

## **Data Supplement**

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**Table e-1. Composite vascular outcome criteria**

<b>Trial</b>	<b>Composite vascular outcome</b>
<b>CLOSURE I</b>	Stroke or transient ischemic attack during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years
<b>PC</b>	Death, non-fatal stroke, transient ischemic attack, or peripheral embolism
<b>RESPECT</b>	Recurrent non-fatal ischemic stroke, fatal ischemic stroke, or early death after randomization
<b>CLOSE</b>	Ischemic stroke, transient ischemic attack, or systemic embolism
<b>Gore REDUCE</b>	Brain infarction defined as clinical ischemic stroke or silent brain infarction only

**Table e-2. Characteristics of the included studies**

Study	Enrolment	Study population
<b>CLOSURE I</b>	2003-2008 Multicenter United States and Canada	<i>Inclusion criteria:</i> age 18-60 years, history of ischemic stroke/clinically confirmed TIA within the previous 6 months, evidence of PFO as documented by TEE with a bubble study showing right-to-left shunting during a Valsalva maneuver. <i>Exclusion criteria:</i> any potential cause of stroke/TIA other than PFO; any medical condition (other than index stroke), such as deep vein thrombosis, requiring anticoagulation; any coagulopathy (i.e., prothrombin G20210A, protein C, protein S, anti-thrombin III deficiency, factor V Leiden deficiency) or moderate/high positive titer of antiphospholipid antibodies that require long-term anticoagulation, mRS score $\geq 3$ .
<b>PC</b>	2000-2009 Multicenter Europe, Canada, Brazil and Australia	<i>Inclusion criteria:</i> age <60 years, history of both clinically and radiologically verified ischemic stroke/TIA or extra-cranial peripheral thromboembolic event, evidence of PFO as documented by TEE with a right-to-left shunt during the bubble test or color Doppler flow imaging either spontaneously or with a Valsalva or cough maneuver. <i>Exclusion criteria:</i> any identifiable cause for thromboembolic event other than PFO; chronic anticoagulant therapy for another disease entity; severe disability from previous stroke (Barthel-Index <50, mRS score >3).
<b>RESPECT</b>	2003-2011 Multicenter United States and Canada	<i>Inclusion criteria:</i> age 18-60 years, history of ischemic stroke/radiologically verified TIA within the previous 270 days, evidence of PFO defined as TEE visualization of microbubbles in the left atrium within three cardiac cycles from the right atrial opacification, at rest and/or during Valsalva release <i>Exclusion criteria:</i> any potential cause of stroke/TIA other than PFO; uncontrolled hypertension or diabetes mellitus; small vessel infarct; positive test for hypercoagulable states (i.e. IgG or IgM anticardiolipin antibodies, lupus anticoagulant, B2-glycoprotein-1 antibodies, or persistently elevated fasting plasma homocysteine despite medical therapy); severe disability from previous stroke (mRS score >3).
<b>CLOSE</b>	2007-2016 Multicenter France and Germany	<i>Inclusion criteria:</i> age 16-60 years, history of ischemic stroke (or retinal ischemia)/radiologically verified TIA within the previous 6 months, evidence of PFO with an associated ASA on TEE or large shunt (>30 microbubbles in the left atrium within three cardiac cycles from the right atrial opacification) on TTE or TEE, spontaneously or during provocation maneuvers. <i>Exclusion criteria:</i> any identifiable cause of stroke (or retinal ischemia) other than PFO; small artery disease; coagulopathy requiring long-term anticoagulation; long-term anticoagulant or antiplatelet therapy for another reason; mRS score >3.
<b>Gore REDUCE</b>	2008-2015 Multicenter United States, Canada, United Kingdom, Finland, Norway, Sweden and Denmark	<i>Inclusion criteria:</i> age 18-59 years; history of ischemic stroke/radiologically verified TIA within the previous 180 days; evidence of PFO on TEE with bubble study demonstrating right-to-left shunting, spontaneously or during Valsalva maneuver. <i>Exclusion criteria:</i> any identifiable mechanism of stroke other than PFO; uncontrolled diabetes mellitus or systemic hypertension; small-vessel infarct; hypercoagulable states requiring anticoagulation; any other reason requiring chronic anticoagulation; mRS score $\geq 3$ .

Abbreviations: ASA=atrial septal aneurysm; mRS=modified Ranking score; PFO=patent foramen ovale;

TEE=transesophageal echocardiography; TIA=transient ischemic attack; TTE=transthoracic echocardiography.

**Table e-3. Risk of bias summary table**

<b>Bias</b> \ <b>Study</b>	<b>CLOSURE I</b>	<b>PC</b>	<b>RESPECT</b>	<b>CLOSE</b>	<b>Gore REDUCE</b>
Random sequence generation (Selection Bias)	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Allocation concealment (Selection Bias)	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Blinding of participants and personnel (Performance Bias)	High risk	High risk	High risk	High risk	High risk
Blinding of outcome assessment (Detection Bias)	Low risk	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data (Attrition Bias)	Low risk	High risk	High risk	Unclear risk	High risk
Selective reporting (Reporting Bias)	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk
Other sources of bias (Funding bias)	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk

## **e-Appendix I**

### **PubMed search strategy<sup>e-1</sup>**

- #1 random\* OR trial\* OR group\* [Title/Abstract]
- #2 "Randomized Controlled Trial"[Publication Type]
- #3 "Controlled Clinical Trial"[Publication Type]
- #4 ((#1) OR #2) OR #3
- #5 "Animals"[Mesh] NOT "Humans"[Mesh]
- #6 #4 NOT #5
- #7 patent foramen ovale [Title/Abstract]
- #8 cryptogenic stroke [Title/Abstract] OR cryptogenic embolism [Title/Abstract] OR  
cryptogenic transient ischemic attack [Title/Abstract]
- #9 #7 AND #8
- #10 #6 AND #9

### **CENTRAL search strategy**

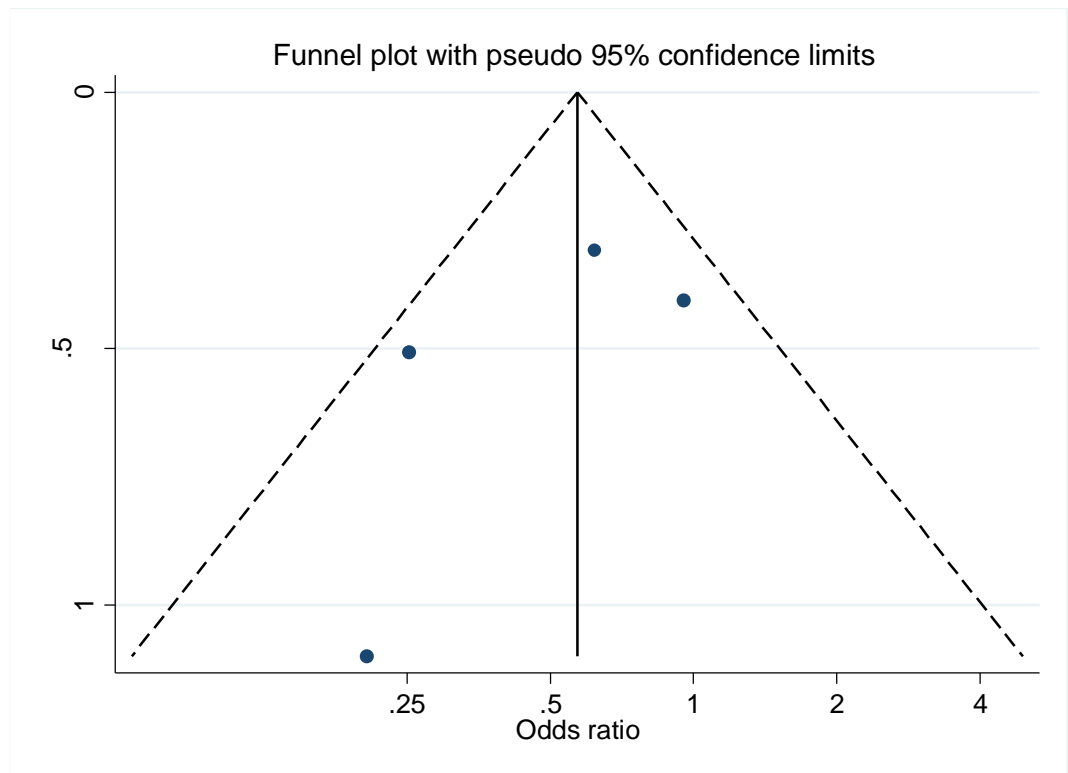
- #1 patent foramen ovale
- #2 cryptogenic stroke OR cryptogenic embolism OR cryptogenic transient ischemic attack
- #3 #1 AND #2

### **ClinicalTrials.gov search strategy**

(patent foramen ovale) AND (stroke) | "Interventional Studies"

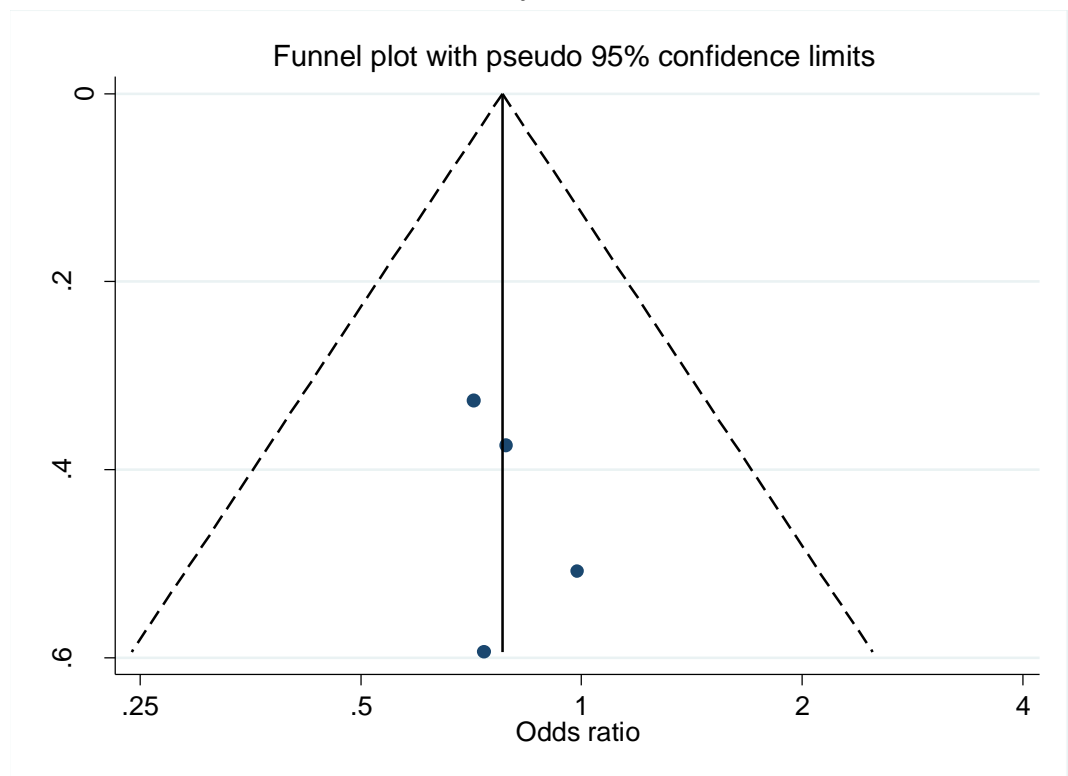
**e-Appendix II**

**Funnel plot of comparison: Device closure versus medical therapy, outcome: stroke occurrence - ITT analysis**



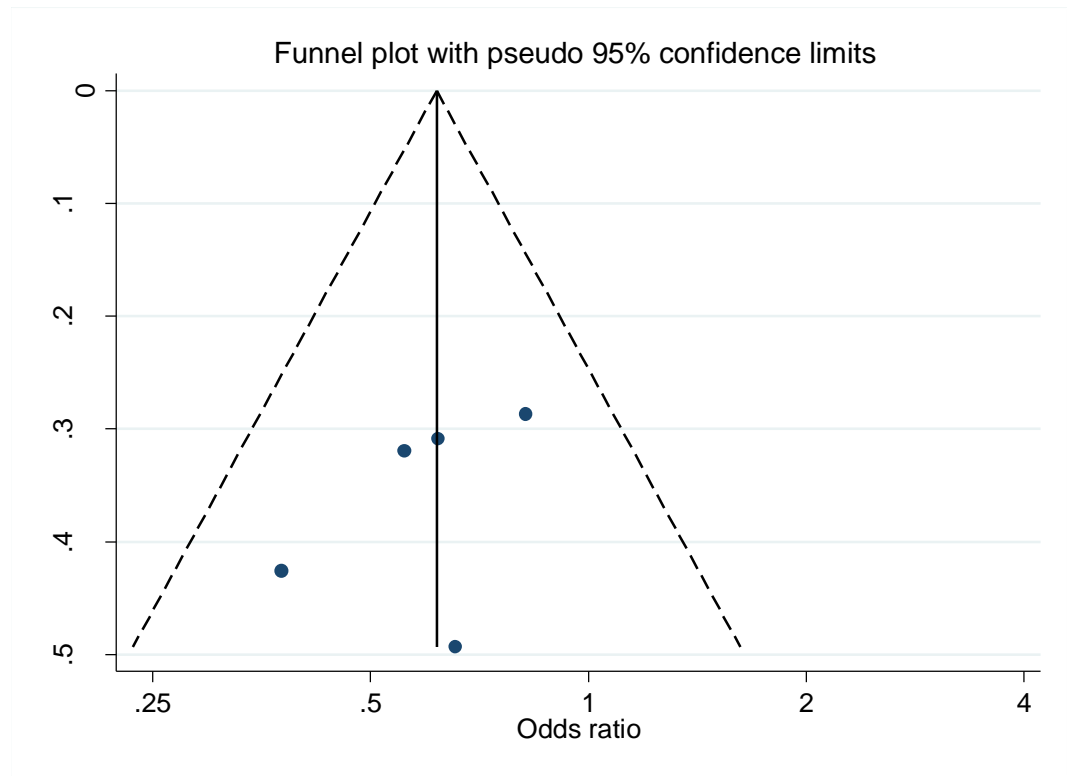
Egger statistical test  $p=0.403$

**Funnel plot of comparison: Device closure versus medical therapy, outcome: transient ischemic attack occurrence - ITT analysis**



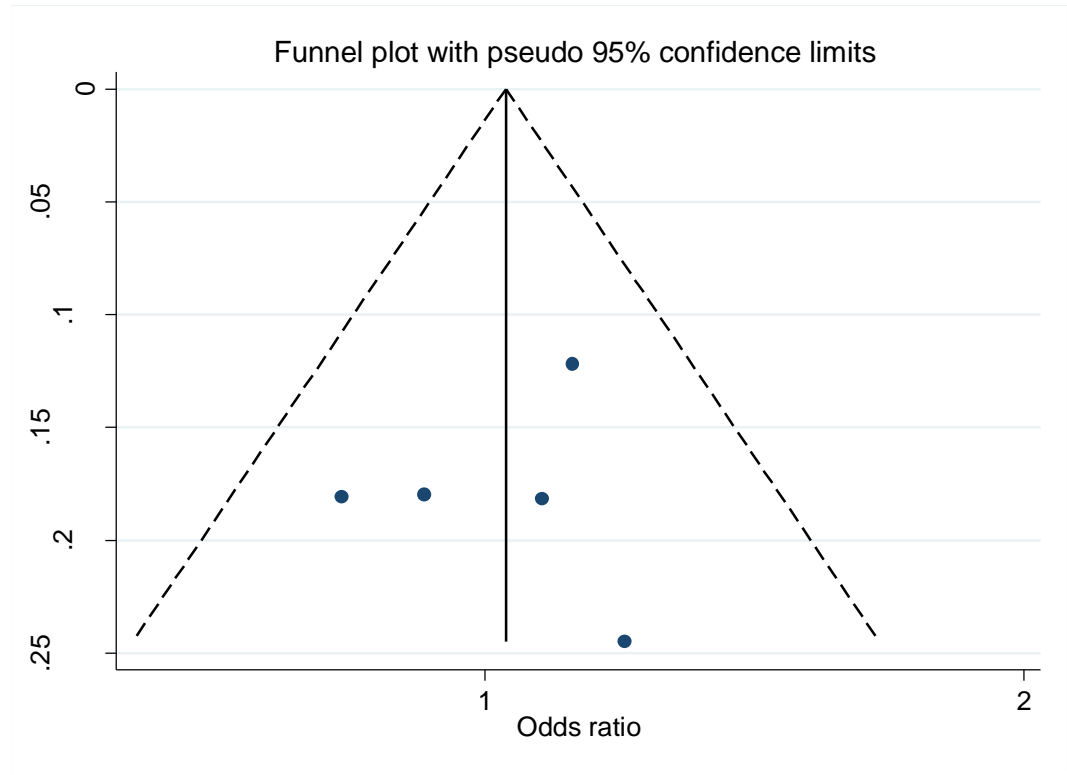
Egger statistical test  $p=0.494$

**Funnel plot of comparison: Device closure versus medical therapy, outcome: composite outcome events - ITT analysis**



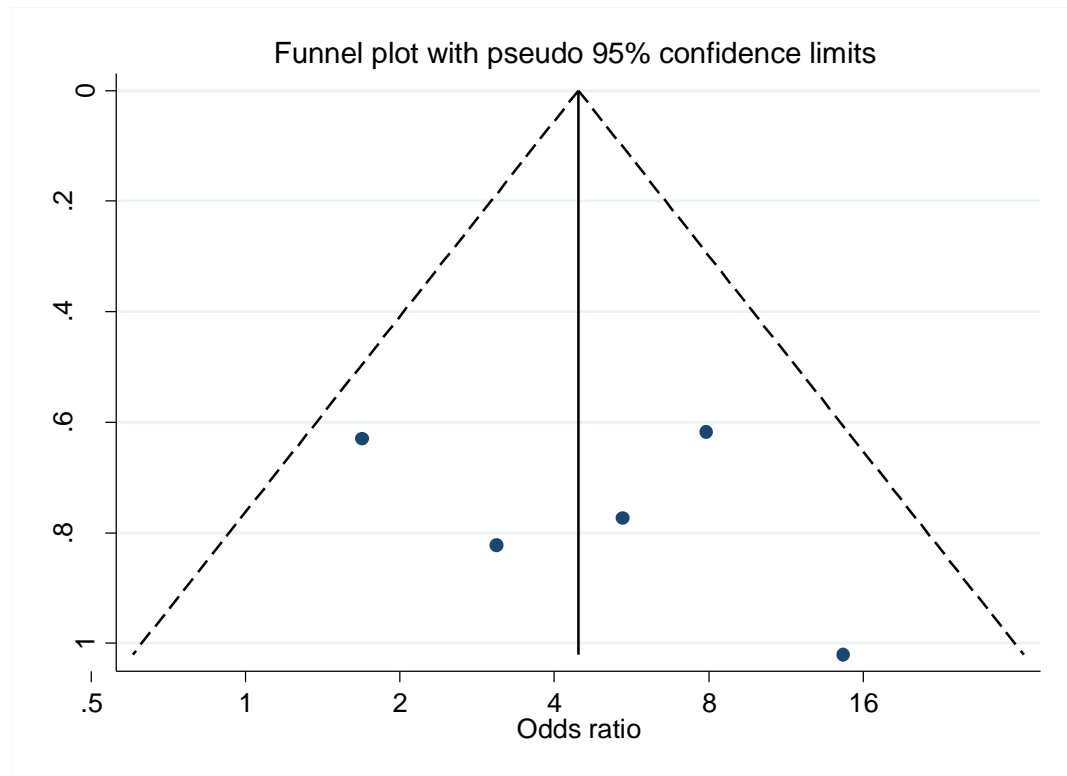
Egger statistical test  $p=0.354$

**Funnel plot of comparison: Device closure versus medical therapy, outcome: any severe adverse event - ITT analysis**



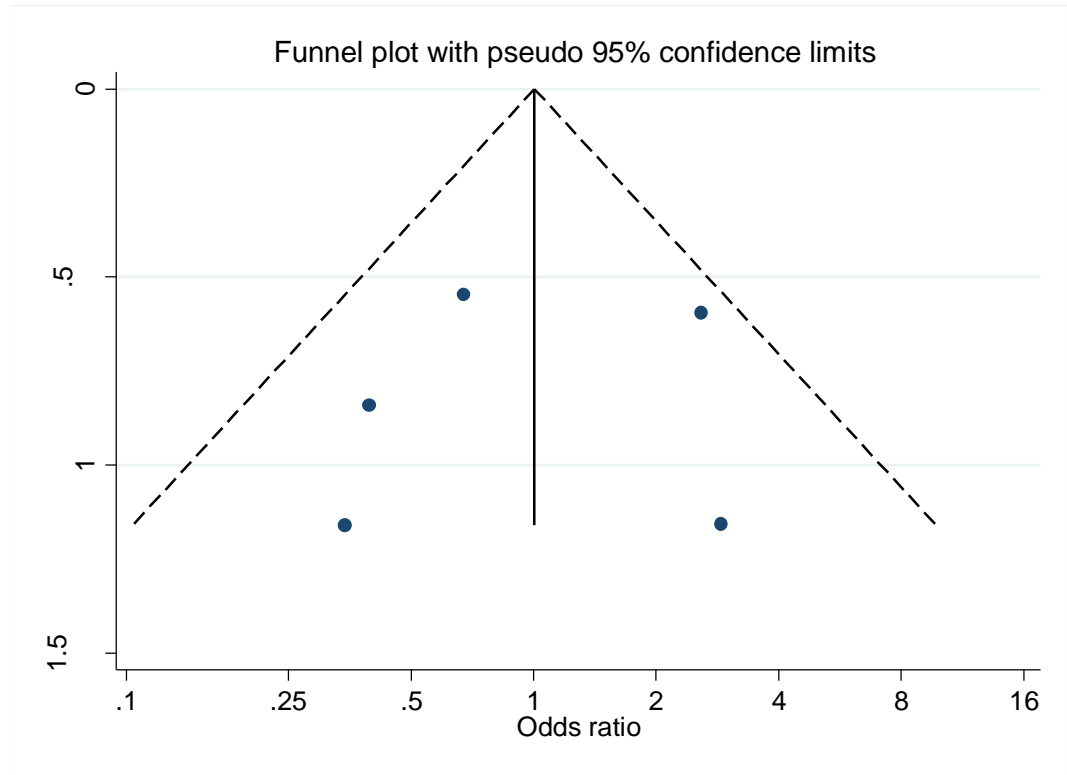
Egger statistical test  $p=0.732$

**Funnel plot of comparison: Device closure versus medical therapy, outcome: atrial fibrillation or flutter - ITT analysis**



Egger statistical test  $p=0.473$

**Funnel plot of comparison: Device closure versus medical therapy, outcome: major bleeding - ITT analysis**



Egger statistical test  $p=0.794$

Abbreviation: ITT=intent to treat.



## **e-Reference**

e-1 Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2* (updated September 2009). The Cochrane Collaboration, 2009. Available from [www.cochranehandbook.org](http://www.cochranehandbook.org).