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Meta-analysis

Sex-specific Long-term Outcomes of Watchman Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation

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ABSTRACT

Background: A recent analysis of a large registry showed differences in periprocedural outcomes of the Watchman left atrial appendage closure device in males compared with females. The objective of our study was to investigate the 5-year event rate in males and females enrolled in the Watchman device premarket clinical studies submitted for US Food and Drug Administration review.

Methods: We conducted a patient-level meta-analysis of 2256 patients from 4 studies: the PROTECT AF (Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation vs Long-Term Warfarin Therapy) randomized controlled trials and their continued-access registries—CAP1 (Continued Access to PROTECT AF) and CAP2 (Continued Access to PREVAIL). The outcomes evaluated were ischemic stroke (IS), IS/systemic embolism, hemorrhagic stroke (HS), and all-cause mortality. Mixed-effects Cox regression models and statistical testing for treatment-by-sex interaction were used to compare left atrial appendage closure vs warfarin in males and females. Hazard ratios adjusted (aHRs) for $CHADS_2$ scores were generated using the same model with $CHADS_2$ score as a covariate. Time-to-event end points were evaluated using the Kaplan-Meier method and log-rank test.

Results: For Watchman vs warfarin in the 2 randomized controlled trials, there was no significant interaction between sex and treatment for IS, IS/systemic embolism, HS, and all-cause mortality ($P > .05$); both males and females in the Watchman group had a lower aHR for HS than that in the warfarin group, which was statistically significant for males (aHR, 0.163; 95% CI, 0.045-0.593). In addition, there were no differences in outcomes between females and males treated with the Watchman device when pooling all studies.

Conclusions: These data suggest that sex does not significantly affect the long-term safety and effectiveness of the Watchman device in patients with nonvalvular atrial fibrillation; however, further studies are needed.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, with an estimated prevalence of 12.1 million people in the United States by the year 2030.[1] Individuals with AF have a 5-fold increased risk of stroke compared with that in individuals without AF.[2] It has been estimated that >80% of AF-related strokes are thromboembolic, and oral anticoagulants (OACs) (warfarin or direct oral anticoagulants [DOACs]) are the standard of care to reduce risks of thromboembolism in patients with nonvalvular atrial fibrillation (NVAF). Because approximately 90% of thrombi are believed to originate in the left atrial appendage (LAA) in AF-associated thromboembolic strokes, left atrial appendage closure (LAAC) has emerged as a treatment to reduce the risk of thromboembolic stroke in patients with AF.[3–5]

Left atrial appendage closure with the Watchman Left Atrial Appendage System (Boston Scientific Corporation) was evaluated in 2 randomized controlled trials (RCTs): PROTECT AF (Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy).[3,5] In

Abbreviations: AF, atrial fibrillation; aHR, adjusted hazard ratio; CAP1, Continued Access to PROTECT AF; CAP2, Continued Access to PREVAIL; DOAC, direct oral anticoagulant; FDA, US Food and Drug Administration; HS, hemorrhagic stroke; IS, ischemic stroke; LAAC, left atrial appendage closure; SE, systemic embolism.

Keywords: atrial fibrillation; females; left atrial appendage closure; meta-analysis; Watchman.

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Table 1. Watchman studies (N = 2256) included in this analysis.

	PROTECT AF	PREVAIL	CAP1	CAP2
Study design	RCT (2:1 randomization, Watchman 2.5: warfarin)	RCT (2:1 randomization, Watchman 2.5: warfarin)	Single-arm Watchman 2.5	Single-arm Watchman 2.5
Enrollment years	2005-2008	2010-2012	2008-2010	2012-2014
Total subjects enrolled (% female, number of females/number of enrolled)	707 (29.7%, 210/707)	407 (30.0%, 122/407)	–	–
Warfarin subjects enrolled (% female, number of females/number of enrolled)	warfarin 244 (29.9%, 73/244)	warfarin 138 (25.4%, 35/138)	–	–
Watchman 2.5 subjects enrolled (% female, number of females/number of enrolled)	Watchman 2.5 463 (29.6%, 137/463)	Watchman 2.5 269 (32.3%, 87/269)	Watchman 2.5 566 (34.4%, 195/566)	Watchman 2.5 576 (39.4%, 227/576)
Total follow-up (patient-years)	2793	1675	1954	1297
Database lock date	8 April, 2014	8 Nov, 2017	14 May, 2014	9 June, 2016

CAP1, Continued Access to PROTECT AF; CAP2, Continued Access to PREVAIL; PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF, Embolic Protection in Patients with Atrial Fibrillation; RCT, randomized controlled trial.

addition, there were 2 accompanying single-arm continued-access registry studies: CAP1 (Continued Access to PROTECT AF) and CAP2 (Continued Access to PREVAIL).[6–8] Results from the 2 RCTs and their respective continued-access studies supported US Food and Drug Administration (FDA) approval of the Watchman LAAC device as the first percutaneous transcatheter closure device intended for nonsurgical closure of LAA in 2015.

It is generally recognized that there are sex-specific differences in the underlying epidemiology of stroke and AF.[9,10] Although females have a lower incidence of AF than that in males, strokes are more common in females.[2,11] In addition, females (particularly elderly females) undergoing invasive cardiovascular procedures tend to have a higher risk of complications than that in males. More recently, a large registry analysis showed a higher periprocedural adverse event rate in women undergoing LAAC with the Watchman device than in men.[12] The objective of the present study was to evaluate the longer-term (5-year) stroke and mortality rates by sex in all patients with NVAF treated with the Watchman device by pooling data from the PROTECT AF and PREVAIL RCTs and their continued-access registries (CAP1 and CAP2).

Methods

Data collection and study designs

We focused our analysis on 4 data sets, 2 pivotal RCTs (PROTECT AF and PREVAIL) and the 2 continued-access registries (CAP1 and CAP2), which were conducted and submitted to the FDA by Boston Scientific Corporation in the Watchman premarket approval application and subsequent supplements. These data sets include deidentified patient-level data with long-term (4-5 years) follow-up periods. The study designs of these trials have been previously described.[3,5,6,13,14]

Study populations

Subject disposition in each of the 4 trials is shown in Table 1. Participants were enrolled from 2005 to 2014. The 2 RCTs had longer average follow-up durations than those of their respective continued-access registries. For pooled analyses, the following 2 populations were analyzed: (1) the combined 2 RCTs—ie, PROTECT AF plus PREVAIL (both the LAAC device and warfarin arms, N = 1114 total patients), and (2) the combined 4 trials—ie, the RCTs and their corresponding continued-access registries (only the LAAC device arm, N = 1874 total patients).

Clinical outcomes and definitions

The clinical outcomes investigated were ischemic stroke (IS), IS or systemic embolism (SE) (IS/SE, whichever occurred first), hemorrhagic stroke (HS), and all-cause mortality. The definition of each end point was identical in each study and has been described previously.[3,5,14] Patients who were event-free at the time of the last known status were censored.

Statistical analyses

Analyses were based on the intent-to-treat population. Between-study and within-study heterogeneities for each of the 4 end points were quantitatively and qualitatively evaluated by assessing the following: (1) the eligibility criteria for each trial, (2) the balance of baseline characteristics between males and females and between the device and control groups within each trial and in the pooled data, and (3) a heterogeneity test using the Cox regression model applied to data of the RCTs with appropriate study-by-treatment and study-by-sex interaction terms.

Regarding sex subgroup analysis, a 1-stage meta-analysis of individual participant data was performed to investigate sex-by-treatment interaction using the 2 RCT data sets. Mixed-effects Cox models with a random intercept for trials to account for study heterogeneity were used. $CHADS_2$ scores were also included as covariates in these models to adjust for multiple risk factors of stroke. The $CHADS_2$-adjusted hazard ratios (aHRs) were summarized in tables and forest plots. Statistical testing for sex-by-treatment interaction terms in these models was also performed.

Kaplan-Meier curves were generated and log-rank tests were performed to evaluate the time–to–first event end points using data from all 4 studies. Statistical significance was based on a 2-sided significance level of .05 (a 2-sided P value of $<.05$ without correction for multiplicity) and a 95% CI.

Statistical analyses were performed using R version 3.4.4 (R Core Team, R Foundation for Statistical Computing) and SAS 9.4 software (SAS Institute). The Coxme package in R was used for mixed-effects Cox models. Counts and percentages were reported for categorical variables, and additional mean and standard deviations were reported for continuous variables.

Results

Baseline characteristics

Baseline demographics and clinical characteristics for all participants stratified by sex are summarized in Table 2 and Figure 1. Specifically, the enrollment of male patients was nearly 2-fold higher (1502 males, 67% of the total enrollment) than that of female patients (754 females, 33% of the total enrollment). More than 90% of patients in the 4 studies were Caucasian in both the male and female subgroups. In the

Table 2. Baseline demographics and clinical characteristics (pooled studies, males and females).

	Males (n = 1502)	Females (n = 754)	*P* value[a]
Age, y	72.8 ± 8.6	75.6 ± 7.7	<.001
Age ≥65 y	1293 (86.1%)	701 (93.0%)	<.001
Age ≥75 y	694 (46.2%)	465 (61.7%)	<.001
Caucasian	1403 (93.4%)	690 (91.5%)	.120
BMI, kg/m^2	30.4 ± 5.6	29.4 ± 6.8	.001
$CHADS_2$ score	2.4 ± 1.1	2.6 ± 1.1	<.001
CHA_2DS_2-$VASc$	3.6 ± 1.4	4.8 ± 1.3	<.001
Medical history			
Congestive heart failure	364 (24.2%)	185 (24.5%)	.916
Hypertension	1363 (90.7%)	680 (90.2%)	.724
Diabetes	452 (30.1%)	200 (26.5%)	.087
Stroke/TIA	357 (23.8%)	230 (30.5%)	<.001
Myocardial infarction[b]	205 (17.8%)	56 (10.6%)	<.001

Values are presented as mean ± SD or n (%).
BMI, body mass index; TIA, transient ischemic attack.
[a] The 2-sample *t* test for continuous variables and the 2-sample proportion z-test for categorical variables. [b] Counts, percentages, and testing include all 4 trials except CAP2 (Continued Access to PREVAIL) (data not available).

2 RCTs, 782 (70.2%) of 1114 patients were males and 332 (29.8%) of 1114 patients were females. Compared with the males in all 4 trials combined, females were older (75.6 ± 8 vs 72.8 ± 9 years, $P < .001$), had statistically significantly higher $CHADS_2$ scores (2.6 ± 1.1 vs 2.4 ± 1.1, $P < .001$), had higher CHA_2DS_2-$VASc$ scores (4.8 ± 1.3 vs 3.6 ± 1.4, $P < .001$), had a higher proportion of prior stroke or transient ischemic attack (30.5% vs 23.4%, $P < .001$), and had a lower proportion of prior myocardial infarction or vascular disease (10.6% vs 17.8%, $P < .001$).

Heterogeneity assessment

The between-study heterogeneity of the 4 trials was assessed by evaluating the eligibility criteria of each study, the balance in the baseline characteristics, and the direction and magnitude of treatment effect across the 2 RCTs via statistical modeling. The eligibility criteria of all 4 studies were similar except that PREVAIL and CAP2 recruited patients with higher $CHADS_2$ scores (score ≥2 required for enrollment, average score 2.6) than those of the patients recruited by PROTECT AF and CAP1 (a score of ≥1 was required for enrollment; average score, 2.2). The variation of the random factor in the mixed-effects Cox regression (random intercept for trials) for the pooled analysis was minimal.

Sex-specific analysis of Watchman device vs warfarin groups

Sex-specific analyses based on the data from the 2 RCT trials were conducted to evaluate whether the treatment effect differed by sex subgroup. The aHRs from the mixed-effects Cox models with a random intercept are shown in Tables 3-5 and the Central Illustration. The point estimates for the aHRs for IS and IS/SE comparing the device with warfarin in each RCT and in the combined RCTs favored the warfarin group for both males and females because all aHRs were >1.0; however, they had wide CIs that crossed 1.0 and, thus, were not statistically significant (Table 3 and Central Illustration). The aHRs for HS favored the Watchman group for both males and females and reached statistical significance for males (aHR, 0.163; 95% CI, 0.045-0.593; $P = .0059$) (Table 4). For all-cause mortality, the point estimates for the aHRs nominally favored the Watchman group for males and females but did not reach statistical significance (Table 5).

Next, Kaplan-Meier time-to-event curves for the pooled 4 studies were plotted by sex and by treatment (Figure 2A-C). There was a trend toward a higher probability of IS/SE in females compared with in males in the LAAC device data pooled from the 4 trials ($P = .0598$); this trend was not observed in the warfarin control group pooled from the 2 RCTs ($P = .2163$) (Figure 2A). In addition, there was a trend toward a higher probability of IS and IS/SE in males treated in the device group compared with males treated in the warfarin control group (Figure 2A) (*P* values of the device vs control groups are .17 in males and .53 in females). There was a significantly higher probability of HS in the

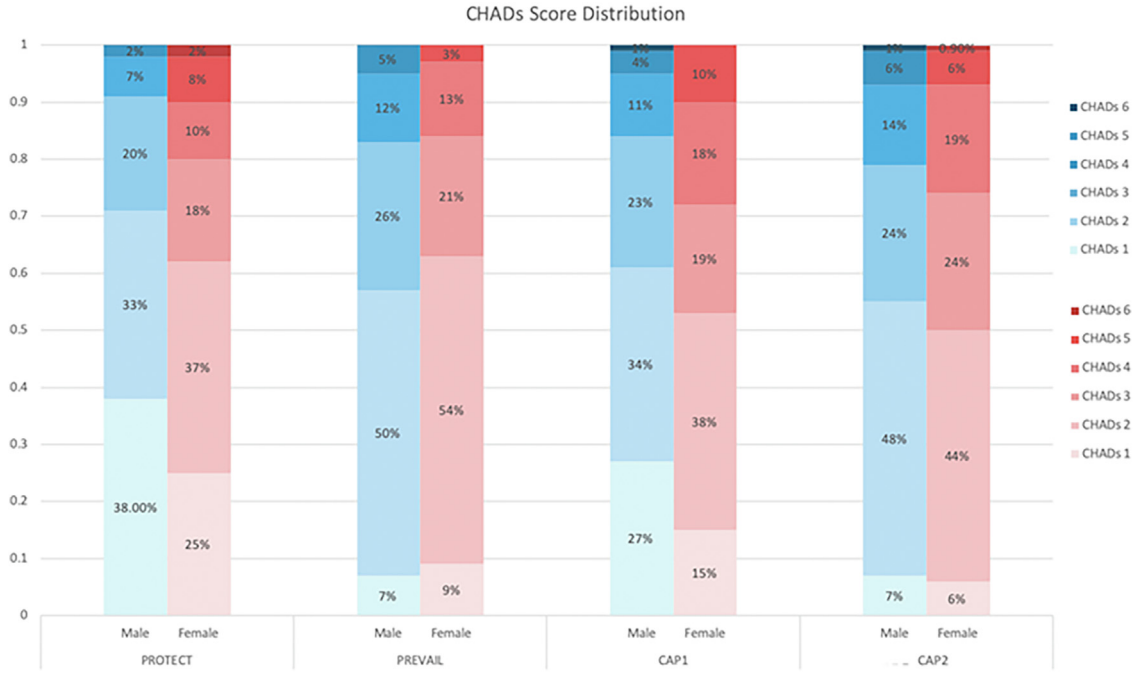
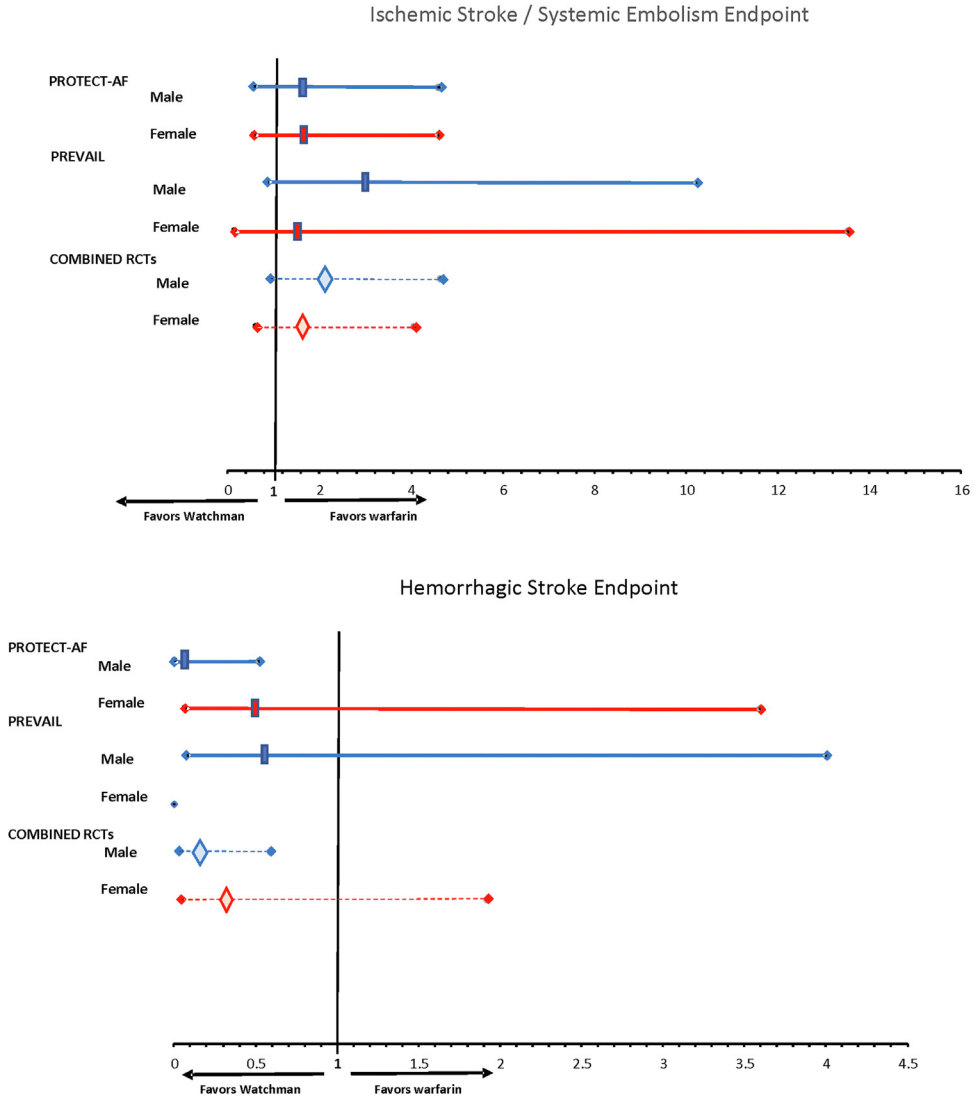


Figure 1.
$CHADS_2$ score distribution in males (blue) and females (red) for all 4 studies. CAP1, Continued Access to PROTECT AF; CAP2, Continued Access to PREVAIL; PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF, Embolic Protection in Patients with Atrial Fibrillation.

Table 3. Hazard ratios for ischemic stroke/systemic embolism adjusted for $CHADS_2$ score, Watchman versus warfarin (control) patients within each sex subgroup, and 95% CIs via mixed-effects Cox model on pooled randomized controlled trials

Trial	Sex	Number of events/total PY (event rate per 100 PY)		aHR (95% CI)	Interaction test *P* value
		Device group (Watchman 2.5), n/N (%)	Control group, n/N (%)		
PROTECT AF	Male n = 497	13/1292 (1.01)	5/656.3 (0.76)	1.621 (0.570-4.606) *P* = .3646	.875
	Female n = 210	13/496.9 (2.62)	5/277.1 (1.81)	1.639 (0.582-4.619) *P* = .3495	
PREVAIL	Male n = 285	15/714 (2.10)	3/409.9 (0.73)	2.966 (0.858-10.247) *P* = .0857	NC
	Female n = 122	4/357.2 (1.12)	1/136.5 (0.73)	1.508 (0.168-13.535) *P* = .7135	
Pooled RCTs	Male n = 782	28/2006 (1.40)	8/1066.2 (0.75)	2.113 (0.961-4.648) *P* = .0630	.470
	Female n = 332	17/854.2 (1.99)	6/413.7 (1.45)	1.596 (0.626-4.068) *P* = .3783	

aHR, adjusted hazard ratio; NC: not calculated; PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF, Embolic Protection in Patients with Atrial Fibrillation; PY, patient-year; RCT, randomized controlled trial.



Central Illustration.
Forest plots for sex-differences analyses for each end point in individual and combined 2 RCTs. PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF, Embolic Protection in Patients with Atrial Fibrillation; RCT, randomized controlled trial.

Table 4. Hazard ratios for hemorrhagic stroke adjusted for $CHADS_2$ score, Watchman versus warfarin (control) patients within each sex subgroup, and 95% CIs via mixed-effects Cox model on pooled randomized controlled trials.

Trial	Sex	No. of events/total PY (event rate per 100 PY)		aHR (95% CI)	Interaction test *P* value
		Device group (Watchman 2.5), n/N (%)	Control group, n/N (%)		
PROTECT AF	Male n = 497	1/1321.6 (0.08)	8/664.8 (1.20)	0.065 (0.008-0.522) *P* = .0101	.143
	Female n = 210	2/523.9 (0.38)	2/281.5 (0.71)	0.496 (0.068-3.602) *P* = .4885	
PREVAIL	Male n = 285	2/754.8 (0.27)	2/412.8 (0.48)	0.565 (0.080-4.010) *P* = .5671	NC
	Female n = 122	0/364.5 (0)	1/140.8 (0.71)	0 (NA)	
Pooled RCTs	Male n = 782	3/2076.4 (0.14)	10/1077.6 (0.93)	0.163 (0.045-0.593) *P* = .0059	.220
	Female n = 332	2/888.4 (0.23)	3/422.3 (0.71)	0.319 (0.053-1.923) *P* = .2126	

aHR, adjusted hazard ratio; NA, not available; NC, not calculated; PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF, Embolic Protection in Patients with Atrial Fibrillation; PY, patient-year; RCT, randomized controlled trial.

warfarin group than in the device group for both males and females (Figure 2B) (*P* values are <.0001 for males and .0327 for females), and time-to-HS event curves were similar in males and females within each treatment arm. All-cause mortality time-to-event curves were similar in males and females as well as in the device and control groups (Figure 2C).

Sex-specific analysis of the Watchman-only group

Figure 3 shows the analysis of aHRs between males and females treated with the Watchman device from the pooled data sets—ie, the 2 RCTs and the combined 4 studies. There were no statistically significant differences in any of the clinical outcomes stratified by sex in the pooled RCTs or when pooling the RCTs with the continued-access studies (all aHRs crossed 1.0).

Discussion

In the present study, we performed a meta-analysis of major clinical outcomes associated with the implantation of the Watchman device stratified by sex in patients with NVAF. A total of 7719 patient-years of data from the 2 RCTs with 5-year follow-up and their respective continued-access studies with 4 to 5 years follow-up were used.

In the pooled analysis of the 2 RCTs, we found that for IS/SE, event rate point estimates favored warfarin versus Watchman for males and females; however, these estimates had wide CIs and were not statistically significant. For HS, there was a statistically significant lower risk in males and numerically lower but not statistically significant risk in females.

When pooling the 2 RCTs with the 2 continued-access studies, there was a trend toward a higher probability of IS/SE in males and females treated in the Watchman group than in the warfarin group. For HS, there was a statistically significant higher risk of HS in both males and females in the warfarin group than in the Watchman group. All-cause mortality was similar between treatment groups for males and females. Importantly, in the pooled analysis of the 2 RCTs and the 2 continued-access studies, considering only Watchmen-treated patients, there were no noticeable differences in any of the clinical outcomes stratified by sex.

The baseline demographics and clinical characteristics of our pooled populations are consistent with those in several studies that have evaluated differences in the epidemiology of AF and stroke stratified by sex. Dagres et al,[9] in an analysis of approximately 5000 patients from the Euro Heart Survey on AF, showed that compared with males, females were older, had a lower quality of life, had more comorbidities, and had a higher risk of stroke. In an Israeli registry including more than 89,000 patients with NVAF, females were older and had a higher incidence of hypertension.[15] The overall risk of stroke was similar between males and females. However, females aged >75 years had a 2-fold higher risk of stroke than that in males. In addition, the mortality rate was higher in females than in males.[15] In the Framingham

Table 5. Hazard ratios for all-cause mortality adjusted for $CHADS_2$ score, Watchman versus warfarin (control) patients within each sex subgroup, and 95% CIs via mixed-effects Cox model on pooled randomized controlled trials.

Trial	Sex	No. of events/total PY (event rate per 100 PY)		aHR (95% CI)	Interaction test *P* value
		Device group (Watchman 2.5), n/N (%)	Control group, n/N (%)		
PROTECT AF	Male n = 497	41/1321.6 (3.10)	33/667.2 (4.95)	0.656 (0.414, 1.042) *P* = .0743	.312
	Female n = 210	19/524.0 (3.63)	11/282.4 (3.90)	1.074 (0.509, 2.265) *P* = .8508	
PREVAIL	Male n = 285	37/755.0 (4.90)	20/415.6 (4.82)	1.004 (0.583, 1.731) *P* = .9872	.072
	Female n = 122	9/364.5 (2.47)	9/140.9 (6.39)	0.364 (0.144, 0.920) *P* = .0326	
Pooled RCTs	Male n = 782	78/2076.4 (3.76)	53/1082.8 (4.90)	0.779 (0.549, 1.105) *P* = .1610	.150
	Female n = 332	28/888.5 (3.15)	20/423.2 (4.73)	0.719 (0.404, 1.280) *P* = .2624	

aHR, adjusted hazard ratio; PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF, Embolic Protection in Patients with Atrial Fibrillation; PY, patient-year; RCT, randomized controlled trial.

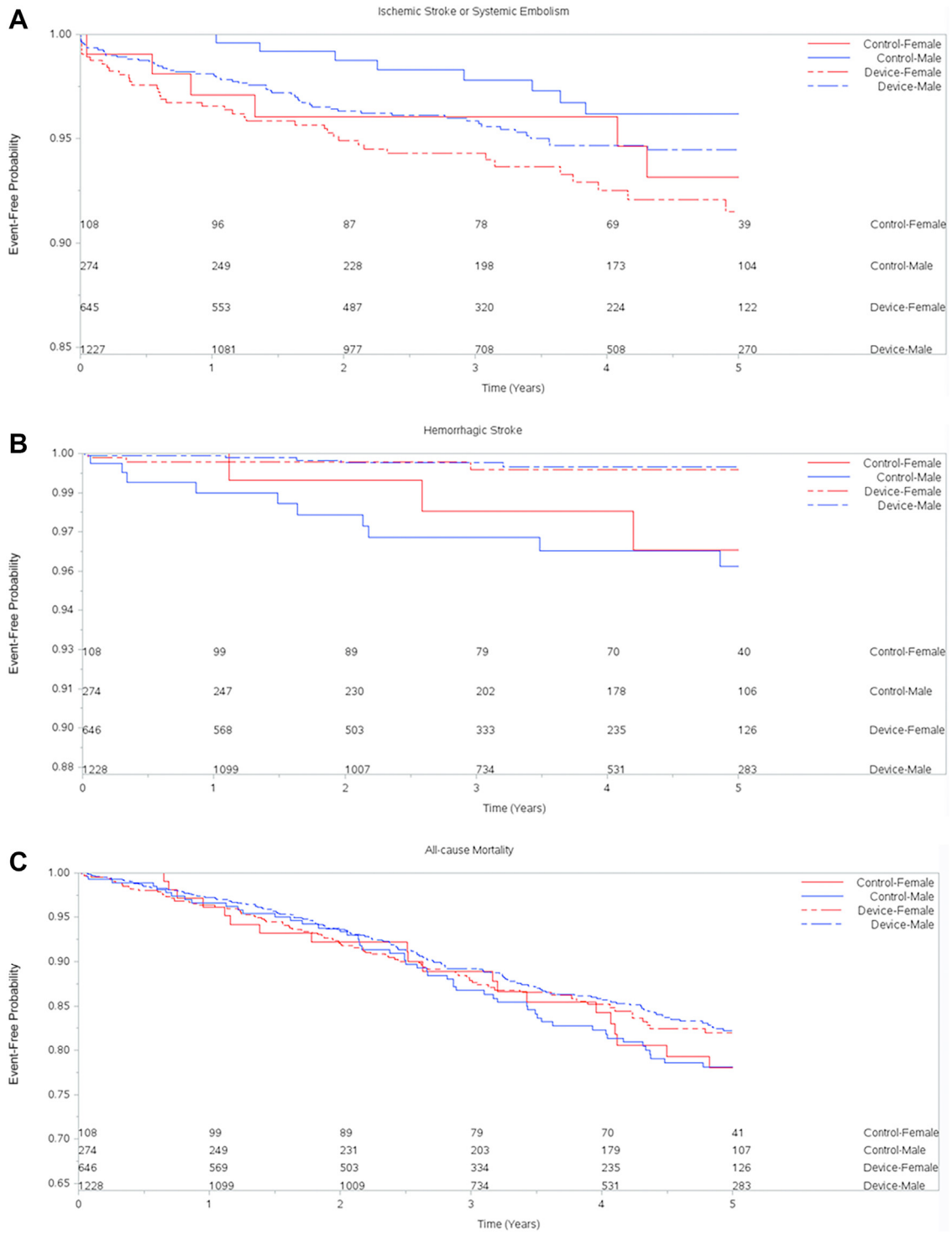


Figure 2.

Kaplan-Meier curves for 3 clinical outcomes in all 4 studies (N = 2256). For each end point, the curves, number of patients at risk, and event-free probabilities are provided and compared using the log-rank test. The *P* values are not adjusted for multiplicity. The dashed lines correspond to 1874 patients treated with the Watchman device in all 4 pooled trials (device group), 1228 males (blue dashed line) and 646 females (red dashed line). The solid lines correspond to 382 patients treated with warfarin (control group) in the 2 randomized controlled trials (RCTs), 274 males (blue, solid line) and 108 females (red, solid line). (**A**) The log-rank test results for ischemic stroke/systemic embolism: device group in 4 pooled studies, male vs female: $P = .0598$; control group in 2 RCTs, male vs female: $P = .2163$. *P* values of the device vs. control are .1732 in males and .5306 in females. (**B**) The log-rank test results for hemorrhagic stroke: device group in all 4 trials, male vs female: $P = .8084$; control group in 2 RCTs, male vs female: $P = .6866$. *P* values of the device vs control are <.0001 for males and .0327 for females. (**C**) The log-rank test results for all-cause mortality: dvice group in all 4 trials, male vs female: $P = .6793$; control group in 2 RCTs, male vs female: $P = .8976$. *P* values of the device vs control are .1763 in the male group and .5770 in the female group.

Heart Study and 2 additional cohort studies, the female sex compared with the male sex was associated with an increased risk of stroke in patients not receiving anticoagulation.[11,16,17]

Data on sex differences in clinical outcomes with OACs and with DOACs are limited. In general, females have been underrepresented in clinical trials evaluating DOACs, representing approximately 37% of the

Endpoint	Trial	Event : Women	Event : Men	aHR (95% CI)
IS	two RCTs	16 : 224	26 : 508	1.27 (0.68-2.37)
	all four	38 : 646	50 : 1228	1.34 (0.89-2.03)
IS or SE	two RCTs	17 : 224	28 : 508	1.25 (0.60-2.29)
	all four	40 : 646	54 : 1228	1.34 (0.89-2.03)
HS	two RCTs	2 : 224	3 : 508	1.58 (0.26-9.50)
	all four	3 : 646	5 : 1228	1.19 (0.27-4.86)
All-cause Mortality	two RCTs	28 : 224	78 : 508	0.78 (0.51-1.21)
	all four	84 : 646	162 : 1228	0.96 (0.74-1.25)

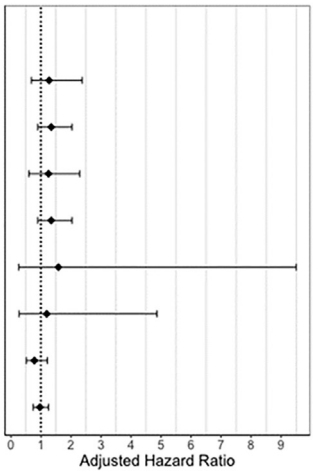


Figure 3.
Sex differences in Watchman patients only for each end point from pooled analyses. Adjusted hazard ratios (aHRs) (adjusted for $CHADS_2$ score; hazard ratio = female/male) and 95% CIs via mixed-effects Cox model for the 2 combined randomized controlled trial (RCTs) and for the 2 RCTs combined with the corresponding registries (all 4 studies). HS, hemorrhagic stroke; IS, ischemic stroke; SE, systemic embolism.

overall population enrolled in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF–TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trials,[18,19] which is similar to the percentage observed in the 4 clinical trials included in our study (30%-39%). In addition, similar to our study, each trial was not powered to evaluate sex-related differences in treatment outcomes. A meta-analysis of the 4 randomized trials found a lower risk of stroke in both males and females treated with DOACs than that in those treated with warfarin, which was primarily driven by a reduction in HS.[18] Other studies have suggested that males might benefit more from a reduction in stroke, and females might benefit more from a reduction in major bleeding.[19,20]

The introduction of LAAC in the management of patients with NVAF has provided a new treatment option to reduce the risk of stroke in patients with NVAF. In line with short-term studies that have shown higher rates of periprocedural adverse events in women than in men undergoing invasive procedures, a recent large LAAC registry analysis including 49,357 patients undergoing LAAC with the Watchman device showed higher rates of periprocedural serious adverse events in women than in men.[12] Data from this registry on long-term outcomes stratified by sex/gender are not yet available.

A strength of our study is that we were able to perform a meta-analysis on potential sex differences in the long-term performance of this first-of-its-kind LAAC device for each individual end point using the most complete long-term follow-up data sets available to the FDA. The incorporation of patient-level data across multiple studies increases the precision of the estimated treatment effects. In addition, consistent findings across different subgroup analyses and the relatively comparable quality of each of the 4 trials support the validity of our findings of a generally similar long-term performance of LAAC in females compared with in males.

Further research on the benefits and risks of LAAC between males and females and between LAAC and DOACs is needed. The ongoing "Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants" (CATALYST; NCT04226547) is evaluating the safety and effectiveness of the Amulet LAA occluder (Abbott) compared with NOAC (non-vitamin K antagonist oral anticoagulants) in patients with NVAF at an increased risk for IS. A similar evaluation is being conducted in the "WATCHMAN FLX Versus NOAC for Embolic ProtectION in the Management of Patients With Non-Valvular Atrial Fibrillation" trial (CHAMPION-AF; NCT04394546). Evaluation of sex-specific outcomes from analyses of large LAAC registries (eg, the US LAAO (Left Atrial Appendage Occlusion) Registry; the EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the Watchman Left Atrial Appendage Closure Technology) Registry in Europe, Russia, and the Middle East; the WASP (The Asia-Pacific Registry on WATCHMAN Outcomes in Real-Life Utilization) Registry in Southern Asia, South Korea, Australia, and Saudi Arabia; the Canadian Watchman Registry in Canada; and the China Registry of Watchman) is encouraged.

Limitations

Similar to prior reports, our study has several limitations. Most importantly, the total enrollment of female patients in these premarket studies was relatively small (n = 754 patients). Additional study limitations include the following: (1) a limited number of studies (2 randomized and 2 nonrandomized trials) that were combined in the meta-analysis; (2) an exploratory sex subgroup analysis that was not powered for statistical inference; (3) an imbalance in the sample sizes of the Watchman and warfarin groups, with the Watchman cohort being nearly 5-times larger than the warfarin group; (4) analyses adjusted for $CHADS_2$ score, but there may be other unmeasured confounding covariates; and (5) warfarin was used in the PROTECT AF and PREVAIL control groups, such that comparing the Watchman device to OAC stratified by sex cannot be extrapolated to all DOAC treatments. Finally, it should be noted that these trials involved the Watchman 2.5 device. In July 2020, FDA approved the Watchman FLX device, which is the current-generation Watchman device that is being implanted in the United States. In summary, because of relatively small sample sizes in premarket trials of patients treated with the first-generation Watchman 2.5 device and control patients treated with warfarin, the results of the present study may not be generalizable to the newer Watchman device and alternative antithrombotic treatment strategies.

Conclusion

The present study supports the hypothesis that sex does not significantly impact the long-term safety and effectiveness of the Watchman LAAC device in patients with NVAF. Further studies that include larger numbers of women treated with the current-generation WATCHMAN FLX device and comparisons of LAAC with DOACs are needed to confirm these findings.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

This study was conducted in accordance with ethical regulatory requirements. The institutional review boards at each participating center approved the trials. This meta-analysis does not meet the requirements of research involving human subjects as defined in 45 CFR 46. The study does not involve interaction or intervention with human subjects. The data obtained were deidentified, and all private health information was removed before it was available for analysis, therefore exempt per 45 CFR 46 (b).

Disclaimer

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