Circulation

ORIGINAL RESEARCH ARTICLE

Comparative Effectiveness of Left Atrial Appendage Occlusion Versus Oral Anticoagulation by Sex

Emily P. Zeitler, MD, MHS; Stephen Kearing, MS; Megan Coylewright, MD, MPH; Devi Nair, MD; Jonathan C. Hsu, MD, MAS; Douglas Darden, MD; A. James O'Malley, PhD; Andrea M. Russo, MD; Sana M. Al-Khatib, MD, MHS

BACKGROUND: The comparative real-world outcomes of older patients with atrial fibrillation (AF) treated with anticoagulation compared with left atrial appendage occlusion (LAAO) may be different from those in clinical trials because of differences in anticoagulation strategies and patient demographics, including a greater proportion of women. We sought to compare real-world outcomes between older patients with AF treated with anticoagulation and those treated with LAAO by sex.

METHODS: Using Medicare claims data from 2015 to 2019, we identified LAAO-eligible beneficiaries and divided them into sex subgroups. Patients receiving LAAO were matched 1:1 to those receiving anticoagulation alone through propensity score matching. The risks of mortality, stroke or systemic embolism, and bleeding were compared between matched groups with adjustment for potential confounding characteristics in Cox proportional hazards models.

RESULTS: Among women, 4085 LAAO recipients were matched 1:1 to those receiving anticoagulation; among men, 5378 LAAO recipients were similarly matched. LAAO was associated with a significant reduction in the risk of mortality for women and men (hazard ratio [HR], 0.509 [95% CI, 0.447–0.580]; and HR, 0.541 [95% CI, 0.487–0.601], respectively; $P<0.0001$), with a similar finding for stroke or systemic embolism (HR, 0.655 [95% CI, 0.555–0.772]; and HR, 0.649 [95% CI, 0.552–0.762], respectively; $P<0.0001$). Bleeding risk was significantly greater in LAAO recipients early after implantation but lower after the 6-week periprocedural period for women and men (HR, 0.772 [95% CI, 0.676–0.882]; and HR, 0.881 [95% CI, 0.784–0.989], respectively; $P<0.05$).

CONCLUSIONS: In a real-world population of older Medicare beneficiaries with AF, compared with anticoagulation, LAAO was associated with a reduction in the risk of death, stroke, and long-term bleeding among women and men. These findings should be incorporated into shared decision-making with patients considering strategies for reduction in AF-related stroke.

Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ mortality ■ stroke

The first left atrial appendage occlusion (LAAO) device, the WATCHMAN, was approved for commercial use in 2015 for reducing thromboembolism in patients with nonvalvular atrial fibrillation (AF). During the design phase for premarket clinical evaluation of this technology, the standard of care for stroke risk reduction in AF was systemic anticoagulation, with the only commercially available option in the United States being warfarin. Thus, comparative clinical trials were designed against this standard of care, and ultimate approval by the Food and Drug Administration included initial recommendations for continued warfarin plus aspirin for 6 weeks after implantation.[1,2] Notably, partially on the basis of recognition of a changing demographic and therapeutic landscape in AF care, LAAO was covered by the Centers for Medicare & Medicaid Services through a national coverage determination, which requires formal

Correspondence to: Emily P. Zeitler, MD, MHS, 1 Medical Center Dr, Lebanon, NH 03756. Email emily.p.zeitler@hitchcock.org

This manuscript was sent to Kenneth Ellenbogen, MD, guest editor, for review by expert referees, editorial decision, and final disposition.

This article is part of the Science Goes Red™ collection. Science Goes Red™ is an initiative of Go Red for Women®, the American Heart Association's global movement to end heart disease and stroke in women.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.122.062765.

For Sources of Funding and Disclosures, see page 595.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Women were under-enrolled in clinical trials of left atrial appendage occlusion, so specific risks and benefits in this important subgroup are uncertain.
- This analysis represents the largest group of older women treated with left atrial appendage occlusion in clinical practice.

What Are the Clinical Implications?

- Left atrial appendage occlusion was associated with a reduced risk of death, stroke/systemic embolism, and late bleeding compared with anticoagulation in women and men.
- Decision making at the point of care requires incorporation of patient and clinical factors, like sex, that are not modifiable, so understanding risks and benefits in specific groups is critically important, and therefore the results of this study can inform clinical decision making.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
DAOC	direct-acting oral anticoagulant
HR	hazard ratio
LAAO	left atrial appendage occlusion
PREVAIL	Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
PROTECT-AF	WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation

shared decision-making and structured data collection as conditions of coverage for Medicare beneficiaries.[3,4] This requirement resulted in the development of the National Cardiovascular Data Registry (NCDR) LAAO Registry, and findings from this registry and others, as well as medium- to long-term outcomes from trial participants, have been sources of contemporary LAAO outcomes data.[5–8]

Direct-acting oral anticoagulants (DOACs) are now the preferred anticoagulants to reduce stroke risk among most patients with AF on the basis of superior efficacy, safety, and convenience of administration and management, and relevant guidelines by professional societies reflect this evolution.[9,10] Data from the NCDR LAAO Registry reflect this change in clinical practice.[8] Thus, there is a discrepancy between the comparator used to assess the safety and effectiveness of LAAO for market authorization and the comparator considered in contemporary clinical practice. Comparisons in outcomes between eligible patients who are treated with DOACs and those treated with non-WATCHMAN LAAO devices suggest that benefits of LAAO over contemporary anticoagulation remain.[11,12] Although randomized trials are underway to address this evolution,[13–16] real-world evidence using Medicare claims may improve our understanding of the comparative risks and benefits of LAAO compared with contemporary oral anticoagulation.

Consistently, outcomes for LAAO have been reported in a mostly male population, with women accounting for fewer than half of studied cohorts, despite similar lifelong prevalence. Women generally have greater risk of stroke and bleeding in AF compared with men,[17] suggesting that potential benefits of LAAO may be greater in this subgroup. This is balanced by reports that female sex is associated with greater risk of complications of cardiovascular procedures,[18,19] including LAAO.[20–22] We seek to build on these previous investigations to report outcomes in separate male and female subgroups undergoing LAAO compared with patients treated with contemporary anticoagulation in clinical practice to inform point-of-care decision-making.

METHODS

Data Source and Patient Population

The population of interest was the Medicare fee-for-service population with a diagnosis of AF (2015–2019), as defined by the chronic conditions warehouse (Table S1). This investigation was approved by the Dartmouth-Hitchcock institutional review board; informed consent was waived. Because of the sensitive nature of the data collected for this study, extensive precautions taken to preserve privacy, and rules enforced by Centers for Medicare & Medicaid Services, the data used in this analysis may not be available to all interested parties. Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author. This population of Medicare beneficiaries was further narrowed to those patients with a CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex) score of at least 2 for men and 3 for women to align with US guideline recommendations for anticoagulation and LAAO.[23] Patients with a history of surgical left atrial appendage removal or occlusion were excluded. The population was limited to a subset of patients with Medicare Part D data to obtain information on prescription drugs. From this cohort, the population was divided into an LAAO cohort and an anticoagulation cohort. The LAAO cohort included those with any claim for a LAAO procedure (*International Classification of Diseases, 9th/10th revisions* procedure codes 37.90/02L73DK). The anticoagulation cohort were those without a claim for an LAAO procedure and evidence of continuous anticoagulation prescription defined as at least 75% covered days.

Table 1. Characteristics by Treatment Group, 2015 to 2019 in Women and Men Before and After 1:1 Propensity Matching

	All observations					Matched patients (1:1)		
	LAAO		Anticoagulation		Standard difference	Anticoagulation		Standard difference
Women								
Total								
n (row %)	4085	1.0%	396 555	99.0%		4085	50.0%	
Age, y								
n, mean (SD)	75.8 (6.1)		79.2 (7.6)		−0.50	75.9 (6.5)		−0.03
65–74	1785	43.7%	117 992	29.8%		1785	43.7%	
75–84	1962	48.0%	170 388	43.0%		1962	48.0%	
≥85	338	8.3%	108 175	27.3%		338	8.3%	
Race/ethnicity								
White, non-Hispanic	3702	90.6%	353 969	89.3%	−0.01	3702	90.6%	0.00
Geography								
South	1655	40.5%	146 222	36.9%	0.07	1689	41.3%	−0.02
Midwest	925	22.6%	101 788	25.7%	−0.07	936	22.9%	−0.01
Northeast	659	16.1%	89 060	22.5%	−0.16	640	15.7%	0.01
West	846	20.7%	59 485	15.0%	0.15	820	20.1%	0.02
Medical history								
CHA_2DS_2-VASc								
n, mean (SD)	5.1 (1.3)		4.8 (1.2)		0.24	5.2 (1.3)		−0.07
AF history								
1 y	646	15.8%	82 819	20.9%	0.12	646	15.8%	0.00
2 y	1181	28.9%	112 284	28.3%		1181	28.9%	
≥3 y	2258	55.3%	201 452	50.8%		2258	55.3%	
Chronic conditions								
History of ischemic stroke	959	23.5%	50 872	12.8%	−0.11	1020	25.0%	0.01
Heart failure	2607	63.8%	213 749	53.9%	−0.09	2767	67.7%	0.04
Diabetes	1767	43.3%	149 813	37.8%	−0.05	1887	46.2%	0.03
Hypertension	3992	97.7%	363 326	91.6%	−0.06	3929	96.2%	−0.02
Vascular disease	1446	35.4%	117 876	29.7%	−0.06	1575	38.6%	0.03
Ischemic heart disease	2965	72.6%	226 890	57.2%	−0.15	3292	80.6%	0.08
Obesity	1784	43.7%	106 290	26.8%	−0.17	1795	43.9%	0.00
Chronic kidney disease	2284	55.9%	172 764	43.6%	−0.12	2438	59.7%	0.04
COPD	1314	32.2%	96 315	24.3%	−0.08	1390	34.0%	0.02
Neurological disease	772	18.9%	98 395	24.8%	0.06	798	19.5%	0.01
Medications (≥30-d supply)								
Warfarin	1961	48.0%	181 369	45.7%	−0.02	1978	48.4%	0.004
DOAC	2221	54.4%	205 650	51.9%	−0.03	2309	56.5%	0.02
P2Y12-inhibitor	2972	72.8%	57 426	14.5%	−0.58	2982	73.0%	0.002
Male								
Total								
n (row %)	5378	1.4%	368 848	98.6%		5378	50.0%	
Age, y								
n, mean (SD)	75.3 (6.0)		76.6 (7.1)		−0.19	75.3 (6.3)		0.00
65–74	2530	47.0%	156 034	42.3%		2530	47.0%	

(*Continued*)

Table 1. Continued

	All observations					Matched patients (1:1)		
	LAAO		Anticoagulation		Standard difference	Anticoagulation		Standard difference
75–84	2443	45.4%	155 524	42.2%		2443	45.4%	
≥85	405	7.5%	57 290	15.5%		405	7.5%	
Race								
White, non-Hispanic	4945	91.9%	333 470	90.4%	−0.02	4945	91.9%	0.00
Geography								
South	2113	39.3%	136 101	36.9%	0.05	2080	38.7%	0.01
Midwest	1052	19.6%	90 101	24.4%	−0.12	1067	19.8%	−0.01
Northeast	1028	19.1%	81 792	22.2%	−0.08	1010	18.8%	0.01
West	1185	22.0%	60 854	16.5%	0.14	1221	22.7%	−0.02
Medical history								
CHA_2DS_2-VASc								
n, mean (SD)	4.1 (1.2)		3.8 (1.2)		0.33	4.2 (1.3)		−0.06
AF history								
1 y	924	17.2%	84 501	22.9%	−0.10	924	17.2%	0.00
2 y	1553	28.9%	104 015	28.2%		1553	28.9%	
≥3 y	2901	53.9%	180 332	48.9%		2901	53.9%	
Chronic conditions								
History of ischemic stroke	1141	21.2%	41 094	11.1%	−0.10	1191	22.1%	0.01
Heart failure	3423	63.6%	187 404	50.8%	−0.13	3618	67.3%	0.04
Diabetes	2576	47.9%	159 271	43.2%	−0.05	2718	50.5%	0.03
Hypertension	5254	97.7%	332 414	90.1%	−0.08	5182	96.4%	−0.01
Vascular disease	2171	40.4%	109 921	29.8%	−0.11	2296	42.7%	0.02
Ischemic heart disease	4470	83.1%	259 533	70.4%	−0.13	4744	88.2%	0.05
Obesity	2166	40.3%	101 477	27.5%	−0.13	2138	39.8%	0.01
Chronic kidney disease	3198	59.5%	173 589	47.1%	−0.12	3352	62.3%	0.03
COPD	1597	29.7%	88 261	23.9%	−0.06	1637	30.4%	0.01
Neurological disease	920	17.1%	64 655	17.5%	0.00	957	17.8%	0.01
Medications (≥30-d supply)								
Warfarin	2565	47.7%	175 132	47.5%	0.00	2575	47.9%	0.002
DOAC	2788	51.8%	181 460	49.2%	−0.03	2841	52.8%	0.01
P2Y12-inhibitor	3947	73.4%	70 920	19.2%	−0.54	3962	73.7%	0.003

AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous troke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex; COPD, chronic obstructive pulmonary disease; DOAC, direct-acting oral anticoagulant; and LAAO, left atrial appendage occlusion.

End Points

There were 3 end points of interest: mortality, ischemic stroke or systemic embolism, and bleeding. Mortality was determined by the death index and was treated as a censoring event. Remaining end points were defined according to relevant *International Classification of Diseases, 9th* or *10th revision* codes (Table S2). The bleeding end point included any bleeding, regardless of whether it could be attributed to the procedure. The list of bleeding codes was compiled from an exhaustive review of the literature. Given the extensive list of diagnosis codes meeting the definition of bleeding, events were further characterized into categories of gastrointestinal, neurological, respiratory, and other.

Statistical Analysis

Patient characteristics based on treatment and sex category were compared with the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. For medications of interest, beneficiaries were identified as taking the medication if there was at least one 30-day prescription filled for the medication during the index year. Summary statistics were reported as percentages for categorical variables and as means and SDs for continuous variables. The standardized difference between groups for each variable was defined as the absolute value of the difference in group means or proportions divided by the average SD and expressed as a percentage. Meaningful differences between the LAAO and anticoagulation

groups were anticipated, so a propensity score–matched analysis was planned.

The methods of Rosenbaum and Rubin[24] were used to separately develop matched groups of patients receiving LAAO and anticoagulation among the female and male subgroups. First, for continuous variables, patients receiving anticoagulation whose value was below the minimum or above the maximum for patients receiving LAAO were excluded. Second, a propensity model was built using logistic regression (PSMATCH procedure), in which the dependent variable (outcome) was an indicator of whether each patient belonged to the LAAO or anticoagulation group, and the independent variables (predictors) were the baseline characteristics listed in Table 1. From the logistic regression model, an estimated propensity score and corresponding logit for the propensity score were calculated for each patient. Third, for the matching process, a caliper width of 0.6 was used. For a given patient receiving LAAO, all patients receiving anticoagulation whose logit differed from that patient's logit by less than the caliper width were considered. Among these patients, the patient receiving anticoagulation with the shortest Mahalanobis distance from the patient receiving LAAO was selected as a match. Each patient receiving LAAO was matched no more than once, and no patients receiving LAAO were left unmatched.

A Cox proportional hazards model was used to evaluate the association of LAAO with the risks of all-cause mortality, stroke or systemic thromboembolism, and bleeding. To account for censoring, the survival time of each end point of interest is represented with a separate Kaplan-Meier plot. Time 0 for the LAAO and anticoagulation groups was defined as coincident with the LAAO procedure for the patient receiving LAAO in each matched pair.

Differences were declared statistically significant at $P<0.05$, and all statistical tests were 2 sided. For all analyses, SAS version 9.4 was used.

Sensitivity Analyses

Landmark Analysis

In recognition that the LAAO group would experience procedure-related complications (eg, groin hematoma) and consistent with previous work,[25] a landmark analysis was planned to begin at 45 days after implantation. Although procedure-related complications are included in the overall comparative assessment of LAAO versus anticoagulation therapy, consideration of long-term comparative outcomes with these events excluded was expected to offer additional insights.

Second, it was expected that survival bias would affect the assessment of outcomes between groups. So, after the removal of data of patients who died within one year of the index date, outcomes were recalculated within the matched groups.

Falsification End Points

Because of the observational nature of these analyses, confounding cannot be completely eliminated. Falsification end points are variables that are hypothesized to be effects of the same unmeasured confounders that are concerns for the study outcomes but are not expected to be affected by the treatment. If these dual assumptions hold, then a null association between the treatment and the falsification end points provides a level of assurance that no unmeasured confounders are present, whereas a (significant) non-0 association is an indication that unmeasured confounders are present and that less trust should be placed in the results of the study. As with the study outcomes, the falsification end points were prespecified as one measure of residual confounding. We chose the diagnoses of shingles and osteoarthritis because whether a patient undergoes LAAO is not expected to affect them[26] and because they are thought to be similarly affected by potential unmeasured confounders, including fitness for a procedural intervention.

RESULTS

Patient Cohorts

The patient cohorts identified for inclusion in these analyses were typical of a contemporary population of Medicare beneficiaries with AF (Table 1). The overall LAAO group was 43% female. Before matching, the LAAO cohort was, on average, younger than the anticoagulation cohort but had a greater burden of comorbidity. After propensity matching, the female cohort had a mean age of 76 years and was 91% White and non-Hispanic. The mean CHA_2DS_2VASc score was 5, reflecting high stroke risk. About half of patients (48%) were treated with warfarin. Men were numerically younger than women on average (mean age, 75 years), with a lower mean CHA_2DS_2VASc score (4). In both the male and female subgroups, the LAAO group had a greater burden of comorbidity based on a higher rate of nearly every comorbidity measured. Propensity matching was successful (Figure 1), with a standardized mean difference of <0.1 for all measured variables in both sex subgroups. After matching, a subset of patient pairs (31 of 4085 women [0.76%] and 44 of 5378 men [0.82%]) had an anticoagulation death date before the corresponding LAAO procedure date and were excluded from outcome analysis.

Outcomes

Death

LAAO was associated with a significantly reduced risk of death compared with anticoagulation alone in the female (n=4054; hazard ratio [HR], 0.509 [95% CI, 0.447–0.580]) and male (n=5334; HR, 0.541 [95% CI, 0.487–0.601]; $P<0.0001$ for both) subgroups (Figure 2A).

Stroke or Systemic Embolism

Stroke or systemic embolism occurred in 6.0% of women (n=245) treated with LAAO and 8.3% of those treated with anticoagulation (n=335). There was a reduced risk of stroke or systemic embolism associated with LAAO compared with anticoagulation in women (HR, 0.655 [95% CI, 0.555–0.772]) and men (HR, 0.649 [95% CI, 0.552–0.762]; $P<0.0001$ for both; Figure 2B).

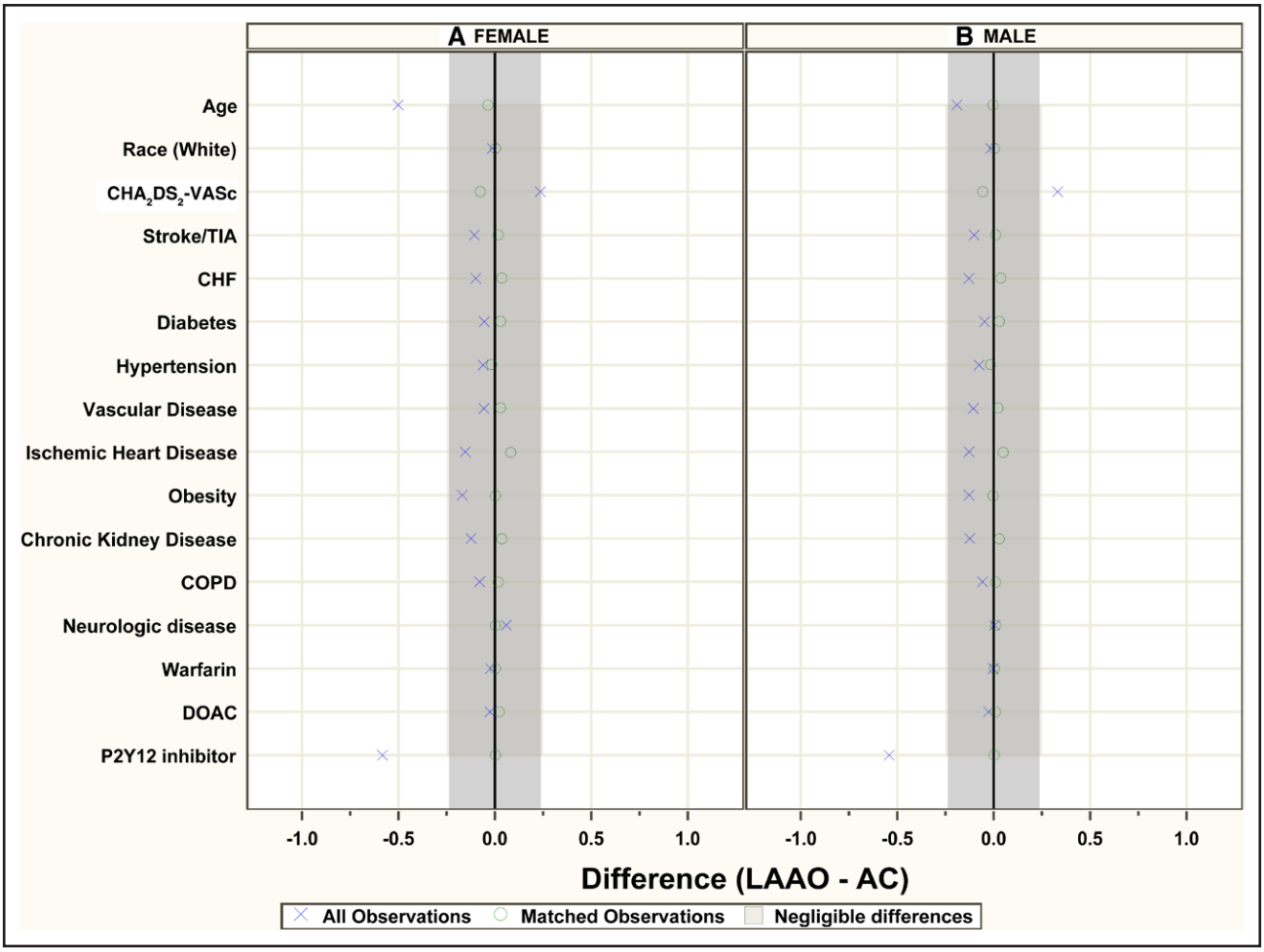

Figure 1. Standardized mean differences before and after propensity score matching within the sex subgroups.
AC indicates anticoagulation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DAOC, direct-acting oral anticoagulant; LAAO, left atrial appendage occlusion; and TIA, transient ischemic attack.

Bleeding

An initial examination of results for the bleeding end point suggested a violation of the proportional hazards assumption. This was confirmed with the supremum test ($P<0.0001$). On visual inspection, the curves crossed at ≈12 months, so this end point was divided into periods of 0 to 12 and ≥13 months. In the first 12 months, there was an increased risk of bleeding associated with LAAO compared with anticoagulation in both women and men (HR, 1.223 [95% CI, 1.068–1.401] and HR, 1.246 [95% CI, 1.104–1.407], respectively; $P<0.01$ for both). In the remaining follow-up period, this relationship was reversed: LAAO was associated with reduced risk of bleeding compared with anticoagulation alone after 12 months of follow-up in both women (HR, 0.611 [95% CI, 0.483–0.775]) and men (HR, 0.678 [95% CI, 0.557–0.824]; $P<0.0001$ for both; Figure 2C).

In both men and women across all follow-up, gastrointestinal bleeding events were the most common and were more common in the LAAO group than the anticoagulation group, whereas all other forms of bleeding were more common in the anticoagulation cohort (Table 2).

Because of the pattern of differential bleeding risk before and after 12 months after LAAO, additional analyses were pursued, including an assessment of anticoagulation and antiplatelet drug use during follow-up. Among patients taking warfarin at the index date, nearly all patients receiving anticoagulation were still taking warfarin 6 months later compared with only 2% of the LAAO cohort. A similar pattern was seen among those taking a DOAC, with only 5% of the LAAO cohort still taking a DOAC 6 months after the procedure compared with stable DOAC use in the anticoagulation cohort. The pattern of P2Y12-inhibitor prescriptions over time differed from this pattern, with an increase in P2Y12-inhibitor prescriptions in the LAAO cohorts to ≈50% after the index date, reflecting the typical postimplantation anticoagulation protocol with little change in P2Y12-inhibitor prescriptions among patients receiving anticoagulation over time. At 12 months, P2Y12-inhibitor prescriptions fell in the LAAO cohorts to 14% and 18% of female and

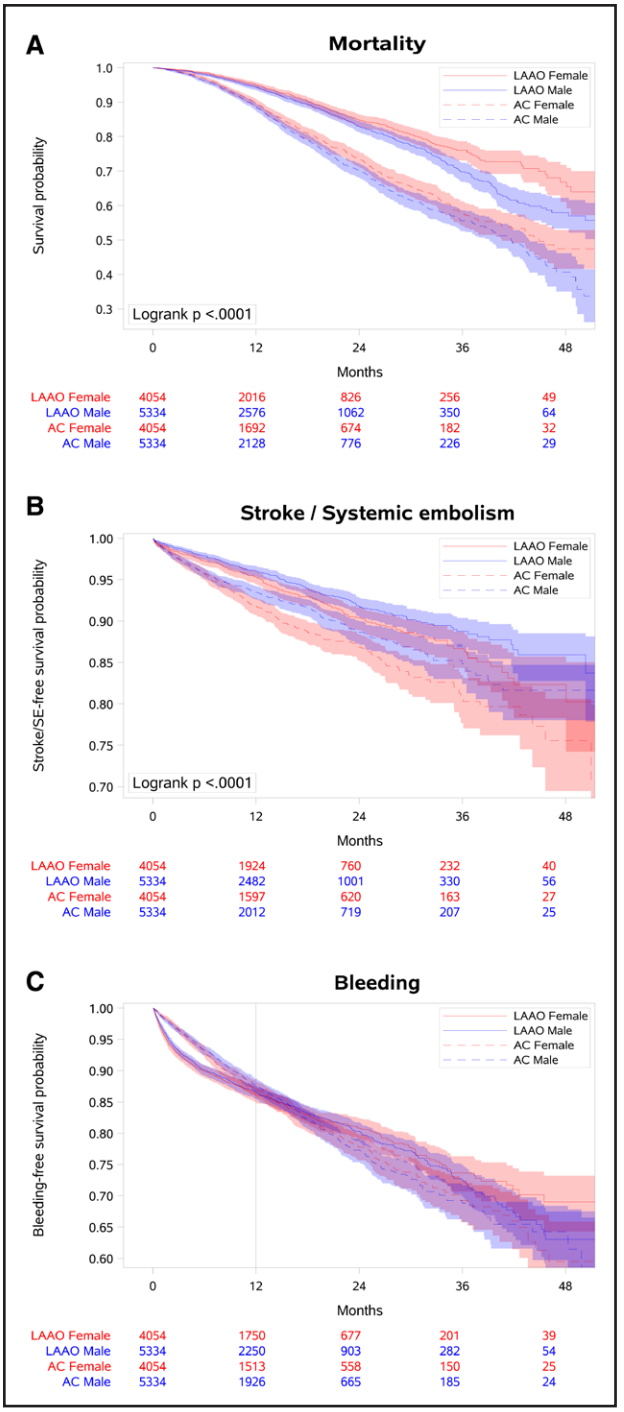

Figure 2. Kaplan-Meier survival curves between treatment groups within the female (red) and male (blue) subgroups comparing (A) mortality, (B) stroke/SE, and (C) bleeding. Log-rank tests performed to compare outcomes of interest between left atrial appendage occlusion (LAAO; solid line) and anticoagulation (AC; dashed line) within the sex subgroups. **A**, The probability of mortality is significantly lower in the group treated with LAAO compared with AC within the sex subgroups ($P<0.0001$ for both). **B**, The probability of stroke or systemic embolism (SE) is significantly lower in the group treated with LAAO compared with the group treated with AC within the sex subgroups ($P<0.0001$ for both). **C**, For both sex subgroups, the probability of bleeding was greater in the LAAO compared with AC group during the initial period of follow-up and lesser during the later follow-up, which violated the proportional hazards assumption, so log-rank tests were not performed.

Table 2. Bleeding Event Frequency by Category in Females and Males

	LAAO		Anticoagulation	
	n	%	n	%
Female (n=4054)				
Gastrointestinal	428	72.5	288	53.3
Neurological	58	9.8	81	15.0
Respiratory	58	9.8	76	14.1
Other	42	7.1	80	14.8
Total	590	100.0	540	100.0
Male (n=5334)				
Gastrointestinal	461	59.2	297	43.8
Other	166	21.3	177	26.1
Neurological	81	10.4	112	16.5
Respiratory	71	9.1	92	13.6
Total	779	100.0	678	100.0

LAAO indicates left atrial appendage occlusion.

male LAAO recipients compared with 43% and 51% of female and male anticoagulation patients still prescribed P2Y12-inhibitor (Table 3).

To assess the comparative risk of bleeding with exclusion of periprocedural bleeding and the effect of recommended post-LAAO anticoagulation strategy during the period of investigation eliminated, a landmark analysis was performed at 45 days. From 45 days to 48 months, LAAO was associated with a significant reduction in the risk of bleeding among both the female (HR, 0.772 [95% CI, 0.676–0.882]) and male (HR, 0.881 [95% CI, 0.784–0.989]; $P<0.05$) cohorts.

Finally, in the matched cohorts, 414 women and 599 men died within 1 year of the index date. The average age was no different in these groups compared with the groups of women and men still alive at 1 year. After the removal of data of patients who died within 1 year of the index date, no difference was seen in the comparative risk of bleeding, systemic embolism, or mortality within the sex subgroups (Table S3).

Falsification End Points

In the matched cohorts, there was no difference in the risk of shingles among women (HR, 0.634 [95% CI, 0.326–1.230]; $P=0.18$) or men (HR, 1.132 [95% CI, 0.514–2.495]; $P=0.76$). Similarly, there was no difference in the risk of osteoarthritis in the propensity-matched cohort of women (HR, 1.270 [95% CI, 0.718–2.247]; $P=0.68$) or men (HR, 1.867 [95% CI, 0.849–4.108]; $P=0.13$).

DISCUSSION

Since the design and completion of premarket LAAO device studies for reduction of AF-related stroke, the DOACs have become increasingly favored, and the

Table 3. Proportion of Patients Prescribed Anticoagulants or Antiplatelet Drugs After the Index Date in the Female and Male Subgroups by Treatment Cohort

	Anticoagulation strategy at index date											
	Warfarin				DOAC				$P2Y_{12}$			
	LAAO		Anticoagulant		LAAO		Anticoagulant		LAAO		Anticoagulant	
	n	%	n	%	n	%	n	%	n	%	n	%
Women: follow-up drug Rx by treatment and drug group (at least 1 Rx within ±45 d)												
Patients with Rx: index	1733	43	1446	36	1648	41	1716	42	1440	36	2018	50
Total patients	4054	100	4054	100	4054	100	4054	100	4054	100	4054	100
Patients with Rx: 6 mo	58	2	1024	36	149	5	1328	47	1597	53	1475	52
Patients with 6-mo follow-up	3016	74	2842	70	3016	74	2842	70	3016	74	2842	70
Patients with Rx: 12 mo	25	1	651	38	86	4	832	49	281	14	732	43
Patients with 12-mo follow-up	2016	50	1693	42	2016	50	1693	42	2016	50	1693	42
Patients with Rx: 24 mo	13	2	287	42	64	8	358	53	108	13	257	38
Patients with 24-mo follow-up	827	20	677	17	827	20	677	17	827	20	677	17
Men: follow-up drug Rx by treatment and drug group (at least 1 Rx within ±45 d)												
Patients with Rx: index	2206	41	1852	35	2030	38	2099	39	1991	37	2813	53
Total patients	5334	100	5334	100	5334	100	5334	100	5334	100	5334	100
Patients with Rx: 6 mo	90	2	1372	38	174	5	1582	44	1994	52	2008	56
Patients with 6-mo follow-up	3857	72	3589	67	3857	72	3589	67	3857	72	3589	67
Patients with Rx: 12 mo	48	2	879	41	126	5	1020	48	453	18	1086	51
Patients with 12-mo follow-up	2576	48	2130	40	2576	48	2130	40	2576	48	2130	40
Patients with Rx: 24 mo	17	2	355	46	52	5	381	49	201	19	362	47
Patients with 24-mo follow-up	1063	20	777	15	1063	20	777	15	1063	20	777	15

DOAC indicates direct-acting oral anticoagulant; LAAO, left atrial appendage occlusion; and Rx, prescription.

clinical population receiving LAAO is older, has more comorbidities, and includes more women than clinical trial populations. Premarket randomized trials of LAAO included insufficient populations of women to perform well-powered subgroup analyses. These factors limit the applicability of these previous trial results. Studying the safety and effectiveness of LAAO among women is of particular importance because previous work suggests a higher risk of both AF-related stroke and LAAO procedure–related complications compared with men.[22] Because sex is not a modifiable risk factor, this analysis was designed to address questions at the point of care by comparing differences in outcomes between LAAO and anticoagulation in sex subgroups.

In the early randomized trials of WATCHMAN, for example, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy) and PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), ≈70% of enrolled patients were male, and only 224 women were implanted with the device in randomized trials before US Food and Drug Administration approval.[1,27] Subsequent reports of real-world US and European experience with LAAO devices have consistently demonstrated the distribution of female recipients to be ≈40%,[8,28] which more closely reflects the prevalence of AF in Medicare beneficiaries.[29] Furthermore, these early clinical trials of LAAO included patients with a lower burden of comorbidity, including, for example, less prevalence of heart failure (≈25% versus 65%) and diabetes (≈25%–35% versus 45%), than a typical clinical population of patients with AF. This discrepancy between clinical trial and clinical practice populations is critically important because the comparative outcomes may be different according to baseline risk, and postmarket assessments suggest that procedure-related risk is higher for women than for men.[22,30] Whether longer follow-up in a real-world population would reflect sufficient benefit to justify this increased procedural risk was unknown. Findings in this analysis, which included >4000 female LAAO recipients followed up for an average of >1 year, can begin to answer this question. Indeed, these comparative outcomes are essential to inform formal shared-decision making, as is required for Medicare beneficiaries before implantation.[4] Thus, women were propensity matched to similar women in a cohort 20 times larger than randomized trials, providing data on the outcomes after LAAO implantation compared with the best alternative.

In this comparative-effectiveness study, over an average follow-up of ≈1 year, LAAO was associated with a significantly lower risk of mortality than anticoagulation

in both the female and male subgroups. The mortality rate in the overall group was high, consistent with previous assessments of mortality risk in older all-comer patients with AF.[29] The hazard for death was reduced by nearly 50% in the LAAO group in both sex subgroups. This significant reduction in mortality is greater than the mortality reduction observed in PROTECT-AF (34%).[27] The comparator group in PROTECT-AF was warfarin, which represented only 50% of this cohort, so the observed difference in mortality risk was greater than expected. However, other observational comparative analyses of LAAO and contemporary anticoagulation strategies have demonstrated similar findings,[12,31] and preliminary data suggest benefits of LAAO over anticoagulation when delivered exclusively with DOACs overall and in sex subgroups.[32] Future randomized data are forthcoming to better define this comparative relationship in all comers.[11,33]

The pattern of comparative risk reduction of stroke or systemic embolism between the LAAO and anticoagulation groups (both female and male) mirrored that of mortality: there was a significant reduction in the hazard of stroke or systemic embolism associated with LAAO implantation. Unlike mortality, the difference in stroke risk was evident early (Figure 2B) and persisted over the course of follow-up. Furthermore, although the risk of stroke was unsurprisingly higher among women, the magnitude of the stroke risk reduction associated with LAAO was similar between the sex subgroups. This significant difference in associated stroke or systemic embolism is in contrast to the landmark clinical trials of LAAO that failed to demonstrate a difference between LAAO and warfarin therapy on this end point. Subsequent observational studies exploring this comparison have produced heterogeneous results, reflecting, at least in part, the difficulty in addressing all potential confounding in the relatively older and comorbid population of patients with AF at a time when AF management is rapidly evolving.

Finally, bleeding was common overall in the LAAO and anticoagulation cohorts, with nearly 15% of all patients experiencing a bleeding event, and this was higher than the rate of bleeding observed in LAAO clinical trials. However, the comparative risk of bleeding between the LAAO and anticoagulation cohorts was more complex than the mortality or ischemic stroke or embolism outcomes. In both the male and female cohorts, the risk of bleeding was greater among LAAO recipients during the early period after the index procedure but was lesser thereafter. Although the present study cannot determine the causes of bleeding, there are multiple potential explanations for this finding. One likely possibility is that procedure-related bleeding accounts for the early differential. This hypothesis is supported by the analysis of periprocedural bleeding (within 45 days of the index procedure), during which time bleeding risk was greater in the LAAO groups, reflecting, in part, the labeled anticoagulation strategy of the time: OAC plus aspirin. A second compounding possibility is that early post-LAAO bleeding occurred in patients who had previous severe bleeding that led to discontinuation of anticoagulation, LAAO referral, and reinitiation of anticoagulation as part of the required postimplantation regimen. Notably, both clinical practice and regulatory approval for anticoagulation in the postprocedural period have recently changed, with labeling now supporting the use of dual antiplatelet therapy alone without an oral anticoagulant.[34,35] Conversely, outside the periprocedural period (after 45 days), the risk of bleeding was greater in the anticoagulation groups. This finding is consistent with previous work demonstrating a similar pattern.[25] The upper limit of the 95% CI for bleeding risk in the male cohort nearly included 1.0, making this finding most vulnerable to unmeasured confounders. However, because the LAAO cohort reflected a sicker group more prone to bleeding, unmeasured confounding would be expected to contribute to underestimation of effect.

As with any procedural intervention, procedural risks are expected, and in the case of LAAO, bleeding risks are related to femoral venous access, procedural anticoagulation, large sheath manipulation in the thin-walled left atrium, and protocols for ongoing anticoagulation and antiplatelet therapy for a period after device implantation. In the time that followed LAAO, there was a considerable reduction in the prescription of anticoagulation and P2Y12-inhibitor drugs, but reasons for this are unknown (Table 3). These drugs may have been discontinued in response to bleeding events or as a matter of postprocedural routine. Thus, in this case, the reduction in the risk of mortality and ischemic stroke associated with LAAO, along with the reduced risk of bleeding outside the periprocedural period, may justify procedural risks for many patients. It remains to be seen whether this balance between procedural risks and longer-term benefits is accentuated by improved procedural safety, as typically occurs with operator experience and device iteration.

Limitations

Limitations of the analyses include residual confounding attributable to the observational nature of the data set despite the use of propensity score matching to reduce confounding resulting from observed predictors. Selection bias is also relevant, given that an interventional procedure (LAAO) is compared with a medical therapy (anticoagulation), and not all factors that could potentially affect this bias are included in the propensity model (eg, HAS-BLED score). A falsification end points analysis failed to detect a difference in groups but does not rule out that one exists. The inability to capture aspirin use limits both matching and comparing outcomes, particularly bleeding. Furthermore, only prescription fills are

captured; claims data do not assess actual medication intake and lack precision on drug initiation or discontinuation. Moreover, although Medicare claims data do not include specific device information, on the basis of commercial availability from 2015 to 2019, LAAO in this analysis is largely synonymous with the first-generation WATCHMAN device, and comparative risks and benefits with next-generation or alternative devices or labeling may be different. In addition, the population presented is not representative of all those eligible for LAAO, including those who are younger or insured by Medicare Advantage. Because the propensity model included P2Y12-inhibitor therapy, patients in the anticoagulation group with greater risk may have been selected because they would have had an indication for taking this medication, including previous percutaneous coronary intervention or stroke, for example, whereas the patients on P2Y12-inhibitor receiving LAAO were more likely prescribed the drug as part of routine postprocedural therapy. Finally, some factors that contribute to AF-related stroke are not measurable in Medicare claims data and therefore do not contribute to modeling, including, but not limited to, left atrial size and AF duration.

Conclusions

In this analysis of comparative outcomes among eligible Medicare beneficiaries, the risk of mortality and stroke or systemic embolism was significantly reduced with LAAO compared with anticoagulation in both the male and female cohorts. The risk of bleeding was also reduced among patients receiving LAAO outside the 6-week periprocedural period. These findings reflect real-world outcomes in an all-comer Medicare population that includes more women with greater comorbidity burden than LAAO clinical trial populations. Thus, these data serve to further inform real-world shared decision-making for patients with AF at the point of care when deciding between LAAO and anticoagulation for stroke risk reduction, and may serve as a counterpoint to concerns of LAAO procedural risk, especially among women.

ARTICLE INFORMATION

Received October 6, 2022; accepted January 6, 2023.

Affiliations

Dartmouth Health (E.P.Z., S.K.), Lebanon, NH. Dartmouth Institute, Lebanon, NH (E.P.Z., A.J.O.). Erlanger Heart and Lung Institute, Chattanooga, TN (M.C.). St. Bernard's Heart and Vascular Center, Jonesboro, AR (D.N.). University of California San Diego, La Jolla (J.C.H.). Kansas City Heart Rhythm Institute, Overland Park (D.D.). Geisel School of Medicine at Dartmouth College, Hanover, NH (A.J.O.). Cooper Medical School of Rowan University, Camden, NJ (A.M.R.). Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (S.M.A.-K.).

Acknowledgments

The authors acknowledge the tremendous work done by Dr Alex Iribarne in compiling the list of *International Classification of Diseases, 9th* and *10th revisions,* bleeding codes used in this analysis. That compilation reflects an exhaustive review of the literature for claims-based bleeding outcome codes.

Sources of Funding

This project was funded by an investigator-initiated grant from Boston Scientific.

Disclosures

Dr Coylewright reports research funding from Edwards LifeSciences and Boston Scientific, as well as consulting fees from Edwards LifeSciences, Medtronic, Occlutech, American College of Cardiology, and Boston Scientific. Dr Hsu reports honoraria from Medtronic, Abbott, Boston Scientific, Biotronik, Janssen Pharmaceuticals, Bristol-Myers Squibb, Pfizer, Zoll Medical, Galvanize Therapeutics, Acutus Medical, and Biosense-Webster, as well as research grants from Biotronik and Biosense-Webster, and equity interest in Vektor Medical. Dr Zeitler reports research funding from Boston Scientific, consulting fees from Medtronic, Biosense Webster, Boston Scientific, and Sanofi, and nonfinancial research support from Biosense Webster and Sanofi. Dr Al-Khatib reports research funding from Boston Scientific paid to her institution. The other authors report no conflicts.

Supplemental Material

Tables S1–S3

REFERENCES

1. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the WATCHMAN left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol.* 2014;64:1–12. doi: 10.1016/j.jacc.2014.04.029
2. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet.* 2009;374:534–542. doi: 10.1016/S0140-6736(09)61343-X
3. Zeitler EP, Gilstrap LG, Coylewright M, Slotwiner DJ, Colla CH, Al-Khatib SM. Coverage with evidence development: where are we now? *Am J Manag Care.* 2022;28:382–389. doi: 10.37765/ajmc.2022.88870
4. Jensen T, Chin J, Ashby L, Long K, Schafer J, Hakim R. *Decision Memo for Percutaneous Left Atrial Appendage (LAA) Closure Therapy (CAG-00445N).* Centers for Medicare and Medicaid Services; 2016.
5. Holmes DR Jr, Reddy VY, Gordon NT, Delurgio D, Doshi SK, Desai AJ, Stone JE Jr, Kar S. Long-term safety and efficacy in continued access left atrial appendage closure registries. *J Am Coll Cardiol.* 2019;74:2878–2889. doi: 10.1016/j.jacc.2019.09.064
6. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, et al. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol.* 2017;70:2964–2975. doi: 10.1016/j.jacc.2017.10.021
7. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, Poloczek M, Stasek J, Haman L, Branny M, et al. 4-Year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol.* 2022;79:1–14. doi: 10.1016/j.jacc.2021.10.023
8. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, et al. The NCDR left atrial appendage occlusion registry. *J Am Coll Cardiol.* 2020;75:1503–1518. doi: 10.1016/j.jacc.2019.12.040
9. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42:4194373–4194194. doi: 10.1093/eurheartj/ehab648
10. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019;74:104–132. doi: 10.1016/j.jacc.2019.01.011
11. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, Poloczek M, Stasek J, Haman L, Branny M, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol.* 2020;75:3122–3135. doi: 10.1016/j.jacc.2020.04.067

12. Nielsen-Kudsk JE, Korsholm K, Damgaard D, Valentin JB, Diener HC, Camm AJ, Johnsen SP. Clinical outcomes associated with left atrial appendage occlusion versus direct oral anticoagulation in atrial fibrillation. *JACC Cardiovasc Interv*. 2021;14:69–78. doi: 10.1016/j.jcin.2020.09.051
13. ClinicalTrials.gov. CHAMPION-AF clinical trial (CHAMPION-AF). Accessed October 5, 2022. https://www.clinicaltrials.gov/ct2/show/NCT04394546?term=NCT04394546&draw=2&rank=1
14. ClinicalTrials.gov. Left Atrial Appendage Occlusion Versus Novel Oral Anticoagulation for Stroke Prevention in Atrial Fibrillation (OCCLUSION-AF). Accessed October 5, 2022. https://www.clinicaltrials.gov/ct2/show/NCT03642509?term=NCT03642509&draw=2&rank=1
15. ClinicalTrials.gov. Amplatzer Amulet LAAO vs. NOAC (CATALYST). Accessed October 5, 2022. https://www.clinicaltrials.gov/ct2/show/NCT04226547?term=NCT04226547&draw=2&rank=1
16. Alkhouli M. Moving the needle forward for more relevant evidence on left atrial appendage occlusion. *JACC Cardiovasc Interv*. 2021;14:79–82. doi: 10.1016/j.jcin.2020.10.044
17. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 2016;532:h7013. doi: 10.1136/bmj.h7013
18. Russo AM, Daugherty SL, Masoudi FA, Wang Y, Curtis J, Lampert R. Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation: findings from the National Cardiovascular Data Registry (NCDR). *Am Heart J*. 2015;170:330–338. doi: 10.1016/j.ahj.2015.02.025
19. Elayi CS, Darrat Y, Suffredini JM, Misumida N, Shah J, Morales G, Wilson W, Bidwell K, Czarapata M, Parrott K, et al. Sex differences in complications of catheter ablation for atrial fibrillation: results on 85,977 patients. *J Interv Card Electrophysiol*. 2018;53:333–339. doi: 10.1007/s10840-018-0416-1
20. Osman M, Patel B, Munir MB, Kawsara A, Kheiri B, Balla S, Daggubati R, Michos ED, Alkhouli M. Sex-stratified analysis of the safety of percutaneous left atrial appendage occlusion. *Catheter Cardiovasc Interv*. 2021;97:885–892. doi: 10.1002/ccd.29282
21. Schmidt B, Betts TR, Sievert H, Bergmann MW, Kische S, Pokushalov E, Schmitz T, Meincke F, Mazzone P, Stein KM, et al. Incidence of pericardial effusion after left atrial appendage closure: the impact of underlying heart rhythm: data from the EWOLUTION study. *J Cardiovasc Electrophysiol*. 2018;29:973–978. doi: 10.1111/jce.13626
22. Darden D, Duong T, Du C, Munir MB, Han FT, Reeves R, Saw J, Zeitler EP, Al-Khatib SM, Russo AM, et al. Sex differences in procedural outcomes among patients undergoing left atrial appendage occlusion: insights from the NCDR LAAO registry. *JAMA Cardiol*. 2021;6:1275–1284. doi: 10.1001/jamacardio.2021.3021
23. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
24. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Statistician*. 1985;39:33–38. doi: 10.2307/2683903
25. Price MJ, Reddy VY, Valderrabano M, Halperin JL, Gibson DN, Gordon N, Huber KC, Holmes DR Jr. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the WATCHMAN randomized trial experience. *JACC Cardiovasc Interv*. 2015;8:1925–1932. doi: 10.1016/j.jcin.2015.08.035
26. Jena AB, Prasad V. Falsification end points for observational studies: reply. *JAMA*. 2013;309:1770–1771. doi: 10.1001/jama.2013.3112
27. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B, Kar S, Swarup V, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312:1988–1998. doi: 10.1001/jama.2014.15192
28. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol*. 2019;12:e006841. doi: 10.1161/CIRCEP.118.006841
29. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. 2012;5:85–93. doi: 10.1161/CIRCOUTCOMES.111.962688
30. Osman M, Patel B, Munir MB, Kawsara A, Kheiri B, Balla S, Daggubati R, Michos ED, Alkhouli M. Sex-stratified analysis of the safety of percutaneous left atrial appendage occlusion. *Catheter Cardiovasc Interv*. 2021;97:885–892. doi: 10.1002/ccd.29282
31. Gloekler S, Furholz M, de Marchi S, Kleinecke C, Streit SR, Buffle E, Fankhauser M, Haner JD, Nietlispach F, Galea R, et al. Left atrial appendage closure versus medical therapy in patients with atrial fibrillation: the APPLY study. *EuroIntervention*. 2020;16:e767–e774. doi: 10.4244/eij-d-20-00201
32. Noseworthy PA, Van Houten HK, Krumholz HM, Kent DM, Abraham NS, Graff-Radford J, Alkhouli M, Henk HJ, Shah ND, Gersh BJ, et al. Percutaneous left atrial appendage occlusion in comparison to non-vitamin K antagonist oral anticoagulant among patients with atrial fibrillation. *J Am Heart Assoc*. 2022;11:e027001. doi: 10.1161/JAHA.121.027001
33. ClinicalTrials.gov. CHAMPION-AF. Accessed September 26, 2022. https://www.clinicaltrials.gov/ct2/show/NCT04394546
34. Freeman JV, Higgins AY, Wang Y, Du C, Friedman DJ, Daimee UA, Minges KE, Pereira L, Goldsweig AM, Price MJ, et al. Antithrombotic therapy after left atrial appendage occlusion in patients with atrial fibrillation. *J Am Coll Cardiol*. 2022;79:1785–1798. doi: 10.1016/j.jacc.2022.02.047
35. US Food and Drug Administration. Premarket approval of WATCHMAN and WATCHMAN FLX left atrial appendage closure devices with delivery systems. Accessed September 2, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130013S043