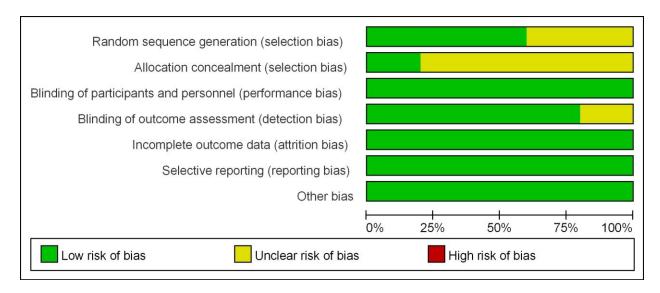
Supplementary Appendix

Supplementary Figures



Supplementary Figure 1. Risk of bias graph using the Cochrane Risk Assessment Tool.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CLOSE 2017	•	?	+	?	•	•	•
Closure I 2012	+	?	+	+	+	+	•
PC Trial 2013	+	+	+	+	+	+	+
REDUCE 2017	?	?	+	+	+	+	•
RESPECT 2017	?	?	+	+	+	+	+

Supplementary Figure 2. Risk of bias summary using the Cochrane Risk Assessment Tool.

Primary endpoint: sensitivity analysis

Study name	S	Statistics	with stu	udy remo	ved	Risk ratio (95% CI)							
	Point	Lower limit	Upper limit	Z-Value	p-Value		with study removed						
Closure I (2012)	0.51	0.36	0.71	-3.89	0.00								
PC Trial (2013)	0.58	0.43	0.78	-3.57	0.00								
CLOSE (2017)	0.60	0.45	0.80	-3.48	0.00								
RESPECT (2017)	0.57	0.41	0.80	-3.30	0.00								
REDUCE (2017)	0.68	0.48	0.97	-2.11	0.04								
Fixed-effects model	0.58	0.44	0.78	-3.67	0.00			\blacklozenge					
						0.01	0.1	1	10	100			
						Favor clos	s PFC sure) F		medical rapy			

Supplementary Figure 3. Sensitivity analysis for primary endpoint(s).

Strokes: sensitivity analysis

Study name	5	Statistics	with st	udy remo	Risk ratio (95% CI)					
	Point	Lower limit	Upper limit	Z-Value	p-Value		with study removed			
Closure I (2012)	0.46	0.31	0.70	-3.72	0.00					
PC Trial (2013)	0.56	0.39	0.80	-3.15	0.00					
CLOSE (2017)	0.57	0.38	0.86	-2.67	0.01					
RESPECT (2017)	0.50	0.32	0.79	-2.99	0.00					
REDUCE (2017)	0.61	0.42	0.90	-2.49	0.01					
ixed-effects model	0.54	0.38	0.78	-3.35	0.00			lack		
						0.01	0.1	1	10	100

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Supplementary Figure 4. Sensitivity analysis for strokes.

Transient ischemic attacks: sensitivity analysis

Study name	5	Statistics	with stu	udy remo	ved	Risk ratio (95% CI)					
	Point	Lower limit	Upper limit	Z-Value	p-Value		with study removed				
Closure I (2012)	0.80	0.51	1.24	-1.00	0.32						
PC Trial (2013)	0.80	0.54	1.20	-1.07	0.28						
CLOSE (2017)	0.74	0.48	1.13	-1.41	0.16						
RESPECT (2017)	0.85	0.53	1.37	-0.67	0.50						
REDUCE (2017)	0.80	0.55	1.17	-1.14	0.26						
Fixed-effects model	0.80	0.55	1.16	-1.19	0.23			\Diamond			
						0.01	0.1	1	10	100	
						Favors PFO closure		Fa	vors r	nedical apv	

Supplementary Figure 5. Sensitivity analysis for TIAs.

Atrial fibrillation or flutter: sensitivity analysis

Study name	5	Statistics	with stu	udy remo	ved	d Risk ratio (95% CI)						
	Point	Lower limit	Upper limit	Z-Value	p-Value		with study removed					
Closure I (2012)	1.65	1.05	2.60	2.15	0.03							
PC Trial (2013)	1.94	1.25	3.02	2.95	0.00							
CLOSE (2017)	2.38	1.41	4.02	3.25	0.00			-	-			
RESPECT (2017)	2.06	1.31	3.24	3.12	0.00							
REDUCE (2017)	2.24	1.33	3.78	3.02	0.00				.			
Fixed-effects model	2.01	1.31	3.08	3.22	0.00			•				
						0.01	0.1	1	10	100		
						Favors PFO closure		Fav	ors r	nedical apy		

Supplementary Figure 6. Sensitivity analysis for atrial fibrillation or flutter.

All bleeding: sensitivity analysis

Study name	s	tatistics	Rate ratio (95% CI)									
	Point		Upper limit	Z-Value	p-Value		wit	th stud	dy r	emov	ed	
Closure I (2012)	0.709	0.372	1.353	-1.043	0.297			+	-			
PC Trial (2013)	0.953	0.383	2.375	-0.103	0.918			+		+		
CLOSE (2017)	1.085	0.566	2.080	0.246	0.805			-		\dashv		
RESPECT (2017)	0.755	0.327	1.740	-0.660	0.509			+		-		
REDUCE (2017)	0.968	0.405	2.313	-0.073	0.942			+		+		
Random-effects model	0.887	0.442	1.779	-0.337	0.736					-		
						0.1	0.2	0.5	1	2	5	10
							Favors PFO closure		F		s m	edical ov

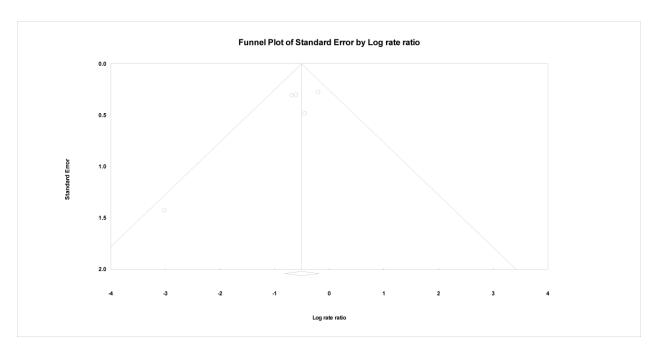
Supplementary Figure 7. Sensitivity analysis for bleeding.

Gastrointestinal bleeding, ulceration or ulcer perforation: sensitivity analysis

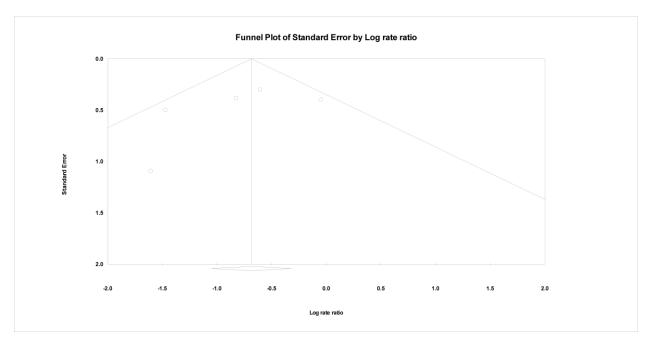
Study name	5	Statistics	with stu	ıdy remo	Risk ratio (95% CI)						
	Point	Lower limit	Upper limit			with study removed					
CLOSE (2017)	1.21	0.38	3.80	0.32	0.75				-		
RESPECT (2017)	0.43	0.06	3.24	-0.82	0.41		+	■┼	.		
REDUCE (2017)	1.17	0.37	3.72	0.26	0.79			-	-		
Fixed-effects model	1.03	0.35	3.00	0.05	0.96			~	.		
						0.01	0.1	1	10	100	

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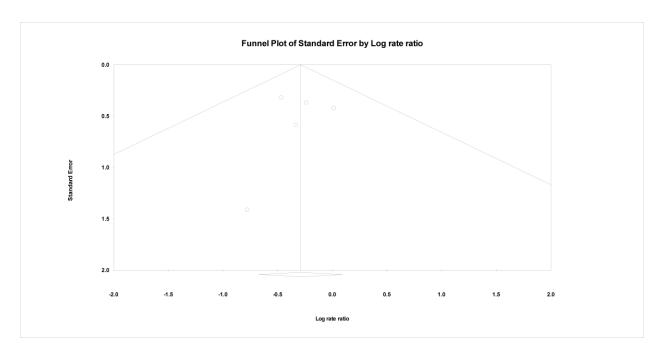
Supplementary Figure 8. Sensitivity analysis for gastrointestinal complications.



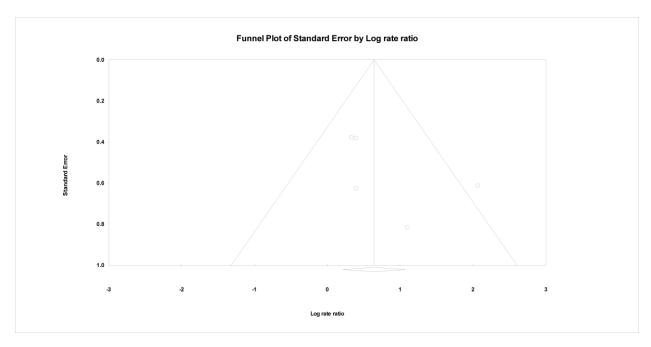
Supplementary Figure 9. Funnel plot for primary endpoint(s).



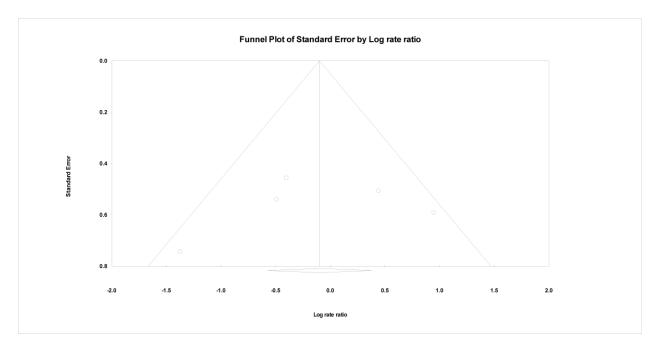
Supplementary Figure 10. Funnel plot for strokes.



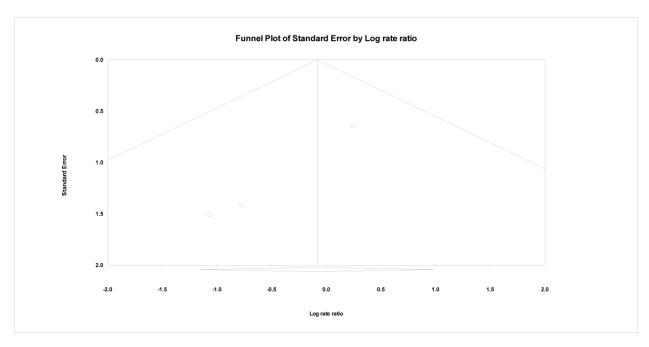
Supplementary Figure 11. Funnel plot for TIAs.



Supplementary Figure 12. Funnel plot for atrial fibrillation or flutter.



Supplementary Figure 13. Funnel plot for bleeding.



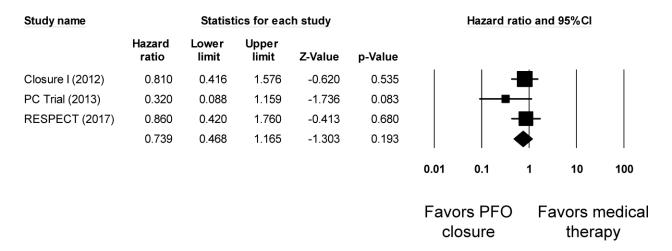
Supplementary Figure 14. Funnel plot for gastrointestinal complications.

Atrial septal aneurysm and primary endpoint events

Study name		<u>Statist</u>	ics for eac	:h study		Hazard ratio and 95%CI						
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value							
Closure I (2012)	0.780	0.293	2.078	-0.497	0.619		-					
PC Trial (2013)	2.090	0.382	11.447	0.850	0.396		-	╅	\rightarrow			
CLOSE (2017)	0.050	0.003	0.949	-1.995	0.046	 	-	-				
RESPECT (2017)	0.200	0.059	0.683	-2.568	0.010		+=-	-				
	0.464	0.135	1.596	-1.219	0.223							
						0.01	0.1	1	10	100		
						Favors PFO closure		Fa	vors n thera	nedical		

Supplementary Figure 15. Subgroup analysis for the presence of atrial septal aneurysm.

No atrial septal aneurysm and primary endpoint events



Supplementary Figure 16. Subgroup analysis for the absence of atrial septal aneurysm.

Large shunt size and primary endpoint events

Study name		Statist	ics for eac	ch study	ly Hazard ratio and			d 95%CI		
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value					
Closure I (2012)	0.720	0.148	3.513	-0.406	0.685		I —	=	-	
RESPECT (2017)	0.260	0.098	0.693	-2.694	0.007			\vdash		
REDUCE (2017)	0.180	0.058	0.560	-2.963	0.003			-		
	0.274	0.140	0.537	-3.773	0.000			▶		
						0.01	0.1	1	10	100

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Supplementary Figure 17. Subgroup analysis for large shunt size.

Small shunt size and primary endpoint events

Study name		Statist	ics for eac	h study	Hazard ratio and 95%Cl					
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value					
Closure I (2012)	0.770	0.398	1.489	-0.777	0.437			-		
RESPECT (2017)	0.960	0.438	2.102	-0.102	0.919			-		
REDUCE (2017)	0.270	0.027	2.713	-1.112	0.266	-	 -	-		
	0.801	0.489	1.311	-0.883	0.377					
						0.01	0.1	1	10	100

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Supplementary Figure 18. Subgroup analysis for small shunt size.