Cryptogenic stroke vs. PFO Stroke? Neurology perspectives

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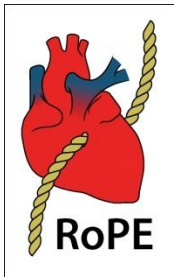
Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Research Support for clinical trial	• WL Gore Associates
• Research Support for clinical trial	• St. Jude Medical
• Consulting Fees for RESPECT Steering Committee	• St. Jude Medical
• Grant Support for RoPE Study	• NINDS (NIH)



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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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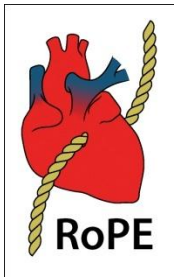
We need to identify factors that:

1) Predict that the PFO is pathogenic and
2) Predict the risk of recurrence of CS



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Cryptogenic stroke with PFO

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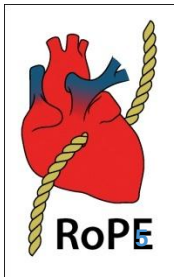
Paradoxical embolism



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We believe that paradoxical embolism is related to stroke because PFO is over-represented in populations of CS v stroke of known cause

BUT

Are there patient-level variables that predict PFO from within the CS population?

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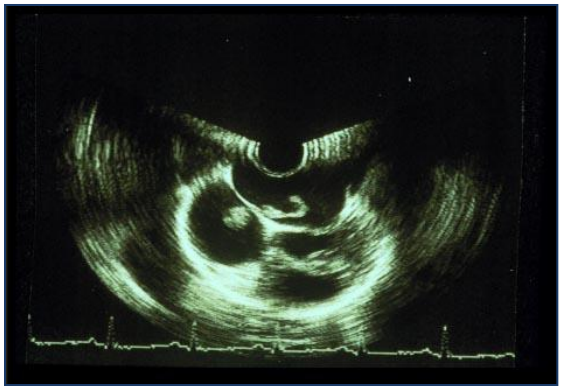
Support for diagnosis of paradoxical embolism

Thrombus *in* PFO



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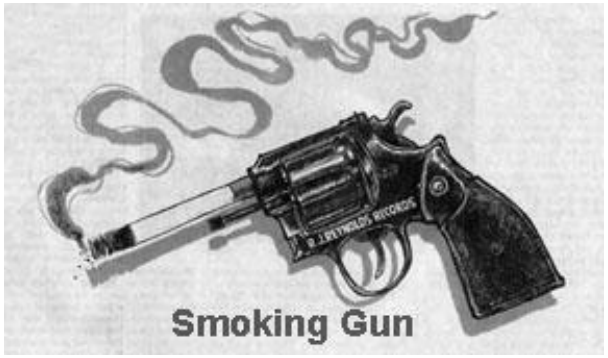

= very rare

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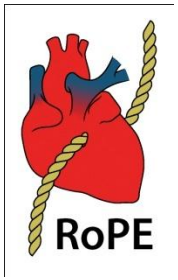
Suggested predictors of pathogenic PFO

- Cryptogenic stroke
- Absence of conventional vascular RFs
- Young age
- Prior immobility (eg airplane travel)
- Valsalva at onset
- Associated features
  - Atrial septal aneurysm
  - Shunt at rest
  - Size of shunt



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Predictors of pathogenic PFO ≠ predictors of recurrence

- ~~Cryptogenic stroke~~
- ~~Absence of conventional vascular RFs~~
- ~~Young age~~
- ?? Prior immobility (eg airplane travel)
- ?? Valsalva at onset
- ?? Associated features
  - Atrial septal aneurysm
  - Shunt at rest
  - Size of shunt

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“Precurrent stroke” is not associated with “provoked” paradoxical embolism

Neurology 2012 78:993-997

- Precurrence = chronic stroke seen on imaging at the time of the index event (surrogate for recurrent stroke)

- Provoked paradoxical embolism = CS+PFO in the setting of 1) Immobility/DVT, 2) Valsalva, or 3) Both

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Neurology 2012 78:993-997

Table 1 Descriptive characteristics of subjects included in the Tufts PFO Registry

Baseline variables in the Tufts PFO Registry (n = 224)	
Men, n (%)	127 (57)
Age, y, mean (SD)	52.3 (14.3)
Clinical conditions for provoked paradoxical embolism, n (%)	
Prothrombotic conditions	83 (37)
Concurrent deep vein thrombosis	13 (6)
Prolonged immobility or postoperative period	73 (33)
Valsalva maneuver	60 (27)
Either prothrombotic conditions or Valsalva maneuver	121 (54)
Both prothrombotic conditions and Valsalva maneuver	22 (10)

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Neurology 2012 78:993-997

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Valsalva maneuver
Either prothrombotic conditions or Valsalva maneuver
Both prothrombotic conditions and Valsalva maneuver

Table 2 Associations between radiologic endpoints of interest and clinical indicators of paradoxical embolism[a]

Clinical conditions	Strokes of different radiologic ages	Silent strokes	Large acute strokes
All patients			
1: Valsalva maneuver	1.30 (0.55–3.09) [1.23 (0.58–2.60)]	1.03 (0.45–2.32) [0.97 (0.44–2.14)]	0.67 (0.31–1.47) [0.74 (0.36–1.52)]
2: Prothrombotic conditions	1.19 (0.54–2.67) [1.01 (0.49–2.04)]	0.61 (0.27–1.33) [0.65 (0.30–1.38)]	1.44 (0.73–2.86) [1.41 (0.73–2.68)]
1 or 2	1.29 (0.59–2.79) [1.37 (0.68–2.73)]	0.78 (0.38–1.59) [0.82 (0.41–1.65)]	1.01 (0.52–1.95) [1.04 (0.56–1.93)]
1 and 2	1.25 (0.30–5.14) [0.66 (0.18–2.37)]	0.52 (0.11–2.40) [0.46 (0.10–2.06)]	1.12 (0.32–3.93) [1.18 (0.34–4.04)]
Patients with index cortical stroke			
1: Valsalva maneuver	1.68 (0.61–4.62)	1.49 (0.55–4.03)	0.83 (0.32–2.12)
2: Prothrombotic conditions	1.16 (0.50–2.74)	0.99 (0.41–2.39)	2.17 (0.93–5.06)
1 or 2	1.84 (0.74–4.59)	1.34 (0.56–3.22)	1.57 (0.71–3.42)
1 and 2	1.04 (0.19–5.64)	0.95 (0.18–4.96)	1.78 (0.29–10.8)

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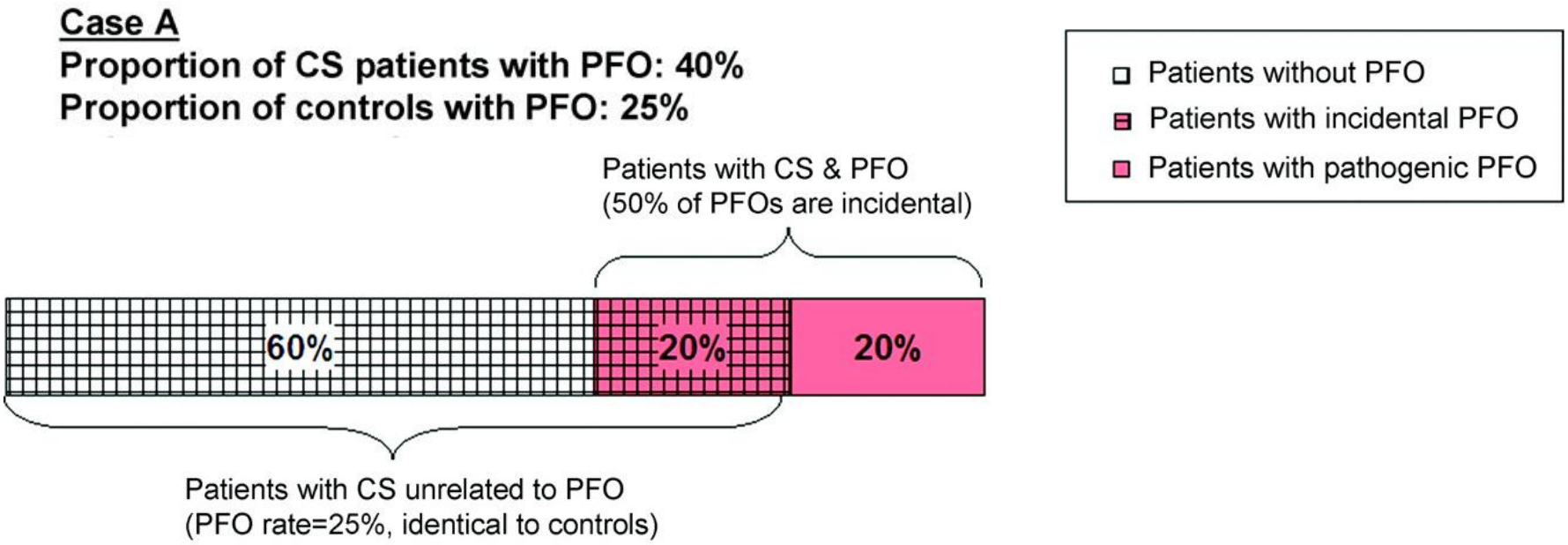
Proportion of CS patients with incidental PFO

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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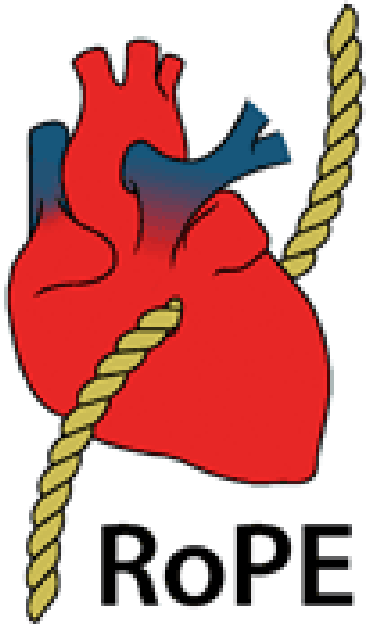
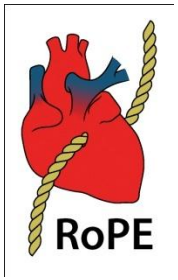
Risk of Paradoxical Embolism (RoPE) Study

NINDS R01 NS062153-01





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RoPE Study premise:

PFO closure can only benefit patients with a high

"PFO attributable recurrence risk"

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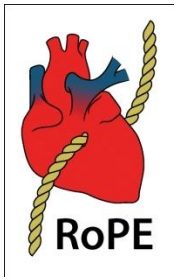
Likelihood of pathogenic PFO *x* recurrence risk



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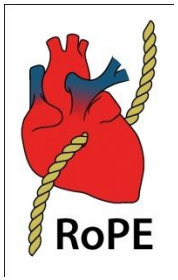
Attributable fraction

While it is rarely possible to establish in an individual patient whether a PFO discovered in a CS patient is incidental or pathogenic, one can estimate the attributable fraction using Bayes' theorem



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Attributable fraction

So, the attributable fraction is dependent on the excess prevalence of PFO in the CS population.

BUT (!)

PFO prevalence among CS patients varies based on other characteristics

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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 (CLOSURE I, RESPECT, PC-Trial, REDUCE)

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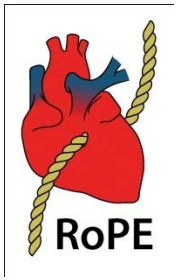
Methods – 9 steps to the RoPE database

1. Selected published and unpublished data bases
2. Developed a collaborative team of international investigators
3. Determined availability and characteristics of data in each data base
4. Specified dependent variables
5. Determined and specified the independent variables
6. Specified inclusion/exclusion criteria for data base inclusion
7. Added new data bases if discovered and suitable
8. Acquired new primary data (re-read MRI, TEE, etc)
9. Checked for “missingness” and consistency of effects



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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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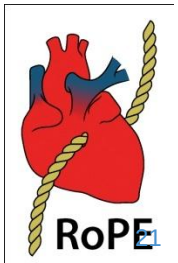
Results: Clinical Variables

- 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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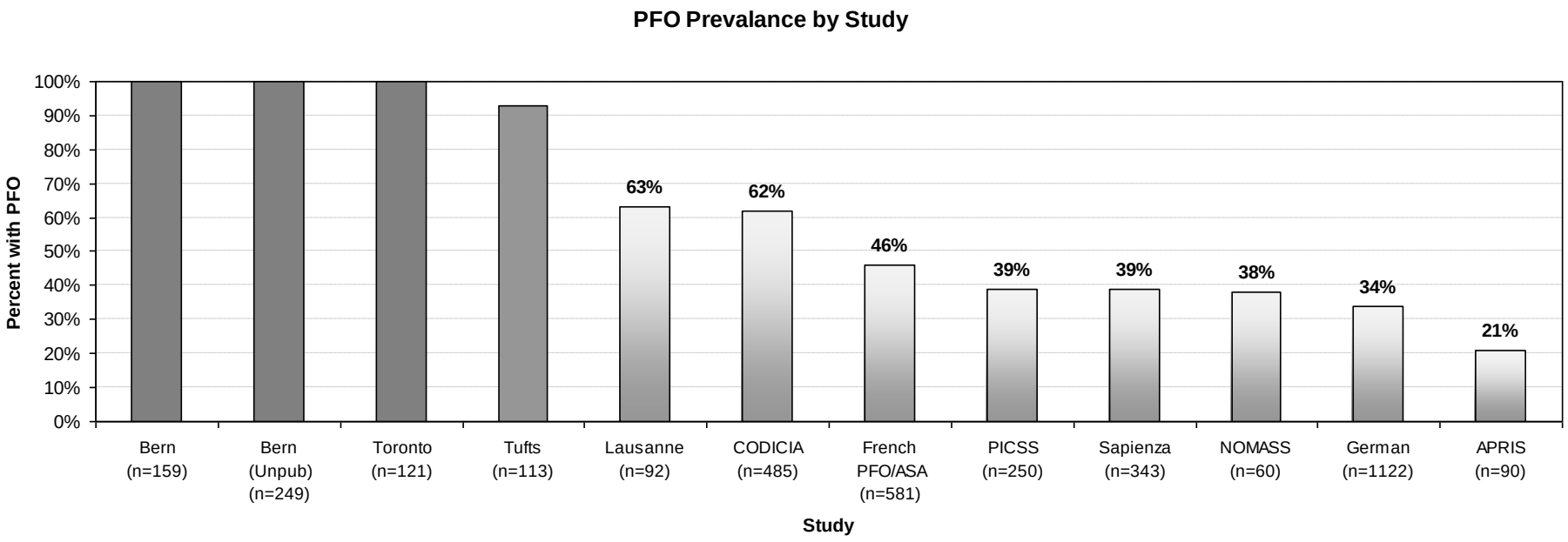
Results: PFO prevalence by site according to RoPE PFO definition



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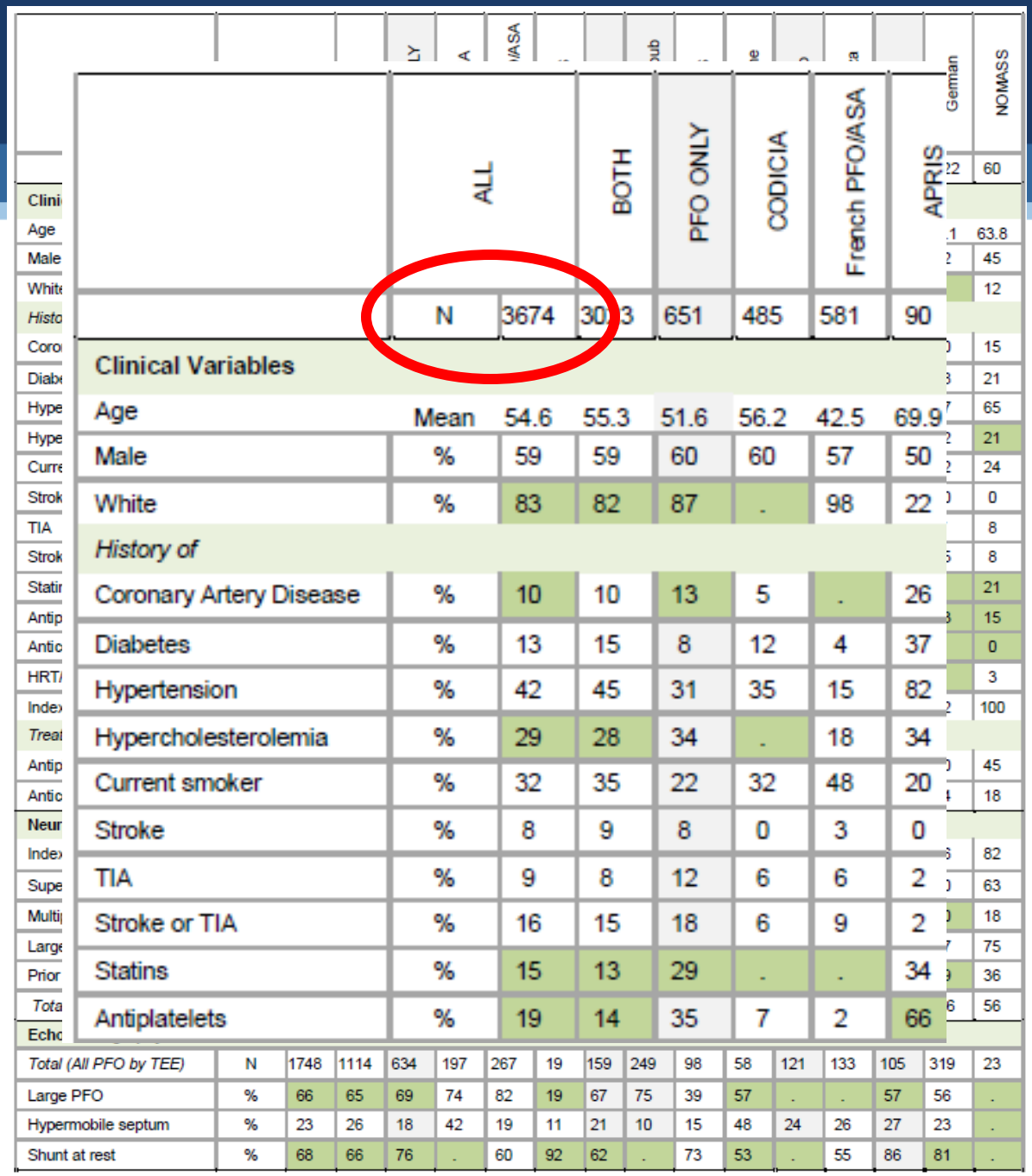

		ALL	BOTH	PFO ONLY	CODICIA	French PFO/ASA	APRIS	German	NOMASS
	N	3674	303	651	485	581	90	22	60
Clinical Variables									
Age	Mean	54.6	55.3	51.6	56.2	42.5	69.9	1	63.8
Male	%	59	59	60	60	57	50	2	45
White	%	83	82	87	.	98	22		12
History of									
Coronary Artery Disease	%	10	10	13	5	.	26	0	15
Diabetes	%	13	15	8	12	4	37	3	21
Hypertension	%	42	45	31	35	15	82	7	65
Hypercholesterolemia	%	29	28	34	.	18	34	2	21
Current smoker	%	32	35	22	32	48	20	2	24
Stroke	%	8	9	8	0	3	0	0	0
TIA	%	9	8	12	6	6	2		8
Stroke or TIA	%	16	15	18	6	9	2	5	8
Statins	%	15	13	29	.	.	34		21
Antiplatelets	%	19	14	35	7	2	66	3	15
									0
									3
								2	100
								0	45
								4	18
								6	82
								0	63
								0	18
								7	75
								9	36
								6	56
Total (All PFO by TEE)	N	1748	1114	634	197	267	19	159	249	98	58	121	133	105	319	23
Large PFO	%	66	65	69	74	82	19	67	75	39	57	.	.	57	56	.
Hypermobile septum	%	23	26	18	42	19	11	21	10	15	48	24	26	27	23	.
Shunt at rest	%	68	66	76	.	60	92	62	.	73	53	.	55	86	81	.

Table 1. Prevalence of each variable by database.

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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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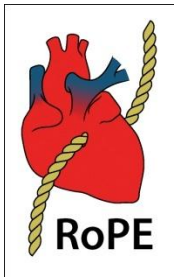
Model 1: “PFO propensity”



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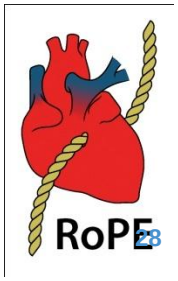
Generalized linear models to develop an index estimating PFO prevalence conditional on patient characteristics.

Bayes' theorem transforms the stratum-specific PFO prevalence to a stratum-specific estimate of PFO-attributable fraction.



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Model Assumptions

1) If not for those strokes that are PFO-attributable, the probability of a PFO in a CS patient would be the same as in the general population (controls)

2) The rate of PFO-attributable strokes in PFO-negative CS patients is near-zero

3) PFO prevalence is unrelated to patient characteristics in the general population (i.e. control rate is constant)

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Database	# of subjects	# w/ PFO	# w/o PFO
APRIS[27]*	90	19	71
CODICIA[28]	485	300	185
French PFO-ASA[29]	581	267	314
German[30]	1122	376	746
Lausanne	92	58	34
NOMASS[31]	60	23	37
PICSS[32]*	250	98	152
Sapienza[33]*	343§	133§	210
Bern (published)[34]	159	159	0
Bern (unpublished)	249	249§	0
Toronto[35]	121	121	0
Tufts[36]	122	122	0

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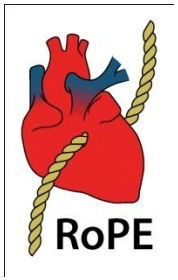
Model 1:
Clinical variables



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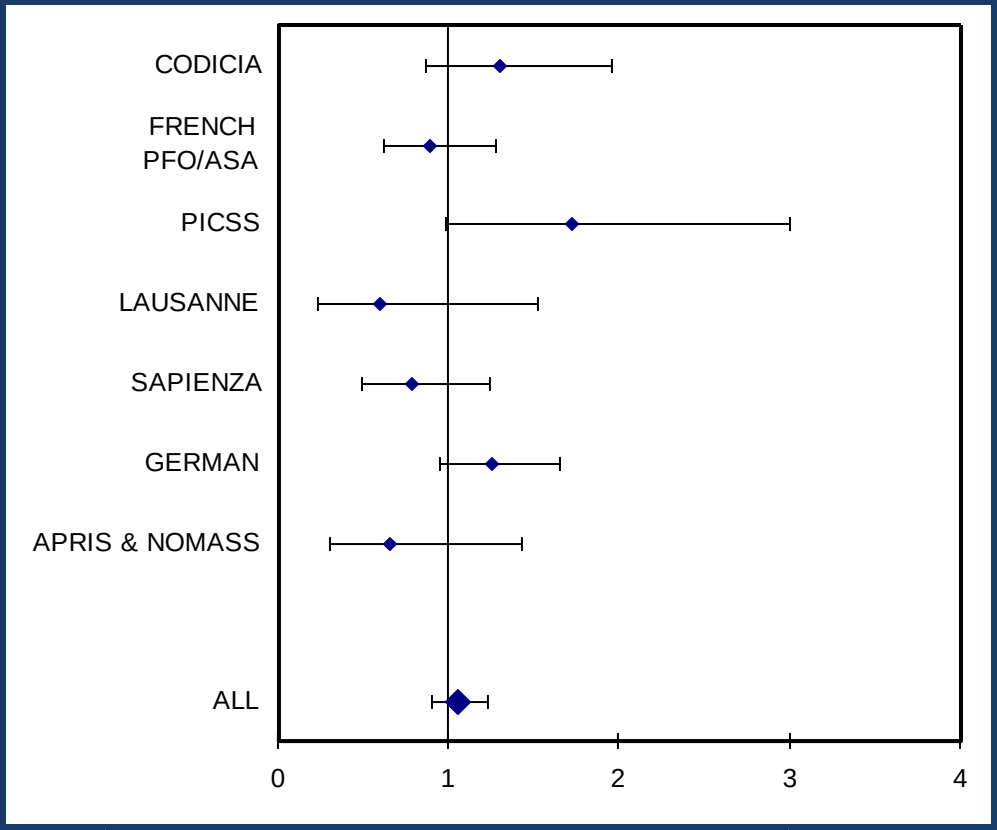
Consistency Across Sites of Relationship of *Gender* (Male v. Female) and Odds of having a PFO



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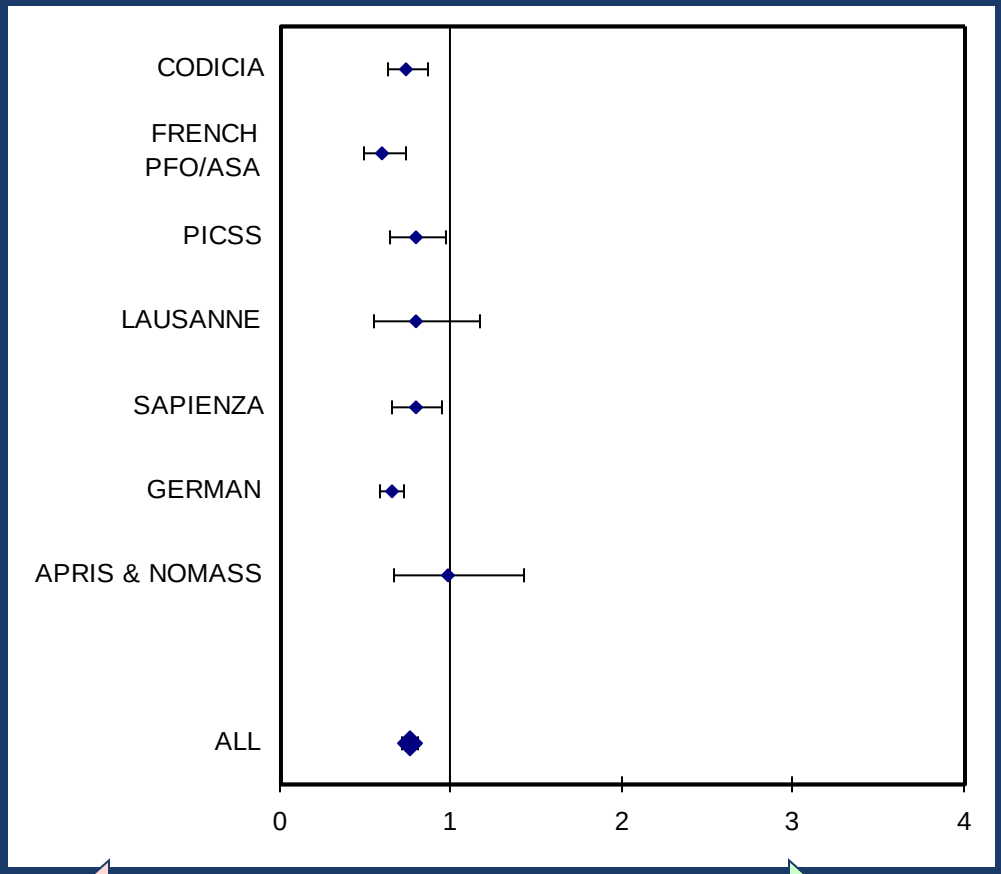
Consistency Across Sites of Relationship of *Age* and Odds of having a PFO



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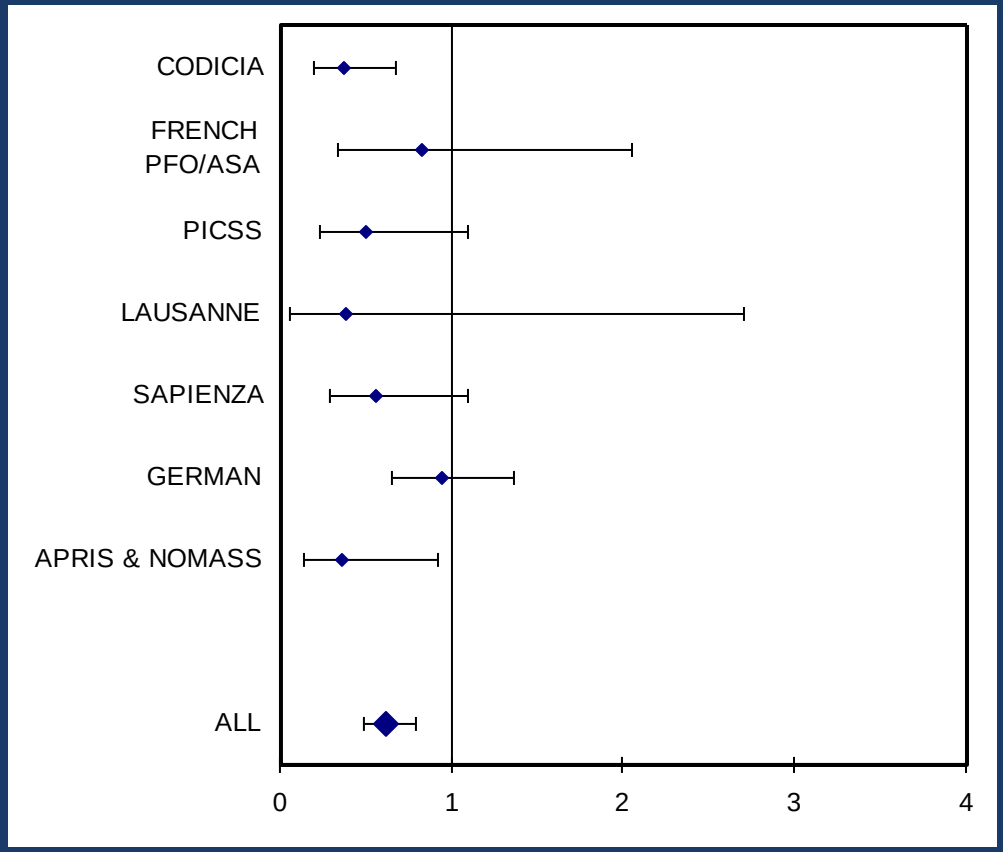
Consistency Across Sites of Relationship of *Diabetes* and Odds of having a PFO



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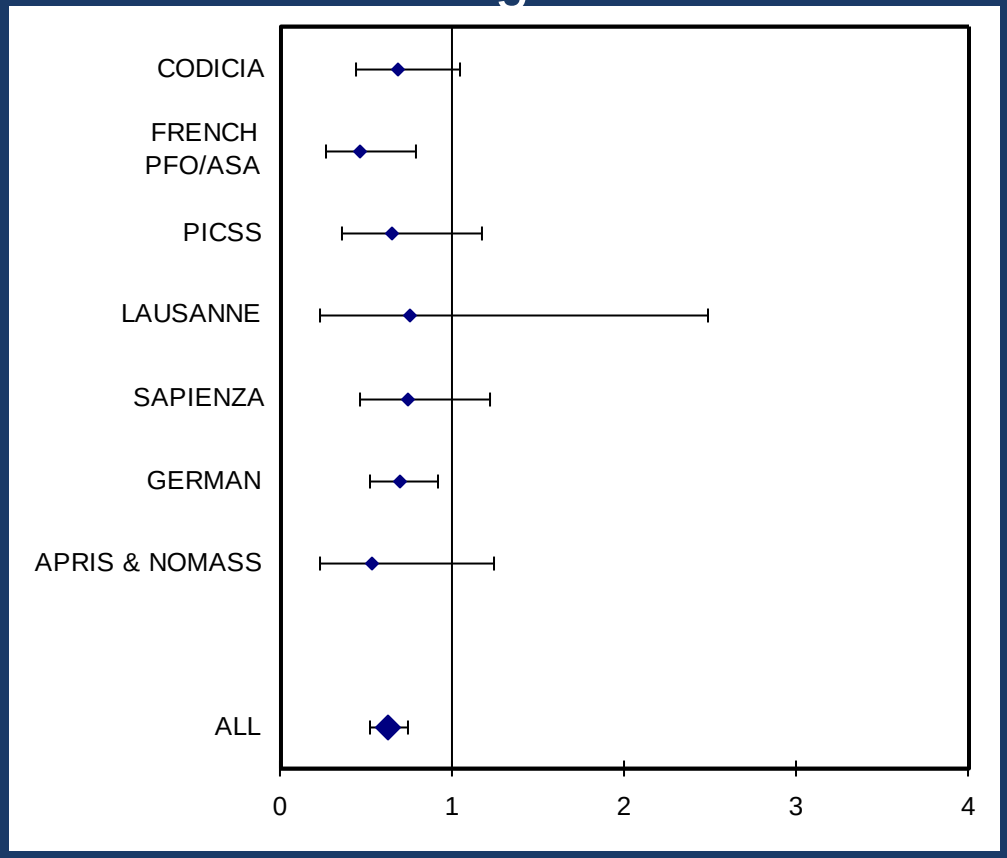
Consistency Across Sites of Relationship of *Hypertension* and Odds of having a PFO



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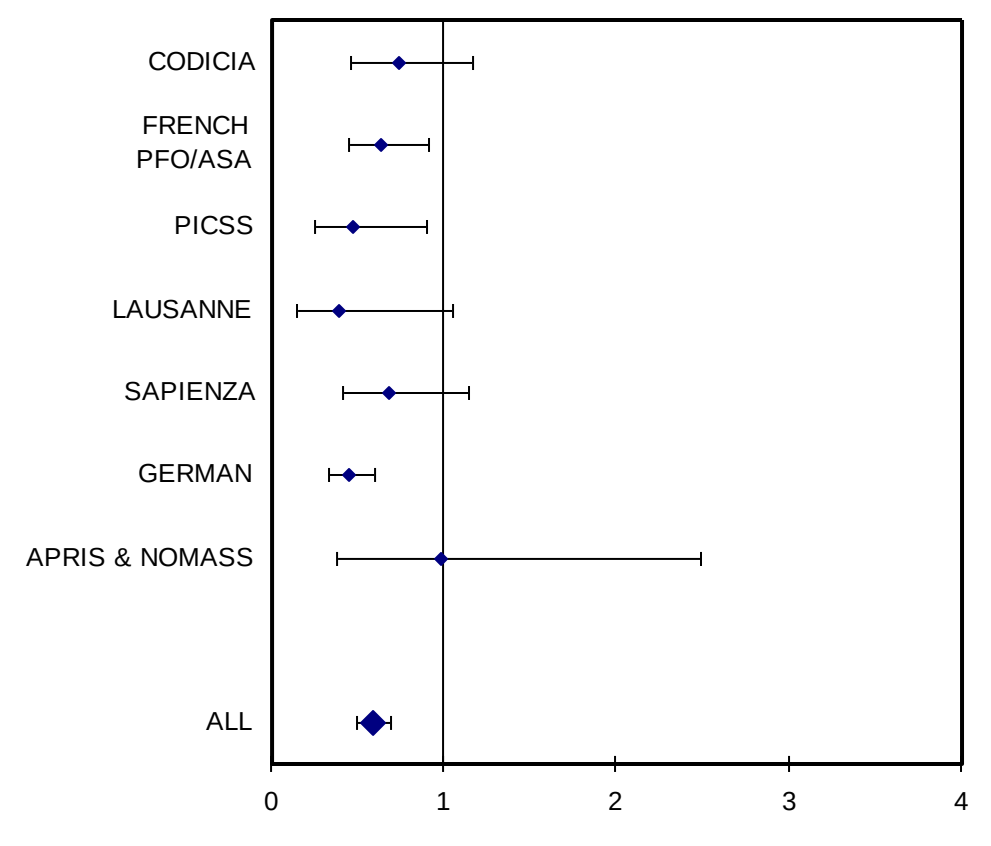
Consistency Across Sites of Relationship of *Smoking* and Odds of having a PFO



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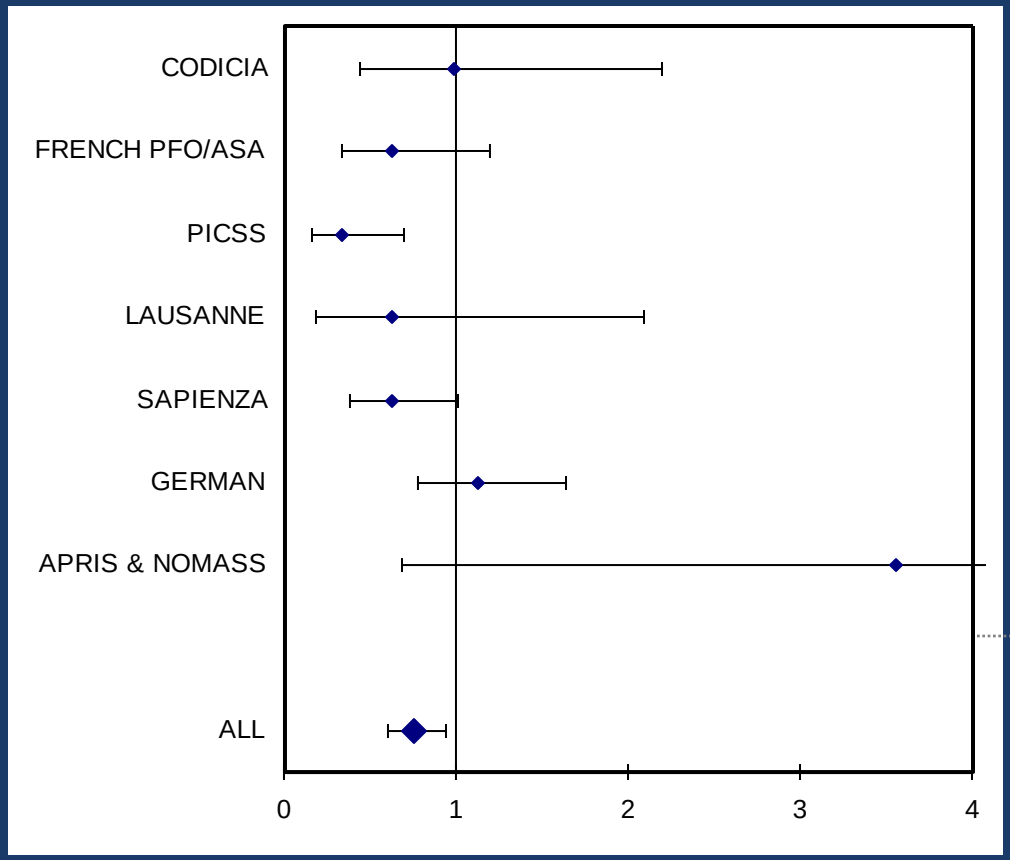
Consistency Across Sites of Relationship of *History of Stroke or TIA* and Odds of having a PFO*



** 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:
Neuroradiological variables

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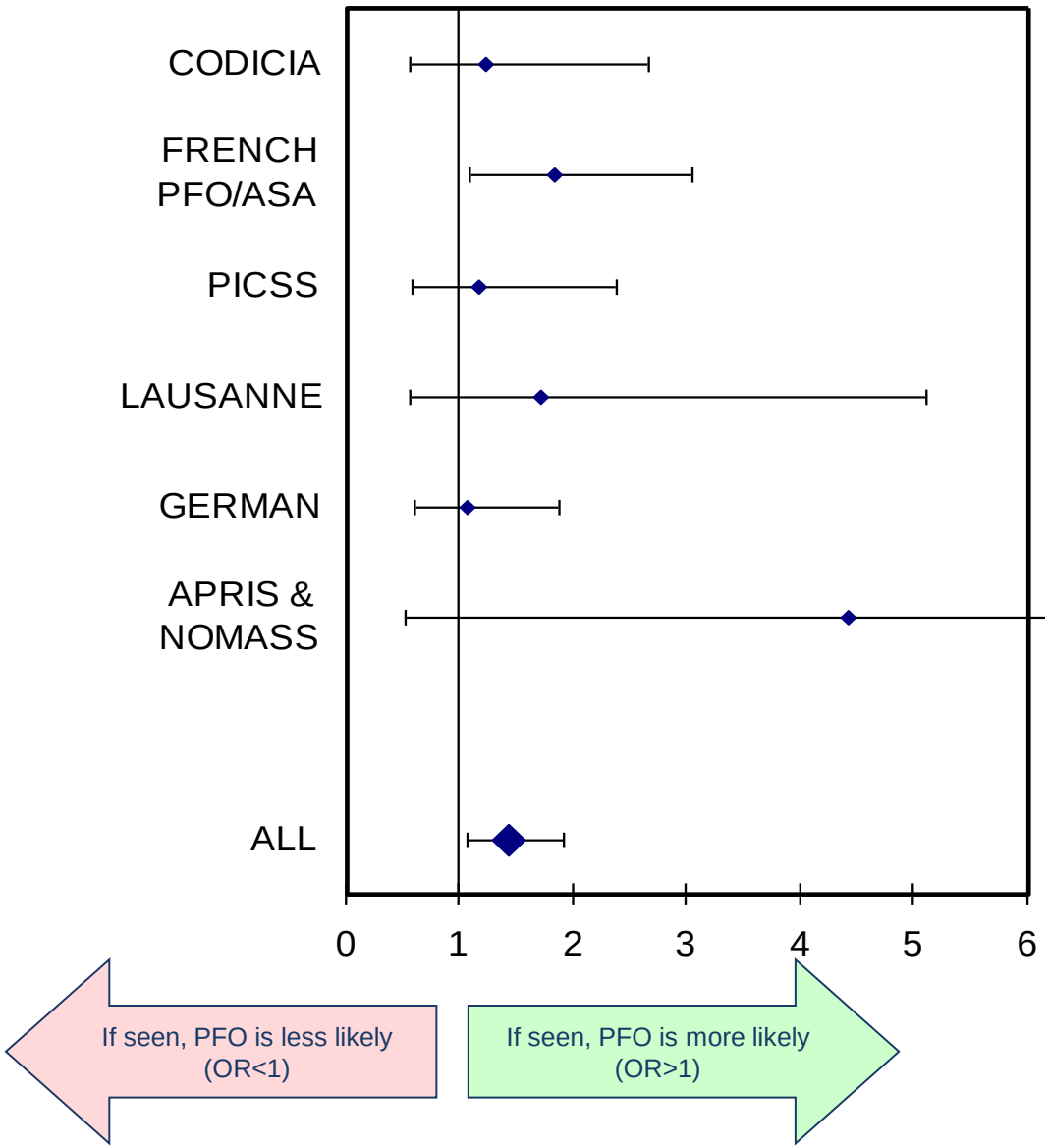
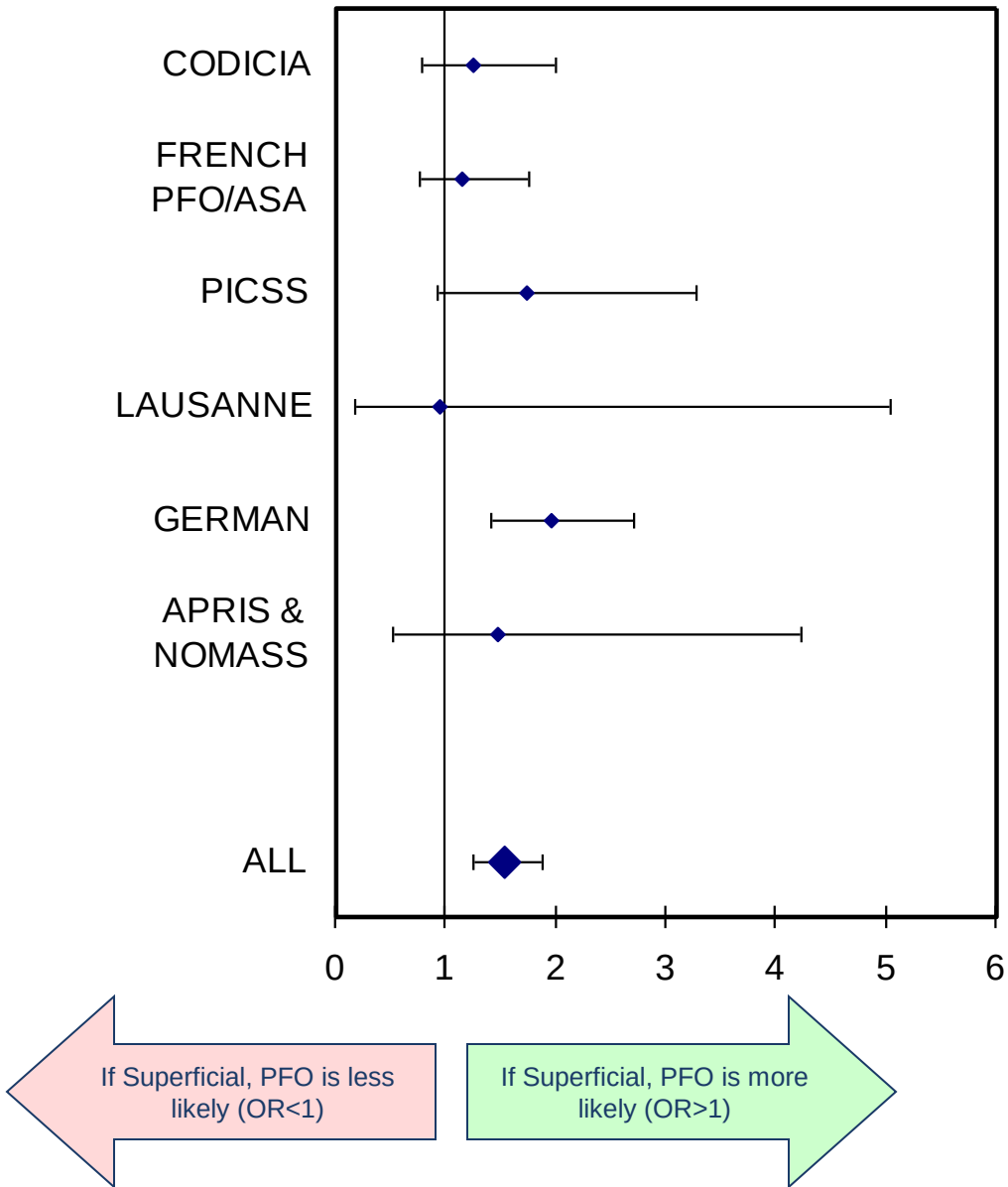
Consistency Across Sites of Relationship of *Having Stroke Seen* (per radiology) and Odds of having a PFO*

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



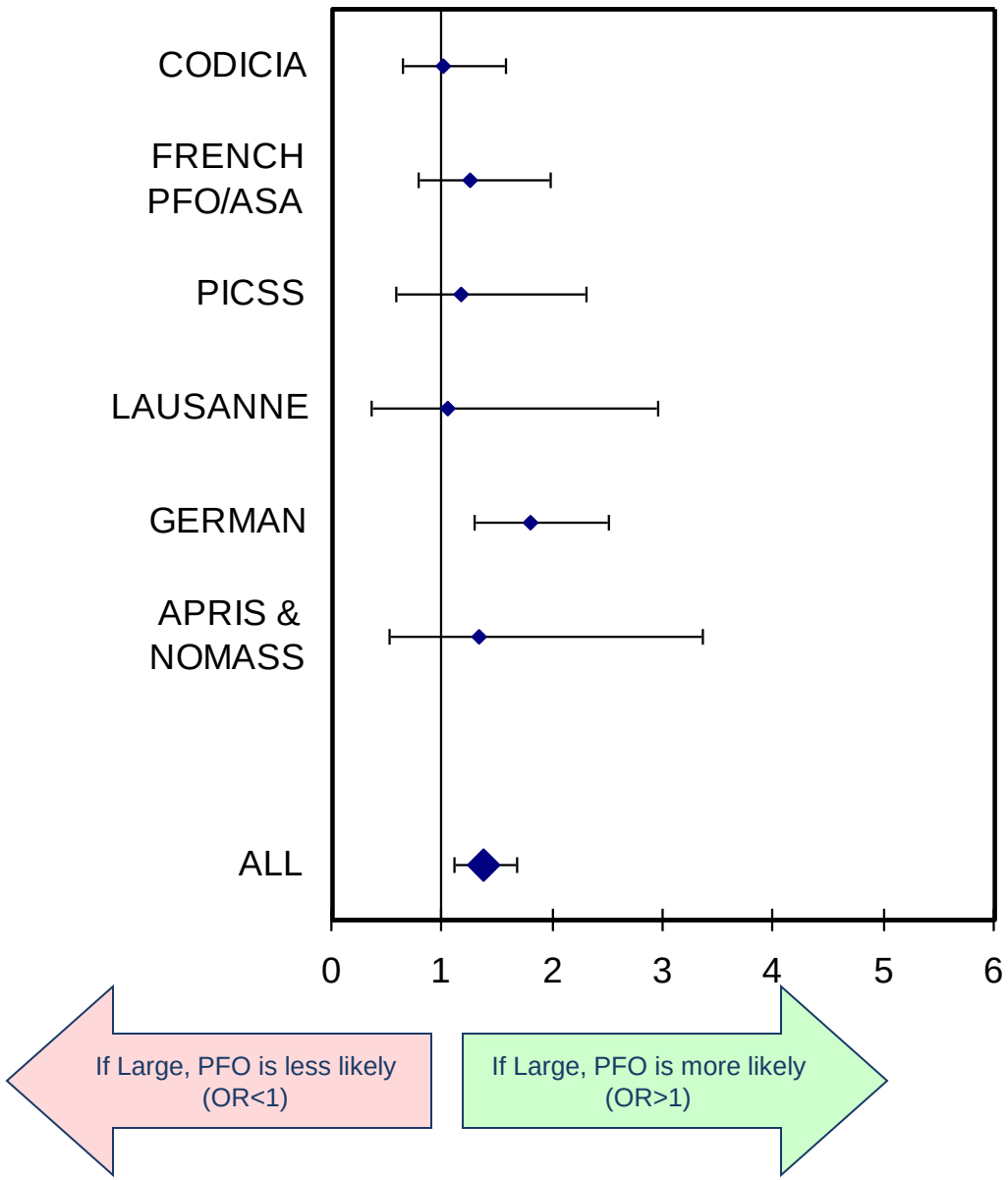
Consistency Across Sites of Relationship of *Superficial vs. Deep (per radiology)* and Odds of having a PFO*

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



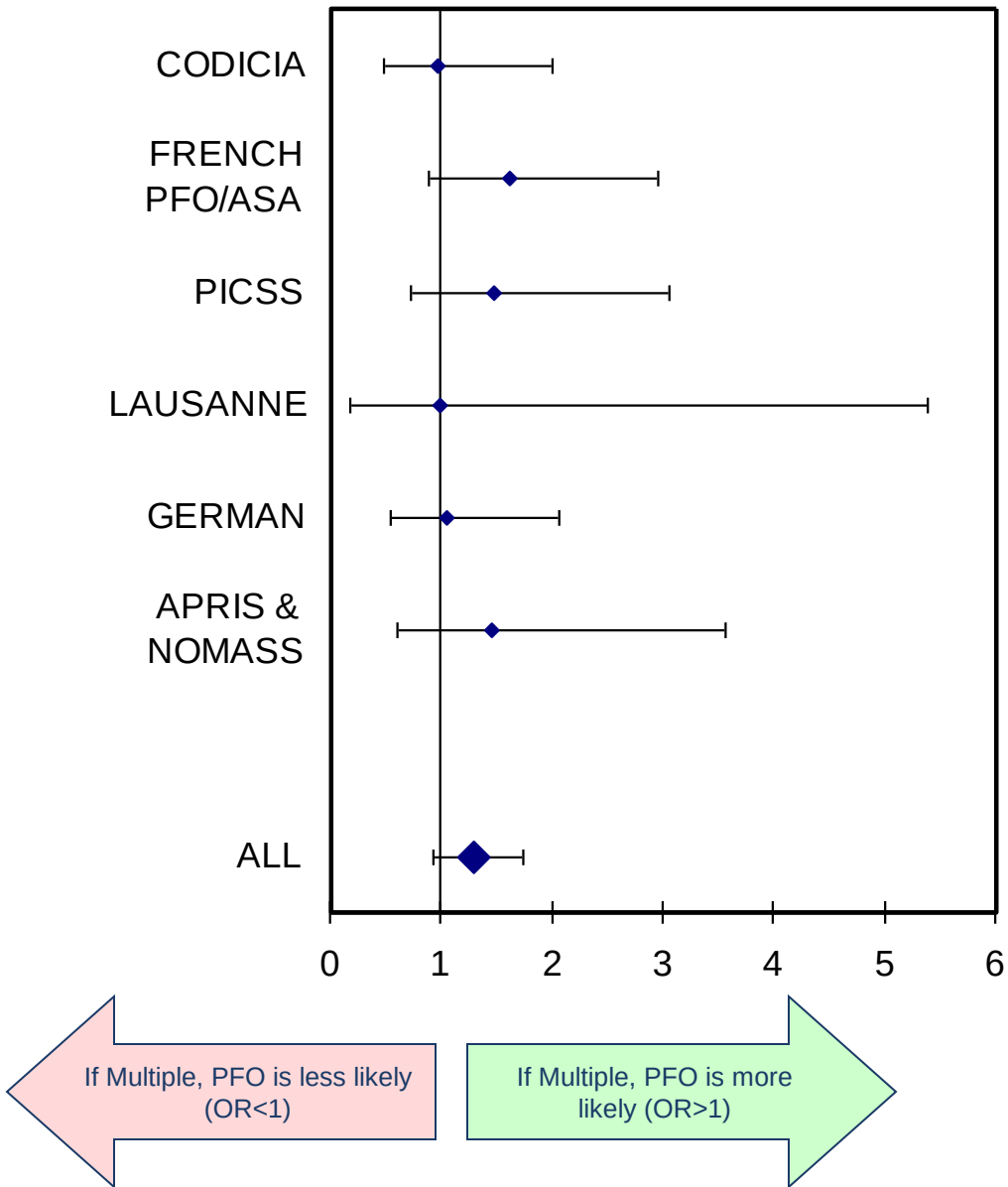
Consistency Across Sites of Relationship of *Large vs. Small/not seen (per radiology)* and Odds of having a PFO*

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



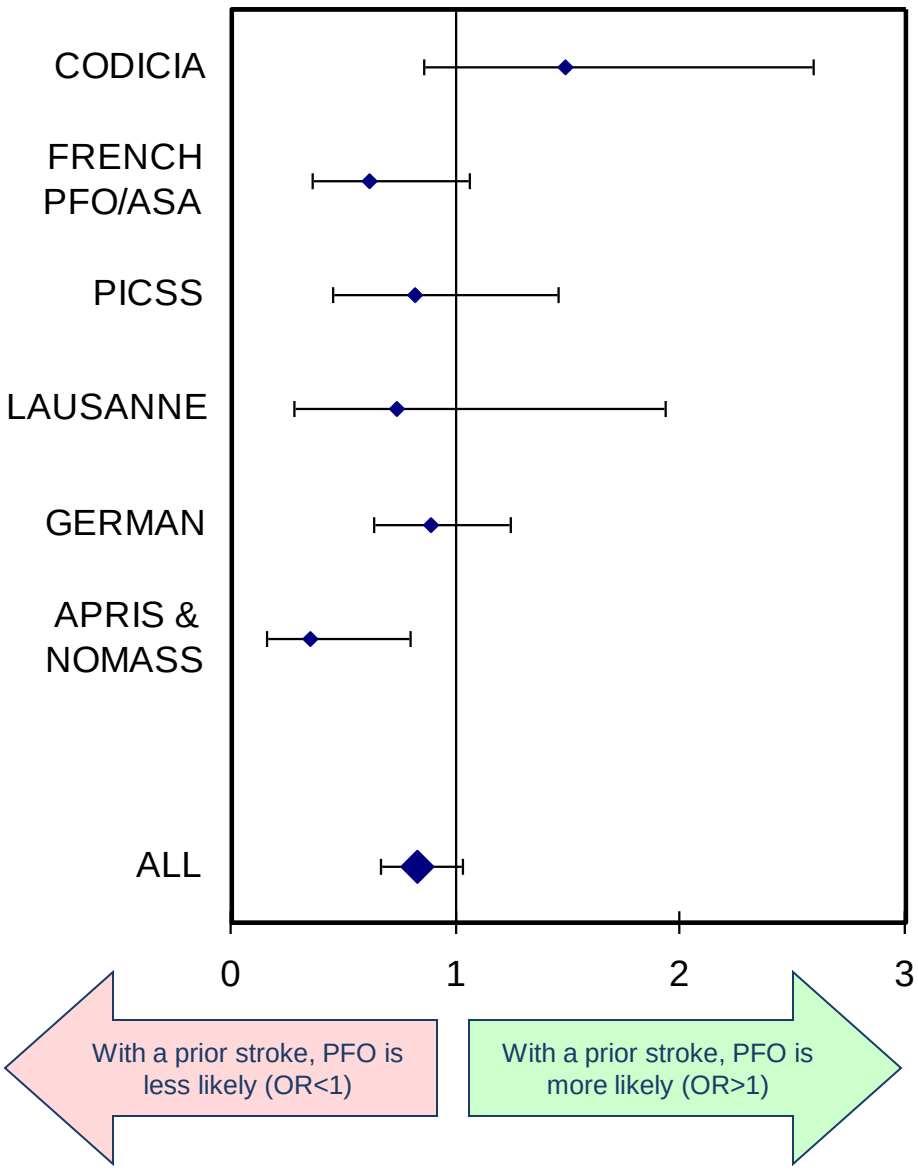
Consistency Across Sites of Relationship of *Multiple vs. Single/not seen (per radiology)* and Odds of having a PFO*

**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 Stroke (per radiology)* 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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	PFO (n=1274)	Non-PFO (n=1749)	P-value
Patient Characteristics			
Male	58.9% (751/1274)	59.3% (1038/1749)	0.8251
Age over 65	21.5% (274/1274)	35.9% (627/1748)	<.0001
White	86.1% (515/598)	79.3% (649/818)	0.0010
Diabetes	8.9% (113/1269)	18.6% (325/1746)	<.0001
Coronary artery disease	6.7% (67/1005)	12.0% (172/1434)	<.0001
Hypertension	32.7% (415/1271)	53.2% (927/1744)	<.0001
Hypercholesterolemia	22.5% (195/866)	30.6% (425/1387)	<.0001
Current smoker	32.5% (410/1263)	36.0% (622/1727)	0.0435
History of stroke/TIA	11.9% (151/1270)	18.0% (314/1740)	<.0001
Radiology Variables			
Prior stroke, % yes	22.6% (196/867)	31.1% (396/1272)	<.0001
Number of lesions	N=901	N=1261	0.3255
- Multiple	13.3% (120)	12.5% (158)	
- Not multiple	72.5% (653)	75.2% (948)	
- TIA	14.2% (128)	12.3% (155)	
Size	N=930	N=1324	0.0189
- Large	59.1% (550)	55.9% (740)	
- Not large	27.1% (252)	32.4% (429)	
- TIA	13.8% (128)	11.7% (155)	
Location	N=907	N=1173	<.0001
- Superficial	54.1% (491)	44.9% (527)	
- Deep	31.8% (288)	41.9% (491)	
-TIA	14.1% (128)	13.2% (155)	

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RoPE – Model 1 – “Pathogenic PFO”

Term in Model	OR	(95 % CI for OR)	p-value
Age (per 10 year increase)	0.72	(0.67 to 0.77)	<.0001

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The RoPE Score

Points are subtracted from 10 for each risk factor: • A patient less than 30 years with no risk factors has a score of 10; • A patient ≥ 70 years with all 5 risk factors has a score of 0	**SCORE**
Maximum Score:	10
Risk Factor Count (0 to 5 points):	-
Hypertension (1)	
Diabetes (1)	
Prior Stroke or TIA (1)	
Current Smoker (1)	
Absence of visible cortical infarct on CT or MRI (1)	
Age (0 to 5 points):	-
<30 years (0)	
30 to 39 years (1)	
40 to 49 years (2)	
50 to 59 years (3)	
60 to 69 years (4)	
≥ 70 years (5)	
Total Score =	

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Confidential

RoPE Score distribution and PFO prevalence

POINT SCORE	A. Cryptogenic Stroke (N=3023)		
	Number of Patients	Prevalence of Patients with a PFO % (95% CI*)	PFO-Attributable Fraction % (95% CI*)
0-3	613	23% (19% to 26%)	0% (0% to 4%)
4	511	35% (31% to 39%)	38% (25% to 48%)
5	516	34% (30% to 38%)	34% (21% to 45%)
6	482	47% (42% to 51%)	62% (54% to 68%)
7	434	54% (49% to 59%)	72% (66% to 76%)
8	287	67% (62% to 73%)	84% (79% to 87%)
9-10	180	73% (66% to 79%)	88% (83% to 91%)

RoPE Scores and Recurrence rates

POINT SCORE	A. Cryptogenic Stroke (N=3023)			B. CS Patients with PFO (N=1324)	
	Number of Patients	Prevalence of Patients with a PFO % (95% CI*)	PFO-Attributable Fraction % (95% CI*)	# CS patients with PFO*	Estimated Two Year Survival/TIA Recurrence Rate (Kaplan-Meier, with 95% CI)
0-3	613	23% (19% to 26%)	0% (0% to 4%)	108	20% (12% to 28%)
4	511	35% (31% to 39%)	38% (25% to 48%)	148	12% (6% to 18%)
5	516	34% (30% to 38%)	34% (21% to 45%)	186	7% (3% to 11%)
6	482	47% (42% to 51%)	62% (54% to 68%)	236	8% (4% to 12%)
7	434	54% (49% to 59%)	72% (66% to 76%)	263	6% (2% to 10%)
8	287	67% (62% to 73%)	84% (79% to 87%)	233	6% (2% to 10%)
9-10	180	73% (66% to 79%)	88% (83% to 91%)	150	2% (0% to 4%)

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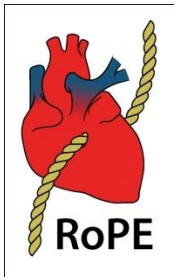
RoPE Scores and Recurrence rates for those <60y

Appendix 5: For Subset Under Age 60, PFO prevalence, attributable fraction and estimated two year risk of stroke/TIA by point score strata, using control rate of 25%.

POINT SCORE	A. Cryptogenic Stroke (N=1809)			B. CS Patients with PFO (N=981)	
	Number of Patients	Prevalence of Patients with a PFO % (95% CI*)	PFO-Attributable Fraction, % (95% CI*)	# CS patients with PFO*	Estimated Two Year Survival/TIA Recurrence Rate (Kaplan-Meier, with 95% CI)
0-3	41	24% (11% to 38%)	0% (0% to 45%)	8	0%
4	132	28% (20% to 36%)	14% (0% to 40%)	25	5% (0% to 15%)
5	301	28% (23% to 33%)	15% (0% to 33%)	97	7% (3% to 12%)
6	434	46% (42% to 51%)	61% (53% to 68%)	205	8% (4% to 12%)
7	434	54% (49% to 59%)	72% (66% to 76%)	263	6% (2% to 10%)
8	287	67% (62% to 73%)	84% (79% to 87%)	233	6% (2% to 10%)
9-10	180	73% (66% to 79%)	88% (83% to 91%)	150	2% (0% to 4%)

**Note: 95% CI for PFO prevalence based on normal approximation to the binomial distribution. Attributable risk and 95% CI for Atributable risk based on PFO prevalence and 95% CI for that estimate.!*



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RoPE Conclusions (so far)

- Among patients with CS, there is considerable variation in PFO prevalence based on easily obtainable clinical characteristics, with large subgroups varying from ~20% to >70%.
- This prevalence suggests stratum-specific (i.e. RoPE Scores) attributable fractions that range from 0% to 90% among patients with CS and PFO.
- Among patients with PFO, stroke recurrence rates are highest in the stratum least likely to have a PFO-attributable CS, and lowest in the stratum most likely to have a PFO-attributable CS.

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Future Work

- More work is needed to identify those patients with PFO-attributable CS that are most likely to recur.
- *Nota bene:*
  - None of these data address “high risk” echo characteristics
  - Early looks at Model 2 suggest we might be WRONG about what constitutes high risk

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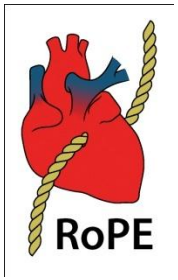
Final thought

“Science is the great antidote to the poison of enthusiasm and superstition.”

Adam Smith, *The Wealth of Nations*, 1776



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Acknowledgments

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