PFO detection in young stroke patients

Massimo Del Sette

DINOG

University of Genova, Italy

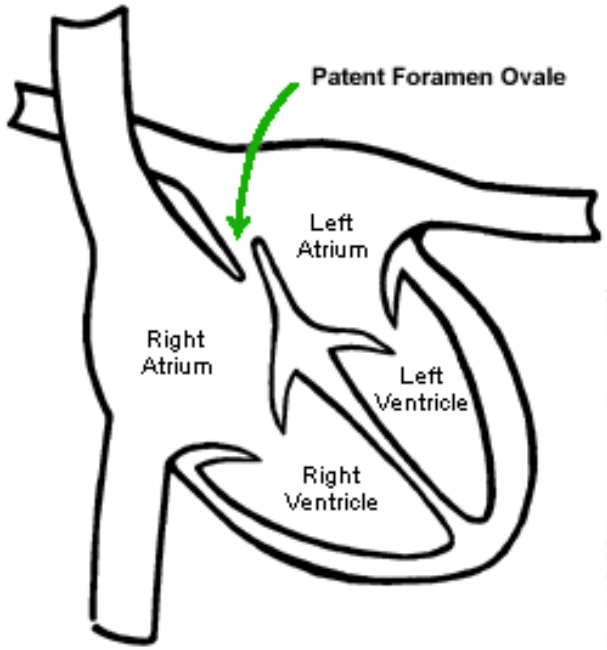
1st Residential Training Course - ESNCH

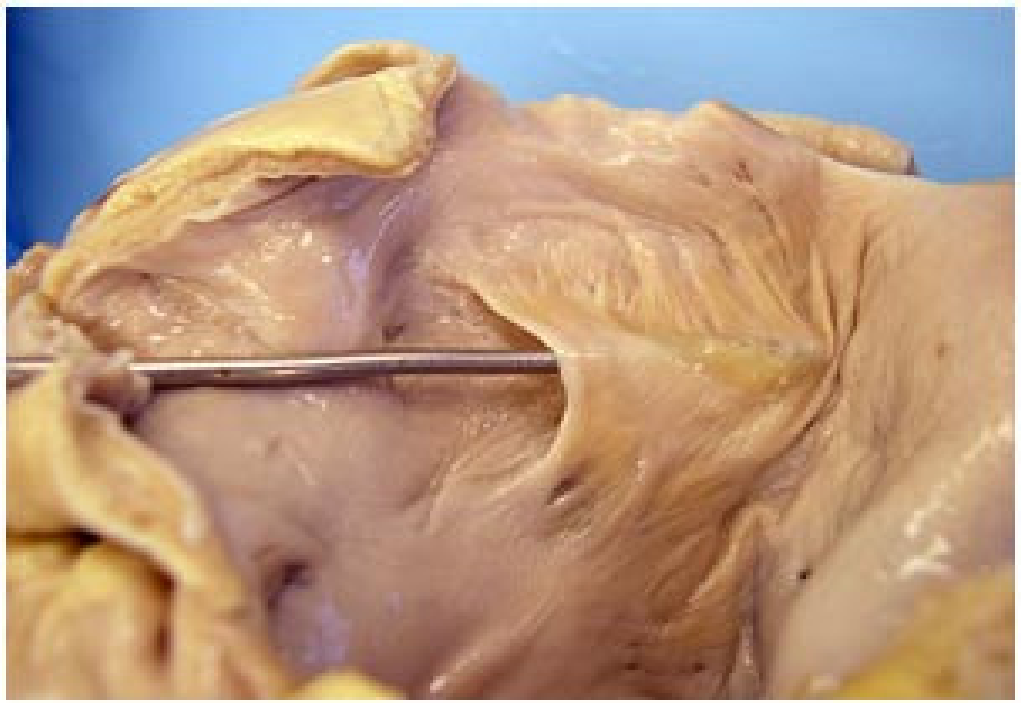
Bertinoro, Italy. September 7-12

Summary

- What is PFO
- How to diagnose it
- Why to diagnose it
- When to diagnose it

What is PFO: neither foramen, nor patent





Prevalence of PFO

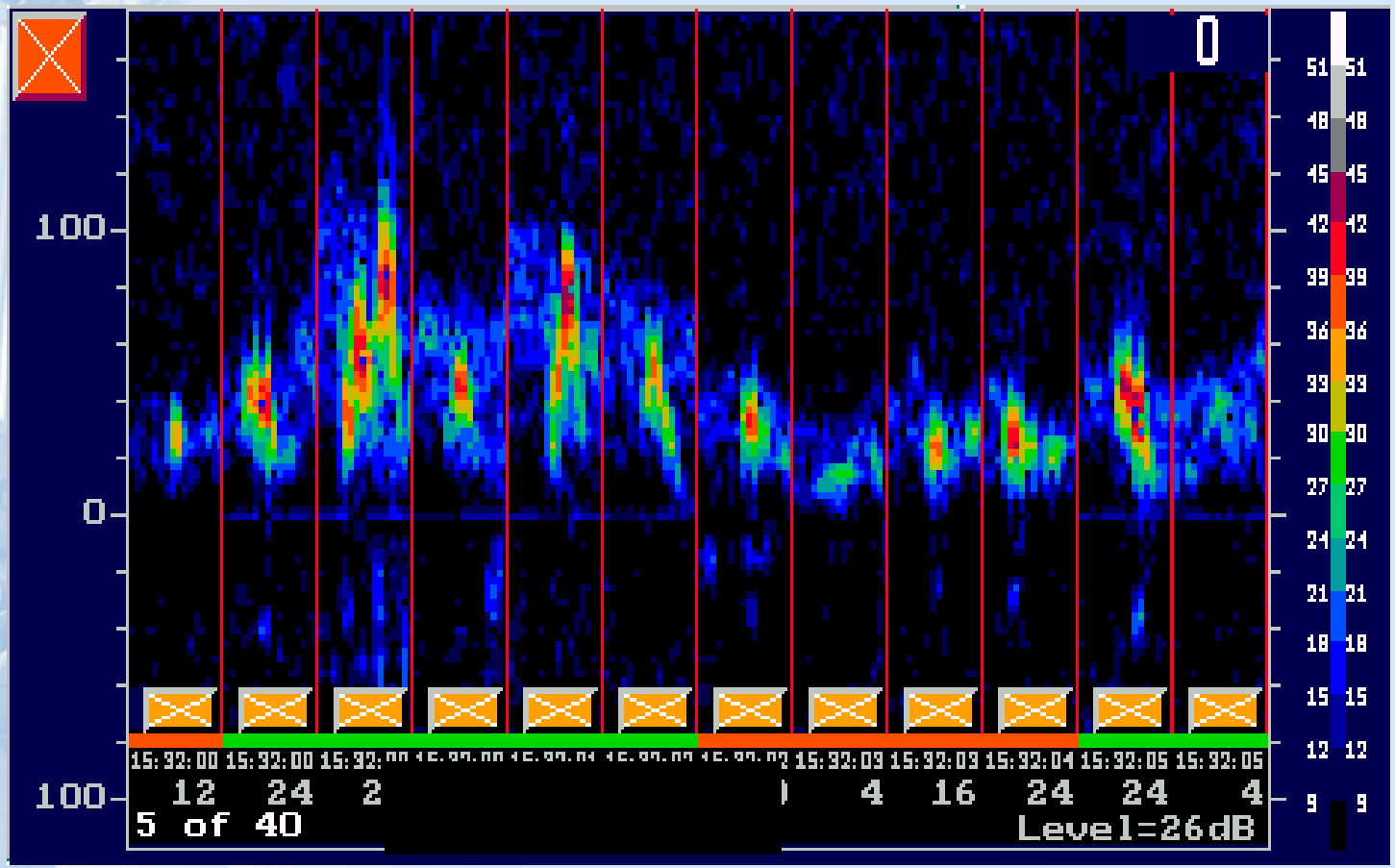
- Ischemic stroke: 40% (range: 32%-50%)
- Cryptogenic ischemic stroke: 50% (49%-62%)
- Normal controls: 20% (17%-35%)

- Population study *(Petty et al , Mayo Clin Proc 2006)* : 1072 subjects (TEE)
  - Controls: 20.8%
  - Heart disease 8.4%
  - Non-cryptogenic stroke 10.8%
  - Cryptogenic stroke 16.5%

Relationship PFO- Age

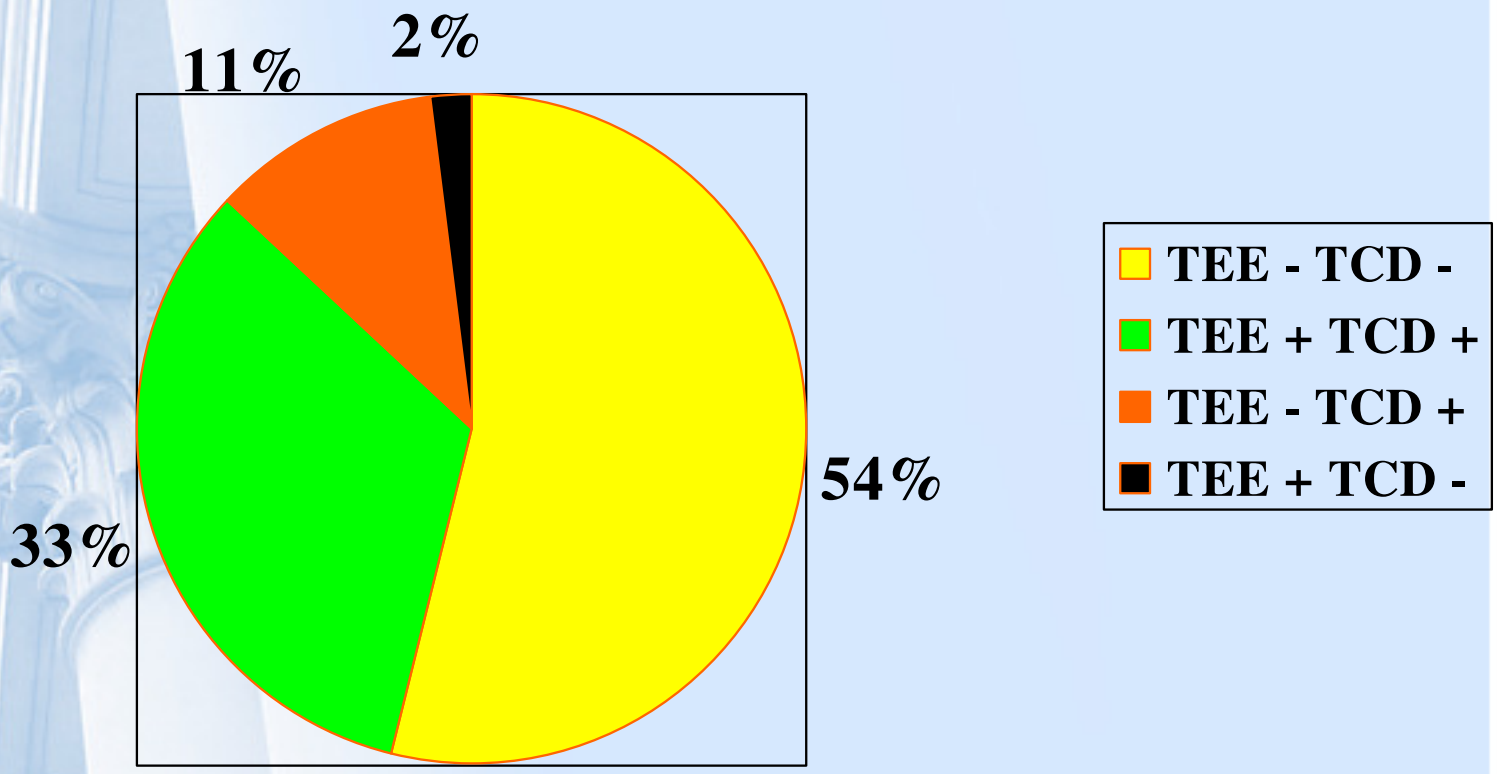
- Prevalence falls with age: over 80years = 20%
- Dimension increases with age:
  - 1-10years = 3.4 mm
  - over 90years = 5.8 mm

Consensus Meeting, ESNCH ’99 *(Jauss et al., 2000)*


0
100
0
100
51 51
48 48
45 45
42 42
39 39
36 36
33 33
30 30
27 27
24 24
21 21
18 18
15 15
12 12
9 9
15:32:00 15:32:00 15:32:03 15:32:03 15:32:04 15:32:05 15:32:05
12 24 2 4 16 24 24 4
5 of 40
Level=26dB

sensitivity: 95%

specificity:75%



Droste et al., '99

Comparison of VBC and MCA Recording at Rest

(Del Sette et al., Stroke 2007)

	MCA +	MCA -	TOT
VBC+	16	0	16
VBC–	12	155	167
Total	28	155	183

Sensitivity 57.14%; specificity 100%; positive predictive value 100%; negative predictive value 92.81%.

Comparison of VBC and MCA Recording After the Valsalva Maneuver

(Del Sette et al., Stroke 2007)

	MCA+	MCA-	Total
VBC+	36	0	36
VBC–	7	140	147
Total	43	140	183

Sensitivity 83.72%; specificity 100%; positive predictive value 100%; negative predictive value 95.24%.

Comparison of VBC and MCA Recording for Medium and Large Shunts (>10 Mb)

(Del Sette et al., Stroke 2007)

	MCA+	MCA -	Total
VBC+	22	0	22
VBC–	0	161	161
Total	22	161	183

Sensitivity 100%; specificity 100%; positive predictive value 100%; negative predictive value 100%.

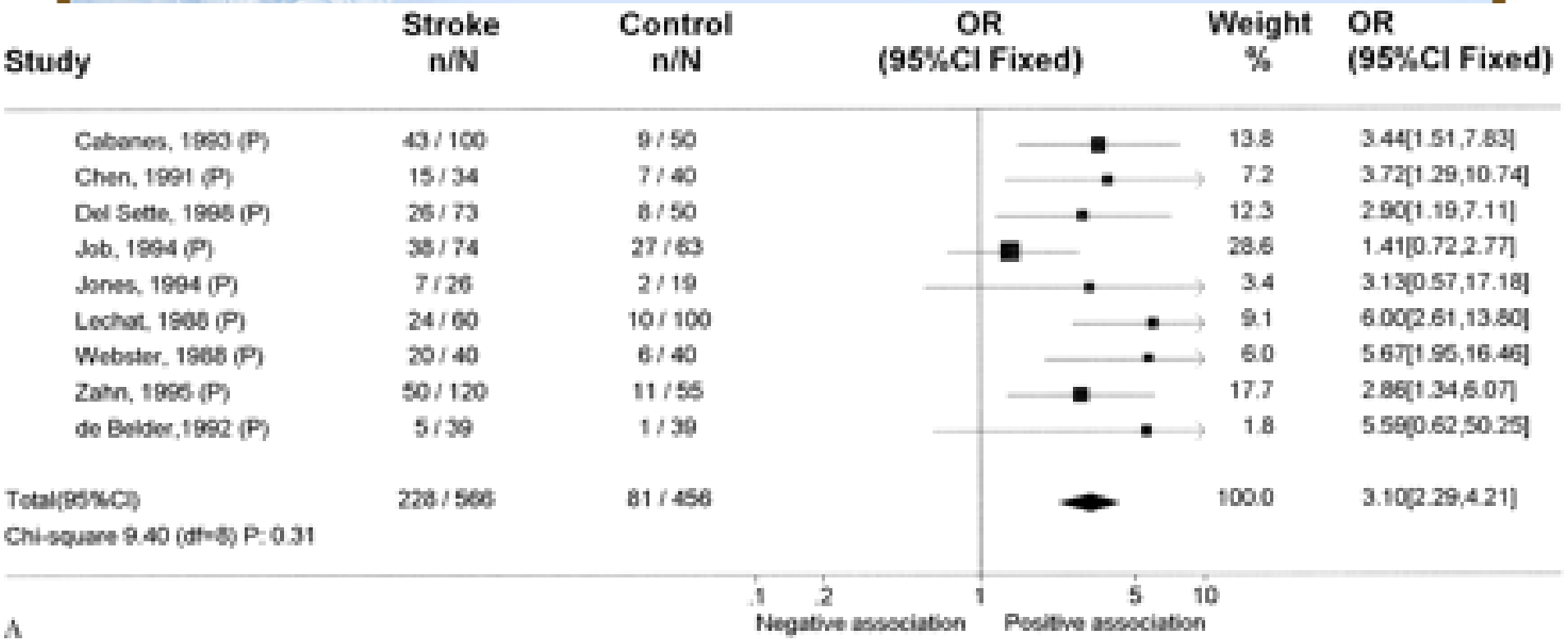
Other techniques

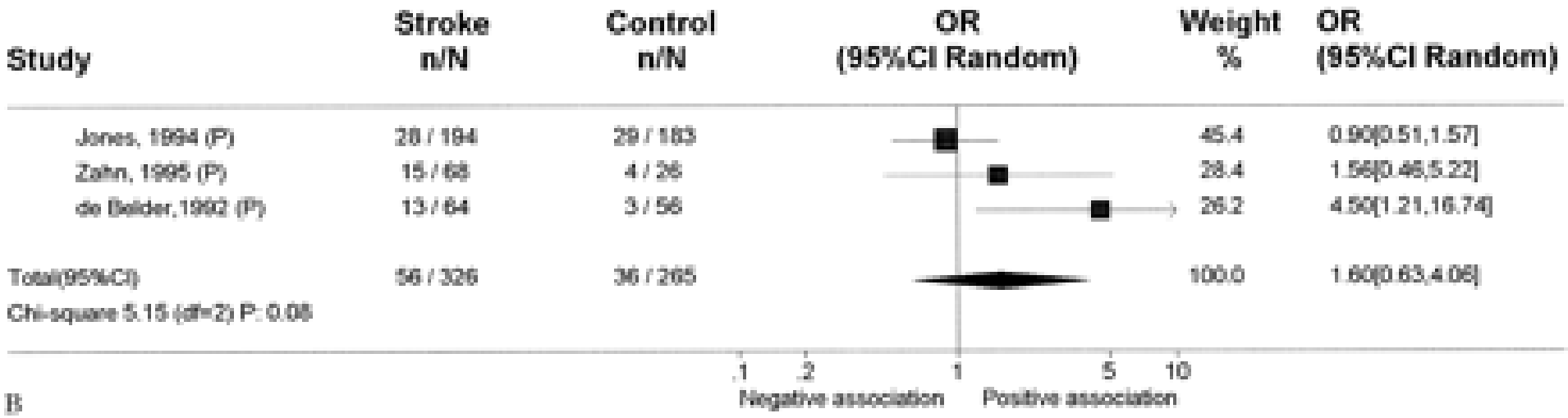
- Cardiac MR: inferior to TEE for PFO and ASA *(Nusser et al., JACC 2006)*
- 3D echo: useful for large atrial septal defects *(Mehmood et al, Ecocard. 2004)*
- Intra Cardiac Echography: Useful during procedure *(Ponnuthuray Int J Cardiol 2007)*

In which conditions?

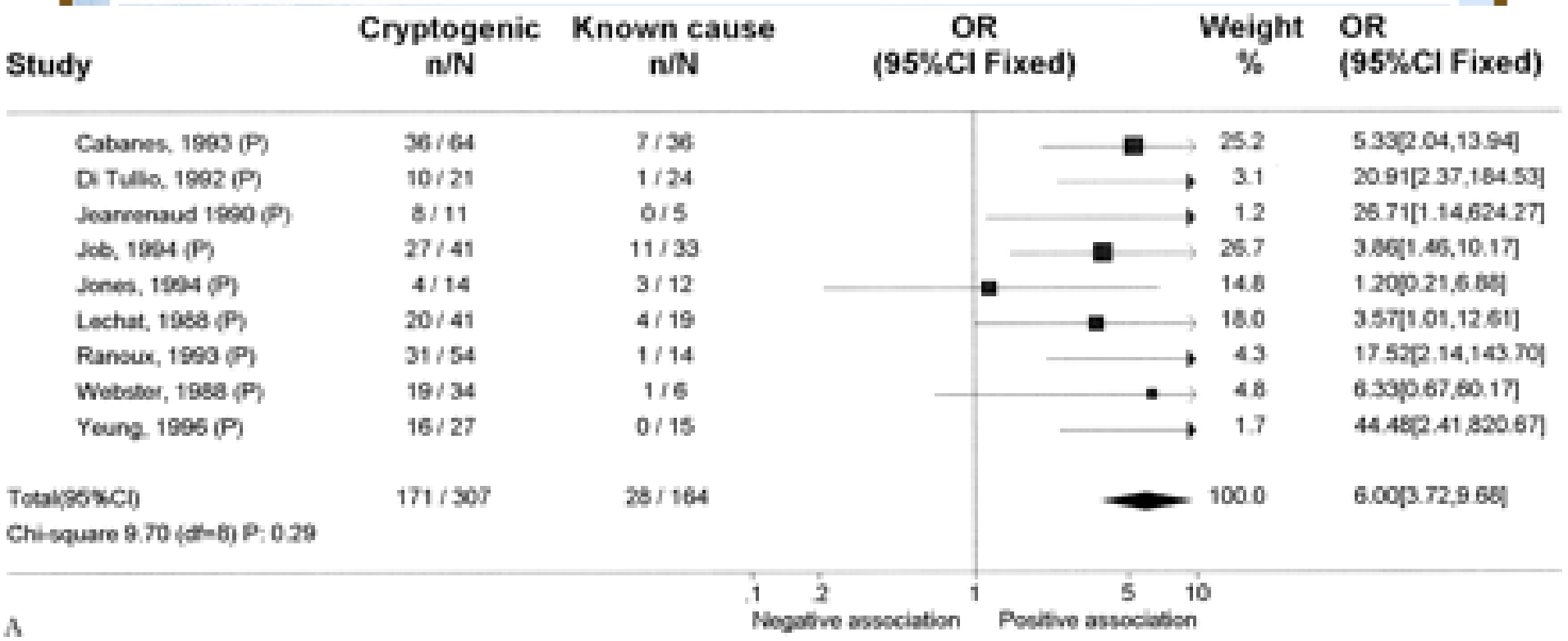
- Ischemic stroke
- Migraine with aura
- CADASIL
- Transiet global amnesia
- Pneumopathies and obstructive sleep apnoea syndrome (OSAS)

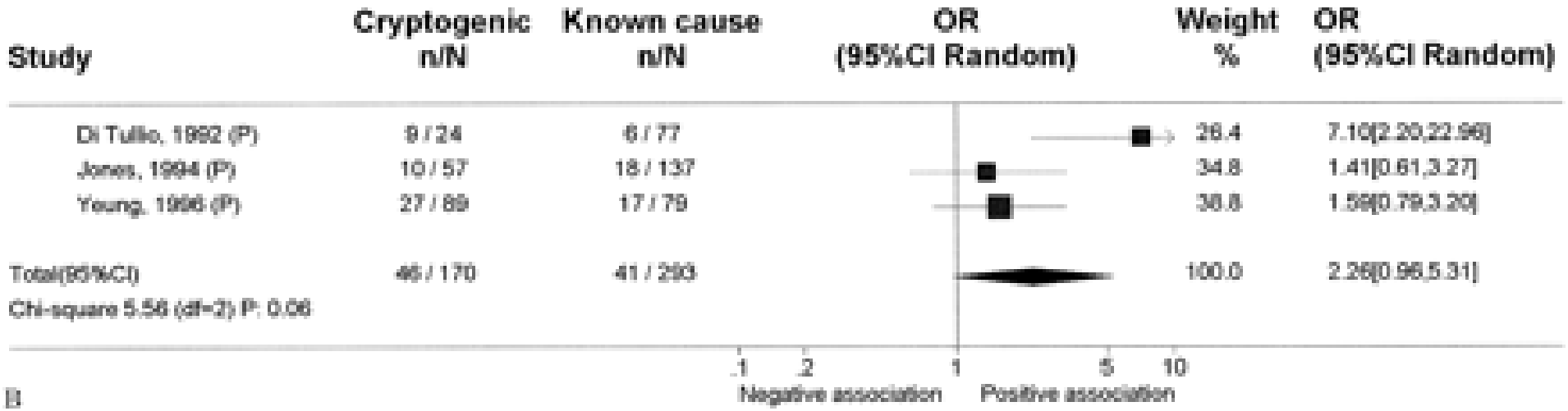
Methanalysis (Overell et al, Neurology 2000;55:1172-1179)





Methanalysis (Overell et al, Neurology 2000;55:1172-1179)





Which variables for stratification of risk?

- Atrial Septal Aneurysm (ASA)
- Magnitude of shunt

PFO -ASA
(Meissner et al., JACC 2006)

- 585 subjects (population-based)
- Prevalence:
  - PFO: 24.3%
  - ASA: 1.9%
- Risk of having stroke (HR)
  - PFO: 1.46 (0.74 - 2.88) p=0.28
  - ASA: 3.72 (0.88 - 15.71) p=0.074

Functional characteristics of PFO and risk of stroke

- 101 patients
- Symptomatic PFO vs. asymtom.
- Symptomatic PFO:
  - More frequent shunt at rest
  - Higher septal mobility (>6.5 mm)
- Risk at 3 years:
  - 4.3% for low-risk group
  - 12.3% for high-risk group

(De Castro et al., '00)

ASA, PFO, stroke risk

- 100 pat. (<55 years): strong association with stroke if PFO + ASA (O.R. 33.3 – 95% C.I. 4.1-270)

  (Cabanes et al., '93)

- 581 pat.: recurrence risk at 4 years
  - FOP: 5.6%
  - FOP + ASA: 19.2%

  (Mas et al., 2001)

Magnitude of shunt and stroke risk

- **Large PFO (cTEE >5 mm) have higher risk (45% vs. 23% p=.02)**

  (Steiner et al., '98)

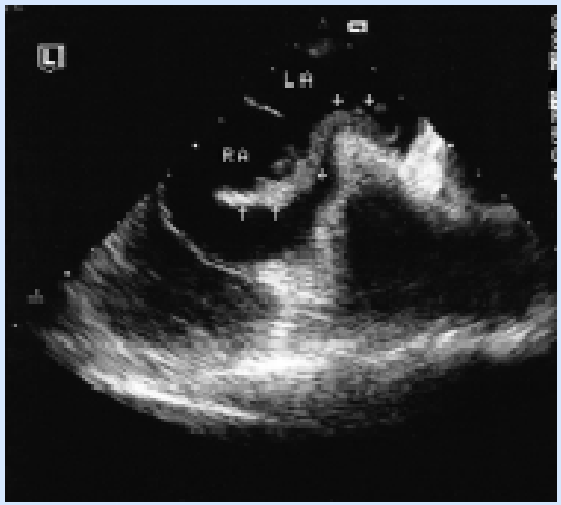
- **Large shunt ampio ("shower" or "curtain" pattern on cTCD) associated to higher risk**

  (O.R. 3.5; C.I.: 1.29-9.87)

  (Serena et al., '98)

Why is PFO an independent cause of stroke?

- Paradoxical embolism
- “In situ” thrombus formation
- Arrithmya (“atrial vulnerability”)
- Comorbidities:
  - Coagulopathies
  - Migraine
  - Pneumopathies and OSAS



Embolic lesions due to patent foramen ovale in young subjects are frequently distributed in vertebrobasilar circulation

(Del Sette et al., submitted)

Vascular territory of lesions	Patients with PFO-related stroke (n=40)	Patients with PFO-unrelated stroke (n=68)
Anterior Circulation Only	26 (65.00 %)	51 (75.00 %)
Anterior and Posterior Circulation	0 (0.00 %)	6 (8.82 %)
Posterior Circulation Only	14 (35.00 %)	11 (16.18 %)

Pneumopathies and PFO

- Platypnea-orthodeoxia syndrome (POS): desaturation in ortostatic position due to PFO
  (Legras et al., '99; Kubler et al., '00)

- COPD: PFO in 70%. In half of them desaturation during Valsalva
  (Soliman et al., '99)

OSAS and PFO

- PFO in 33/48 OSAS (69%) vs. 4/24 (17%) ($p<0.0001$)

  (Shanoudy et al., '98)

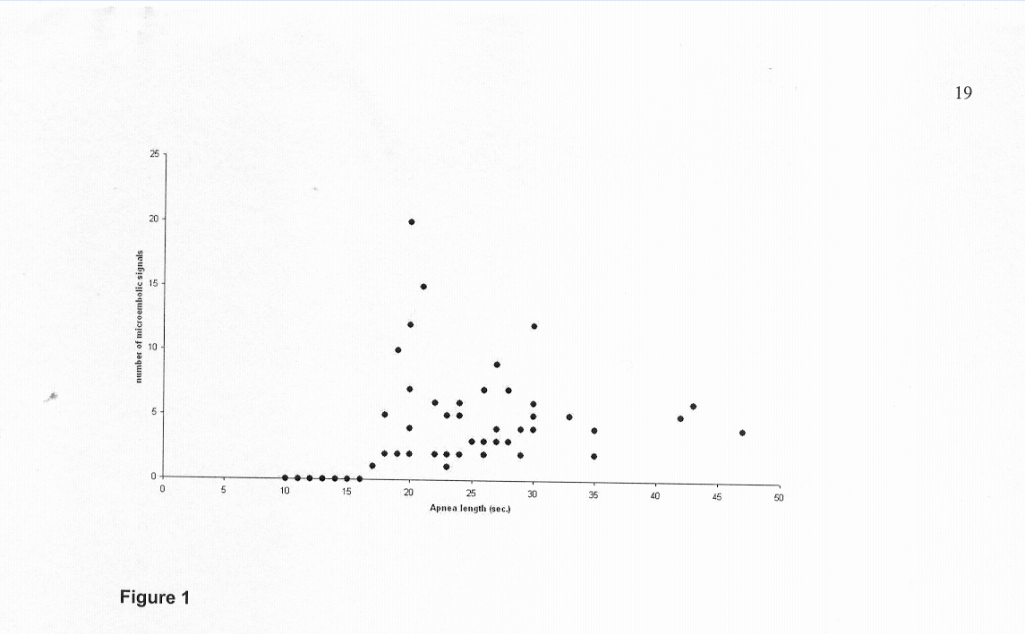
- SHUNT: 21/78 OSAS (27%) vs. 13/89 controlli (15%) ($p<0.05$)

  (Beelke et al., '02)

SHUNT during apnoea

- 10 subjects OSAS + FOP:
  - 9/10: shunt during apnoea, if duration > 17 seconds

(Beelke et al., '02)



Magnitude of shunt in apnoea is proportional to Valsalva

- Number of Mb apnoea-Valsalva significantly correlated ($p<0.0001$)

(Beelke et al., '02)

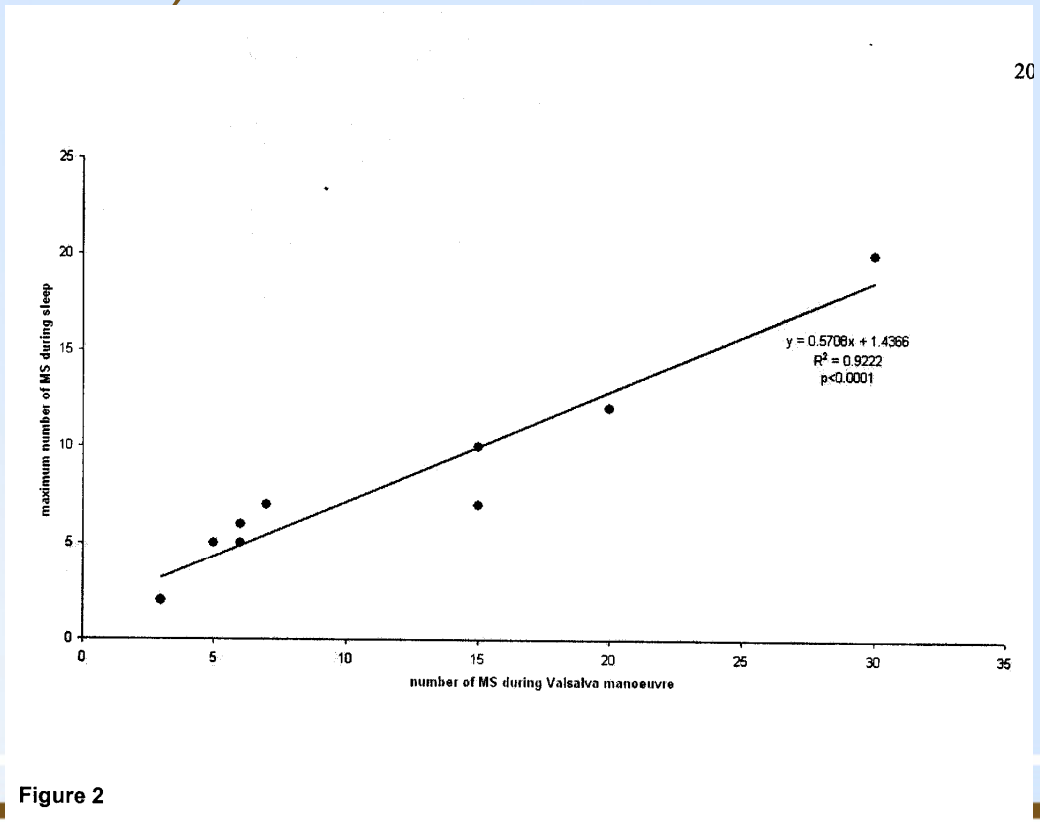
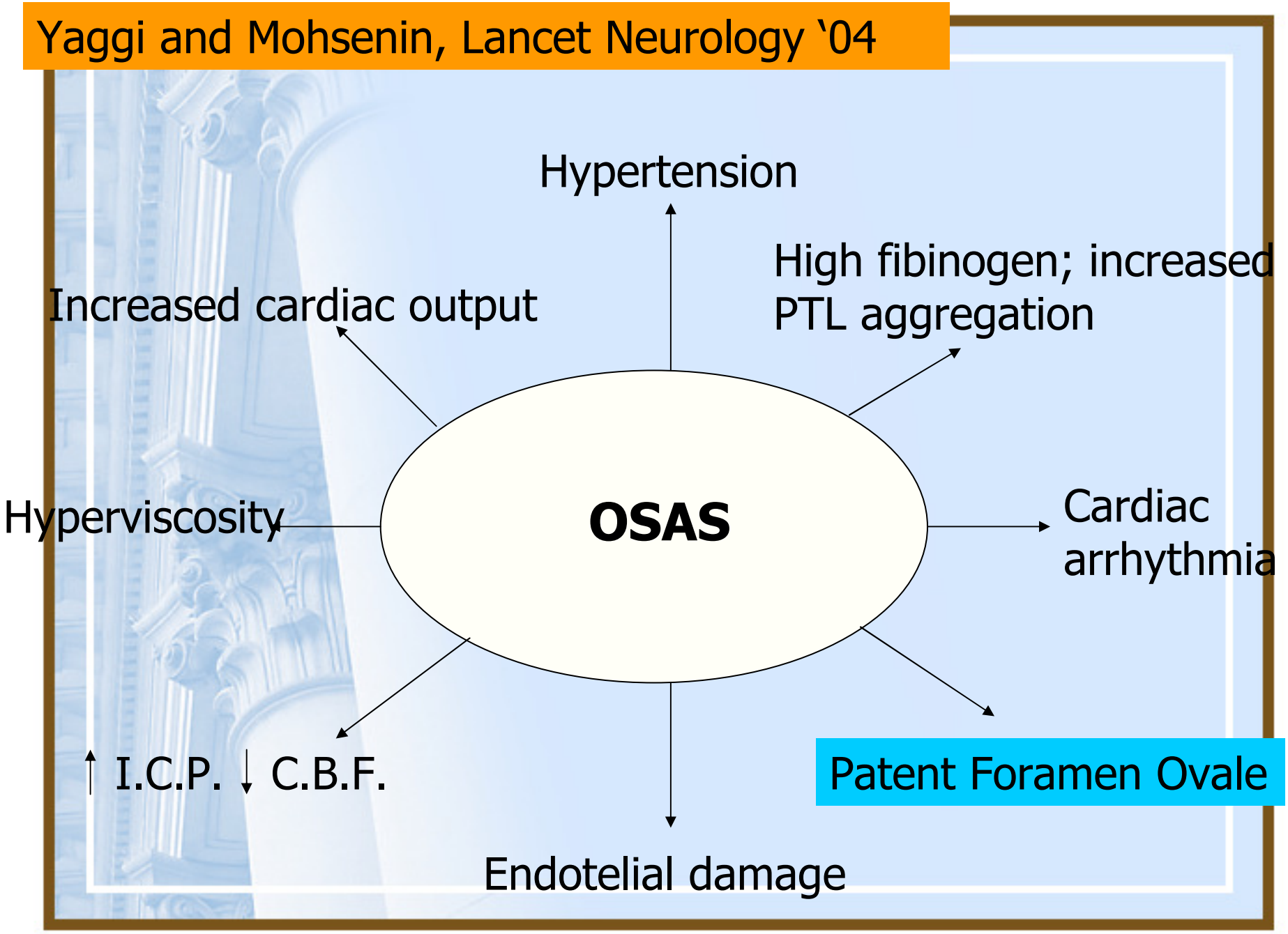


Figure 2

Yaggi and Mohsenin, Lancet Neurology '04



Case report

- 2 subjects with stroke on awakenig
- Both had OSAS + PFO

Treatment

- Medical

(second event within 1 year despite medical treatment: 4.22%, 95% CI 3.43-5.01)

- Transcatheter closure

(event rate after closure at 1 year: 1.62%, 95% CI 1.13-2.24)

*S. R. Messé, et al Neurology, Apr **2004**; **62**: **1042** - 1050.*

	Lausanne study (Bogousslavsky et al., 1996[27])	La Sapienza study (De Castro et al., 2000[21])	French PFO/ASA study (Mas et al., 2001[6])	PICSS (Homma et al., 2002[31]) cryptogenic strokes	PICSS (Homma et al., 2002[31]) all stroke subtypes
Type of study	Cohort	Case-control	Cohort	RCT	RCT
Follow-up (months)	36 (10-91)	31 (4- 58)	37.8 ± 9.7	24	24
N	340	160	581	265	630
Annual risk (no pfo)	-	4.5	1.8	6.3	7.7
Annual risk (pfo)	3.1	3.7	1.5	7.2	7.4

5 retrospective studies (1966 to 1999)

- **Warfarin better than ASA (OR 0.37; 95% CI, 0.23 - 0.60).**
- **Similar efficacy warfarin-surgery (OR 1.19; 95% CI, 0.62 - 2.27).**

METHANALYSIS

(Orgera et al., South Med J 2001;94:699-703)

French PFO- ASA study group

(Mas JL, et al., N Engl J Med. 2001; 345: 1740–1746)

- **216 patients (18 – 55 anni)**
- **Cryptogenic stroke + PFO**
- **vs. 304 no PFO**
- **All treated with ASA 300 mg**
- **FOP (only): risk at 2 years (2.3% PFO[+] vs 4.2% PFO[-]).**
- **FOP + ASA: (15.2%; OR 4.17; 1.47 - 11.84)**

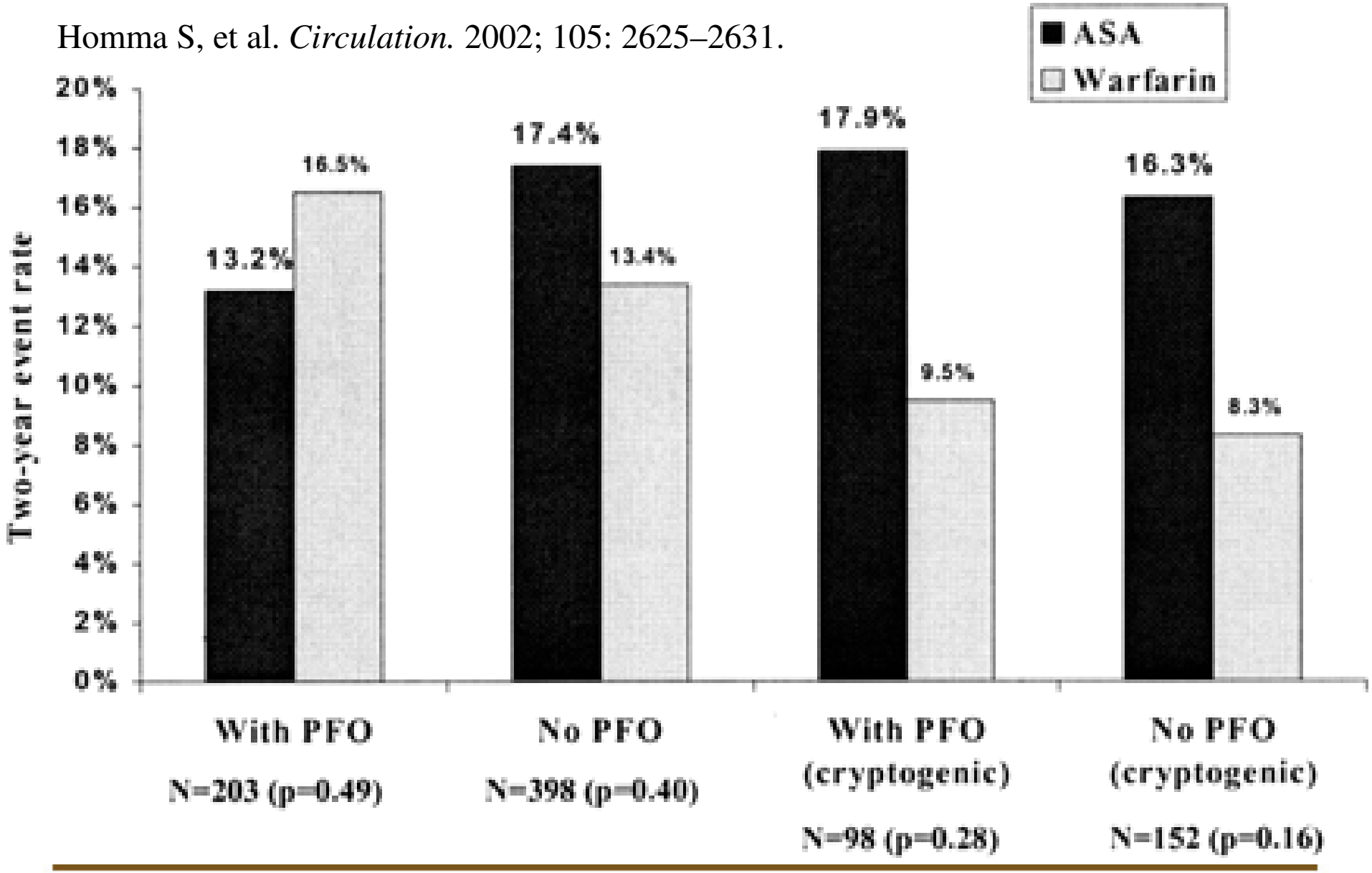
PICSS

- Substudy of Warfarin Aspirin Recurrent Stroke Study (WARSS)
- 630 non-young stroke(age30- 85, mean 59): cryptogenic (42%) or lacunar (39%) stoke.
- Randomized
- ASA (325 mg) vs. warfarin (INR 1.7 to 2.2).
- No difference
- Large PFO: low recurrence (9.5% vs. 18.5%)
- PFO + ASA: not increased risk

Homma S, et al. Circulation. 2002; 105: 2625–2631.

PICSS Two-Year Stroke or Death Rate*

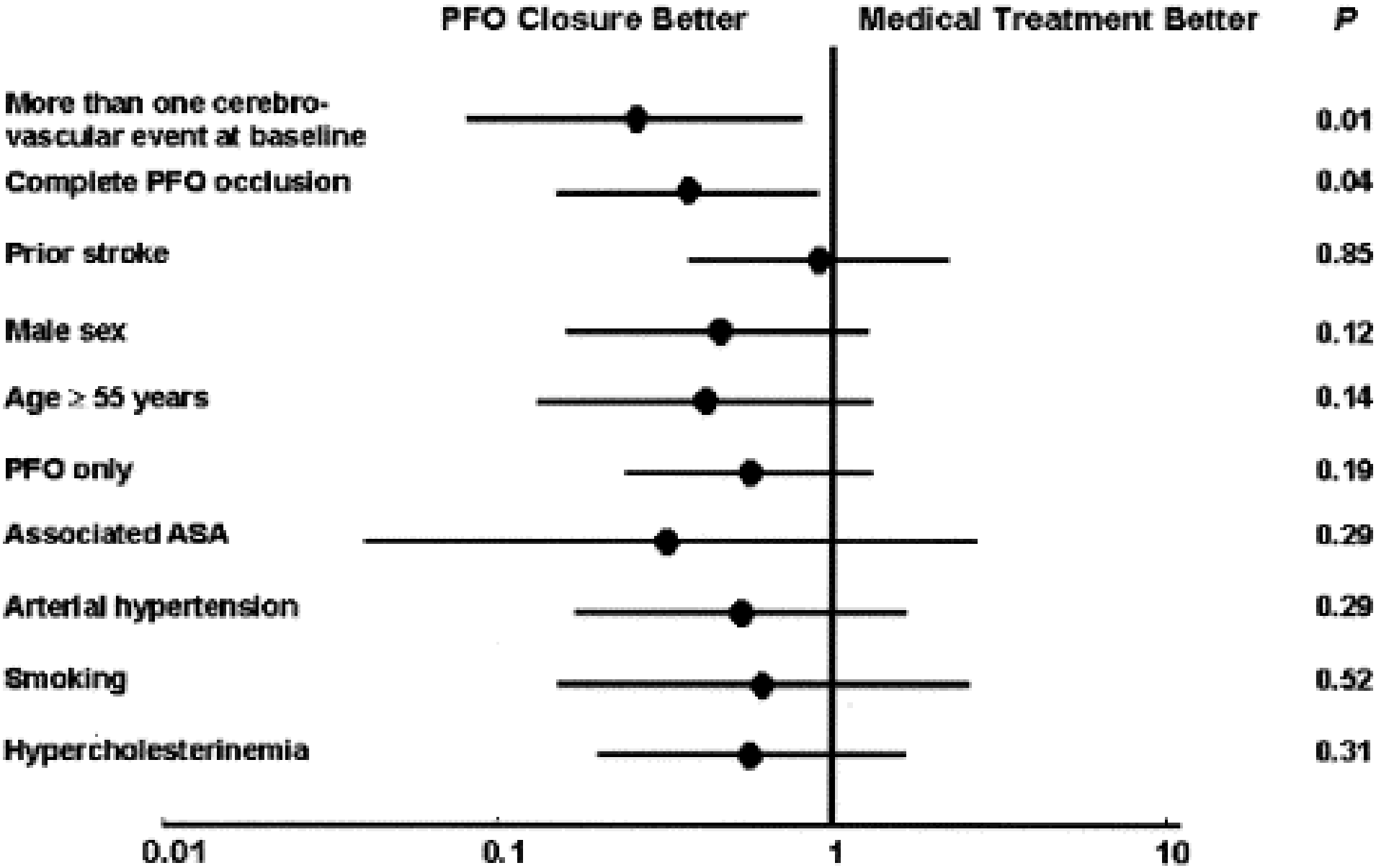
Homma S, et al. *Circulation.* 2002; 105: 2625–2631.



Windecker et al., Journal of the American College of Cardiology 2004 Aug;44:750-758

- 308 subjects
  - 158: antiplatelets
  - 150: closure

- Follow-up (4 years):
- Global trend to less deaths, stroke and TIA (8.5% vs. 24.3%; p=n.s.)
- Significant difference:
  - Multiple events (7.3% vs. 33.2%; p=0.01)
  - Complete closure (6.5% vs. 22.%; p=0.04)



Windecker et al., JACC 2004;44:750-758

Closure: synthesis

- Success rate: 86% - 100%
- Recurrent stroke: 0% - 3.8%
- Complications:
  - Major: < 1.5%
  - Minor: 7.9%
- Closure complete at 6 months in 95% of patients
- No sufficent comparison between devices to indicate preference

(Wilson et al, Circulation 2007)

Anthony J. Furlan
Patent Foramen Ovale and Recurrent Stroke: Closure is the Best Option: Yes
Stroke, Mar 2004; 35: 803 - 804.

Geoffrey A. Donnan and Stephen M. Davis
Patent Foramen Ovale and Stroke: Closure by Further Randomized Trial Is Required!
Stroke, Mar 2004; 35: 806.

Tong and Becker
Patent Foramen Ovale and Recurrent Stroke: Closure Is the Best Option: No
Stroke, Mar 2004; 35: 804 - 805.

Closure of patent foramen ovale in cryptogenic stroke. Ready or not, here come the trials
Joseph L. Blackshear – JACC 2004;44:759-761

ONGOING TRIALS

- PC trial (Amplatzer)
- Respect PFO Trial (Amplatzer - AGA Medical, Golden Valley, Minnesota)
- Closure I Trial (CardioSeal - NMT Medical, Boston, Massachusetts)
- CARDIA (PFO- STAR)

AHA/American Stroke Association guidelines

- First choice: antiplatelets
- Warfarin: only in presence of DVT or hypercoagulability
- Closure: after second event or high-risk

(Albers et al. Chest 2004; Messe et al., Neurology 2004; Slottow et al, Circulation 2007)

New percutaneous options

- Radio-frequency
  - Complete closure in 43% after 6 months (Sievert et al, Circulation 2007)
- HeartStich PFO I (automatic suture)
- BioTREK (bioabsorbable)

Conclusions - I

- Diagnosis of PFO possible with cTCD
- PFO is risk factor when:
  - Stroke is cryptogenic (and juvenile)
  - Large (>2 mm)
  - With large shunt (>25 Mb)
  - Associated to Atrial Septal Aneurysm

Conclusions - II

- Subgroup with high prevalence:
  - **Migraine**
  - **OSAS**
- There is still uncertainty for PFO closure