Meta-analyses of PFO Closure Trials for Stroke: What is the Evidence?

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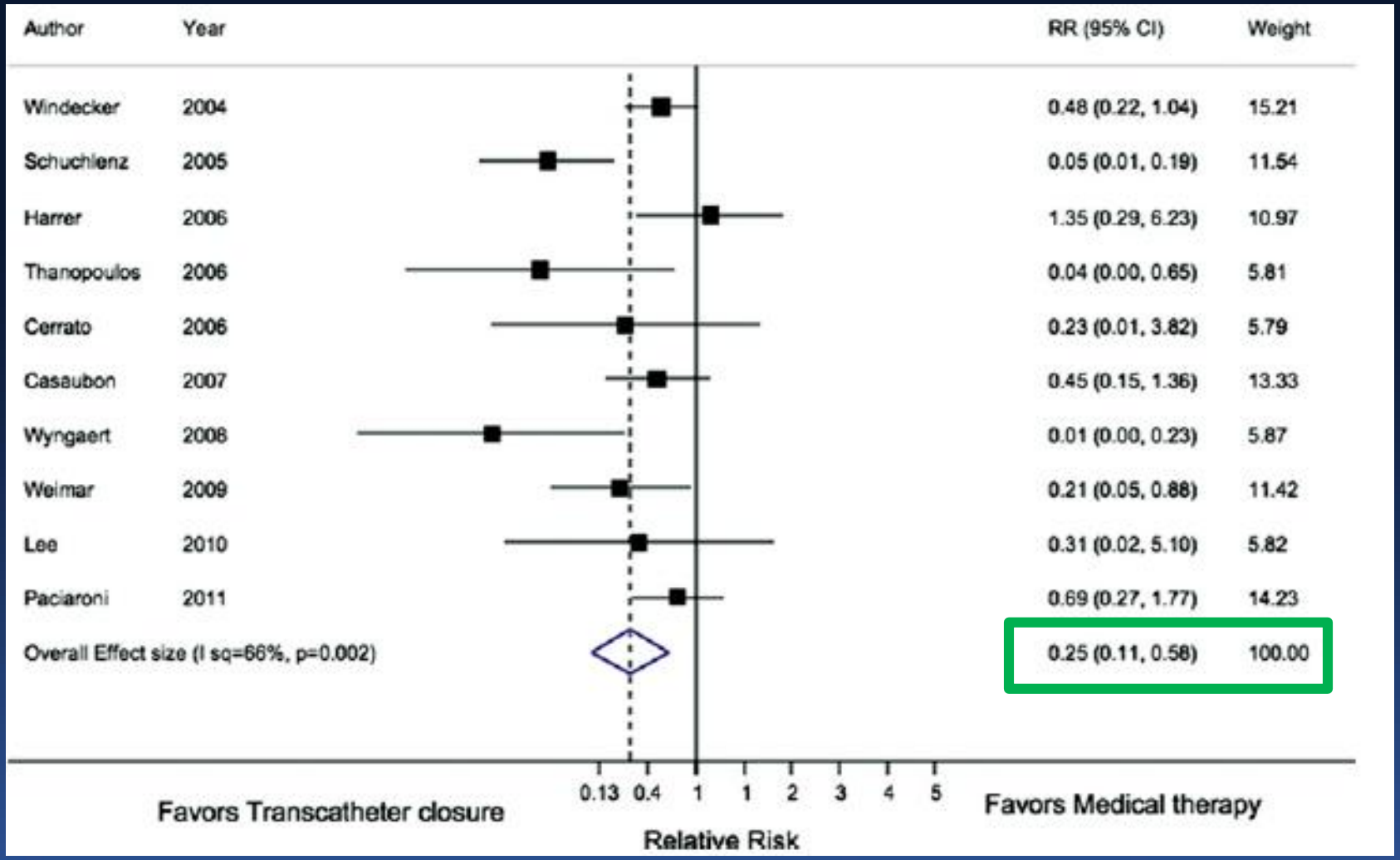
I, Abel Romero-Corral DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

- PFO common in healthy adults
  - 66% compared to stroke of know causes[1]
- Transcatheter closure to prevent events
- Meta-analyses of observational studies: 75% reduction in events vs. medical management[2]

1.-Khairy P, et al. Ann Intern Med 2003.
2.-Agarwal S, et al. J Am Coll Cardiol Intv 2012.

Background



Agarwal S, et al. *J Am Coll Cardiol Intv* 2012.

Background

- 3 RCT failed to show clear benefit[1,2,3]
- Many controversies including type 2 error
- Systematic Review and Meta-analyses of RCT

1.-Furlan AJ, et al. *N Engl J Med* 2012. (CLOSURE I)
2.-Carroll JD, et al. *N Engl J Med* 2013. (RESPECT)
3.-Meier B, et al. *N Engl J Med* 2013. (PC Trial)

A Meta-Analysis of Transcatheter Closure of Patent Foramen Ovale versus Medical Therapy for Prevention of Recurrent Thromboembolic Events in patients with Cryptogenic Cerebrovascular Events

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Running Title: Meta-analysis of PFO closure vs medical therapy

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Results

- Wolfrum M, et al. Heart: Borderline significant risk reduction in stroke in PFO TC closure (3RCT + 2non-RCT) HR=0.58 (0.33-0.99), p=0.047

- Rengifo-Moreno P, et al. Eur Heart J: Significant risk reduction in TIA/Stroke in PFO TC closure (3RCT) HR=0.59 (0.36-0.97), p=0.04

- Pineda AM, et al. CCI: Trend in favor of PFO TC closure (3RCT), OR=0.7 (0.47-1.05) ,p=0.08 in the composite endpoint

3 RCT Interventions and Baseline Characteristics

Author	Study acronym	Enrolment	Country	Number of patients	Mean follow-up (months)	Lost to F/U	Intervention group	Medical therapy group

Trial		Number of patients	Age (years) means ± SD	Men (%)	ASA (%)	Hypertension (%)	Hyperlipidaemia (%)	Smoking (%)	Diabetes (%)
RESPECT, $n = 980$	Device group	499	45.7 ± 9.7	268 (53.7)	180 (36.1)	158 (31.7)	194 (38.9)	75 (15)	33 (6.6)
	Medical therapy	481	46.2 ± 10.0	268 (55.7)	169 (35.1)	150 (31.2)	193 (40.1)	55 (11.4)	40 (8.3)
PC, $n = 414$	Device group	204	44.3 ± 10.2	92 (45.1)	47 (23.0)	49 (24.0)	50 (24.5)	52 (25.5)	5 (2.5)
	Medical therapy	210	44.6 ± 10.1	114 (54.3)	51 (24.3)	58 (27.6)	62 (29.5)	47 (22.4)	6 (2.9)
CLOSURE I, $n = 909$	Device group	447	46.3 ± 9.6	233 (52.1)	168 (37.6)	151 (33.8)	212 (47.4)	96 (21.5)	NR
	Medical therapy	462	45.7 ± 9.1	238 (51.5)	165 (35.7)	131 (28.4)	189 (40.9)	104 (22.6)	NR

ASA, atrial septal aneurysm.

Rengifo-Moreno P, et al. *Eur Heart J* 2013.

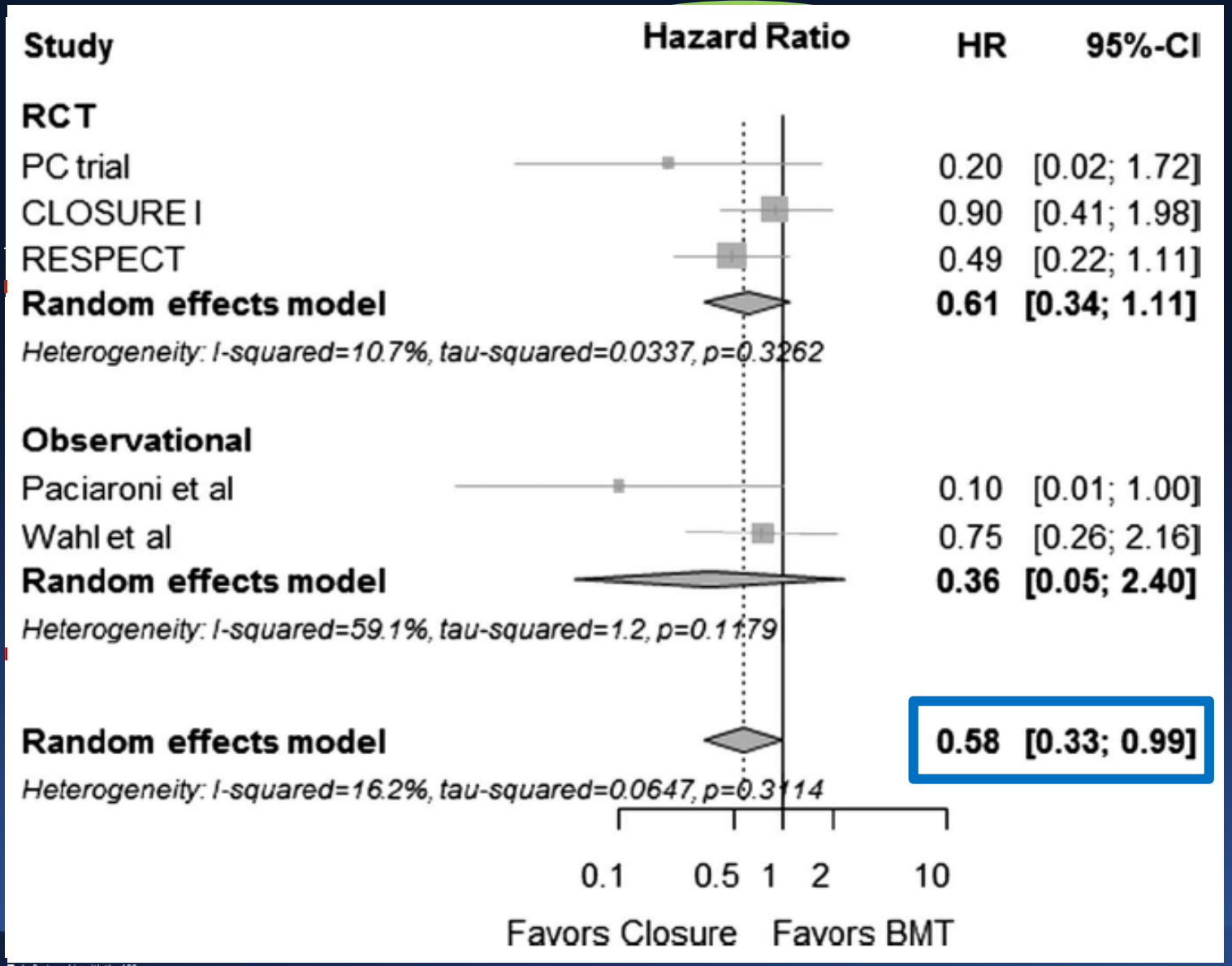
3 RCT Outcomes

	Events	Intervention group (%)	Medical therapy (%)	Hazard ratio	Confidence interval	*P*-value
RESPECT intention-to-treat	Non-fatal ischaemic stroke	9/499	16/481	0.49	0.22–1.11	0.08
RESPECT per protocol		6/471	14/473	0.37	0.14–0.96	0.03
RESPECT as-treated		5/474	16/484	0.27	0.1–0.75	0.007
PC	Composite: death, stroke, TIA or peripheral embolism	7 (3.4)	11 (5.2)	0.63	0.24–1.62	0.34
	Death	2 (1.0)	0	5.2	0.25–107.61	0.24
	Stroke	1 (0.5)	5 (2.4)	0.2	0.02–1.72	0.14
	TIA	5 (2.5)	7 (3.3)	0.71	0.23–2.24	0.56
	Composite stroke, TIA, peripheral embolism	5 (2.5)	11 (5.2)	0.45	0.16–1.29	0.14
CLOSURE I intention-to-treat	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	23 (5.5)	29 (6.8)	0.78	0.45–1.35	0.37
	Stroke	12 (2.9)	13 (3.1)	0.9	0.41–1.98	0.79
	TIA	13 (3.1)	17 (4.1)	0.75	0.36–1.55	0.44
CLOSURE I modified intention-to-treat	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	22/400 (5.6)	29/451 (6.9)	0.78	0.44–1.35	0.37
	Stroke	12/400 (3.1)	13/451 (3.1)	0.94	0.43–2.07	0.88
	TIA	12/400 (3.0)	17/451 (4.2)	0.72	0.34–1.51	0.38
CLOSURE I per protocol	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	22/378	29/375	0.74	0.42–1.29	0.28
	Stroke	12/378	13/375	0.91	0.41–1.99	0.8
	TIA	12/378	17/375	0.68	0.33–1.43	0.31

TIA, transient ischaemic attack.

Rengifo-Moreno P, et al. *Eur Heart J* 2013.

Results - STROKE



Results – TIA/STROKE

RESULTS

STUDY PATIENTS

From August 23, 2003, through December 28, 2011, a total of 980 patients were enrolled; 499 were randomly assigned to the closure group and 481 to the medical-therapy group (Fig. S2 in the Supplementary Appendix). The median time from the index stroke to randomization was 120 days (interquartile range, 74 to 179). A total of 2559 patient-years of follow-up were accumulated, with a mean (±SD) follow-up period of 2.6±2.0 years, a median of 2.1 years (interquartile range, 1.0 to 4.1), and a range of 0 to 8.1 years. At the time the database was locked, 851 patients (86.8%) remained in active follow-up. The dropout rate was 17.2% in the medical-therapy group and 9.2% in the intention-to-treat cohort, 9 events occurred in patients in the closure group, and 16 in patients in the medical-therapy group. The difference between the two groups in the number of patient-years of follow-up met the criteria for considering the raw-count analysis of the intention-to-treat cohort invalid. In the primary time-to-event analysis of the 980 patients in the intention-to-treat cohort (499 in the closure group and 481 in the medical-therapy group) with 25 primary end-point events (9 in the closure group and 16 in the medical-therapy group), the rate of the primary end point was 0.66 events per 100 patient-years in the closure group as compared with 1.38 events per 100 patient-years in the medical-therapy group (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22 to 1.11; P=0.08) (Fig. 1A).

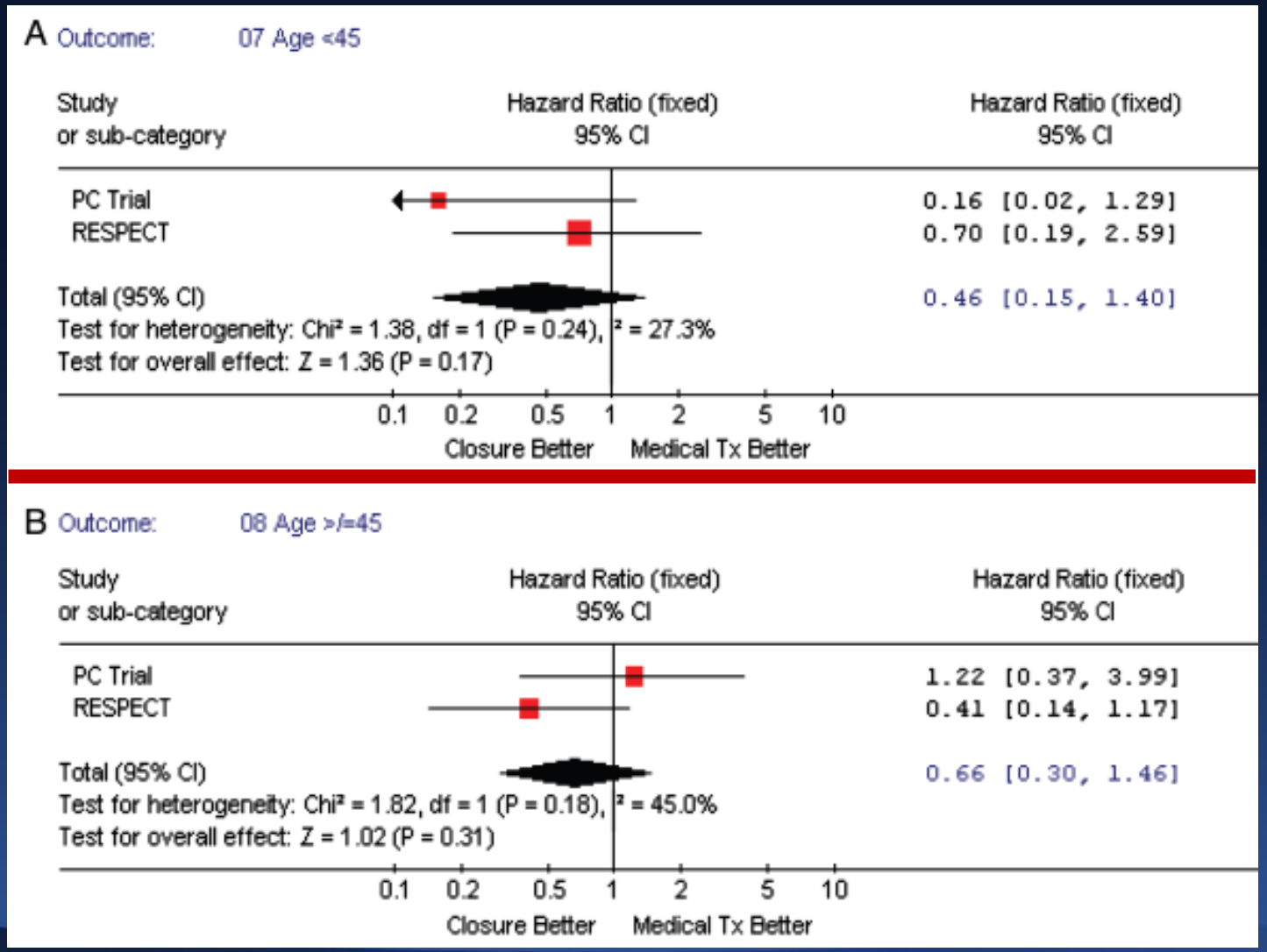
Carroll JD, et al. *N Engl J Med* 2013. (RESPECT)

Results – New Onset A. fib

Trial	Events	Intervention group (%)	Medical therapy (%)	Hazard ratio	Confidence interval (95% CI)	*P*-value
PC trial	New-onset atrial fibrillation	6 (2.9) Two transient, 2 required pharmacological cardioversion, 1 required electrical cardioversion, and 1 sustained AF	2 (1)	3.15	0.64–15.6	0.16
	Myocardial infarction	2 (1)	1 (0.5)	2.04	0.19–22.5	0.62
	Hospital admission related to patent foramen ovale	13 (6.4)	13 (6.3)	1.02	0.48–2.21	0.95
	Bleeding	8 (3.9)	12 (5.7)	0.66	0.27–1.62	0.40
	Vascular procedural complication	2 (1)	N/A	N/A	N/A	N/A
CLOSURE 1	New-onset atrial fibrillation	23 (5.7) Only 14 during the initial 30 days of follow-up, it was transient in 17 patients and persistent in 6 patients	3 (0.7)	N/A	N/A	<0.001
	Major bleeding episode	10/378 (2.6)	4/374 (1.1)	N/A	N/A	0.11
	Death other than endpoint	2 (0.5)	4 (0.9)	N/A	N/A	0.51
	Nervous system disorder	6 (1.5)	16 (3.5)	N/A	N/A	0.15
	Vascular procedural complication	8 (1.7)	N/A	N/A	N/A	N/A
	Cardiac perforation	1 (0.2)	0	N/A		
RESPECT	New-onset atrial fibrillation	(3)	(1.5)	N/A	N/A	N/A
	Pulmonary embolism	6 (1.2)	1 (0.2)	N/A	N/A	0.12
	Major bleeding episode	8 (1.6)	9 (1.9)	N/A	N/A	0.81
	Vascular procedural complication	3 (0.6)	0	N/A	N/A	0.124
	Cardiac perforation	1 (0.2)	0	N/A	N/A	0.124

Rengifo-Moreno P, et al. *Eur Heart J* 2013.

High-Risk Features



Rengifo-Moreno P, et al. *Eur Heart J* 2013.

Limitations

- Lack of individual data
- Medical arm heterogeneous treatment
  - Antiplatelet: single vs. dual vs. Coumadin
- Individual data to asses high-risk PFO features
- Atrial fibrillation?

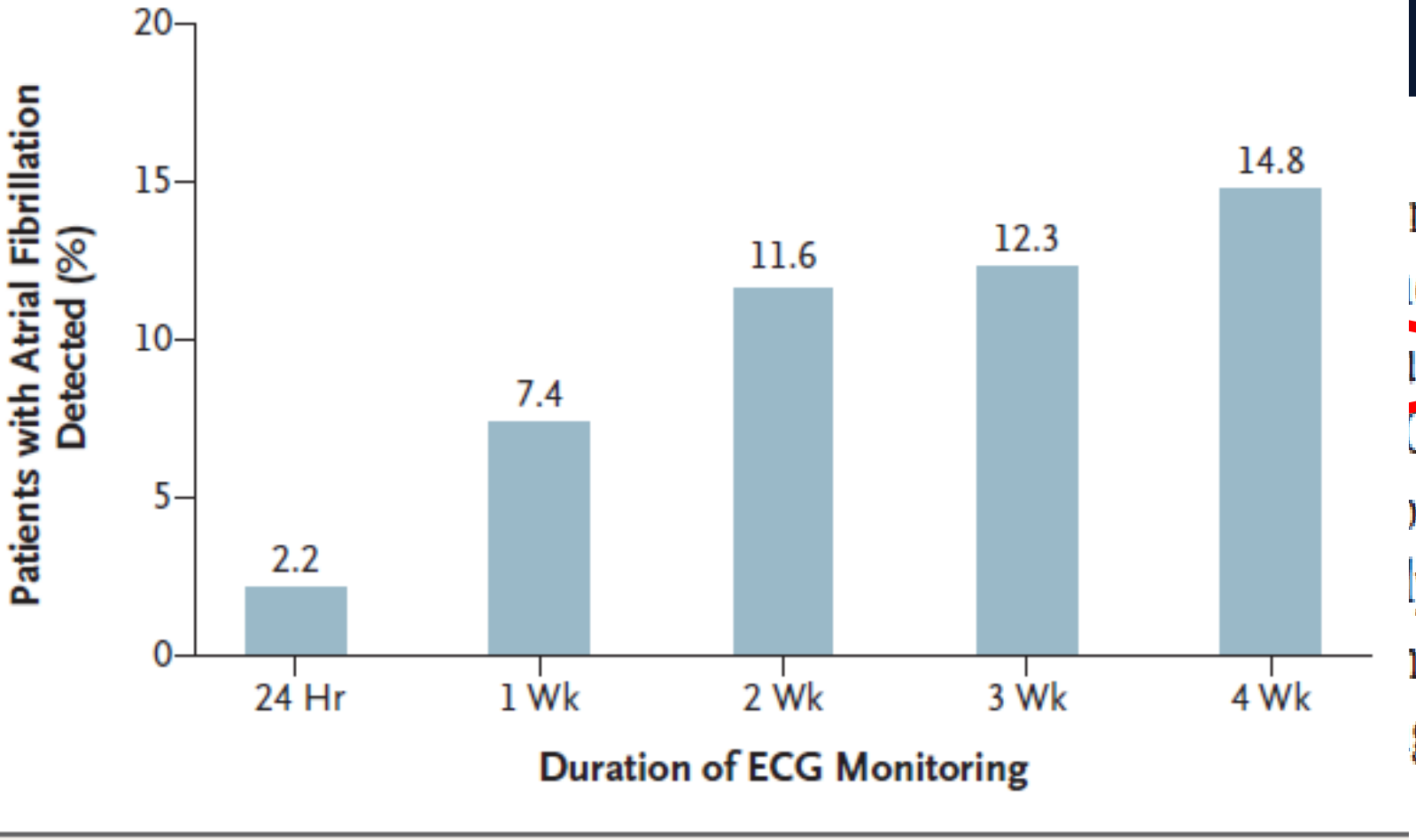


Figure 2. Incremental Yield of Prolonged ECG Monitoring for the Detection of Atrial Fibrillation in Patients with Cryptogenic Stroke or TIA.

Upcoming Data

GORE® HELEX® Septal Occluder / GORE® Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients - The Gore REDUCE Clinical Study (HLX 06-03)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2014 by W.L.Gore & Associates

Sponsor:
W.L.Gore & Associates

Information provided by (Responsible Party):
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ClinicalTrials.gov Identifier:
NCT00738894

First received: August 19, 2008
Last updated: August 19, 2014
Last verified: August 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The primary objective is to determine that **patent foramen ovale** (PFO) closure with the GORE® HELEX® Septal Occluder / GORE® Septal Occluder plus antiplatelet medical management is safe and effective and reduces the risk of recurrent stroke or imaging-confirmed transient ischemic attack (TIA) when compared to antiplatelet medical management alone in patients with a PFO and history of cryptogenic stroke or imaging-confirmed TIA.

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Questions?