

Supplementary Table 5. Interaction effects between treatment modalities and different patient enroll periods in the overall and high-risk PFO population

Outcomes	Overall population							P for interaction effect
	HR (95% CI)	P	Index stroke year <2016		Index stroke year ≥2016			
			HR (95% CI)	P	HR (95% CI)	P		
Primary outcome								
Ischemic stroke or TIA	0.45 (0.24–0.84)	0.012	0.54 (0.22–1.29)	0.164	0.32 (0.13–0.80)	0.014	0.422	
Secondary outcomes								
Death	0.40 (0.09–1.89)	0.247	NE	-	NE	-	-	
Ischemic stroke	0.58 (0.30–1.12)	0.107	0.66 (0.26–1.64)	0.367	0.43 (0.16–1.20)	0.107	0.557	
Ischemic stroke, TIA, or systemic embolization	0.47 (0.26–0.87)	0.017	0.59 (0.26–1.35)	0.212	0.32 (0.13–0.80)	0.014	0.333	
Intracranial bleeding	0.46 (0.12–1.77)	0.258	0.49 (0.05–4.60)	0.531	0.40 (0.04–4.54)	0.461	0.918	
Major bleeding	0.72 (0.27–1.90)	0.505	1.19 (0.33–4.34)	0.790	0.30 (0.06–1.56)	0.152	0.229	
Atrial fibrillation	1.97 (0.76–5.09)	0.162	2.25 (0.64–7.96)	0.209	1.55 (0.39–6.19)	0.538	0.688	
Outcomes	High-risk PFO population							P for interaction effect
	HR (95% CI)	P	Index stroke year <2016		Index stroke year ≥2016			
			HR (95% CI)	P	HR (95% CI)	P		
Primary outcome								
Ischemic stroke or TIA	0.40 (0.21–0.77)	0.006	0.45 (0.17–1.16)	0.097	0.31 (0.12–0.80)	0.016	0.583	
Secondary outcomes								
Death	0.55 (0.11–2.72)	0.461	NE	-	NE	-	-	
Ischemic stroke	0.47 (0.23–0.95)	0.035	0.50 (0.19–1.36)	0.176	0.37 (0.13–1.09)	0.072	0.698	
Ischemic stroke, TIA, or systemic embolization	0.42 (0.22–0.81)	0.009	0.50 (0.21–1.23)	0.131	0.31 (0.12–0.81)	0.016	0.462	
Intracranial bleeding	0.29 (0.05–1.59)	0.154	NE	-	NE	-	-	
Major bleeding	0.51 (0.17–1.54)	0.235	0.69 (0.13–3.57)	0.657	0.31 (0.06–1.67)	0.173	0.535	
Atrial fibrillation	2.31 (0.85–6.24)	0.099	2.16 (0.61–7.63)	0.234	2.47 (0.51–11.96)	0.261	0.892	

Hazard ratios are for the PFO closure group as compared with the medical therapy alone group. PFO, patent foramen ovale; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; NE, non-estimable.

Supplementary Table 6. Hazard ratios adjusted for the participating center effect in the propensity-score matched cohorts

	Overall cohort			High-risk PFO cohort		
	HR*	95% CI	P	HR*	95% CI	P
Primary outcome						
Ischemic stroke or TIA	0.37	0.21–0.96	0.005	0.33	0.16–0.71	0.004
Secondary outcome						
Death	0.41	0.08–1.97	0.264	0.55	0.11–2.86	0.479
Ischemic stroke	0.45	0.21–0.96	0.038	0.37	0.16–0.85	0.018
Ischemic stroke, TIA, or systemic embolization	0.39	0.20–0.77	0.007	0.36	0.18–0.75	0.006
Intracranial bleeding	0.42	0.08–2.23	0.310	0.27	0.03–2.42	0.241
Major bleeding	0.44	0.14–1.37	0.155	0.33	0.09–1.22	0.097
Atrial fibrillation	1.82	0.70–4.74	0.223	2.24	0.83–6.06	0.113

PFO, patent foramen ovale; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack. *Hazard ratios are for the PFO closure as compared with the medical therapy alone group. Cox proportional hazards regression with a shared frailty factor.