Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Impact of Female Sex on Clinical Outcomes in the FIRE AND ICE Trial of Catheter Ablation for Atrial Fibrillation

BACKGROUND: Data on predictors of long-term clinical outcomes after catheter ablation of atrial fibrillation (AF) are limited. We sought to assess the association of baseline covariates with clinical outcomes in the 750 patients with drug-refractory paroxysmal AF enrolled in FIRE AND ICE.

METHODS: In a 2-part analysis, univariate and multivariable Cox regression models were first used to identify baseline patient characteristics predictive of catheter ablation efficacy determined by the clinical end points of (1) atrial arrhythmia recurrence (primary efficacy failure), (2) cardiovascular rehospitalization, and (3) repeat ablation. Propensity score stratification methods were then used to account for differences in baseline characteristics between sexes.

RESULTS: Female sex (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.08–1.73; *P*=0.010) and prior direct current cardioversion (HR, 1.40; 95% CI, 1.07–1.82; *P*=0.013) were independently associated with atrial arrhythmia recurrence. Female sex (HR, 1.36; 95% CI, 1.02–1.80; *P*=0.035) and hypertension (HR, 1.48; 95% CI, 1.09–2.00; *P*=0.013) independently predicted cardiovascular rehospitalization. A longer history of AF (HR, 1.03; 95% CI, 1.00–1.06; *P*=0.039) increased the rate of repeat ablation. Women continued to have higher rates of primary efficacy failure and cardiovascular rehospitalization after propensity score adjustment, with adjusted HRs of 1.51 (95% CI, 1.16–2.18; *P*<0.05) and 1.40 (95% CI, 1.15–2.17; *P*<0.05), respectively.

CONCLUSIONS: After catheter ablation of paroxysmal AF, female sex was associated with an almost 40% increase in the risks of primary efficacy failure and cardiovascular rehospitalization. Primary efficacy failure was also adversely impacted by a history of direct current cardioversion, whereas hypertension had a negative impact on cardiovascular rehospitalization. History of AF was the only predictor of repeat ablation.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01490814.

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Key Words: atrial fibrillation ■ catheter ablation ■ humans ■ risk ■ sex

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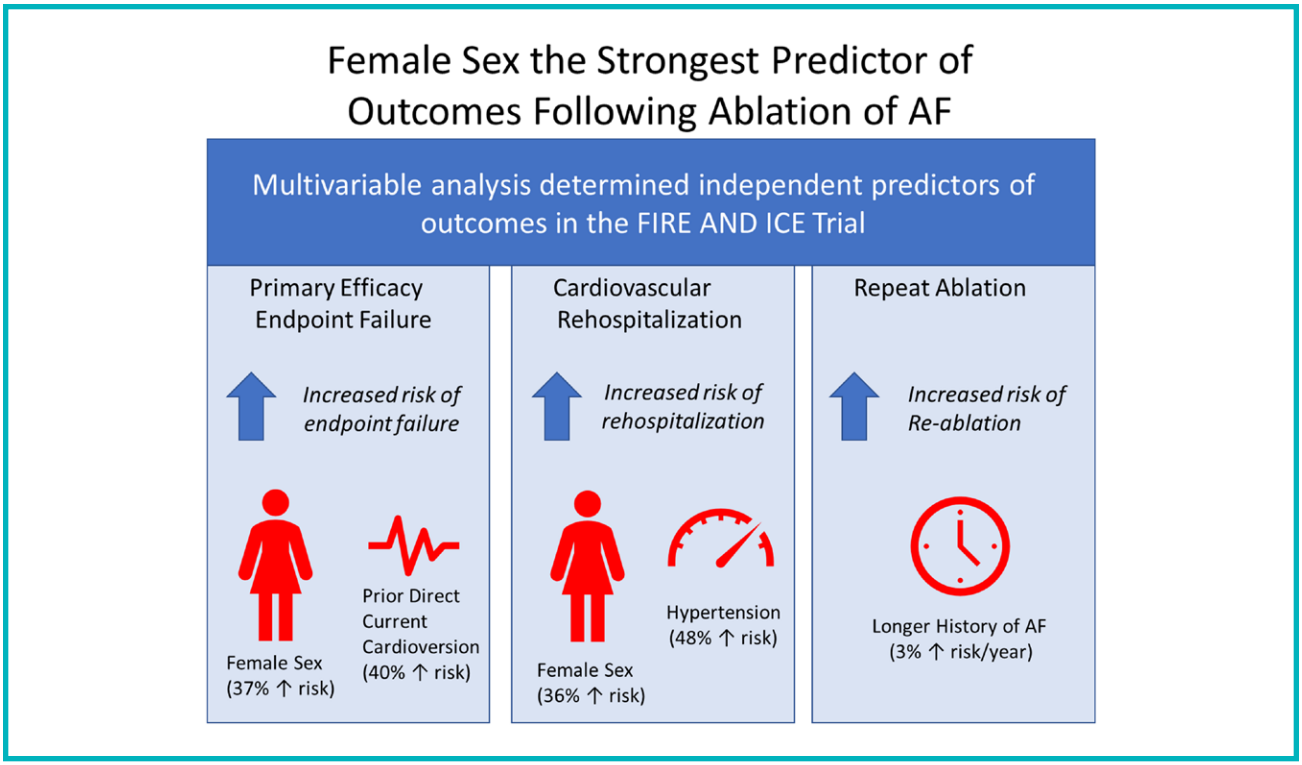

WHAT IS KNOWN?

- Pulmonary vein isolation is the cornerstone of catheter ablation for the treatment of patients with paroxysmal atrial fibrillation; yet, some patients still experience arrhythmia recurrence and undergo repeat ablation and cardiovascular rehospitalization after pulmonary vein isolation.
- Previous database reviews have shown that long-term clinical outcome failures of catheter ablation are associated with select baseline patient characteristics.

WHAT THE STUDY ADDS?

- Female sex is associated with a ≈40% higher risk than male sex of primary efficacy failure and cardiovascular rehospitalization after catheter ablation of atrial fibrillation, indicating a need for increased efforts in monitoring and earlier treatment of women to reduce the risk of arrhythmia recurrence.
- A history of direct current cardioversion, hypertension, and a longer history of atrial fibrillation independently predicted poorer clinical outcomes after catheter ablation of atrial fibrillation.

Pulmonary vein isolation via catheter ablation is accepted as a safe and effective treatment for atrial fibrillation (AF), but a better understanding of patients who are/are not likely to benefit from catheter ablation may further advance treatment strategies. Several database reviews have identified sex, age, socioeconomic, and racial/ethnic dependent differences in long-term outcomes of catheter ablation for AF.[1–4] Although the number of subjects examined in these studies have been robust, the analyses have been limited to the few patient baseline characteristics previously recorded in these medical database reviews.[1–4] There is a lack of large cohort analyses that evaluate an extensive set of baseline data to identify preprocedural patient characteristics predictive of long-term outcomes after catheter ablation for AF.

The present study evaluates the 750 subjects treated in the FIRE AND ICE trial (without differentiating by catheter ablation modality)[5–8] across 22 distinct baseline patient characteristics. All 22 characteristics were associated with 3 separate, predefined, long-term measures of clinical outcome: atrial arrhythmia recurrence (primary efficacy failure), cardiovascular rehospitalization, and repeat catheter ablation. Secondary analyses were utilized to test differences in male and female outcomes for a more comprehensive understanding of the impact sex has on clinical success after catheter ablation of AF.

METHODS

As additional publications of FIRE AND ICE data are in preparation, the current data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Data Source

FIRE AND ICE was a multicenter (16 centers in 8 European countries) randomized (1:1) comparison of 2 catheter ablation modalities (cryoballoon versus radiofrequency current ablation) used to treat patients with drug-refractory symptomatic paroxysmal AF.[5–8] The study design, procedural methods, and predefined primary and secondary study end points have been published previously.[5–8] Approval for this study was granted by each local institution's review board, and informed consent was obtained from each subject. In brief, 762 subjects were enrolled and randomized, 750 of whom were treated with catheter ablation and comprised the modified intention-to-treat cohort.[5] The ablation strategy used in both treatment groups was pulmonary vein isolation without any further ablation in the left atrium.[5] Subjects were enrolled from January 2012 to January 2015 and were followed for a maximum of 33 months, with an average follow-up of 1.5 years.[5]

In the trial, the primary efficacy end point was the time to first documented occurrence, outside the landmark 90-day blanking period, of (1) recurrence of atrial arrhythmia (AF >30 seconds, atrial flutter, or atrial tachycardia), (2) prescription of an antiarrhythmic drug, or (3) repeat catheter ablation.[5] Predefined secondary end points included cardiovascular rehospitalization and repeat catheter ablation for atrial arrhythmias that occurred throughout the entire study follow-up (including the blanking period; these measurements were total observed events rather than time to first recordings).[5–7] The primary objectives of the current data analyses were to identify the baseline patient demographic characteristics predictive of clinical patient outcomes, specifically primary efficacy, cardiovascular rehospitalization, and repeat catheter ablation. The current analyses utilized the same definition of outcomes as those previously published for the primary and secondary end points.[5–8]

Statistics

Previous publications reporting subgroup interaction tests concluded that the treatment effect (difference between cryoballoon and radiofrequency current efficacy) was consistent across predefined subgroups;[5,6] therefore, the randomization arms from the FIRE AND ICE trial (cryoballoon and radiofrequency current) were pooled into a single, large cohort of patients for statistical examination in this study. All patients who were enrolled, randomized, and treated with catheter ablation (modified intention-to-treat cohort) were included, which is consistent with previous publications of this data set.[5–8] Continuous data are presented as means and SDs, and discrete data are presented as counts and percentages. Demographic and procedural differences between sexes were assessed with a *t* test for continuous variables and Fisher exact test for categorical variables.

Two types of analysis were completed in this study. The first analysis identified baseline patient characteristics predictive of efficacy after catheter ablation. The second analysis further investigated differences in outcomes by sex. The distribution of patients included in these analyses is given in Figure 1.

Univariate and multivariable Cox regression models were used to assess the association between baseline patient characteristics and the risk of a study end point occurring in a subject. Each patient baseline characteristic was examined by univariate analysis with the study outcome denoted as the dependent variable and baseline patient characteristic as the covariate. Significant covariates ($P<0.05$) identified from the univariate analyses were then included in a multivariable Cox regression model. Covariates that were significant in the multivariable model ($P<0.05$) were considered independently associated with the study outcome. Separate univariate and multivariable models were utilized for each of the 3 clinical outcomes, and hazard ratios (HRs) were estimated with Cox regression from both the univariate models (HR) and multivariable models ($HR_{MV\ adj}$). Kaplan–Meier plots were used to illustrate the significant patient characteristics.

To account for differences in baseline characteristics between men and women, propensity score (PS) stratification methods were utilized to estimate an adjusted HR for efficacy between men and women.[9] Seventeen baseline covariates were included in the PS analysis (Table I in the Data Supplement). Patients were divided equally into 5 strata using PS quintiles, HRs were calculated by Cox proportional hazards regression for each strata, and the overall adjusted HR was obtained using inverse-variance weighting. Interaction tests (with sex by PS quintile as an interaction term) were conducted with Cox regression models to check the balance of demographics within each quintile and the consistency of outcomes across quintiles. Bootstrap methods were used to calculate a 95% confidence interval (CI).

All analyses were conducted using SAS/STAT software (version 13.1; 2012 SAS Institute) and R statistical package, version 3.2.2 (https://www.r-project.org).

RESULTS

Baseline Characteristics

A total of 750 subjects with symptomatic paroxysmal AF refractory to class I or III antiarrhythmic drugs or

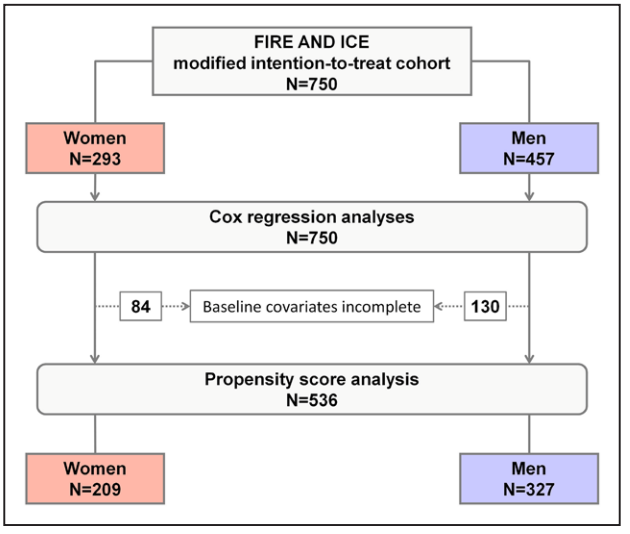

Figure 1. Flowchart of patients enrolled and included in analyses. The total cohort of 750 patients was entered into univariate and multivariable Cox regression analyses. Propensity score-matched patients were subsequently analyzed to assess the impact of sex on outcomes.

Table 1. Baseline Patient Characteristics

	Total (N=750)	Women (n=293)	Men (n=457)	*P* Value*
Age, y	60±10	64±8	57±10	<0.001
Body mass index, kg/m^2	28±5	28±5	28±4	0.157
Systolic BP, mm Hg	134±18	135±19	133±18	0.142
Diastolic BP, mm Hg	79±11	77±11	80±11	<0.001
Diabetes mellitus, type I or II	60 (8)	21 (7)	39 (9)	0.582
GFR, mL/min per 1.73 m^2	79±19	74±18	82±19	<0.001
History of AF, y	4.6±5.2	4.6±5.2	4.6±5.2	0.987
History of atrial flutter	128 (17)	32 (11)	96 (21)	<0.001
History of CAD	63 (8)	16 (5)	47 (10)	0.022
Hyperlipidemia	221 (29)	90 (31)	131 (29)	0.566
Hypertension	436 (58)	183 (62)	253 (55)	0.058
Left atrial volume, mL†	59±30	59±31	58±30	0.923
LVEDD, mm†	50±7	48±5	51±7	<0.001
LVEF, %†	63±7	64±6	62±7	0.004
Left atrial diameter, mm†	40.7±6.1	39.9±6.5	41.2±5.8	0.012
NYHA functional class				0.002
No heart failure	540 (72)	194 (66)	346 (76)	
NYHA class I	87 (12)	34 (12)	53 (12)	
NYHA class II	122 (16)	65 (22)	57 (12)	
No NYHA class available	1 (0.1)	0 (0)	1 (0.2)	
PCI	40 (5)	12 (4)	28 (6)	0.248
Peripheral artery disease	4 (0.5)	2 (0.7)	2 (0.4)	0.646
Prior DCCV	174 (23)	63 (22)	111 (24)	0.425
Prior myocardial infarction	18 (2)	4 (1)	14 (3)	0.220
Prior stroke or TIA	28 (4)	12 (4)	16 (4)	0.696

Values are mean±SD or n (%). AF indicates atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; DCCV, direct current cardioversion; GFR, glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*2-sample *t* test for continuous variables and Fisher exact test for categorical variables.

†Left atrial diameter data reported for 584 subjects, left ventricular ejection fraction data reported for 510 subjects, left ventricular end-diastolic diameter data reported for 411 subjects, and left atrial volume data reported for 87 subjects.

β-blockers were enrolled, randomized, and treated in the study. The mean patient age was 60.0±9.5 years, and 457 patients (61%) were men. Patients were diagnosed with AF for a mean of 4.6±5.2 years before the index ablation, and 174 patients (23%) had a history of direct current cardioversion (DCCV; Table 1).

Predictors of Efficacy: Relationship Between Baseline Characteristics and the Primary Outcome

The impact of the 22 baseline demographic characteristics on recurrence of AF assessed by univariate statistical testing (Table 2) revealed that both sex (*P*=0.015) and prior DCCV (*P*=0.021) were significant predictors of AF recurrence. Subsequent multivariable modeling confirmed that both sex and prior DCCV were independent predictors of AF recurrence (Table 3; Figure 2). Specifically, female sex was associated with a 37% increase in the risk of primary efficacy end point failure ($HR_{MV\ adj}$, 1.37; 95% CI, 1.08–1.73; *P*=0.010), and DCCV before enrollment was associated with a 40% increase in the risk of primary efficacy failure ($HR_{MV\ adj}$, 1.40; 95% CI, 1.07–1.82; *P*=0.013).

Predictors of Efficacy: Relationship Between Baseline Characteristics and Secondary Outcomes

Univariate statistical testing determined that age (*P*=0.012), body mass index (*P*=0.035), sex (*P*=0.008), hypertension (*P*=0.001), and systolic blood pressure (*P*=0.034) were all significantly associated with cardiovascular rehospitalization; the only predictor of repeat ablation was history of AF (*P*=0.039; Table 2).

Table 2. Univariate Analysis of Clinical Outcomes (Primary Efficacy End Point, Cardiovascular Rehospitalization, and Repeat Ablation) Against 22 Baseline Patient Characteristics

Baseline Characteristics* (N=750)	Primary End Point		CV Rehospitalization		Repeat Ablation	
	HR (95% CI)	Univariate *P* Value	HR (95% CI)	Univariate *P* Value	HR (95% CI)	Univariate *P* Value
Age, y	1.01 (1.00–1.02)	0.168	1.02 (1.00–1.04)	0.012†	1.00 (0.98–1.03)	0.653
Body mass index, kg/m^2	0.99 (0.97–1.02)	0.505	1.03 (1.00–1.06)	0.035†	1.00 (0.96–1.04)	0.994
Systolic BP, mm Hg	1.00 (0.99–1.01)	0.689	1.01 (1.00–1.01)	0.034†	1.00 (0.99–1.01)	0.627
Diastolic BP, mm Hg	1.00 (0.99–1.01)	0.814	1.00 (0.98–1.01)	0.451	0.99 (0.98–1.01)	0.379
Diabetes mellitus, type I or II	1.10 (0.73–1.66)	0.640	1.33 (0.85–2.06)	0.209	1.12 (0.59–2.15)	0.730
GFR, mL/min per 1.73 m^2	1.00 (0.99–1.01)	0.822	1.00 (0.99–1.01)	0.476	1.00 (0.99–1.01)	0.718
Female sex	1.34 (1.06–1.70)	0.015‡	1.43 (1.10–1.86)	0.008†	1.19 (0.81–1.73)	0.370
History of AF, y	1.02 (1.00–1.04)	0.052	1.00 (0.98–1.03)	0.900	1.03 (1.00–1.06)	0.039§
History of atrial flutter	0.98 (0.72–1.34)	0.913	1.14 (0.82–1.59)	0.447	1.21 (0.77–1.92)	0.410
History of CAD	0.69 (0.42–1.10)	0.121	1.20 (0.77–1.87)	0.414	0.61 (0.27–1.40)	0.245
Hyperlipidemia	1.13 (0.88–1.46)	0.329	1.31 (1.00–1.73)	0.054	1.11 (0.75–1.67)	0.596
Hypertension	1.07 (0.84–1.35)	0.603	1.63 (1.23–2.16)	0.001†	1.23 (0.84–1.82)	0.287
NYHA I or Ⅲ	1.25 (0.97–1.60)	0.079	1.21 (0.91–1.60)	0.186	1.04 (0.69–1.56)	0.861
Left atrial volume, mL¶	1.00 (0.99–1.01)	0.479	1.01 (1.00–1.02)	0.122	1.01 (0.99–1.02)	0.560
LVEDD, mm¶	1.00 (0.98–1.02)	0.949	1.01 (0.99–1.04)	0.258	1.01 (0.98–1.05)	0.489
LVEF, %¶	0.99 (0.97–1.01)	0.209	0.99 (0.97–1.01)	0.279	0.99 (0.96–1.02)	0.536
Left atrial diameter, mm¶	1.02 (1.00–1.04)	0.051	1.02 (1.00–1.04)	0.111	1.00 (0.97–1.04)	0.885
PCI	0.80 (0.45–1.43)	0.455	1.13 (0.65–1.98)	0.665	0.52 (0.16–1.64)	0.263
Peripheral artery disease	1.82 (0.45–7.32)	0.398	0.91 (0.13–6.50)	0.926	2.30 (0.32–16.5)	0.406
Prior DCCV	1.37 (1.05–1.78)	0.021‡	1.32 (0.98–1.77)	0.067	1.16 (0.75–1.78)	0.508
Prior myocardial infarction	0.40 (0.13–1.24)	0.111	0.52 (0.17–1.64)	0.266	0.39 (0.05–2.80)	0.350
Prior stroke or TIA	0.88 (0.47–1.66)	0.703	1.47 (0.80–2.70)	0.210	1.00 (0.37–2.70)	0.992

AF indicates atrial fibrillation; AVS, aortic valve stenosis; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DCCV, direct current cardioversion; GFR, glomerular filtration rate; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*AVS and CABG were not included in the analysis because prevalences were too low for meaningful statistical evaluation (0.1% of subjects had AVS and 0.6% of subjects had prior CABG at baseline).

†Significant univariate terms when cardiovascular rehospitalization is the outcome.

‡Significant univariate terms when primary efficacy is the outcome.

§Significant univariate terms when repeat ablation is the outcome.

ⅡNYHA III and IV were excluded from the trial.

¶Left atrial dimension data reported for 584 subjects, left ventricular ejection fraction data reported for 510 subjects, left ventricular end-diastolic dimension data reported for 411 subjects, and left atrial volume data reported for 87 subjects.

Sex and hypertension remained statistically significant in multivariable modeling, indicating that they were independent predictors of cardiovascular rehospitalization. Female sex was associated with a 36% increase ($HR_{MV\ adj}$, 1.36; 95% CI, 1.02–1.80; *P*=0.035), and a baseline history of hypertension was associated with a 48% increase ($HR_{MV\ adj}$, 1.48; 95% CI, 1.09–2.00; *P*=0.013) in the risk of cardiovascular rehospitalization. History of AF (in years) was the only statistically significant covariate predicting repeat ablation, and thus, no multivariable model was estimated. The HR for years with AF was 1.03 (95% CI, 1.00–1.06; *P*=0.039), indicating that each additional year of diagnosed AF history was associated with a 3% increased risk of repeat ablation.

Outcomes According to Sex: Baseline Patient Characteristics

In the FIRE AND ICE data set, female and male patients presented with similar histories of AF (4.6±5.2 versus 4.6±5.2 years; *P*=0.987), body mass index (28±5 versus 28±4 kg/m^2; *P*=0.157), and baseline systolic blood pressure (135±19 versus 133±18 mm Hg; *P*=0.142), respectively (Table 1). However, women exhibited baseline clinical characteristics predisposing them to an adverse outcome after catheter ablation for AF. Specifically, women were on average older (64±8 versus 57±10 years; *P*<0.001) and had a lower glomerular filtration rate (74±18 versus 82±19 mL/min per 1.73 m^2;

Table 3. Multivariable Analysis of Outcomes (Primary Efficacy End Point, Cardiovascular Rehospitalization, and Repeat Ablation) Against Baseline Patient Characteristics With Significant Univariate Association

Study End Point	Baseline Characteristics (N=750)	Univariate		Multivariable	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary efficacy failure	Female sex	1.34 (1.06–1.70)	0.015	1.37 (1.08–1.73)	0.010
	Prior DCCV	1.37 (1.05–1.78)	0.021	1.40 (1.07–1.82)	0.013
Cardiovascular rehospitalization*	Age, y	1.02 (1.00–1.04)	0.012	1.01 (0.99–1.03)	0.241
	BMI, kg/m^2	1.03 (1.00–1.06)	0.035	1.02 (0.99–1.05)	0.215
	Female sex	1.43 (1.10–1.86)	0.008	1.36 (1.02–1.80)	0.035
	Hypertension	1.63 (1.23–2.16)	0.001	1.48 (1.09–2.00)	0.013
Repeat ablation†	History of AF, y	1.03 (1.00–1.06)	0.039	NA	NA

AF indicates atrial fibrillation; BMI, body mass index; BP, blood pressure; CI, confidence interval; DCCV, direct current cardioversion; HR, hazard ratio; and NA, not applicable.

*To avoid collinearity, systolic BP has been excluded from the multivariable model because it is highly correlated with hypertension.

†History of AF was the only variable significant in univariate testing.

P<0.001) than men. Although not statistically significant, there was also a trend for a clinical history of hypertension to be more prevalent in women (62% versus 55%; *P*=0.058). By contrast, the female cohort also presented with clinically favorable baseline characteristics, namely, a lower prevalence of prior atrial flutter (11% versus 21%; *P*<0.001) and coronary artery disease (5% versus 10%; *P*=0.022), and smaller left atria (left atrial diameter, 39.9±6.5 versus 41.2±5.8 mm; *P*=0.012). Additional statistically different but clinically similar differences emerged between female and male cohorts, including left ventricular end-diastolic diameter (48±5 versus 51±7 mm; *P*<0.001), left ventricular ejection fraction (64±6% versus 62±7%; *P*=0.004), and diastolic blood pressure (77±11 versus 80±11 mm Hg; *P*<0.001).

Efficacy After PS Adjusting for Baseline Differences

All female (n=209) and male (n=327) subjects with complete baseline covariates were included in the PS analysis (Figure 1). PS stratified into 5 quintiles balanced across the baseline covariates revealed no statistical differences between groups (all interaction tests, *P*>0.05; Table I in the Data Supplement). Women continued to have worse outcomes than men. Specifically, the female cohort had a higher risk of primary efficacy failure (HR, >1) in 4 of 5 quintiles and a higher risk of cardiovascular rehospitalization in all 5 quintiles. The overall PS-adjusted HRs for both the primary efficacy end point ($HR_{PS\ adj}$, 1.51; 95% CI, 1.16–2.18) and cardiovascular rehospitalization ($HR_{PS\ adj}$, 1.40; 95% CI, 1.15–2.17) were statistically significant at *P*<0.05 (Table 4).

Procedural Characteristics by Sex

Table 5 presents the index AF ablation procedural measurements. Mean procedure time during the index AF ablation was similar between female and male cohorts (131±46 versus 134±50 minutes, respectively; *P*=0.533). Similarly, there were no statistical differences between female and male cohorts when examining left atrial dwell time (98±37 versus 102±41 minutes, respectively; *P*=0.157) and fluoroscopy time (20±19 versus 19±14 minutes, respectively; *P*=0.179). However, the length of stay during the index ablation hospitalization was significantly longer in women than in men (2.4±2.0 versus 1.8±1.2 days; *P*<0.001).

Safety Events by Sex

The primary safety end point was protocol defined as a composite of death from any cause, stroke or transient ischemic attack from any cause, and serious adverse events.[5–7] Serious adverse events included 2 major categories: (1) cardiac arrhythmias (other than a recurrence of AF) that were causally related to the therapeutic intervention and (2) procedure-related serious adverse events that were judged by the end point review committee to be causally related to the treatment. In this study, more women experienced a primary safety adverse event end point throughout the trial than men (16% versus 10%; *P*=0.017; Table 6). Of the 6% difference in safety event rate between men and women, 2.8% was attributed to groin site complications.

DISCUSSION

The primary objective of this study was to evaluate the association of baseline patient characteristics in the FIRE AND ICE data set with 3 clinical outcome measurements of catheter ablation for AF (ie, atrial arrhythmia recurrence, cardiovascular rehospitalization, and repeat catheter ablation). The study revealed that female sex was associated with a 37% increase in the risk of atrial arrhythmia recurrence and that subjects with a histo-

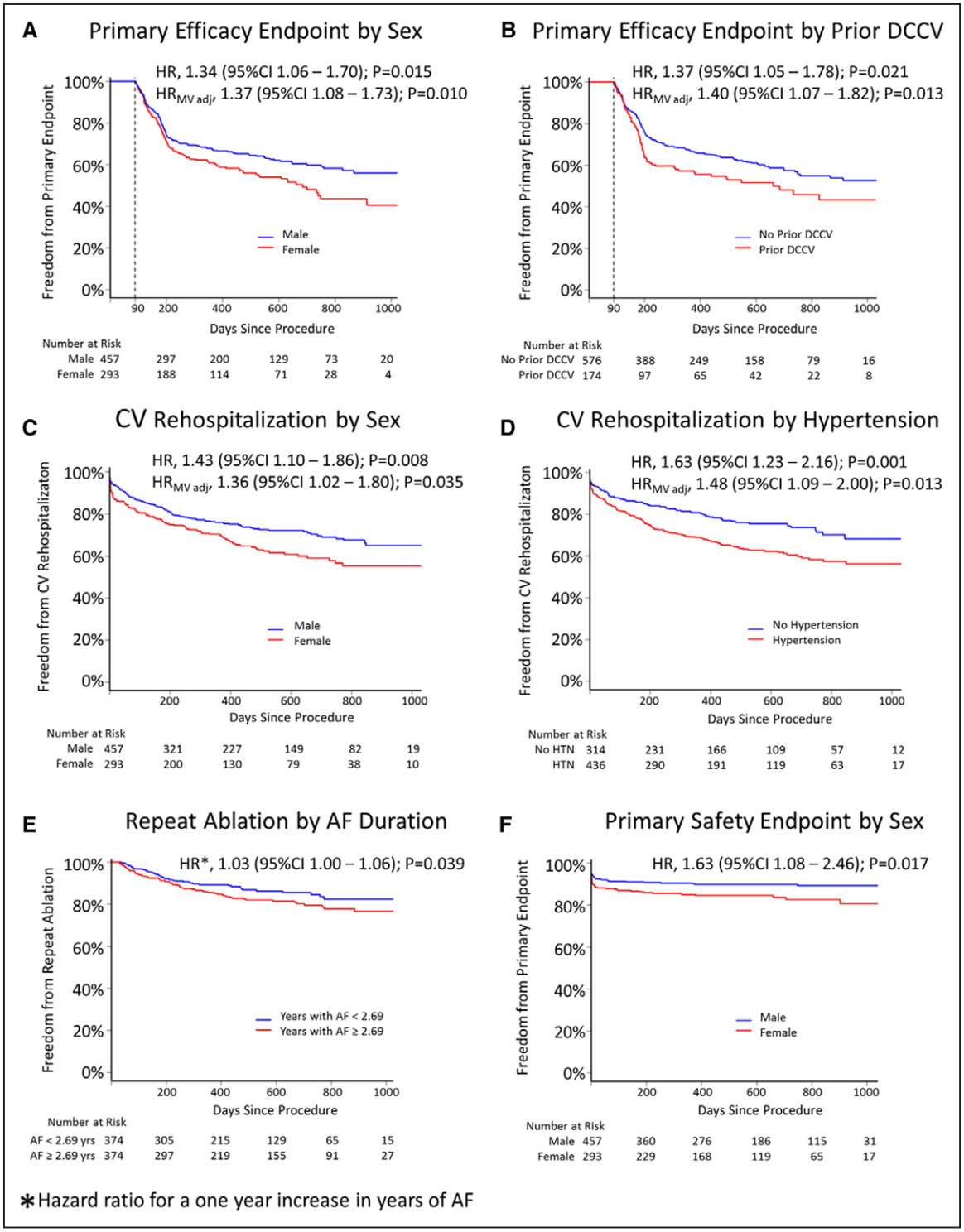

Figure 2. Kaplan–Meier event-free survival after the index catheter ablation.
A and **B**, Primary efficacy end point according to sex and history of direct current cardioversion (DCCV), respectively. Vertical dotted line at 90 d is the predefined landmark blanking period used for the primary efficacy end point. Adjusted hazard ratio (HR) from multivariable model ($HR_{MV\ adj}$) includes sex and prior DCCV as covariates. **C** and **D**, Cardiovascular (CV) rehospitalization according to sex and history of hypertension, respectively. $HR_{MV\ adj}$ includes age, sex, BMI, and hypertension as covariates. **E**, Repeat catheter ablation according to prior duration of atrial fibrillation (AF) symptoms (history of AF) before index catheter ablation. History of AF is dichotomized at the median value (2.69 y) for the Kaplan–Meier plot, and the data analyses retained the continuous measurements. **F**, Primary safety end point according to sex. CI indicates confidence interval.

ry of DCCV had a 40% increase in the risk of atrial arrhythmia recurrence. In addition to increased primary efficacy failure, female sex was associated with a 36% increased risk, and a history of hypertension was associated with a 48% increased risk of cardiovascular rehospitalization. A longer history of AF was the only

Table 4. Efficacy Outcomes by Sex-Adjusted Baseline Differences (Propensity Score Method)

Propensity Score Quintile	Total	Women	Men	HR (95% CI)	
				Primary End Point*†	CV Hospitalization*‡
Quintile 1	107	10	97	0.84 (0.30–2.35)	1.43 (0.50–4.08)
Quintile 2	107	25	82	1.75 (0.88–3.48)	1.48 (0.68–3.23)
Quintile 3	108	37	71	1.32 (0.71–2.45)	1.02 (0.49–2.13)
Quintile 4	107	57	50	1.94 (1.04–3.62)	1.70 (0.84–3.43)
Quintile 5	107	80	27	1.30 (0.66–2.57)	1.37 (0.68–2.77)
Adjusted overall (inverse-variance weighted)	536	209	327	1.51 (1.16–2.18)§; $P<0.05$	1.40 (1.15–2.17)§; $P<0.05$

CI indicates confidence interval; CV, cardiovascular; HR, hazard ratio; and PS, propensity score.

*Cox proportional hazards regression utilized to calculate HR (95% CI).

†Consistency of HR across quintiles tested by interaction term within a Cox regression model. Primary efficacy is the dependent variable. Sex, PS quintile, and sex×PS quintile interaction are covariates. The interaction term is not significant ($P=0.64$).

‡Consistency of HR across quintiles tested by interaction term within a Cox regression model. CV hospitalization is the dependent variable. Sex, PS quintile, and sex×PS quintile interaction are covariates. The interaction term is not significant ($P=0.91$).

§95% CI calculated by bootstrap methods (10 000 bootstrap samples).

baseline characteristic associated with an increased risk of repeat catheter ablation. Specifically, the analysis revealed that each additional year of diagnosed AF before the index ablation increased the risk of repeat ablation by 3%. Collectively, these data suggest that female sex, a history of DCCV or hypertension, and a longer history of AF are indicative of a lower success rate of catheter ablation for AF and may substantiate specialized monitoring or earlier treatment for certain patient populations to maximize treatment success.

Predictors of Primary and Secondary AF Ablation Outcomes

Analysis of baseline patient characteristics that predict secondary end points (eg, cardiovascular rehospitalization and repeat catheter ablation) more carefully identifies patients likely to experience clinical success after catheter ablation of AF than identifying predictors of primary efficacy alone. Studies and subsequent scoring systems designed to predict primary efficacy after ablation have been reported,[4,10] but here, a large cohort of patients was investigated to identify characteristics that predict a more complete depiction of clinical success. This study demonstrated that a history of DCCV in addition to female sex increased the risk of AF recurrence and that a longer history of AF increased the risk of repeat ablation. These results agree with other studies that determined history of DCCV, a long history of AF, and female sex were associated with AF recurrence after catheter ablation.[10–12] Additionally, this study determined that female sex and hypertension independently increased the risk of cardiovascular rehospitalization. The observation that hypertension increased the risk of cardiovascular rehospitalization is consistent with previous reports that demonstrate an association between hypertension and both AF- and cardiovascular-related hospitalization.[12,13] In our study, we identified female sex as the strongest predictor of outcomes after catheter ablation of AF.

Impact of Sex

Our data indicate that female sex was associated with ≥36% risk of both primary efficacy failure and cardiovascular rehospitalization. However, it was challenging to assess whether the female cohort had a poorer overall health status at the time of enrollment. On average, enrolled women were older and had a lower glomerular filtration rate than men. Although a host of poorly understood, sex-dependent physiological and pathophysiological mechanisms may predispose women to develop AF later in life, a review of differences between men and women who underwent cardiac ablation pro-

Table 5. Procedural Measurements by Sex

Procedure Characteristics	Total (N=750)	Women (n=293)	Men (n=457)	*P* Value*
Procedure time, min	133±48	131±46	134±50	0.533
Left atrial dwell time, min†	100±40	98±37	102±41	0.157
Fluoroscopy time, min†	19±16	20±19	19±14	0.179
Index ablation length of stay, d	2.1±1.5	2.4±2.0	1.8±1.2	<0.001

Values are mean±SD.

*2-sample *t* test.

†Left atrial dwell time reported for 711 subjects and fluoroscopy time reported for 744 subjects.

Table 6. Safety Events by Sex

Primary Safety Event	Total (N=750)	Women (n=293)	Men (n=457)	*P* Value*
Total	91 (12.1)	46 (15.7)	45 (9.8)	0.017
Groin site complication	23 (3.1)	14 (4.8)	9 (2.0)	0.048
Atrial arrhythmia	21 (2.8)	9 (3.1)	12 (2.6)	0.821
Unresolved phrenic nerve injury	10 (1.3)	5 (1.7)	5 (1.1)	0.524
Cardiac tamponade or pericardial effusion	6 (0.8)	4 (1.4)	2 (0.4)	0.216
Pulmonary or bronchial complication	6 (0.8)	1 (0.3)	5 (1.1)	0.413
Stroke or TIA from any cause	4 (0.5)	2 (0.7)	2 (0.4)	0.646
Transient neurological complication	4 (0.5)	2 (0.7)	2 (0.4)	0.646
Dyspnea	3 (0.4)	1 (0.3)	2 (0.4)	1.000
Gastrointestinal complication	3 (0.4)	2 (0.7)	1 (0.2)	0.564
Other, nonarrhythmia cardiac complications	3 (0.4)	1 (0.3)	2 (0.4)	1.000
Death	2 (0.3)	1 (0.3)	1 (0.2)	1.000
Anxiety	1 (0.1)	1 (0.3)	0 (0)	0.391
Contrast media reaction	1 (0.1)	0 (0)	1 (0.2)	1.000
Contusion	1 (0.1)	1 (0.3)	0 (0)	0.391
Esophageal ulcer	1 (0.1)	1 (0.3)	0 (0)	0.391
Hematuria	1 (0.1)	0 (0)	1 (0.2)	1.000
Local edema	1 (0.1)	1 (0.3)	0 (0)	0.391

Values are n (%). TIA indicates transient ischemic attack.
**P* value for total safety events calculated by log-rank test. *P* value for safety event components calculated with Fisher exact test.

cedures suggested that women are referred to catheter ablation less frequently and at more symptomatic disease states than men,[14] which may play a role in the observed age difference between sexes.

Although old age and a lower glomerular filtration rate may contribute to adverse outcomes after AF ablation, the differences observed were not large enough to account for the entire difference in outcomes between women and men observed in our study. For example, the 7-year age difference between sexes was univariately associated with a 7% increase in primary efficacy failure, much less than the observed 37% increase in risk. Furthermore, the difference between sexes does not seem to be explained by a composite of the baseline characteristics; the increased risk of primary efficacy failure and cardiovascular rehospitalization remained increased in women even after PS stratification of patients. Together, these data suggest that, regardless of baseline health conditions, sex influences clinical outcomes after AF ablation.

Our finding that female sex independently predicted both primary efficacy failure and cardiovascular rehospitalization is consistent with other reports of an association between female sex and an increased risk of recurrent AF.[1–4,10,15] The ORBIT-AF registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) examined the difference between sexes regarding AF symptoms, quality of life, AF treatment, and outcomes and found that in addition to baseline characteristic differences between sexes, women had more often symptomatic AF, more functional limitations, and a lower quality of life.[16] Interestingly, our data indicate that early primary efficacy of catheter ablation for AF is similar in both men and women up until ≈6 months, at which point ablation efficacy diverges in favor of men (Figure 2). This sex-dependent late divergence in longer term efficacy is not well understood, but it may indicate a less-durable lesion in women and a propensity for developing non–pulmonary vein triggers after catheter ablation.

We did not observe statistical differences between women and men in either procedure duration or fluoroscopy time during the index ablation, but women did have a longer length of stay during the index ablation procedure and a higher rate of primary safety end points, driven by a higher rate of groin site complications. Overall, the total number of groin site complications was low, but the mechanisms that underlie the observed sex difference in the incidence of groin site complications are unknown.

There is limited data to inform our understanding of the sex-related AF disparity and the role sex hormones may play in AF disease progression; however, there is evidence of an association between low levels of testosterone and risk of AF and progression of atrial remodeling during AF in men.[17,18] More research needs to be conducted on the sex dependence of AF disease parameters that affect efficacy and safety when women undergo any type of catheter ablation for AF. Further, a referral bias against catheter ablation treatment for female patients with AF may result in catheter ablation of older and disease-progressed women and ultimately

impair successful outcomes in this patient population.[14] As future clinical evaluations are conducted, it will be important to acknowledge that female sex in addition to a history of DCCV or hypertension or a long duration of AF may decrease the likelihood of a successful ablation outcome and skew clinical trial results. Consequently, more aggressive monitoring and effective treatment is necessary in these patient cohorts.

Study Limitations

This study utilized the database from the FIRE AND ICE trial to assess the association between baseline patient characteristics and clinical outcomes. Multivariable models were used to investigate associations between baseline characteristics and patient outcomes. Statistically significant associations in the multivariable models do not necessarily prove any hypothesis, but they do provide supporting evidence to other publications. Indeed, a sex effect was observed in this trial, but it may be limited by the data that were available.

Although sex had the largest impact of the 22 characteristics that were collected at baseline, other (potentially important) uncollected baseline characteristics may have had important contributions to our observations. A PS analysis method was used in an attempt to understand the difference in efficacy observed between sexes, and the results suggested that the large differences in efficacy we observed could not be explained by the baseline covariates collected (including the mean age difference). However, there may be additional baseline variables that underlie the observed differences, such as the frequency and duration of AF episodes, which were not collected at the time of enrollment.

Conclusions

Our study identified select baseline patient characteristics that were associated with relevant clinical outcomes after catheter ablation of AF. Regardless of the catheter ablation modality, female sex and a history of DCCV were independently associated with recurrence of AF. Also, female sex and hypertension independently predicted an increased rate of cardiovascular rehospitalization. Lastly, the patient's history (duration) of AF was associated with a higher risk of repeat ablation. Although the risk of an adverse outcome after catheter ablation in female patients with AF mandates further investigation (because it is possible that not all critical baseline covariates were collected), these results join a growing collection of literature that supports earlier AF detection and treatment to enhance efficacy in populations that predict poorer clinical outcomes.

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