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Posterior versus anterior circulation infarct location and outcomes after breakthrough ischemic stroke in orally anticoagulated patients for atrial fibrillation: An ASPERA-R inverse probability–weighted analysis

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ABSTRACT

Introduction and aims: Breakthrough ischemic stroke may occur despite ongoing oral anticoagulation (OAC) in patients with atrial fibrillation (AF). Whether infarct location influences prognosis remains unclear. We aimed to compare clinical characteristics and outcomes of posterior versus anterior circulation infarct (PCI vs ACI).
Methods: Multicentre retrospective analysis from the ASPERA cohort, including patients with AF and ischemic stroke despite continuous OAC (Feb. 2020 to Feb. 2025). Patients were classified as PCI or ACI according to infarct location. The primary outcome was a 90-day composite of recurrent ischemic stroke, myocardial infarction, or vascular death. Secondary outcomes included modified Rankin Scale (mRS) shift and all-cause mortality. Safety outcomes included 24-h hemorrhagic transformation (HT) and symptomatic intracranial hemorrhage (sICH), 90-day ICH. Inverse-probability weighting with truncation of extreme weights and additional adjustment for residual imbalance were applied.
Results: Among 1649 patients (mean age 78.0 ± 10.7 years; 47.8% men), 165 (10.0%) had PCI. PCI patients were more often on vitamin K antagonists and had lower stroke severity. After weighting, PCI was associated with a higher risk of the composite outcome (aHR 1.50, 95% CI 1.19–1.90; $p < 0.001$), vascular death (aHR 1.46, 95% CI 1.12–1.91; $p = 0.005$), all-cause mortality (aHR 1.85, 95% CI 1.51–2.27; $p < 0.001$), and worse mRS shift (aOR 1.79, 95% CI 1.51–2.13; $p < 0.001$). PCI was also associated with an increased risk of ICH (aHR 2.25, 95% CI 1.08–4.70; $p = 0.031$), whereas 24-HT and sICH were similar between groups.
Conclusions: In AF patients with breakthrough stroke on OAC, PCI identifies a subgroup with worse 90-day outcomes. These findings support the prognostic relevance of infarct location.

1. Introduction

Ischemic stroke may occur despite ongoing oral anticoagulant therapy in patients with atrial fibrillation (AF), a phenomenon commonly

[1] These authors equally contributed to the manuscript and share first authorship.

referred to as breakthrough stroke [1,2]. These events represent a major clinical challenge, as they are associated with substantial risks of recurrent vascular events, disability, and mortality despite apparently adequate secondary prevention. Understanding the factors influencing prognosis after breakthrough stroke is therefore essential to improve risk stratification and optimize post-stroke management.

Approximately one fifth of ischemic strokes involve the posterior circulation, affecting the brainstem, cerebellum, thalamus, and occipital lobes [3]. Compared with anterior circulation infarctions, posterior circulation strokes often present with lower apparent stroke severity but greater diagnostic uncertainty because of nonspecific symptoms such as dizziness, diplopia, or imbalance [4,5]. In addition, differences in vascular anatomy, collateral circulation, and underlying stroke mechanisms suggest that posterior and anterior circulation infarctions represent biologically and clinically distinct entities [6,7]. While anterior circulation infarctions are more commonly related to embolic occlusions of large intracranial arteries, posterior circulation strokes frequently involve vertebrobasilar pathology or small-vessel disease [7]. In patients experiencing breakthrough stroke, infarct location may therefore reflect different mechanisms of anticoagulation failure and identify subgroups with distinct risks of recurrent vascular events and adverse outcomes. Furthermore, involvement of structures critical for autonomic, respiratory, and consciousness regulation may influence prognosis independently of initial stroke severity.

Despite these considerations, limited evidence exists regarding the prognostic implications of infarct location in patients experiencing breakthrough ischemic stroke while receiving oral anticoagulation for AF. Most studies comparing posterior and anterior circulation stroke have focused on non-cardioembolic populations or specific therapeutic settings, such as antiplatelet therapy or reperfusion treatments, leaving an important knowledge gap in anticoagulated patients [8–10]. Clarifying whether infarct location influences outcomes in this population may improve understanding of breakthrough stroke mechanisms and inform post-stroke management strategies. Therefore, we aimed to compare the clinical characteristics and 90-day outcomes of patients with posterior versus anterior circulation infarction occurring despite ongoing oral anticoagulation for AF in a large multicenter cohort of breakthrough ischemic stroke.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

The *Advancing Knowledge in Ischemic Stroke Patients on Oral Anticoagulants* (ASPERA) study received ethical approval from the Abruzzo Regional Ethics Committee (CEtRA) in February 2025 (approval number 033054/25). Further approvals were obtained from the local ethics committees of the participating centers when required. Given the retrospective design and exclusive use of data derived from medical record review, informed consent was waived in most participating countries following approval by local ethics committees. In countries where consent is required for retrospective research, including Italy, written informed consent was obtained from patients or their legally authorized representatives. For patients who were deceased or could not be contacted, a consent waiver was granted by the ethics committee. The study protocol was prospectively registered at ClinicalTrials.gov (identifier: NCT06823466).

2.2. Study design

The ASPERA study is a large, multicenter, real-world observational investigation coordinated by the University of L'Aquila. The study comprises two complementary cohorts: a retrospective arm (ASPERA-R), designed to characterize baseline features and 90-day outcomes following breakthrough ischemic stroke occurring during oral anticoagulation for atrial fibrillation, and a prospective arm (ASPERA-P), intended to evaluate long-term outcomes over a follow-up period of up to five years.

The present analysis reports findings from the ASPERA-R cohort, based on retrospectively collected data from 35 stroke centers across nine countries in Europe and North Africa (**Appendix S1**). Eligible patients were identified after the index breakthrough stroke event, and 90-day outcomes were obtained through retrospective review of routine clinical follow-up documentation. The ASPERA-P arm is currently ongoing. The dataset used for this analysis was locked on September 1, 2025. Study reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.3. Study population

The ASPERA-R arm retrospectively enrolled adult patients who experienced a breakthrough ischemic stroke, defined as an ischemic stroke occurring despite continuous OAC therapy for AF, irrespective of whether the event represented a first-ever or recurrent stroke, between February 2020 and February 2025. Continuous OAC therapy was defined as a documented prescription with uninterrupted treatment during the 7 days preceding the index event and intake of the last dose within 48 h before symptom onset. Patients with a history of ischemic stroke or TIA were eligible, including those whose prior cerebrovascular event had occurred while receiving OAC therapy. For patients with multiple qualifying events during the study period, the first breakthrough stroke was considered the index event for ASPERA-R.

Eligibility criteria included: (1) age $\geq$ 18 years; (2) documented AF; (3) an ischemic stroke diagnosed according to World Health Organization criteria and confirmed by non-contrast computed tomography (NCCT) and/or magnetic resonance imaging (MRI); (4) occurrence of the event during OAC treatment, including either direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs), within the study period (February 2020–February 2025); (5) availability of baseline extracranial and intracranial vascular imaging, including CT or MR angiography (CTA/MRA), color Doppler ultrasonography (CDU), or digital subtraction angiography (DSA); and (6) availability of a standardized clinical follow-up assessment at 90 $\pm$ 10 days after the index stroke conducted through an in-person visit.

Conversely, we excluded patients with 1) inadequate DOAC dosing, as defined by any regimen not meeting guideline criteria based on renal function, age, body weight, or drug interactions (including underdosing or unjustified dose reductions); 2) poor compliance with anticoagulant therapy, defined as missed or uncertain OAC intake during the 7 days preceding the stroke based on patient/caregiver report or medical records. A full list of mandatory and optional baseline variables is provided in **Appendix S2**.

2.4. Data collection, quality and study definitions

Data were extracted from medical records collected during the index hospitalization and routine follow-up visits. To minimize selection bias, all consecutive hospital admissions and emergency department evaluations occurring within the study period were systematically screened, and all eligible patients were included. Clinical information was recorded using a standardized Research Electronic Data Capture (REDCap) case report form (CRF).

Data quality was ensured through weekly data validation checks and centralized monitoring procedures, with queries issued to participating centers when clarification or correction was required. The analytical dataset was finalized and locked on September 1, 2025.

Participation in the ASPERA consortium was restricted to centers with demonstrated high-level stroke expertise and established comprehensive diagnostic pathways. Centers lacking a designated lead investigator with recognized stroke expertise or without routinely implemented exhaustive diagnostic evaluations were not included. Likewise, participation to the ASPERA-R study was restricted to centres

with an established and routinely implemented 90-day follow-up pathway for all stroke patients, including standardized in-person outcome assessment and structured telephone contact for patients unable to attend in-person consultations. In addition, participating centres followed predefined case identification procedures to ensure consecutive inclusion of eligible patients and to minimize the risk of selection bias.

Patients were categorized as having ACI or PCI according to the anatomical location of the index acute infarct(s). ACI was defined as infarct(s) involving territories supplied by the anterior cerebral artery, middle cerebral artery, or internal carotid artery, whereas PCI included infarct(s) affecting territories supplied by the posterior cerebral artery, cerebellar arteries, basilar artery, or vertebral artery. In patients presenting with multiple acute infarcts involving both anterior and posterior circulation territories, classification was determined by the predominant clinical syndrome, as defined by the Oxford Vascular Study (OXVASC) criteria [11]. Accordingly, total anterior circulation infarction (TACI) and partial anterior circulation infarction (PACI) were classified as ACI, whereas posterior circulation infarction (POCI) was classified as PCI.

2.5. Study outcomes

The primary outcome was the occurrence within 90 days of a composite endpoint including new ischemic stroke, myocardial infarction, or vascular death, defined as any death attributable to cardiovascular or cerebrovascular causes, including fatal ischemic or hemorrhagic stroke, sudden cardiac death, myocardial infarction, or other vascular events. Secondary outcomes comprised the individual components of the primary endpoint, the shift across the 90-day modified Rankin Scale (mRS) scores, and all-cause mortality at 90 days. Safety outcomes included hemorrhagic transformation (HT) and symptomatic ICH (sICH) within 24 h, and 90-day intracranial hemorrhage (ICH). HT was defined as any category according to the Heidelberg bleeding classification system [12]; sICH was defined as any intracranial hemorrhage associated with a $\geq$ 4-point worsening on the National Institutes of Health Stroke Scale (NIHSS) not attributable to alternative causes [12]. ICH during follow-up was defined as any intracranial bleeding event, including intraparenchymal hemorrhage, subarachnoid hemorrhage, subdural hematoma, or intraventricular hemorrhage, confirmed by neuroimaging, regardless of symptom severity. All primary, secondary and safety outcomes were adjudicated by investigators through systematic review of 90-day follow-up assessments using prespecified operational definitions.

2.6. Statistical analysis

Categorical variables were summarized as counts (percentages), and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. To mitigate baseline imbalances between patients with PCI and ACI, inverse probability weighting (IPW) based on propensity scores was applied. Propensity scores were estimated using logistic regression including prespecified demographic, clinical, and treatment-related variables. Stabilized weights were calculated, truncated at the 1st and 99th percentiles to limit the influence of extreme values, and normalized to generate a weighted pseudo-population. Covariate balance was assessed using standardized mean differences (SMDs). All weighted analyses were additionally adjusted for covariates with residual imbalance after weighting (SMD >0.10), consistent with a doubly robust framework. Center-level clustering was accounted for using cluster-robust variance estimators.

Time-to-event outcomes were analyzed using weighted Cox proportional hazards models, reporting hazard ratios (HRs) and 95% confidence intervals (CIs). Kaplan–Meier curves and log-rank tests were used for graphical and unadjusted comparisons, and the proportional hazards assumption was assessed using Schoenfeld residuals. Fine–Gray competing-risk models were used for recurrent ischemic stroke and intracranial hemorrhage, considering all-cause mortality as a competing event. Functional outcome at 90 days was analyzed using ordinal logistic regression and reported as adjusted odds ratios (aORs). Twenty-four–hour hemorrhagic transformation (HT) and symptomatic intracranial hemorrhage (sICH) were analyzed using generalized linear models, reporting adjusted risk differences (aRDs).

Several sensitivity analyses were performed to assess the robustness of the primary findings: (1) additional adjustment for baseline neuroimaging modality (NCCT alone, MRI alone, or NCCT plus MRI) in the propensity score model; (2) exclusion of patients with lacunar and isolated PCA-territory infarcts to address potential OXVASC-related misclassification; (3) propensity score matching using 1:2 (PCI:ACI) nearest-neighbor matching; and (4) interaction analyses according to baseline anticoagulant class (VKA versus DOAC).

No formal sample-size calculation was performed, as all eligible patients enrolled during the study period were included. Analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria), and two-sided p values <0.05 were considered statistically significant.

3. Results

A total of 1649 patients (mean age of 78.0 ± 10.7 years, 47.8% males) were included in the analysis, of whom 165 (10.0%) had PCI. The study flow-chart with number of excluded patients is reported in Fig. 1. At least a brain neuroimaging exam was performed in all patients at baseline (brain NCCT 89.1%, brain MRI 7.0%, both 3.9%). Similarly, all patients underwent at least a brain vessels imaging exam (CTA 81.9%, MRA 10.9%, CDU 26.1%, DSA 44.6%) with no significant between-group differences in imaging modality distribution (SMDunw = 0.048).

3.1. Characteristics of patients with posterior versus anterior circulation breakthrough stroke

According to the OXVASC classification, patients with PCI were almost exclusively categorized as POCS (98.8%), with LACI representing the remaining 1.2%. In contrast, ACI patients were predominantly classified as PACI (60.6%), followed by TACI (31.7%) and LACI (7.7%). In the unweighted cohort, large vessel occlusion was less frequent among patients with PCI than among those with ACI (33.3% vs 57.7%;

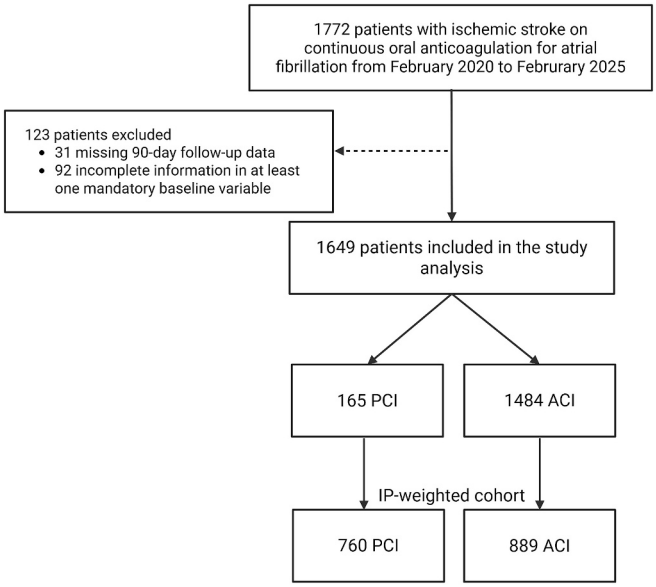

Fig. 1. Study flow-chart. Abbreviations. ACI: anterior circulation infarct; IP: inverse-probability; PCI: posterior circulation infarct.

unweighted standardized mean difference [SMDunw] =0.51). In PCI patients, occlusions most commonly involved the basilar artery (49.1%), whereas in ACI patients they predominantly affected the M1 segment of the middle cerebral artery (46.6%). Moreover, patients with PCI were more often on VKA at the time of breakthrough stroke (29.7% versus 21.9%; SMDunw = 0.18) and had lower median NIHSS scores on admission (5, IQR 2–10 versus 11, IQR 5–18; SMDunw =0.66). Vascular risk factors were similar between groups, except for a modestly lower prevalence of congestive heart failure in PCI compared with ACI (12.7% vs 17.3%; SMDunw = 0.12). Post-stroke secondary prevention strategies also differed between groups. A lower proportion of PCI patients switched to a different DOAC after the index event compared with ACI patients (24.8% vs 29.8%; SMDunw = 0.23). Moreover, the mean time to anticoagulation resumption after the index stroke was shorter in PCI than in ACI patients (6.8 ± 6.8 vs 8.1 ± 9.1 days; SMDunw = 0.18) (Table 1).

3.2. Inverse-probability weighting

The inverse-probability weighted pseudo-population corresponded to 760 patients with PCI and 889 with ACI (weighted sample size). There was no missing data in all variables used in the propensity model, and balance diagnostics indicated excellent performance: the standardized mean difference of the propensity score was 0.12 (<0.25) and the variance ratio was 0.92 (acceptable 0.5–2) [13]. Visual inspection of propensity scores' density overlap between groups and covariate balance confirmed the adequacy of weighting (**Fig. S1 and S2**). Weight diagnostics are reported in **Table S1**. Most weighted SMDs were < 0.10 across baseline characteristics except for NIHSS on admission (Table 1).

3.3. Primary outcome

The composite outcome occurred in 27 (16.4%) patients with PCI and in 251 (16.9%) with ACI in the unweighted cohort, with no significant difference (HR 0.96, 95% CI 0.64–1.42; $p = 0.826$) (Table 2). In the weighted cohort, the 90-day risk was 26.3% versus 14.8%, corresponding to a significantly higher risk in PCI (aHR 1.50, 95% CI 1.19–1.90; $p < 0.001$) (Table 2, Fig. 2).

3.4. Secondary outcomes

For the secondary outcomes, we observed a significantly higher 90-day risk of vascular death and all-cause death among patients with PCI compared with ACI in the weighted cohort (aHR 1.46, 95% CI 1.12–1.91; $p = 0.005$ and aHR 1.85, 95% CI 1.51–2.27; $p < 0.001$, respectively) (Table 2, Fig. 3). Additionally, PCI patients showed a shift toward greater disability both in the unweighted (aOR 1.47, 95% CI 1.12–1.92; $p = 0.006$) and weighted cohorts (aOR 1.79, 95% CI 1.51–2.13; $p < 0.001$) (Table 2, Fig. 4). A non-significant trend toward a higher risk of recurrent ischemic stroke was also observed in the weighted cohort (aHR 1.62, 95% CI 0.93–2.82; $p = 0.086$). In the Fine–Gray competing-risks analysis treating death as a competing event, no significant association was observed between PCI and stroke recurrence (subdistribution HR 1.12, 95% CI 0.61–2.07; $p = 0.718$) (**Fig. S3**). Other secondary outcomes did not significantly differ between patients with PCI and ACI.

3.5. Safety outcomes

For the safety outcomes, patients with PCI showed a significantly higher 90-day incidence of intracranial hemorrhage compared with those with ACI in the weighted cohort (2.6% versus 1.2%; aHR 2.25, 95% CI 1.08–4.70; $p = 0.031$) (Table 2, Fig. 5). In the Fine–Gray competing-risks analysis treating death as a competing event, PCI remained associated with a higher cumulative incidence of intracranial hemorrhage (subdistribution HR 8.44, 95% CI 4.24–16.77; $p < 0.001$)

Table 1
Baseline characteristics.

	Overall cohort (*n* = 1649)	PCI (*n* = 165)	ACI (*n* = 1484)	SMD unweighted	SMD weighted
Demographics					
Age (years), mean ± sd	78.0 ± 10.7	77.8 ± 10.1	78.4 ± 10.4	0.06	0.04
Sex – male, n (%)	789 (47.8)	83 (50.3)	777 (52.4)	0.04	0.00
Ethnicity, n (%)				0.07	0.06
Non-Hispanic White	1303 (79.0)	133 (80.6)	1170 (78.8)		
Hispanic White	113 (6.9)	11 (6.7)	102 (6.9)		
Black	24 (1.5)	5 (3.0)	19 (1.3)		
Asian	9 (0.5)	0 (0.0)	9 (0.6)		
Other	200 (12.1)	16 (9.7)	184 (12.4)		
Baseline oral anticoagulation characteristics					
Type of oral anticoagulation at the time of index stroke, n (%)				0.18	0.03
VKA	374 (22.7)	49 (29.7)	325 (21.9)		
DOAC	1275 (77.3)	116 (70.3)	1159 (78.1)		
Type of DOAC at the time of index stroke, n (%)				0.11	0.04
Apixaban	469/1275 (36.8)	49 (42.2)	420 (36.2)		
Rivaroxaban	428/1275 (33.6)	29 (25.0)	399 (34.3)		
Edoxaban	251/1275 (19.7)	18 (15.5)	233 (20.1)		
Dabigatran	127/1275 (10.0)	20 (17.2)	107 (9.2)		
Time from last DOAC intake to admission, n (%)				0.04	0.01
<12 h	653/1275 (51.2)	58 (50.0)	595 (51.3)		
12–24 h	471/1275 (36.9)	41 (35.3)	430 (37.1)		
24–48 h	151/1275 (11.9)	17 (14.7)	134 (11.6)		
INR on admission, mean ± sd	1.39 ± 0.54	1.41 ± 0.51	1.39 ± 0.55	0.04	0.03
On-label DOAC dosing on admission, n (%)	1094/1275 (85.8)	94/116 (81.0)	1000/1159 (86.2)	0.14	0.08
Clinical characteristics					
NIHSS on admission, median (IQR)	11 (5–18)	5 (2–10)	11 (5–18)	0.66	**0.12**
Pre-stroke mRS score category, n (%)					
No symptoms (score of 0), n (%)	814 (49.4)	92 (55.8)	722 (48.7)	0.08	0.05
Symptoms without any disability (score of 1), n (%)	369 (22.4)	23 (13.9)	346 (23.3)	0.12	

(*continued on next page*)

Table 1 (*continued*)

	Overall cohort (*n* = 1649)	PCI (*n* = 165)	ACI (*n* = 1484)	SMD unweighted	SMD weighted
Symptoms with mild disability (score of 2), n (%)	223 (13.5)	23 (13.9)	200 (13.5)	0.01	
Symptoms with mild-to-moderate disability (score of 3), n (%)	179 (10.9)	22 (13.3)	157 (10.6)	0.07	
Symptoms with moderate-to-severe disability (score of 4), n (%)	59 (3.6)	4 (2.4)	55 (3.7)	0.04	
Symptoms with severe disability (score of 5), n (%)	5 (0.3)	1 (0.6)	4 (0.3)	0.02	
Competing stroke etiology other than cardioembolism, n (%)	401 (24.3)	42 (25.5)	359 (24.2)	0.03	0.04
Type of competing stroke etiology, n (%)*				0.02	0.06
Small-vessel disease	70/401 (17.5)	7 (16.7)	63/359 (17.5)		
Large artery atherosclerosis	240/401 (59.9)	26 (61.9)	214/359 (59.6)		
Other determined etiology	60/401 (15.0)	6 (14.3)	54/359 (15.0)		
Combined competing etiology	31/401 (7.6)	3 (7.1)	28/359 (7.0)		
Large vessel occlusion, n (%)	912 (55.3)	55 (33.3)	857 (57.7)	0.51	0.10
Large vessel occlusion site, n (%)					
ICA	82 (0.9)	–	82/857 (9.6)	–	–
MCA – M1	399 (43.8)	–	399/857 (46.6)	–	–
MCA – M2	209 (22.9)	–	209/857 (24.4)	–	–
MCA – distal than M2	52 (5.7)	–	52/857 (6.1)	–	–
Tandem (ICA + M1)	97 (10.6)	–	97/857 (11.3)	–	–
ACA	18 (2.0)	–	18/857 (2.1)	–	–
VA	8 (0.9)	8/55 (14.5)	–	–	–
BA	27 (3.0)	27/55 (49.1)	–	–	–
PCA	20 (2.2)	20/55 (36.4)	–	–	–
Intravenous thrombolysis, n (%)	139 (8.4)	16 (9.7)	123 (8.3)	0.05	0.06
Endovascular thrombectomy, n (%)	732 (44.4)	37 (22.4)	695 (46.8)	0.53	0.05
Risk factors					
Arterial hypertension, n (%)†	1338 (81.1)	132 (80.0)	1206 (81.3)	0.04	0.03
Dyslipidemia, n (%)‡	845 (51.2)	88 (53.3)	757 (51.0)	0.05	0.04
Diabetes, n (%)§	443 (26.9)	39 (23.6)	404 (27.6)	0.05	0.03
Cigarette smoking, n (%)‖	154 (9.3)	12 (7.3)	142 (9.6)	0.03	0.09
Prior ischemic stroke or TIA, n (%)	410 (24.9)	39 (23.6)	371 (25)	0.03	0.06
Prior intracranial hemorrhage, n (%)	27 (1.6)	1 (0.6)	26 (1.8)	0.04	0.08
Ischemic heart disease, n (%)#	366 (22.2)	37 (22.4)	329 (22.2)	0.01	0.03
Chronic congestive heart failure, n (%)**	277 (16.8)	21 (12.7)	256 (17.3)	0.12	0.05
Chronic kidney disease, n (%)***	268 (16.3)	29 (17.6)	239 (16.1)	0.03	0.07
Chronic liver failure, n (%)****	7 (0.4)	0 (0.0)	7 (0.5)	0.02	0.04
Symptomatic peripheral artery disease, n (%)*****	80 (4.9)	10 (6.1)	70 (4.7)	0.03	0.09
Mechanical heart valve, n (%)	94 (5.7)	13 (7.9)	81 (5.5)	0.09	0.02
Biological heart valve, n (%)	81 (4.9)	10 (6.1)	71 (4.8)	0.02	0.01
Atrial fibrillation type, n (%)******				0.06	0.04
Paroxysmal	335 (20.3)	44 (26.7)	291 (19.6)		
Persistent	200 (12.1)	12 (7.3)	188 (12.7)		
Long-standing persistent	76 (4.6)	16 (9.7)	60 (4.0)		
Permanent	847 (51.4)	84 (50.9)	763 (51.4)		
Unknown	191 (11.6)	9 (5.5)	182 (12.3)		
History of cancer, n (%)	237 (14.4)	27 (16.4)	220 (14.8)	0.02	0.02
Antihypertensive drugs on admission, n (%)	1310 (79.4)	129 (78.2)	1181 (79.6)	0.03	0.09
Lipid-lowering drugs on admission, n (%)	742 (45.0)	82 (49.7)	660 (44.5)	0.10	0.08
Antidiabetic drugs on admission, n (%)	397 (24.1)	33 (20.0)	364 (24.5)	0.10	0.04
Antiplatelet therapy on admission, n (%)	131 (7.9)	11 (6.7)	120 (8.1)	0.05	0.09
Post-stroke secondary prevention					
Post-stroke anticoagulation strategy, n (%)				0.04	**0.15**
No anticoagulation restarted	179 (10.9)	14 (8.5)	165 (11.1)		
Same DOAC restarted	463 (28.1)	55 (33.3)	408 (27.4)		
Switch to different DOAC (anti-Xa ↔ anti-Xa / anti-IIa ↔ anti-IIa)	201 (12.2)	6 (3.6)	195 (13.1)		
Switch to different DOAC (anti-Xa ↔ anti-IIa)	283 (17.2)	35 (21.2)	248 (16.7)		
VKA → DOAC	112 (6.8)	19 (11.5)	93 (6.2)		

(*continued on next page*)

Table 1 (*continued*)

	Overall cohort (*n* = 1649)	PCI (*n* = 165)	ACI (*n* = 1484)	SMD unweighted	SMD weighted
VKA → VKA	179 (10.9)	21 (12.7)	158 (10.6)		
DOAC → VKA	59 (3.6)	3 (1.8)	56 (3.8)		
DOAC → LMWH	36 (2.2)	3 (1.8)	33 (2.2)		
VKA → LMWH	19 (1.2)	0 (0.0)	19 (1.3)		
Left atrial appendage closure	8 (0.5)	2 (1.2)	6 (0.4)		
Unknown	110 (6.7)	7 (4.2)	103 (6.9)		
Days from index stroke to anticoagulation restart, mean ± sd	8.1 ± 9.1	6.8 ± 6.8	8.3 ± 9.3	0.18	**0.20**
Anticoagulation discontinued during follow-up, n (%)	151/1360 (11.1)	19/144 (13.2)	132/1216 (10.9)	0.11	0.10
Post-stroke antihypertensive drugs, n (%)	1346 (81.7)	139 (84.2)	1207 (81.3)	0.08	0.09
Post-stroke lipid-lowering drugs, n (%)	1064 (64.5)	110 (66.7)	954 (64.3)	0.05	0.06
Post-stroke antidiabetic drugs, n (%)	535 (32.4)	35 (21.2)	352 (23.7)	0.06	0.05
Post-stroke antiplatelet therapy, n (%)	250 (15.2)	22 (13.3)	228 (15.4)	0.06	0.08

Abbreviations. ACA: anterior cerebral artery; ACI: anterior circulation infarct; BA: basilar artery; DOAC: direct oral anticoagulant; mRS: modified Rankin Scale; ICA: internal carotid artery; INR: international normalized ratio; IQR: interquartile range; MCA: middle cerebral artery; NIHSS: National Institute of Health Stroke Scale; sd: standard deviation; PCA: posterior cerebral artery; PCI: posterior circulation infarct; SMD: standardized mean difference; VA: vertebral artery; VKA: vitamin K antagonist. SMD >0.10 are reported in bold.*: Competing stroke etiology was classified according to the Trial of Org 10,172 in the Acute Stroke Treatment (TOAST) classification system; †: Arterial hypertension was defined as a history of blood pressure > 140/90 mmHg 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 mellitus 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 last 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 less than 60 for 3 months or more (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 ACC/AHA/HRS guidelines.

(Fig. S3). Given the earlier anticoagulation resumption observed in PCI patients, an exploratory analysis additionally adjusting for time to anticoagulation restart was performed. In this model, PCI remained associated with a numerically increased risk of intracranial hemorrhage (HR 2.68, 95% CI 0.81–8.87; $p = 0.106$), whereas time to anticoagulation restart was not independently associated with hemorrhagic risk (HR 1.03 per day, 95% CI 0.97–1.08; $p = 0.360$). Of note, in the original cohort intracranial hemorrhages occurred predominantly early after the index stroke (median 3 days, IQR 1–8) and generally preceded anticoagulation resumption (median restart time 13 days, IQR 6–27, among patients experiencing intracranial hemorrhage). Early hemorrhagic complications within the infarcted area were not significantly different between groups after weighting. At 24 h, hemorrhagic transformation occurred with similar frequency in PCI and ACI (adjusted risk difference − 0.4%, 95% CI −4.0% to 3.1%; $p = 0.824$). Likewise, 24-h symptomatic intracranial hemorrhage did not differ between groups (adjusted risk difference 0.0%, 95% CI −1.5% to 1.5%; $p = 0.995$) (Table 2).

3.6. Sensitivity analyses

Results were robust across multiple sensitivity analyses. After additional adjustment for baseline neuroimaging modality in the propensity score model, PCI remained associated with recurrent ischemic events, vascular death, all-cause mortality, and worse 90-day functional outcome (**Table S2).** Likewise, after excluding patients with lacunar infarcts and isolated PCA-territory strokes to minimize potential OXVASC-related misclassification, the main findings remained unchanged, with PCI continuing to be associated with a higher risk of adverse outcomes and worse functional status (**Table S3**). A 1:2 propensity score matching analysis yielded effect estimates that were directionally consistent with the primary IPW analysis, although attenuated and generally no longer statistically significant (**Fig. S4**, **Table S4**). Finally, no evidence of effect modification according to baseline anticoagulant class (VKA versus DOAC) was observed for any outcome (all interaction *p*-values >0.50; **Table S5**).

4. Discussion

In this large multicentre cohort of patients with AF experiencing breakthrough ischemic stroke despite ongoing oral anticoagulation, we identified differences in baseline characteristics between posterior and anterior circulation infarctions and found that infarct location was associated with distinct clinical outcomes. After inverse-probability weighting, posterior circulation infarction was associated with higher risks of adverse 90-day outcomes, including recurrent vascular events, mortality, disability, and intracranial hemorrhage. These findings support the prognostic relevance of infarct location in patients with breakthrough ischemic stroke and suggest that posterior and anterior circulation events may represent clinically heterogeneous subgroups warranting further investigation.

Within the unweighted cohort, patients with PCI exhibited lower NIHSS scores, fewer large vessel occlusions, and less frequent use of endovascular thrombectomy compared with ACI. Although this may suggest a milder clinical phenotype, such interpretation should be made cautiously, as the NIHSS is less sensitive to clinically relevant deficits typical of posterior circulation stroke. Accordingly, the lower apparent severity of PCI may be misleading and may not fully capture the true burden of ischemia. PCI was also more frequently associated with VKA therapy at stroke onset. This finding raises the possibility that posterior circulation breakthrough strokes may reflect a distinct pathophysiological profile. In particular, variability in anticoagulation intensity with VKA may predispose to the formation of larger or more embolic thrombi, which could preferentially reach the vertebrobasilar circulation due to anatomical and flow-related factors [14,15]. Moreover, PCI showed modest differences in post-stroke management, including slightly earlier resumption of anticoagulation. This shorter time to anticoagulation may reflect the lower perceived stroke severity or smaller infarct burden at presentation.

Despite the lower apparent clinical severity, in our inverse-probability weighted analysis, posterior circulation strokes were

Table 2
Outcomes comparison in the unweighted and weighted cohort.

	Unweighted cohort		Weighted cohort						
	PCI (n = 165)	ACI (n = 1484)	PCI (*n* = 760)	ACI (*n* = 889)	Statistical metric[§]	Unweighted difference [95% CI]	P value	Weighted difference [95% CI]	P value
Primary outcome									
90-day composite outcome	27 (16.4)	251 (16.9)	220 (26.3)	120 (14.8)	Hazard ratio	0.96 [0.64–1.42]	0.826	1.50 [1.19–1.90]	**<0.001**
Secondary outcomes									
90-day new ischemic stroke, n (%)	7 (4.2)	50 (3.4)	29 (3.8)	22 (2.4)	Hazard ratio	0.75 [0.44–1.29]	0.305	1.62 [0.93–2.82]	0.086
90-day myocardial infarction, n (%)	2 (1.2)	19 (1.3)	4 (1.5)	12 (1.3)	Hazard ratio	0.28 [0.08–1.02]	0.052	0.40 [0.13–1.25]	0.117
90-day vascular death, n (%)	18 (10.9)	197 (13.3)	118 (15.5)	99 (11.1)	Hazard ratio	0.81 [0.50–1.31]	0.381	1.46 [1.12–1.91]	**0.005**
90-day all-cause death, n (%)	32 (19.4)	302 (20.4)	222 (29.2)	154 (17.3)	Hazard ratio	0.93 [0.65–1.34]	0.703	1.85 [1.51–2.27]	**<0.001**
90-day mRS score distribution									
No symptoms (score of 0), n (%)	23 (13.9)	162 (10.9)	70 (9.2)	104 (11.7)					
Symptoms without any disability (score of 1), n (%)	32 (19.4)	252 (17.0)	109 (14.3)	157 (17.7)					
Symptoms with mild disability (score of 2), n (%)	28 (17.0)	213 (14.4)	119 (15.7)	141 (15.9)					
Symptoms with mild-to-moderate disability (score of 3), n (%)	27 (16.4)	242 (16.3)	113 (14.9)	149 (16.8)	Odds ratio			1.79 [1.51–2.13]	**<0.001**
Symptoms with moderate-to-severe disability (score of 4), n (%)	15 (9.1)	205 (13.8)	73 (9.6)	125 (14.1)		1.47 [1.12–1.92]	**0.006**		
Symptoms with severe disability (score of 5), n (%)	8 (4.8)	108 (7.3)	54 (7.1)	59 (6.6)					
Death (score of 6), n (%)	32 (19.4)	302 (20.4)	222 (29.2)	154 (17.3)					
Safety outcomes									
90-day intracranial hemorrhage, n (%)	5 (3.0)	24 (1.6)	20 (2.6)	11 (1.2)	Hazard ratio	1.86 [0.71–4.89]	0.205	2.25 [1.08–4.70]	**0.031**
24-h hemorrhagic transformation, n (%)	99 (11.8)	137 (16.9)	122 (16.1)	152 (17.1)	Risk difference (%)	−5.0 [−8.3 to −1.5]	**0.007**	−0.4 [−4.0 to 3.1]	0.824
24-h symptomatic intracranial hemorrhage, n (%)	3 (1.8)	38 (2.6)	19 (2.5)	24 (2.7)	Risk difference (%)	−1.2 [−2.7 to 0.2]	0.088	0.0 [−1.5 to 1.5]	0.995

Abbreviations. ACI = anterior circulation infarct; CI = confidence interval; PCI = posterior circulation infarct. Global Schoenfeld residuals p-values (weighted cohort): 90-day composite outcome = 0.890; 90-day ischemic stroke = 0.086; 90-day myocardial infarction = 0.120; 90-day vascular death = 0.050; 90-day all-cause death 0.511; 90-day intracranial hemorrhage = 0.330.§: All analyses in the weighted cohort were controlled for pre-stroke variables that remained imbalanced after weighting (SMD > 0.10), specifically NIHHS score on admission, and incorporated center-level clustering using robust variance estimators. Statistically significant p-values are reported in bold.

associated with a significantly increased risk of the composite endpoint at 90 days. Notably, the observed excess risk was driven primarily by mortality, whereas recurrent ischemic stroke showed only a modest, non-significant increase. The higher mortality observed in PCI is consistent with previous observational evidence indicating worse long-term outcomes in this subgroup. In a large prospective cohort from the Athens Stroke Registry, posterior circulation stroke was associated with substantial long-term mortality, with cumulative risks exceeding 50% at 10 years in specific topographic subtypes. Several mechanisms may account for these findings [16]. First, PCI may reflect a greater burden of systemic vascular disease, including diffuse atherosclerosis and impaired collateral capacity, which could predispose to fatal vascular events beyond the index stroke. Second, the involvement of brainstem structures, critical for autonomic and respiratory regulation, may confer a higher vulnerability to early clinical deterioration and death, even in the absence of high NIHSS scores. Third, the often subtle or atypical clinical presentation of posterior circulation stroke may lead to delays in recognition or differences in acute management, potentially influencing early outcomes. Of note, nearly half of posterior circulation large-vessel occlusions in our cohort involved the basilar artery. Given the poor prognosis traditionally associated with basilar artery occlusion, this subgroup may have contributed disproportionately to the excess mortality observed in PCI. Recent randomized trials, including the Basilar Artery International Cooperation Study (BASICS) [17] and the Basilar Artery Occlusion Chinese Endovascular Trial (BAOCHE) [18], have demonstrated the major influence of reperfusion strategies on outcomes in this setting, suggesting that differences in occlusion site and treatment responsiveness may partly contribute to the prognostic heterogeneity of posterior circulation stroke.

Furthermore, we observed a worse distribution of 90-day mRS scores in patients with posterior versus anterior circulation stroke, consistent with previous studies and in line with the higher mortality observed in this subgroup. Posterior circulation infarcts often involve brainstem, cerebellar, or thalamic structures, leading to disabling non-motor deficits such as ataxia, dysphagia, and oculomotor dysfunction, which may substantially impair functional independence even in the absence of significant motor weakness. This finding further highlight a mismatch between initial stroke severity and functional outcome, as the NIHSS underestimates posterior circulation deficits, whereas the mRS better captures their impact on daily functioning. In addition, delayed recognition, lower use of reperfusion therapies, and less tailored rehabilitation may further contribute to worse outcomes in this subgroup.

For the safety outcomes, patients with posterior circulation breakthrough stroke showed no significant differences in early hemorrhagic complications compared with anterior circulation strokes, with similar rates of both HT and sICH within the first 24 h. This finding contrasts with previous studies reporting a lower incidence of early hemorrhagic complications in PCI, often attributed to smaller infarct volumes, vertebrobasilar vascular anatomy, and a lower frequency of large vessel occlusions requiring aggressive reperfusion therapies [19]. However,

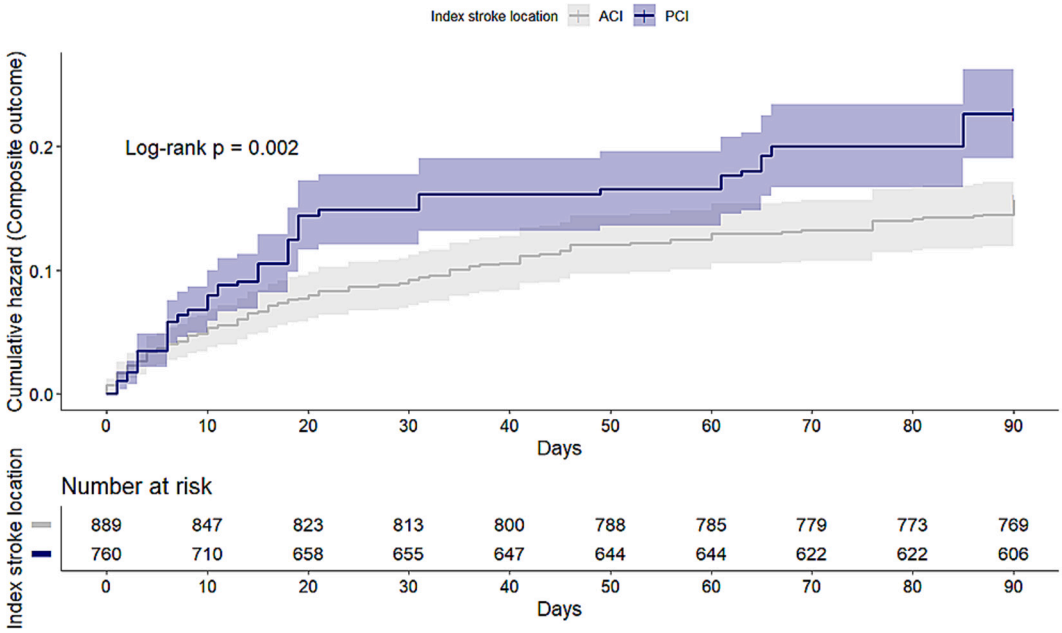

Fig. 2. Kaplan-Meier cumulative hazard curve of 90-day composite outcome. Abbreviations. ACI: anterior circulation infarct; PCI: posterior circulation infarct. P value indicates log-rank test statistical significance. Dashed areas indicate 95% confidence interval.

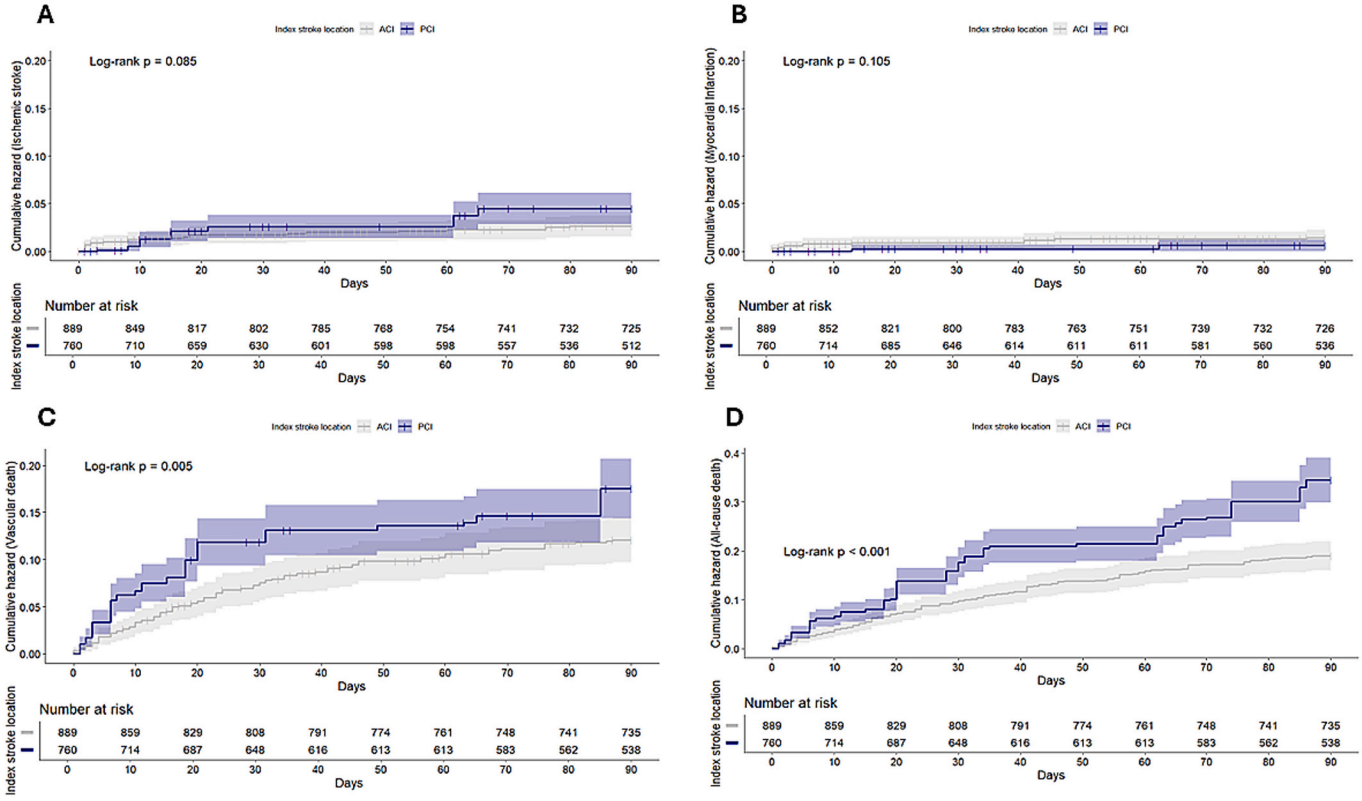

Fig. 3. Kaplan-Meier cumulative hazard curve of 90-day A) ischemic stroke, B) myocardial infarction, C) vascular death, D) all-cause death. Abbreviations. ACI: anterior circulation infarct; PCI: posterior circulation infarct. P value indicates log-rank test statistical significance. Dashed areas indicate 95% confidence interval.

our cohort included exclusively patients with breakthrough stroke, a population characterized by a distinct bleeding risk profile [18], and our inverse-probability weighting may have attenuated baseline imbalances and reduced apparent differences between groups. Despite comparable early bleeding risk, PCI was associated with a higher risk of intracranial hemorrhage during follow-up. This finding should be interpreted cautiously given the limited number of hemorrhagic events. However, the association persisted after accounting for time to anticoagulation resumption, while restart timing itself was not independently associated with hemorrhagic risk. Furthermore, most intracranial hemorrhages occurred early after the index stroke, whereas anticoagulation was typically resumed later, suggesting that differences in anticoagulation

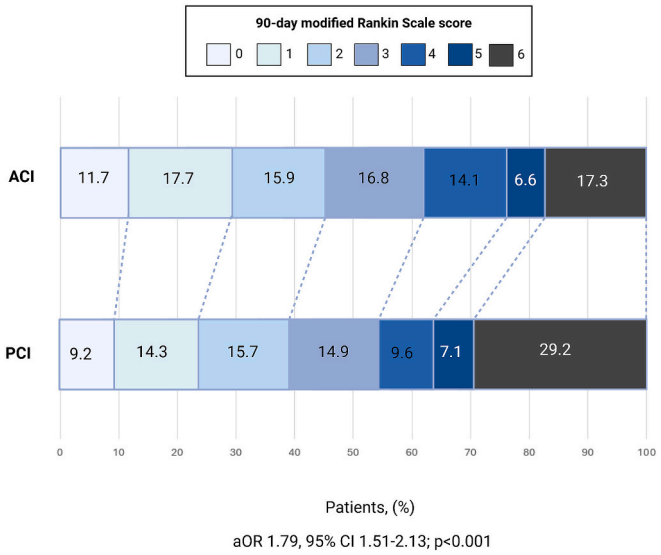

Fig. 4. 90-day modified Rankin Scale (mRS) scores distribution. Abbreviations. ACI: anterior circulation infarct; CI: confidence interval; PCI: posterior circulation infarct. aOR: adjusted odds ratio.

management alone are unlikely to fully explain the observed association.

The robustness of our estimates was supported by multiple sensitivity analyses. The observed associations remained largely unchanged after accounting for baseline neuroimaging modality and after excluding patients most susceptible to OXVASC-related infarct-location misclassification. Likewise, no evidence of effect modification according to baseline anticoagulant class was observed. Importantly, a propensity score–matched analysis yielded effect estimates that were directionally consistent with those of the primary inverse-probability weighted analysis, although generally attenuated and no longer statistically significant, likely reflecting the reduced sample size and number of outcome events in the matched cohort.

Our study has some limitations. First, the retrospective design of the ASPERA-R cohort may introduce residual confounding despite we implemented a rigorous inverse-probability weighting with truncation of extreme weights to reduce the influence of outliers. Although the propensity model included a wide range of demographic and clinical variables, unmeasured confounders cannot be entirely excluded. Information on time in therapeutic range (TTR) was not available for VKA-treated patients, and DOAC plasma levels were not systematically collected, precluding assessment of the contribution of anticoagulation quality or intensity to the observed differences between PCI and ACI. In addition, MRI was not routinely performed across participating centers, and most patients (89.1%) underwent NCCT alone at baseline. Consequently, underrecognition of milder posterior circulation infarcts cannot be excluded and may partly explain the lower PCI prevalence observed in our cohort. However, a sensitivity analysis incorporating baseline neuroimaging modality into the propensity score model yielded similar results, suggesting that differential imaging ascertainment is unlikely to fully explain the observed associations. Finally, although baseline NIHSS was included in both the propensity score model and outcome analyses, residual confounding related to stroke severity cannot be entirely excluded, as NIHSS may underestimate the clinical severity of posterior circulation strokes. Third, management decisions, including the timing of anticoagulation resumption, were not standardized across participating centers and may reflect local clinical practice patterns. In addition, the limited number of intracranial hemorrhages reduced the precision of safety analyses and precluded reliable mediation analyses exploring the potential role of anticoagulation restart timing. Fourth, a small proportion of patients presented with multiple acute infarcts involving both anterior and posterior circulation territories. In these cases, classification was based on the predominant clinical syndrome according to OXVASC criteria. However, these cases represented only a very small fraction of the cohort (26/1649 patients, 1.5%) and are therefore unlikely to have influenced the overall findings. Fifth, anatomical variants such as fetal PCA configuration were not systematically collected. Consequently, some PCA-territory infarcts supplied by the internal carotid circulation, as well as lacunar infarcts involving posterior structures, may have been misclassified within the OXVASC framework. However, a sensitivity analysis excluding patients with lacunar and isolated PCA-territory stroke yielded results consistent with the primary analysis. Finally, although the multicentre design enhances

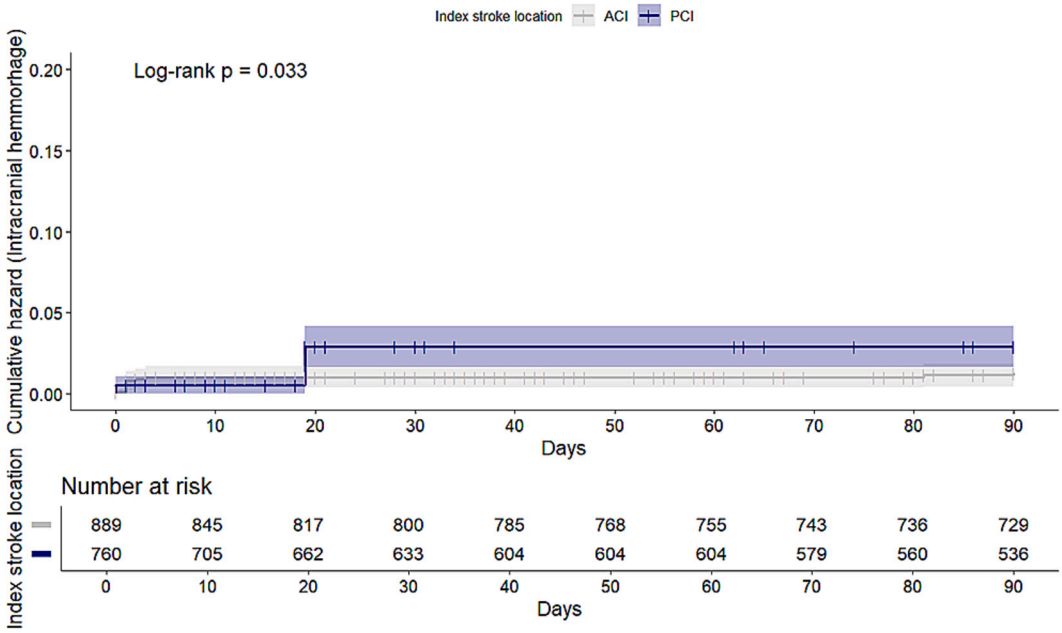

Fig. 5. Kaplan-Meier cumulative hazard curve of 90-day intracranial hemorrhage (ICH) Abbreviations. ACI: anterior circulation infarct; PCI: posterior circulation infarct. P value indicates log-rank test statistical significance. Dashed areas indicate 95% confidence interval.

generalizability, variations in diagnostic pathways and treatment strategies across centers could have influenced outcomes. Despite these limitations, our study has several strengths, including the large sample size, the international multicentre design with standardized data collection procedures and centralized data validation.

In conclusion, among patients with AF experiencing breakthrough ischemic stroke despite ongoing oral anticoagulation, PCI was associated with worse 90-day outcomes, including higher risks of mortality, disability, and intracranial hemorrhage during follow-up. These findings suggest that infarct location may provide additional prognostic information in this population and support the need for prospective studies to clarify the mechanisms underlying these outcome differences and their potential clinical implications.

Disclosures

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CRediT authorship contribution statement

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Appendix A. Supplementary data

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Data availability

The complete dataset used for this study will be shared upon request from any qualified researcher to the corresponding author.

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