PFO Closure for Stroke Prevention: Meta-Analysis Evidence from Non-Randomized Trials

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Conflicts

RESPECT Trial	Steering Committee
AGA Medical Corporation	Consultant (modest)
WL Gore Associates	Consultant (modest)
RoPE Study, NINDS	Co-PI

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Points of agreement

- PFO is common in the general population
- PFO is causally related to stroke – probably via paradoxical embolism
- Not all discovered PFOs in *stroke patients* are pathogenic
- Not all discovered PFOs in *cryptogenic stroke patients* are pathogenic
- Closing incidental PFOs is not likely to offer benefit
- For any treatment the benefit (reduced stroke) must outweigh the risks (hemorrhage, procedural complications, late device complications) in a medically meaningful way

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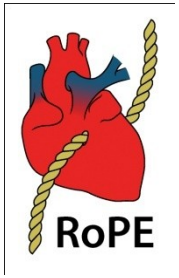
Current literature RE: PFO Closure

- Mostly case series
- Poor, non-standard case selection
- Small numbers
- Unblinded outcomes adjudication by non-neurologists
- Clinical (not scheduled) f/u



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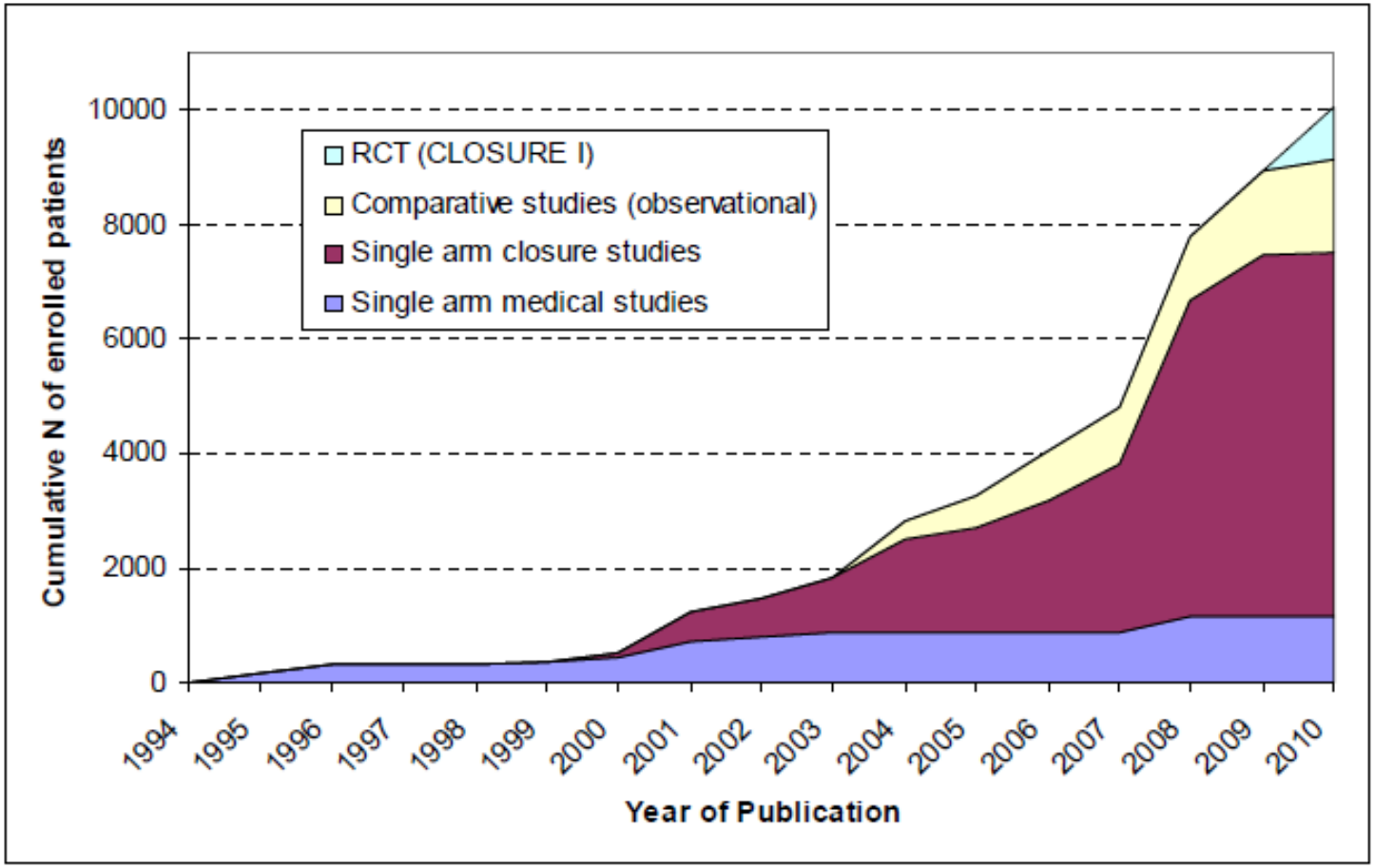
Meta-Analysis of Observational Studies

(Kitsios et al, in press)

Figure 2. Cumulative number of patients recruited in studies of different designs over a period of 16 years.



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(Kitsios et al, in press)

Table 1. Summary characteristics of studies examining medical treatment and percutaneous closure.

	Medical treatment studies	Percutaneous closure studies	P-value*
N of studies	19	50	
Total N of included patients	2020	7104	
Prospective design	68%	76%	
Mean age of patients (median, (25^{th} -75^{th} percentile), n)	47 (43-53), n=19	46.8 (43-50.5), n=48	0.711
% Males (median, (25^{th} -75^{th} percentile), n)	56.7 (51-60), n=18	53 (48-56), n=45	0.052
% Atrial septal aneurysm (median, (25^{th} -75^{th} percentile), n)	20.9 (15.9-33.6), n=12	31.2 (22.7-36.2), n=44	0.069
% Hypertension (median, (25^{th} -75^{th} percentile), n)	23.9 (16.5-31.3), n=16	22.5 (17-33), n=33	0.945
% Diabetics (median, (25^{th} -75^{th} percentile), n)	5 (3-9), n=15	5.5 (3.5-7.5), n=28	0.895
% Hyperlipidemia (median, (25^{th} -75^{th} percentile), n)	16.1 (13.1-28.9), n=12	24 (15-32), n=25	0.496
% Smoking (median, (25^{th} -75^{th} percentile), n)	32.5 (24.5-41.9), n=15	22.7 (16.4-33), n=29	0.024
% with stroke as the index event (median, (25^{th} -75^{th} percentile), n)	75.8 (67.7-100), n=18	65 (47.3-72), n=40	0.009
Use of structured screening instrument for recurrent stroke detection	79%	46%	0.014
Recurrent events ascertained by Neurologist	79%	54%	0.058
Recurrent events documented by neuroimaging	53%	44%	0.521

Table 1. Characteristics of cohort studies investigating incidence rates of recurrent cerebrovascular events in patients with PFO and under medical treatment or PFO closure.

* Mann-Whitney test or Chi-square test, as appropriate.

IQR: interquartile range

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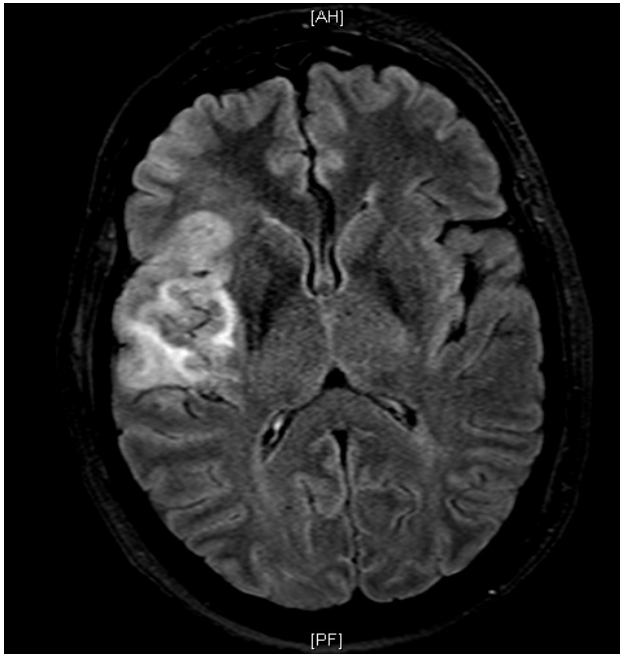
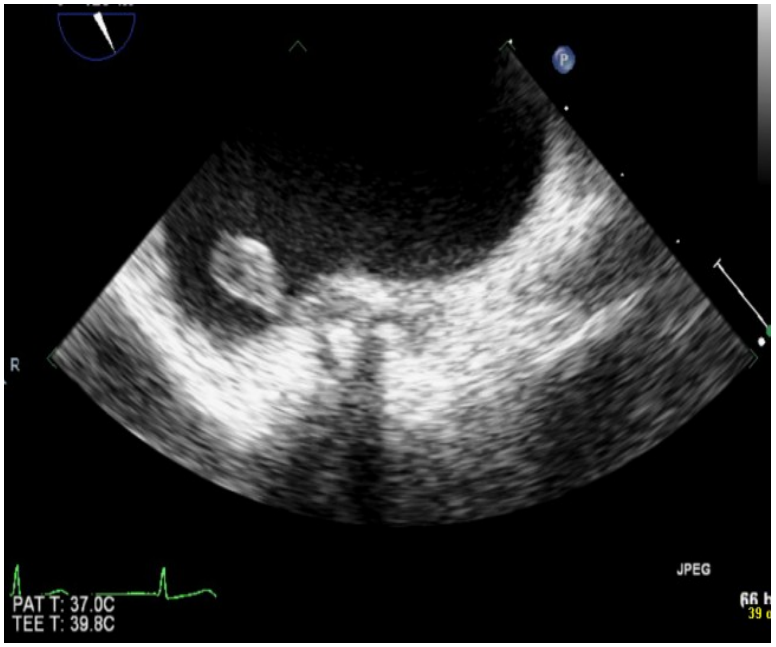
Infection 8y after CardioSEAL implantation by Dr. X complicated by stroke





"Dr. X told me that he's never had a long term complication of a PFO closure." – My patient enrolled in RESPECT

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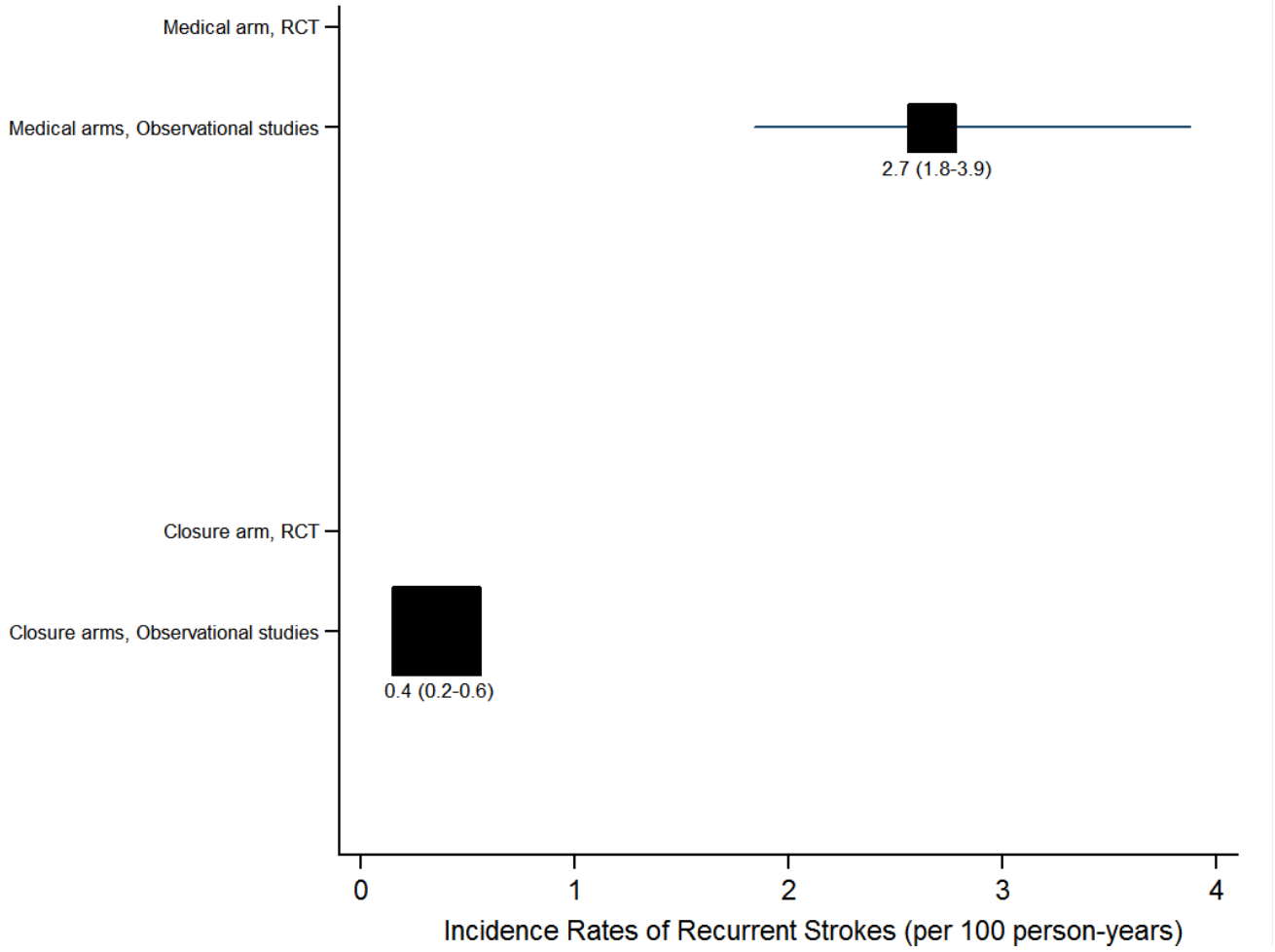
Meta-Analysis of Observational Studies

(Kitsios et al, in press)



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Meta-Analysis of Observational Studies

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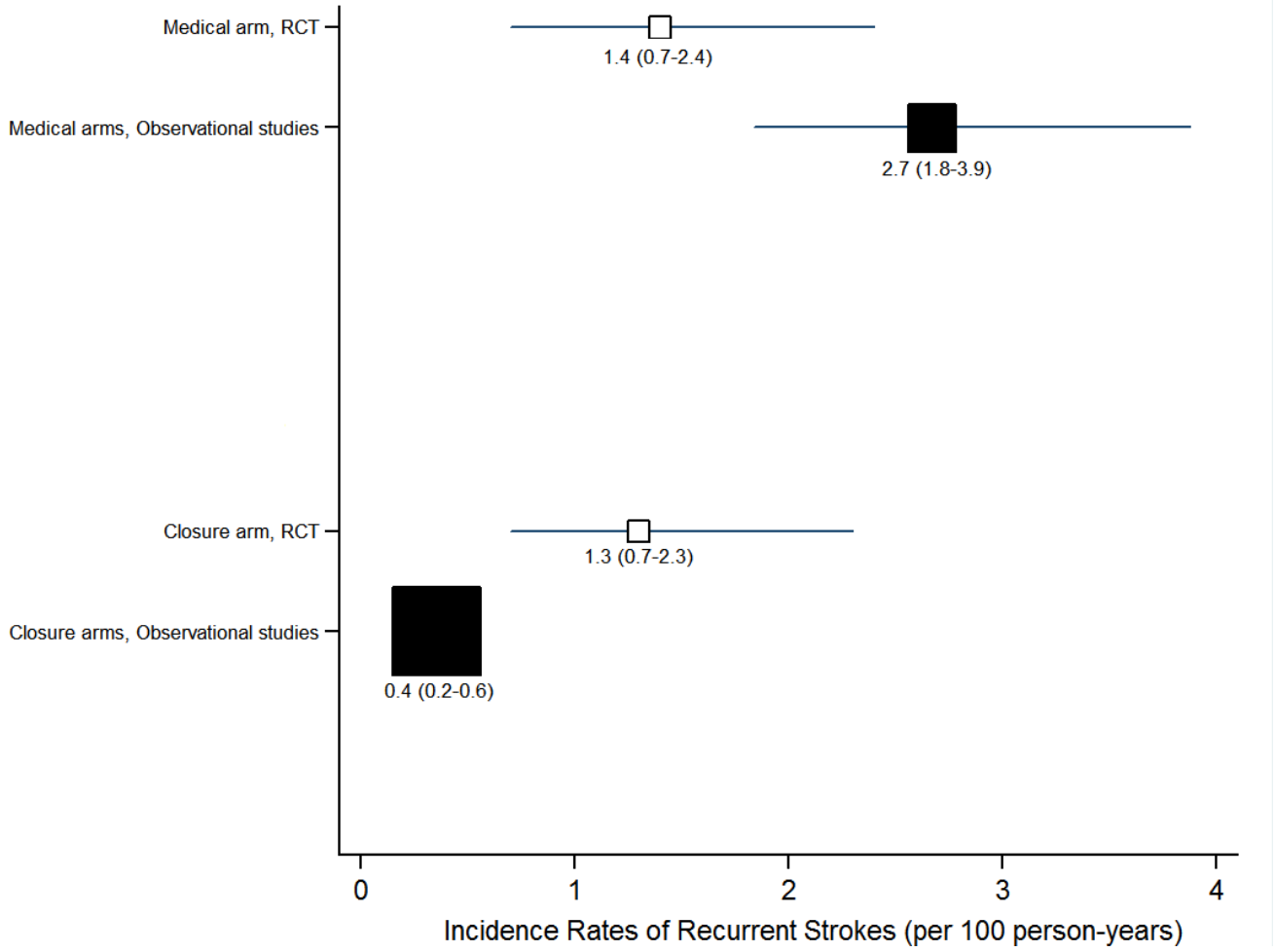

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Meta-Analysis of Observational Studies

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- The results of CLOSURE I challenge the credibility of a substantial body of observational evidence strongly favoring mechanical closure over medical therapy.
- Further randomized trial data are needed to determine precisely the effects of closure on stroke recurrence.

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The endpoint of interest is recurrent paradoxical embolism *not* recurrent stroke.

PFO May Be Causal For The First Stroke But Unrelated To Subsequent Ischemic Events

Mono et al and CLOSURE I

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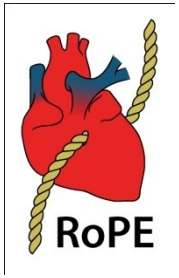
What happens when you have multiple causes of recurrent events?

The PICSS conundrum



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PICSS: Results

2-year rates of recurrent stroke or death in patients with different PFO size and shunt

	No PFO (n=398)	Small PFO (n=119)	Large PFO (n=84)
Event rate	15.4	18.5	9.5

Combination of PFO and atrial septal aneurysm (n=44) no riskier than PFO alone (n=159)

Mohr *et al* NEJM 345: 1444, 2001

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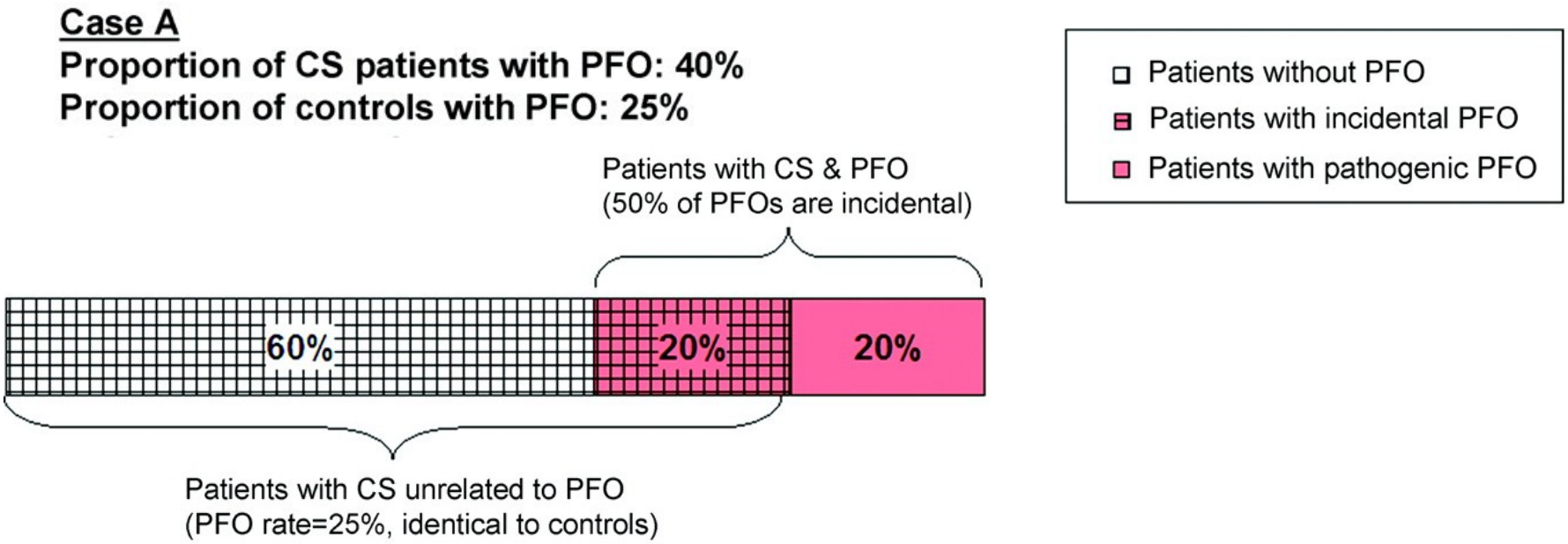
Proportion of patients with CS and PFO with incidental PFO

Case A
Proportion of CS patients with PFO: 40%
Proportion of controls with PFO: 25%



Probability PFO is incidental in CS cases=

$$\frac{\text{Prevalence of PFO in controls}*(1-\text{Prevalence of PFO in CS cases})}{\text{Prevalence of PFO in CS cases}*(1-\text{Prevalence of PFO in controls})}$$

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Alsheikh-Ali, A. A. et al. Stroke 2009;40:2349-2355

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Outcome risk

Risk of recurrent paradoxical embolism

=

“PFO propensity” x Probability of stroke recurrence

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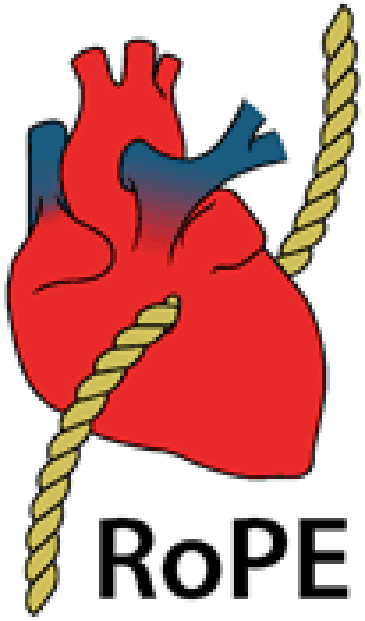
Risk of Paradoxical Embolism (RoPE) Study

NINDS R01 NS062153-01



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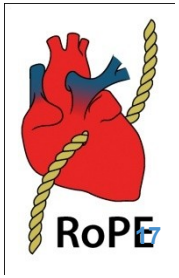
Risk of Paradoxical Embolism (RoPE) Study

1. To build the largest database of CS using existing cohort studies of patients with CS studied with TEE, both with and without PFO.
2. Model 1: Characteristics that predict PFO
3. Model 2: Characteristics that predict recurrent CS
4. Combine Models 1 & 2: Characteristics that predict PFO-related recurrence
5. Validation of the combined model on clinical trial populations (RESPECT, PC-Trial, CLOSURE I, REDUCE)



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Results: Component databases

Database	Collaborator(s)
CODICIA	Joaquin Serena
French PFO/ASA	Jean-Louis Mas
APRIS	Marco DiTullio
Bern (published)	Krassen Nedeltchev, Marie-Luise Mono
Bern (unpublished)	Heinrich Mattle
PICSS	Shunichi Homma
Lausanne	Patrik Michel
Toronto	Cheryl Jaigobin
Sapienza	Emanuele Di Angelantonio, Federica Papetti
Tufts	David Thaler
German	Christian Weimar
NOMASS	Mitchell Elkind

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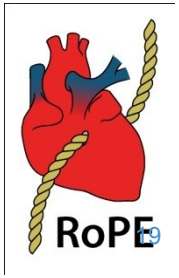
Results: Clinical Variables

- Age (at time of stroke)
- Gender
- Sex
- Race
- Coronary artery disease
- Diabetes
- Hypertension
- Hyperlipidemia

- Prior spells: number, date(s), event(s)
- Smoking status: current
- Medication at time of spell:
  Statin Antiplatelet

  Anticoagulant
  OCP/HRT
- Index event: date



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Results: Neuroradiological variables

1. **Index stroke seen:** yes, no
2. **Location**: superficial, deep
3. **Size**: large, small
4. **Multiple:** yes, no
5. **Prior stroke:** yes, no

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Results: Echocardiographic variables

1.	**Mobility of septum**	hypermobile (ASA), normal
2.	**PFO size**	large, small
3.	**Shunt at rest**	yes, no

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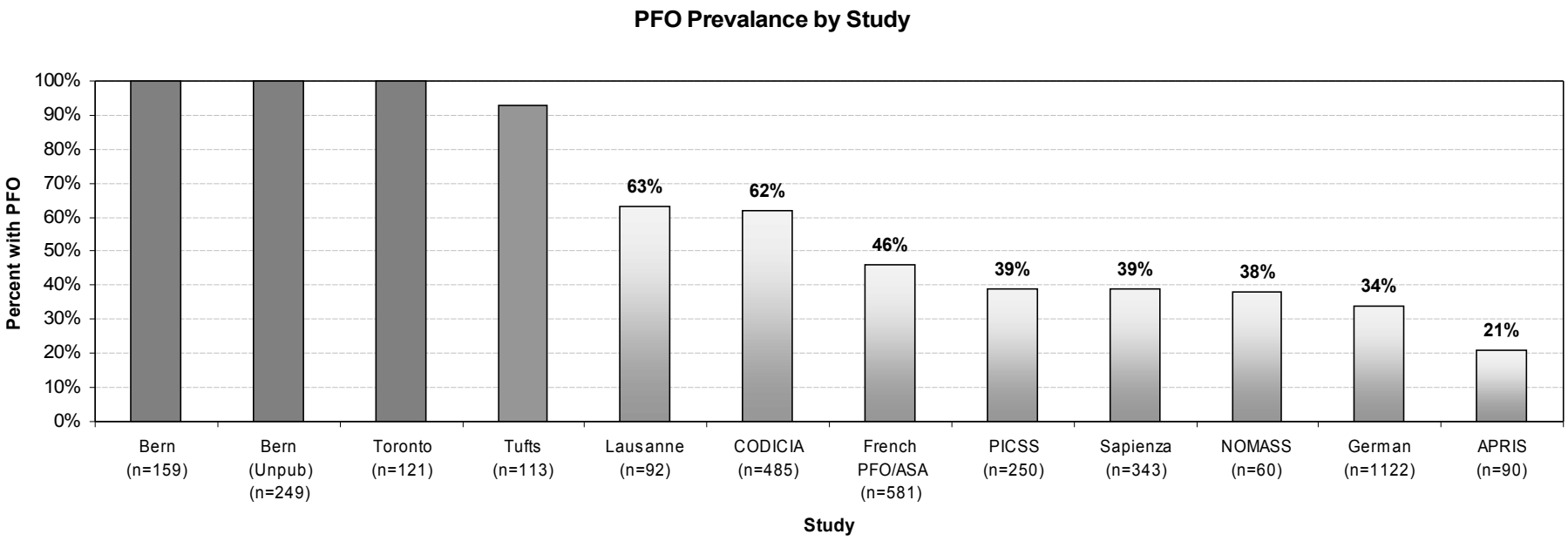
Results: PFO prevalence by site according to RoPE PFO definition



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Results: Prevalence of clinical variables

Incident event type, % stroke	All	Study Status		Study											
		BOTH	PFO ONLY	01.CODICIA	02.French PFO/ASA	03.APRIS	04.Bern	05.Bern_Unpub	06.PICSS	07.Lausanne	08.Toronto	09.Sapienza	10.Tufts	11.German	12.NOMASS
n=	3665	3023	642	485	581	90	159	249	250	92	121	343	113	1122	60
Age in years, mean	54.6	55.3	51.6	56.2	42.5	69.9	51	51.9	57.8	46.7	46.2	61.6	57.3	58.1	63.8
Gender, % male	59%	59%	60%	60%	57%	50%	59%	65%	57%	58%	53%	58%	59%	62%	45%
Race, % white	83%	82%	87%	.	98%	22%	.	.	57%	92%	.	100%	87%	.	12%
CAD, % yes	10%	10%	13%	5%	.	26%	8%	18%	18%	0%	.	8%	6%	10%	15%
DM, % yes	13%	15%	8%	12%	4%	37%	9%	6%	19%	5%	6%	17%	14%	18%	21%
HTN, % yes	42%	45%	31%	35%	15%	82%	32%	33%	47%	28%	17%	57%	42%	57%	65%
Cholesterolemia, % yes	29%	28%	34%	.	18%	34%	30%	40%	.	49%	23%	24%	37%	32%	21%
Current Smoker, % yes	32%	35%	22%	32%	48%	20%	33%	22%	29%	33%	15%	34%	16%	32%	24%
History of Stroke, % yes	8%	9%	8%	0%	3%	0%	9%	6%	10%	8%	3%	28%	14%	10%	0%
History of Tia, % yes	9%	8%	12%	6%	6%	2%	19%	10%	15%	14%	6%	16%	11%	7%	8%
Hx Stroke or Tia, % yes	16%	15%	18%	6%	9%	2%	26%	14%	23%	18%	9%	39%	23%	15%	8%
Statins, % yes	15%	13%	29%	.	.	34%	.	.	8%	3%	.	13%	29%	.	21%
Antiiplatelets, %yes	19%	14%	35%	7%	2%	66%	16%	66%	21%	8%	9%	28%	27%	23%	15%
Anticoagullants, % yes	4%	1%	12%	.	0%	12%	2%	25%	0%	1%	7%	2%	6%	1%	0%
Incident event type, % stroke	87%	89%	76%	83%	100%	100%	74%	77%	100%	100%	69%	.	87%	82%	100%
HRT/OCP, % yes (females only)	20%	23%	5%	11%	46%	0%	3%	.	0%	34%	.	.	7%	.	3%

Results: Outcomes

	Before Adjudication			
	Total	Stroke	TIA	Death
APRIS	21	9		12
Bern (pub)	25	7	14	4
CODICIA	40	10	18	12
French PFO/ASA	42	23	13	6
Lausanne	5	2	2	1
PICSS	47	24	14	9
Tufts	9	7	1	1
German	133	61	43	29
Total	**322**	**143**	**105**	**74**

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Model 1: “PFO propensity”

Clinical variables

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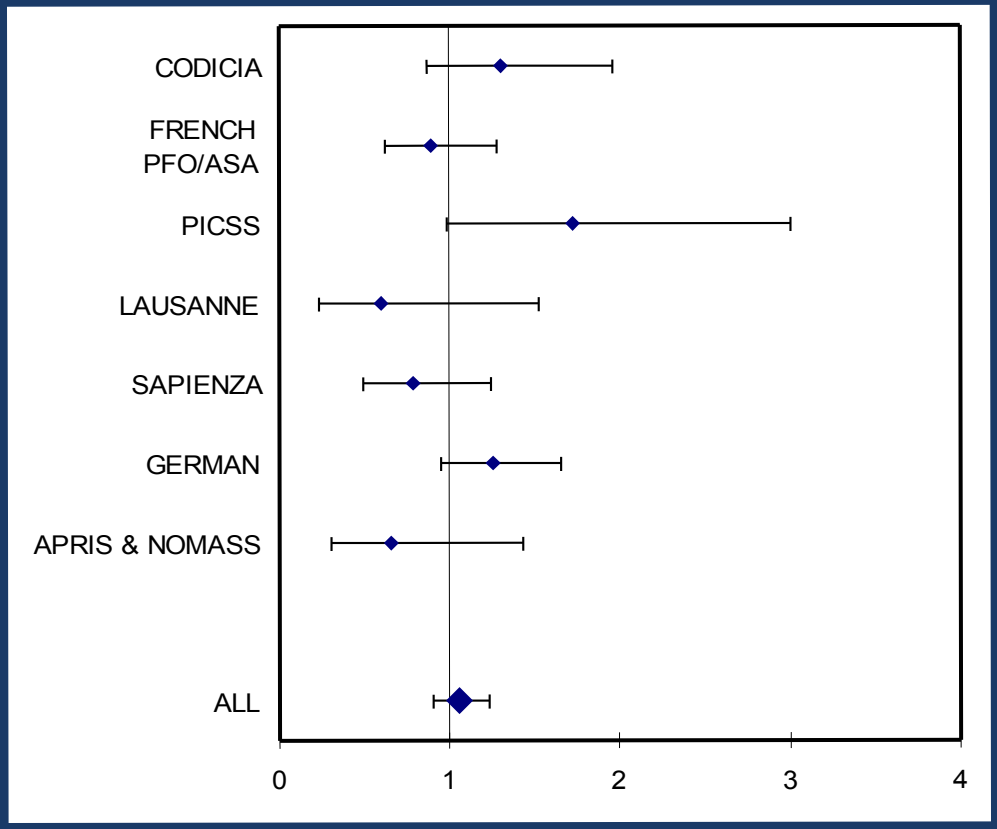
Consistency Across Sites of Relationship of *Gender* (Male v. Female) and Odds of having a PFO



** adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*

In Males, PFO is less likely (OR<1)

In Males, PFO is more likely (OR>1)

Odds Ratio (OR) for Male (vs. Female)

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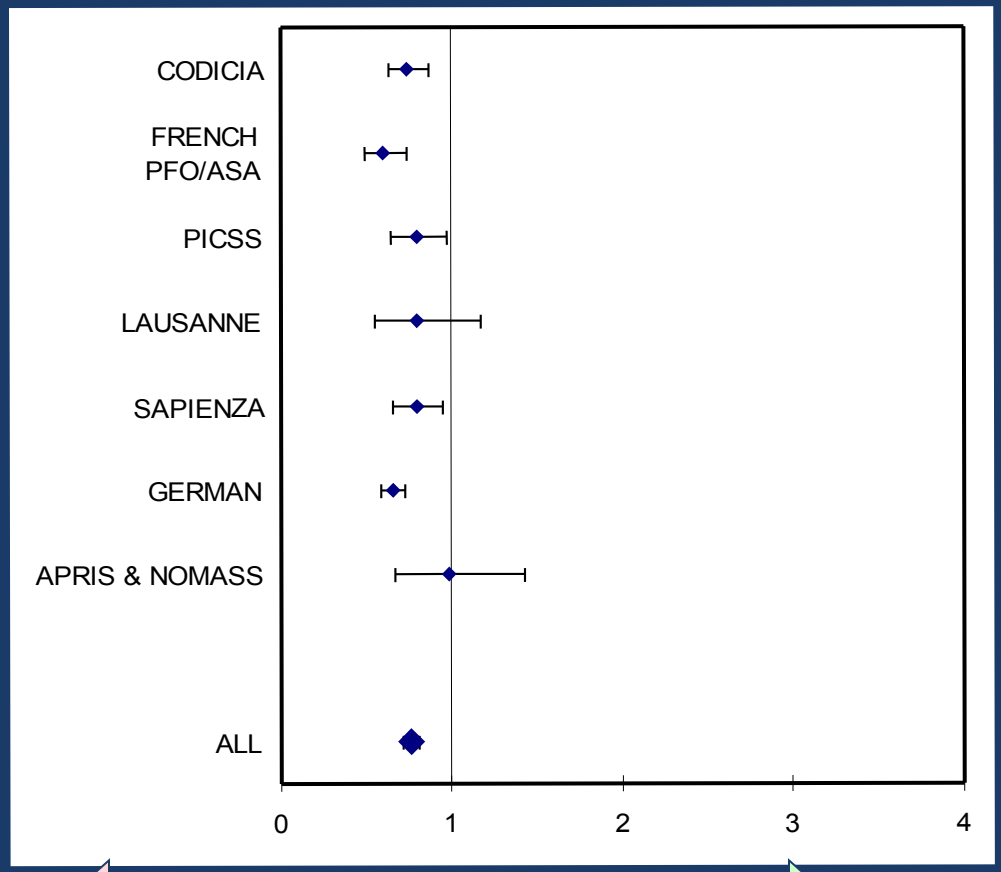
Consistency Across Sites of Relationship of *Age* and Odds of having a PFO



** adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*

In Older cases, PFO is less likely (OR<1)

In Older cases, PFO is more likely (OR>1)

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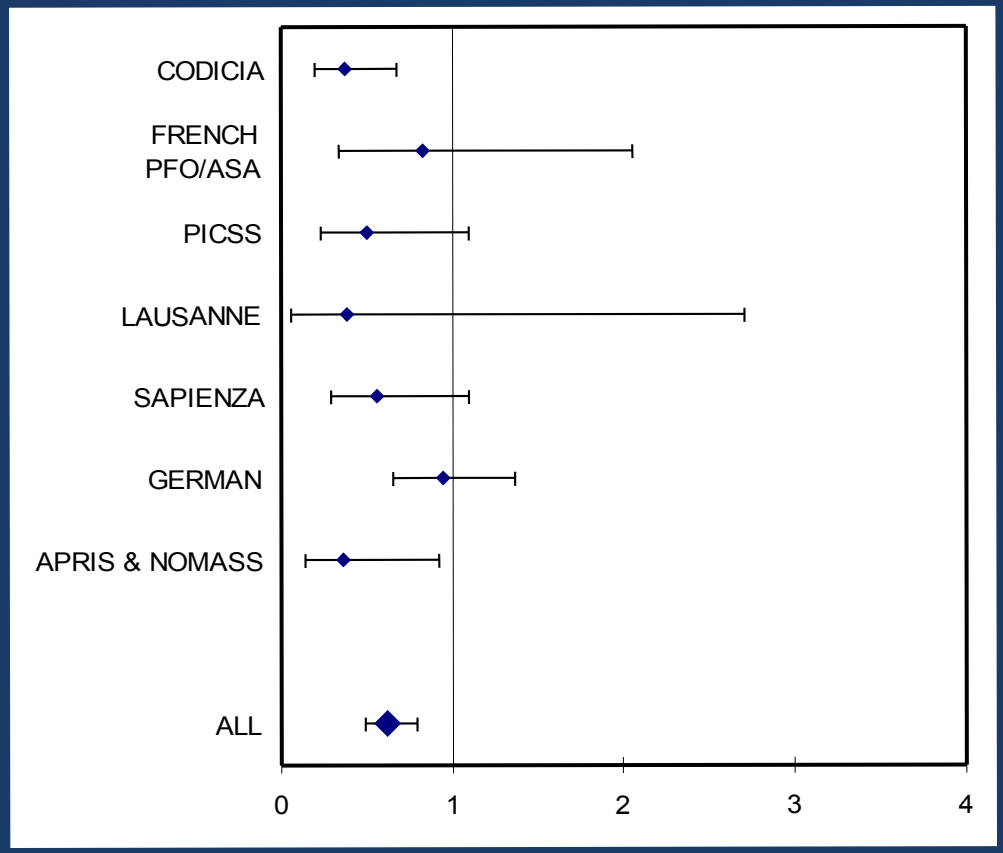
Consistency Across Sites of Relationship of *Diabetes* and Odds of having a PFO



** adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*

Odds Ratio (OR) for DM (vs. no DM)

In cases with DM, PFO is less likely (OR<1)

In cases with DM, PFO is more likely (OR>1)

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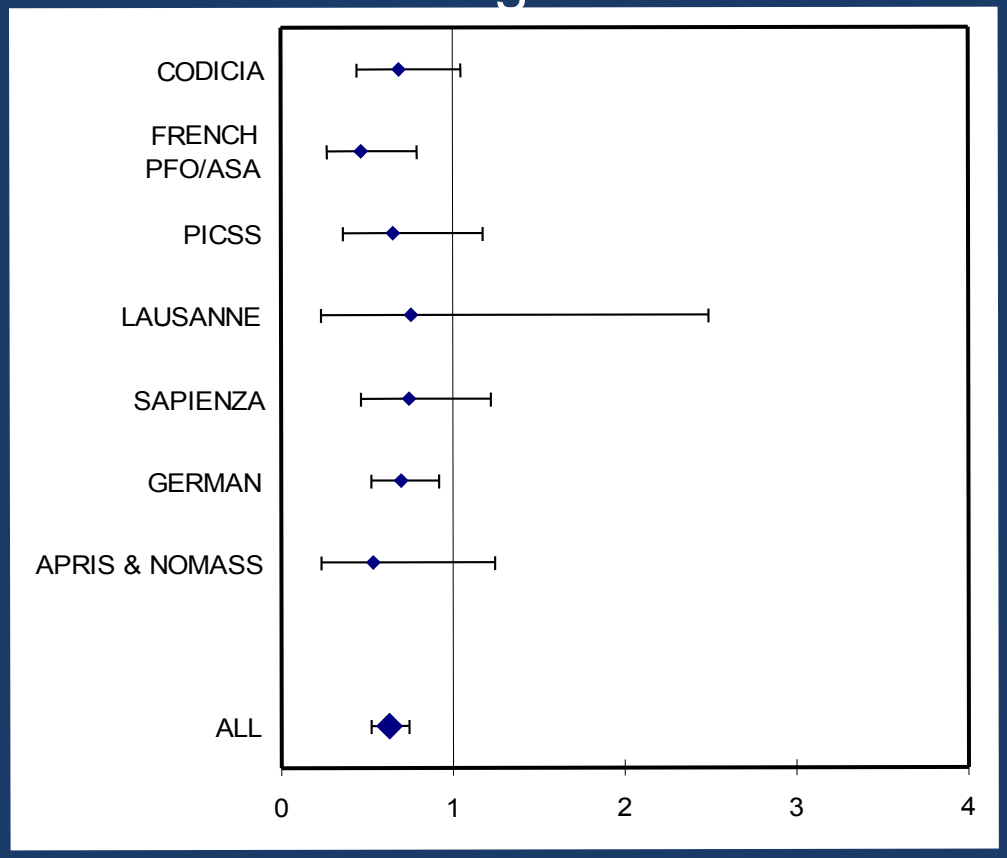
Consistency Across Sites of Relationship of *Hypertension* and Odds of having a PFO



** adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*

Odds Ratio (OR) for HTN (vs. no HTN)

In cases with HTN, PFO is less likely (OR<1)

In cases with HTN, PFO is more likely (OR>1)

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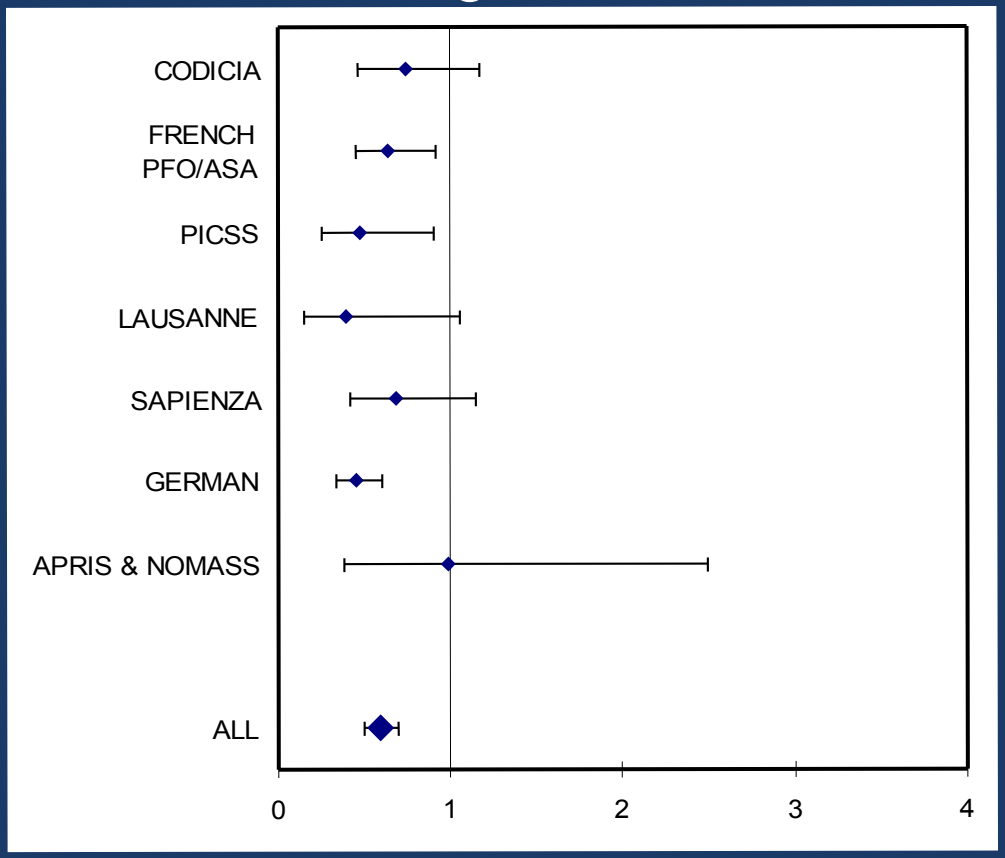
Consistency Across Sites of Relationship of *Smoking* and Odds of having a PFO



** adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*

Odds Ratio (OR) for Current Smoking (vs. not)

In cases with Smoking, PFO is less likely (OR<1)

In cases with Smoking, PFO is more likely (OR>1)

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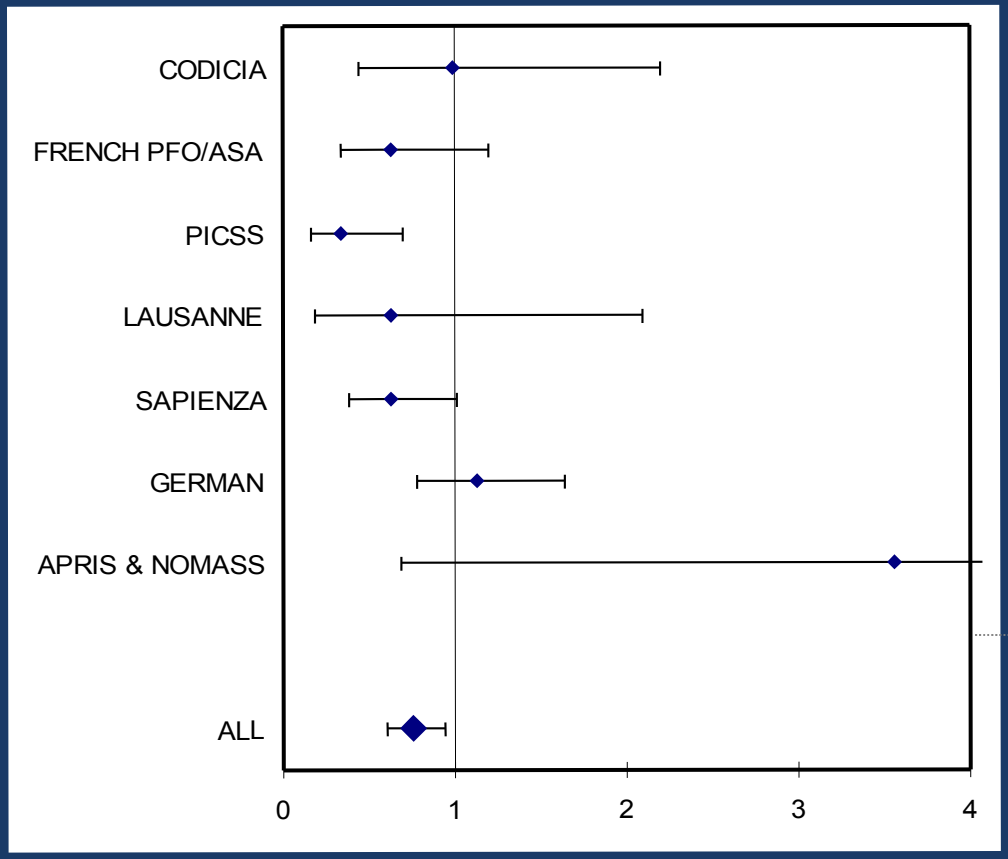
Consistency Across Sites of Relationship of *History of Stroke or TIA* and Odds of having a PFO*



** adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*

Odds Ratio (OR) for History of Stroke or TIA (vs. not)

In cases with Hx Stroke/TIA, PFO is less likely (OR<1)

In cases with Hx Stroke/TIA, PFO is more likely (OR>1)

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Clinical variables: Findings & Results

- Subjects were significantly *more likely to have a PFO* if they had:
  - Younger age
  - No DM
  - No HTN
  - No smoking
  - No prior h/o stroke/TIA
- A *trend to more likely to have a PFO* if they had:
  - No hyperlipidemia
  - No CAD
  - No statin use at time of index event
  - No antiplatelet use at time of index event
- There was *no effect* of:
  - Gender
  - Race

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Model 1: “PFO propensity”

Neuroradiological variables

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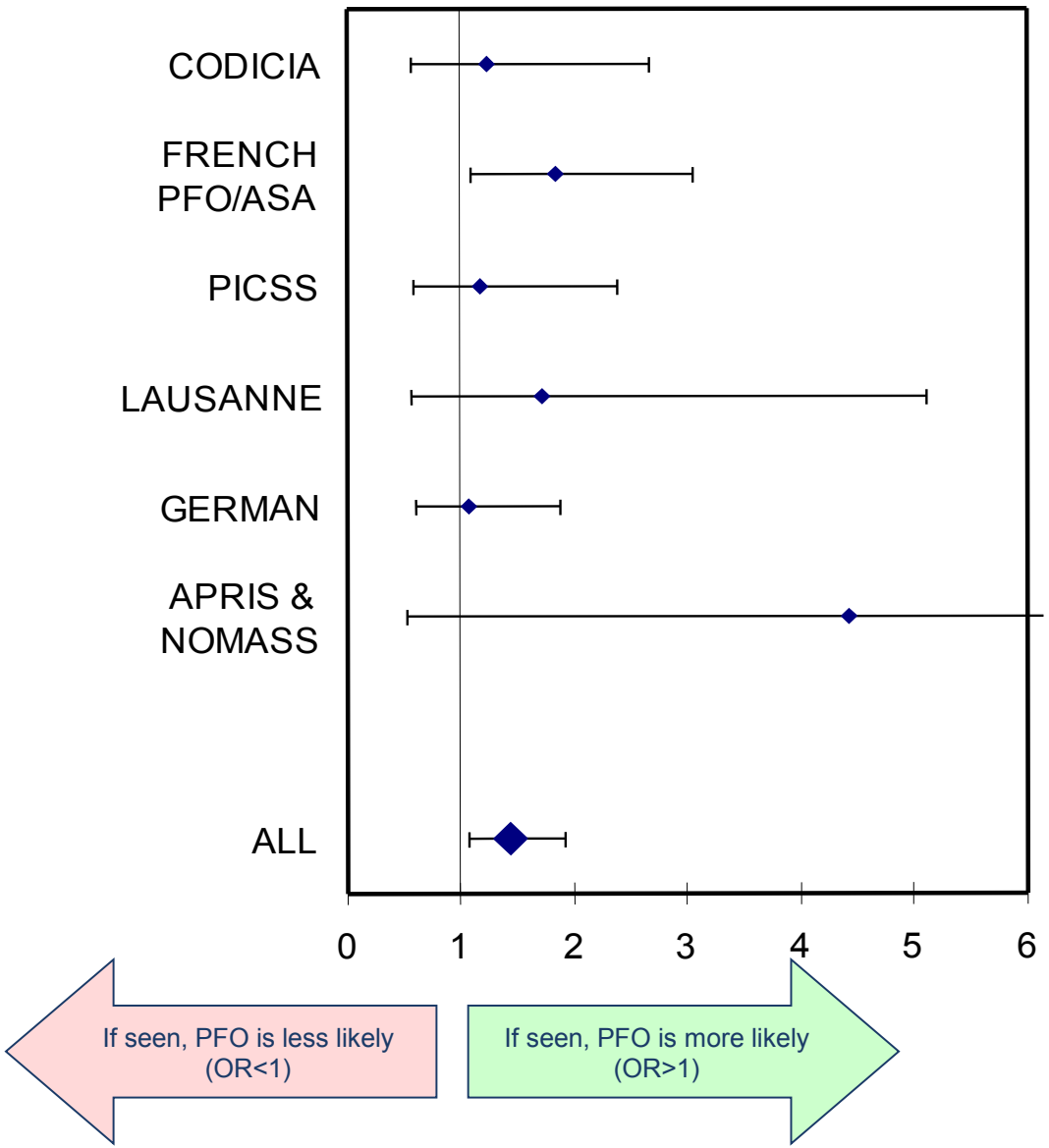
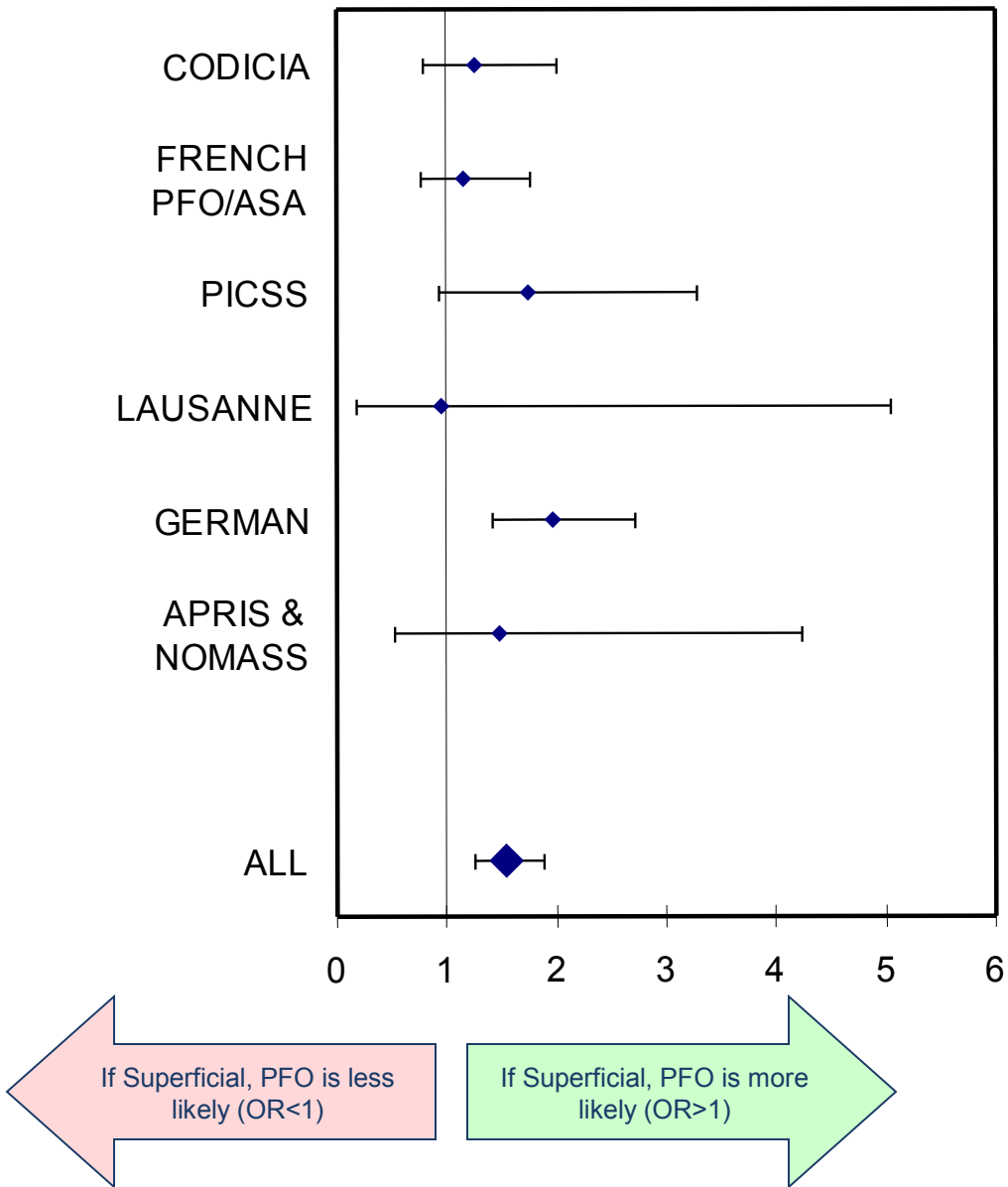
Consistency Across Sites of Relationship of *Having Stroke Seen On Index Image* and Odds of having a PFO*

**Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*



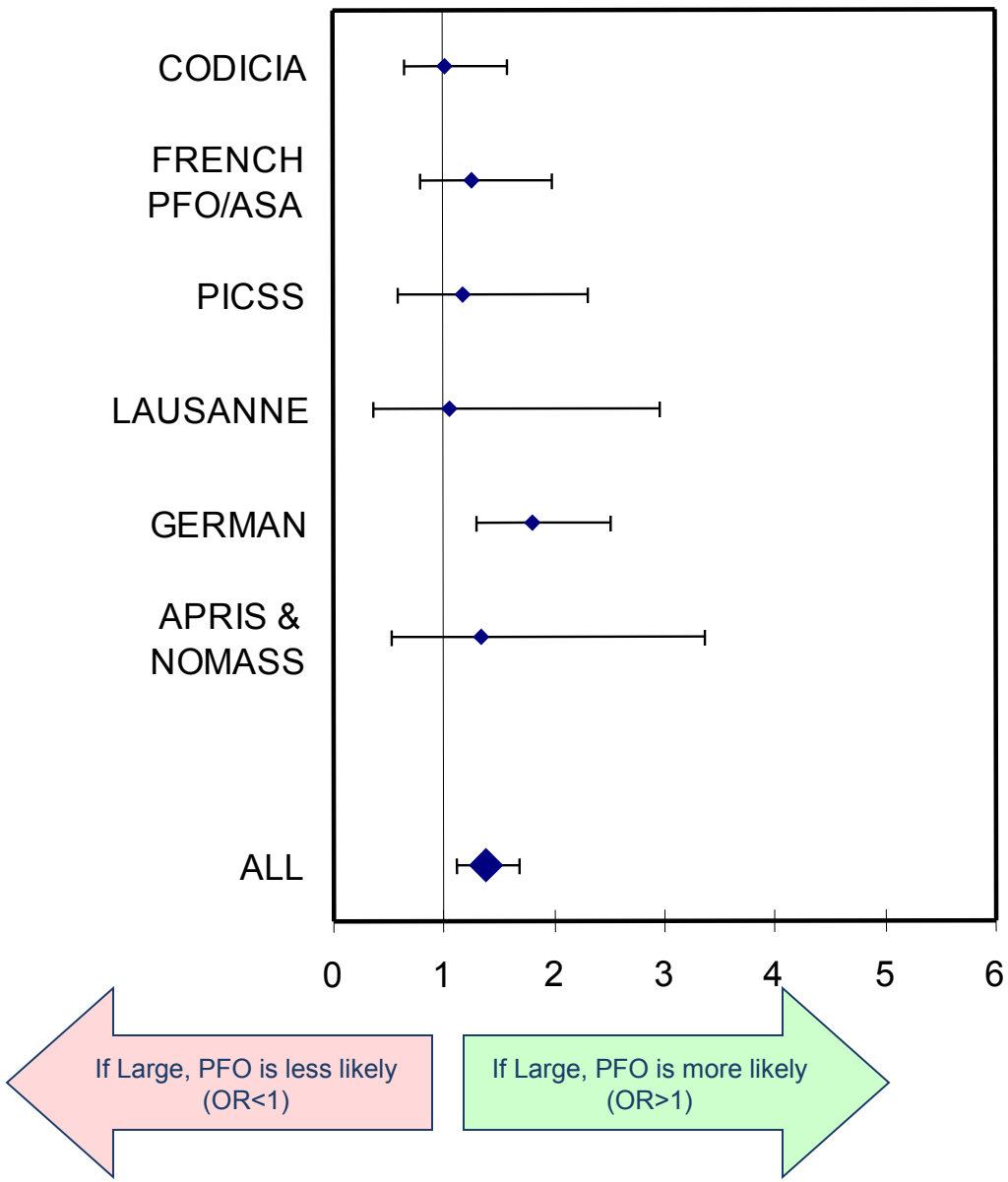
Consistency Across Sites of Relationship of *Superficial vs. Deep Location of Infarct* and Odds of having a PFO*

**Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*



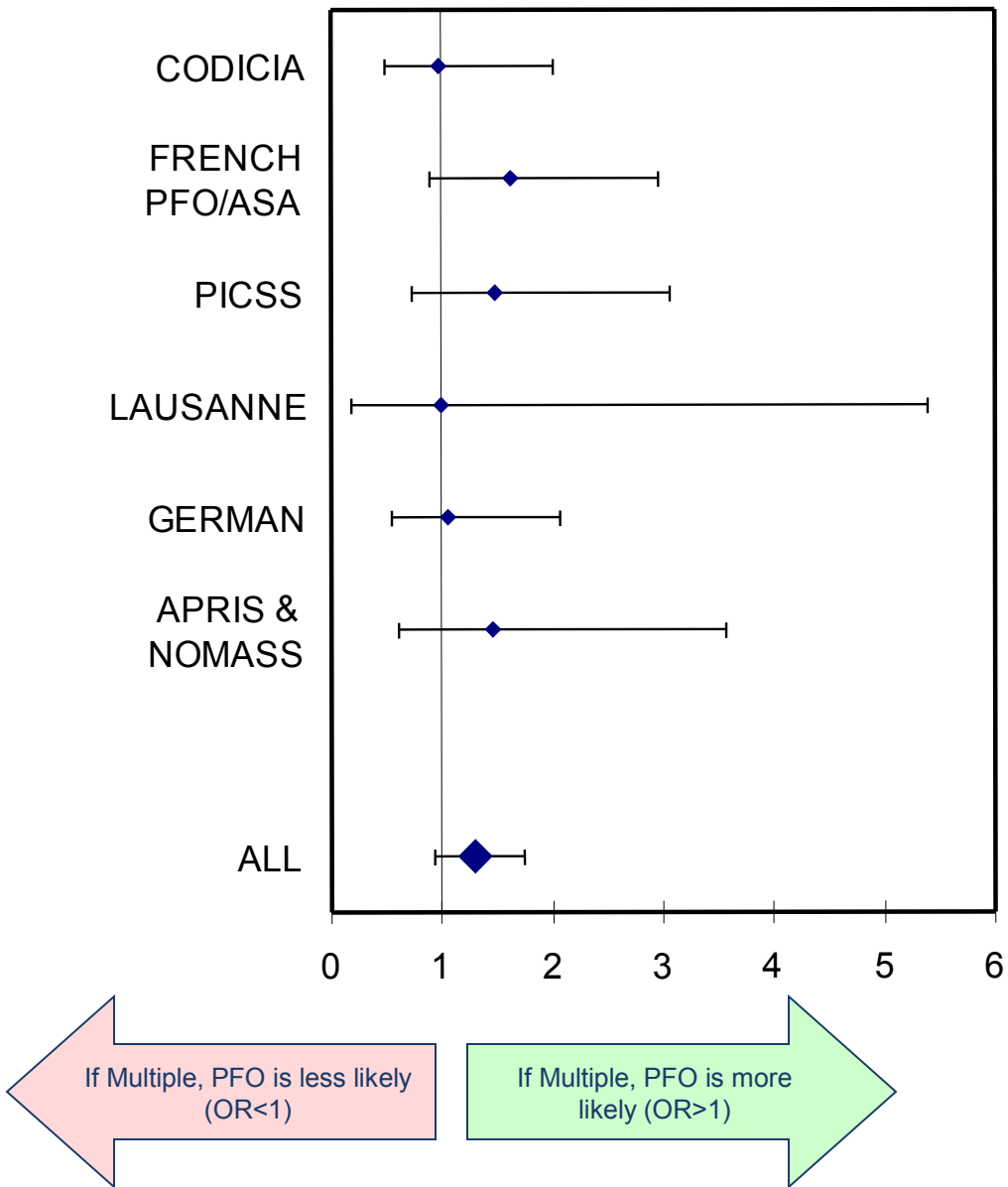
Consistency Across Sites of Relationship of *Large Infarct vs. Small/not seen* and Odds of having a PFO*

**Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*



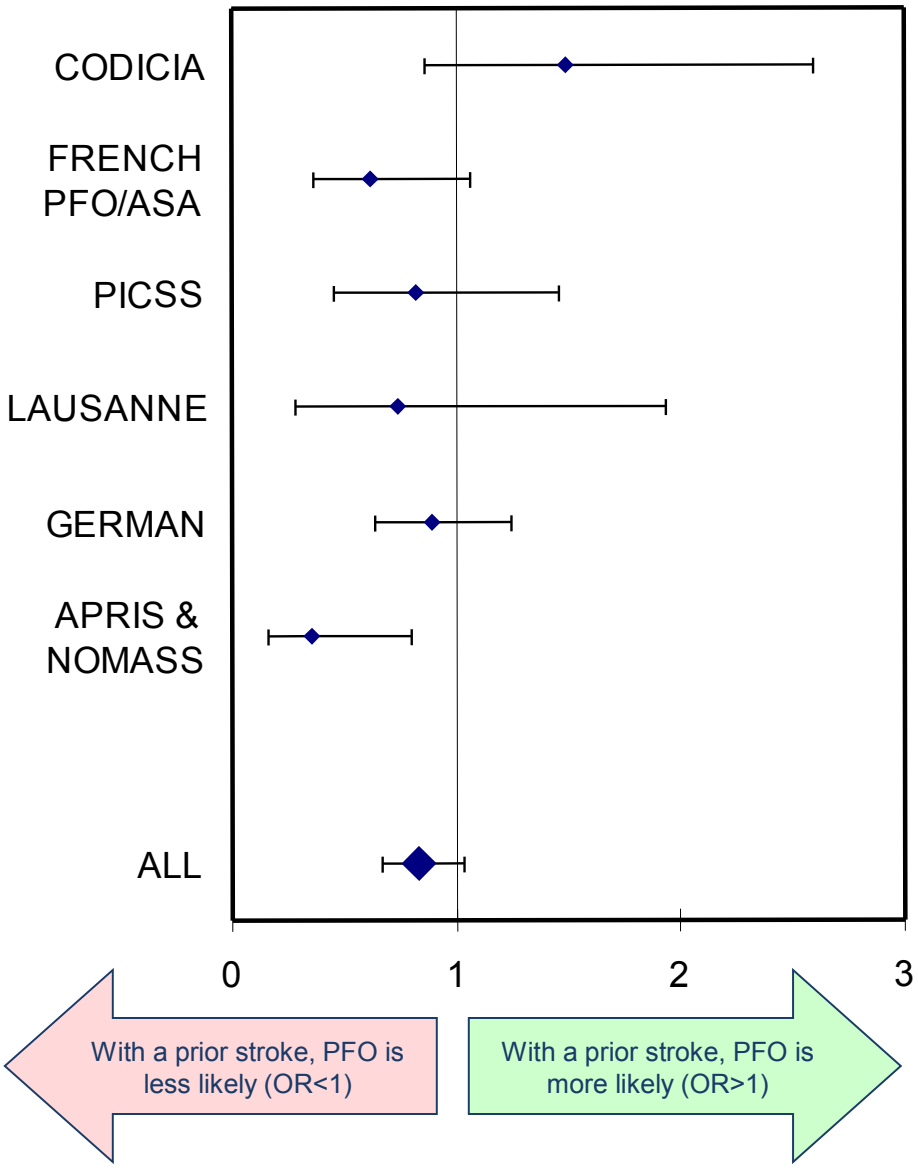
Consistency Across Sites of Relationship of *Infarcts are Multiple vs. Single/Not Seen* and Odds of having a PFO*

**Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*



Consistency Across Sites of Relationship of *Prior (chronic) Stroke on Index Imaging* and Odds of having a PFO*

**Age adjusted odds ratios (and 95% confidence intervals) for each site, and pooled across sites, are shown as blue diamonds and black whiskers*



Neuroradiological variables: Findings & Results

- Subjects were significantly *more likely to have a PFO* if they had:
  - An index stroke seen on neuroimaging
  - A large stroke
  - A superficial stroke
- A *trend to more likely to have a PFO* if they had:
  - No prior (*i.e.* chronic) infarct seen
- There was *no effect* of:
  - Multiple v single infarcts

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Estimated Probability of Pathogenic PFO by Propensity Quartile

		All	Rank for Variable predpfo			
			q1:less pfo	q2	q3	q4:more pfo
Variable	Total Sample Size	3022	755	756	756	755
pred	%Predicted PFO	42%	22%	35%	47%	66%
pfo_03	%Observed PFO	42%	25%	30%	48%	66%
	CR=15%	76%	46%	59%	81%	91%
	CR=20%	**66%**	**24%**	**42%**	**73%**	**87%**
	CR=25%	54%	0%	23%	64%	83%

CR = control rate (i.e. prevalence in the general population)

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Conclusion

- The RoPE Study has successfully merged several databases of existing cohort studies.
- This is the largest database in existence of patients with CS and PFO that includes detailed clinical, neuroradiological, and echocardiographic data.
- Further analysis to model PFO propensity and the risk of recurrent CS are ongoing.
- These data will inform decisions regarding CS diagnosis and (hopefully) treatment decisions.

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Boston RoPE Team

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Marcia Landa

Robin Ruthazer

John Griffith

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Cardiology

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Jessica Haffajee

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Neuroradiology

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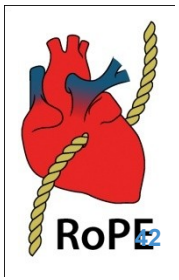

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What is certain?

- Predictors of recurrence are *not* firmly established
- Devices close holes
- Some FOs remain P after “closure”
- Devices seem to be LOW risk (but *not* NO risk)
- Even a low rate of procedure or device-related adverse events could nullify most or all of the potential benefit
- Case series are completely inadequate (and possibly misleading) for determining the risk:benefit of closure
- We must be honest with patients about what is known
- ***More data are needed!***

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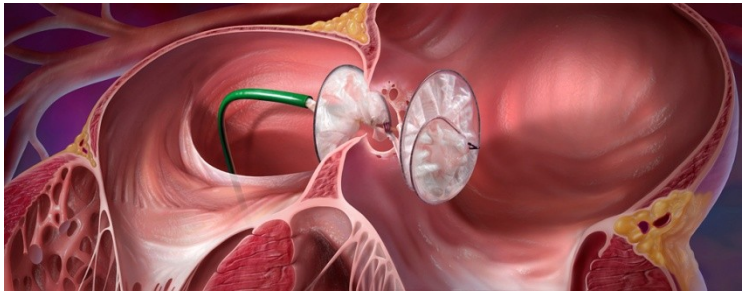
Ongoing trials

- RESPECT: www.respectstudy.com

- REDUCE: www.clinical.goremedical.com/REDUCE



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What's the difference between a chicken and a pig's approach to ham & eggs for breakfast?


The chicken has an interest but the pig is truly committed!

Thank you!

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