

Appendix Material

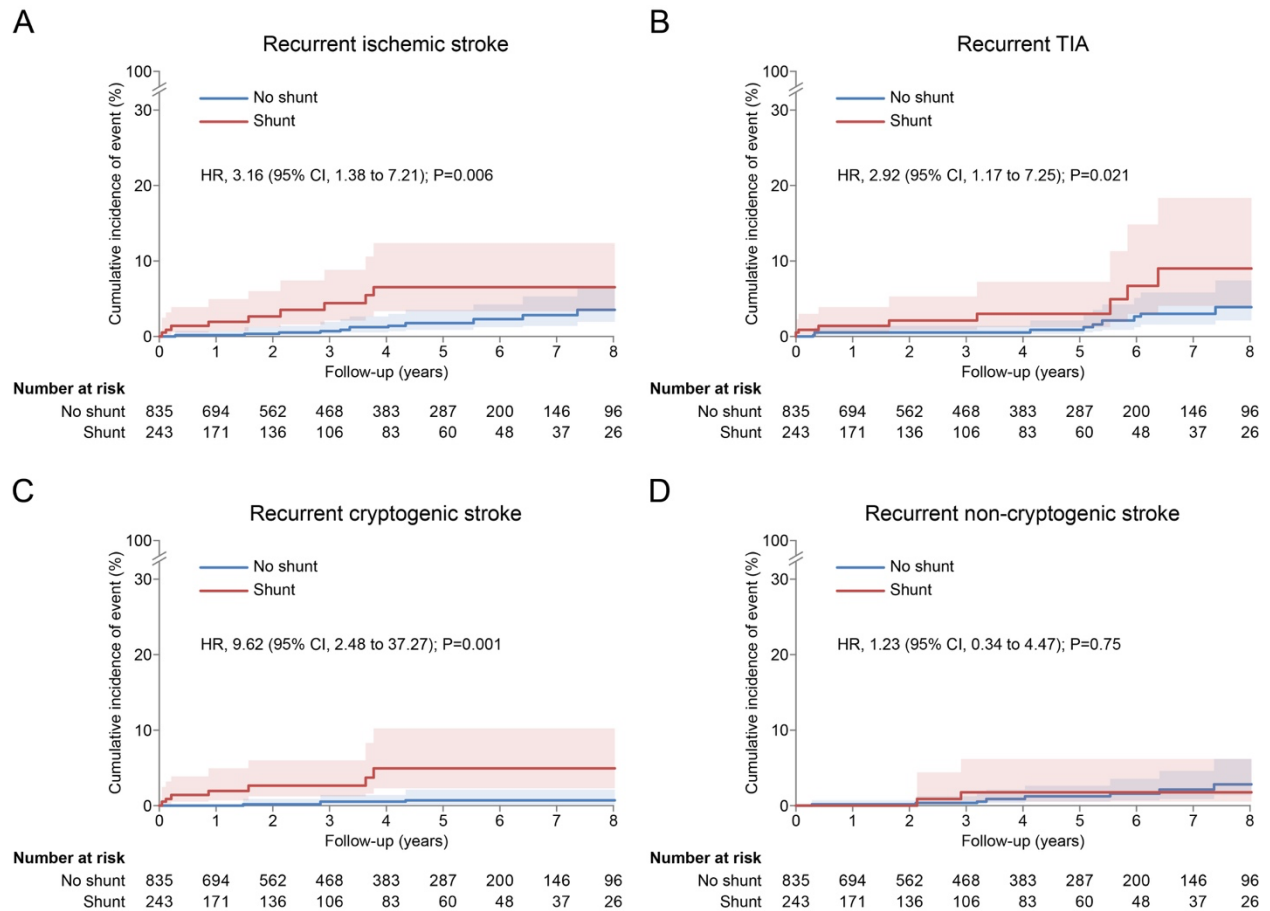
Deng W, Yin S, McMullin D, et al. Residual Shunt post Patent Foramen Ovale Closure and Long-term Stroke Recurrence: A Prospective Cohort Study

Appendix Methods

Transthoracic echocardiogram bubble study

Transthoracic echocardiogram (TTE) with agitated saline microbubbles was performed under a standardized protocol to evaluate residual shunt at rest and during Valsalva maneuver per American Society of Echocardiography guidelines. 9 mL of sterile saline and 1 mL of room air are agitated and injected as an intravenous bolus with cannula no less than 20 gauge. To ensure the effectiveness of Valsalva maneuver, the sonographer explained the Valsalva maneuver to the patient and had the patient do practice maneuvers prior to saline injection, which allowed the sonographer to be aware of, and adjust for, changes in views during the Valsalva maneuver. Effectiveness of Valsalva maneuver was determined by the visible increase in saline contrast on the right side of the heart with leftward bowing of the interatrial septum upon release of Valsalva. If this did not occur, the maneuver was reperformed until there was adequate opacification of the right atrium and leftward bowing of the septum. If the suspicion of residual shunt persisted despite negative echocardiographic studies, saline contrast injections were repeated to ensure that the negative results were true.

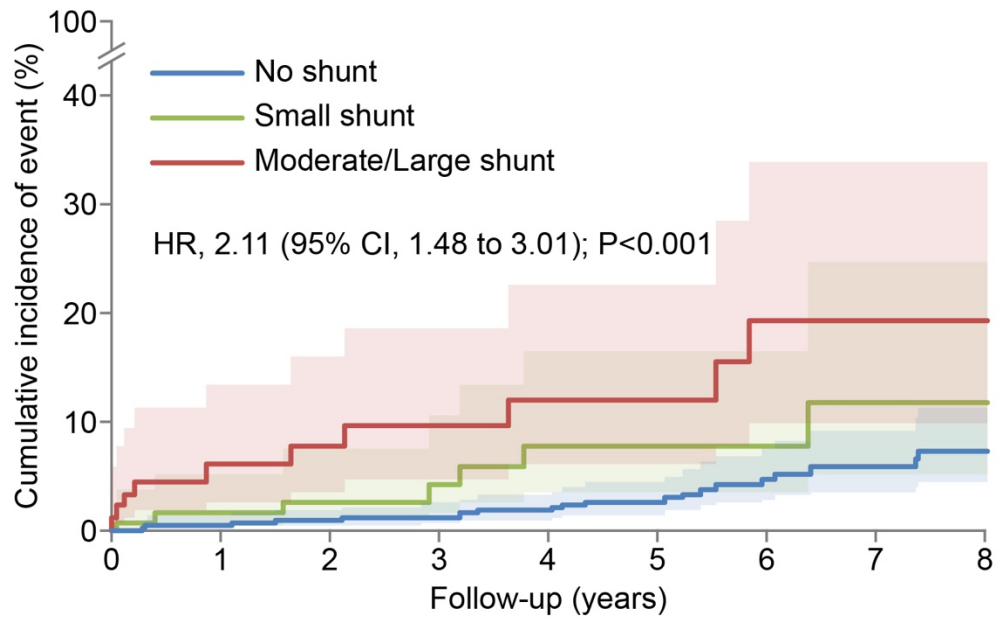
Appendix Figure 1.



Appendix Figure 1. Secondary outcome in patients with and without residual shunt post percutaneous PFO closure. Cumulative incidence of recurrent ischemic stroke (**A**), recurrent TIA (**B**), recurrent cryptogenic stroke (**C**) and recurrent non-cryptogenic stroke (**D**) in patients with and without shunt post closure. TIA = transient ischemic attack; HR = hazard ratio; CI = confidence interval.

Appendix Figure 2.

Recurrent ischemic stroke and TIA

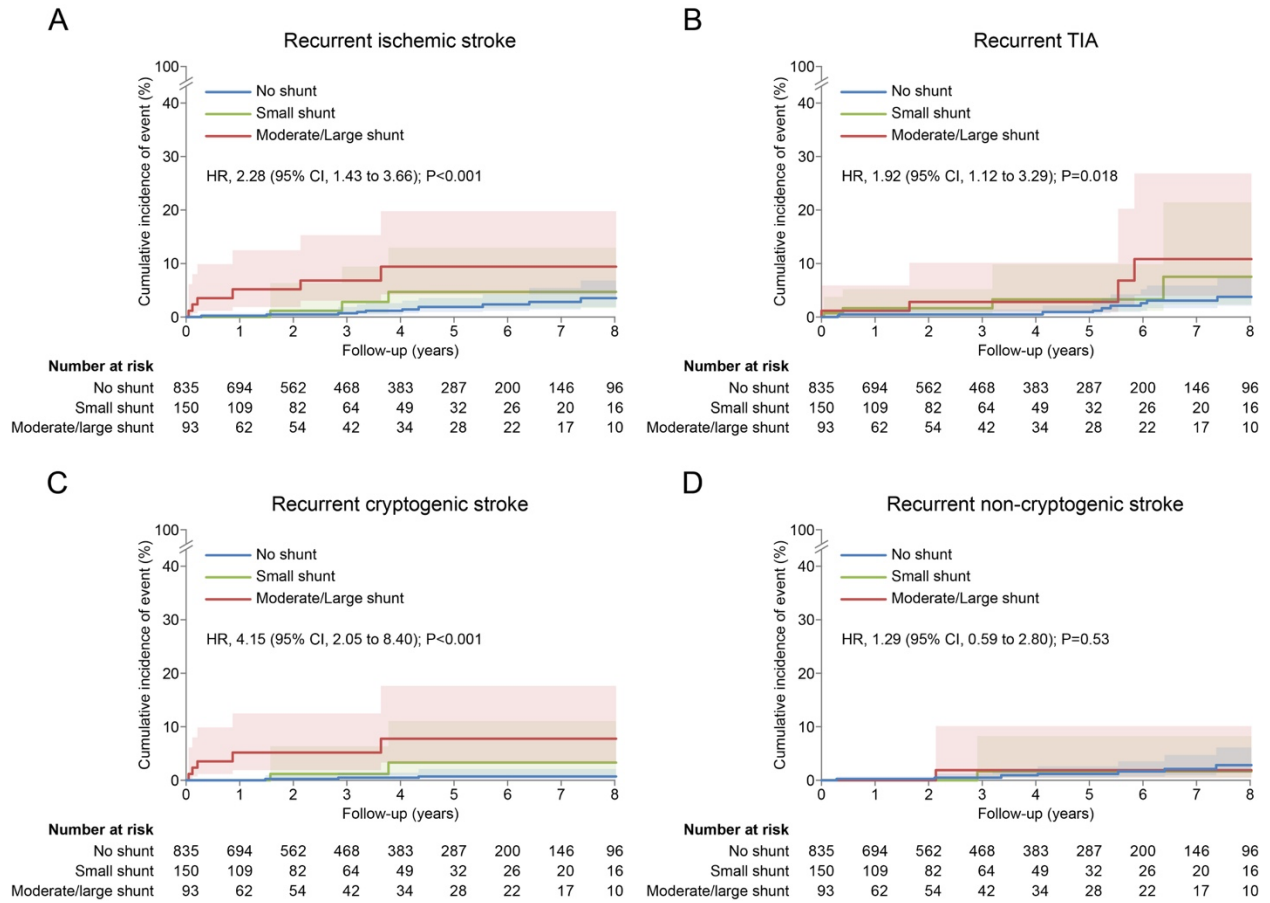


Number at risk									
No shunt	835	694	562	468	383	287	200	146	96
Small shunt	150	109	82	64	49	32	26	20	16
Moderate/large shunt	93	62	54	42	34	28	22	17	10

Appendix Figure 2. Primary outcome (composite stroke/TIA) by shunt size.

TIA = transient ischemic attack; HR = hazard ratio; CI = confidence interval.

Appendix Figure 3.



Appendix Figure 3. Secondary outcome by shunt size. Cumulative incidence of recurrent ischemic stroke (A), recurrent TIA (B), recurrent cryptogenic stroke (C) and recurrent non-cryptogenic stroke (D) in patients with different shunt sizes. TIA = transient ischemic attack; HR = hazard ratio; CI = confidence interval.

Appendix Table 1. Hypercoagulable state and device usage in patients with and without residual shunt.

Characteristic	Total (n=1078)	No shunt (n=835)	Shunt (n=243)
Hypercoagulable state, n (%)			
Prothrombin gene mutation	28 (2.6)	25 (3.0)	3 (1.2)
Factor V Leiden	39 (3.6)	31 (3.7)	8 (3.3)
Protein C deficiency	30 (2.8)	26 (3.1)	4 (1.6)
Protein S deficiency	130 (12.1)	94 (11.3)	36 (14.8)
Antithrombin III deficiency	56 (5.2)	44 (5.3)	12 (4.9)
Antiphospholipid syndrome	172 (16.0)	143 (17.1)	29 (11.9)
Lipoprotein (a)	103 (9.6)	81 (9.7)	22 (9.1)
Hyperhomocysteinemia	81 (7.5)	58 (6.9)	23 (9.5)
Device, n (%)			
Amplatzer	700 (64.9)	563 (67.4)	137 (56.4)
STARFlex	225 (20.9)	175 (21.0)	50 (20.6)
HELEX	100 (9.3)	71 (8.5)	29 (11.9)
Sideris button	53 (4.9)	26 (3.1)	27 (11.1)

Appendix Table 2. The association of covariates with residual shunt and recurrent event.

Covariates	Residual shunt		Recurrent stroke/TIA	
	Odds Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Study period	0.71 (0.56-0.91)	0.007	0.79 (0.44-1.40)	0.41
Age	1.00 (0.99-1.01)	0.71	1.01 (0.99-1.04)	0.21
Gender	0.81 (0.61-1.08)	0.153	1.54 (0.83-2.87)	0.174
Device				
Amplatzer*	1.00		1.00	
STARFlex	1.17 (0.81-1.69)	0.39	0.72 (0.31-1.68)	0.45
HELEX	1.68 (1.05-2.69)	0.031	1.84 (0.64-5.34)	0.26
Sideris button	4.27 (2.41-7.55)	<0.001	2.36 (1.00-5.59)	0.051
Hypercoagulability	0.90 (0.67-1.20)	0.47	1.05 (0.57-1.94)	0.86
Atrial septal aneurysm	1.28 (0.94-1.75)	0.116	0.78 (0.38-1.59)	0.50
Hypermobile septum	1.32 (0.95-1.83)	0.095	1.51 (0.81-2.83)	0.197
Hypertension	0.84 (0.60-1.17)	0.30	1.56 (0.83-2.92)	0.171
Hyperlipidemia	0.78 (0.56-1.08)	0.131	1.81 (0.99-3.32)	0.055
Diabetes	1.23 (0.70-2.19)	0.47	2.75 (1.16-6.54)	0.022
Aspirin	1.63 (0.84-3.16)	0.145	1.66 (0.40-6.88)	0.48
Clopidogrel	0.72 (0.42-1.24)	0.24	1.83 (0.81-4.12)	0.145
Warfarin	0.97 (0.78-1.22)	0.82	0.85 (0.52-1.39)	0.51

* Reference category.

Appendix Table 3. Sensitivity analysis for differential follow-up

Outcomes*	Original analysis		Sensitivity analysis‡	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Recurrent ischemic stroke/TIA	3.05 (1.65-5.62)	<0.001	2.53 (1.37-4.67)	0.003
Ischemic stroke	3.16 (1.38-7.21)	0.006	2.57 (1.12-5.87)	0.025
Cryptogenic†	9.62 (2.48-37.27)	0.001	8.02 (2.07-31.04)	0.003
Non-cryptogenic†	1.23 (0.34-4.47)	0.75	0.98 (0.27-3.55)	0.97
Transient ischemic attack	2.92 (1.17-7.25)	0.021	2.49 (1.00-6.20)	0.049

CI = confidence interval; TIA = transient ischemic attack.

* Outcomes are the first event occurred in the patients post PFO closure.

† Recurrent ischemic strokes were adjudicated as “cryptogenic” and “non-cryptogenic” according to TOAST criteria.

‡ Sensitivity analysis was performed by simulating an additional event-free year for patients lost to follow-up in shunt group.

Appendix Table 4. Residual shunt rate over time.

Shunt size	24 hr	1 m	6 m	1 yr	2 yr	3 yr	4 yr	5 yr
No shunt	53.5%	64.0%	70.5%	80.2%	83.0%	86.4%	88.5%	88.9%
Small shunt	31.4%	24.8%	21.2%	12.6%	11.7%	8.4%	6.3%	6.3%
Moderate/large shunt	15.0%	11.1%	8.3%	7.2%	5.4%	5.2%	5.2%	4.8%

Appendix Table 5. Residual shunt and recurrent event by study period.

Study period	Total number of patients	No shunt, n (%)	Shunt, n (%)		Events	Event rate per 100 patient-years
			Small shunt	Moderate/large shunt		
1995~2002	134	87 (64.9)	32 (23.9)	15 (11.2)	9	1.38
2003~2010	696	551 (79.2)	83 (11.9)	62 (8.9)	29	1.02
2011~2017	248	197 (79.4)	35 (14.1)	16 (6.5)	4	0.79

Appendix Table 6. Primary and secondary outcomes by shunt size.

Shunt size	Outcomes		Unadjusted		Adjusted [‡]	
	Events	Event rate per 100 patient-years	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
<i>Primary outcome (the composite of recurrent ischemic stroke and TIA)</i>						
Overall	42	1.05	2.11 (1.48-3.01)	<0.001	2.06 (1.43-2.96)	<0.001
No shunt*	24	0.75	1.00		1.00	
Small shunt	7	1.52	2.02 (0.87-4.69)	0.102	1.90 (0.80-4.49)	0.146
Moderate/large shunt	11	3.49	4.50 (2.20-9.20)	<0.001	4.28 (2.07-8.88)	<0.001
<i>Ischemic stroke</i>						
Overall	23	0.58	2.28 (1.43-3.66)	<0.001	2.23 (1.37-3.62)	0.001
No shunt*	13	0.40	1.00		1.00	
Small shunt	3	0.65	1.60 (0.46-5.62)	0.46	1.49 (0.41-5.38)	0.54
Moderate/large shunt	7	2.22	5.42 (2.16-13.6)	<0.001	5.12 (2.00-13.15)	<0.001
<i>Cryptogenic stroke[†]</i>						
Overall	10	0.25	4.15 (2.05-8.40)	<0.001	4.26 (2.09-8.72)	<0.001
No shunt*	3	0.09	1.00		1.00	
Small shunt	2	0.44	4.54 (0.76-27.20)	0.098	4.82 (0.79-29.55)	0.089
Moderate/large shunt	5	1.59	17.39 (4.15-72.80)	<0.001	18.42 (4.28-79.17)	<0.001
<i>Non-cryptogenic stroke[†]</i>						
Overall	13	0.33	1.29 (0.59-2.80)	0.53	1.16 (0.51-2.63)	0.72
No shunt*	10	0.31	1.00		1.00	
Small shunt	1	0.22	0.70 (0.09-5.51)	0.74	0.56 (0.07-4.56)	0.58
Moderate/large shunt	2	0.63	1.96 (0.43-8.95)	0.39	1.63 (0.34-7.76)	0.54
<i>Transient ischemic attack</i>						
Overall	19	0.48	1.92 (1.12-3.29)	0.018	1.87 (1.08-3.25)	0.027
No shunt*	11	0.34	1.00		1.00	
Small shunt	4	0.87	2.51 (0.80-7.90)	0.115	2.38 (0.73-7.71)	0.149
Moderate/large shunt	4	1.27	3.47 (1.10-10.90)	0.033	3.33 (1.04-10.64)	0.043

CI = confidence interval; TIA = transient ischemic attack

* Reference category.

† Recurrent ischemic strokes were adjudicated as “cryptogenic” and “non-cryptogenic” according to TOAST criteria.

‡ All values were adjusted for age, study period, device, the presence or absence of atrial septal aneurysm, hypertension, hyperlipidemia, diabetes, hypercoagulable status and hypermobile septum, as well as medication usage (aspirin, clopidogrel, warfarin) using propensity score method.

Appendix Table 7. Comparison between patients with small shunt and moderate/large shunt.

Characteristic	Small shunt (n=150)	Moderate/large shunt (n=93)	Odds Ratio (95% CI)	P Value
Age, mean (SD), y	47.1 (13.6)	52.2 (15.4)	1.02 (1.01-1.04)	0.009
Male sex, n (%)	75 (50.0)	48 (51.6)	1.07 (0.64-1.79)	0.81
Hypercoagulability, n (%)	61 (40.7)	40 (43.0)	1.10 (0.65-1.86)	0.72
Atrial septal aneurysm, n (%)	38 (25.3)	40 (43.0)	2.22 (1.28-3.86)	0.004
Hypermobility septum, n (%)	40 (26.7)	27 (29.0)	1.12 (0.63-2.00)	0.69
Hypertension, n (%)	22 (14.7)	36 (38.7)	3.67 (1.99-6.80)	<0.001
Hyperlipidemia, n (%)	31 (20.7)	31 (33.3)	1.92 (1.07-3.44)	0.029
Diabetes, n (%)	5 (3.3)	12 (12.9)	4.30 (1.46-12.63)	0.008
Aspirin, n (%)	143 (95.3)	89 (95.7)	1.09 (0.31-3.83)	0.89
Clopidogrel, n (%)	7 (4.7)	10 (10.8)	2.46 (0.90-6.71)	0.078
Warfarin, n (%)			1.22 (0.81-1.83)	0.35
Short-term	26 (17.3)	19 (20.4)		
Long-term	11 (7.3)	9 (9.7)		

SD = standard deviation; CI = confidence interval.

Appendix Table 8. Recurrent events over time.

	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	11 yr	Total
Event, n (%)	11 (26.2)	4 (9.5)	4 (9.5)	5 (11.9)	3 (7.1)	6 (14.3)	4 (9.5)	2 (4.8)	1 (2.4)	2 (4.8)	0 (0)	42