Electrophysiology

Use of implantable cardioverter defibrillators for primary prevention in the community: Do women and men equally meet trial enrollment criteria?

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Background Fewer women than men undergo implantable cardioverter defibrillator (ICD) implantation for the primary prevention of sudden cardiac death. The criteria used to select patients for ICD implantation may be more permissive among men than for women. We hypothesized that women who undergo primary prevention ICD implantation more often meet strict trial enrollment criteria for this therapy.

Methods We studied 59,812 patients in the National Cardiovascular Data Registry ICD registry undergoing initial primary prevention ICD placement between January 2005 and April 2007. Patients were classified as meeting or not meeting enrollment criteria of either the MADIT-II or SCD-HeFT trials. Multivariable analyses assessed the association between gender and concordance with trial criteria adjusting for demographic, clinical, and system characteristics.

Results Among the cohort, 27% (n = 16,072) were women. Overall, 85.2% of women and 84.5% of men met enrollment criteria of either trial ($P = .05$). In multivariable analyses, women were equally likely to meet trial criteria (OR 1.04, 95% CI 0.99-1.10) than men. Significantly more women than men met the trial enrollment criteria among patients older than age 65 (86.6% of women vs 85.3% of men, OR 1.11, 95% CI 1.03-1.19), but this difference was not found among younger patients (82.5% of women vs 83.0% of men, OR 0.97, 95% CI 0.89-1.07).

Conclusions In a national cohort undergoing primary prevention ICD implantation, older women were only slightly more likely then men to meet the enrollment criteria for MADIT II or SCD-HeFT. Relative overutilization in men is not an important explanation for gender differences in ICD implantation. (Am Heart J 2009;158:224-9.)

Recent clinical trials have expanded indications for implantable cardioverter defibrillators (ICDs) for the primary prevention of sudden cardiac death.[1,2] However, many eligible patients do not receive this therapy,[3-5] and previous studies have demonstrated that certain groups, specifically women, are less likely to be referred for primary prevention ICD therapy.[3-7]

Existing evidence and guidelines do not support the differential use of ICD therapy according to gender. Although women constitute only approximately 20% of the patient population in the large primary prevention trials for ICD therapy, there is no evidence that the benefits of ICD therapy vary by gender.[1,2,8,9] Current practice guidelines based on these trials recommend primary prevention ICD therapy in both women and men with severe left ventricular systolic dysfunction.[10,11] Possible explanations for observed gender differences in ICD implantation rates include that fewer women may be truly eligible for ICD therapy, that a disproportionately smaller number of eligible women are referred for ICD therapy, or that the criteria used to select women for ICD implantation in practice are more stringent.

We sought to compare the extent to which women and men receiving ICD therapy in the United States conform to the criteria for patient selection based on major clinical trials. We hypothesized that, given prior evidence that women are less likely to be referred for primary prevention ICD therapy, women who actually

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undergo ICD implantation would be more likely to meet these criteria.

Methods

Data source

We used data from the National Cardiovascular Data Registry's (NCDR) ICD Registry, which was developed in 2005 in response to a mandate by the Center for Medicaid and Medicare Services to characterize patients receiving primary prevention ICD therapy.[12] Implanting centers must enter data into the registry on Medicare beneficiaries receiving primary prevention ICDs to obtain reimbursement for these procedures. Enrollment of non-Medicare patients is voluntary, although approximately 80% of participating hospitals register all ICD recipients, regardless of indication or insurance status.[13] Implanting centers submit data quarterly using American College of Cardiology certified software and data quality is examined using the data quality reporting process.[13,14] Implanting centers must enter complete and accurate data to receive Medicare reimbursement. The registry contains detailed and standardized data elements related to baseline patient clinical characteristics, device used, and in-hospital outcomes.

Study population

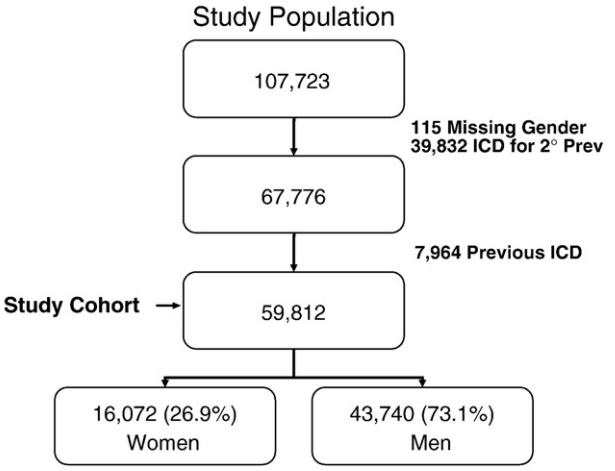
All patients within the NCDR-ICD registry who underwent ICD implantation between January 2005 and April 2007 were considered for inclusion. Patients with missing gender information and those receiving ICD therapy for secondary prevention were excluded from the analyses. Patients were also excluded if they had received a prior ICD. Thus, all patients in the study cohort underwent first-time ICD implantation for the primary prevention of sudden cardiac death.

Independent variables

For all analyses, the primary independent variable was patient gender. Additional variables considered in the multivariable models included hospital admission characteristics (age, race, insurance payer, reason for hospitalization); patient comorbidities and risk factors (history of congestive heart failure, atrial fibrillation or flutter, cardiac transplantation, etiology of cardiomyopathy, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, valvular surgery, cerebrovascular disease, pacemaker insertion, chronic lung disease, diabetes, hypertension, estimated glomerular filtration rate [from the Modification of Diet in Renal Disease Study equation][15] and admission New York Heart Association [NYHA] classification); diagnostic and procedural information (ejection fraction, whether an electrophysiology study was performed, electrophysiology study results, QRS duration, PR interval, presence of atrial or ventricular conduction delays, blood urea nitrogen, sodium level, brain natriuretic peptide level, systolic blood pressure, ICD type [single-chamber, dual-chamber, or biventricular device], and lead implantation method); and physician and hospital characteristics (whether implanting physician is certified in electrophysiology per self report, for-profit or not-for-profit hospital, rural or nonrural hospital, hospital teaching status, number of beds, and number of ICD implantations at each hospital).

The rate of missing data was extremely low for all variables (<0.5%, with the exception of left ventricular ejection fraction, which was missing in 1.5%). To avoid case-wise deletion of those cases with missing data points, the missing values were imputed. The missing categorical variables were imputed as the most common value among those with the data present. For example, in the categorical variable NYHA class (missing = 0.15%), missing variables were imputed as "class I." For continuous variables, the missing values were imputed as the median among those with the data present. Dummy variables were constructed to indicate when the variable was missing. In the multivariable models, both the imputed values and the dummy variable were included.

Figure 1



Study population of women and men from 1107 sites in the United States.

Dependent variables

For all analyses, the primary dependent variable of interest was whether enrollment criteria for either the MADIT II or SCD-HeFT trial were met. Patients were considered to have met MADIT II criteria if they had (1) a prior myocardial infarction (MI); (2) the MI occurred >40 days before implantation; (3) a left ventricular ejection fraction (LVEF) ≤30%; and (4) NYHA class I, II, or III symptoms.[2] Patients were considered to have met SCD-HeFT criteria if they had (1) a history of heart failure regardless of etiology, (2) an LVEF ≤35%; and (3) NYHA class II or III symptoms.[1] Patients meeting either of these definitions were designated as meeting trial enrollment criteria. Patients with NYHA class IV symptoms were also considered to qualify if (1) they met either MADIT II or SCD-HeFT indications other than symptom severity, (2) had an intraventricular conduction delay, and (3) received a biventricular ICD.[10]

Statistical analysis

Baseline clinical characteristics between women and men were compared using the χ^2 test for categorical variables and *t* tests for continuous variables. To assess the independent relationship between gender and concordance with trial enrollment criteria for ICD therapy, hierarchical logistic regression was used, adjusting for patient, provider, hospital,

Table I. Baseline characteristics

Description	Gender		P
	Male (n = 43740)	Female (n = 16072)	
Admission characteristics			
Age (mean ± SD)	68.2 ± 12.2	67.6 ± 12.8	<.001
Race			<.001
White	83.2	76.5	
Black	11.3	18.2	
Other	5.5	5.3	
Hispanic ethnicity	5.4	5.4	.95
Insurance payer			<.001
Medicare	70.7	70.8	
Medicaid	3.8	5.8	
Commercial	16.2	15.0	
Health maintenance organization	6.1	5.6	
Other	3.2	2.8	
History and risk factors			
Congestive heart failure	83.2	88.3	<.001
New York Heart Association current status			<.001
Class I	10.1	7.3	
Class II	35.3	29.8	
Class III	50.0	57.2	
Class IV	4.7	5.7	
Nonischemic dilated cardiomyopathy	28.1	47.0	<.001
Ischemic cardiomyopathy	71.6	51.1	<.001
Atrial fibrillation/flutter	32.3	25.7	<.001
Previous myocardial infarction			<.001
Within 40 d of ICD implant	5.7	4.5	
More than 40 d before ICD implant	50.1	34.3	
Previous coronary artery bypass grafting	41.5	23.1	<.001
Previous percutaneous coronary intervention	34.0	25.9	<.001
Cerebrovascular disease	14.3	13.4	.005
Chronic lung disease	21.3	22.4	.003
Diabetes	37.3	39.1	<.001
Hypertension	73.3	72.0	.001
Glomerular filtration rate <60 mL/min	40.3	54.7	<.001
Diagnostics			
% Ejection fraction (mean ± SD)	24.9 ± 7.8	24.8 ± 8.5	.26
Electrophysiology study done	10.1	8.6	<.001
QRS duration (ms) (mean ± SD)	128.5 ± 34.6	128.2 ± 34.6	.36
Abnormal intraventricular conduction	56.7	58.7	<.001
BNP level (pg/mL), when drawn (mean ± SD)	1033.6 ± 1119.2	1099.5 ± 1164.1	.004
ICD type			<.001
Single chamber	25.8	23.9	
Dual chamber	35.1	30.2	
Biventricular	38.8	45.7	

All expressed as percent unless otherwise specified.
BNP, Brain natriuretic peptide.

procedural characteristics, and accounting for the clustering of patients within hospitals. Because of the large sample size, nonparsimonious models could be used.

Given current Center for Medicaid and Medicare Services reimbursement rules, it is possible that gender differences may vary based on Medicare coverage. Therefore, in secondary analyses, patients were stratified by age (<65 and ≥65 years old). Multivariable hierarchical logistic regression models were constructed considering the same covariates as the primary analysis models. The statistical significance of differences among strata was tested with 2-way interaction terms in the full model. All analyses were performed using the SAS statistical package version 9.1 (SAS Institute, Cary, NC). A *P* value of <.05 was deemed significant, and all reported *P* values are 2-sided except where appropriate.

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Results

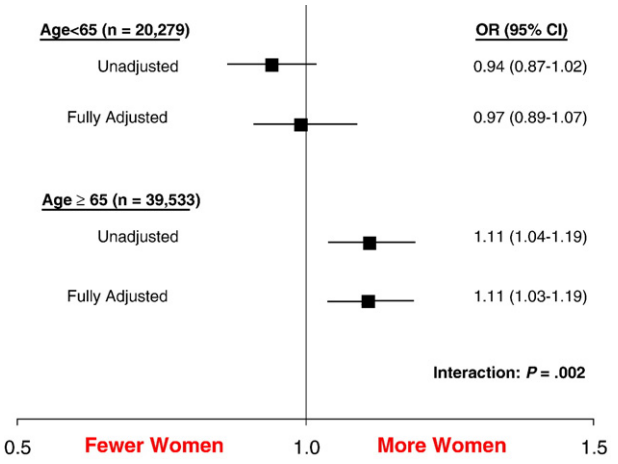
Study population

A total of 107,723 patients (26% women vs 74% men) who underwent ICD implantation from January 2005

Table II. Characteristics of women and men receiving ICDs who did not meet either the MADIT II or SCD-HeFT trial enrollment criteria

Baseline charcteristics	Men N = 6769	Women N = 2382	*P* value
NYHA Class			<.001
I	36.3	35.0	
II	31.7	28.0	
III	18.1	20.7	
IV	13.9	16.2	
Left Ventricular Ejection Fraction			<.001
>35%	21.1	23.3	
30-35%	31.7	22.8	
<30%	47.3	53.9	
Prior Heart Failure			<.001
No	60.8	54.5	
Yes	39.2	45.5	
Prior MI			<.001
No	58.4	72.9	
Yes; ≤40 days of implant	11.2	7.6	
Yes; >40 days of implant	30.4	19.4	

Figure 2



Adjusted odds of meeting trial enrollment criteria in women and men stratified by age group.

through April 2007 were considered for inclusion into the study cohort. Among these, 115 were missing gender information. Another 39,832 were excluded for secondary prevention ICD indications (22,281 with secondary prevention indicated on case reporting form; another 12,485 with history of syncope, 1,602 with history of tachycardic cardiac arrest, and 3,464 with history of sustained ventricular tachycardia). A total of 7,964 patients had received a prior ICD resulting in a final study cohort of 59,812 patients undergoing first-time ICD implantation for primary prevention, of which 27% were women and 73% were men (Figure 1).

Demographic and clinical characteristics

Women were slightly younger (mean age ± SD: women 67.6 ± 12.8, men 68.2 ± 12.2, $P < .001$) and more often black (18.2% vs 11.3%, $P < .001$) compared with men. Substantially more women had a nonischemic cardiomyopathy (47.0% vs 28.1%, $P < .001$) and slightly more had a history of heart failure (88.3% vs 83.2%, $P < .001$). Women had more advanced heart failure symptoms (NYHA class III or IV 62.9% vs 54.7%, $P < .001$) than men. The mean ejection fraction (%) was not significantly different between women and men (mean ± SD 24.8 ± 8.5 vs 24.9 ± 7.8, $P = .26$) (Table I).

Concordance with trial criteria

Among the final study cohort receiving primary prevention ICD therapy, 84.7% met either the MADIT-II or SCD-HeFT trial enrollment criteria. The overall proportion of patients meeting trial criteria was slightly higher for women than for men (85.2% vs 84.5%, $P = .05$). In the group of patients who did not meet inclusion criteria for either trial, women tended to have a higher NYHA symptom class, lower ejection fractions, were more likely to have a history of heart failure, and were less likely to have a prior MI compared to men (Table II).

In multivariable analyses, women and men were equally likely to meet overall trial criteria after accounting for admission characteristics; medical history; NYHA class; diagnostic, physician, and hospital characteristics; and clustering of patients among hospitals (OR, 1.04; 95% CI 0.99-1.10).

Secondary analyses

A significant interaction was found between gender and age group ($P = .002$). When stratified into groups of ≤65 years old, younger women and men were equally likely to meet trial enrollment criteria (crude proportions of 82.5% vs 83.0%, $P = .37$; fully adjusted OR 0.97, 95% CI 0.89-1.07). However, among those ≥65 years old, women were significantly more likely than men to meet these criteria (crude proportions of 86.6% vs 85.3%, $P < .01$; adjusted OR 1.11, 95% CI 1.03-1.19) (Figure 2).

Discussion

This study of patterns of care in 1107 institutions in the United States found that most patients receiving primary prevention ICD therapy in practice meet enrollment criteria for the major clinical trials. Furthermore, after adjustment for patient and health system factors, men were as likely to meet these criteria as women. This finding varied according to age group with older women having 11% greater odds than men of meeting trial criteria. However, the absolute difference in this proportion (1.3%) was modest, suggesting that relative overutilization in men is not a major contributor to gender differences in the use of ICD therapy.

Our study suggests women represent 27% of patients receiving ICDs for primary prevention in contemporary clinical practice in the United States. This proportion is similar to that identified in single-center studies that have found that women represent a minority of those receiving ICD therapy for either primary or secondary prevention, with the greatest gender differences among those receiving primary prevention therapy.[4,6,7,16] More recently, reports using data from the Medicare population also demonstrate consistently lower rates of ICD use in women over time.[4,5] The lower rates of ICD therapy in women raises important questions as to why these gender differences occur.

One possible explanation for lower ICD implantation rates in women is that the criteria used to select patients for implantation are applied more stringently to women. Possible reasons for such a difference might include provider belief that women are less likely to benefit from ICD therapy, provider concern for higher complications rates of ICD implantation in women, or provider gender bias.[16] For example, if there were widespread belief that ICD therapy is less efficacious in women then in men, then we would expect that women who actually receive ICD therapy would be more likely to meet stringent trial criteria or that trial criteria would be applied more permissively in men. In this study, we found that women and men were equally likely to meet trial criteria after consideration of a wide range of other patient characteristics. Therefore, a relative overuse of ICDs in men does not appear to explain the large variation seen in the overall use of ICD therapy among women and men.

A second possible explanation for the lower use of ICD therapy in women is a disproportionate underreferral of eligible women compared to men. Prior work has shown women are less commonly referred for invasive cardiac procedures compared to men.[17-20] A recent study by Hernandez et al investigated whether women are less often referred for ICD therapy. Using American Heart Association Get With The Guidelines data for patients hospitalized for heart failure, they found that among eligible patients, only 35% received ICD therapy and eligible women were 40% less likely to receive an ICD than eligible men.[3] Although this study provides significant evidence for disparate ICD referral patterns among women and men hospitalized for heart failure, questions still remain regarding gender differences in eligible outpatients. The findings of this study suggest that most of the variation in ICD use by gender may be related to upstream factors such as an underreferral of women who meet ICD eligibility criteria or fewer women than men in the general population actually meet ICD eligibility criteria.

Another important finding of our study is the influence of age on the gender differences identified. Our findings suggest trial criteria are being applied more stringently among older women than older men with no significant gender differences among younger patients. Given that the NCDR provides clear guidelines for the reimbursement of ICD therapy among Medicare beneficiaries, our finding that gender differences are confined to the older cohort and not found in the younger cohort where reimbursement guidelines are less stringent is unexpected. Similar to other invasive procedures, this finding may reflect providers' reluctance to recommend ICD therapy among older women who may have more coexisting illnesses and higher complication rates and are therefore viewed as less likely to benefit from therapy.[16,21] However, even after controlling for many important clinical characteristics, including coexisting illnesses, this difference persisted. Another possible explanation for this age-specific finding is that older women may be more likely to refuse ICD therapy compared to men. Some studies have suggested older women are slightly more likely to refuse certain invasive cardiac procedures; yet, the absolute differences in refusal rates in these studies were small and unlikely to explain all of the gender variation observed in the use of invasive technologies.[22,23] Additional studies are needed to distinguish the extent to which differences in provider and patient attitudes toward ICD therapy account for variation in ICD implantation between women and men.

Finally, this study highlights the value of large, contemporary national registries to study the application of new technologies applied in real world settings. National registries are ideal for monitoring technology utilization, safety, and effectiveness on a national scale in representative populations. Furthermore, results from this and other studies using the NCDR registries overcome the potential lack of applicability of single-center studies or those confined only to Medicare beneficiaries, and extend the findings of existing studies by focusing on ICD use in contemporary practice.

When considering these results, a few limitations should be noted. First, although we were able to study a large national cohort of patients who underwent primary prevention ICD therapy, we were not able to study eligible patients who were not referred for therapy or who were referred but did not undergo ICD implantation. Thus, we were unable to examine whether referral bias or patient preferences explain the differences observed. Furthermore, among patients who did not meet trial criteria, it is possible that extenuating circumstances not reflected in the data collection motivated the decision to pursue ICD implantation. Finally, data in the NCDR registry are self-reported by hospitals and failure to meet trial enrollment criteria may be underreported. However, there is no substantial incentive to underreport cases that do not meet trial criteria as reimbursement is not dependent on achieving trial concordance. Furthermore, it is unlikely that patterns of reporting trial concordance would vary by patient gender.

Conclusion

We found that among patients undergoing ICD implantation for primary prevention, older women were only slightly more likely to conform to the enrollment criteria of clinical trials than older men, suggesting that gender differences in ICD therapy is not related to a disproportionate overutilization among men who do not meet trial criteria. Additional studies are needed to further define the extent to which other factors, such as a smaller population of eligible women, the underreferral of eligible women, or gender differences in patient preferences contribute to gender differences in the use of ICD therapy.

Disclosures

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