RESPECT: Insights into Ischemic Stroke and Its Treatment

RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

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FOR THE RESPECT INVESTIGATORS

Disclosure Statement of Financial Interest

- Within the past 12 months, the University of California, JLS' employer, has had a financial interest/arrangement or affiliation with the organization listed below:

Affiliation/ Financial Relationship	Company
Research Support to Perform Clinical Trial Work (RESPECT)	AGA Medical/ St. Jude Medical
Professional Consulting Fees for Steering Committee Work	AGA Medical/ St. Jude Medical

Goals of Presentation – Neurovascular Aspects of RESPECT Trial Results

- Review RESPECT patient selection methods
  - To enroll patients with cryptogenic cerebral infarct
  - To exclude patients with infarcts of defined non-PFO cause
- Characterize study qualifying ischemic strokes
  - Size, location, severity
- Characterize study efficacy endpoint ischemic strokes
  - Size, location, severity
- Discuss implications for clinical practice

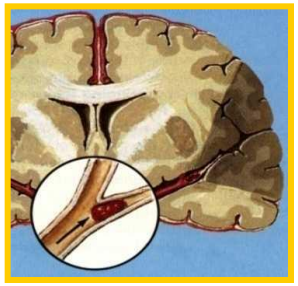
Causes of Stroke

RESPECT CLINICAL TRIAL

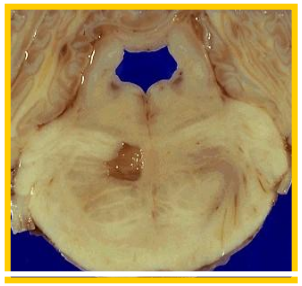
Ischemic Stroke (83%)

Atherothrombotic Cerebrovascular Disease (15-30%)

Cardioembolic (15-30%)



Lacunar- small vessel disease (15-30%)

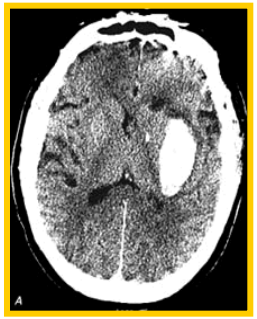


Other (vasculitis, dissection, hyper-coagulable, etc (10%)

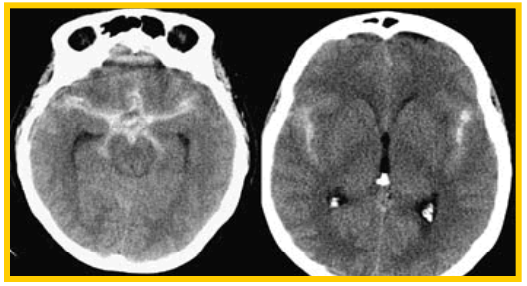
Cryptogenic (10-40%)

Hemorrhagic Stroke (17%)

Intracerebral Hemorrhage (70%)



Subarachnoid Hemorrhage (30%)



RESPECT Entry Criteria – Ischemic Stroke, not TIA

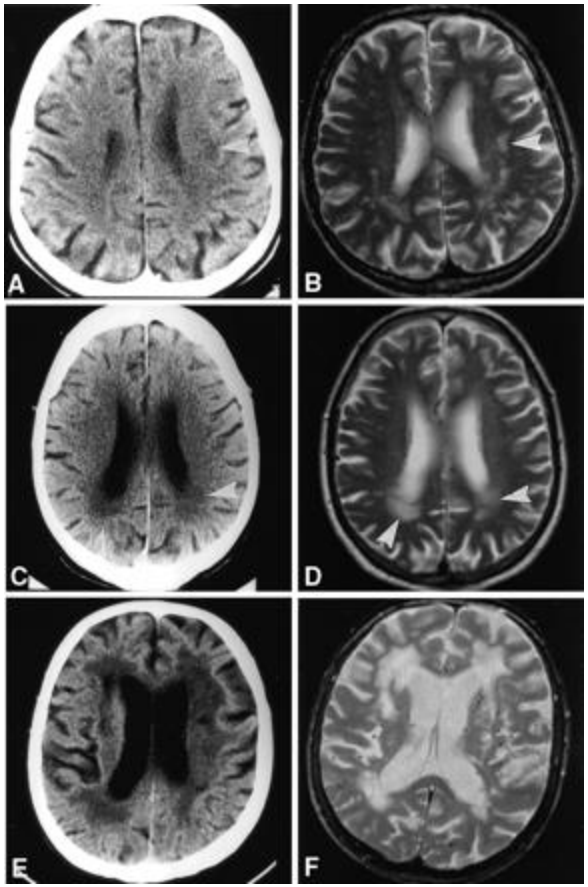
- Ischemic stroke: acute focal neurological deficit, presumed to be due to focal ischemia, and either:
  - Symptoms persisting 24 hours or greater, or
  - Symptoms persisting less than 24 hours but associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct

RESPECT Entry Criteria – Stroke Mechanism

- Inclusion criteria
  - Age 18-60
- Exclusion criteria
  - Arteriopathy
    - Atherosclerosis or other arteriopathy of intracranial or extracranial vessels >50% supplying the involved lesion
    - Aortic arch plaque > 4 mm
    - Arterial dissection as qualifying event
  - Cardioembolic source
    - A fib/flutter chronic/intermittent; Intracardiac thrombus or tumor; MI within last 6 mos; LV aneurysm or akinesis; Valve vegetation or prosthesis; LVEF < 35%; Endocarditis
  - Arterial hypercoagulable state
    - Antiphospholipid Abs, Homocysteinemia
  - Lacunar infarct probably due to intrinsic small vessel disease

Lacunar Infarct Probably Due to Intrinsic Small Vessel Disease

- Ischemic stroke in the distribution of a single, small, deep penetrating vessel AND ANY of the following:
  - HTN (except in 1st week post stroke)
  - DM
  - Age ≥ 50
  - MRI or CT shows leukoaraiosis greater than symmetric, well-defined periventricular caps or bands (European Task Force on Age-Related White Matter Changes rating scale score > 0)



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Wahlund LO et al, Stroke 2001

Trial Results:
Qualifying Cerebral Infarcts

Qualifying Ischemic Stroke Timing and Severity

Characteristic	Device Group N=499	Medical Group N=481	All Subjects N=980	P-value
Days from stroke to randomization[a]	130 (70)	130 (69)	130 (70)	0.89
NIHSS stroke deficit score[b]	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	
Barthel Index ADL score[b]	100 (100 – 100)	100 (100 – 100)	100 (100 – 100)	
mRS disability score[b]	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)	

a. Data represented as mean (standard deviation) for months from randomization to event
b. Data presented in terms of median (interquartile range) for NIHSS, Barthel and mRS.

Topography of Qualifying Ischemic Stroke

Topography	Device Group N=442	Medical Group N=448	All Subjects N=890	P- value[a]
Superficial Only	53.8%	52.7%	53.3%	0.64
Mixed Superf - Deep	9.5%	7.4%	8.4%	
Large Deep Only	4.1%	4.5%	4.3%	
Small Deep Only	12.9%	15.6%	14.3%	
Other	19.7%	19.9%	19.8%	

a. P-values calculated using Chi-Squared Test

Lesion Size of Qualifying Ischemic Infarcts

Lesion size	Device Group N=443	Medical Group N=446	All Subjects N=889	P-value
Small (<0.5 cm)	17.6%	20.6%	19.1%	0.057[a]
Intermediate (0.5-1.5 cm)	33.0%	31.2%	32.1%	
Moderate (1.6-3.0 cm)	19.9%	28.5%	24.2%	
Large (3.1-6.0 cm)	24.4%	16.6%	20.5%	
Massive (>6.0 cm)	5.2%	3.1%	4.2%	
Larger (≥1.5 cm)	49.4%	48.2%	48.8%	0.71[b]

a. P-values calculated using Mann-Whitney-Wilcoxon Test
b. P-values calculated using Fisher's Exact test

Trial Results:
Endpoint Cerebral Infarcts

Endpoint Ischemic Stroke Timing and Severity

RESPECT CLINICAL TRIAL

Characteristic	Device Group n=9	Medical Group n=16	All Subjects n=25	P-value[a]
Months from randomization to event	16 (22.4)	17.9 (15.5)	17.2 (17.9)	0.38
NIHSS stroke deficit score[b]	2 (2 - 3)	2 (0 - 4)	2 (0 - 4)	0.70
Barthel Index ADL score[b]	100 (95 - 100)	100 (85 - 100)	100 (90 - 100)	0.59
mRS disability score[b]	1 (1 - 3)	1 (0 - 2)	1 (0 - 3)	0.56

a. P-values calculated using Mann-Whitney-Wilcoxon test
b. Data presented in terms of median (interquartile range) for NIHSS, Barthel and mRS. Data represented as mean (standard deviation) for months from randomization to event

Topography of Endpoint Ischemic Strokes

Topography	Device Group n=7	Medical Group n=13	All Subjects n=20	P-value[a]
Superficial Only	57.1%	61.5%	60%	0.04
Mixed Superf - Deep	0.0%	15.4%	10%	
Large Deep Only	0.0%	0.0%	0.0%	
Small Deep Only	42.9%	0.0%	15%	
Other	0.0%	23.1%	15%	

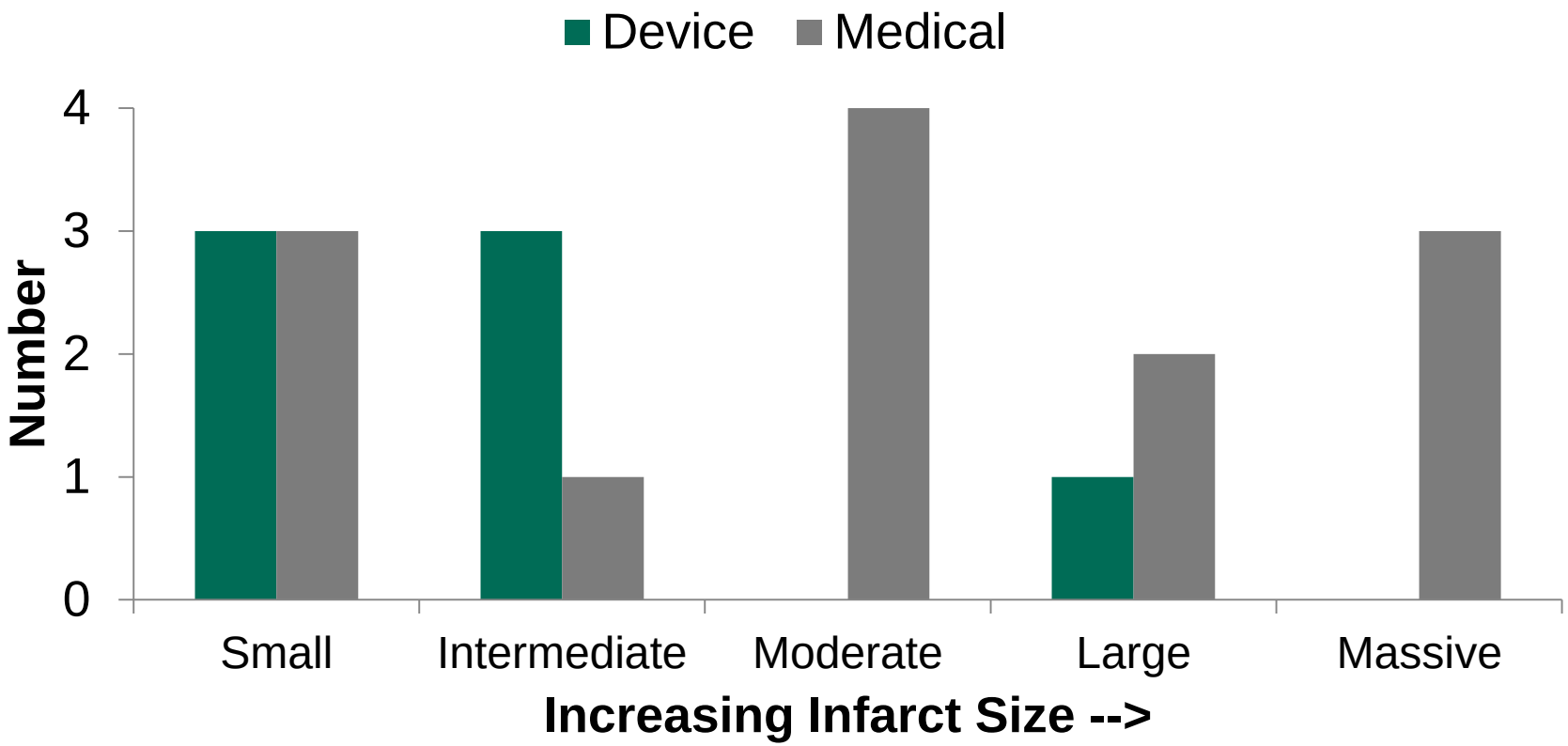
a. P-values calculated using Chi-Squared Test

Lesion Size of Endpoint Ischemic Strokes

Lesion size	Device Group n=7	Medical Group n=13	All Subjects n=20	P-value
Small (<0.5 cm)	42.9%	23.1%	30%	0.09[a]
Intermediate (0.5-1.5 cm)	42.9%	7.7%	20%	
Moderate (1.6-3.0 cm)	0.0%	30.8%	20%	
Large (3.1-6.0 cm)	14.3%	15.4%	15%	
Massive (>6.0 cm)	0.0%	23.1%	15%	
Larger (≥ 1.5 cm)	14.3%	69.2%	50%	0.06[b]

a. P-values calculated using Mann-Whitney-Wilcoxon Test
b. P-values calculated using Fisher's Exact test

Lesion Size of Endpoint Ischemic Strokes



Stroke Mechanism Aspects of Endpoint Ischemic Strokes – Device Arm

- 3 of the 9 device arm ischemic strokes occurred in patients without a device in place
  - 1 after randomization but prior to PFO occluder implant
  - 1 in patient who declined procedure and crossed to medical therapy
  - 1 in patient who required a CABG after randomization but prior to study procedure and who underwent bovine pericardium patch PFO repair during the surgery instead of device closure
- Of the remaining 6 device arm ischemic strokes, 3 were small, deep only infarcts

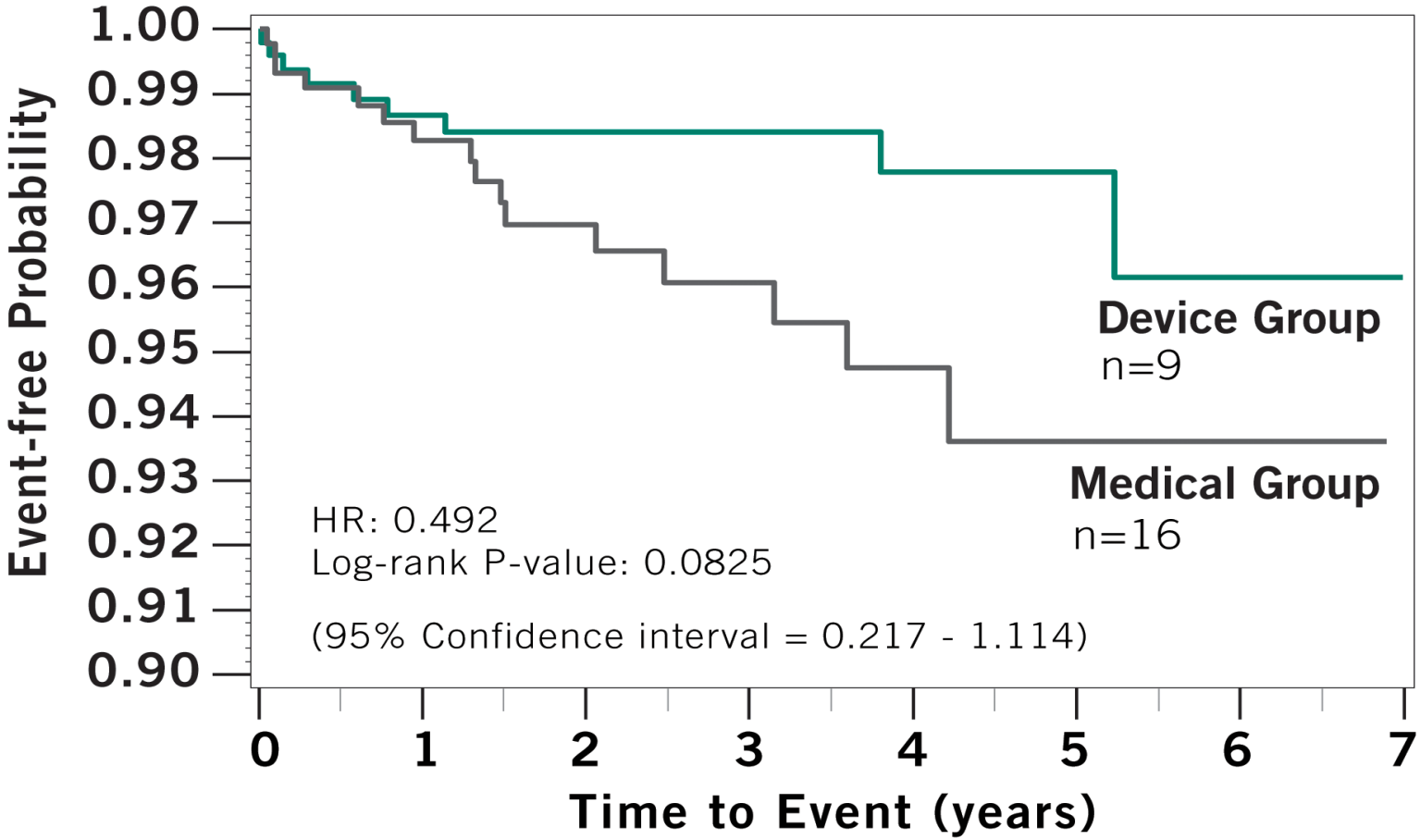
Ischemic Strokes in Device Arm without PFO Occluder Implanted

Event	ITT	PP	AT	DIP
Ischemic stroke prior to PFO occluder Implant	Dev	Dev	Exc	Med
Ischemic stroke post cross-over to medical management	Dev	Exc	Med	Med
Ischemic stroke post CABG bovine pericardium patch repair	Dev	Exc	Exc	Med

Dev = Device Group
Med = Medical Group
Exc = Excluded from analysis

Primary Endpoint Analysis – ITT Cohort

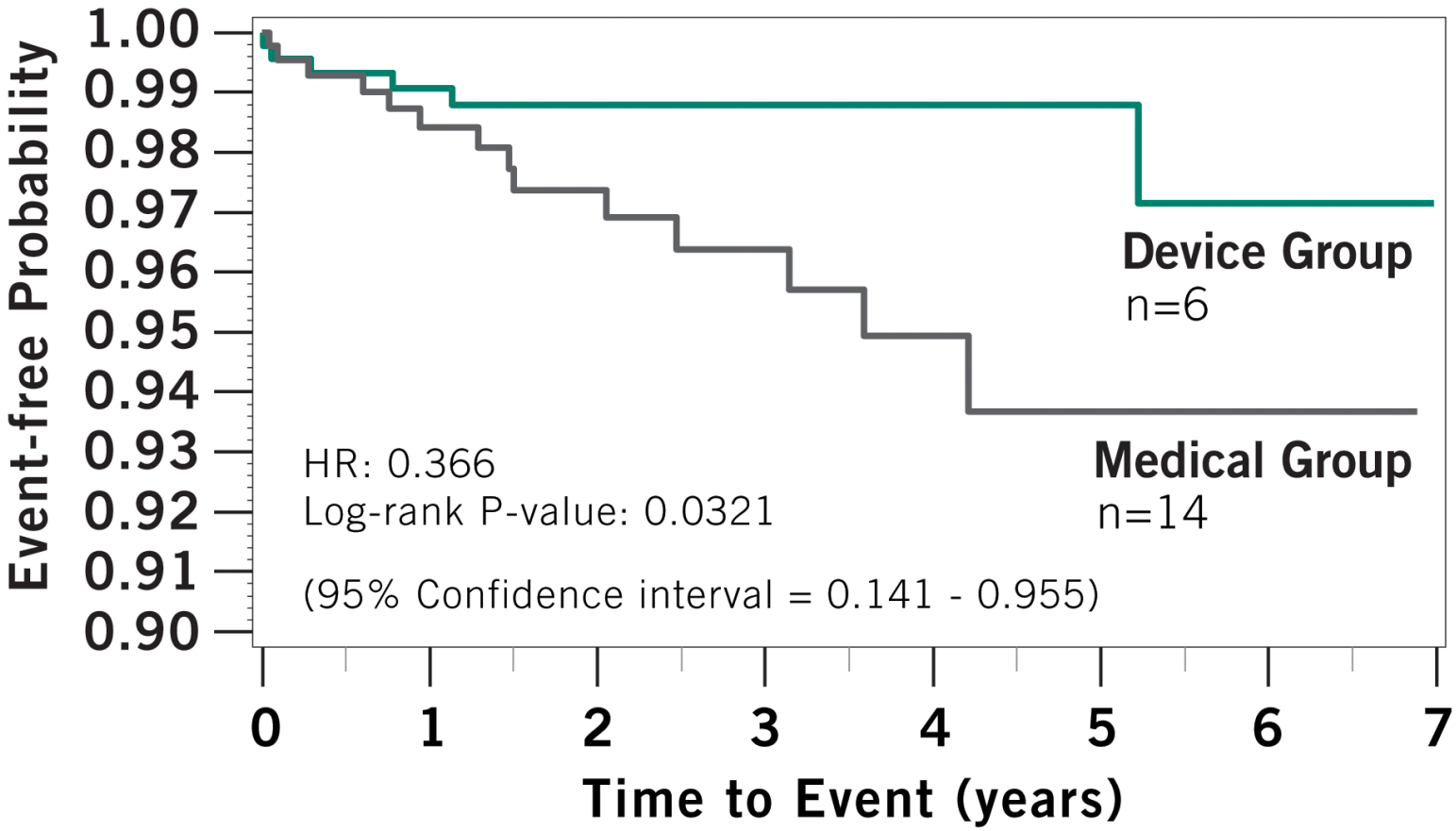
50.8% risk reduction of stroke in favor of device



- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

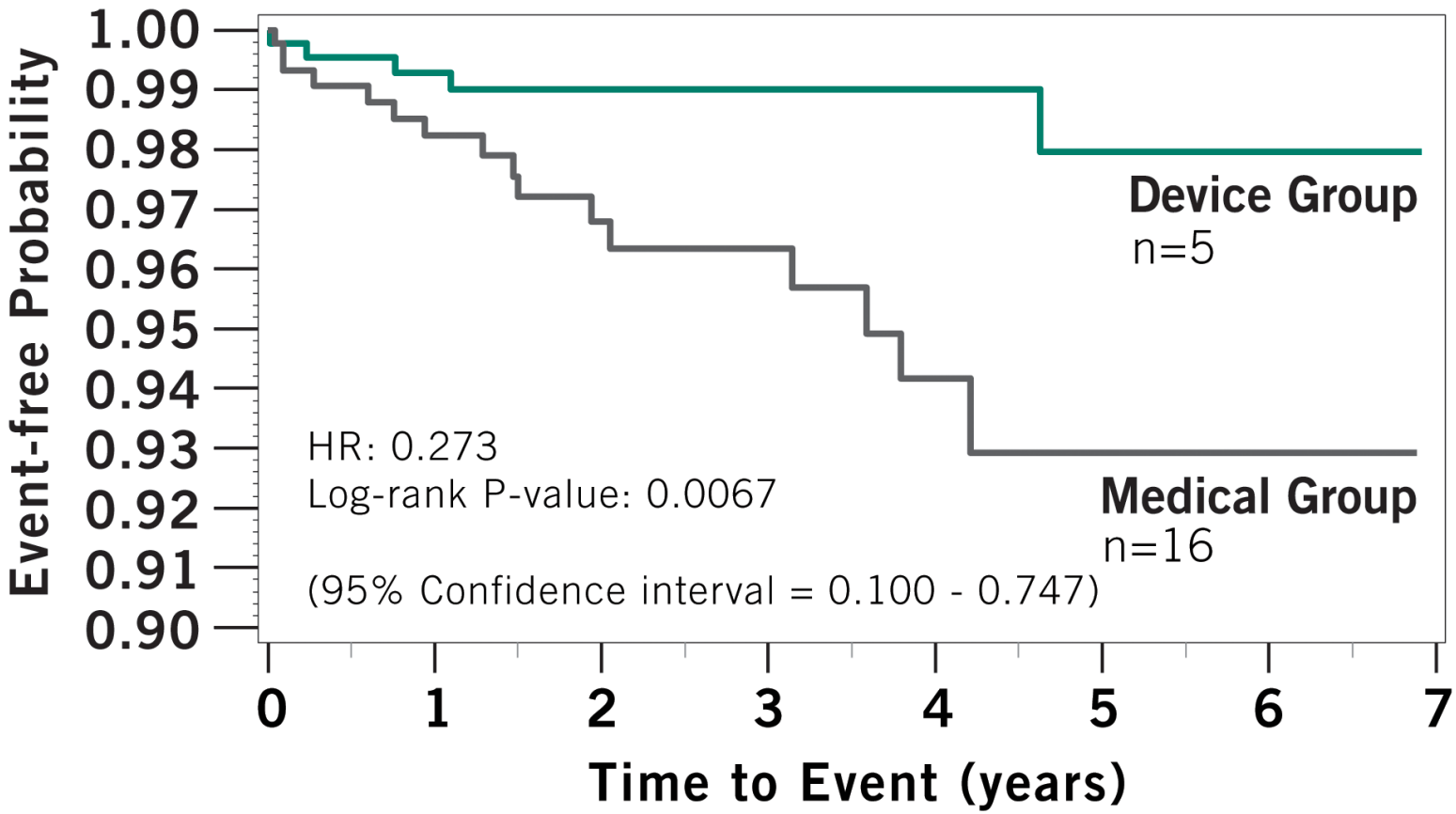
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

1. Cox model used for analysis

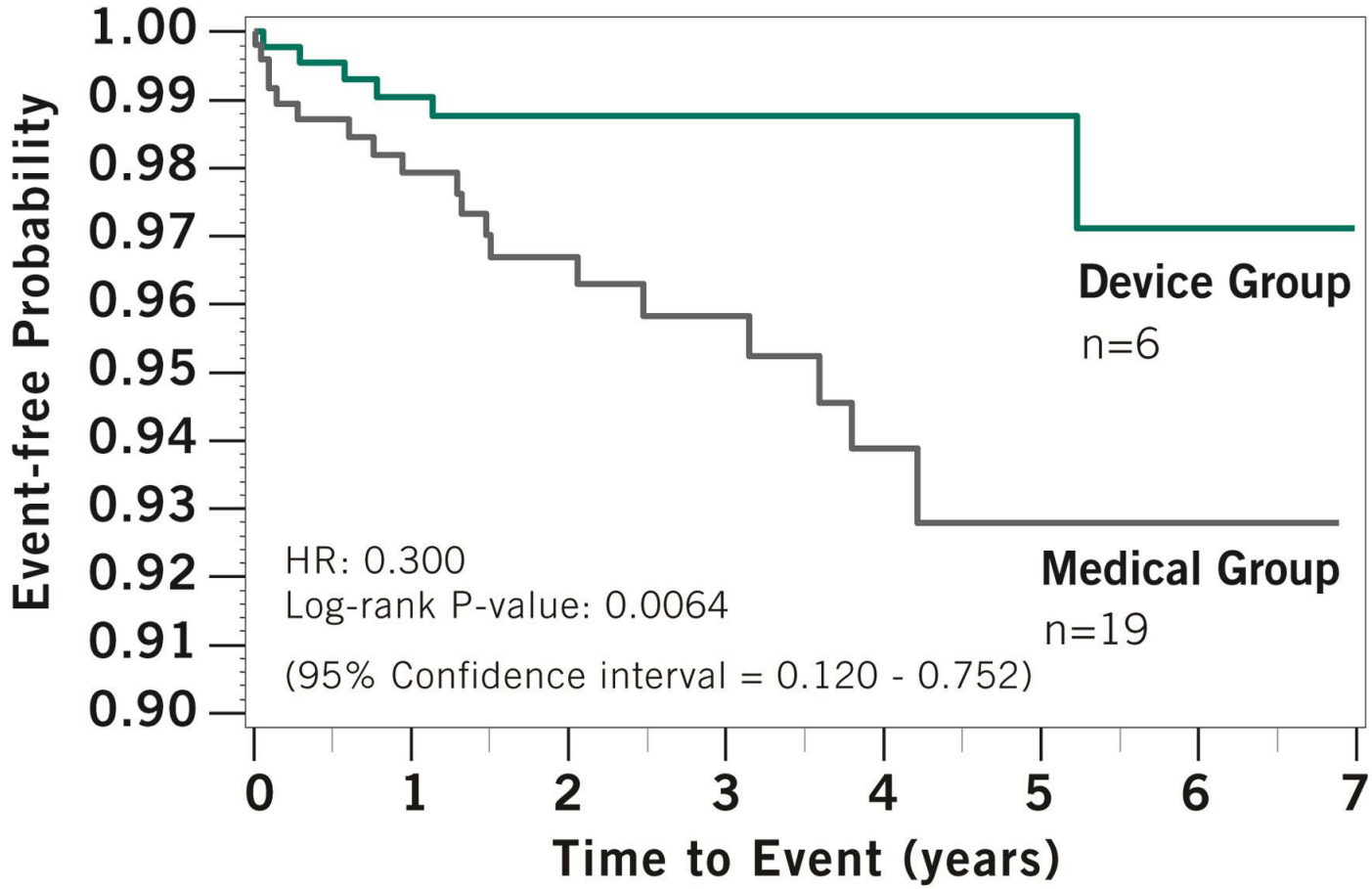
Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device



- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

1. Cox model used for analysis

Post-hoc Analysis – Device in Place Cohort
70% risk reduction of stroke in favor of device



- The Device in Place cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually present at time of each observation, regardless of the randomization assignment

1. Cox model used for analysis

Discussion

- The RESPECT population was stringently selected to identify patients with cryptogenic ischemic stroke
  - Excluding TIA patients from entry (and from primary endpoint analysis) reduced noise from “mimic” conditions
  - The exclusion of small deep infarcts likely due to intrinsic small vessel disease was successful in limiting recurrent small deep infarcts as endpoint events
- The types of infarcts particularly averted in the device group were those associated with paradoxical embolic stroke mechanism
  - Superficial vascular distribution
  - Large infarct size
- In ITT analysis, event rate was low in medical arm (1.25% per patient-year) but even lower in device arm (0.61% per patient-year)

Conclusions

- Consideration of neurovascular aspects of the RESPECT trial reinforce the primary analysis
- With stringent patient selection to identify patients with a history of cryptogenic stroke and PFO, closure with the AMPLATZER PFO Occluder showed evidence of benefit over medical management alone
- Indications of magnified effect in averting superficial cerebral infarcts and larger cerebral infarcts provide additional evidence of a genuine biological effect of closure with the AMPLATZER PFO Occluder in preventing recurrent cerebral infarcts due to paradoxical emboli