Atrial Fibrillation: Risk factor or risk marker? What are the differences?

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Disclosures

- **Research Grants**
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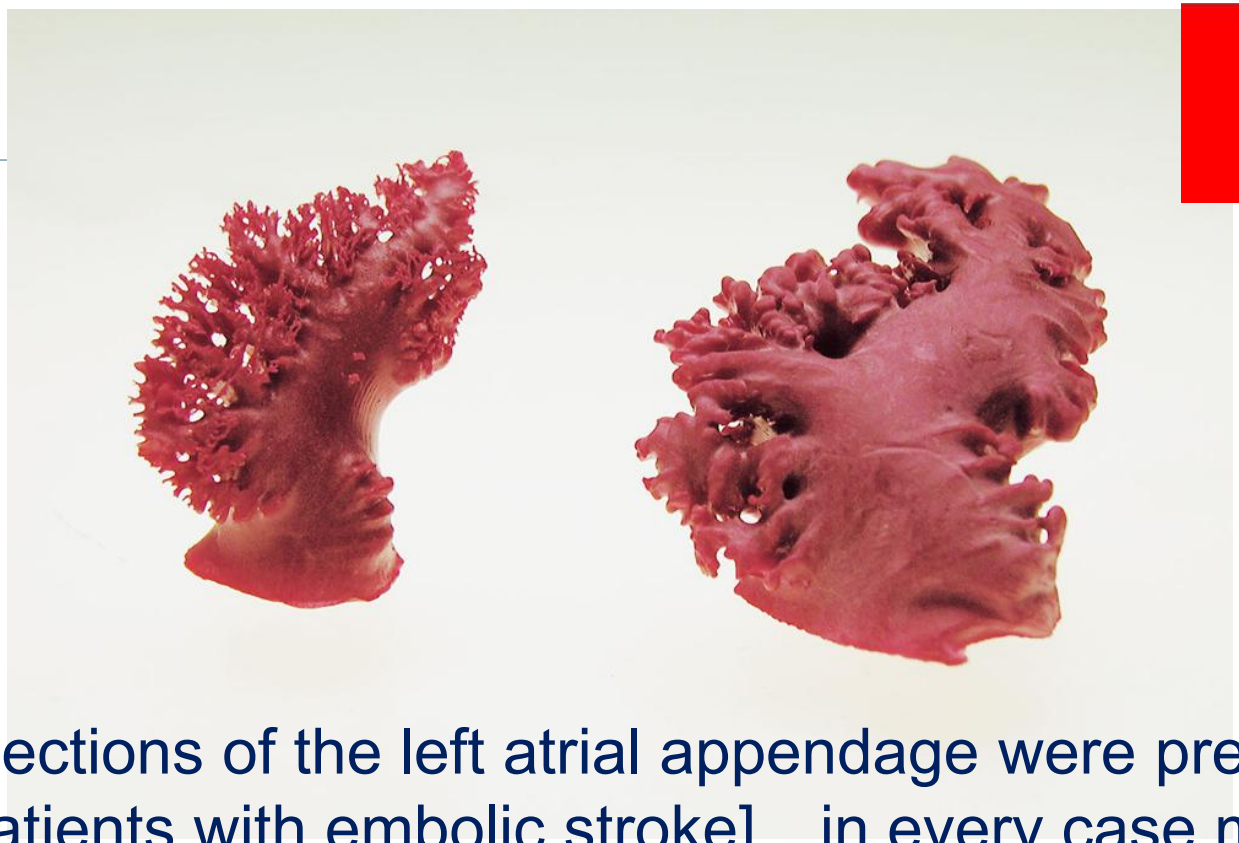
  - Medtronic, Boston Scientific, St. Jude Medical, Boehringer-Ingelheim, Bayer, Bristol-Meyers-Squibb

What is Causality?

- **Aristotle**
  - Formal, Material, Efficient and Final causes
- **Hume**
  - Can never be sure;
  - Cause and effect must be contiguous in space and time; cause must occur before the effect and there be a constant union between the two
- **Similar constructs in Hindu and Buddhist philosophy**
- **Multiple causal models and theories to help "prove" causation**

Criteria for Causation: Sir Austin Bradford Hill

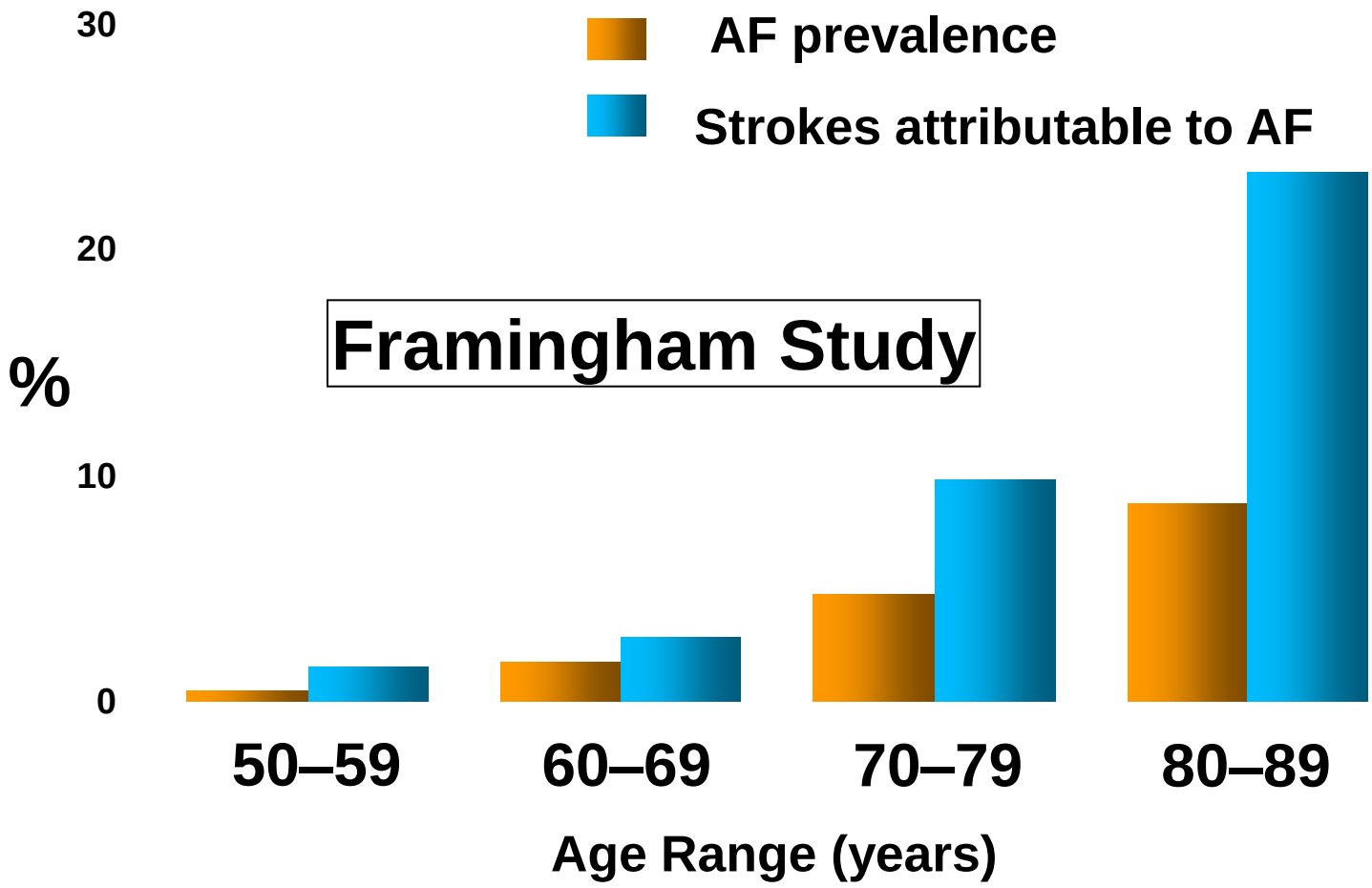
Factor	AF and Stroke
Strength	2-6-fold increased RR, OR, HR; PAR high, but **confounding**
Consistency	Observation in **many** populations, CHADS-VASc
Specificity	**Difficult** –many types and "causes" of stroke
Temporality	**Difficulty** defining all AF; post-stroke monitoring studies
Biological gradient	**Unclear** AF threshold for clinical AND sub-clinical AF
Plausibility	Pathology and TE echo studies; **but small and/or old; cannot see all thrombi**
Coherence	Animal models; **but easy to adapt; relevance to SCAF?**
Experimental	**Data lacking**, RCTs in AF – both drug and device
Analogy	**Many but not specific**



"Serial sections of the left atrial appendage were prepared [in AF-patients with embolic stroke]…in every case mural thrombus, not obvious to the naked eye, was found in the interstices of the trabeculae carneae."

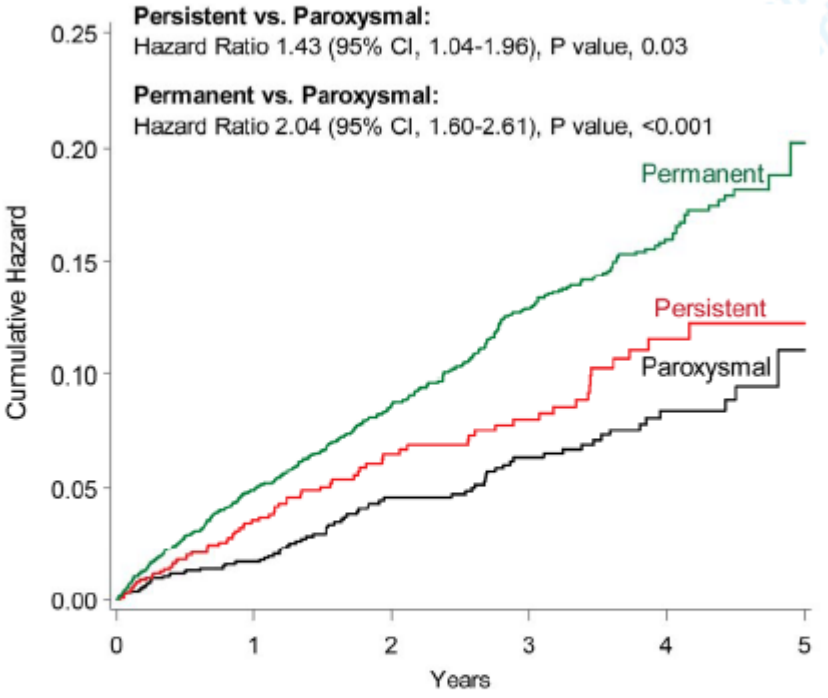
C.M. Fisher. Can Med Assoc J 1953; 69: 257.
1913-2012 (b. Waterloo, Ontario)

Strokes Attributable to AF



Wolf et al. Stroke 1991;22:983-988.

ACTIVE-AVERROES
N=6563, ASA-treated



No. at Risk						
Paroxysmal	1576	1226	766	604	310	17
Persistent	1136	846	502	386	174	7
Permanent	3854	2909	1975	1505	685	31

Figure 1. Kaplan-Meier cumulative hazard rates of embolic events according to pattern of AF occurence.

Venassche T. Eur Heart J. 2014

ASSERT: Clinical Outcomes
Healey JS, NEJM 2012

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N=2319		Present N= 261				
	events	%/year	events	%/ year	RR	95% CI	p
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.49	1.28 – 4.85	0.007
Vascular Death	153	2.62	19	2.92	1.11	0.69 – 1.79	0.67
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.25	0.85 – 1.84	0.27
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.56	3.78 – 8.17	<0.001

ASSERT: Time-Dependent Analysis

Duration of AT ≥ 190 Beats per Minute	Ischemic Stroke or Embolism: Atrial Tachyarrhythmia Present vs. Absent		
	RR	95% CI	P-Value
≥ 6 minutes	1.77	1.01-3.10	0.047
≥ 30 minutes	2.01	1.12-3.60	0.02
≥ 6 hours	2.99	1.55-5.77	0.001
≥ 24 hours	4.96	2.39-10.3	<0.001

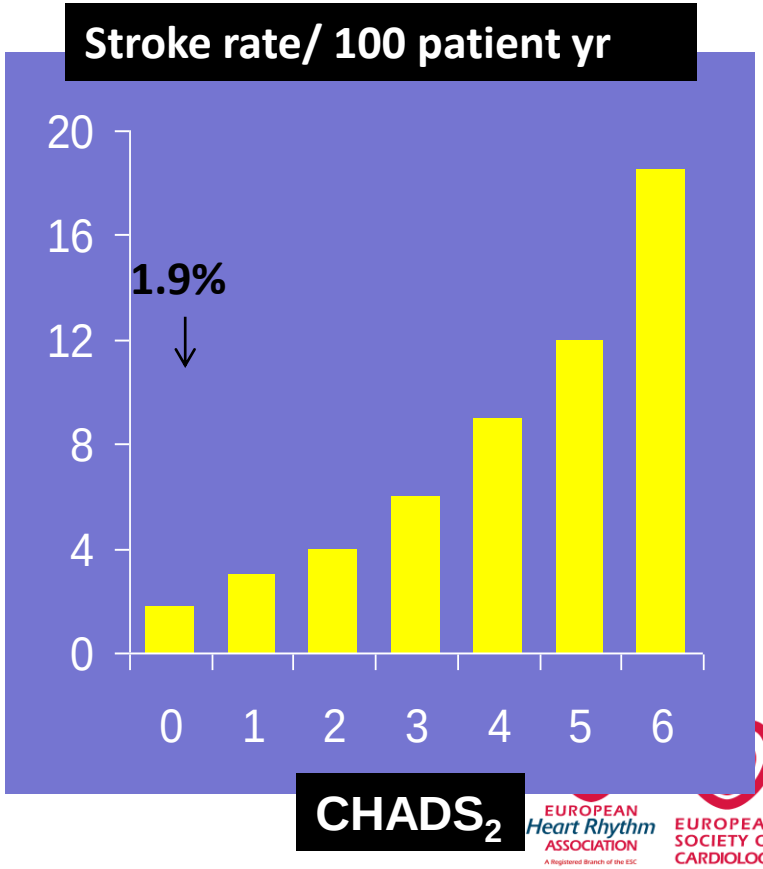
ASSERT: Outcomes by $CHADS_2$

Healey JS, NEJM 2012

$CHADS_2$ Score	Total Pts.	Sub-clinical Atrial Tachyarrhythmia between enrollment and 3 months						Sub-clinical Atrial Tachyarrhythmia Present vs. absent		
		Present			Absent					
		Pts.	events	%/year	Pts.	events	%/year	HR	95% CI	P (trend)
1	600	68	1	0.56	532	4	0.28	2.11	0.23 – 18.9	
2	1129	119	4	1.29	1010	22	0.77	1.83	0.62 – 5.40	0.35
>2	848	72	6	3.78	776	18	0.97	3.93	1.55 – 9.95	

Stroke Risk by Clinical Factors

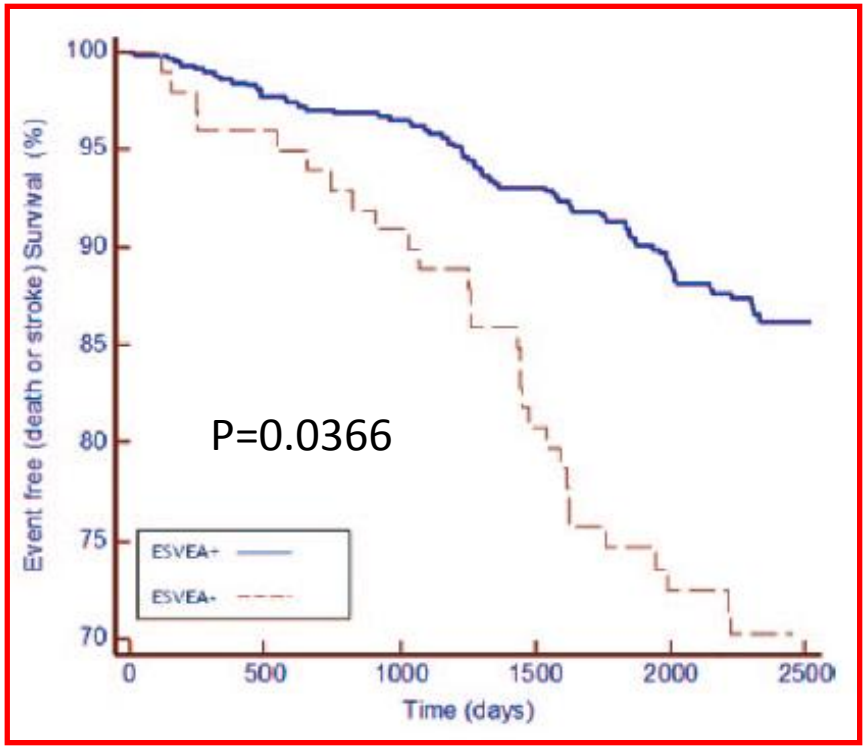
Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke/TIA/ Thromboembolism	2
Maximum Score	6

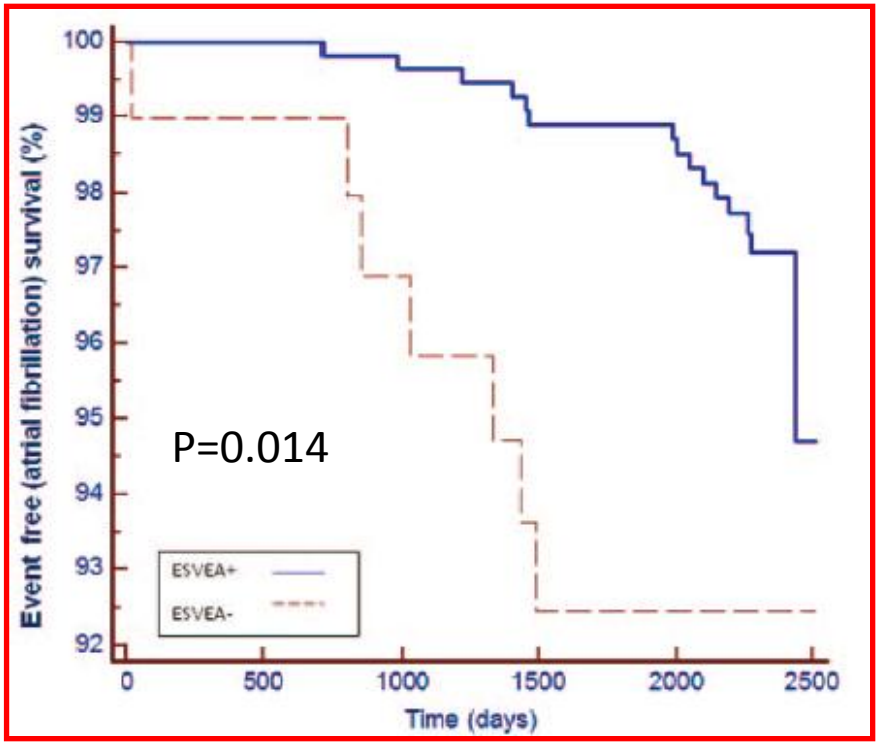


Outcomes of Cohort Study

Binici, Circulation 2010

Copenhagen Holter Study: Age 55-75. One 48 hour Holter.
Positive defined as > 30 PACs per hour or any run ≥ 20 beats.
Mean follow-up of 6.3 years

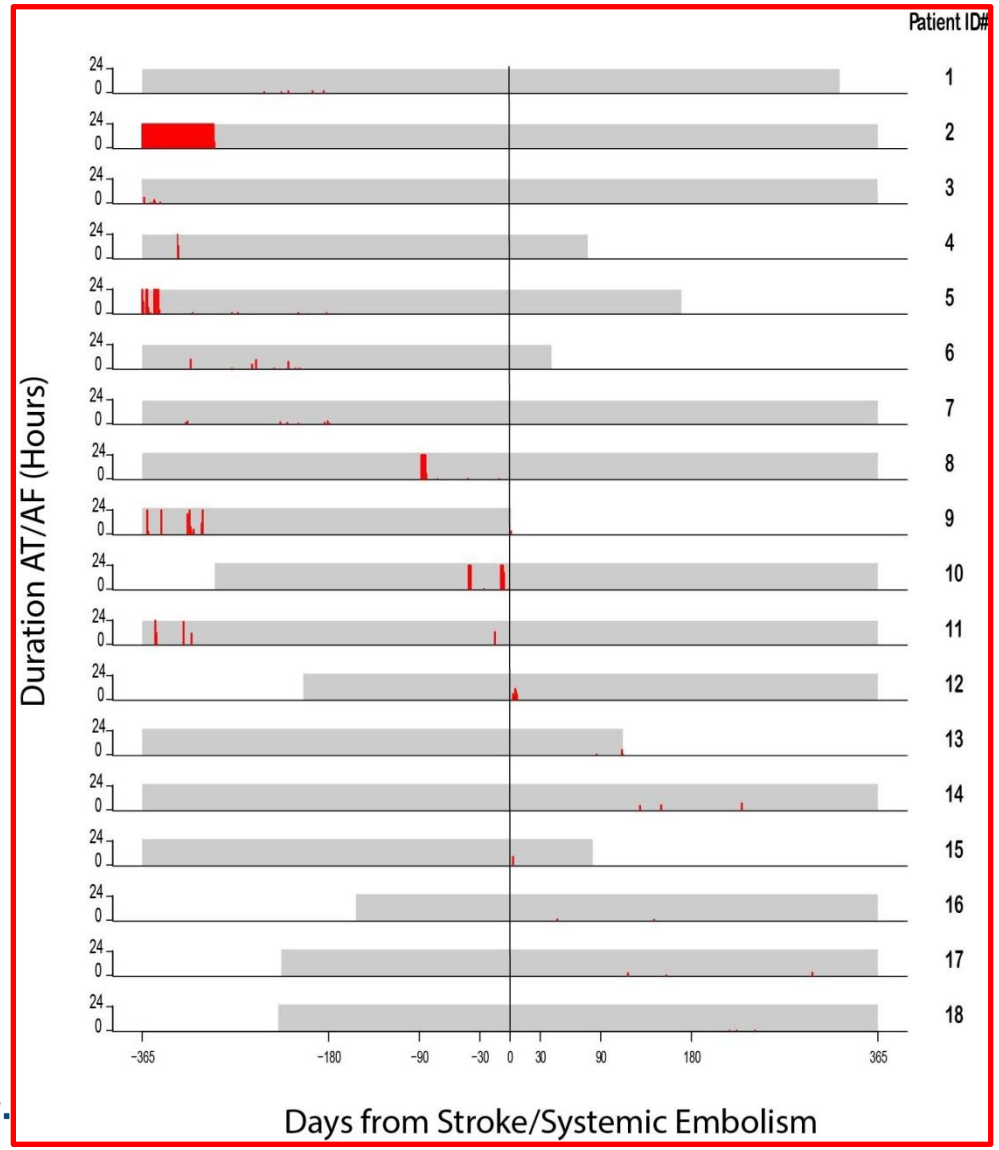




Death or Stroke

Hospitalization for AF

Relationship between AF and Stroke



Brambatti M
Circulation 2014

Trans-Esophageal Echo: A. Klein, NEJM 2001

Variable	Transesophageal-Echocardiography Group (N=619)	Conventional-Treatment Group (N=603)	Relative Risk (95% CI)	P Value
All embolic events — no. (%)	5 (0.8)	3 (0.5)	1.62 (0.39–6.76)	0.50
Cerebrovascular accident	4 (0.6)	2 (0.3)	1.95 (0.36–10.60)	0.43
Transient ischemic attack	1 (0.2)	1 (0.2)	0.97 (0.06–15.54)	0.99
Peripheral embolism	0	0	—	—
Hemorrhagic events — no. (%)	18 (2.9)†	33 (5.5)	0.53 (0.30–0.93)	0.03
Major	5 (0.8)	9 (1.5)	0.54 (0.18–1.61)	0.26
Minor	14 (2.3)	24 (4.0)	0.57 (0.30–1.09)	0.08
Death from all causes — no. (%)	15 (2.4)	6 (1.0)	2.44 (0.95–6.24)	0.06
Cardiac-related	8 (1.3)	4 (0.7)	1.95 (0.59–6.44)	0.27
Noncardiac-related	5 (0.8)	2 (0.3)	2.44 (0.47–12.50)	0.27
Unknown cause	2 (0.3)	0	4.87 (0.23–101.25)	0.16

Treatment	Age (yr)/ Sex	Coexisting Conditions and Risk Factors for Embolism	Adjudicated Event	Days after Enrollment	DC Cardioversion	Spontaneous Cardioversion	Days after Cardioversion	Recurrence of Atrial Fibrillation after DC Cardioversion	Death	Anticoagulation at Time of Event	
										Warfarin (INR)	Heparin (PTT)
TEE	70/M	HTN, DM, SEC	CVA	2	Yes	No	1	Yes	No	Yes (1.9)	Yes (58)
TEE	77/F	SEC	CVA	5	Yes	No	5	Yes	No	Yes (1.7)	No
TEE	73/M	HTN, cancer, SEC	CVA	28	Yes	No	26	Yes	No	No	No
TEE	58/M	HTN, complex AP	CVA	55	Yes	No	52	No	No	No	No
TEE	65/M	HTN, LVEF <40%, complex AP, SEC	TIA	16	No	Yes	16	NA	No	Yes (2.5)	No
Conventional	65/F	None	CVA	12	Yes	No	6	No	No	Yes (2.4)	No
Conventional	68/F	HTN, DM, LVEF <40%	CVA	20	No	No	NA	NA	Yes	Yes (2.7)	No
Conventional	57/M	HTN, DCM, LVEF <40%	TIA	7	No	No	NA	NA	No	Yes (2.7)	No

*TEE denotes transesophageal echocardiography, DC direct current, INR international normalized ratio, PTT partial-thromboplastin time (in seconds), HTN hypertension, DM diabetes mellitus, SEC smoke-like echoes on transesophageal echocardiography, CVA cerebrovascular accident, AP aortic plaque, LVEF left ventricular ejection fraction, TIA transient ischemic attack, NA not applicable, and DCM dilated cardiomyopathy.

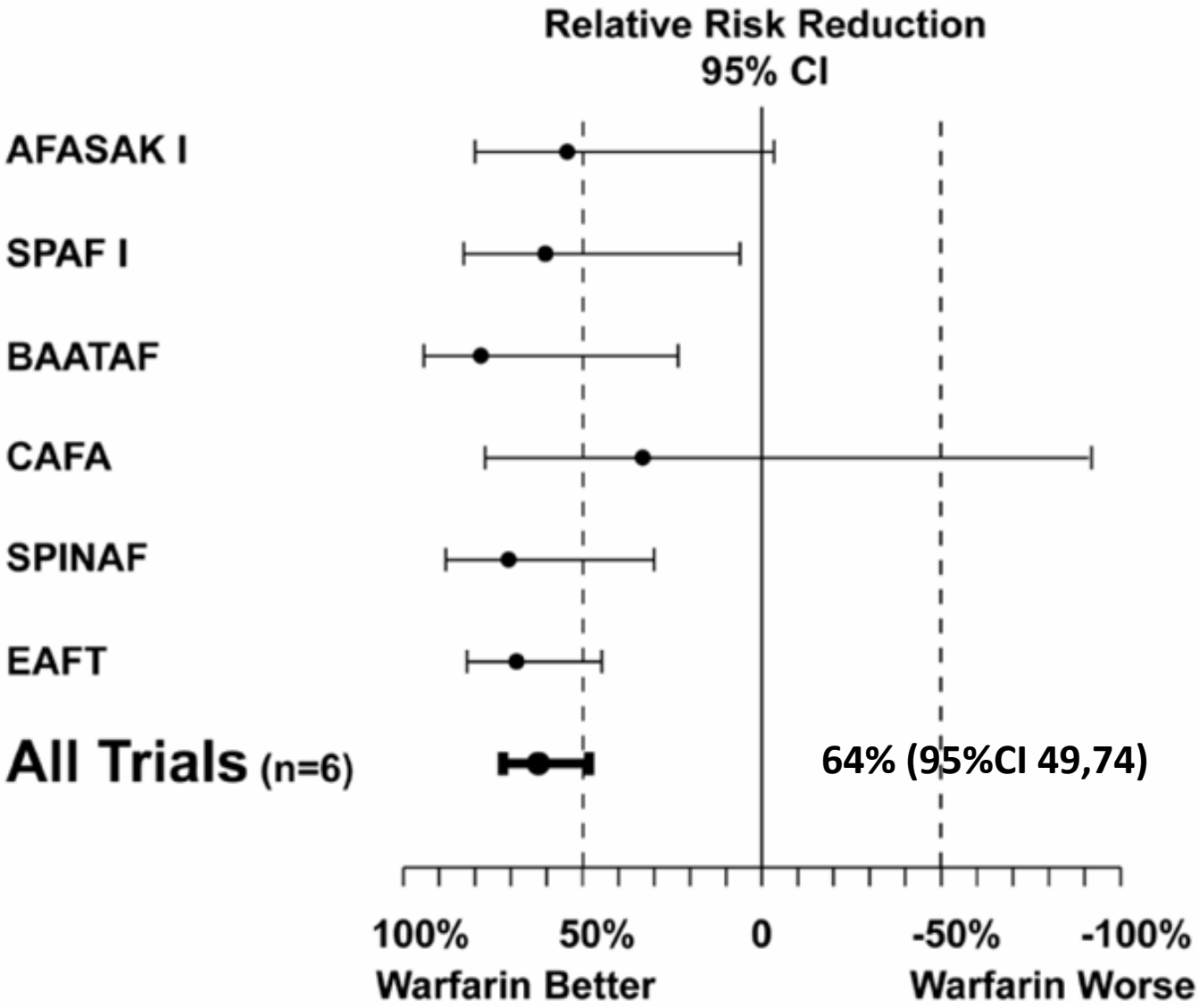
Speaker

The 2 mm thrombus…..

Challenges to Proof of Causality

- **Defining AF**
  - Monitoring studies
  - AF vs. SCAF vs. atrial tachycardia vs. PACs
  - Historical studies mostly persistent/permanent AF
- **Defining Surrogates**
  - LAA clot vs. spontaneous echo contrast (smoke)
- **Defining Outcomes**
  - Stroke
  - Covert stroke
  - Cognitive decline
- **Determining Temporal Relationship**
- **Experiment…**

Adjusted-dose Warfarin Compared with Placebo/Control



Hart RG, Pearce LA, Aguilar MI. *Ann Intern Med* 2007: 146: 857-67.

Drug-Based Rhythm Control

TABLE 3. ADVERSE EVENTS.*

EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
		no. of patients (%)		
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68
Disabling anoxic encephalopathy	9 (0.3)	4 (0.2)	5 (0.4)	0.74
Myocardial infarction	140 (5.5)	67 (4.9)	73 (6.1)	0.60
Hemorrhage not involving the central nervous system	203 (7.3)	107 (7.7)	96 (6.9)	0.44
Systemic embolism	16 (0.5)	9 (0.5)	7 (0.4)	0.62
Pulmonary embolism	8 (0.3)	2 (0.1)	6 (0.5)	0.16
Hospitalization after base line	2594 (76.6)	1220 (73.0)	1374 (80.1)	<0.001

*Percentages were derived from a Kaplan–Meier analysis. P values were derived from the log-rank statistic.

†The P value in the case of death was based on the square root of the log-rank statistic, adjusted for 10 interim monitoring analyses.

‡One patient had crossed over to the rhythm-control group and was taking quinidine, and one patient had torsade de pointes 72 hours after mitral-valve replacement.

§Information on warfarin therapy was missing for two patients in the rate-control group and three patients in the rhythm-control group. Information on the presence of atrial fibrillation with the event was missing for 16 patients in the rate-control group and 13 patients in the rhythm-control group.

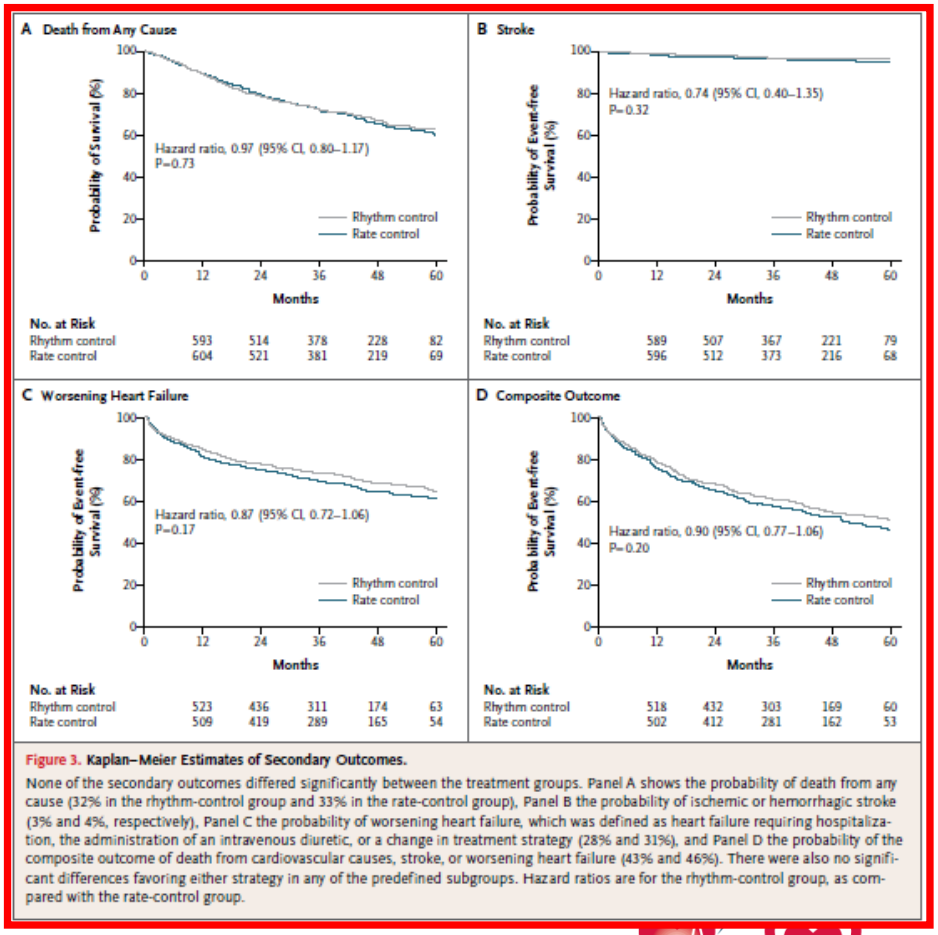


Figure 3. Kaplan–Meier Estimates of Secondary Outcomes.

None of the secondary outcomes differed significantly between the treatment groups. Panel A shows the probability of death from any cause (32% in the rhythm-control group and 33% in the rate-control group), Panel B the probability of ischemic or hemorrhagic stroke (3% and 4%, respectively), Panel C the probability of worsening heart failure, which was defined as heart failure requiring hospitalization, the administration of an intravenous diuretic, or a change in treatment strategy (28% and 31%), and Panel D the probability of the composite outcome of death from cardiovascular causes, stroke, or worsening heart failure (43% and 46%). There were also no significant differences favoring either strategy in any of the predefined subgroups. Hazard ratios are for the rhythm-control group, as compared with the rate-control group.

AFFIRM: G. Wyse, NEJM 2002

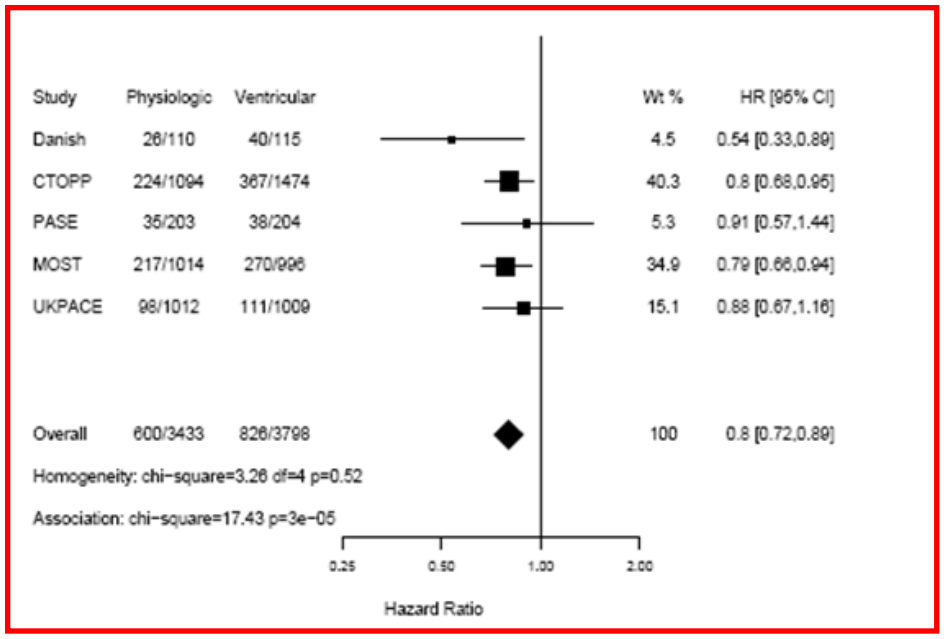
AF-CHF: D. Roy, NEJM 2008

Stroke risk after AF ablation

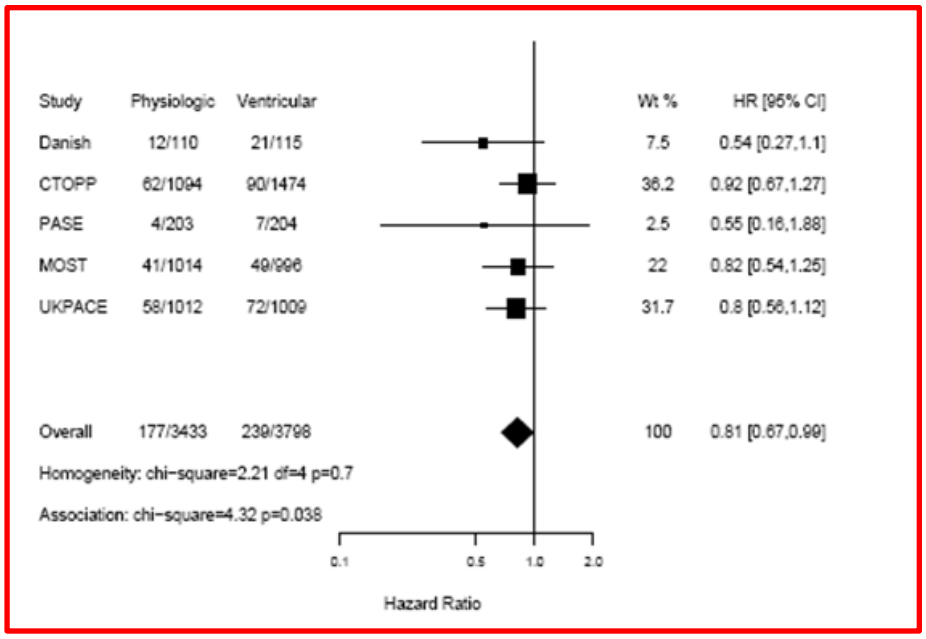
	Centres	N	Follow-up (mo)	$CHADS_2$ score	OAC stopped	Events per year in OAC stopped
Oral 2006[44]	Single US	522	25	Not stated	78% of CHADS 0 and 68% ≥1	0
Nademanee 2008[45]	Single US	517	26	Not stated; mean about 1	84%	0.4% per year
Themistoclakis 2010[46]	5 US/ Europe	3555	28	60%=0, 27%=1, 13% =2	80.2%	0.04% strokes per year
Chao 2011[47]	Single Taiwan	565	39	Median 1	Not clear	1.5% stroke/TIA per year for whole group (i.e on and off OAC)
Saad 2011[48]	Single Brazil	327	46	Mean 1.89	91%	0
Yagishita 2011[49]	Single Japan	524	44	0-1=85%, 2 or more=15%	82%	0.16% per year
Hunter 2012[50]	7 UK/ Australia	1273	36	(in those stopping OAC) 57% =0, 34% =1, 7% >1	64%	0.16% stroke/TIA Per year
Guiot 2012[51]	Single US	1016	34	Mean 1.1	60%	1% stroke per year
Reynolds 2012[52]	US multicenter	812	36		40%	3.4 % stroke/TIA per year for whole group (i.e. on and off OAC)
Bunch 2013[53]	Single US	4212	36	20%=0, 20%=1, 5%=2, 56%>2	Not included	1.5% risk of stroke per year in ablation arm
Gaita 2014[54]	Single Italy	766	60.5	84%=0 or 1, 16%= 2+, 5%=3+	64% (all pts with CHADS or more)	0.2 per 100 patient years for those off OAC

Pacing Mode and Outcomes

Atrial Fibrillation



Stroke



Healey JS, Circulation 2006

Does atrial fibrillation cause stroke?

- Difficult to say with certainty in all cases where the two conditions are sequentially associated
- In some cases, the conventional paradigm is undoubtedly true
- In others, it is undoubtedly false
- Some strategies to prevent AF-associated stroke depend on our understanding of causality, while others do not

C-SPIN

Canadian Stroke Prevention Intervention Network

ARTESiA

APIXABAN FOR THE REDUCTION OF THROMBO-EMBOLISM DUE TO SUB-CLINICAL ATRIAL FIBRILLATION

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LAAOS-III

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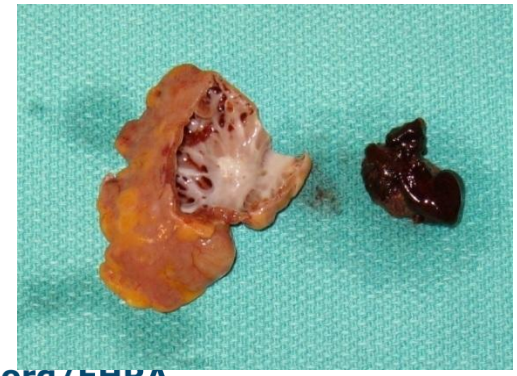
- Most strokes (70%) in AF patients are cardio-embolic originating from the LAA
- 90% of the clots are in the LAA in AF patients
- N=3500; both receiving and not receiving OAC



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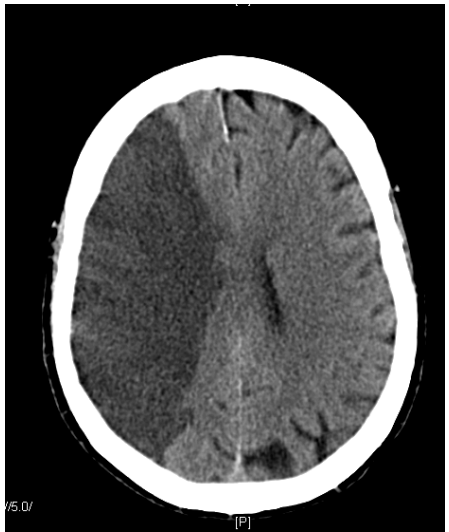

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O C E A N

The Optimal Anticoagulation for Enhanced Risk Patients Post-AF Ablation Trial

David Birnie, Ottawa Heart Institute

Atul Verma, Southlake Regional Health Centre

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