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Changing or Retaining Direct Oral Anticoagulant After Ischemic Stroke Despite Direct Oral Anticoagulant Treatment

Shin-Yi Lin, MS*; Yun-Tsz Liao, MPH*; Sung-Chun Tang, MD, PhD; Ching-Ching Claire Lin, PhD; Chi-Chuan Wang, PhD

BACKGROUND: The optimal antithrombotic strategies for patients with atrial fibrillation who experience ischemic stroke (IS) despite direct oral anticoagulant (DOAC) therapy remain inconclusive. This study compared outcomes for patients with DOAC treatment failure who changed or retained their prestroke DOAC.

METHODS AND RESULTS: This retrospective cohort study analyzed data from the National Health Insurance Research Database from 2012 to 2020. Patients with atrial fibrillation who experienced IS during DOAC therapy were assigned to either (1) the DOAC-change group: changing prestroke DOAC or (2) the DOAC-retain group: retaining prestroke DOAC. The primary outcome was a composite of recurrent IS and transient ischemic attack. The secondary outcomes included intracranial hemorrhage, major bleeding, systemic thromboembolism, and all-cause death. Propensity score–based inverse probability of treatment weighting was applied to balance the baseline characteristics between the DOAC-change and DOAC-retain groups. The Cox proportional hazards model compared the risk of outcomes between the 2 groups. In total, 1979 patients were enrolled (609 DOAC-change patients and 1370 DOAC-retain patients). The incidence rates of recurrent IS or transient ischemic attack were 7.20 and 6.56 per 100 person-years in the DOAC-change and DOAC-retain groups, respectively (hazard ratio [HR], 1.07 [95% CI, 0.87–1.30]). A nonsignificantly higher incidence rate of intracranial hemorrhage was observed in the DOAC-change group compared with the DOAC-retain group (0.75 versus 0.53 per 100-person-years; HR, 1.49 [95% CI, 0.78–2.83]). The systemic thromboembolism, major bleeding, and death rates were comparable between the DOAC-change and DOAC-retain groups.

CONCLUSIONS: Changing prestroke DOAC does not reduce the risk of recurrent cerebral ischemia in patients with atrial fibrillation who develop IS during DOAC therapy. However, future studies should continue to observe the potential trends of increased intracranial hemorrhage risk.

Key Words: atrial fibrillation ■ changing DOAC ■ direct oral anticoagulant ■ ischemic stroke

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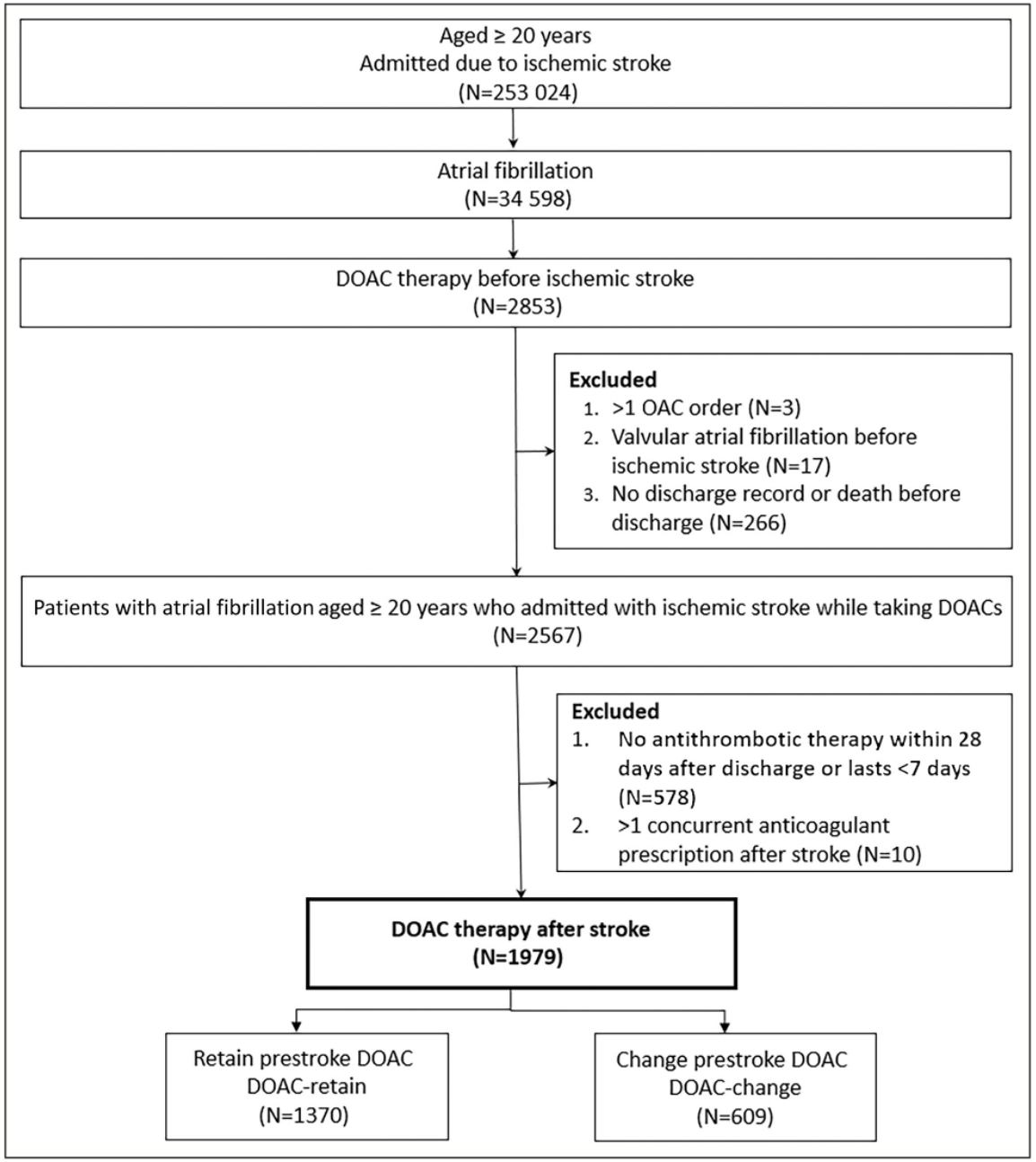

Figure 1. The process of study sample selection.
DOAC indicates direct oral anticoagulant; and OAC, oral anticoagulant.

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Table 1. Baseline Characteristics of Patients with Changed and Retained Pre-stroke DOAC

Characteristics	Before IPTW			After IPTW		
	Change prestroke DOAC (N=609)	Retain prestroke DOAC (N=1370)	SMD	Change prestroke DOAC (N=1980.01)	Retain prestroke DOAC (N=1978.69)	SMD
Age (years), mean (SD)	77.15 (9.47)	77.47 (9.26)		77.00 (17.08)	77.57 (11.12)	
≥65	558 (91.63%)	1,252 (91.39%)	0.009	1,822 (92.01%)	1,811 (91.54%)	0.017
Sex, male	314 (51.56%)	726 (52.99%)	0.029	1,047 (52.89%)	1,040 (52.56%)	0.007
CHA_2DS_2-VASc score, mean (SD)	3.86 (1.44)	3.85 (1.46)		3.82 (2.64)	3.86 (1.74)	
≥3	514 (84.40%)	1,130 (82.48%)	0.052	1,637 (82.65%)	1,643 (83.04%)	0.011
HAS-BLED score, mean (SD)	2.64 (1.07)	2.66 (1.03)		2.64 (1.91)	2.65 (1.23)	
≥3	331 (54.35%)	763 (55.69%)	0.027	1,081 (54.60%)	1,090 (55.10%)	0.010
Stroke severity index, mean (SD)	10.76 (6.42)	8.23 (5.61)		9.09 (10.97)	8.94 (7.10)	
≤5	222 (36.45%)	733 (53.50%)	**0.348**	957 (48.31%)	955 (48.27%)	0.001
>5 to ≤12	119 (19.54%)	287 (20.95%)	0.035	406 (20.48%)	406 (20.52)	0.001
>12	268 (44.01%)	350 (25.55%)	**0.395**	618 (31.21%)	618 (31.21%)	0.000
Comorbidities						
Congestive heart failure	190 (31.20%)	419 (30.58%)	0.013	596 (30.08%)	607 (30.66%)	0.013
Coronary artery disease	171 (28.08%)	391 (28.54)	0.010	581 (29.33%)	566 (28.60%)	0.016
Ischemic stroke	98 (16.09%)	243 (17.74%)	0.044	341 (17.22%)	342 (17.27%)	0.001
Hypertension	409 (67.16%)	908 (66.28%)	0.019	1,303 (65.79%)	1,314 (66.40%)	0.013
Diabetes mellitus	192 (31.53%)	428 (31.24%)	0.006	613 (30.97%)	620 (31.35%)	0.008
Renal disease	55 (9.03%)	125 (9.12%)	0.003	183 (9.22%)	181 (9.13%)	0.003
Venous thromboembolism	13 (2.13%)	19 (1.39%)	0.057	31 (1.58%)	32 (1.60%)	0.001
Intracranial hemorrhage	7 (1.15%)	17 (1.24%)	0.008	28 (1.41%)	25 (1.24%)	0.015
Gastrointestinal bleeding	35 (5.75%)	78 (5.69%)	0.002	112 (5.66%)	112 (5.68%)	0.001
Baseline medication history						
Agents acting on the renin-angiotensin system	397 (65.19%)	882 (64.38%)	0.017	1,282 (64.75%)	1,278 (64.56%)	0.004
Antiarrhythmics	187 (30.71%)	464 (33.87%)	0.068	649 (32.75%)	651 (32.88%)	0.003
Beta blockers	408 (67.00%)	845 (61.68%)	**0.111**	1,251 (63.17%)	1,253 (63.30%)	0.003
Calcium channel blockers	280 (45.98%)	630 (45.99%)	0.000	905 (45.69%)	909 (45.93%)	0.005
Digitalis glycosides	119 (19.54%)	258 (18.83%)	0.018	370 (18.67%)	376 (19.00%)	0.008
Antiepileptic drugs	18 (2.96%)	56 (4.09%)	0.061	74 (3.72%)	74 (3.72%)	0.000
HMG-CoA reductase inhibitors	214 (35.14%)	471 (34.38%)	0.016	685 (34.59%)	686 (34.66%)	0.001
NSAIDs	319 (52.38%)	716 (52.26%)	0.002	1,025 (51.76%)	1,031 (52.11%)	0.007
Proton pump inhibitors	80 (13.14%)	176 (12.85%)	0.009	263 (13.27%)	257 (12.99%)	0.008

Bold value indicates significant difference between the DOAC-change and DOAC-retain groups.

DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; and SMD, standardized mean difference.

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Table 2. Number of Events and Incidence Rates of Outcomes in Patients With Changed and Retained Prestroke DOAC (As-Treated Analysis)

	Number of events		Person-years		Follow-up years, median (IQR)		Incidence rates (per 100 person-years)			
							Before IPTW		After IPTW	
	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain	DOAC-change	DOAC-retain
Primary outcome										
Recurrent IS and TIA	60	131	839.25	2072.01	1.09 (0.28–1.98)	1.12 (0.35–2.24)	7.15	6.32	7.20	6.56
Secondary outcome										
Effectiveness										
STE	82	175	828.35	2022.78	1.08 (0.28–1.97)	1.07 (0.32–2.18)	9.90	8.65	10.20	8.84
Safety										
ICH	6	10	883.89	2185.58	1.13 (0.33–2.07)	1.19 (0.39–2.33)	0.68	0.46	0.75	0.53
Major bleeding	28	62	867.36	2133.76	1.11 (0.32–2.04)	1.16 (0.38–2.27)	3.23	2.91	2.82	2.93
All-cause death	87	158	886.51	2190.95	1.13 (0.39–2.33)	1.19 (0.33–2.07)	9.81	7.21	8.57	7.76

DOAC indicates direct oral anticoagulant; ICH, intracranial hemorrhage; IPTW, inverse probability of treatment weighting; IQR, interquartile range; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

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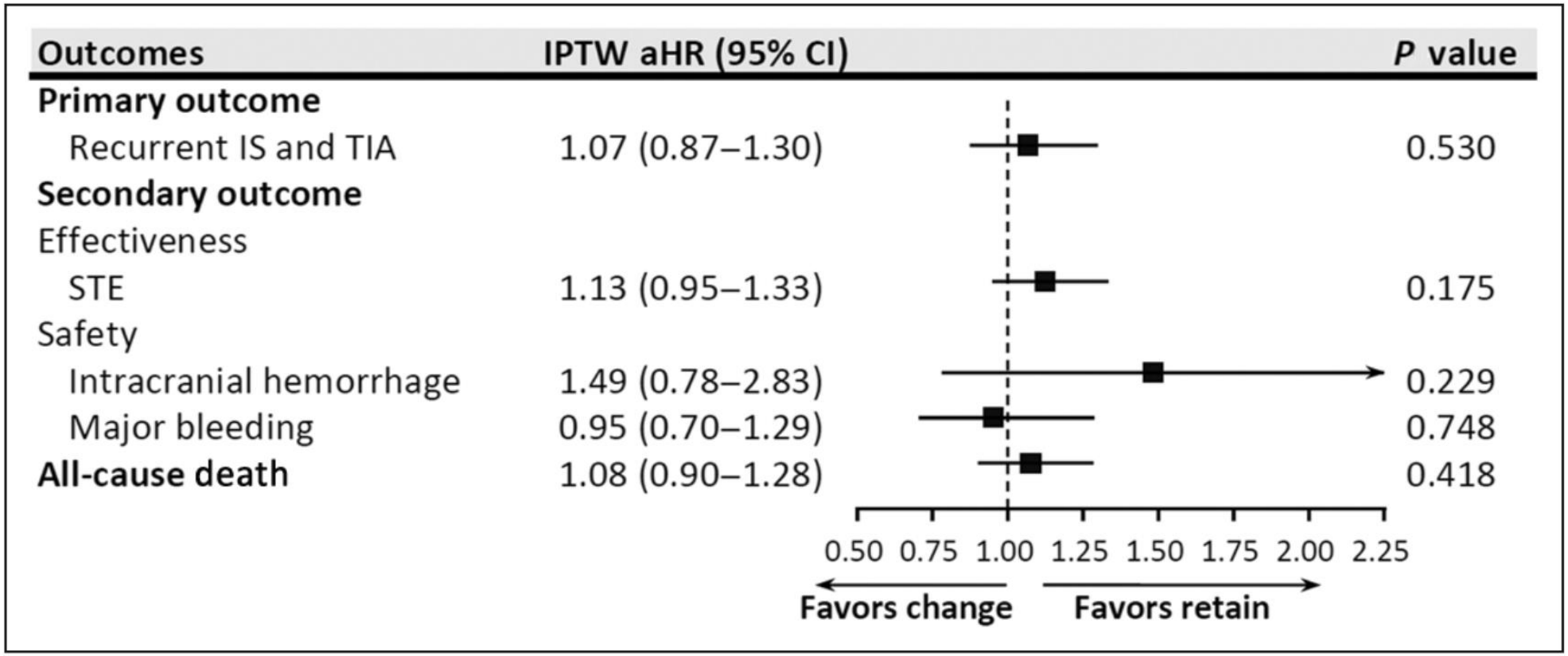

Figure 2. Hazard ratio for outcomes of patients with changed and retained prestroke direct oral anticoagulant prescription.
aHR indicates adjusted hazard ratio; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

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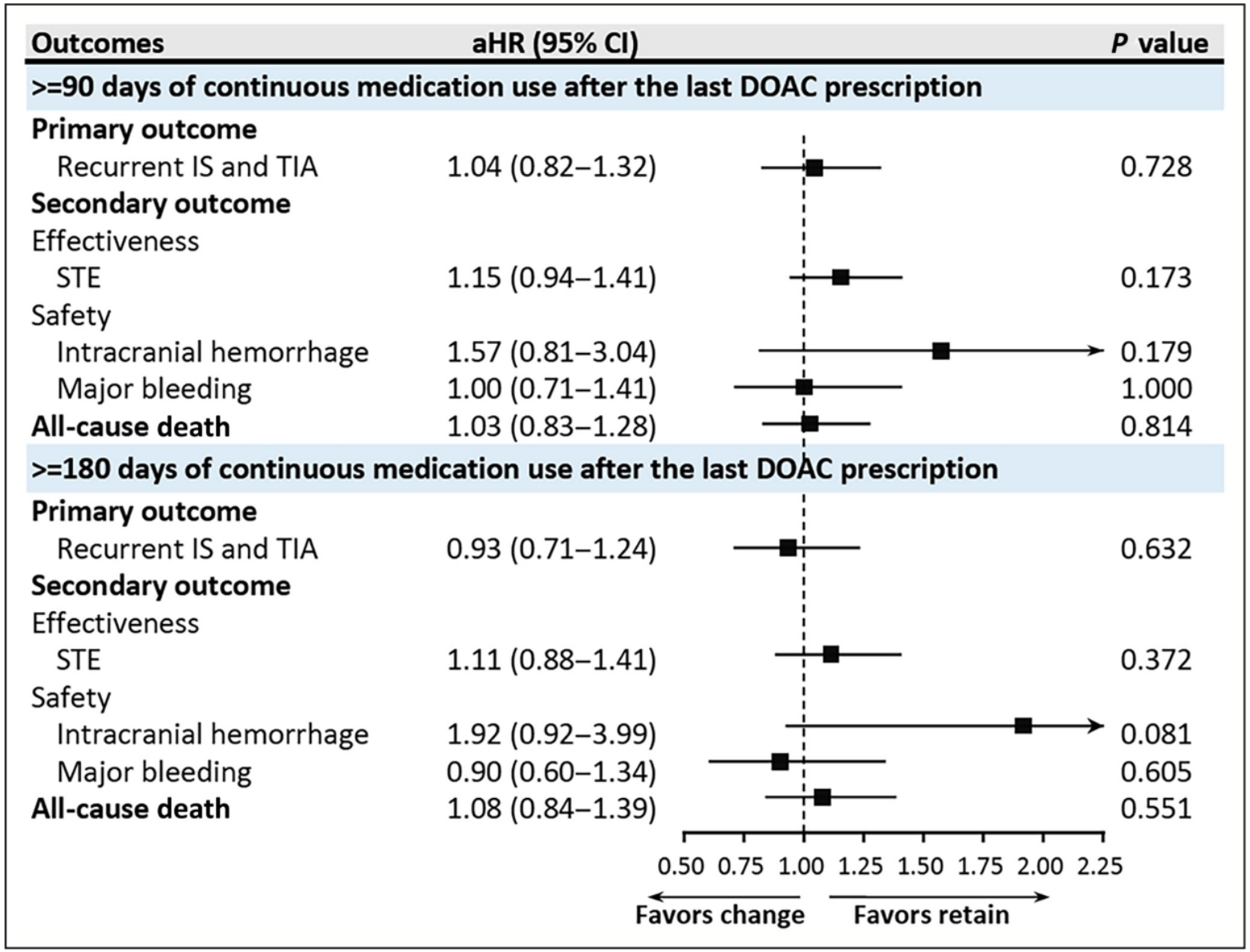

Figure 3. Hazard ratios for outcomes in patients with changed and retained prestroke DOAC (≥90 and ≥180 days of continuous medication use after the last DOAC prescription).

aHR, adjusted hazard ratio; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

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CLINICAL PERSPECTIVE

What Is New?

- Changing a prestroke direct oral anticoagulant (DOAC) does not reduce the risk of recurrent cerebral ischemia in patients with atrial fibrillation who develop ischemic stroke during DOAC therapy.
- Instead, a potential trend of increased intracranial hemorrhage risk was observed among patients whose prestroke DOAC was changed.

What Are the Clinical Implications?

- The type of DOAC might not be the underlying cause of treatment failure. Prescribing an on-label DOAC regimen or improving DOAC adherence is more important.
- Monitoring of the potential risk of intracranial hemorrhage is crucial when considering a change of prestroke DOAC.