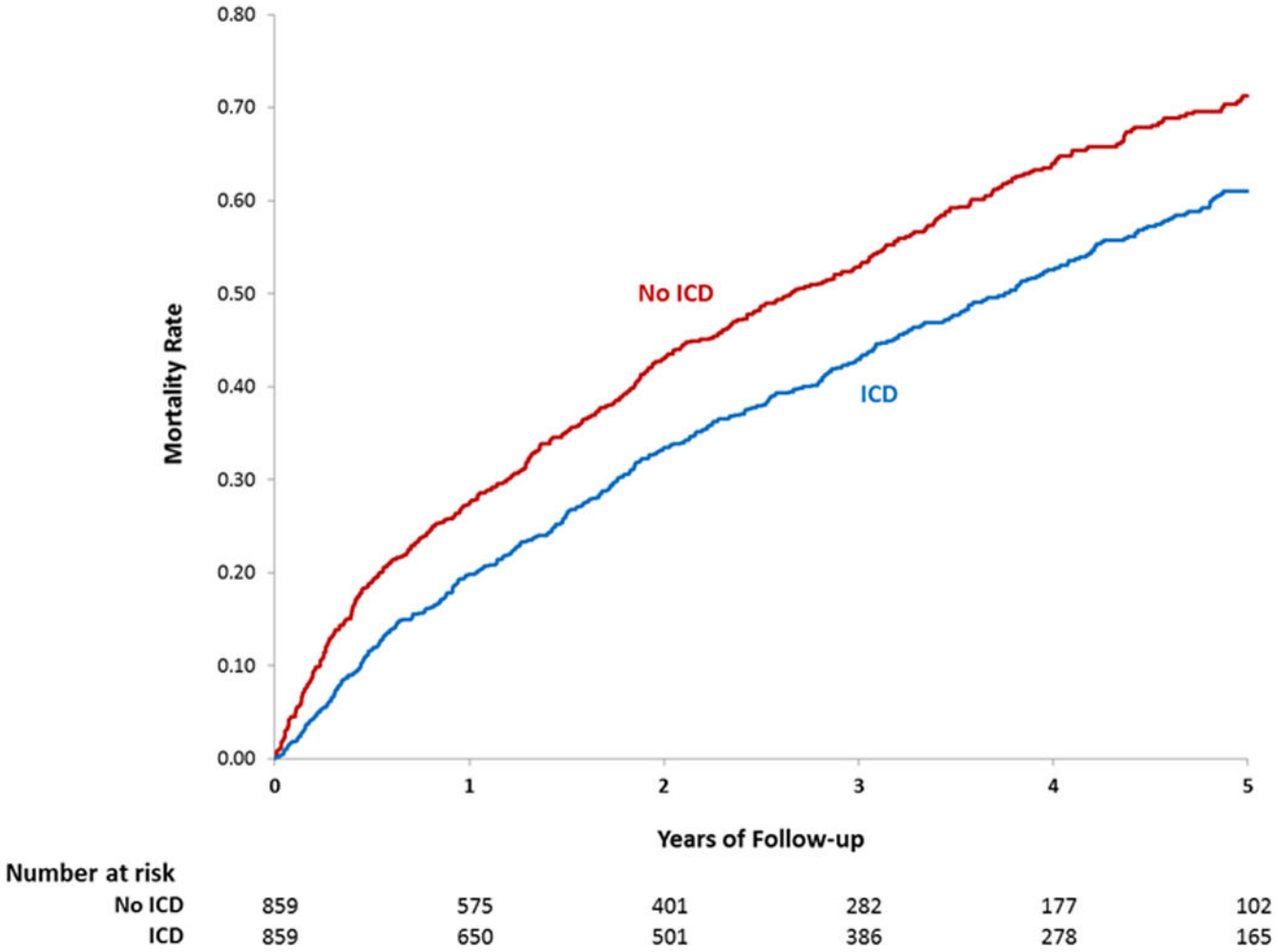


Figure 2. Unadjusted Kaplan-Meier estimates of mortality with and without an ICD placed during or after a HF hospitalization (A) Women (B) Men

Table 1
Baseline characteristics for women with or without an ICD

Baseline characteristic	ICD N=430	No ICD N=3358
Age, years	76 (71, 81)	80 (73, 86)
White race	76% (317)	77% (2534)
Presentation		
Systolic BP	133 (117, 149)	139 (121, 157)
Heart rate	80 (70, 94)	86 (74, 101)
LVEF (%)	25 (20, 30)	28 (20, 32)
BMI	26.3 (22.0, 30.9)	25.0 (21.3, 29.6)
QRS duration, ms	113 (94, 140)(n=124)	114 (94, 145)(n=1126)
Medical history		
Anemia	12% (53)	15% (517)
Ischemic heart disease	58% (251)	57% (1897)
Prior atrial arrhythmia	28% (119)	29% (963)
Diabetes	41% (177)	38% (1270)
Hypertension	76% (328)	75% (2519)
Smoking in past 12 months	13% (55)	10% (323)
Chronic renal insufficiency	16% (67)	15% (504)
Dialysis	2% (7)	3% (94)
COPD or asthma	27% (114)	25% (851)
Prior CVA or TIA	13% (56)	14% (465)
PAD	9% (39)	11% (354)
Depression	6% (24)	9% (289)
Medications		
ACE-inhibitor or ARB	91% (331)	89% (2432)
Anticoagulant therapy	32% (119)	32% (894)
Beta blocker	95% (387)	92% (2845)
Calcium channel blocker	13% (49)	18% (504)
Digoxin	37% (146)	29% (824)
Diuretic	79% (308)	83% (2488)
Statin	49% (193)	39% (1198)
Labs		
BNP (pg/mL)	1119 (453, 2106)	1290 (664, 2343)
Sodium (mEq/L)	138 (136, 140)	138 (135, 141)
Hemoglobin (g/dL)	12.3 (11.0, 13.3)	12.0 (10.8, 13.2)
Creatinine (mg/dl)	1.2 (0.9, 1.5)	1.2 (0.9, 1.6)
BUN (mg/dl)	23 (17, 33)	24 (17, 35)
Hospital characteristics		

Baseline characteristic	**ICD N=430**	**No ICD N=3358**
Geographic region		
Northeast	41% (175)	29% (977)
Midwest	19% (83)	22% (751)
South	32% (139)	36% (1205)
West	8% (33)	13% (425)
Teaching hospital	75% (321)	62% (2077)
Rural site	2% (10)	7% (224)
Number of beds	438 (339, 593)	372 (236, 536)
Performs PCI for acute MI	92% (378)	85% (2679)
Performs cardiac surgery	90% (377)	73% (2303)
Performs heart transplants	18% (75)	8% (268)

Continuous variables are shown as median (25^{th}, 75^{th} percentiles) and are compared with Wilcoxon rank sum tests. Categorical variables are shown as percent (number) and are compared with Pearson chi-square tests. Only non-imputed values are used.

*QRS duration has been collected in the GWTG-HF registry since February 2008, and has been required since Oct 2011.

†Medications are from discharge where available, otherwise from admission.

‡Labs are from admission where available, otherwise from discharge.

Table 2

Variables used in the propensity model for women and men with standardized differences after matching

Baseline characteristic	Women with ICDN=430	Women after 1:1 matching		Men with ICDN=859	Men after 1:1 matching	
		No ICDN=430	% standardized difference*		No ICDN= 859	% standardized difference*
Age, years	76 (71, 81)	76 (71, 80)	0	75 (70, 80)	75 (71, 80)	4
White race	76% (325)	75% (324)	1	84% (720)	85% (731)	4
LVEF (%), mean (SD)	24.4 (6.93)	24.9 (6.7)	7	24.8 (6.9)	24.9 (6.4)	1
Systolic BP	133 (116, 150)	135 (120, 151)	3	130 (112, 148)	130 (114, 146)	2
Ischemic heart disease	58% (251)	59% (254)	1	74% (633)	77% (661)	8
Prior atrial arrhythmia	28% (119)	26% (112)	4	32% (274)	32% (273)	0
Diabetes	41% (177)	44% (189)	6	36% (310)	37% (315)	1
Hypertension	76% (328)	78% (335)	4	67% (577)	70% (598)	5
Chronic renal insufficiency	16% (67)	17% (73)	4	16% (138)	16% (138)	0
Depression	6% (24)	5% (20)	4	5% (47)	5% (46)	1
COPD/asthma	27% (114)	28% (121)	4	23% (201)	21% (184)	5
Anemia	12% (53)	13% (56)	2	8% (70)	8% (71)	0
Prior CVA or TIA	13% (56)	12% (50)	4	12% (102)	11% (95)	3
ACE-inhibitor or ARB	77% (331)	76% (325)	3	77% (661)	78% (672)	3
Beta blocker	90% (387)	92% (396)	7	90% (769)	90% (772)	1
Calcium channel blocker	13% (55)	16% (67)	3	13% (114)	13% (109)	2
Digoxin	37% (158)	37% (158)	3	35% (297)	31% (270)	7
Diuretic	79% (339)	81% (349)	2	78% (666)	82% (701)	10
Statin	47% (201)	47% (203)	0	47% (400)	47% (408)	2
Sodium	138 (136, 140)	138 (136, 140)	1	138 (136, 141)	138 (136, 141)	2
BUN	24 (17, 35)	25 (18, 35)	2	26 (19, 37)	27 (20, 38)	5
Creatinine	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	1	1.4 (1.1, 1.9)	1.4 (1.1, 1.9)	2
Hemoglobin	12.3 (11.0, 13.4)	12.0 (10.9, 13.3)	5	13.0 (11.8, 14.3)	12.8 (11.7, 14.0)	10
Site: Northeast	41% (175)	39% (169)	3	138 (136, 141)	138 (136, 141)	2
Site: Teaching hospital	75% (321)	72% (311)	5	26 (19, 37)	27 (20, 38)	5

Baseline characteristic	Women with ICDN=430	Women after 1:1 matching		Men with ICDN=859	Men after 1:1 matching	
		No ICDN=430	% standardized difference*		No ICDN= 859	% standardized difference*
Site: Number of beds	438 (339, 593)	435 (311, 559)	8	1.4 (1.1, 1.9)	1.4 (1.1, 1.9)	2
Site: Advanced cardiac procedures performed†	92% (397)	93% (398)	1	13.0 (11.8, 14.3)	12.8 (11.7, 14.0)	10

Dataset used in matching is shown here, i.e., with a single imputation for missing data, which affects race, systolic BP, medications, labs, and site performance of cardiac procedures (no other variables had missing data); therefore slight differences may be noted in these variables between this table and Table 1. For medications, patients with noted contraindications are counted as “no” in Table 2 but as missing in Table 1.

*The standardized difference is the absolute difference in means (or proportions) divided by the average standard deviation.

†Hospital performs PCI, cardiac surgery, or heart transplants. Continuous variables are shown as median (25th, 75th percentiles), except where noted, and categorical variables as percent (number).

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Table 3

Results of mortality analysis in women and men. (A) Primary analysis propensity matched (B) Propensity matched and adjusted model (C) Propensity matched 30-day landmark analysis

	Women		Men	
	ICD	No ICD	ICD	No ICD
N	430	430	859	859
Follow-up duration among survivors (years)				
Median	3.4	3.0	3.9	2.9
25th, 75th percentiles	1.9, 5.3	1.7, 4.7	2.1, 5.2	1.6, 4.7
Min, max	0.03, 7.8	0.01, 7.9	0.04, 7.7	0.01, 8.0
(A) Propensity matched (primary results)				
Mortality rate (KM) at 1 year (95% CI)	17.0% (13.7, 21.0)	24.5% (20.7, 29.0)	19.8% (17.3, 22.7)	27.5% (24.6, 30.7)
Mortality rate (KM) at 3 years (95% CI)	40.2% (35.4, 45.4)	48.7% (43.7, 53.9)	42.9% (39.5, 46.5)	52.9% (49.3, 56.6)
Unadjusted HR (95% CI) for ICD vs. no ICD	0.78 (0.66, 0.92), p=0.003		0.76 (0.67, 0.87), p<0.001	
P-value for interaction of sex with ICD	0.79			
(B) Propensity matched and adjusted				
Adjusted mortality rate at 1 year (95% CI)	18.3% (17.6,19.0)	23.1% (22.3,23.9)	21.3% (20.7,21.8)	26.7% (26.0,27.3)
Adjusted mortality rate at 3 years (95% CI)	39.1% (38.0,40.3)	47.1% (45.9,48.3)	44.2% (43.3,45.0)	52.5% (51.6,53.4)
Adjusted HR (95% CI) for ICD vs. no ICD	0.75 (0.63, 0.90), p=0.002		0.76 (0.67, 0.86), p<0.001	
p-value for interaction of sex with ICD	0.97			
(C) Propensity matched 30-day landmark analysis				
N	422	422	839	839
Mortality rate at 1 year (95% CI)	17.3% (13.9, 21.3)	23.6% (19.8, 28.1)	19.4% (16.8, 22.3)	25.0% (22.2, 28.2)
Mortality rate at 3 years (95% CI)	40.1% (35.3, 45.3)	48.6% (43.6, 54.0)	43.3% (39.9, 47.0)	50.9% (47.3, 54.7)
Unadjusted HR (95% CI) for ICD vs no ICD	0.80 (0.68, 0.94), p=0.007		0.81 (0.71, 0.92), p=0.002	
p-value for interaction of sex with ICD	0.86			