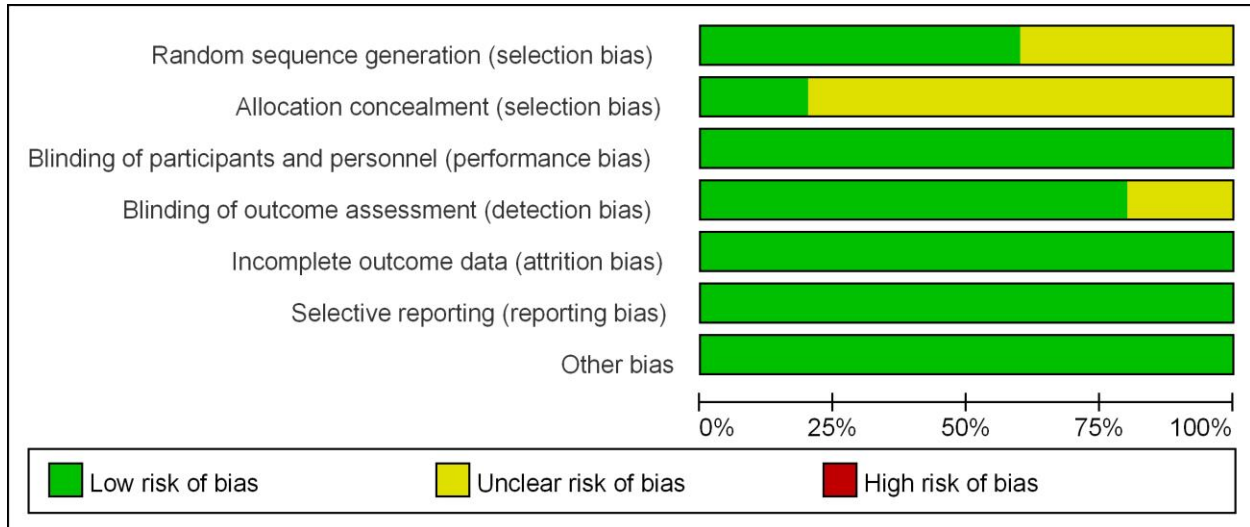


Supplementary Appendix

Supplementary Figures

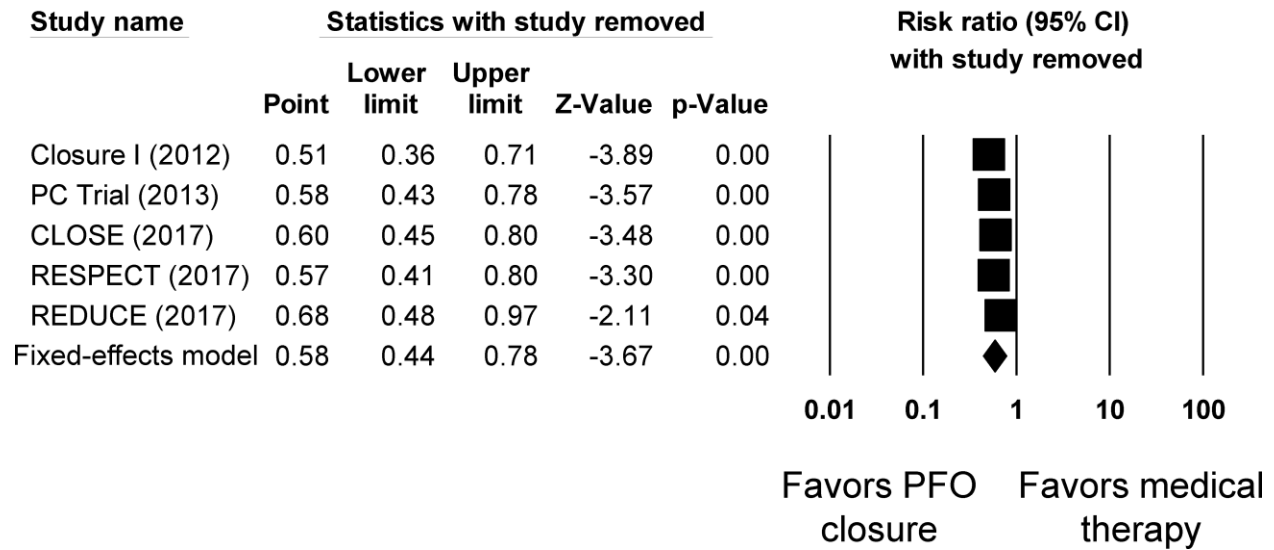


Supplementary Figure 1. Risk of bias graph using the Cochrane Risk Assessment Tool.

	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	?	?	+	+	+	+	+

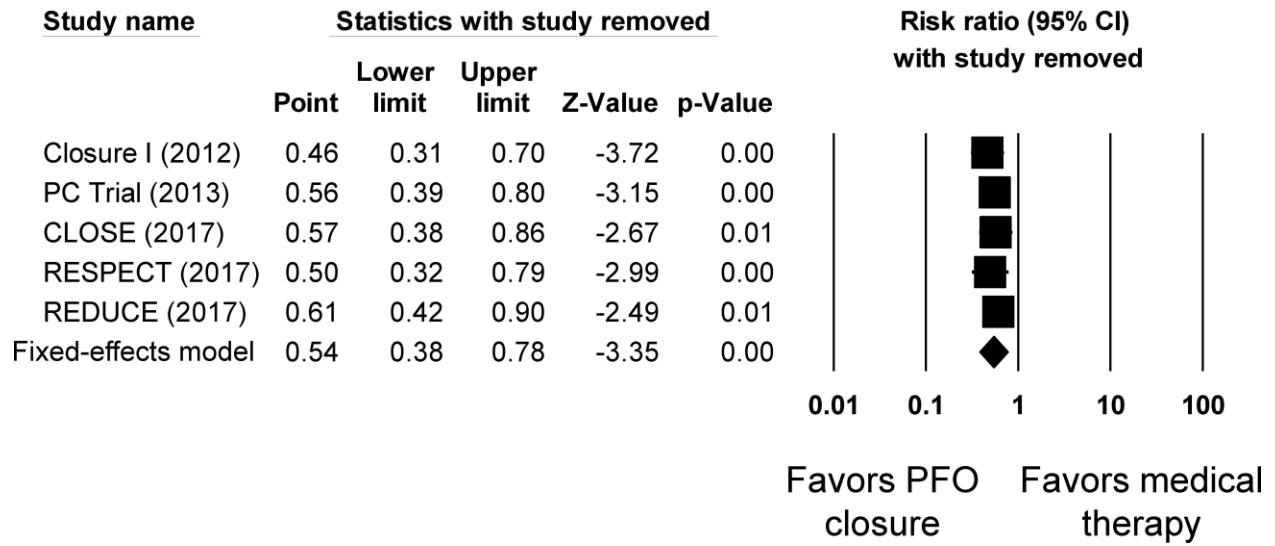
Supplementary Figure 2. Risk of bias summary using the Cochrane Risk Assessment Tool.

Primary endpoint: sensitivity analysis



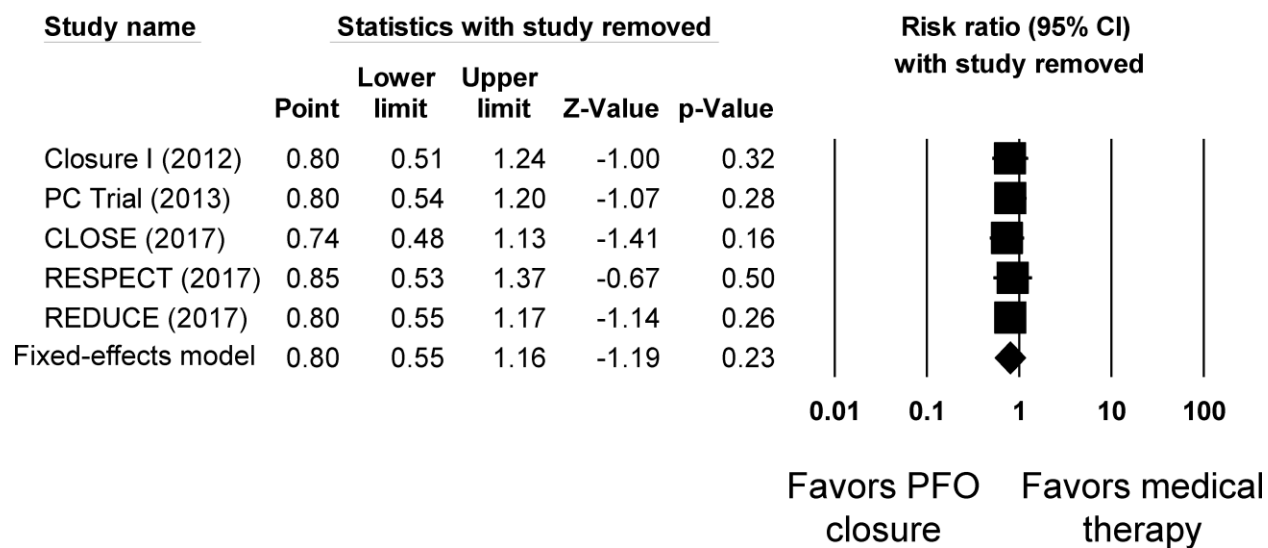
Supplementary Figure 3. Sensitivity analysis for primary endpoint(s).

Strokes: sensitivity analysis



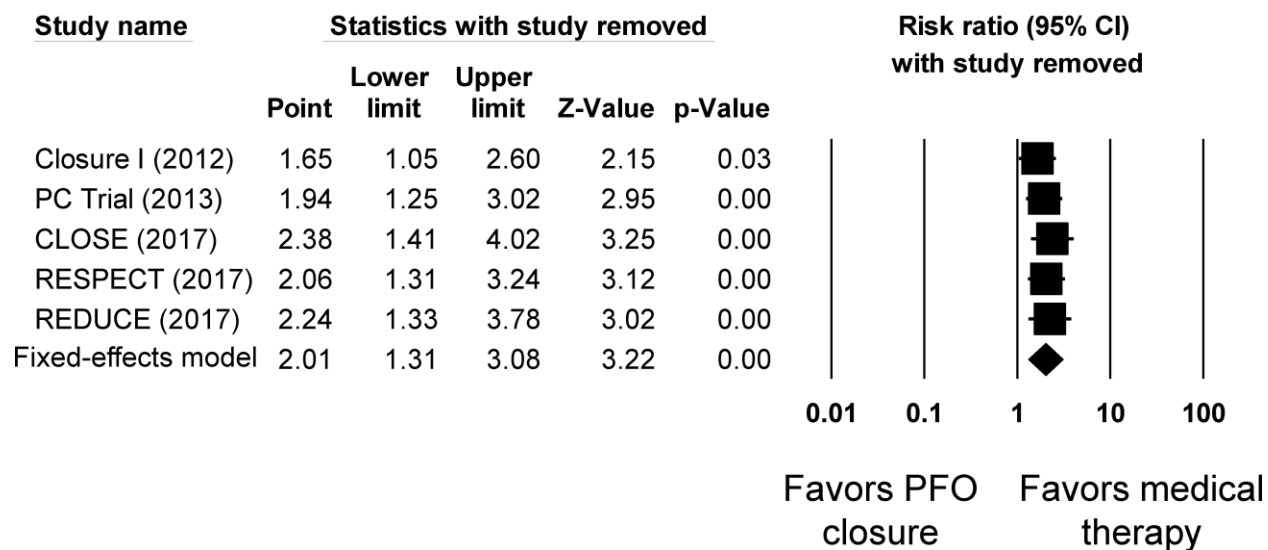
Supplementary Figure 4. Sensitivity analysis for strokes.

Transient ischemic attacks: sensitivity analysis



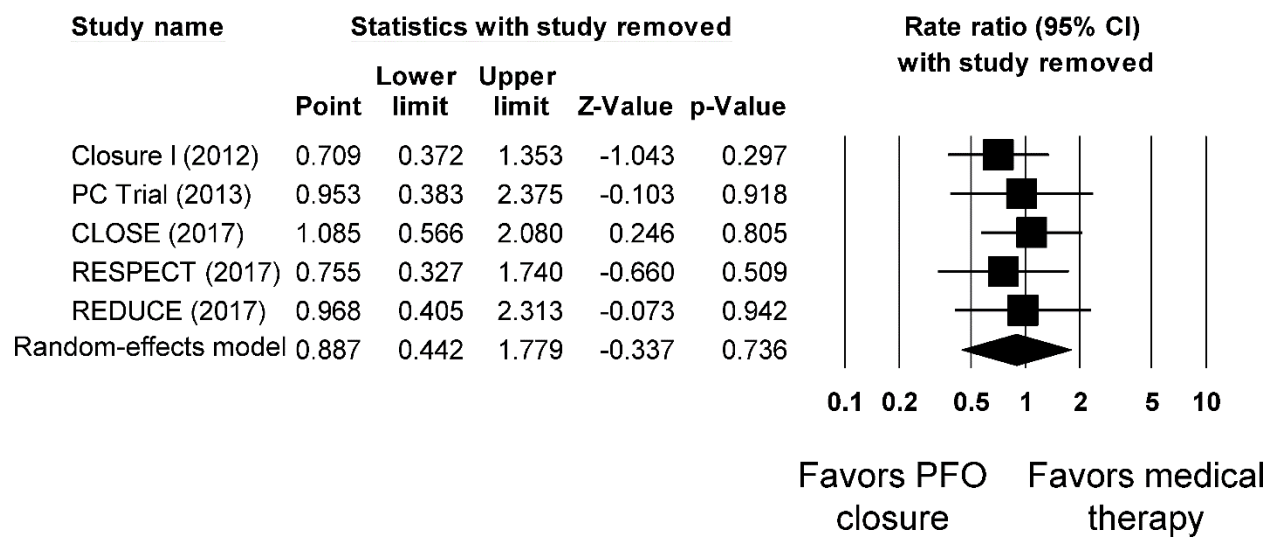
Supplementary Figure 5. Sensitivity analysis for TIAs.

Atrial fibrillation or flutter: sensitivity analysis



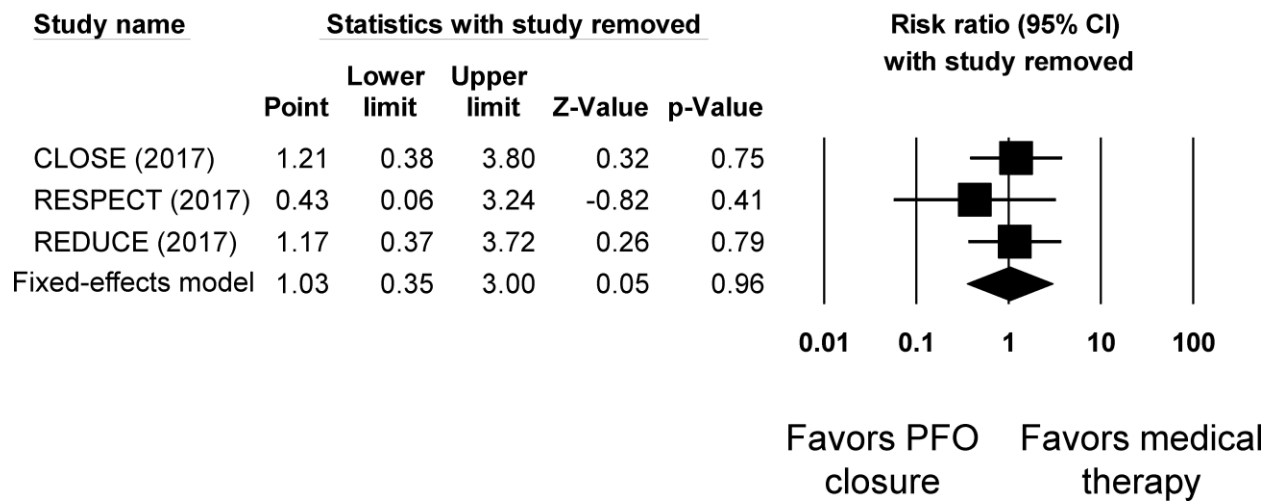
Supplementary Figure 6. Sensitivity analysis for atrial fibrillation or flutter.

All bleeding: sensitivity analysis

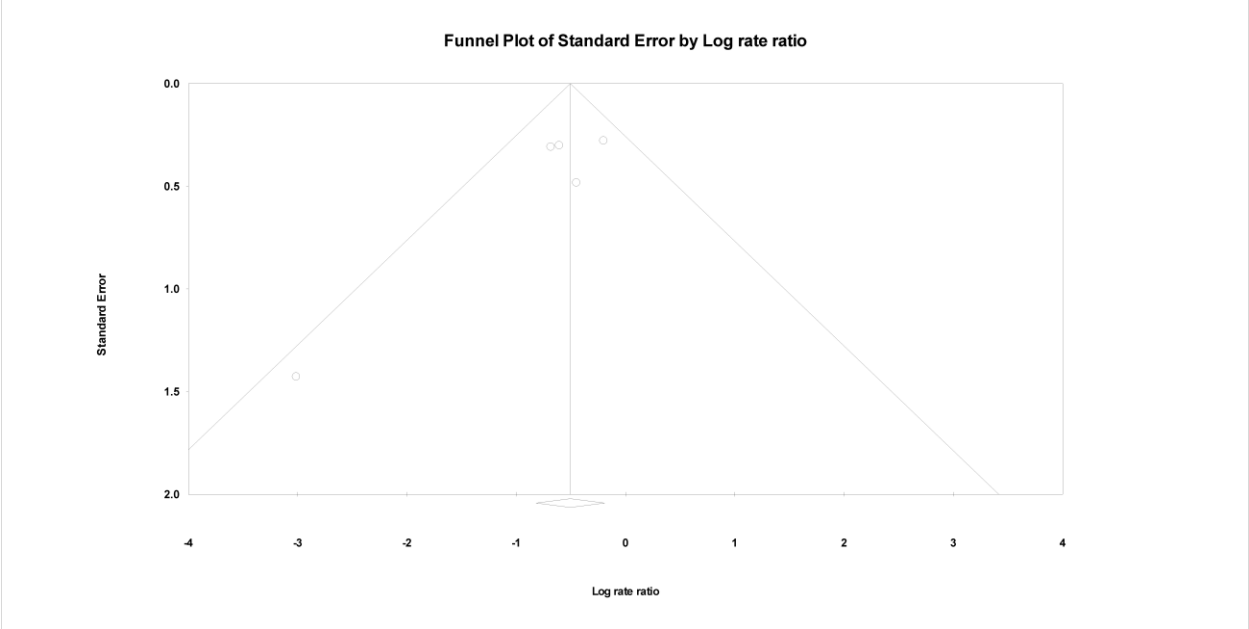


Supplementary Figure 7. Sensitivity analysis for bleeding.

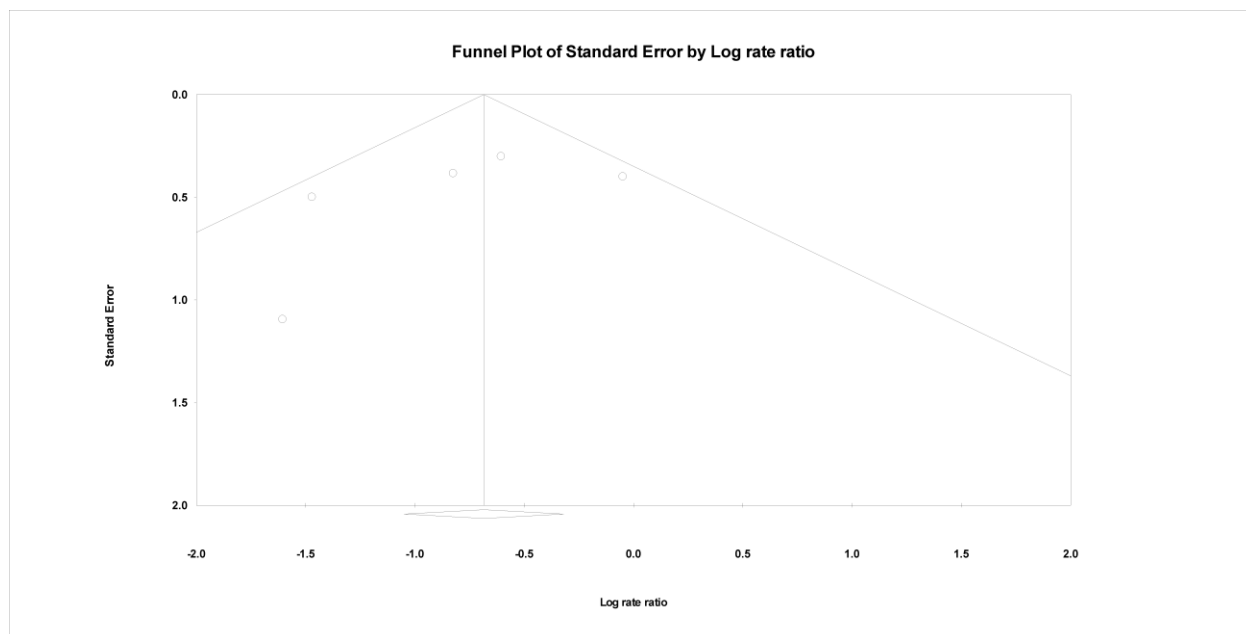
Gastrointestinal bleeding, ulceration or ulcer perforation: sensitivity analysis



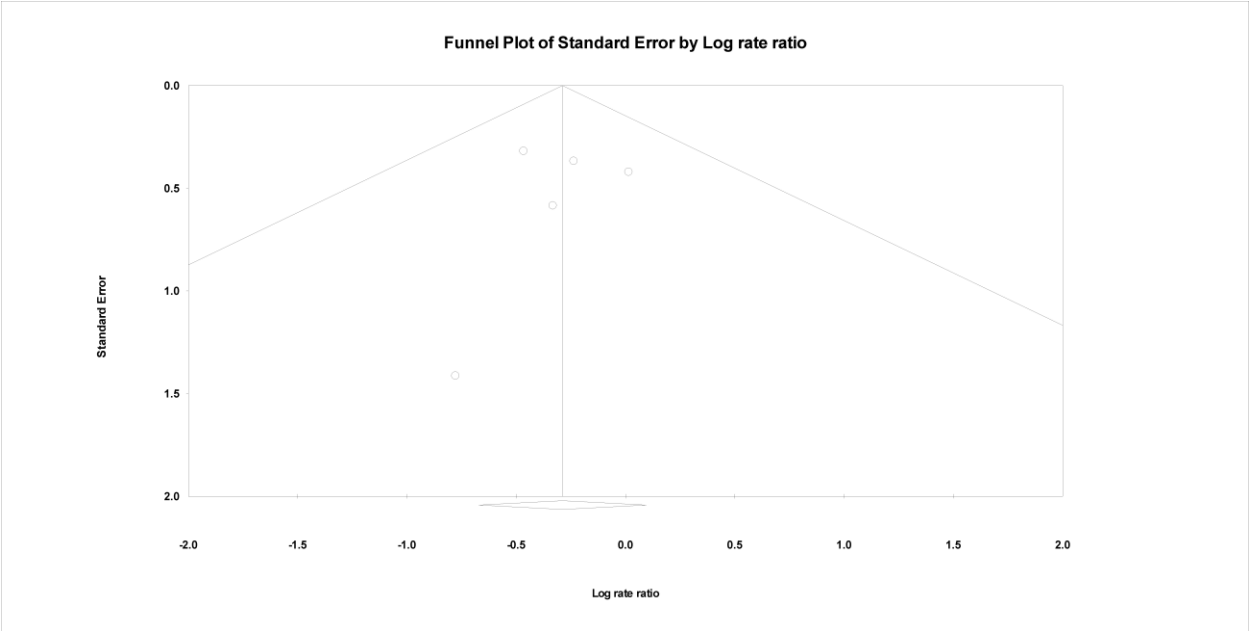
Supplementary Figure 8. Sensitivity analysis for gastrointestinal complications.



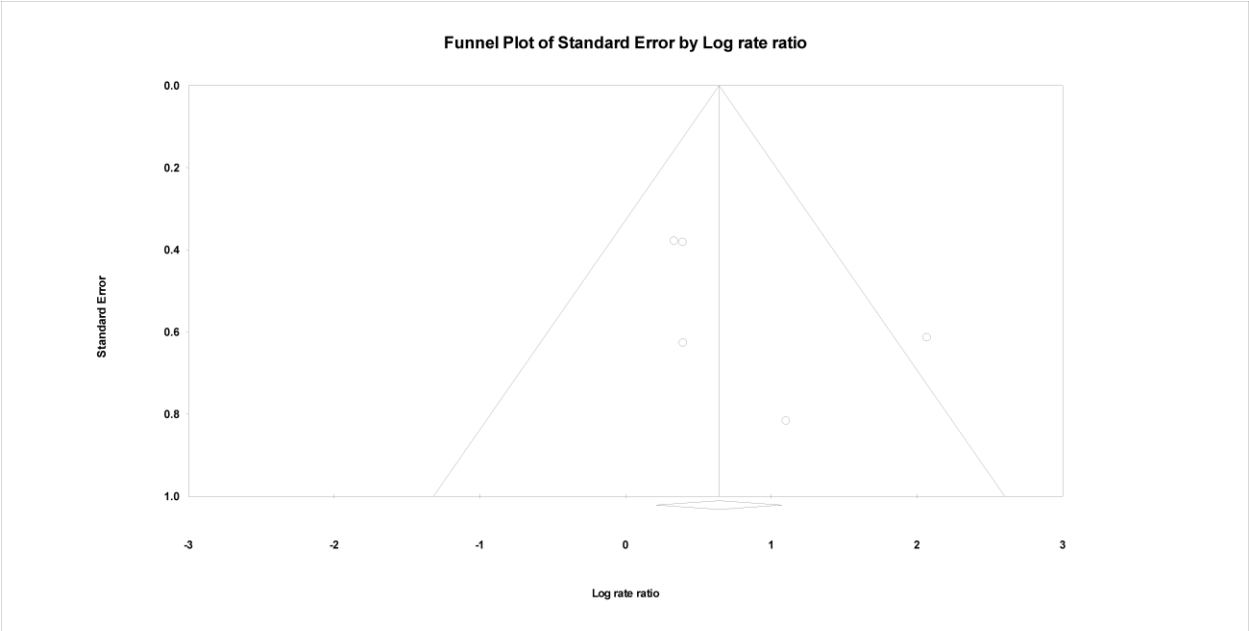
Supplementary Figure 9. Funnel plot for primary endpoint(s).



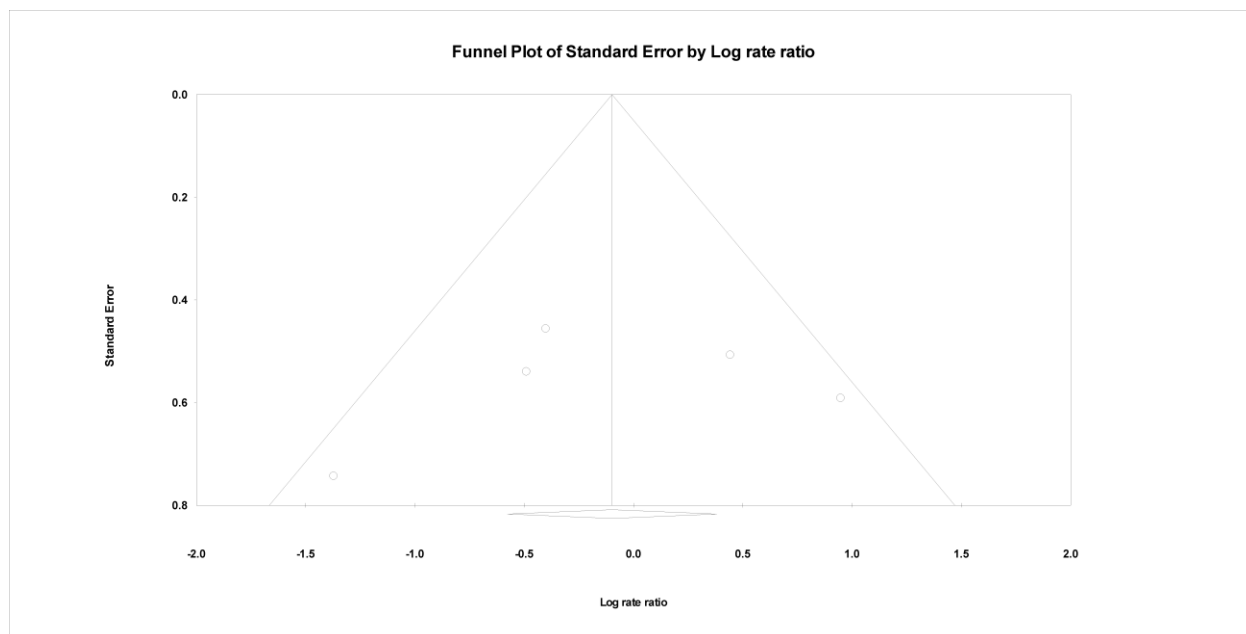
Supplementary Figure 10. Funnel plot for strokes.



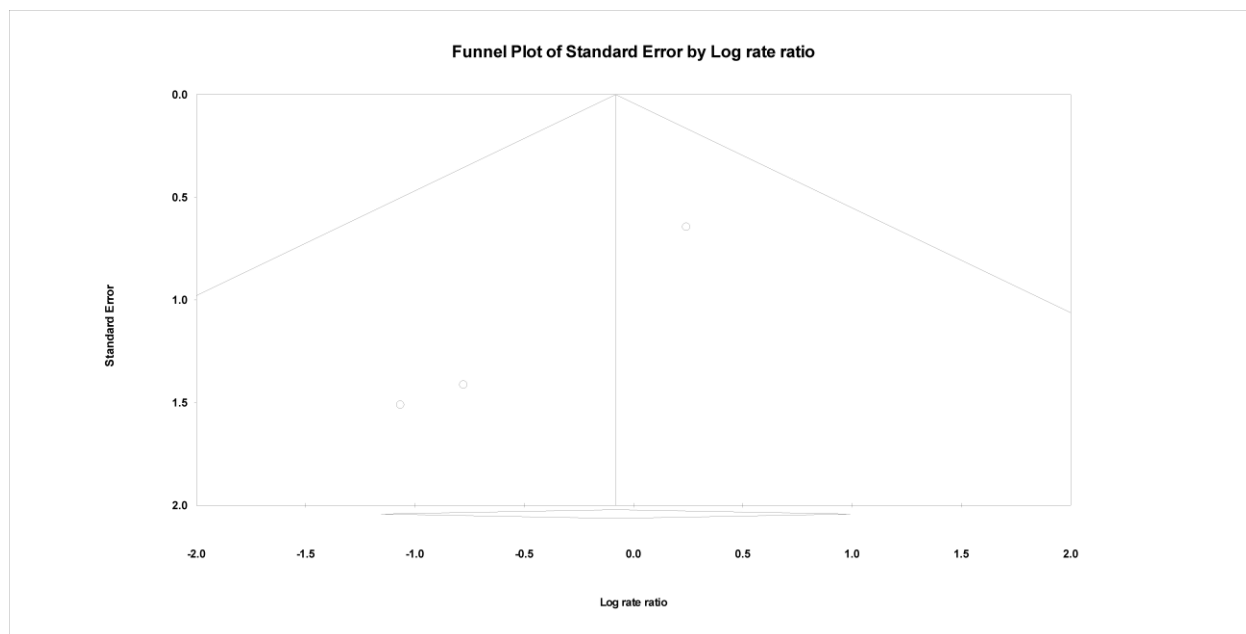
Supplementary Figure 11. Funnel plot for TIAs.



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

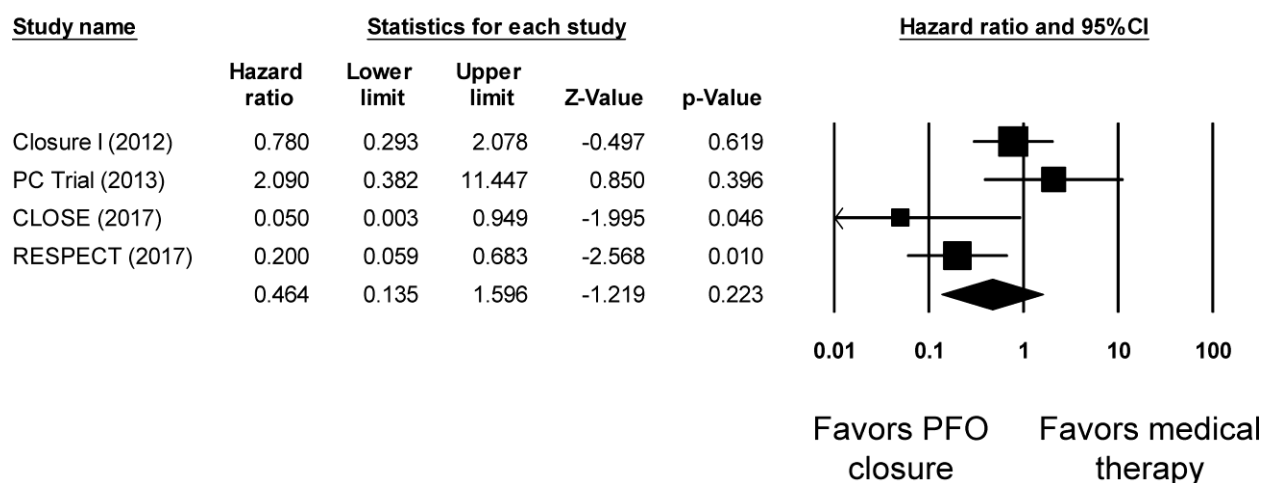


Supplementary Figure 13. Funnel plot for bleeding.



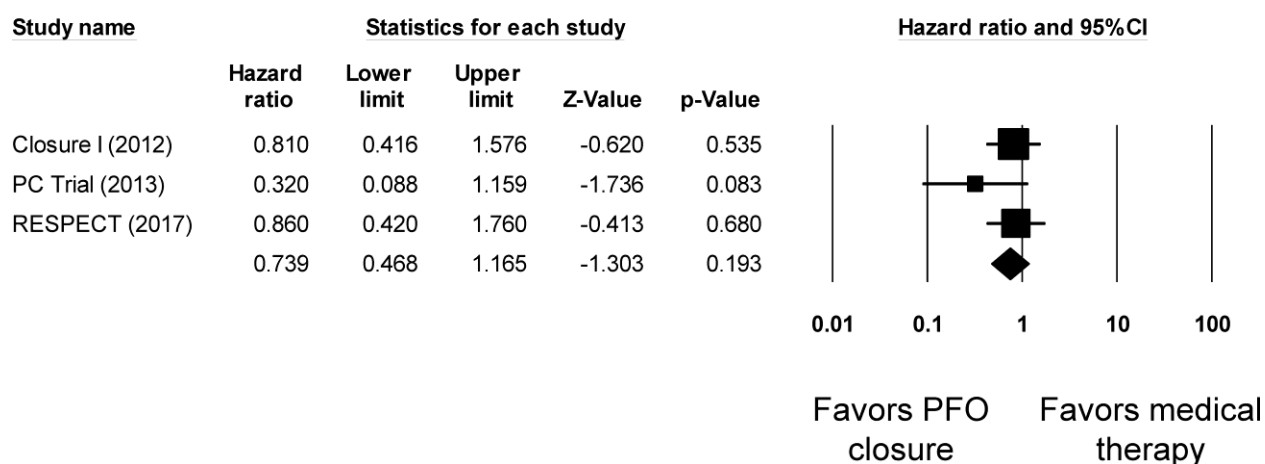
Supplementary Figure 14. Funnel plot for gastrointestinal complications.

Atrial septal aneurysm and primary endpoint events



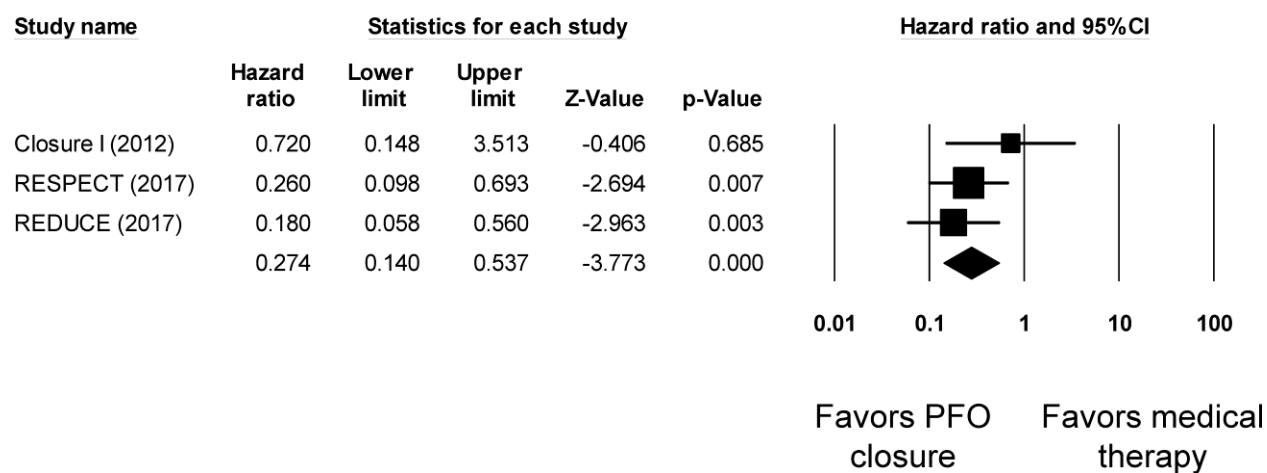
Supplementary Figure 15. Subgroup analysis for the presence of atrial septal aneurysm.

No atrial septal aneurysm and primary endpoint events



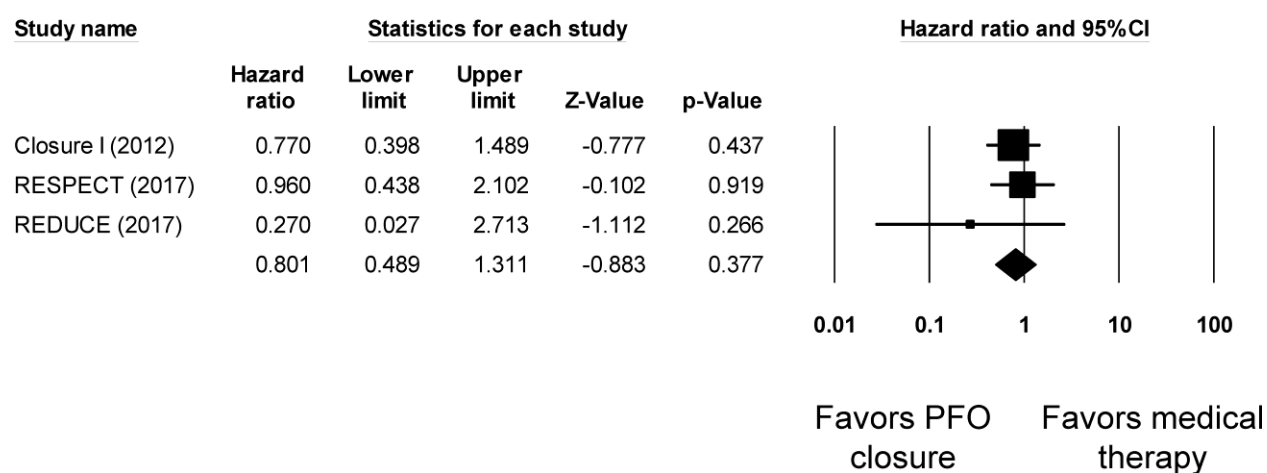
Supplementary Figure 16. Subgroup analysis for the absence of atrial septal aneurysm.

Large shunt size and primary endpoint events



Supplementary Figure 17. Subgroup analysis for large shunt size.

Small shunt size and primary endpoint events



Supplementary Figure 18. Subgroup analysis for small shunt size.