Circulation

ORIGINAL RESEARCH ARTICLE

Association Between Sex and Treatment Outcomes of Atrial Fibrillation Ablation Versus Drug Therapy

Results From the CABANA Trial

BACKGROUND: Among patients with atrial fibrillation (AF), women are less likely to receive catheter ablation and may have more complications and less durable results. Most information about sex-specific differences after ablation comes from observational data. We prespecified an examination of outcomes by sex in the 2204-patient CABANA trial (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation).

METHODS: CABANA randomized patients with AF age ≥65 years or <65 years with ≥1 risk factor for stroke to a strategy of catheter ablation with pulmonary vein isolation versus drug therapy with rate/rhythm control agents. The primary composite outcome was death, disabling stroke, serious bleeding, or cardiac arrest, and key secondary outcomes included AF recurrence.

RESULTS: CABANA randomized 819 (37%) women (ablation 413, drug 406) and 1385 men (ablation 695, drug 690). Compared with men, women were older (median age, 69 years versus 67 years for men), were more symptomatic (48% Canadian Cardiovascular Society AF Severity Class 3 or 4 versus 39% for men), had more symptomatic heart failure (42% with New York Heart Association Class ≥II versus 32% for men), and more often had a paroxysmal AF pattern at enrollment (50% versus 39% for men) (P<0.0001 for all). Women were less likely to have ancillary (nonpulmonary vein) ablation procedures performed during the index procedure (55.7% versus 62.2% in men, P=0.043), and complications from treatment were infrequent in both sexes. For the primary outcome, the hazard ratio for those who underwent ablation versus drug therapy was 1.01 (95% CI, 0.62–1.65) in women and 0.73 (95% CI, 0.51–1.05) in men (interaction P value=0.299). The risk of recurrent AF was significantly reduced in patients undergoing ablation compared with those receiving drug therapy regardless of sex, but the effect was greater in men (hazard ratio, 0.64 [95% CI, 0.51–0.82] for women versus hazard ratio, 0.48 [95% CI, 0.40–0.58] for men; interaction P value=0.060).

CONCLUSIONS: Clinically relevant treatment-related strategy differences in the primary and secondary clinical outcomes of CABANA were not seen between men and women, and there were no sex differences in adverse events. The CABANA trial results support catheter ablation as an effective treatment strategy for both women and men.

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Clinical Perspective

What Is New?

- In a large, randomized controlled study of catheter ablation versus drug-based treatment for atrial fibrillation (AF), there was no significant treatment strategy–related difference in the primary outcome of death, disabling stroke, serious bleeding, or cardiac arrest in men versus women.
- Adverse events related to ablation or drug therapy were low in both men and women, without significant sex differences.
- Catheter ablation compared with drug therapy reduced AF recurrence in both men and women, although a greater reduction in AF burden was noted in men, likely related to greater prevalence of paroxysmal (as opposed to persistent) AF noted at baseline in women.

What Are the Clinical Implications?

- Although previous nonrandomized data suggested higher procedural complications in women compared with men, this was not seen in this randomized trial, and recommendations for ablation should not be discouraged based on concern for adverse events in women.
- As ablation offers comparable benefits for women and men, sex should not be used as a basis for selecting a management strategy for treatment of AF.

The role that sex plays in determining the risks and benefits of catheter-based versus drug-based management of atrial fibrillation (AF) remains controversial.[1,2] Nonrandomized data suggest that women may have a greater risk of procedural complications when compared with men.[3,4] Explanations offered for this difference usually include older age and greater number of comorbidities in women versus men along with smaller vessels and smaller heart size that could potentially make vascular access more difficult or increase risk for perforation during transseptal puncture or catheter manipulation in the left atrium. Whether such factors adequately account for reported differences is unclear. In addition, some studies suggest that women may have higher rates of AF recurrence after ablation than men.[5–7] Postulated reasons for sex differences in ablation effectiveness include less frequent or delayed referral for ablation, greater atrial fibrosis, older age with more complex clinical profile, and higher prevalence of nonpulmonary vein triggers in women.[7–11]

The CABANA trial (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) was an National Institutes of Health–funded, randomized, controlled trial designed to test the hypothesis that ablative therapy of AF is more effective than drug-based therapy for reduction of a composite primary outcome of death, disabling stroke, serious bleeding, or cardiac arrest.[12] CABANA enrolled the largest cohort of women in a randomized trial of catheter ablation and offers an important resource to determine if clinically important differences in response to ablation or drug therapy exist between men and women.

METHODS

Study Population

All patients enrolled in the CABANA trial were included in this study, and all supporting data are available within the article and its online supplementary file. This was a post hoc analysis of the CABANA trial for which each site's institutional review board or ethics committee approved the study, and written informed consent was obtained from all patients. As reported previously,[13] CABANA enrolled patients age 18 years or older who had electrocardiographic evidence of at least 2 episodes of paroxysmal AF or 1 episode of persistent AF in the 6-month period preceding enrollment. Patients also had to be eligible for both catheter ablation and drug therapy. Patients were further required to be age 65 years or older, or to have at least 1 risk factor for stroke. Patients were classified by sex group (men versus women) recorded in the case report forms and by randomized treatment arm. On the basis of an assessment of clinical relevance, in some instances, these categorizations were used to evaluate outcomes of ablation versus drug within sex subgroups including AF recurrence and complications. In other cases, categorizations were used to evaluate outcomes in men versus women within randomized treatment groups including primary and secondary outcomes.

Treatment Strategies

Details of the treatment strategies tested in CABANA have been described previously.[13] Ablation procedures had to include pulmonary vein isolation, but other (ancillary) ablative procedures were at the discretion of the treating physicians. Ancillary ablation procedures include ablation of complex fragmented electrograms, ganglion plexus and lines including the roof, mitral isthmus, left atrial septum, mitral annulus, cavotricuspid isthmus, coronary sinus, and right atrium or other ancillary strategy. In the drug therapy arm, the treating physician made the decision about use of specific rhythm or rate control agents. Use of anticoagulation therapy in accordance with prevailing guidelines was advised for all patients in CABANA.

Primary and Secondary Clinical Outcomes

The primary CABANA outcome was a composite of death, disabling stroke, serious bleeding, or cardiac arrest, as previously described.[12] Key secondary outcomes included all-cause mortality, death or cardiovascular hospitalization, and recurrent AF.

Ambulatory ECG monitoring, as previously described, was used to determine AF recurrence and AF burden.[14] Patient-triggered, symptom-driven recordings were obtained

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throughout the trial, and autodetect 24-hour loop recordings were obtained once per month during the first year and then quarterly throughout the remainder of the trial. Every 6 months, the monitor was programmed to provide up to 96 hours of monitoring to assess AF burden. Symptomatic and autodetect rhythms meeting the definition of an end point (atrial arrhythmia duration ≥30 s) were sent to the CABANA ECG Core Laboratory for reading by 2 expert physicians, with disagreements settled by a third reviewer.

Recurrence of AF was defined as any episode of atrial arrhythmia outside the 90-day blanking period lasting 30 s or longer with or without symptoms. Primary AF recurrence estimates were generated with the subset of patients who used the specific CABANA study recording system (86% of enrolling sites). Standardized 96-hour Holter monitor recordings were also used for assessment of AF burden biannually. Rhythm assessment was performed by an ECG Core Laboratory with embedded quality assurance mechanisms.[14]

Statistical Methods

Descriptive characteristics are reported as medians (25th, 75th percentiles) for continuous variables, and counts (percentages) for categorical variables. Comparisons between groups were performed using the Pearson χ^2 test or Fisher exact test for categorical data, and the Wilcoxon rank-sum test for continuous data.

Comparisons of treatment effects were performed using the randomized treatment assignment (intention to treat) and are reported by treatment strategy stratified by sex. Cumulative event rates were estimated from the time of randomization and depicted as Kaplan-Meier curves.[15] The Cox proportional hazards model was used to estimate hazard ratios (HRs) with 95% CIs.[16] The Cox model included terms for treatment, sex, and treatment and sex interaction and was adjusted for the following prespecified baseline characteristics: age, race/ethnicity, AF type, years since onset of AF, history of heart failure, structural heart disease, CHA_2DS_2-VASc score, history of coronary artery disease, and hypertension. Statistical testing of treatment outcome differences was performed using the Wald test from the Cox model. Proportional hazards assumptions were tested in all models, and no violations were found. Restricted cubic splines were used in the Cox model when the linearity assumption was violated for the primary composite, death or cardiovascular hospitalization, and atrial fibrillation or flutter or tachycardia recurrence outcomes. Counts of events and event rates per 100 patient-years are presented. Where missing covariate data did occur (<1%), continuous variables were imputed using the median, and categorical variables were imputed using the mode.

Prespecified subgroup comparisons were performed using multivariable Cox models including a treatment by covariable interaction term and were summarized using a forest plot.

Recurrent AF incidence rates were estimated using the method of Fine and Gray, with death treated as a competing risk and adjusted for the baseline covariates enumerated previously.[17] AF burden was calculated as the proportion of time (0%–100%) in each biannual Holter recording that patients were in AF. Recurrence and AF burden analyses were performed exclusively on patients who used the proprietary CABANA ECG event recorders (the CABANA box).

P values, where provided, are intended as supplemental interpretive aids reflecting the unexpectedness of the observed effects or differences under the assumption that the null hypothesis is true.[18] No adjustments were made for multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline and Procedural Characteristics

Baseline characteristics of the 819 (37%) women and 1385 (63%) men enrolled in CABANA are presented in Table 1. A total of 413 women and 695 men were randomized to catheter ablation and 406 women and 690 men to drug therapy. On average, women were older (median age, 69 years versus 67 years) and were more often white (94% versus 91%). Women were more likely to have paroxysmal AF than men (50% versus 39%, respectively) but reported more severe AF symptoms by Canadian Cardiovascular Society class (48% class III–IV for women versus 39% for men). Women also had more symptomatic heart failure (New York Heart Association class ≥II in 42% of women and 32% of men). Women were less likely to have coronary artery disease, left ventricular ejection fraction ≤35%, or sleep apnea (Table 1). Prevalence of diabetes, hypertension, and previous stroke/transient ischemic attack was similar between men and women. The number of years since first onset of AF was also similar in men and women. Women were less likely to have undergone previous cardioversion of AF, although there was no difference in the number of previous antiarrhythmic drugs used before ablation when compared with men.

Procedural Characteristics and Treatment-Related Adverse Events

Of the 413 women randomized to ablation, 373 (90%) received the procedure. Of the 695 men randomized to ablation, 633 (91%) received the procedure. In patients who received ablation treatment, men were more likely to have ancillary ablation procedures performed during the index procedure (55.7% in women versus 62.2% in men, *P*=0.043). The likelihood of undergoing repeat ablation among patients who were randomized to and had an initial procedure was not different in women and men (women 22.8% versus men 20.5%, *P*=0.400). The time from the initial ablation procedure to the repeat procedure did not differ between sexes (median of 372 days in women and 452 days in men, *P*=0.853).

For patients randomized to ablation therapy who received ablation, the overall rate of adverse events was low, with complications occurring in 22/373 (5.9%) of women and 35/633 (5.5%) of men (*P*=0.807) (Table 2). Vascular access complications were recorded in 14/373 (3.8%) of women and 23/633 (3.6%) of men.

Table 1. Baseline Characteristics of Intention to Treat, by Sex and Randomized Treatment

Characteristics	Men			Women			*P* value*
	Overall (N=1385)	Ablation (N=695)	Drug (N=690)	Overall (N=819)	Ablation (N=413)	Drug (N=406)	
Age							<0.0001
Median (Q1, Q3)	66.5 (60.1, 70.9)	66.6 (59.8, 71.2)	66.4 (60.9, 70.8)	69.4 (65.1, 73.7)	69.4 (65.3, 74.0)	69.4 (64.8, 73.3)	
N	1385	695	690	819	413	406	
Age category, y							<0.0001
<65	568/1385 (41.0%)	281/695 (40.4%)	287/690 (41.6%)	198/819 (24.2%)	94/413 (22.8%)	104/406 (25.6%)	
≥65 to <75	662/1385 (47.8%)	343/695 (49.4%)	319/690 (46.2%)	468/819 (57.1%)	234/413 (56.7%)	234/406 (57.6%)	
≥75	155/1385 (11.2%)	71/695 (10.2%)	84/690 (12.2%)	153/819 (18.7%)	85/413 (20.6%)	68/406 (16.7%)	
Race							0.0520
White	1259/1384 (91.0%)	629/694 (90.6%)	630/690 (91.3%)	766/816 (93.9%)	389/413 (94.2%)	377/403 (93.5%)	
Black or African American	55/1384 (4.0%)	31/694 (4.5%)	24/690 (3.5%)	22/816 (2.7%)	8/413 (1.9%)	14/403 (3.5%)	
Other	70/1384 (5.1%)	34/694 (4.9%)	36/690 (5.2%)	28/816 (3.4%)	16/413 (3.9%)	12/403 (3.0%)	
Minority: Hispanic or non-White	158/1381 (11.4%)	81/692 (11.7%)	77/689 (11.2%)	67/817 (8.2%)	32/412 (7.8%)	35/405 (8.6%)	0.0154
Body mass index, kg/m^2							0.8296
Median (Q1, Q3)	30.0 (26.6, 34.3)	30.0 (26.8, 33.9)	30.1 (26.6, 34.6)	30.1 (26.1, 35.2)	30.0 (26.1, 34.9)	30.5 (26.2, 35.6)	
N	1370	685	685	800	401	399	
Atrial fibrillation severity (Canadian Cardiovascular Society class)							<0.0001
Class 0	160/1375 (11.6%)	73/688 (10.6%)	87/687 (12.7%)	63/816 (7.7%)	32/412 (7.8%)	31/404 (7.7%)	
Class 1	246/1375 (17.9%)	124/688 (18.0%)	122/687 (17.8%)	93/816 (11.4%)	42/412 (10.2%)	51/404 (12.6%)	
Class 2	433/1375 (31.5%)	210/688 (30.5%)	223/687 (32.5%)	270/816 (33.1%)	140/412 (34.0%)	130/404 (32.2%)	
Class 3	457/1375 (33.2%)	239/688 (34.7%)	218/687 (31.7%)	326/816 (40.0%)	162/412 (39.3%)	164/404 (40.6%)	
Class 4	79/1375 (5.7%)	42/688 (6.1%)	37/687 (5.4%)	64/816 (7.8%)	36/412 (8.7%)	28/404 (6.9%)	
Heart function severity, New York Heart Association class≥II	433/1373 (31.5%)	207/686 (30.2%)	226/687 (32.9%)	345/813 (42.4%)	171/411 (41.6%)	174/402 (43.3%)	<0.0001
Medical history							
Hypertension (>140/90 mm Hg)	1100/1385 (79.4%)	538/695 (77.4%)	562/690 (81.4%)	676/818 (82.6%)	338/413 (81.8%)	338/405 (83.5%)	0.0649
Baseline left ventricular hypertrophy	444/1025 (43.3%)	223/540 (41.3%)	221/485 (45.6%)	218/619 (35.2%)	111/324 (34.3%)	107/295 (36.3%)	0.0012
Diabetes (glucose ≥126 mg/dL)	360/1385 (26.0%)	179/695 (25.8%)	181/690 (26.2%)	201/818 (24.6%)	101/413 (24.5%)	100/405 (24.7%)	0.4596
Previous cerebral vascular accident or transient ischemic attack	129/1385 (9.3%)	65/695 (9.4%)	64/690 (9.3%)	91/818 (11.1%)	52/413 (12.6%)	39/405 (9.6%)	0.1708
Coronary artery disease	332/1385 (24.0%)	160/695 (23.0%)	172/690 (24.9%)	92/818 (11.2%)	48/413 (11.6%)	44/405 (10.9%)	<0.0001
Sleep apnea	372/1385 (26.9%)	189/695 (27.2%)	183/690 (26.5%)	136/818 (16.6%)	73/413 (17.7%)	63/405 (15.6%)	<0.0001
Left ventricle ejection fraction ≤35	58/948 (6.1%)	33/486 (6.8%)	25/462 (5.4%)	11/582 (1.9%)	5/304 (1.6%)	6/278 (2.2%)	0.0001
Comorbidities							

(*Continued*)

Table 1. Continued

Characteristics	Men			Women			*P* value*
	Overall (N=1385)	Ablation (N=695)	Drug (N=690)	Overall (N=819)	Ablation (N=413)	Drug (N=406)	
CHA_2DS_2-VASc score							<0.0001
Median (Q1, Q3)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	
N	1385	695	690	819	413	406	
Arrhythmia history							
Years since first onset of atrial fibrillation							0.4818
Median (Q1, Q3)	1.0 (0.3, 3.9)	1.0 (0.3, 4.2)	1.0 (0.3, 3.7)	1.2 (0.3, 3.8)	1.1 (0.3, 3.8)	1.4 (0.3, 3.9)	
N	1373	690	683	812	410	402	
Type of atrial fibrillation							
Paroxysmal	540/1385 (39.0%)	276/695 (39.7%)	264/690 (38.3%)	406/818 (49.6%)	194/413 (47.0%)	212/405 (52.3%)	<0.0001
Persistent	690/1385 (49.8%)	338/695 (48.6%)	352/690 (51.0%)	352/818 (43.0%)	186/413 (45.0%)	166/405 (41.0%)	0.0020
Long-standing persistent	155/1385 (11.2%)	81/695 (11.7%)	74/690 (10.7%)	60/818 (7.3%)	33/413 (8.0%)	27/405 (6.7%)	0.0032
Previous direct current cardioversion of atrial fibrillation	547/1384 (39.5%)	267/694 (38.5%)	280/690 (40.6%)	262/818 (32.0%)	131/413 (31.7%)	131/405 (32.3%)	0.0004
Current or past use of rhythm control therapy reported at time of enrollment	638/1312 (48.6%)	301/651 (46.2%)	337/661 (51.0%)	400/782 (51.2%)	187/395 (47.3%)	213/387 (55.0%)	0.2640
≥2 Rhythm control drugs	109/638 (17.1%)	43/301 (14.3%)	66/337 (19.6%)	79/400 (19.8%)	47/187 (25.1%)	32/213 (15.0%)	0.2778
Crossover	263/1385 (19.0%)	62/695 (8.9%)	201/690 (29.1%)	140/819 (17.1%)	40/413 (9.7%)	100/406 (24.6%)	0.2660
Study withdrawal	138/1385 (10.0%)	54/695 (7.8%)	84/690 (12.2%)	101/819 (12.3%)	49/413 (11.9%)	52/406 (12.8%)	0.0840
Follow-up time							0.0136
Median (Q1, Q3)	49.7 (30.4, 62.5)	49.7 (31.0, 61.9)	49.8 (30.0, 63.2)	47.3 (28.7, 61.4)	47.8 (28.5, 61.4)	44.0 (29.4, 61.6)	
N	1385	695	690	819	413	406	

Q1 and Q3 indicate quartiles 1 and 3 (25th and 75th percentiles).
**P* value for comparison between overall men and overall women.

Complications related to ablation or catheter manipulation in the heart occurred in 2.4% of women and 2.1% of men. This included esophageal ulceration in 4 (1.1%) women and 1 (0.2%) man. There were no reports of cardiac tamponade with perforation, atrial esophageal fistula, cardiac arrest, or disabling stroke, and transient ischemic attack was rare (0.3% women and 0.3% men).

For patients receiving drug therapy, adverse events occurred in 19/405 (4.7%) of women and 27/687 (3.9%) of men (Table 3). Ventricular proarrhythmia was rare in both sexes (women, 0.5%; men, 1.2%).

Primary and Secondary CABANA Outcomes

Median follow-up in CABANA was 48.5 months (women 47.3 months, men 49.7 months) (Table 1). The rates of crossover and withdrawal for women were similar to those of men (crossover rate of women 17.1% versus men 19.0%; withdrawal rate of women 12.3% versus men 10.0%).

For the primary outcome of death, disabling stroke, serious bleeding, or cardiac arrest, the HR for an ablation treatment strategy versus a drug treatment strategy in the intention-to-treat subgroup of women was 1.01 (95% CI, 0.62–1.65), and in the subgroup of men, the HR was 0.73 (95% CI, 0.51–1.05; interaction *P* value=0.299) (Figure 1). For the composite secondary outcome of all-cause mortality or cardiovascular hospitalization, the HR was 0.87 (95% CI, 0.72–1.04) in women and 0.80 (95% CI, 0.69–0.92) in men (interaction *P* value=0.49). For all-cause mortality, the HR in women was 0.62 (95% CI, 0.33–1.16) and in men was 0.92 (95% CI, 0.60–1.41) (interaction *P* value=0.313).

AF Recurrence and Burden

Following the blanking period, the risk of recurrent AF was significantly reduced in both women (HR, 0.64 [95% CI, 0.51–0.82]) (Figure 2A) and men (HR, 0.48 [95% CI, 0.40–0.58]) (Figure 2B) undergoing ablation compared with those receiving drug therapy. The magnitude of benefit was larger in men because of both higher freedom from recurrent AF in the ablation arm and lower freedom from AF in the drug therapy arm relative to women (interaction *P* value=0.064). At 12 months, 59% of women and 66% of men randomized to ablation were free from recurrence. The

Table 2. Adverse Events of Ablation, by Sex

Event	Patients with ablation-related adverse event	
	Men (n=633), n (%)*	Women (n=373), n (%)*
Catheter insertion		
Hematoma	13 (2.1)	9 (2.4)
Pseudo aneurysm	6 (0.9)	5 (1.3)
Atrial venous fistula	3 (0.5)	1 (0.3)
Pneumothorax	…	…
Sepsis	1 (0.2)	…
Deep vein thrombosis	…	…
Pulmonary embolus	…	…
Ablation-related events		
Severe pericardial chest pain	9 (1.4)	2 (0.5)
Esophageal ulcer	1 (0.2)	4 (1.1)
Left inferior pulmonary vein stenosis >75%	1 (0.2)	…
Phrenic nerve injury	…	1 (0.3)
Atrial esophageal fistula	…	…
Catheter manipulation within the heart		
Transient ischemic attack	2 (0.3)	1 (0.3)
Myocardial infarction	…	1 (0.3)
Cardiac tamponade with perforation	…	…
Complete heart block	…	…
Coronary occlusion	…	…
Valvular damage	…	…
Medication-related events	…	…
Heparin induced bleeding	…	…

*Percentage is calculated among patients who received ablation.

Table 3. Adverse Events of Drug Therapy, by Sex

Event	Patients with drug-related adverse event	
	Men (n=687), n (%)*	Women (n=405), n (%)*
Hyper- or hypothyroidism	12 (1.7)	6 (1.5)
Major proarrhythmic event (ventricular tachycardia, ventricular fibrillation)	8 (1.2)	2 (0.5)
Allergic reaction	3 (0.4)	4 (1.0)
Gastrointestinal abnormality excluding moderate/severe diarrhea	3 (0.4)	7 (1.7)
Hypotension	2 (0.3)	1 (0.2)
Liver injury or failure	1 (0.1)	2 (0.5)
Atrial proarrhythmic event	1 (0.1)	…
Pulmonary toxicity	1 (0.1)	…
Blindness	…	…
Heart failure	…	…
Kidney damage	…	…
Moderate or severe diarrhea	…	…
Renal failure	…	…
Severe headache	…	…
Torsades des pointes	…	…

*Percentage is calculated among patients who received drug.

corresponding 12-month estimates in the drug arm were 44% in women and 39% in men.

Women had a lower AF burden than men at the time of enrollment: 42% of Holter recording time in AF for women versus 52% in men (P=0.006) (Figure 3). For women, at 12 months, AF was present during 8% of recording time for the patients with ablation and 7% of the patients with drug therapy (Figure IA in the Data Supplement). At 5 years, the corresponding figures were 15% and 18%, respectively. For men, at 12 months, AF was present during 6% of Holter time in the ablation arm and 18% in the drug therapy arm (Figure IB in the Data Supplement). The corresponding figures for 5 years were 14% and 22%, respectively.

Comparison of Outcomes by Sex Stratified by Randomized Treatment Group

In patients randomized to ablation, the women:men HR for the CABANA primary composite outcome was 0.95 (95% CI, 0.60–1.52) (Table 4). In patients randomized to drug therapy, the corresponding HR was 0.69 (95% CI, 0.43–1.11). The women:men HR for the secondary outcome of death or cardiovascular hospitalization was 1.03 (95% CI, 0.85–1.24) for the ablation arm and 0.95 (95% CI, 0.79–1.13) for the drug therapy arm.

Prespecified Subgroup Effects in Women

In the 819 women in CABANA, the estimated treatment effect on the primary composite outcome did not vary significantly by any of the prespecified subgroups proposed for the parent trial (Figure 4).

DISCUSSION

CABANA was a large, randomized, controlled study of catheter ablation versus drug-based treatment strategies for AF in both men and women and provides the largest randomized comparison of these treatment options in women. From this experience, 3 important findings emerge. First, we found that in the women versus men subgroups, as in the overall trial, there was no significant treatment strategy–related difference in the primary outcome of death, disabling stroke, serious bleeding, or cardiac arrest. Second, treatment-related adverse events in both treatment arms were low and did not differ significantly based on sex. Third, AF recurrence was reduced by ablation compared with drug

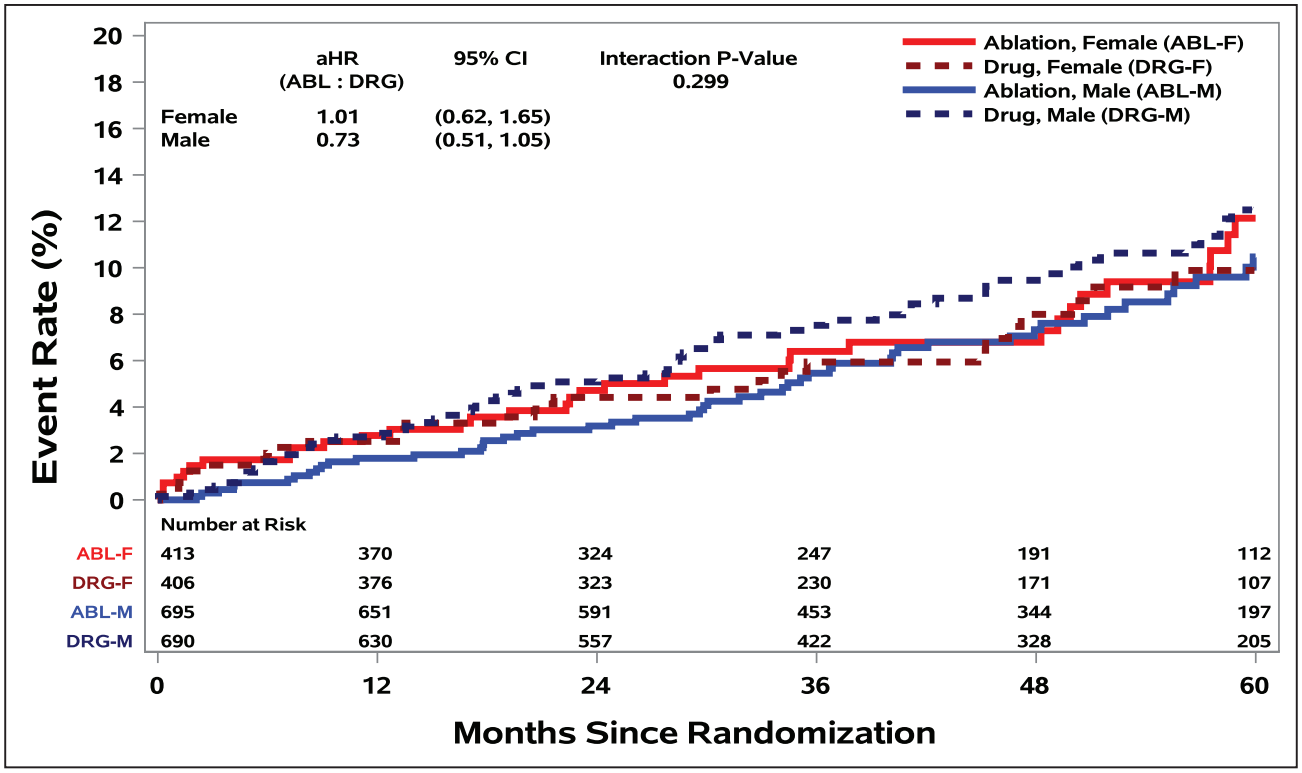

Figure 1. Kaplan-Meier estimates of the incidence of the primary outcome in the intention-to-treat groups, by sex.
ABL indicates ablation; aHR, adjusted hazard ratio; and DRG indicates drug.

therapy in both women and men, but men appeared to achieve greater absolute benefit from ablation both in terms of freedom from AF recurrence and AF burden (defined as percentage of Holter time spent in AF during periodic follow-up recordings).

The CABANA trial previously reported that catheter ablation compared with medical therapy did not significantly reduce the composite outcome of death, disabling stroke, serious bleeding, or cardiac arrest.[12] Outcome comparisons by treatment in the subgroup of women enrolled in CABANA were consistent with this result for the primary outcome and for important secondary outcomes, including death, disabling stroke, and cardiac arrest individually and the composite secondary outcome of death or cardiovascular hospitalization (Figures 1 and 2). Previous work suggested that these outcomes differ between sex subgroups.[4,19–24] When stratified by therapy, there was no difference in primary or secondary outcomes between men and women in CABANA (Table 4). Thus, in the absence of a clear mortality difference, AF management decisions should be made based on alternative considerations including individual patient risk of complications, AF recurrence, AF burden, and quality of life.

Previous analyses of AF ablation have reported that women appear to have a higher risk of procedural complications. Putative explanations for this include smaller cardiac and venous structures making venous access and catheter manipulation more prone to vascular complications and cardiac perforation with tamponade.[25,26] In CABANA, the rate of serious procedure-related complications was low and consistent with other contemporaneous ablation trials and registries[27–29] and did not differ significantly between sex subgroups (5.9% of women and 5.5% of men). In fact, there were no reports of tamponade with perforation, and the majority of adverse events were related to catheter insertion complications in both men and women in this trial. In part, this may reflect evolving safety of AF ablation procedures with improved transseptal puncture techniques, advanced catheter technology, availability of novel oral anticoagulants during the study period, and enrollment of patients at selected sites with experience in catheter ablation. In addition, women have been shown to have greater atrial fibrosis, more comorbidities, and higher prevalence of nonpulmonary vein triggers.[7–11] Although there appears to be a disparity in referral or use of AF ablation in women versus men, reasons for these differences remain unclear. Our findings would not support reduced referral of women based on higher procedural risk or low efficacy of ablation.

This study also demonstrated the comparative safety of antiarrhythmic therapy overall and by sex. Adverse events from antiarrhythmic therapy were rare in the CABANA trial despite the relatively frequent use of amiodarone (32% in the drug group and 17% in the ablation group) and its well-known profile of adverse

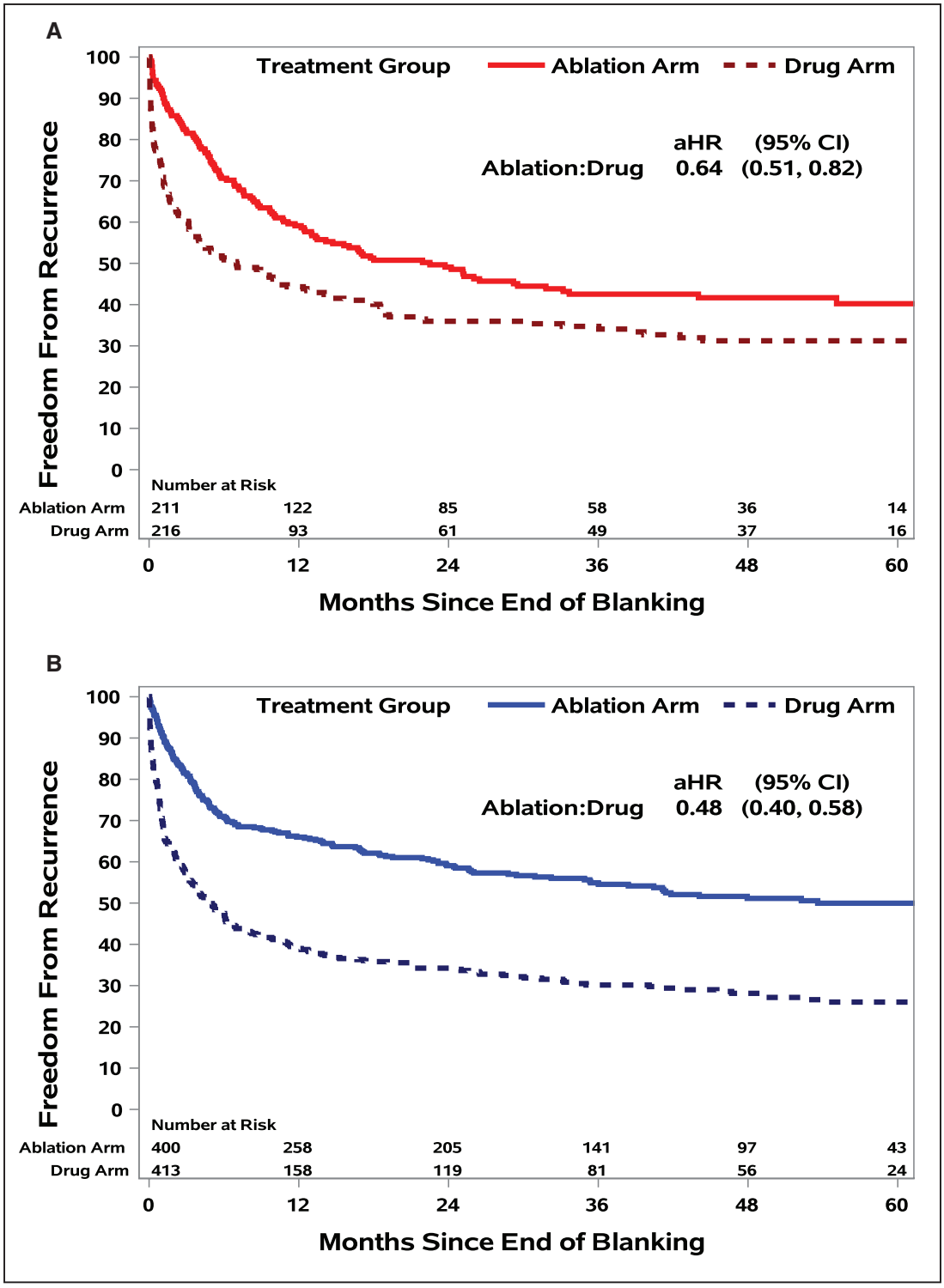

Figure 2. Recurrent atrial arrhythmias postblanking in ablation versus drug intention to treat groups.
Freedom from first recurrence of atrial fibrillation, flutter, or atrial tachycardia following the blanking period in patients who used the study ECG event recorders (CABANA box) in (**A**) women and (**B**) men. aHR indicates adjusted hazard ratio; and CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

effects.[30,31] It is also important to note that ventricular proarrhythmia was rare in both sexes.

CABANA demonstrated that women had a lower AF burden at baseline and less incremental reduction in AF burden from ablation compared with men, especially in the first year after ablation. Reasons for a difference in AF reduction after ablation between men and women are likely multifactorial. Comparisons of women versus men by freedom from AF recurrence (Figure 2A and 2B) show that at 12 months, drug therapy was somewhat

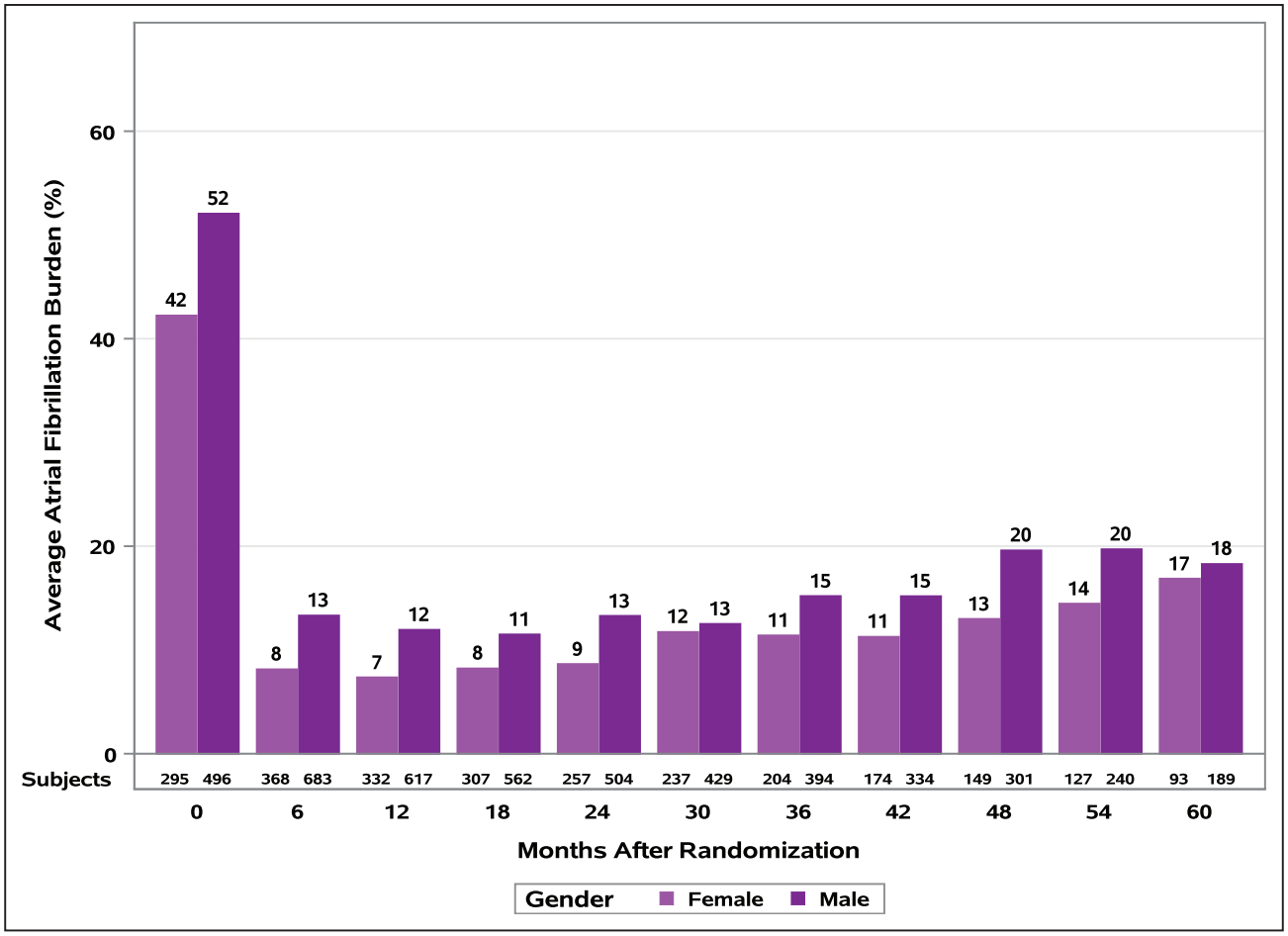

Figure 3. Atrial fibrillation burden, by time, women versus men.

more effective and ablation somewhat less effective, respectively. Both factors contributed to the quantitatively smaller relative and absolute treatment benefit in women. Comparing the burden of AF in men versus women randomized to ablation shows equivalent outcomes at 12 months: 8% of Holter time in AF for women and 6% of time in AF for men. In the drug therapy arm, however, burden at 12 months was 7% of Holter time in women versus 18% in men (Figure IA and IB in the Data Supplement).

Table 4. CABANA Primary and Secondary Outcomes Compared by Sex Stratified by Randomized Treatment Strategies

Event	Adjusted hazard ratio,* (95% CI)	
	Ablation	Drug
Primary composite outcome	0.95 (0.60–1.52)	0.69 (0.43–1.11)
Primary outcome components		
Death	0.67 (0.37–1.22)	0.99 (0.56–1.73)
Disabling stroke	3.44 (0.27–43.85)	0.74 (0.12–4.71)
Serious bleeding	1.10 (0.53–2.28)	0.39 (0.17–0.91)
Cardiac arrest	4.86 (0.92–25.66)	0.44 (0.05–3.93)
Atrial fibrillation recurrence	1.19 (0.93–1.53)	0.89 (0.70–1.13)
Secondary outcomes		
Death or cardiovascular hospitalization	1.03 (0.85–1.24)	0.95 (0.79–1.13)

CABANA indicates Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation.

*Male group as a reference.

Previous studies have suggested that differences between men and women in ablation effectiveness in the control of AF may be related to sex differences in triggers of AF because women may be more likely to have nonpulmonary vein triggers than men.[8,32] Information about AF triggers was not reported in CABANA, but men were somewhat more likely to undergo ancillary ablation during the index procedure than women. Although the value of empirical ancillary ablation procedures remains uncertain, it is certainly possible that women could have higher recurrence rates if specific triggers are not ablated. In addition, differences in treatment-related results between men and women, as in the AF burden results, are most notable in the drug therapy arms results rather than the ablation arms. Our data do not allow us to conclude whether the greater apparent responsiveness of women to drug therapy relative to men suggested by these data has a biological basis, such as a sex difference in disease stage at trial

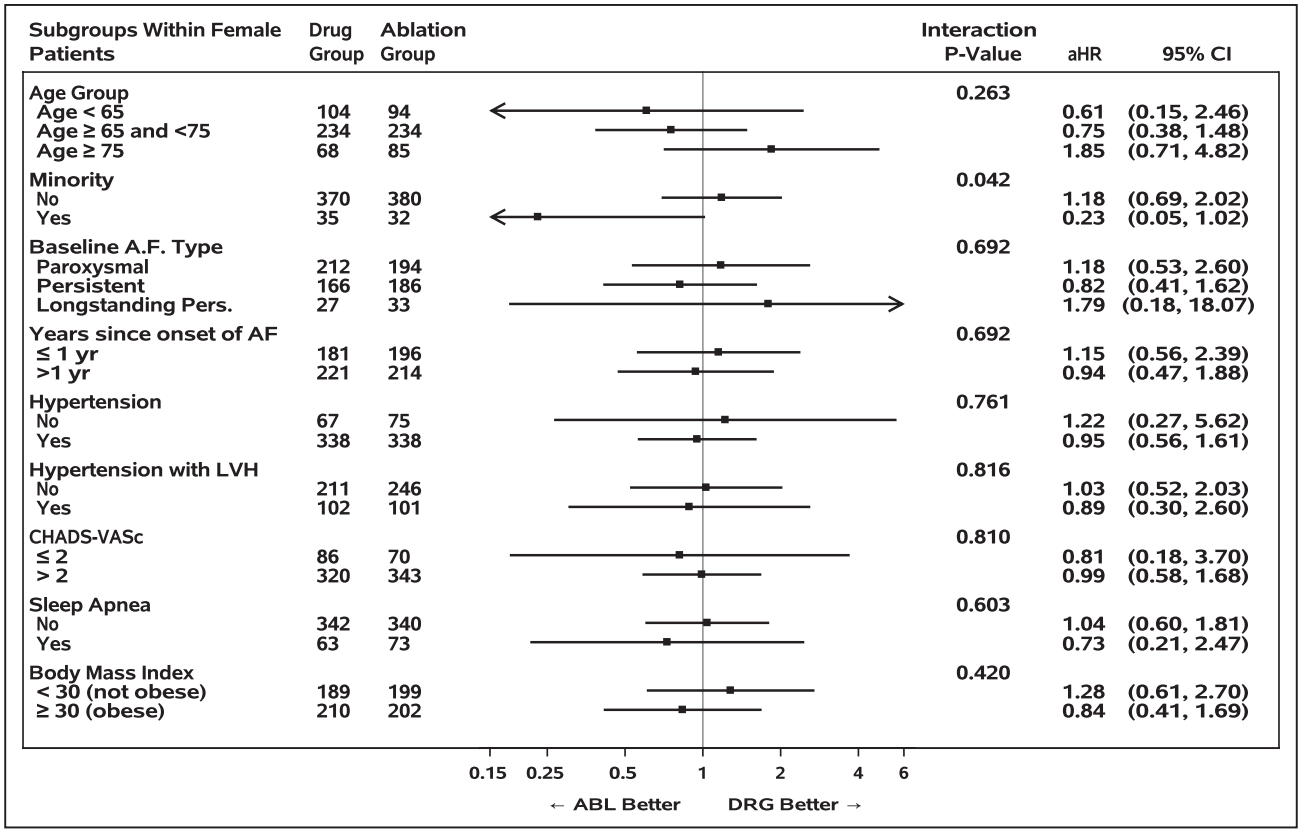

Figure 4. Subgroup effects on primary CABANA composite outcome, by randomized treatment strategy in women.
Prespecified subgroup comparisons were performed using multivariable Cox models including a treatment by covariable interaction term. After finding the maximum likelihood estimator, *P* values were generated based on the associated Wald χ^2 test statistic. ABL indicates ablation; aHR, adjusted hazard ratio; CABANA, Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; and DRG indicates drug.

entry (as reflected in more paroxysmal AF and lower AF burden at baseline).

Alternatively, it is possible that a real difference in AF mechanisms or AF substrate exists between men and women. Previous investigation has suggested that women may have more left atrial fibrosis than men; in multivariate analysis, advancing age and female sex were associated with a higher burden of atrial fibrosis in patients with AF.[9] Potential sex differences in hormonal or autonomic influence on arrhythmias cannot be excluded. Epicardial adipose tissue, which may play a role in AF substrate remodeling, was higher in postmenopausal women than in matched men, and this independently correlated with decreased left atrial voltage and left atrial transport function.[33] If there are differences in AF mechanisms between men and women, ablation strategies may need to be personalized. Further research in this area is warranted.

This analysis has some important limitations. First, subgroup analyses, including the present one, are almost always lacking in precision and power because major clinical trials are powered for the overall treatment comparison. In this context, lack of statistical significance may signal an indeterminate result rather than affirmative evidence of a negative result. Second, CABANA did not use implanted rhythm monitoring devices where truly continuous monitoring of arrhythmias could be used to accurately quantify AF burden. With the greater prevalence of paroxysmal AF in women compared with men at enrollment, reliance on noncontinuous recording capabilities may have resulted in imprecise quantification of brief AF episodes and underestimation of burden. Third, AF burden was quantified as a simple function of time rather than a more comprehensive summation of episode duration, frequency, and intensity. The current analysis did not investigate the impact of AF burden on quality of life measures, which will be reported separately. Fourth, therapy delivered within the clinical trial paradigm does not always approximate care delivered in clinical practice as the former tends to include younger, healthier patients with treatment delivered by more experienced operators/clinicians aware that their results are under careful and ongoing scrutiny. However, CABANA clinical outcome treatment effects for ablation versus drug therapy were reproduced in a large administrative data set, suggesting that the trial results are generalizable.[34]

In summary, compared with men, women in the CABANA trial evidenced some notable differences in AF presentation, ablation treatment, and AF outcomes. Nonetheless, when compared with drug

therapy, ablation offers comparable benefits for women and men. Consequently, sex should not be used as a basis for selecting a management strategy for the treatment of AF.

ARTICLE INFORMATION

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Supplemental Material

Data Supplement Figure I

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