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ORIGINAL RESEARCH

Sex Differences in Outcomes After Breakthrough Ischemic Stroke on Oral Anticoagulants for Atrial Fibrillation: An ASPERA-R Inverse Probability Weighted Analysis

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BACKGROUND: Sex-specific outcomes after breakthrough ischemic stroke on oral anticoagulation (OAC) are unexplored. We compared 90-day outcomes by sex and explored modifiers.

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METHODS: ASPERA-R (Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants retrospective cohort; NCT06823466) was an international, multicenter, retrospective study enrolling adults (aged >18 years) with breakthrough ischemic stroke on OAC for atrial fibrillation. Primary outcome was 90-day return to baseline neurologic function (modified Rankin Scale [mRS] score 0–1 maintained if prestroke 0–1; or same/lower mRS score if prestroke ≥2). Secondary outcomes were 90-day mRS shift, recurrent ischemic stroke/transient ischemic attack, myocardial infarction, and all-cause and vascular death. Safety outcomes included 90-day moderate-to-severe bleeding, intracranial hemorrhage, 24-hour hemorrhagic transformation, and 24-hour symptomatic intracranial hemorrhage. We applied inverse probability weighting and regression models to compare outcomes. Prespecified subgroup analysis tested sex-specific interactions.

RESULTS: We included 1649 patients (women, 52.2%; mean±SD age, 78.0±10.7 years). Women were older (80.2±9.6 versus 76.3±10.8 years; unweighted standardized mean difference=0.376), had higher baseline National Institutes of Health Stroke Scale score (13 [interquartile range, 9–19] versus 9 [interquartile range, 4–17]; unweighted standardized mean difference=0.227), and worse prestroke mRS score (unweighted standardized mean difference=0.237). After weighting, women were less likely to return to baseline neurologic function (35.2% versus 42.7%; adjusted risk ratio, 0.82 [95% CI, 0.71–0.96]; *P*=0.015), had worse mRS distribution (adjusted odds ratio, 1.17 [95% CI, 1.01–1.37]; *P*=0.043), and had higher recurrent ischemic stroke/transient ischemic attack (4.8% versus 2.8%; adjusted hazard ratio [HR], 1.70 [95% CI, 1.01–2.86]; *P*=0.045). Women showed a trend toward more moderate-to-severe bleeding (4.6% versus 2.8%; adjusted HR, 1.63 [95% CI, 0.96–2.72]; *P*=0.070). Subgroup analyses revealed significant sex interactions for OAC type, competing cause, endovascular treatment, and OAC restart.

CONCLUSIONS: Women had worse 90-day outcomes than men after breakthrough ischemic stroke on OAC for atrial fibrillation, highlighting the need for sex-aware management.

Key Words: direct oral anticoagulant ■ ischemic stroke ■ oral anticoagulant ■ outcomes ■ sex differences ■ vitamin K antagonist

See Editorial by XXX.

CLINICAL PERSPECTIVE

What Is New?

- In this large, multinational cohort of patients with atrial fibrillation who experienced breakthrough ischemic stroke despite continuous oral anticoagulation, women had significantly worse 90-day functional outcomes and higher recurrence risk compared with men.

What Are the Clinical Implications?

- Our findings indicate that female sex is an independent determinant of poorer recovery and higher ischemic recurrence after breakthrough stroke on oral anticoagulation, even in contemporary, well-anticoagulated settings.
- We underscore the importance of sex-aware management strategies to improve outcomes in women with atrial fibrillation who experience breakthrough ischemic stroke on oral anticoagulation.

Nonstandard Abbreviations and Acronyms

ASPERA	Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants
ASPERA-P	Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants prospective cohort
ASPERA-R	Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants retrospective cohort
DOAC	direct oral anticoagulant
EVT	endovascular thrombectomy
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery
ICH	intracranial hemorrhage
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OAC	oral anticoagulant
sICH	symptomatic intracranial hemorrhage
SMD	standardized mean difference
SMDunw	unweighted standardized mean difference
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Over the past 2 decades, major advances in secondary prevention, particularly the widespread use of oral anticoagulants (OACs) for atrial fibrillation (AF), have substantially reduced the risk of recurrent

ischemic stroke.[1] Nevertheless, a residual risk of so-called "breakthrough" ischemic stroke persists despite oral anticoagulation. This phenomenon reflects not only to the incomplete protection conferred by direct OACs (DOACs), none of which completely abolish the risk of ischemic events, but also other contributing factors, including poor adherence, off-label dosing, drug–drug interactions, and, in patients on vitamin K antagonists, suboptimal time in therapeutic range.[2] In addition, breakthrough strokes may result from concomitant vascular pathologies, such as carotid atherosclerosis, or small-vessel disease, which can coexist with cardioembolism.[3] Recent European data reported a residual annual risk of ischemic stroke of ≈1.7% among anticoagulated patients with AF, underscoring the clinical relevance of this high-risk phenotype.[4] Overall, incidence rates of breakthrough stroke have ranged from 0.7% to 2.3% per year in randomized clinical trials and ≈1.5% to 2.5% per year in contemporary real-world cohorts.[5] These patients are also at particularly high risk of early recurrent ischemia (up to 7% per year and ~30% over 5 years)[6,7] and poor functional outcomes.[8,9]

Female sex has been repeatedly associated with an increased risk of AF-related stroke in population-based studies, partly reflecting both biological susceptibility and disparities in anticoagulation management.[10] Investigating sex-specific differences in breakthrough stroke is clinically relevant given the well-documented disparities in stroke care and outcomes. Women with ischemic stroke are typically older, present with greater severity, and show worse functional recovery than men across multiple cohorts.[11,12] In populations with AF, female sex is linked to higher residual stroke risk despite OAC, lower rates of appropriate anticoagulant use or dosing, and a greater incidence of bleeding, all of which may amplify disparities.[13] However, the influence of sex on outcomes after breakthrough stroke on OAC remains uncertain, as most prior studies have examined unselected stroke cohorts or general populations with AF.

To address this knowledge gap, we investigated the sex differences in the outcome following breakthrough ischemic stroke on OAC for AF, and evaluated potential effect modification across prespecified clinical strata.

METHODS

The complete data set used for this study will be shared on request from any qualified researcher to the corresponding author.

Ethical Standards

The ASPERA (Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants) study (NCT06823466) received approval from the territorial ethics committee of the Abruzzo region in February 2025 (approval code: 033054/25). All patients provided written informed consent in accordance with the Declaration of Helsinki in countries where consent is required for retrospective observational studies. For patients who were deceased or could not be contacted, consent was obtained from a legally authorized representative when mandated by local regulations; otherwise, a waiver of consent was granted by the responsible ethics committee.

Study Design

The ASPERA study is a large, multicenter, observational, real-world investigation coordinated by the University of L'Aquila. It comprises 2 complementary arms: ASPERA-R (ASPERA retrospective cohort) and ASPERA-P (ASPERA prospective cohort). In the present study, we report results for the ASPERA-R arm with data from 35 stroke centers across 9 countries in Europe and North Africa (Tables S1 and S2). The ASPERA-P arm is still ongoing. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[14]

Study Population

The ASPERA-R arm consecutively enrolled patients with breakthrough ischemic stroke while on OAC for AF between February 2020 and February 2025. All consecutive admissions to hospital wards or evaluations in emergency departments during the study period were screened to minimize selection bias. Eligible patients were adults (aged >18 years) with a diagnosis of ischemic stroke based on World Health Organization criteria, confirmed by brain noncontrast computed tomography and/or brain magnetic resonance imaging and who were on continuous OAC, documented by prescription records and corroborated by patient or caregiver confirmation of uninterrupted intake during the 7 days preceding the index stroke, with the last dose administered within 48 hours before the event. Patients with documented nonadherence were excluded to ensure a focus on those with unexplained anticoagulation failure.

Data Collection and Study Analysis

All information was obtained by medical records during hospitalization and standard follow-up visits. Whenever follow-up information was not documented in the medical records, it was systematically obtained through direct patient contact, thereby ensuring complete outcome ascertainment. For the purposes of this analysis, we included only patients for whom 90-day follow-up outcomes were available. In addition, to minimize potential sources of bias and allow for reliable comparisons, we restricted the cohort to patients

without missing information in any of the predefined mandatory baseline variables. The full list of both mandatory and optional baseline variables is provided in Table S2.

Data were entered into the registry and shared with the coordinating center using a standardized Research Electronic Data Capture case report form to ensure consistency and accuracy. To maintain data quality, the ASPERA-R electronic database was subject to weekly checks and central monitoring procedures. The final data set for this analysis was locked on September 1, 2025.

Study Outcomes

The primary outcome was return to baseline neurologic function, defined as having a modified Rankin Scale (mRS) score of 0 to 1 at baseline and maintaining mRS 0 to 1 at 90 days, or having a baseline mRS score of ≥2 and achieving the same or a lower score at 90 days.[15] The secondary outcomes included the 90-day ordinal mRS scores shift, 90-day occurrence of new ischemic stroke or transient ischemic attack (TIA), myocardial infarction, all-cause death, and vascular death (any death attributable to cardiovascular or cerebrovascular causes, including fatal ischemic or hemorrhagic stroke, sudden cardiac death, myocardial infarction, or other vascular events). Safety outcomes included 90-day moderate-to-severe bleeding, intracranial hemorrhage (ICH), 24-hour hemorrhagic transformation, and 24-hour symptomatic ICH (sICH). Bleeding severity was categorized according to the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery) trial classification.[16] Specifically, we classified the clinical impact of bleeding events as moderate to severe if they involved fatal hemorrhage or hemorrhage that, regardless of hemodynamic compromise, required blood or fluid replacement, inotropic support, or surgical intervention. Hemorrhagic transformation was defined as any category within the Heidelberg bleeding classification system.[17] sICH was defined as any ICH associated with neurologic worsening of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) score, not attributable to other causes.[18]

Statistical Analysis

Categorical variables were summarized as counts (percentages), and continuous variables as mean (SD) or median (interquartile range), according to distribution. To minimize baseline imbalances between sexes, we applied inverse probability weighting based on propensity scores estimated via logistic regression, including prespecified demographic, clinical, and treatment variables (age, race and ethnicity, enrolling center, vascular risk factors, AF type, baseline NIHSS and mRS score, competing stroke causes additional to cardioembolism by the TOAST [Trial of Org 10172 in Acute Stroke Treatment] classification system,[19] and reperfusion therapies). Stabilized weights were used to reduce the influence of extreme values. Balance was assessed through standardized mean differences (SMDs), inspection of propensity score overlap, and covariate balance graphs.

All analyses were performed in the weighted cohort and adjusted for baseline covariates with residual imbalance (SMD >0.10).[20] The primary outcome was analyzed using a binomial generalized linear model with logit link, expressed as adjusted risk ratio with 95% CIs. Secondary outcomes were assessed according to their nature: functional status by 90-day mRS shift (ordinal logistic regression, adjusted odds ratios [ORs] with 95% CIs); and recurrent ischemic events and mortality by Cox regression (adjusted hazard ratios [HRs] with 95% CIs). Safety outcomes were tested with generalized linear models (24-hour hemorrhagic transformation and 24-hour sICH, adjusted risk ratios) or Cox regression (90-day moderate-to-severe bleeding and 90-day ICH, HRs with 95% CIs). Death was treated as a competing risk, as it potentially precluded the occurrence of new ischemic events, with cumulative incidence functions compared by Gray test and Fine–Gray regression used to estimate subdistribution HRs. Proportional hazards were tested with Schoenfeld residuals, and Kaplan–Meier curves illustrated time-to-event outcomes.

Subgroup analyses were conducted across 10 prespecified strata (age, OAC type, baseline NIHSS score, competing cause, prestroke mRS score, hypertension, diabetes, AF type, intravenous thrombolysis, and endovascular thrombectomy [EVT]) for the primary outcome, estimating absolute sex-specific risk ratios and testing for interaction using Wald or likelihood-ratio tests, as appropriate. No formal sample size calculation was performed; the study included all eligible patients enrolled during the study period. Analyses were performed in R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria), with 2-sided $P<0.05$ considered significant.

RESULTS

A total of 1649 patients were included in the analysis, of whom 52.2% were women, with a mean±SD age of 78.0±10.7 years. The ASPERA-R study flowchart with number of excluded patients is displayed in Figure 1. In the unweighted cohort, women were significantly older than men (80.2±9.6 versus 76.3±10.8 years; unweighted SMD [SMDunw]=0.376), presented with greater stroke severity (median NIHSS score,

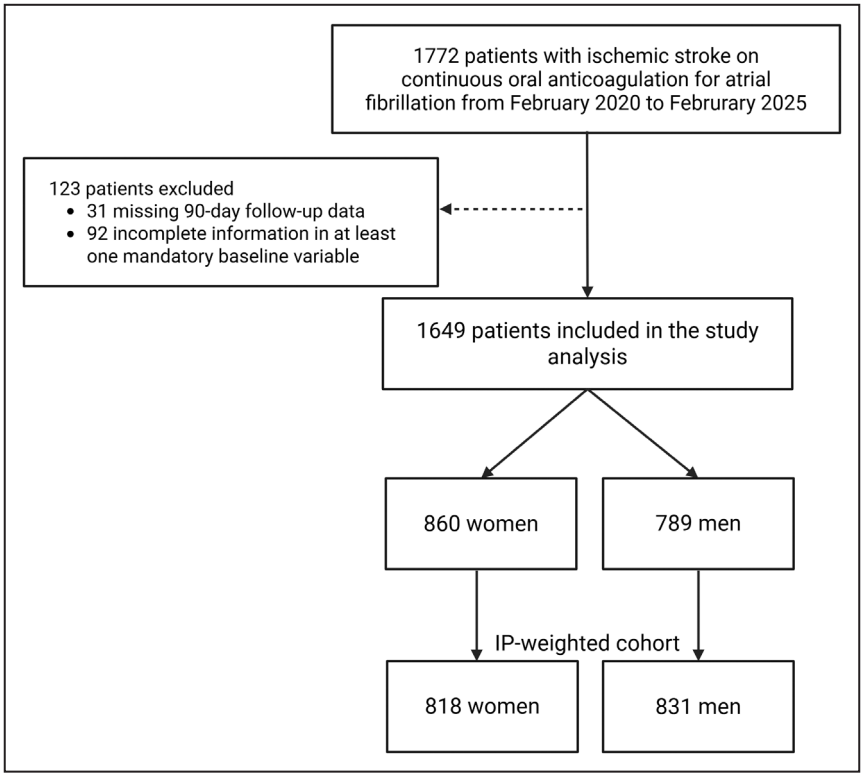

Figure 1. Flowchart of the ASPERA-R study.
ASPERA-R indicates Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants retrospective cohort; and IP indicates inverse probability.

13 [interquartile range, 9–19] versus 9 [interquartile range, 4–17]; SMDunw=0.227), and had worse pre-stroke mRS scores (SMDunw=0.237). Conversely, men were more often current smokers (14.3% versus 4.3%; SMDunw=0.329), more frequently had a competing stroke cause other than cardioembolism (28.1% versus 20.8%; SMDunw=0.171), and were less frequently treated with EVT (50.0% versus 38.3%; SMDunw=0.238) (Table 1).

For secondary stroke prevention, although we did not observe significant differences in the unweighted cohort with respect to the rate of OAC prescription or in the timing of anticoagulation resumption after stroke, women more frequently discontinued oral anticoagulation (SMDunw=0.101), whereas men were more often prescribed antiplatelet (SMDunw=0.119) and lipid-lowering (SMDunw=0.109) agents (Table 1).

Inverse Probability Weighting

After inverse probability weighting matching, the pseudopopulation consisted of 818 women and 831 men. No missing data were present in the variables used to compute propensity scores. Balance diagnostics indicated adequate matching, with a standardized mean difference of propensity scores between groups of 0.005 (good balance defined as <0.25) and a variance ratio of 1.03 (acceptable range, 0.5–2.0).[20] Visual inspection of propensity-score overlap and covariate balance corroborated the adequacy of the matching (Figures S1 and S2). The comparison of baseline characteristics further supported the good balance of our matched cohorts, with a weighted SMD <0.10 in most variables (Table 1).

Primary Outcome

In the unweighted cohort, functional recovery was achieved by 31.9% of women and 42.8% of men. This finding was consistent in the weighted cohort, where women remained significantly less likely to return to baseline function compared with men (35.3% versus 42.7%; adjusted risk ratio, 0.82 [95% CI, 0.71–0.96]; *P*=0.015) (Table 2).

Secondary Outcomes

Results for secondary outcomes in both the unweighted and weighted cohorts are summarized in Table 2. In the weighted cohort, women showed a significantly worse 90-day mRS distribution compared with men (adjusted OR, 1.17 [95% CI, 1.01–1.37]; *P*=0.043) (Figure 2). Women also had a higher risk of recurrent ischemic events: new ischemic stroke or TIA occurred in 39 women (4.5%) versus 18 men (2.3%).

Table 1. Baseline Characteristics

Characteristic	Overall cohort (n=1649)	Women (n=860)	Men (n=789)	SMD unweighted	SMD weighted
Demographics					
Age, mean±SD, y	78.0±10.7	80.2±9.6	76.3±10.8	0.376	0.017
Race and ethnicity, n (%)				0.089	0.088
Non-Hispanic White	1303 (79.0)	693 (80.6)	610 (77.3)		
Hispanic White	113 (6.9)	56 (6.5)	57 (7.2)		
Black	24 (1.5)	13 (1.5)	11 (1.4)		
Asian	9 (0.5)	4 (0.5)	5 (0.6)		
Other	200 (12.1)	94 (10.9)	106 (13.4)		
Baseline oral anticoagulation characteristics					
Type of oral anticoagulation at the time of index stroke, n (%)				0.087	0.029
VKA	374 (22.7)	210 (24.4)	164 (20.8)		
DOAC	1275 (77.3)	650 (75.6)	625 (79.2)		
Type of DOAC at the time of index stroke, n/total (%)				0.011	0.056
Apixaban	469/1275 (36.8)	231/650 (35.5)	238/625 (38.1)		
Rivaroxaban	428/1275 (33.6)	223/650 (34.3)	205/625 (32.8)		
Edoxaban	251/1275 (19.7)	146/650 (22.5)	105/625 (16.8)		
Dabigatran	127/1275 (10.0)	50/650 (7.7)	77/625 (12.3)		
Time from last DOAC intake to admission, n/total (%)				0.004	0.007
<12 h	653/1275 (51.2)	333/650 (51.2)	320/625 (51.2)		
12–24 h	471/1275 (36.9)	239/650 (36.8)	232/625 (37.1)		
24–48 h	151/1275 (11.9)	78/650 (12.0)	73/625 (11.7)		
INR on admission, mean±SD	1.39±0.54	1.39±0.53	1.40±0.55	0.015	0.027
INR on admission for patients on VKAs, n/total (%)				0.045	0.087
<2	205/374 (54.8)	114/210 (54.3)	91/164 (55.5)		
2–3.5	156/374 (41.7)	88/210 (41.9)	68/164 (41.5)		
>3.5	13/374 (3.5)	8/210 (3.8)	5/164 (3.1)		
DOAC levels on admission available, n/total (%)	281/1275 (22.0)	141/650 (21.5)	140/625 (22.6)	0.025	0.084
DOAC levels on admission, n/total (%)				0.021	0.071
Below range	67/281 (23.9)	33/141 (23.4)	34/140 (23.4)		
Within range	197/281 (70.1)	101/141 (68.6)	96/140 (71.6)		
Above range	17/281 (6.0)	7/141 (7.0)	10/140 (5.0)		
On-label DOAC dosing on admission, n/total (%)	1094/1275 (85.8)	545/650 (83.8)	549/625 (87.8)	0.115	0.012
Clinical characteristics					
Hospitalization, n (%)	1596 (96.8)	766 (97.1)	830 (96.5)	0.033	0.086
Hospital setting, n/total (%)				0.008	0.056
Stroke unit	1504/1596 (94.2)	781/766 (94.1)	723/830 (94.4)		
Intensive care unit	42/1596 (2.6)	23/766 (2.8)	19/830 (2.5)		
Other hospital unit	50/1596 (3.1)	26/766 (3.1)	24/830 (3.1)		
NIHSS score on admission, median (IQR)	11 (5–18)	13 (6–19)	9 (4–17)	0.277	0.111*
Prestroke mRS score category, n (%)				0.237	0.088
No symptoms (score of 0)	814 (49.4)	380 (44.2)	434 (55.0)		
Symptoms without any disability (score of 1)	369 (22.4)	196 (22.8)	173 (21.9)		
Symptoms with mild disability (score of 2)	223 (13.5)	130 (15.1)	93 (15.1)		
Symptoms with mild-to-moderate disability (score of 3)	179 (10.9)	115 (13.4)	64 (13.4)		
Symptoms with moderate-to-severe disability (score of 4)	59 (3.6)	37 (4.3)	22 (2.8)		
Symptoms with severe disability (score of 5)	5 (0.3)	2 (0.2)	3 (0.4)		

(*Continued*)

Table 1. Continued

Characteristic	Overall cohort (n=1649)	Women (n=860)	Men (n=789)	SMD unweighted	SMD weighted
OCSP classification, n (%)				0.218	0.080
Total anterior circulation stroke	473 (28.7)	291 (23.1)	182 (28.7)		
Partial anterior circulation stroke	901 (54.6)	442 (58.2)	459 (54.6)		
Posterior circulation syndrome	158 (9.6)	78 (10.1)	80 (9.6)		
Lacunar stroke	117 (7.1)	49 (8.6)	68 (7.1)		
Competing stroke cause other than cardioembolism, n (%)	401 (24.3)	179 (20.8)	222 (28.1)	0.171	0.010
Type of competing stroke cause, n/total (%)†				0.100	0.039
Small-vessel disease	70/401 (17.5)	32/179 (17.9)	38/222 (17.1)		
Large-artery atherosclerosis	240/401 (59.9)	109/179 (60.9)	131/222 (59.0)		
Other determined cause	60/401 (15.0)	29/179 (16.2)	31/222 (15.0)		
Combined competing cause	31/401 (7.6)	9/179 (5.0)	22/222 (9.9)		
Intravenous thrombolysis, n (%)	139 (8.4)	70 (8.0)	69 (8.9)	0.031	0.039
Endovascular thrombectomy, n (%)	732 (44.4)	430 (50.0)	302 (38.3)	0.238	0.109*
Risk factors, n (%)					
Arterial hypertension‡	1338 (81.1)	707 (82.2)	631 (80.0)	0.057	0.017
Dyslipidemia§	845 (51.2)	429 (52.7)	416 (49.9)	0.111	0.057
Diabetes‖	443 (26.9)	224 (26.0)	219 (27.8)	0.039	0.007
Cigarette smoking¶	154 (9.3)	41 (4.8)	113 (14.3)	0.329	0.020
Prior ischemic stroke or TIA	410 (24.9)	204 (23.7)	206 (26.1)	0.055	0.055
Prior intracranial hemorrhage	27 (1.6)	8 (0.9)	19 (2.4)	0.115	0.096
Ischemic heart disease#	366 (22.2)	235 (15.2)	131 (29.8)	0.354	0.041
Chronic congestive heart failure**	277 (16.8)	139 (16.2)	138 (17.5)	0.035	0.050
Chronic kidney disease††	268 (16.3)	144 (16.7)	124 (15.7)	0.028	0.054
Chronic liver failure‡‡	7 (0.4)	4 (0.5)	3 (0.4)	0.013	0.018
Symptomatic peripheral artery disease§§	80 (4.9)	27 (3.1)	53 (6.7)	0.166	0.046
Mechanical heart valve	94 (5.7)	61 (7.1)	33 (4.2)	0.126	0.055
Biological heart valve	81 (4.9)	42 (4.9)	39 (4.9)	0.003	0.052
Atrial fibrillation type, n (%)‖‖				0.206	0.133*
Paroxysmal	335 (20.3)	161 (18.7)	174 (22.1)		
Persistent	200 (12.1)	99 (11.5)	101 (12.8)		
Long-standing persistent	76 (4.6)	30 (3.5)	46 (5.8)		
Permanent	847 (51.4)	481 (55.9)	366 (46.4)		
Unknown	191 (11.6)	89 (10.3)	102 (12.9)		
History of cancer, n (%)	237 (14.4)	124 (15.7)	113 (13.1)	0.073	0.054
Antihypertensive drugs on admission, n (%)	1310 (79.4)	700 (81.4)	610 (77.3)	0.111	0.101*
Lipid-lowering drugs on admission, n (%)	742 (45.0)	362 (42.1)	380 (48.2)	0.122	0.112*
Antidiabetic drugs on admission, n (%)	397 (24.1)	194 (22.6)	203 (25.7)	0.074	0.042
Rhythm control drugs on admission, n (%)	1088 (66.0)	585 (68.0)	503 (63.8)	0.090	0.012
Antiplatelet therapy on admission, n (%)	131 (7.9)	53 (6.2)	78 (9.9)	0.137	0.031
Poststroke secondary prevention					
Poststroke anticoagulation strategy, n (%)				0.082	0.041
No anticoagulation restarted	179 (10.9)	101 (9.5)	78 (8.9)		
Same DOAC restarted	463 (28.1)	223 (21.0)	240 (27.5)		
Switch to different DOAC (anti-Xa ↔ anti-Xa/anti-IIa ↔ anti-IIa)	201 (12.2)	113 (10.7)	88 (10.1)		
Switch to different DOAC (anti-Xa ↔ anti-IIa)	283 (17.2)	134 (12.6)	149 (17.1)		
VKA → DOAC	112 (6.8)	59 (5.6)	53 (6.1)		

(*Continued*)

Table 1. Continued

Characteristic	Overall cohort (n=1649)	Women (n=860)	Men (n=789)	SMD unweighted	SMD weighted
VKA→VKA	179 (10.9)	100 (9.4)	79 (9.1)		
DOAC→VKA	59 (3.6)	33 (3.1)	26 (3.0)		
DOAC→LMWH	36 (2.2)	21 (2.0)	15 (1.7)		
VKA→LMWH	19 (1.2)	13 (1.2)	6 (0.7)		
Left atrial appendage closure	8 (0.5)	6 (0.6)	2 (0.2)		
Unknown	110 (6.7)	57 (5.4)	53 (6.1)		
Time from index stroke to anticoagulation restart, mean±SD, d	8.1±9.1	8.5±9.2	7.8±8.9	0.077	0.085
Anticoagulation discontinued during follow-up, n/total (%)	151/1350 (11.2)	93/695 (13.4)	58/655 (8.9)	0.101	0.048
Poststroke antihypertensive drugs, n (%)	1346 (81.7)	708 (82.3)	638 (80.9)	0.034	0.071
Poststroke lipid-lowering drugs, n (%)	1064 (64.5)	533 (62.0)	531 (67.3)	0.109	0.067
Poststroke antidiabetic drugs, n (%)	535 (32.4)	268 (32.8)	267 (32.1)	0.089	0.013
Poststroke rhythm control drugs, n (%)	1147 (69.6)	520 (72.9)	627 (65.9)	0.160	0.092
Poststroke antiplatelet therapy, n (%)	250 (15.2)	82 (9.5)	137 (17.4)	0.119	0.060
Poststroke carotid intervention, n (%)				0.120	0.095
Endarterectomy, n (%)	18 (1.1)	6 (0.7)	12 (1.5)		
Stenting, n (%)	12 (0.7)	3 (0.3)	9 (1.1)		

DOAC indicates direct oral anticoagulant; INR, international normalized ratio; IQR, interquartile range; LMWH, low-molecular-weight heparin; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire community stroke project; SMD, standardized mean difference; and VKA, vitamin K antagonist.

*SMD >0.10.

†Competing stroke cause was classified according to the TOAST (Trial of Org 10172 in the Acute Stroke Treatment) classification system.

‡Arterial hypertension was defined as a history of blood pressure >140/90 mm Hg or the current use of antihypertensive medications.

§Dyslipidemia was defined as history of total blood cholesterol levels >220 mg/dL and/or total triglycerides levels >130 mg/dL and/or current used lipid-lowering drugs.

‖Diabetes was defined as history of fasting glucose >126 mg/dL or the current use of hypoglycemic medications.

¶Current smoking was defined as the consumption of ≥1 cigarette per day over the past year.

#Ischemic heart disease was defined as history of myocardial infarction, angina, or prior evidence of coronary disease on coronary angiography.

**Chronic congestive heart failure was defined as history of stage C (structural heart disease and current or past history of heart failure symptoms) or stage D (refractory symptoms that interfere with daily life or recurrent hospitalization despite targeted guideline-directed medical therapy) chronic heart failure.

††Chronic kidney disease was defined as history of estimated creatinine clearance of <60 ml/min for ≥3 months (including dialysis).

‡‡Chronic liver failure was defined as history of cirrhosis or end-stage liver disease.

§§Symptomatic atherosclerotic peripheral artery disease was defined as history of intermittent claudication of presumed atherosclerotic origin.

‖‖Atrial fibrillation type was classified according to the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines.

Notably, among women, 90-day ischemic recurrences were mainly observed in those who did not restart OAC (12/39 [30.8%]) or discontinued therapy during follow-up (10/39 [25.6%]). The excess risk in women was confirmed in the weighted cohort (adjusted HR, 1.70 [95% CI, 1.01–2.86]; *P*=0.045). In competing risk analysis, the cumulative incidence of 90-day ischemic stroke or TIA differed significantly by sex (Gray test χ^2=4.62, *P*=0.032), and Fine–Gray regression showed a higher subdistribution hazard in women (subdistribution HR, 1.75 [95% CI, 1.04–2.92]; *P*=0.034). No sex-related differences were observed for death as the competing event (Gray test *P*=0.698) (Figure S3).

The incidence of myocardial infarction was low and similar between sexes (1.6% in women versus 0.7% in men), although women showed a nonsignificant trend toward higher risk (adjusted HR, 2.60 [95% CI, 0.99–6.88]; *P*=0.054). All-cause mortality at 90 days was 20.5% in women and 17.8% in men (adjusted HR, 1.15 [95% CI, 0.92–1.43]; *P*=0.233), and vascular death occurred in 13.1% versus 11.1%, respectively (adjusted HR, 1.16 [95% CI, 0.88–1.54]; *P*=0.297). Kaplan–Meier curves confirmed the increased risk of recurrent ischemic stroke or TIA in women, with comparable incidence of myocardial infarction, all-cause mortality, and vascular death between sexes (Figure 3).

Safety Outcomes

In the weighted cohort, 90-day moderate-to-severe bleeding occurred in 4.6% of women and 2.8% of men, with no significant sex-related difference, although a trend toward higher risk was observed in women (adjusted HR, 1.62 [95% CI, 0.96–2.72]; *P*=0.070) (Figure 4). The incidence of 90-day ICH was similarly low in both groups (1.9% in women versus 1.7% in men; adjusted HR, 0.98 [95% CI, 0.46–2.11]; *P*=0.962) (Figure 4). Hemorrhagic transformation within 24 hours was observed in 20.3% of women and 18.7% of men, with no significant difference (adjusted risk ratio, 1.04 [95% CI, 0.83–1.30]; *P*=0.727). The rate of 24-hour sICH was low and comparable between sexes (2.4%

Table 2. Outcomes Comparison

Variable	Unweighted cohort		Weighted cohort		Statistical metric*	Statistical difference (95% CI)	*P* value
	Women (n=860)	Men (n=789)	Women (n=818)	Men (n=831)			
Primary outcome							
90-d Return to baseline neurologic function, n (%)	274 (31.9)	338 (42.8)	288 (35.2)	355 (42.7)	Adjusted risk ratio	0.82 (0.71–0.96)	0.015†
Secondary outcomes							
90-d mRS score distribution, n (%)					Adjusted odds ratio	1.17 (1.01–1.37)	0.043†
No symptoms (score of 0)	81 (9.4)	113 (14.3)	89 (10.9)	104 (12.5)			
Symptoms without any disability (score of 1)	112 (13.0)	172 (21.8)	134 (16.4)	170 (20.5)			
Symptoms with mild disability (score of 2)	121 (14.1)	118 (15.0)	122 (14.9)	129 (15.5)			
Symptoms with mild-to-moderate disability (score of 3)	151 (17.6)	114 (14.4)	139 (17.0)	115 (13.8)			
Symptoms with moderate-to-severe disability (score of 4)	119 (13.8)	98 (12.4)	98 (12.0)	120 (14.4)			
Symptoms with severe disability (score of 5)	79 (9.2)	37 (4.7)	68 (8.3)	45 (5.4)			
Death (score of 6)	197 (22.9)	137 (17.4)	168 (20.5)	148 (17.8)			
90-d New ischemic stroke or TIA, n (%)	39 (4.5)	18 (2.3)	39 (4.8)	23 (2.8)	Adjusted hazard ratio	1.70 (1.01–2.86)	0.045†
90-d Myocardial infarction, n (%)	12 (1.4)	9 (1.1)	13 (1.6)	6 (0.7)	Adjusted hazard ratio	2.60 (0.99–6.88)	0.054
90-d All-cause death, n (%)	197 (22.9)	137 (17.4)	168 (20.5)	148 (17.8)	Adjusted hazard ratio	1.15 (0.92–1.43)	0.233
90-d Vascular death, n (%)	127 (14.8)	85 (10.8)	107 (13.1)	92 (11.1)	Adjusted hazard ratio	1.16 (0.88–1.54)	0.297
Safety outcomes, n (%)							
90-d Moderate-to-severe bleeding	30 (3.5)	25 (3.2)	38 (4.6)	23 (2.8)	Adjusted hazard ratio	1.62 (0.96–2.72)	0.070
90-d Intracranial hemorrhage	13 (1.5)	15 (1.9)	14 (1.7)	13 (1.6)	Adjusted hazard ratio	0.98 (0.46–2.11)	0.962
24-h Hemorrhagic transformation	167 (19.4)	120 (15.2)	166 (20.3)	155 (18.7)	Adjusted risk ratio	1.04 (0.83–1.30)	0.727
24-h Symptomatic intracranial hemorrhage	21 (2.4)	20 (2.5)	29 (3.5)	30 (3.6)	Adjusted risk ratio	0.97 (0.58–1.64)	0.921

Global Schoenfeld *P* values: 90-day new ischemic stroke or TIA=0.165; 90-day myocardial infarction=0.273; 90-day vascular death=0.433; 90-day all-cause death=0.760; 90-day moderate-to-severe bleeding=0.125; and 90-day intracranial hemorrhage=0.615. Schoenfeld residuals test *P* values: 90-day new ischemic event=0.289; 90-day new stroke or TIA=0.165; 90-day myocardial infarction=0.273; 90-day vascular death=0.433; 90-day all-cause death=0.760; 90-day moderate-to-severe bleeding=0.125; and 90-day intracranial hemorrhage=0.615. mRS indicates modified Rankin Scale; and TIA, transient ischemic attack.

*Adjusted analyses controlled for baseline (prestroke) covariates that remained imbalanced (standardized mean difference >0.10) after weighting (National Institutes of Health Stroke Scale score on admission, endovascular thrombectomy, atrial fibrillation type, and antihypertensive and lipid-lowering drugs on admission).

†Statistically significant *P* values (<0.05).

in women versus 2.5% in men; adjusted risk ratio, 0.97 [95% CI, 0.58–1.64]; *P*=0.921). Rates of safety outcomes in both the unweighted and weighted cohort are reported in Table 2.

Subgroup Analysis for the Primary Outcome

In the weighted cohort, women were less likely than men to achieve the primary outcome in several subgroups. Effect-measure modification was significant for type of oral anticoagulation (*P*=0.025; difference evident among DOAC users but not in vitamin K antagonist users), competing stroke cause (*P*=0.023; driven by no competing cause and lacunar cause), anticoagulation restarted after stroke (*P*=0.048; confined to those who restarted), and EVT (*P*=0.004; difference present only in patients without EVT). In the remaining subgroups, risk ratios were generally consistent in direction, favoring men, with no evidence of a significant interaction (Table 3).

Compared with men, women showed a significantly lower probability of returning to baseline neurologic function both among those with mild stroke severity (baseline NIHSS score, 0–5; risk ratio, 0.87 [95% CI, 0.77–0.99]; *P*=0.037) and among those with small-vessel disease as a competing cause in addition to cardioembolism (risk ratio, 0.68 [95% CI, 0.47–0.97]; *P*=0.034). The proportion of patients who experienced a 90-day recurrent ischemic stroke or TIA did not differ between women and men in either subgroup (4/211 [1.9%] versus 12/289 [4.2%] for NIHSS score 0–5; *P*=0.202; and none in both sexes in the small-vessel disease subgroup; *P*>0.999). However, intravenous thrombolysis was less frequently performed in women with mild stroke compared with men (5/211 [2.4%] versus 16/289 [5.5%]; *P*=0.081), and particularly in those with competing small-vessel disease (0/32 [0.0%]

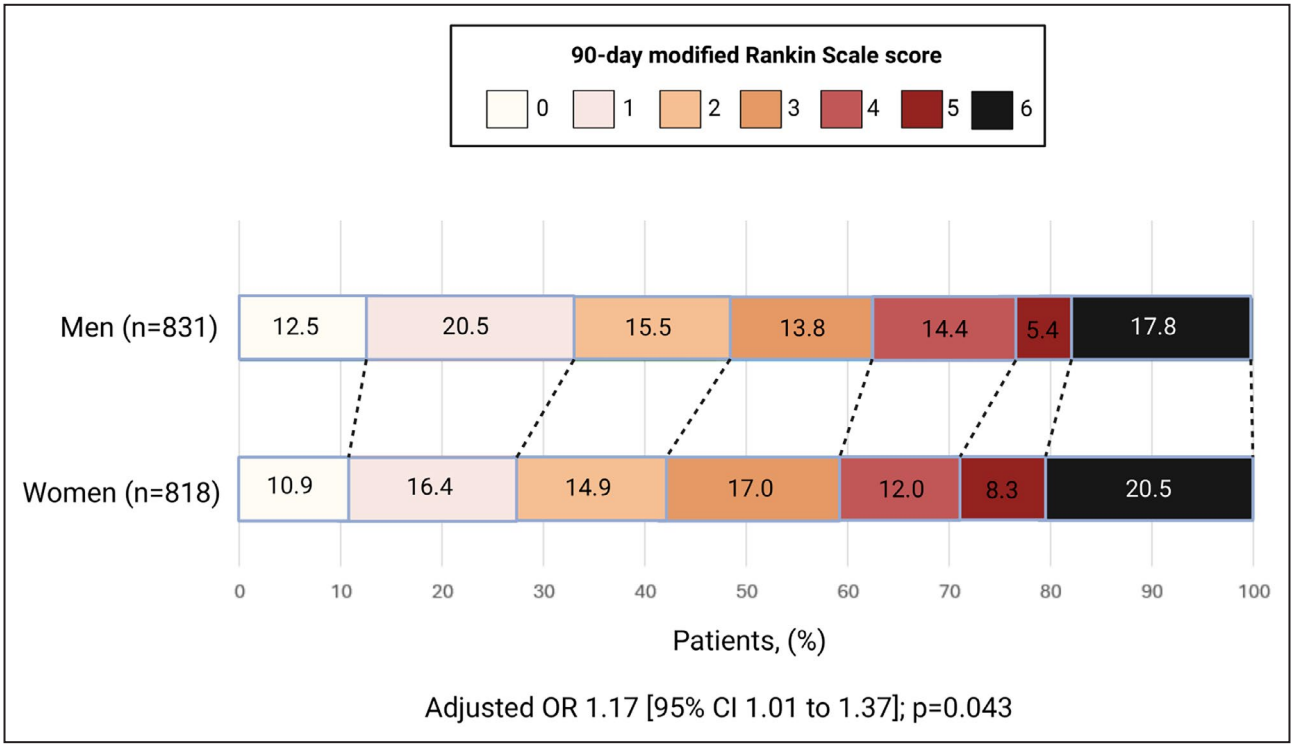

Figure 2. The 90-day mRS score distribution by sex in the weighted cohort.
mRS indicates modified Rankin Scale; and OR, odds ratio.

versus 6/23 [26.1%]; *P*=0.003). In contrast, the proportion of patients with mild stroke undergoing EVT was similar between women and men (19/211 [9.0%] versus 23/289 [8.0%]; *P*=0.707).

DISCUSSION

In this large, international, retrospective cohort of patients with AF who experienced breakthrough ischemic stroke while on continuous OAC, we found consistent sex-specific differences in 90-day outcomes. Indeed, in both the unweighted cohort and after applying inverse probability weighting as well as additional adjustment for residual confounders, women were less likely than men to return to baseline neurologic function, showed a worse overall distribution of functional outcomes, and experienced higher rates of recurrent ischemic stroke or TIA. Mortality did not differ significantly between sexes, and bleeding events were comparable, although women showed a trend toward more moderate-to-severe bleeding after the index event. Our findings for the primary outcome were consistent across several key clinical subgroups, with signals of effect modification by anticoagulant type, competing stroke cause other than cardioembolism, and endovascular treatment. Collectively, these patterns suggest a sex-specific vulnerability after breakthrough events, highlighting the need for secondary prevention strategies that explicitly consider sex-specific factors, extend beyond anticoagulation optimization, and incorporate tailored poststroke rehabilitation approaches.

To date, whether sex influences prognosis specifically after breakthrough ischemic stroke on OAC remains unexplored. The existing literature has primarily examined sex differences in ischemic stroke outcomes across unselected stroke cohorts,[12,21] rather than in the distinct subgroup of patients with AF who experience breakthrough ischemic stroke despite ongoing OAC. Our analysis provides novel evidence that female sex is independently associated with poorer functional recovery after a breakthrough ischemic stroke while on OAC compared with their male counterparts. This observation complements prior evidence from a subanalysis of the RAF (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation) study,[22] which investigated sex differences in outcomes after AF-related stroke irrespective of prior anticoagulation. In that cohort, despite being younger and having lower admission NIHSS scores, women had worse functional outcomes at 90 days. Aligning with prior investigations,[12,21] we documented that women were on average older and presented with greater neurologic severity on admission, factors that may partially account for their reduced likelihood of achieving functional recovery.

Another important finding that may underlie the lower rate of functional recovery observed among

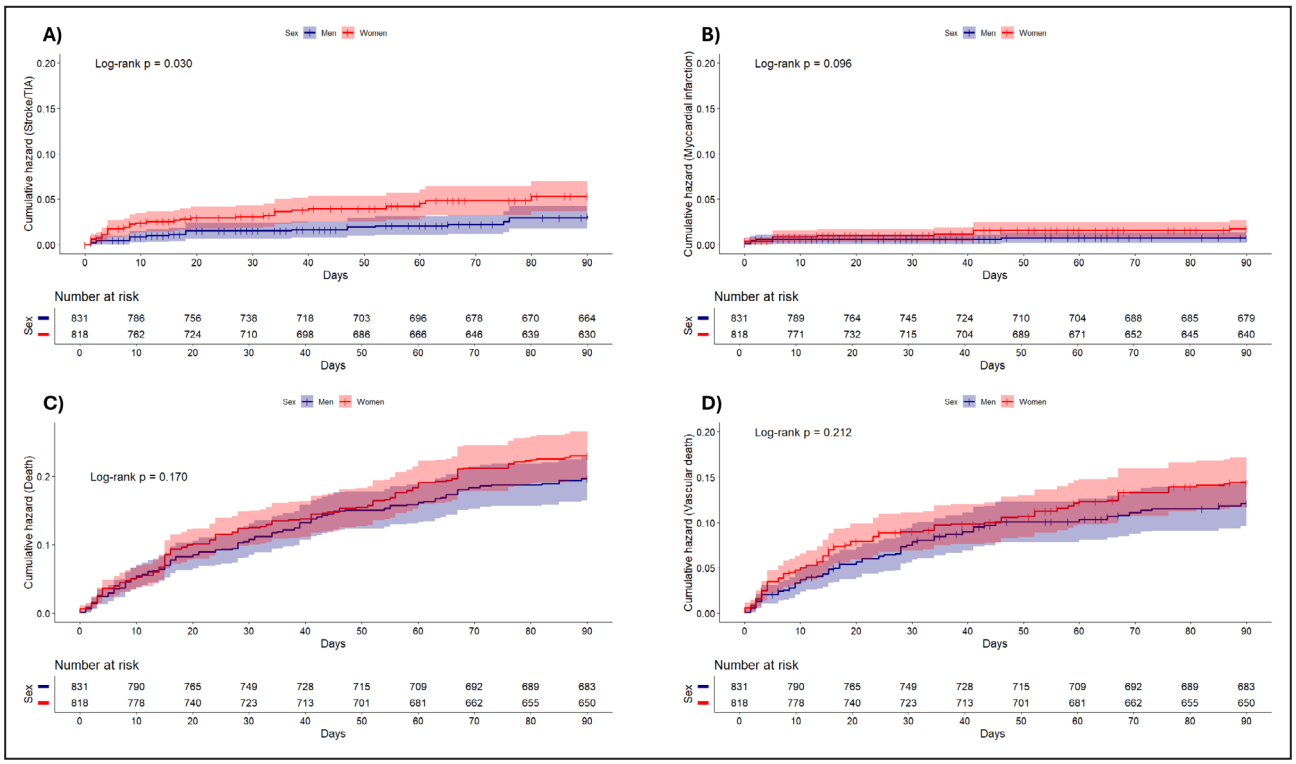

Figure 3. Cumulative hazard curves for outcome comparison in the weighted cohort.
A, The 90-day new ischemic stroke or TIA. **B**, The 90-day myocardial infarction. **C**, The 90-day all-cause death. **D**, The 90-day vascular death. Shaded areas indicate 95% CIs. Number at risk reflects number of patients in the weighted pseudopopulation. HR indicates hazard ratio; and TIA, transient ischemic attack.

women in our cohort is their higher risk of recurrent ischemic stroke or TIA following breakthrough stroke. This observation gains particular relevance in light of the 2024 European Society of Cardiology guidelines on AF, which removed female sex from the CHA_2DS_2-VASc score in favor of the CHA_2DS_2-VA scheme (level of evidence C).[23] Although this change aims to simplify risk stratification and enhance inclusivity, concerns have been raised that it may underestimate thromboembolic risk in women. Although recent studies in well-anticoagulated populations suggest a narrowing of sex-related differences,[24,25] global data continue to show persistently higher stroke rates among women,[26] and real-world evidence from Australia showed that removing the sex criterion was followed by reduced OAC use in women.[27] In our cohort, despite comparable

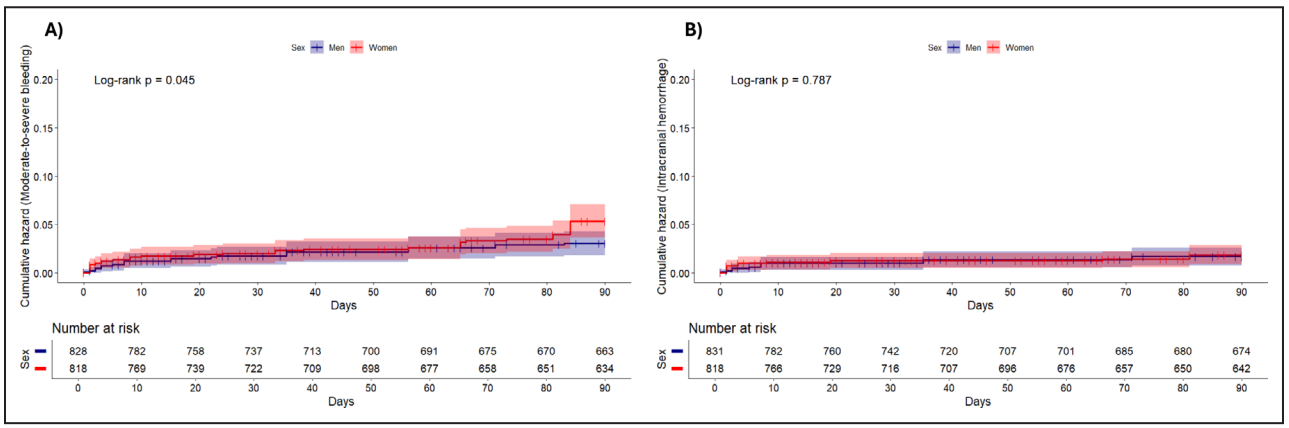

Figure 4. Cumulative hazard curves for outcomes in the weighted cohort.
A, The 90-day moderate-to-severe bleeding. **B**, The 90-day intracranial hemorrhage. Shaded areas indicate 95% CIs. Number at risk reflects number of patients in the weighted pseudopopulation.

Table 3. Primary Outcome by Prespecified Subgroups in the Weighted Cohort

Variable	No. of patients	No. of patients with primary effectiveness outcome/total No. (%)		Risk ratio (95% CI)	*P* value	*P* value interaction
		Women	Men			
Age, y						0.919
<55	70	26/40 (65.0)	22/30 (73.3)	0.88 (0.64–1.22)	0.450	
≥55	1579	262/778 (33.7)	333/801 (41.6)	0.84 (0.73–0.96)	0.010*	
Type of oral anticoagulation						0.025*
VKA	373	77/180 (42.7)	78/193 (40.4)	1.05 (0.82–1.33)	0.710	
DOAC	1276	211/638 (33.1)	277/638 (43.4)	0.76 (0.66–0.88)	<0.001*	
Baseline NIHSS score						0.283
0–5	500	134/211 (63.5)	210/289 (72.7)	0.87 (0.77–0.99)	0.037*	
6–10	336	76/177 (42.9)	67/159 (42.1)	1.03 (0.82–1.30)	0.780	
>10	813	78/430 (18.1)	78/383 (20.4)	0.89 (0.68–1.16)	0.380	
Competing stroke cause						0.023*
None	1235	218/614 (35.5)	266/621 (42.8)	0.83 (0.72–0.95)	0.007*	
Small-vessel disease	55	19/32 (59.4)	20/23 (87.0)	0.68 (0.47–0.97)	0.034*	
Large-artery atherosclerosis	258	40/114 (35.1)	56/144 (38.9)	0.91 (0.65–1.27)	0.590	
Other determined cause	68	11/42 (26.2)	7/26 (26.9)	0.98 (0.45–2.10)	0.960	
Combined competing cause	32	0/15 (0.0)	6/17 (35.3)	0.00 (not estimable)	<0.001*	
Prestroke mRS						0.747
<2	1432	252/723 (34.9)	302/709 (42.6)	0.82 (0.72–0.93)	0.002*	
≥2	217	36/95 (37.9)	53/122 (43.4)	0.88 (0.64–1.21)	0.430	
Arterial hypertension						0.394
Yes	1314	216/649 (33.3)	278/665 (41.8)	0.81 (0.70–0.94)	0.005*	
No	335	72/169 (42.6)	77/166 (46.4)	0.91 (0.72–1.15)	0.420	
Diabetes						0.344
Yes	131	62/218 (28.4)	69/219 (31.5)	0.92 (0.69–1.23)	0.570	
No	512	226/600 (37.7)	286/612 (46.7)	0.77 (0.67–0.88)	<0.001*	
Type of atrial fibrillation						0.884
Paroxysmal	318	61/140 (43.6)	85/178 (47.8)	0.91 (0.71–1.17)	0.450	
Persistent	198	39/108 (36.1)	41/90 (45.6)	0.78 (0.55–1.12)	0.181	
Long-standing persistent	61	7/33 (21.2)	10/28 (35.7)	0.59 (0.24–1.41)	0.233	
Permanent	877	138/445 (31.0)	166/432 (38.4)	0.81 (0.67–0.97)	0.024*	
Unknown	195	43/92 (46.7)	53/103 (51.5)	0.87 (0.67–1.13)	0.301	
Intravenous thrombolysis						0.116
Yes	150	40/79 (50.6)	33/71 (46.5)	1.11 (0.81–1.54)	0.522	
No	1499	248/739 (33.6)	322/760 (42.4)	0.79 (0.70–0.90)	<0.001*	
Endovascular thrombectomy						0.004*
Yes	745	108/392 (27.6)	91/353 (25.8)	1.06 (0.86–1.31)	0.588	
No	904	180/426 (42.3)	264/478 (55.2)	0.77 (0.66–0.89)	<0.001*	

DOAC indicates direct oral anticoagulant; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and VKA, vitamin K antagonist.
*Statistically significant *P* values (<0.05).

OAC prescription rates and timing of reinitiation after the index event, women were more likely to discontinue therapy during follow-up, a potentially modifiable factor contributing to their higher recurrence risk. Notably, most ischemic recurrences occurred in women who either did not restart OAC or discontinued it during follow-up, suggesting that this factor may have contributed to their higher recurrence risk. However, the balance achieved in the weighted cohort indicates that discontinuation alone is unlikely to explain the sex gap. Rather, our findings might point to a multifactorial explanation in which differences in OAC persistence may intersect with biological mechanisms, such as sex-specific variation in coagulation pathways, platelet activity, vascular remodeling, or drug metabolism and clearance. Evidence on sex differences in treatment

persistence after stroke is limited and inconsistent, with some studies reporting no differences,[28,29] others reporting poorer persistence in men,[30,31] and several reporting lower persistence in women.[32–34] Our results align with prior work, including a nationwide analysis reporting that women were more likely to discontinue secondary prevention therapies.[35] The multinational design of the ASPERA-R study further supports that higher discontinuation rates among women are unlikely because of local prescribing practices alone, but instead represent a broader, modifiable factor contributing to their excess recurrence risk.

For safety outcomes, rates of ICH and sICH were similarly low between sexes, consistent with the intrinsically low incidence of major bleeding complications previously reported in predominantly White European cohorts.[36] However, we observed a nonsignificant but clinically relevant trend toward higher moderate-to-severe bleeding in women. This aligns with prior evidence showing greater bleeding susceptibility among female patients with AF treated with DOACs,[37] particularly gastrointestinal tract bleeding, likely driven by older age, higher comorbidity burden, and sex-related pharmacokinetic differences, such as lower body weight, reduced renal clearance, and higher plasma concentrations of factor-Xa inhibitors.[38] Although not always life threatening, these events often lead to OAC discontinuation, an issue especially relevant in our cohort, where women displayed both more bleeding and higher discontinuation rates. Taken together, these findings reinforce the view that although OAC offers comparable intracranial protection across sexes, women may be more vulnerable to extracranial bleeding, underscoring the need for closer monitoring, individualized dosing, and strategies to prevent premature therapy discontinuation.

Finally, in our prespecified subgroup analyses, the reduced likelihood of returning to baseline neurologic function among women compared with men was consistent across most strata. Nonetheless, some subgroups revealed distinct patterns. The observed sex disparity was more pronounced among patients receiving DOACs compared with those on vitamin K antagonists, indicating that sex-related differences in pharmacokinetics, treatment adherence, or therapy discontinuation may exert a greater influence on functional recovery in the context of DOAC therapy. The disparity was also most evident among patients without competing noncardioembolic causes and in those with lacunar strokes, suggesting that women may experience a disproportionate disadvantage when AF-related cardioembolism represents the predominant underlying mechanism. This observation aligns with prior evidence showing that women with AF carry a higher intrinsic risk of stroke than men.[13] Moreover, this sex disparity was evident only in patients who did not undergo EVT, suggesting that effective reperfusion may attenuate sex-related disadvantages in functional recovery and partially neutralize biological or treatment-related differences. Notably, among patients with mild stroke severity and small-vessel disease as a competing cause, women were less likely to receive intravenous thrombolysis, which may partly explain their lower likelihood of returning to baseline neurologic function, as reflected by the risk ratios favoring men in these subgroups.

The main strength of this study lies in the use of rigorous procedures to enhance data accuracy and quality, supported by regular quality checks of the ASPERA-R electronic database. Additional strengths of our study are the large sample size and the use of advanced statistical methods, which yield more robust estimates of clinical outcomes. Nonetheless, several limitations should be acknowledged. First, despite inverse probability weighting and additional adjustment, the observational design cannot exclude residual confounding. For example, information on DOAC resumption or initiation at on-label dosing after the index stroke was incomplete, preventing us from assessing its potential impact on outcomes. Second, the retrospective nature introduces potential selection and measurement bias and limits causal inference; some cases may have been missed, particularly those managed outside the stroke unit and discharged with alternative diagnoses. Furthermore, some participating centers, particularly in Italy, are lower-volume facilities with smaller catchment areas, which may have further limited the total number of enrolled cases. Third, plasma DOAC levels were available in only ~20% of patients, limiting adjustment for on-treatment exposure; in the remainder, estimates from history and medical record review may have introduced misclassification. Moreover, information on time in therapeutic range for patients treated with vitamin K antagonists was not documented, which precluded assessment of the quality of the anticoagulation control in this group. Fourth, detailed reasons for OAC discontinuation were lacking, and in ~5% of cases, OAC resumption remained unknown, precluding a more granular analysis of sex disparities. Fifth, patients with incomplete baseline or follow-up data (6.9%) were excluded, and although no evidence of differential attrition was found, selection bias cannot be ruled out. Sixth, we were unable to perform subgroup analyses for time-to-event secondary outcomes because the number of events for the only end point exhibiting a sex-related difference (n=57 new ischemic strokes/TIAs) was insufficient to support reliable stratified Cox models, which would have led to sparse subgroups and unstable HR estimates. For the remaining time-to-event outcomes, for which no overall sex-related association was detected, undertaking subgroup analyses in the absence of a main effect would have increased

the risk of generating spurious findings. Finally, as 60% of patients were enrolled in Italy, with a cohort strongly imbalanced toward non-Hispanic White ethnicity, generalizability beyond this population may be limited. This is particularly relevant given the intrinsically lower risks of ischemic stroke and major bleedings reported among patients with AF receiving antithrombotic agents compared with Asian and Black populations in large population-based studies.[36,39]

In conclusion, this large, multinational study indicates that women with AF who experience breakthrough ischemic stroke despite continuous OAC face a disproportionate burden of recurrent ischemic events and functional disability compared with men. These disparities persisted despite similar anticoagulant prescription rates and timing of therapy reinitiation and may in part be explained by higher discontinuation rates and greater vulnerability to nonintracranial bleeding among women. Subgroup analyses further revealed that sex differences in the rate of functional recovery were particularly evident in patients treated with DOACs, in those without competing stroke causes, and in patients not undergoing EVT, highlighting clinical contexts where tailored strategies may be most impactful. Our findings underscore the urgent need for sex-specific strategies after breakthrough stroke, encompassing optimized anticoagulant management, measures to mitigate OAC discontinuation, and tailored rehabilitation, alongside investigation into biological determinants of sex-related risk. These priorities will be further addressed by ongoing prospective studies, including ASPERA-P, which are expected to provide further insights on sex-specific differences in breakthrough ischemic stroke.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figures S1–S3
STROBE Checklist

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