LAA Occlusion is Superior to Novel Oral Anticoagulation Antagonist

T. Jared Bunch MD

Medical Director of Heart Rhythm Services for Intermountain Healthcare, SLC, Utah

Stanford University, Palo Alto, CA

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Learning from EP Technologies Past

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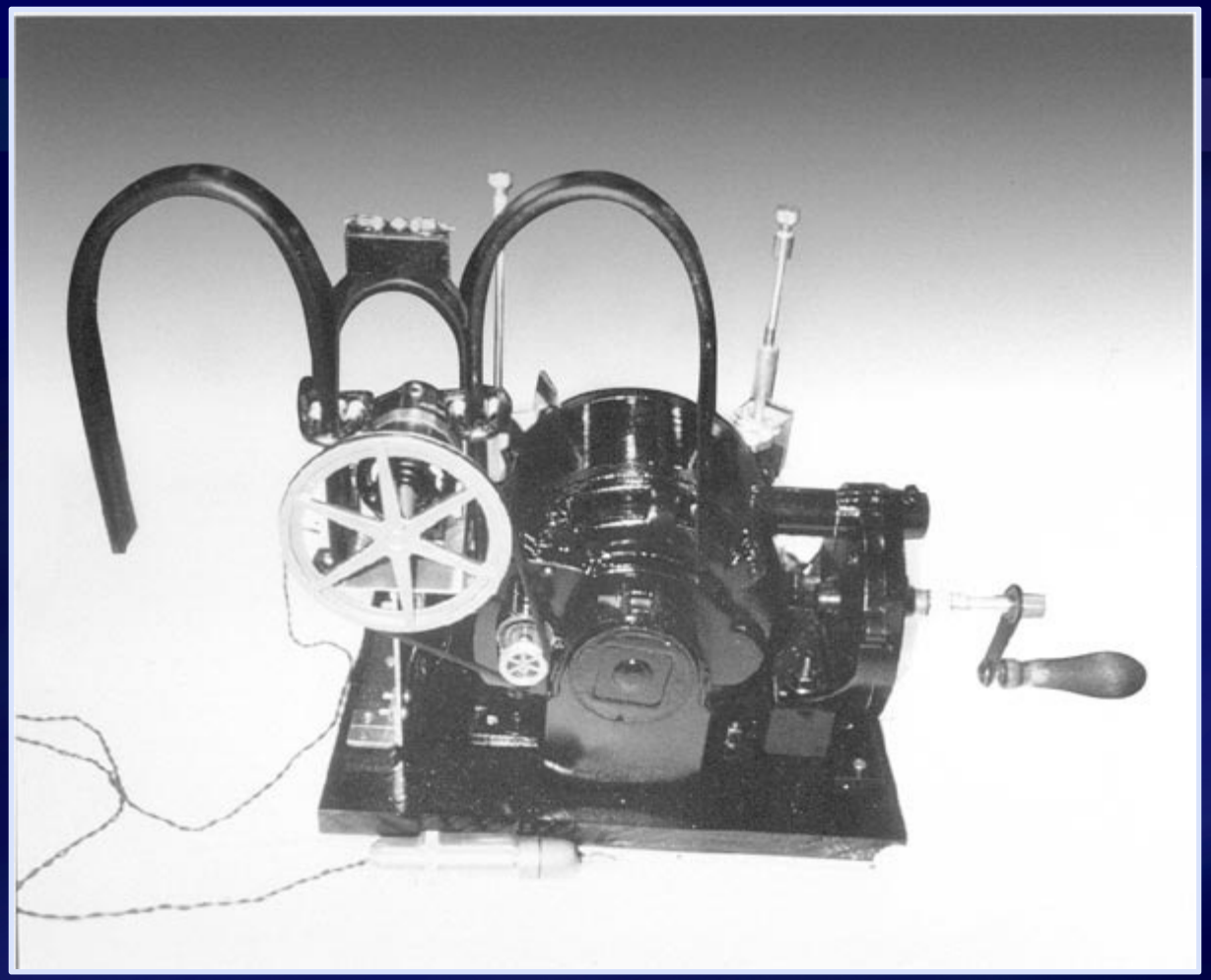
Hyman Pacemaker



Designed for persons whose hearts had entered standstill. He did not distinguish between cardiac arrest and ventricular fibrillation and his published articles did not discuss heart block

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Hyman AS. Resuscitation of the stopped heart by intracardial therapy. II Experimental use of an artificial pacemaker. Arch Intern Med 1932; 50: 283-305

Why the device failed?

A woman is standing looking in the bedroom mirror. She is not happy with what she sees and says to her husband, 'I feel horrible; I look old, fat and ugly. I really need you to pay me a compliment.'

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Harold, the first crank PM recipient

The husband replies, "Your eyesight's nearly perfect."

And then she stopped turning the crank….

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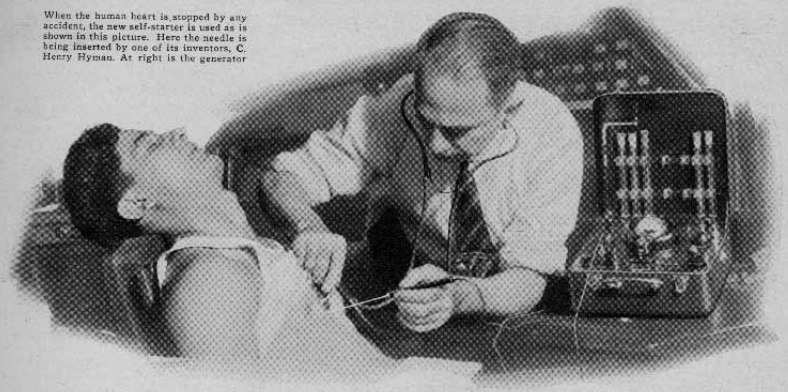
Hyman Pacemaker II – the crank is gone

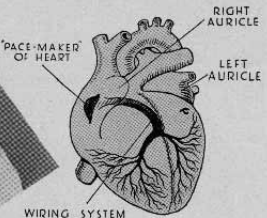
When the human heart is stopped by any accident, the new self-starter is used as is shown in this picture. Here the needle is being inserted by one of its inventors, C. Henry Hyman. At right is the generator



PHYSICIAN INVENTS

SELF-STARTER for Dead Man's Heart

An insulated wire passes through the hollow center of this needle to complete the circuit



WIRING SYSTEM CONVEYING THE ELECTRIC IMPULSES FROM PACE-MAKER TO THE HEART MUSCLES.

Each needle is kept in a sterilized test tube. Diagram of heart shows position of pacemaker

WHAT can be done when the heart ceases to beat? Under all sorts of different conditions, a doctor often is confronted with this urgent question.

The ambulance physician faces it with the victim of heart stroke, drowning, or accident. The surgeon faces it when the pulse of an etherized patient suddenly stops. The family physician faces it when a baby is still born or when a mother's heart stops during childbirth.

Until recently the only answer was the injection of a powerful stimulant into the heart itself, with the result that, not infrequently, the heart failed to respond.

A new answer has just been furnished by the invention of Dr. Albert S. Hyman, heart specialist of the Beth David Hospital of New York, and by C. Henry Hyman, electrical research engineer.

This life-saving device can be compared with the self-starter of a car. When the car's engine stalls, the starter motor turns it over until the cylinders are again firing. In the same way, when the heart stops under any of the conditions named above, the needle of the "Hyman Otor," as it is called, gives the four-cylinder heart engine a rhythmical electrical stimulation. This starts the heart beat and maintains it until the heart's own "electric generator" resumes operation.

This comparison is not far-fetched, for the equivalent of an electrical generator exists in the wall of the right upper chamber (or auricle) of the heart, and a system of "wires" conveys the electrical impulses to the heart muscle. This "ignition system" is called the "pace-maker" of the heart.

The essential feature of the Hyman invention is a hollow steel needle, through which a carefully insulated wire runs to the open point. Both the needle itself and its central wire are connected to the terminals of a light, spring-driven generator, provided with a current-interrupting device. This mechanism can be adjusted to give electrical impulses with the frequency of the heart-beat from infancy to old age.

When the physician faces a case of heart stoppage, he inserts the needle between the first and second ribs into the right auricle of the heart, and starts the generator at the required frequency. The rhythmical current then "cranks" the heart engine by stimulating the "pace-maker" to act in step with the generator, until its normal action is resumed. Usually this occurs quickly.

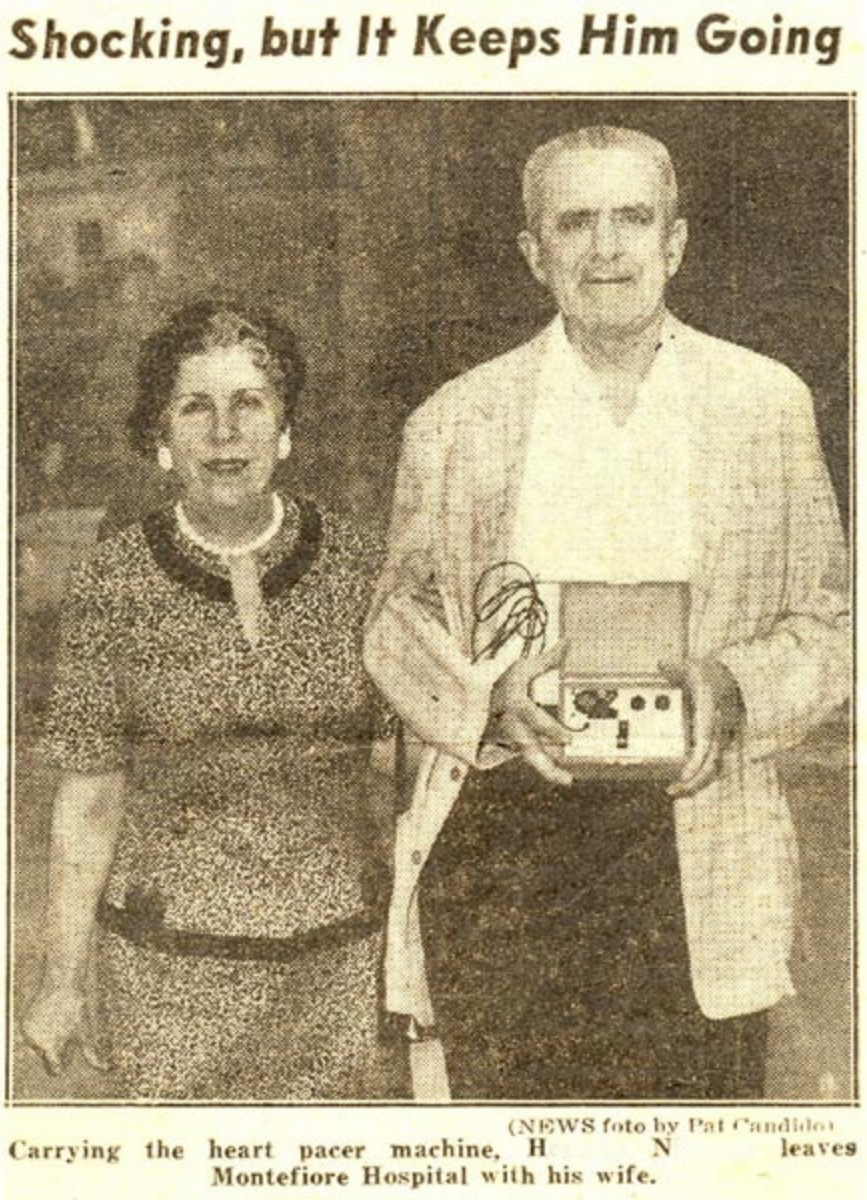
Medical authorities predict a wide usefulness for the "Hyman Otor."

OCTOBER, 1933 25

Popular Science, October 1933

Long Term Ambulatory Exteriorized Transvenous Pacing (Atronic Products Model 902M)

Schwedel JB, Furman S, Escher DJW. Use of an Intracardiac Pacemaker in the treatment of Stokes-Adams Seizures. Prog Cardiovasc Dis 1960;3:170-177.



Shocking, but It Keeps Him Going

(NEWS foto by Pat Candido)

Carrying the heart pacer machine, H N leaves Montefiore Hospital with his wife.

First Working Pacemaker Implant

Implanted by Dr. Robert Rubio on February 3, 1960 (Montevideo, Uruguay). An epicardial electrode was sutured to the left ventricular surface and the pulse generator was placed in the abdominal wall. Improved symptoms (no seizures, better exercise tolerance). Infection developed in the thoracic incision and she died of sepsis 9 1/2 months after implantation.

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Fiandra O. The First Pacemaker Implant in America. PACE 1988;11:1234-1238

Beck Defibrillator

When in doubt – Increase!

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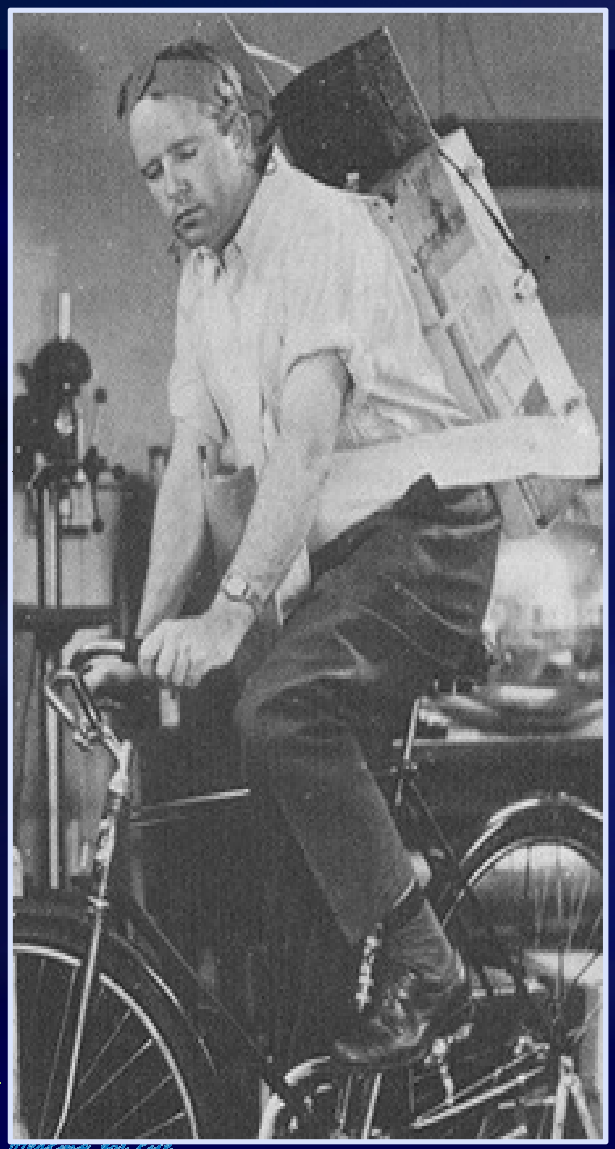
Beck CS, Pritchard WH, Feil HS. Ventricular Fibrillation of Long Duration Abolished by Electric Shock. J Amer Med Assoc. 1947; 135(15):985-986.

Also a rough start for the “ambulatory” ECG

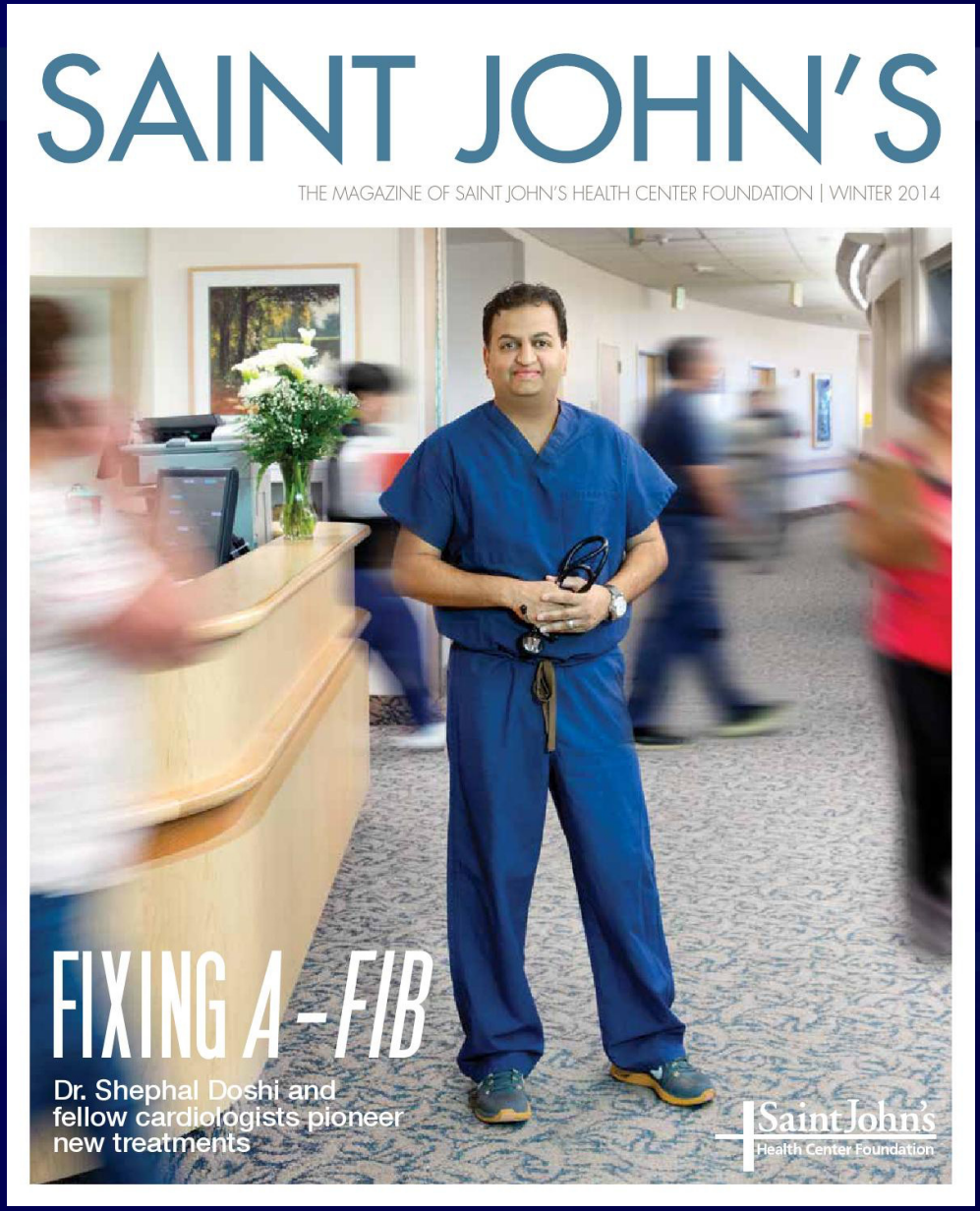


Norman J. "Jeff" Holter - "Father" Of Ambulatory ECG Monitoring (1914 – 1983)

The original 1947 device (shown) had a large ECG radio transmitter and heavy batteries that could not be worn long-term by a patient being monitored.

In 1952 the amplifier and transmitter had been modified and refined from an 85 lb unit to a 2.6 lb amplifier and transmitter.

In Times of Trouble, A Pioneer So Good Time Stands Still



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4 Heart Chambers Open Good

Healthcare
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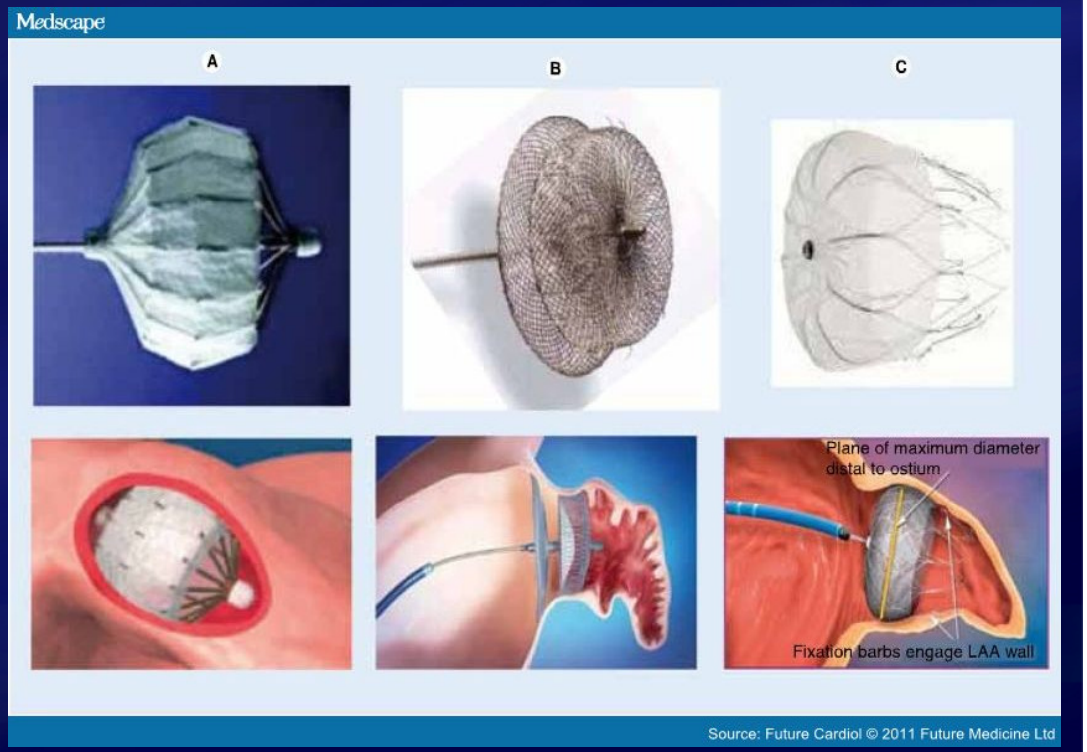
Need Closure – Consider Your Appendage?

Percutaneous LA Appendage Transcatheter Occlusion



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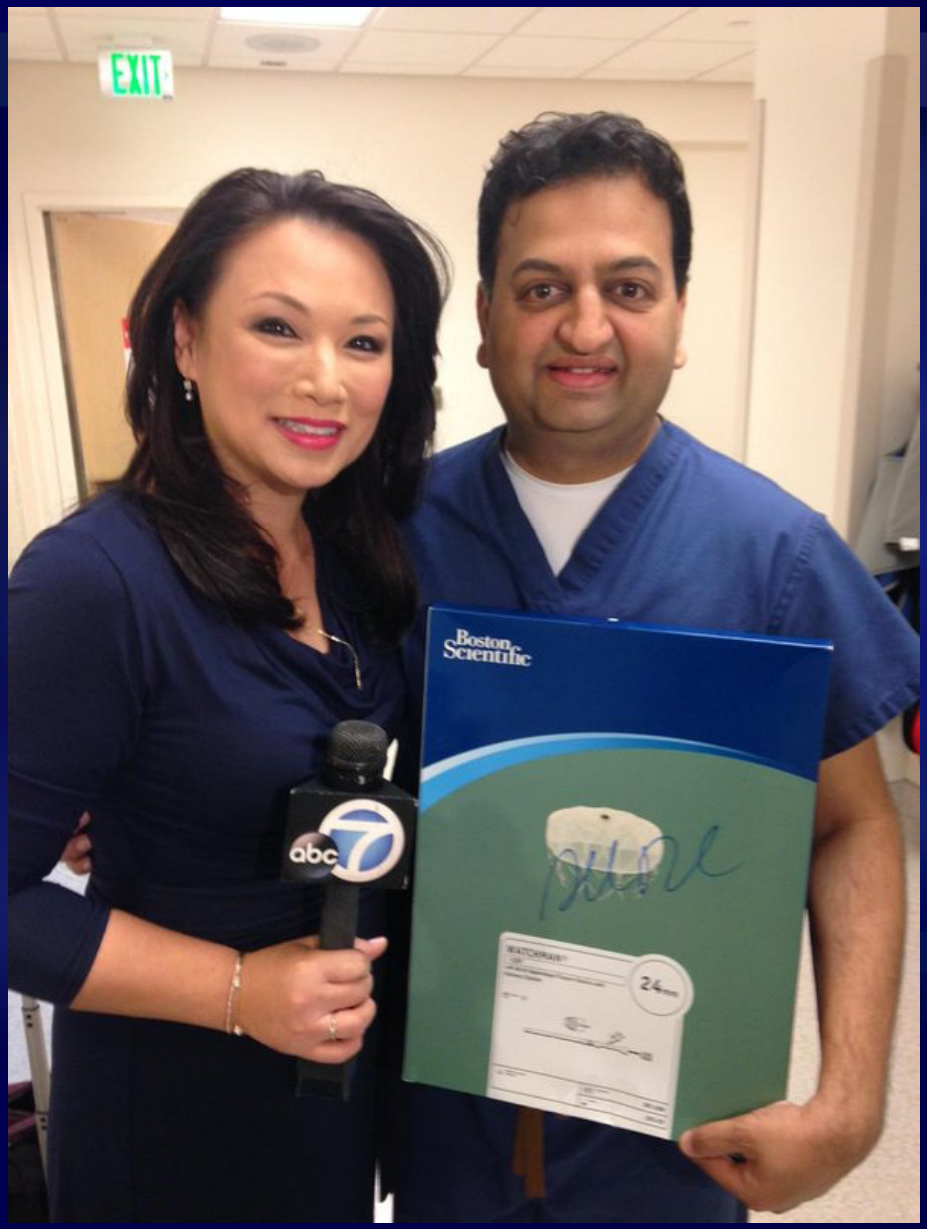
You Get an Autographed Box



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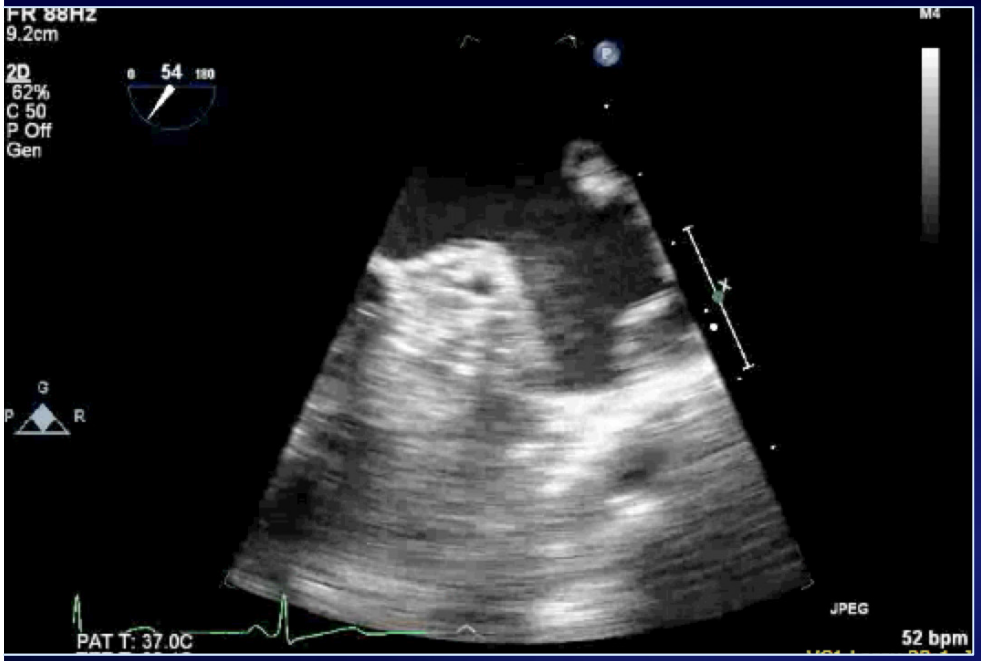
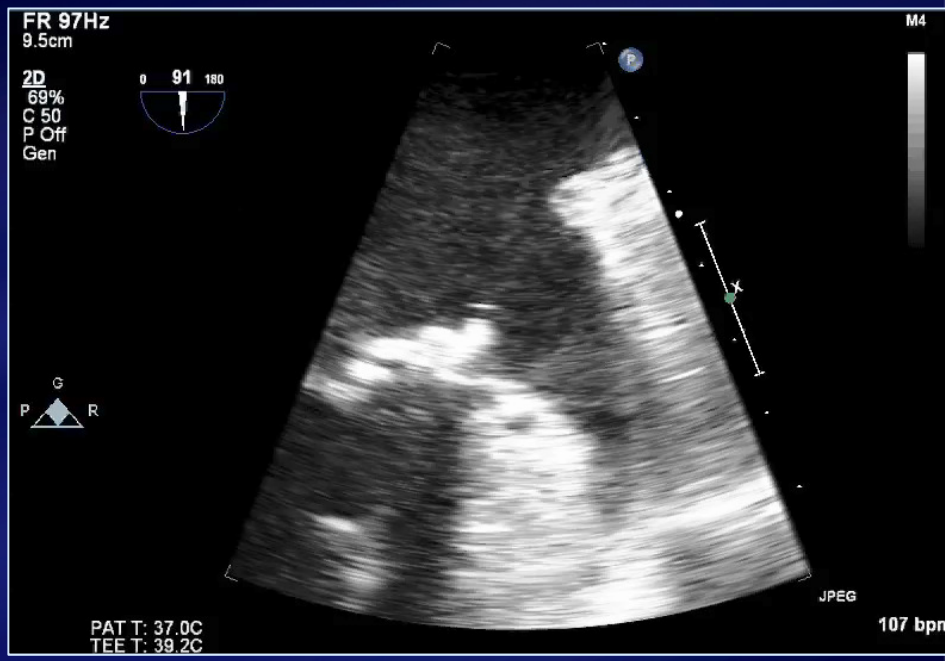
Stroke Paradigm with Atrial Fibrillation – Is It Time to Rethink it?





48 Hours

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Austin Bradford Hill

Atrial Fibrillation and Mechanisms of Stroke
Time for a New Model

Hooman Kamel, MD; Peter M. Okin, MD; Mitchell S.V. Elkind, MD, MS; Costantino Iadecola, MD

To help judge whether one factor causes another or whether the 2 are simply correlated, the epidemiologist Bradford Hill proposed the following widely accepted criteria: (1) strength of association, (2) consistency, (3) speci city, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) accordance with experimental results, and (9) analogy

1. AF has been consistently associated with stroke in different cohorts, and a causal association is biologically plausible based upon Virchows Triangle.
    1. However, risk factors define risk, ? role of burden
2. If AF causes thromboembolism, it should be specially associated with embolic strokes.
    1. However, there does appear to be an especially strong association between AF and embolic strokes
    2. 10% of patients with lacunar strokes have AF
    3. Large-artery atherosclerosis is 2X as common in patients with AF as those without
3. Association between AF and stroke does not fully satisfy Hill's criterion of temporality.
    1. 2 other recent studies found that approximately one third of patients with both AF and stroke do not manifest any AF until after stroke, despite undergoing many months of continuous heart-rhythm monitoring before the stroke
4. If the dysrhythmia is the only cause of thromboembolism, maintaining normal rhythm should eliminate stroke risk

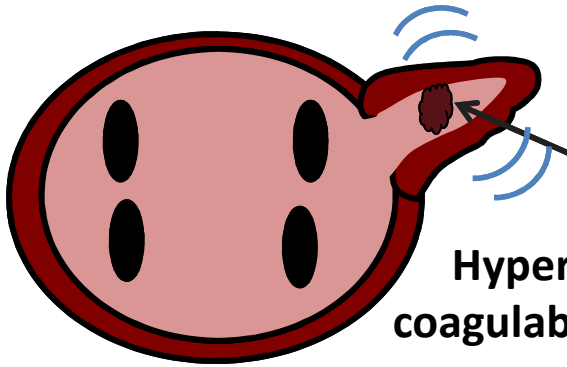
Atrial Fibrillation and Stroke

Focal Electrical Disease

Risk Factor

Reduced LA/LA Appendage Velocities

Atrial Dilitation/Myopathy≈Arrhythmia Burden



Focal Disease

Hyper-coagulability

Stasis

Endothelial Dysfunction

Temporal Association AF & Stroke
As needed Anticoagulation Plausible
Focal Therapy -> Lower Risk
Rhythm Treatments -> Lower Risk

Systemic Disease Symptom

Risk Marker

Obesity

Vascular Disease

Sedentary Lifestyle

Metabolic Syndrome

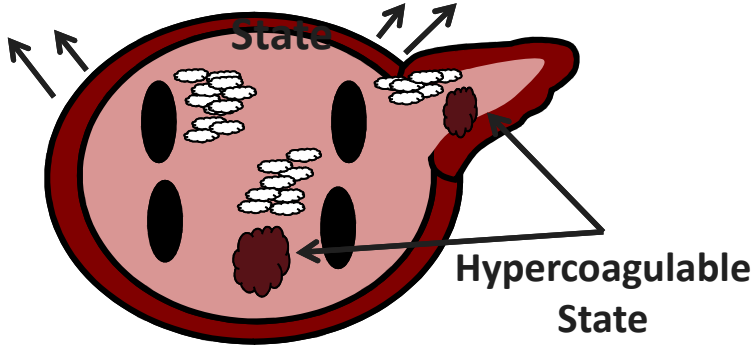
Sleep Apnea

Diabetes

Hypertension

Arterial Stiffness
Microvascular Dysfunction
Diastolic Dysfunction

Atrial Dilatation/Fibrosis/Myopathy≈Disease



Hypercoagulable State

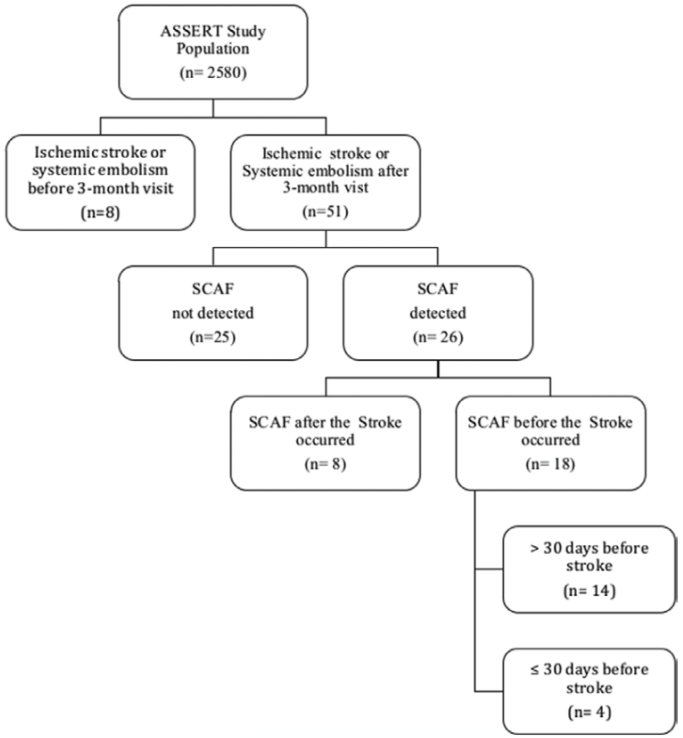
Poor Temporal Association AF & Stroke
Systemic Therapy-> Lower Risk
Risk Persists Despite Rhythm Treatment

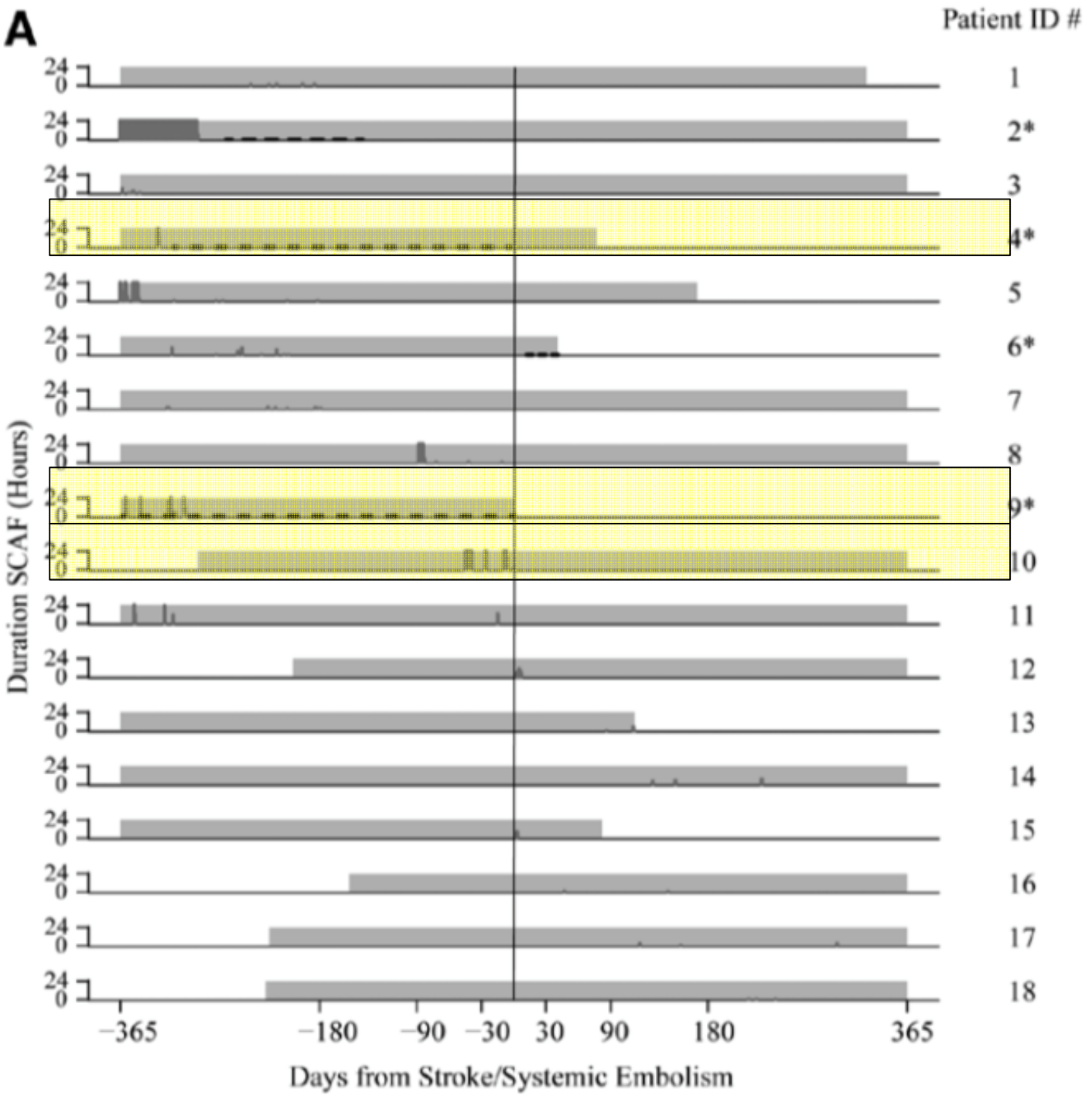
Bunch TJ – Eur Heart J 2016

Temporal Relationship Between Subclinical Atrial Fibrillation and Embolic Events

Michela Brambatti, MD; Stuart J. Connolly, MD; Michael R. Gold, MD; Carlos A. Morillo, MD; Alessandro Capucci, MD; Carmine Muto, MD; Chu P. Lau, MD; Isabelle C. Van Gelder, MD; Stefan H. Hohnloser, MD; Mark Carlson, MD; Eric Fain, MD; Juliet Nakamya, PhD; Georges H. Mairesse, MD; Marta Halytska, BSc; Wei Q. Deng, MSc; Carsten W. Israel, MD; Jeff S. Healey, MD; on behalf of the ASSERT Investigators

Characteristics		SCAF Not Detected (n=25)	SCAF Detected (n=26)	Overall (n=51)	*P* Value
Male sex, No. (%)		20 (80)	8 (31)	28 (55)	<0.001
Age, y	Mean±SD	75.4±6.7	80.3±7.1	77.9±7.3	0.015
Body mass index, kg/m^2	Mean±SD	26.8±3.3	25.8±5.7	26.3±4.6	0.451
Systolic blood pressure, mm Hg	Mean±SD	136±22.6	144±20.4	140±21.7	0.161
$CHADS_2$ score*	Mean±SD	2.8±1.2	2.7±1.1	2.8±1.1	0.944
	Median (P25–P75)	2 (2–4)	2 (2–4)	2 (2–4)	
CHA_2DS_2-VASc score†	Mean±SD	4.3±1.4	4.7±1.0	4.5±1.2	0.331
	Median (P25–P75)	5 (3–5)	5 (4–5)	5 (4–5)	
Risk factors for stroke, No. (%)					
Prior stroke		5 (20)	4 (15)	9 (18)	0.726
Prior transient ischemic attack		4 (16)	2 (8)	6 (12)	0.418
History of heart failure		2 (8)	5 (19)	7 (14)	0.418
Diabetes mellitus		9 (36)	7 (27)	16 (31)	0.555
Prior myocardial infarction		6 (24)	1 (4)	7 (14)	0.049
Sinus node disease, with or without atrioventricular node disease, No. (%)		11 (44)	12 (46)	23 (45)	1.000
Aspirin, No. (%)		13 (52)	15 (58)	28 (55)	0.781
Clinical event type, No. (%)					
Ischemic stroke		21 (84)	25 (96)	46 (90)	0.190
Systemic embolism		4 (16)	1 (4)	5 (10)	0.190
Time from device implantation to primary outcome, d	Mean±SD	580±357	703±394	643±377	0.270
	Median (P25–P75)	570 (263–816)	670 (456–900)	612 (293–890)	
Time from primary outcome to last follow-up, d	Mean±SD	477±399	452±480	464±438	0.565
	Median (P25–P75)	404 (93–866)	350 (41–731)	398 (71–825)	




A
Patient ID #
1
2*
3
4*
5
6*
7
8
9*
10
11
12
13
14
15
16
17
18
24
0
Duration SCAF (Hours)
−365
−180
−90
−30
30
90
180
365
Days from Stroke/Systemic Embolism

Incidence of Newly Detected Atrial Arrhythmias via Implantable Devices in Patients With a History of Thromboembolic Events

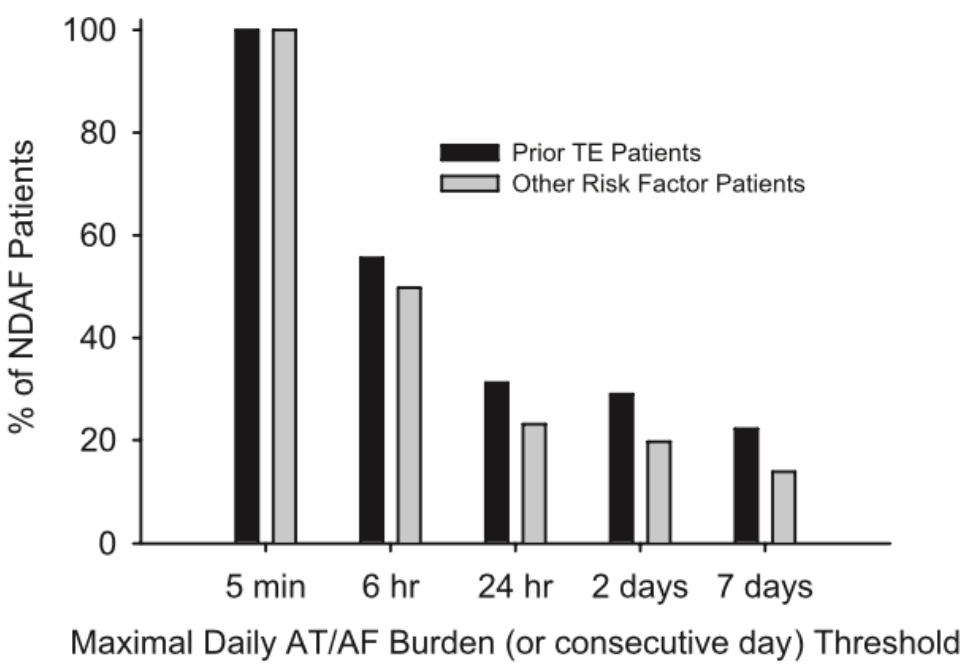
Paul D. Ziegler, MS; Taya V. Glotzer, MD; Emile G. Daoud, MD; D. George Wyse, MD, PhD; Daniel E. Singer, MD; Michael D. Ezekowitz, MD, PhD; Jodi L. Koehler, MS; Christopher E. Hilker, MS

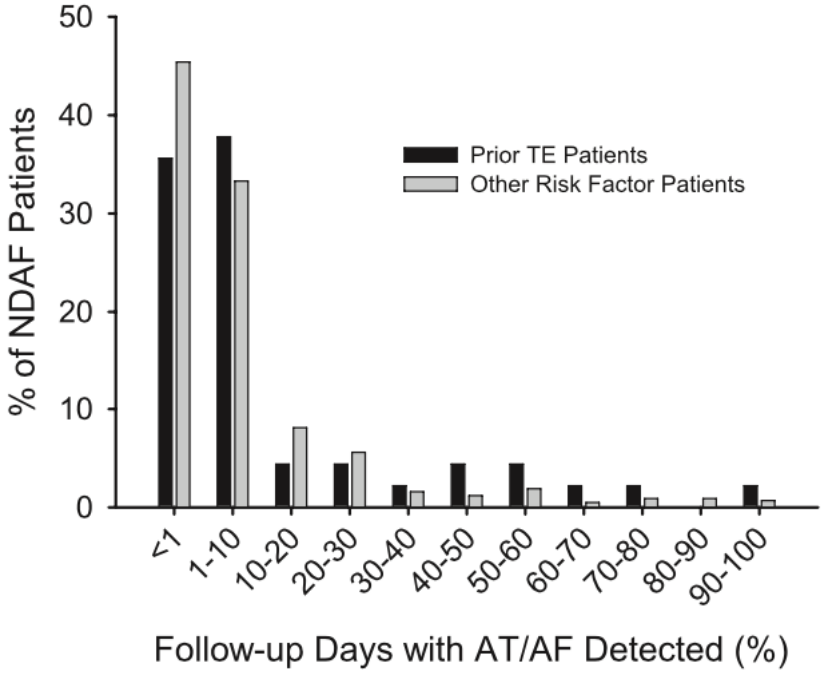
	Previous TE Patients		Other Risk Factor Patients	
Parameter	Patients With NDAF (n=45)	Patients Without NDAF (n=118)	Patients With NDAF (n=432)	Patients Without NDAF (n=996)
Age, yr	74.0±9.1	72.8±9.9	70.8±12.1†	69.7±11.5
Gender, male	32 (71.1%)	74 (62.7%)	299 (69.2%)	647 (65.0%)
$CHADS_2$ score	4.2±0.8	4.1±0.8	2.0±0.9	1.9±0.9
Congestive heart failure	26 (57.8%)*	47 (39.8%)	226 (52.3%)	482 (48.4%)
Hypertension	38 (84.4%)	100 (84.7%)	325 (75.2%)	733 (73.6%)
Age >75 yr	20 (44.4%)	52 (44.1%)	187 (43.3%)†	374 (37.6%)
Diabetes	16 (35.6%)	48 (40.7%)	120 (27.8%)†	341 (34.2%)
Previous stroke/TIA	45 (100%)	118 (100%)	0 (0%)	0 (0%)
Pacemaker	20 (44.4%)	71 (60.2%)	191 (44.2%)	444 (44.6%)
SA node conduction problems	13 (28.9%)	47 (39.8%)	111 (25.7%)	263 (26.4%)
AV conduction problems	7 (15.6%)	20 (16.9%)	67 (15.5%)	158 (15.9%)
Other	0 (0.0%)	4 (3.4%)	13 (3.0%)	23 (2.3%)
Implantable cardioverter defibrillator	25 (55.6%)	47 (39.8%)	241 (55.8%)	552 (55.4%)
Primary prevention	19 (42.2%)	34 (28.8%)	191 (44.2%)	449 (45.1%)
Secondary prevention	6 (13.3%)	13 (11.0%)	50 (11.6%)	103 (10.3%)
Systolic blood pressure, mm Hg	136.3±22.3	136.8±22.3	133.8±22.6	133.3±22.7
Coronary artery disease	34 (75.6%)	81 (68.6%)	267 (61.8%)	636 (63.9%)
Class I/III antiarrhythmics	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Warfarin	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Aspirin	28 (62.2%)	78 (66.1%)	287 (66.4%)	691 (69.4%)
Antiplatelets	21 (46.7%)	58 (49.2%)	94 (21.8%)	241 (24.2%)
Statins	28 (62.2%)	78 (66.1%)	233 (53.9%)	578 (58.0%)

*$P<0.05$, NDAF vs no NDAF in patients with previous TE.
†$P<0.05$, NDAF vs no NDAF in patients with other risk factors.
AV indicates atrioventricular; SA, sino-atrial.

The median time from the previous TE to enrollment in the study was 39 (12–73) months.

Burden and Duration Longer In Patients with Prior TE/Stroke





Majority of patients with prior TE had AF/AT on one day >6 hours

Atrial High Rate Episodes Detected by Pacemaker Diagnostics Predict Death and Stroke

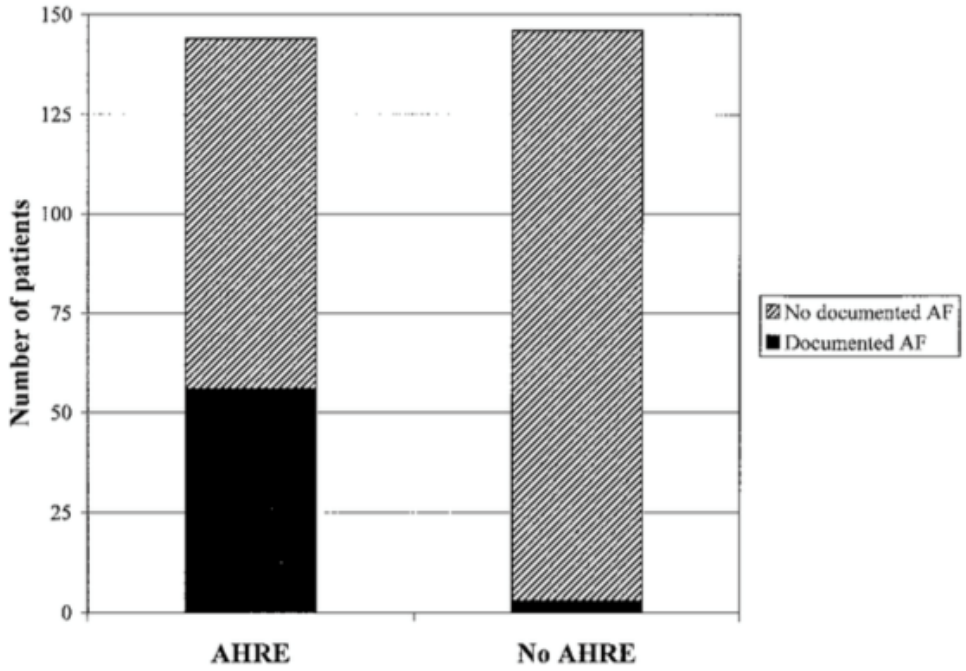
Report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST)

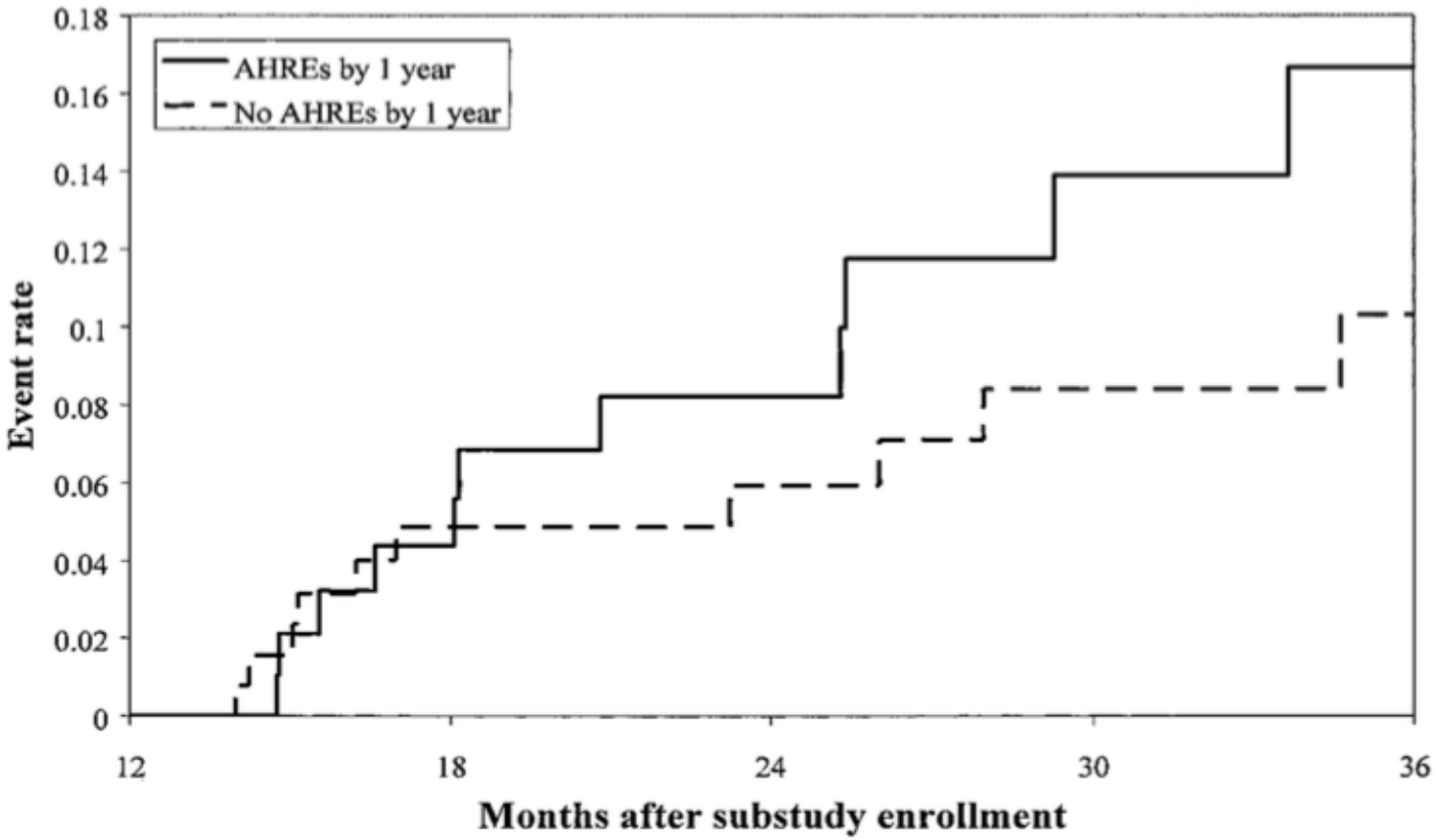
Taya V. Glotzer, MD; Anne S. Hellkamp, MS; John Zimmerman, MD; Michael O. Sweeney, MD; Raymond Yee, MD; Roger Marinchak, MD; James Cook, MD; Alexander Paraschos, MD; John Love, MD; Glauco Radoslovich, MD; Kerry L. Lee, PhD; Gervasio A. Lamas, MD; for the MOST Investigators

Baseline Characteristics for Patients With Atrial High Rate Episodes (AHREs) vs Those Without

Baseline Characteristic	Patients With AHREs (n=160)	Patients Without AHREs (n=152)	*P*
Age, y	75 (68,81)	73 (68, 79)	0.16
Female, % (n)	55 (88)	55 (83)	0.94
Caucasian, % (n)	93 (149)	88 (133)	0.091
Weight, lb	164 (140, 192)	157 (134, 185)	0.067
Prior stroke/TIA/embolism, % (n)	20 (32)	15 (23)	0.26
Charlson Comorbidity Index, % (n)			0.11
0	30 (48)	36 (55)	
1 or 2	48 (76)	51 (77)	
3 or 4	14 (22)	10 (15)	
5 or more	9 (14)	3 (5)	
Diabetes, % (n)	23 (37)	18 (27)	0.24
Systolic blood pressure, mm Hg	133 (120, 150)	140 (124, 150)	0.24
Diastolic blood pressure, mm Hg	70 (62, 80)	73 (68, 82)	0.036
Prior supraventricular arrhythmia, % (n)	81 (129)	39 (59)	0.001
Prior ventricular arrhythmia, % (n)	3 (4)	5 (7)	0.31
Prior atrioventricular block, % (n)	36 (57)	18 (27)	0.001
Antiarrhythmic at admission, % (n)	29 (46)	11 (16)	0.001
Hypertension, % (n)	61 (98)	58 (88)	0.55
Hypercholesterolemia, % (n)	43 (68)	34 (52)	0.13
Prior angina, % (n)	31 (49)	24 (37)	0.21
Prior myocardial infarction, % (n)	23 (37)	28 (42)	0.36
Prior CHF, % (n)	22 (35)	11 (16)	0.006
Prior CABG, % (n)	18 (29)	18 (28)	0.95
Prior PTCA, % (n)	13 (20)	9 (14)	0.36
NYHA CHF class, % (n)			0.51
I	43 (68)	48 (73)	
II	44 (71)	37 (56)	
III	12 (19)	14 (22)	
IV	1 (2)	1 (1)	

Continuous variables are presented as median (25th, 75th percentile). Categorical variables are presented as percent (number). AHRE indicates atrial high rate episode; TIA, transient ischemic attack; CHF, congestive heart failure; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; and NYHA, New York Heart Association.





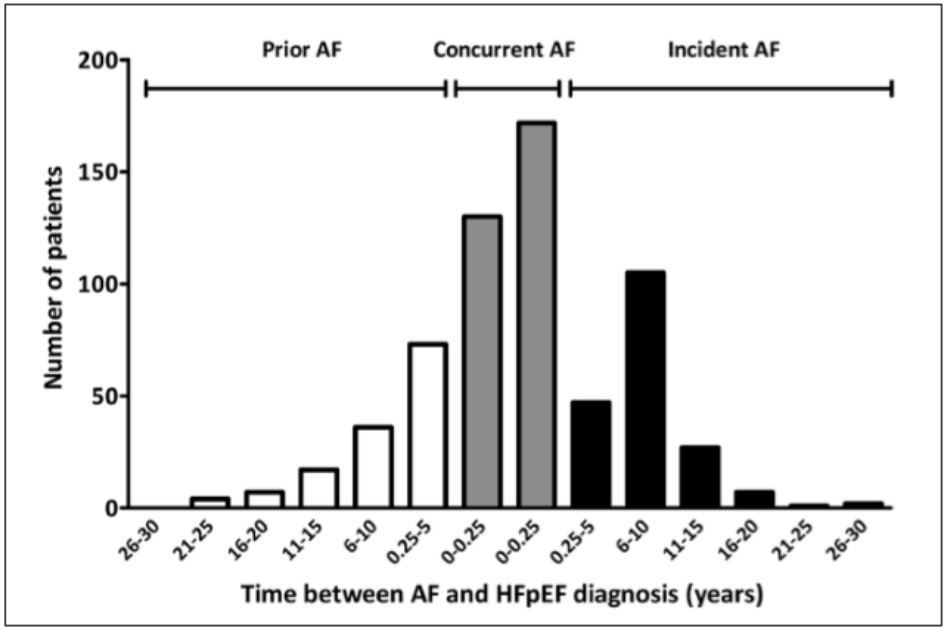
(hazard ratio AHRE versus no AHRE and 95% confidence intervals 2.48 [1.25, 4.91]; *P* 0.0092),

In patients with sinus node dysfunction, pacemaker-detected AHRE, lasting at least 5 minutes, identify patients that are more than twice as likely to die or have a stroke, and are nearly 6 times as likely to develop atrial fibrillation as similar patients without AHRE.

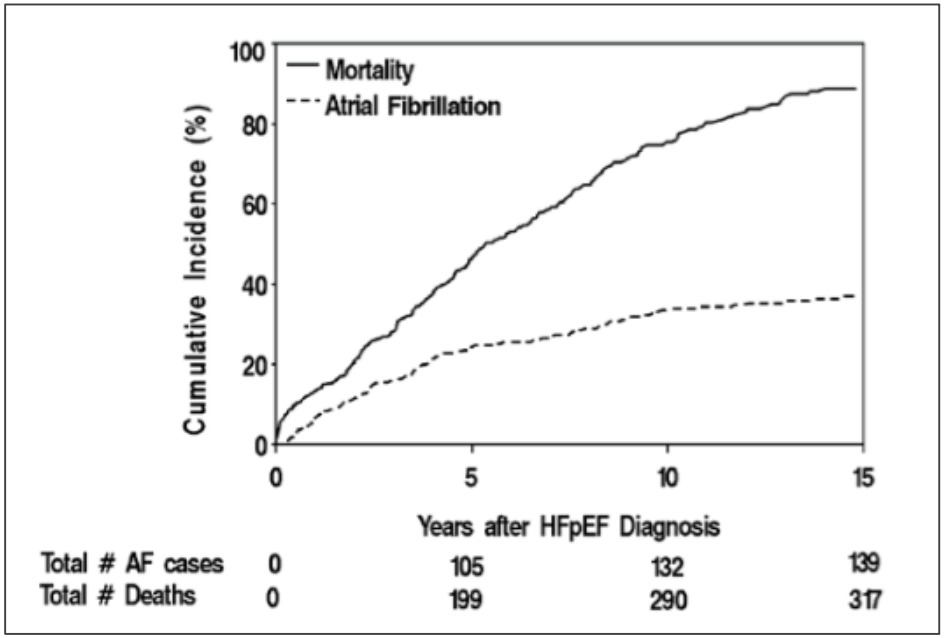
Temporal Relationship and Prognostic Significance of Atrial Fibrillation in Heart Failure Patients With Preserved Ejection Fraction: A Community-Based Study

Rosita Zakeri, Alanna M. Chamberlain, Véronique L. Roger and Margaret M. Redfield

Temporal Relationship of AF and Diastolic HF



Mortality Exceeds AF in Patients with Diastolic HF



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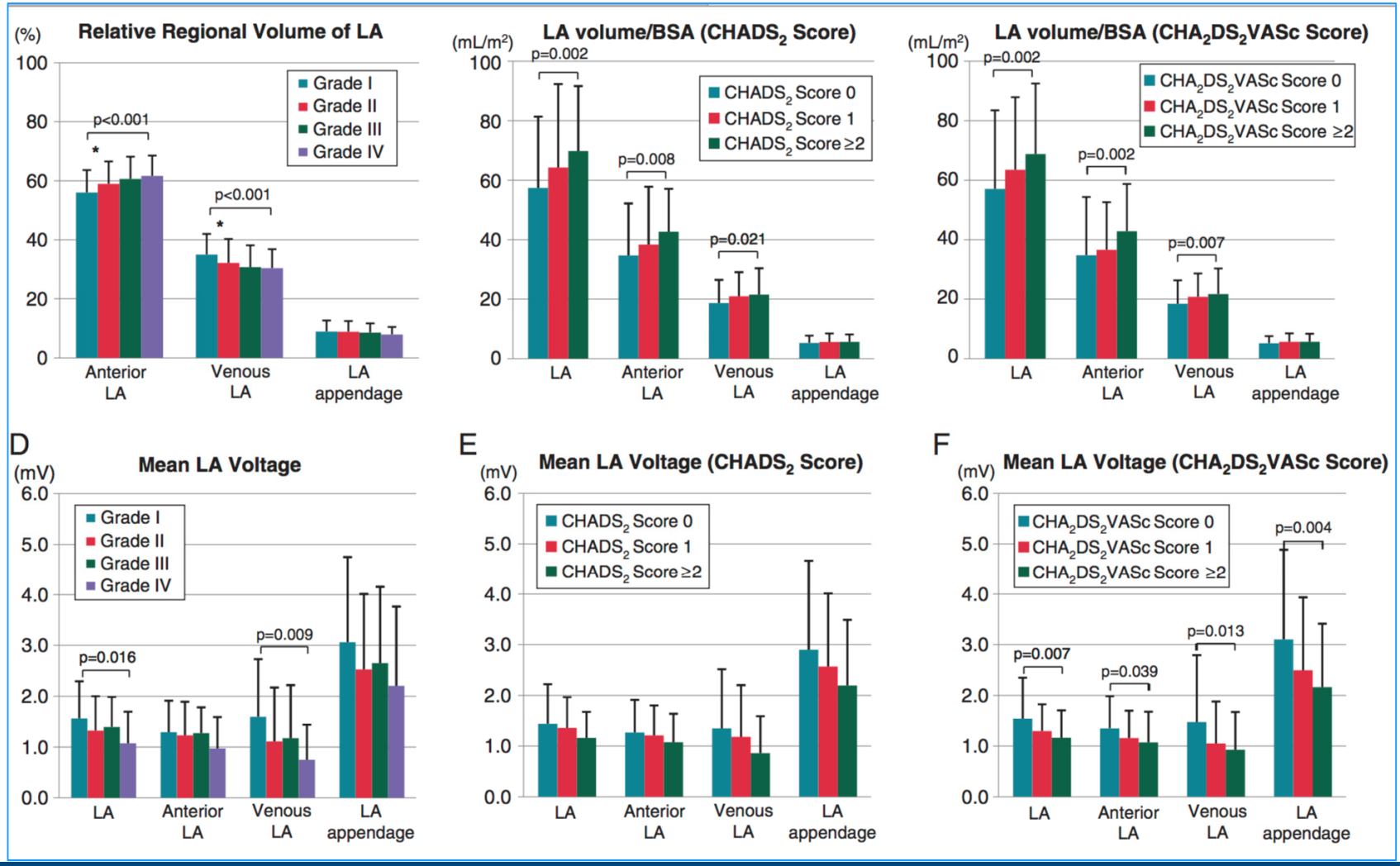
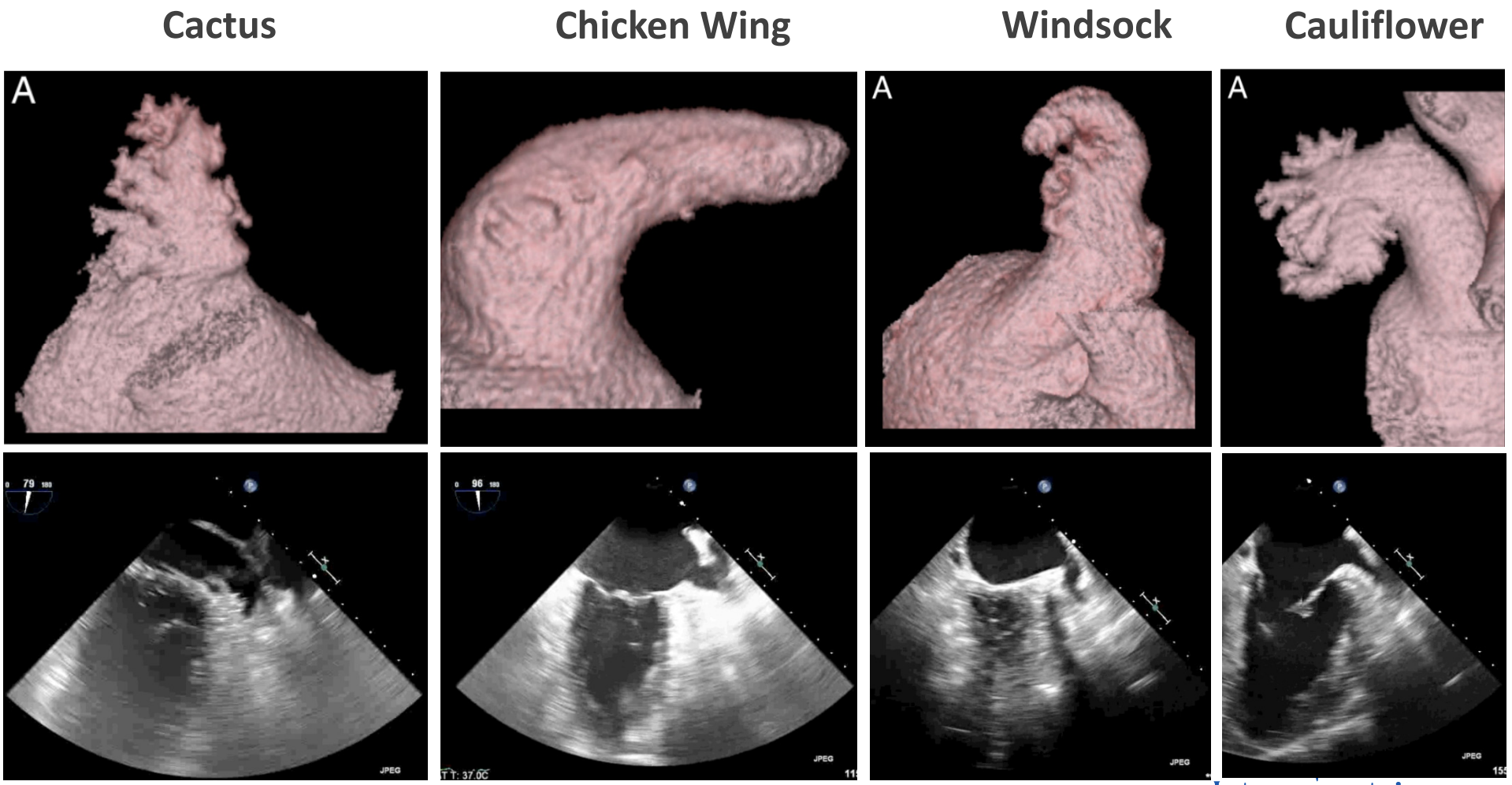
The electroanatomical remodelling of the left atrium is related to $CHADS_2/CHA_2DS_2VASc$ score and events of stroke in patients with atrial fibrillation

Jae Hyung Park[1], Boyoung Joung[1], Nak-Hoon Son[2], Jae Min Shim[1], Moon Hyung Lee[1], Chun Hwang[3], and Hui-Nam Pak[1]*



Left Atrial Appendage Morphologies



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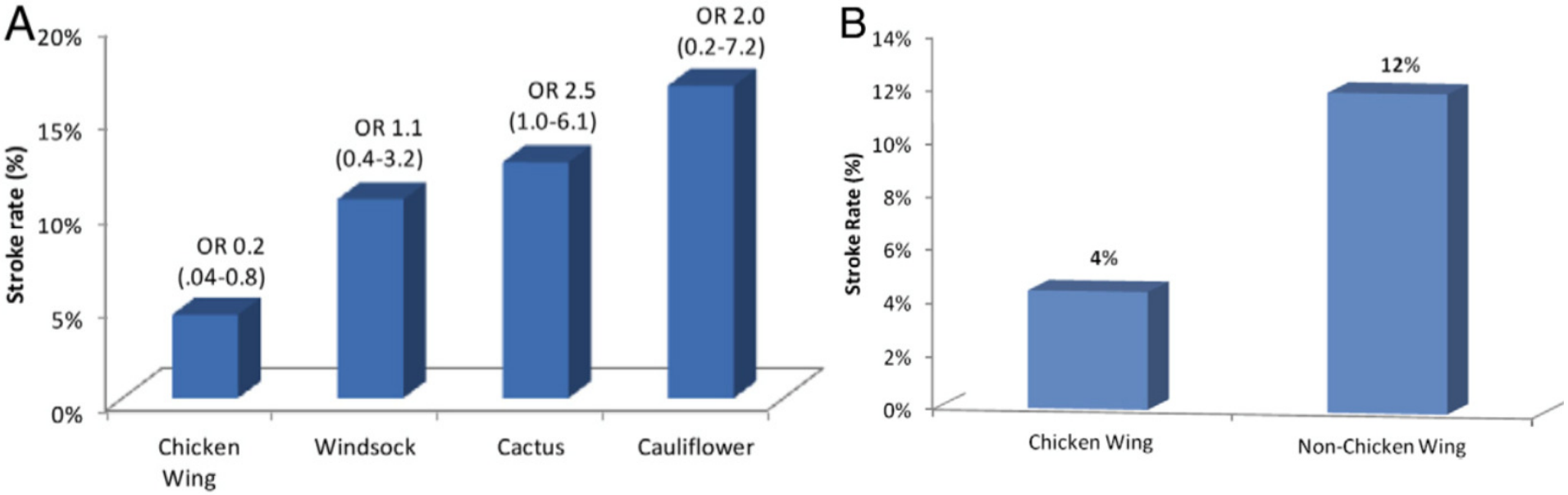
Di Biase L, et al. JACC 2012

Prevalence of Stroke Based Upon Left Atrial Appendage Morphology



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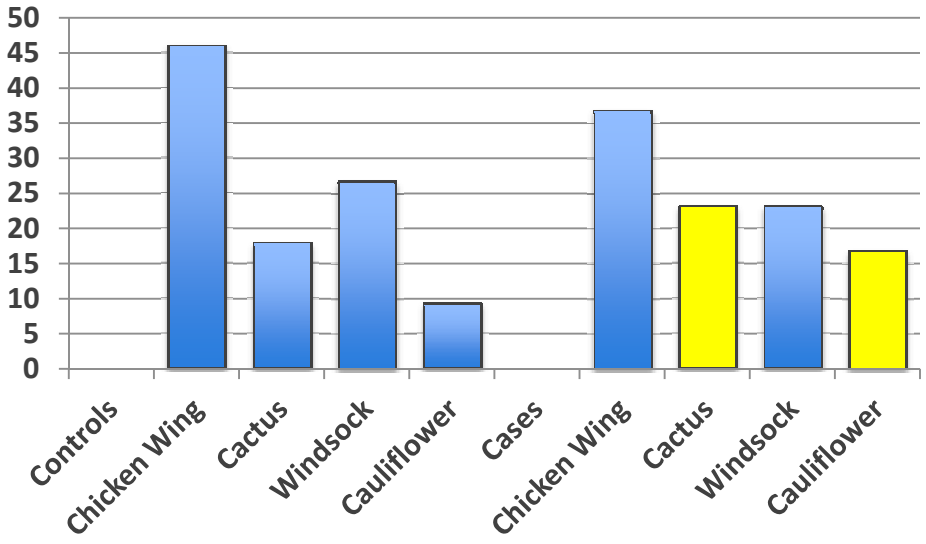
Di Biase L, et al. JACC 2012

Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation

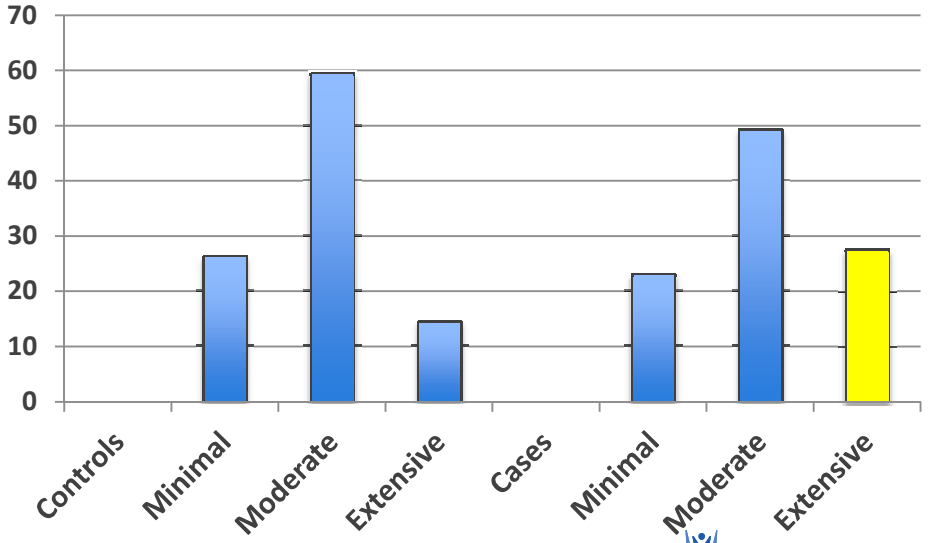
Irfan M. Khurram, MD,[*] Jane Dewire, BA,[*] Michael Mager, RT (R) (MR),[†] Farhan Maqbool, MD,[*] Stefan L. Zimmerman, MD,[†] Vadim Zipunnikov, PhD,[‡] Roy Beinart, MD,[*] Joseph E. Marine, MD, FHRS,[*] David D. Spragg, MD, FHRS,[*] Ronald D. Berger, MD, PhD, FHRS,[*] Hiroshi Ashikaga, MD, PhD,[*] Saman Nazarian, MD, PhD, FHRS,[*] Hugh Calkins, MD, FHRS[*]

From the [*]Department of Medicine/Cardiology, [†]Department of Radiology, and [‡]Department of Biostatistics, Johns Hopkins University, Baltimore, Maryland.

LAA Morphology and Stroke (Cases)



LAA Trabeculations and Stroke (Cases)



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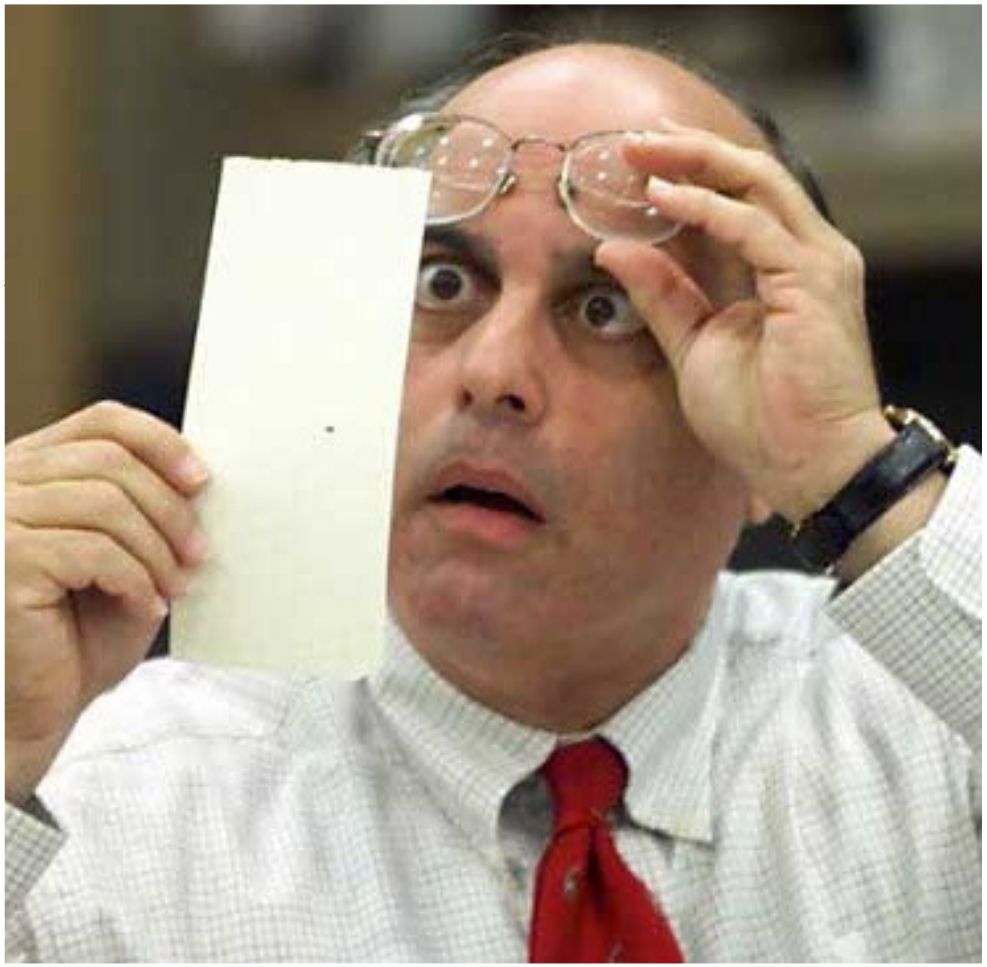
Examining the Evidence

Is it the Appendage – Or is the Appendage A Barometer of the Disease State



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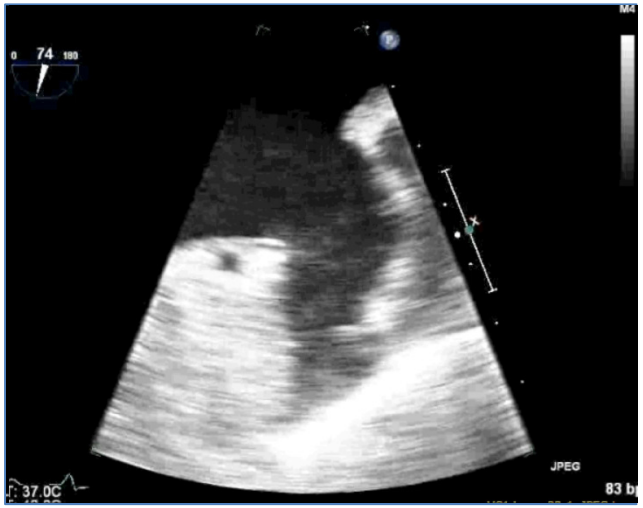
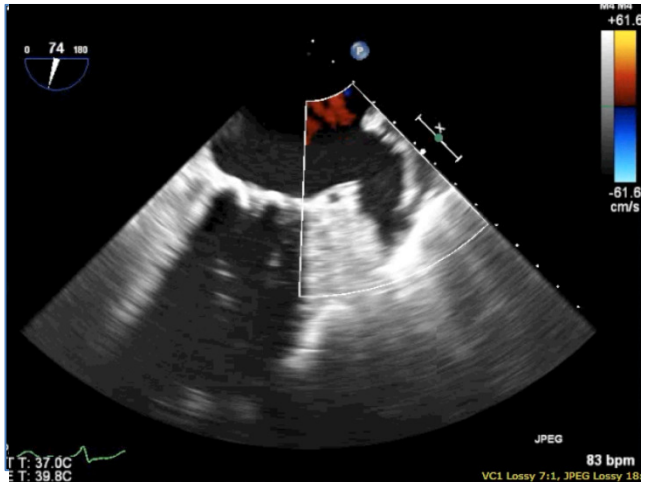
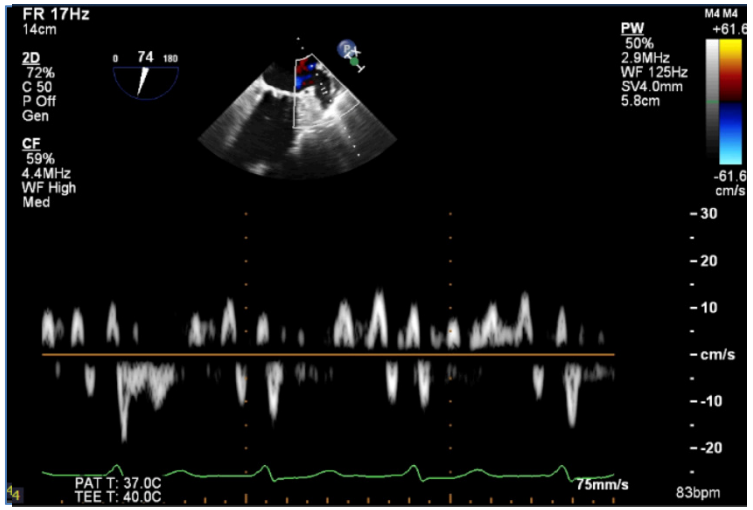
Prevalence of Stroke Based Upon Left Atrial Appendage Function





Normal-Hyperdynamic Function



Hypokinetic – Akinetic Function

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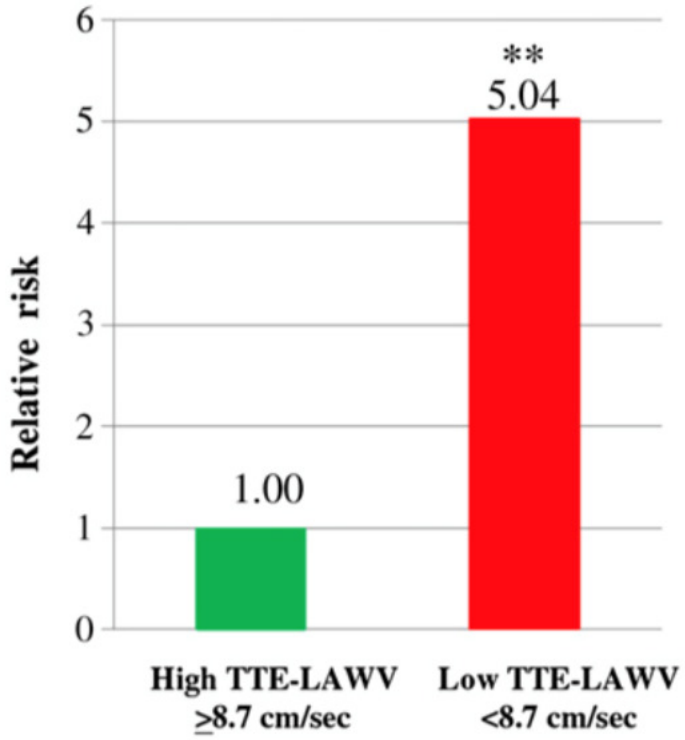
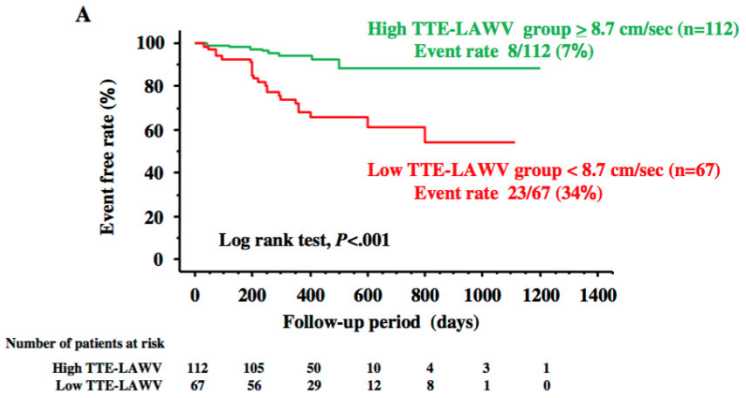
Prognostic Value of Low Left Atrial Appendage Wall Velocity in Patients with Ischemic Stroke and Atrial Fibrillation

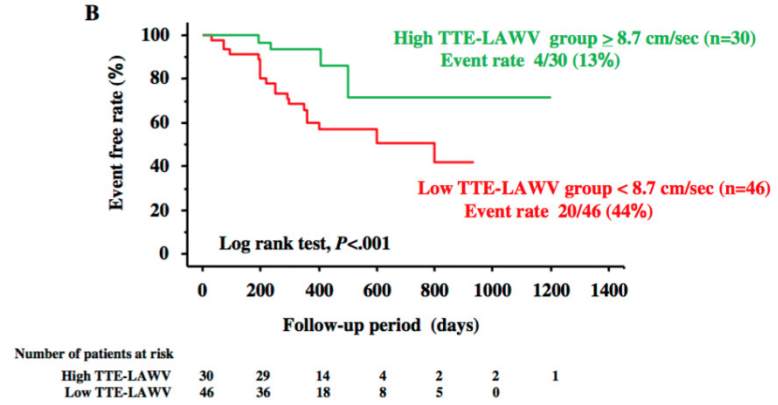
Harutoshi Tamura, MD, Tetsu Watanabe, MD, Satoshi Nishiyama, MD, Shintaro Sasaki, MD, Masahiro Wanezaki, MD, Takanori Arimoto, MD, Hiroki Takahashi, MD, Tetsuro Shishido, MD, Takehiko Miyashita, MD, Takuya Miyamoto, MD, and Isao Kubota, MD, *Yamagata, Japan*



All Patients



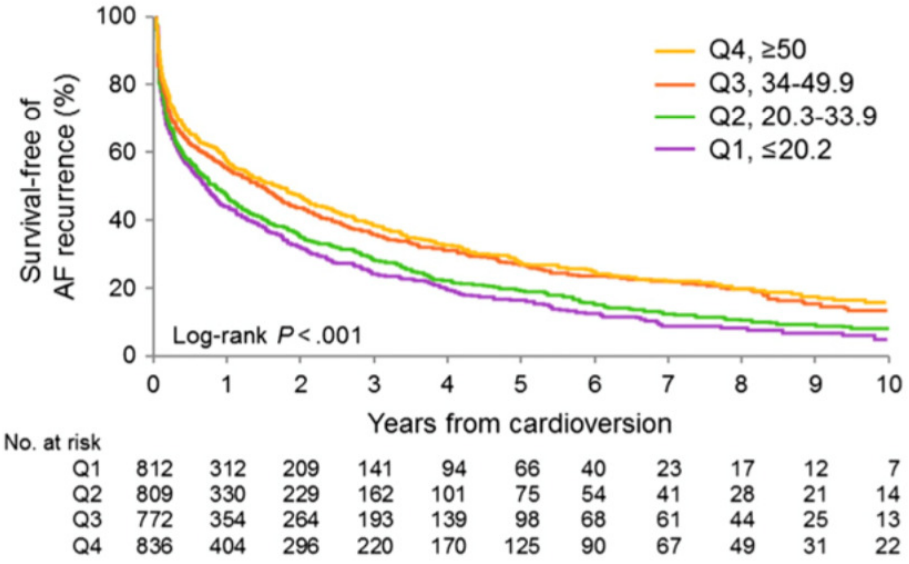
Prior CVA Patients



Real-time physiologic biomarker for prediction of atrial fibrillation recurrence, stroke, and mortality after electrical cardioversion: A prospective observational study

Rowlens M. Melduni, MD, MPH,[a] Hon-Chi Lee, MD, PhD,[a] Kent R. Bailey, PhD,[b] Fletcher A. Miller, Jr., MD,[a] David O. Hodge, MS,[b] James B. Seward, MD,[a] Bernard J. Gersh, MB, ChB, DPhil,[a] and Naser M. Ammash, MD[a]
Rochester, MN and Rochester, FL

Survival Free of AF

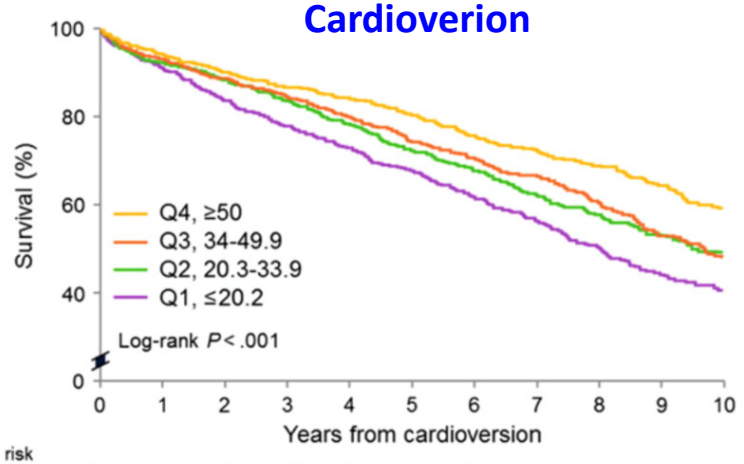


No. at risk

Q1	812	312	209	141	94	66	40	23	17	12	7
Q2	809	330	229	162	101	75	54	41	28	21	14
Q3	772	354	264	193	139	98	68	61	44	25	13
Q4	836	404	296	220	170	125	90	67	49	31	22

3,251 Patients compared by LAA emptying velocity (Q1 <20.2, Q2: 20.3-33.9, Q3: 34-49.9, Q4 >50)

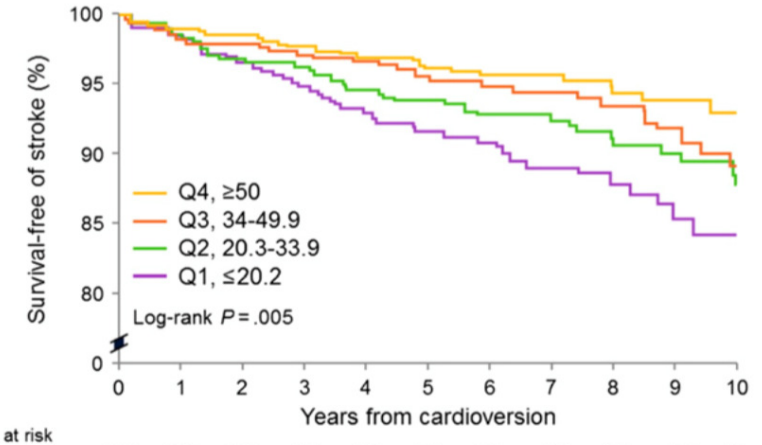
Survival Free AF after Cardioverion



No. at risk

Q1	818	751	696	600	518	425	337	270	210	157	123
Q2	813	763	713	604	514	426	359	298	224	167	125
Q3	777	723	685	606	519	432	361	285	218	163	125
Q4	843	794	752	658	585	500	418	353	273	206	147

Survival Free CVA

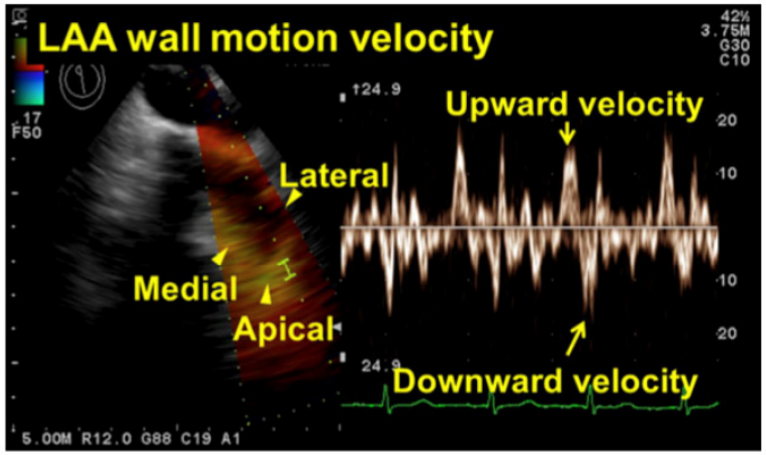


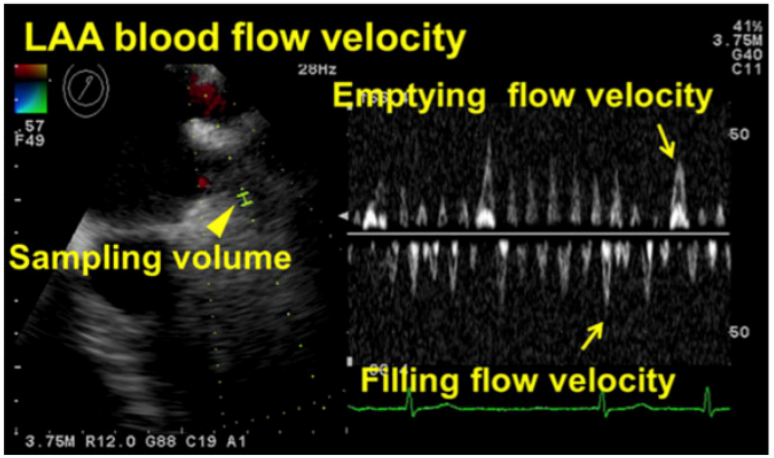
No. at risk

Q1	813	672	586	486	408	314	249	191	141	100	70
Q2	809	688	614	518	410	336	284	220	165	113	82
Q3	772	637	581	498	408	327	260	208	157	114	80
Q4	839	687	627	539	456	382	314	263	200	145	100

Left Atrial Appendage Wall-Motion Velocity Associates with Recurrence of Nonparoxysmal Atrial Fibrillation after Catheter Ablation

Miyuki Ariyama, M.D., Ph.D.,* Ritsushi Kato, M.D., Ph.D.,* Makoto Matsumura, M.D., Ph.D.,* Harumi Yoshimoto, M.D., Ph.D.,* Yoshie Nakajima, M.D., Ph.D.,* Shintaro Nakano, M.D.,* Takatoshi Kasai, M.D., Ph.D.,† Jun Tanno, M.D.,* Takaaki Senbonmatsu, M.D., Ph.D.,* Kazuo Matsumoto, M.D., Ph.D.,* and Shigeyuki Nishimura, M.D., Ph.D.*





Multivariate Logistic Analyses to Identify Factors Associated with Recurrence of Atrial Fibrillation

	OR	95% CI	P-Value
Univariate analyses of variables selected for inclusion			
LAA wall-motion velocity, Apical wall, upward	1.45	1.13–2.01	0.009
Duration of AF	0.96	0.93–0.99	0.03
LVEF	1.03	0.98–1.09	0.21
E-wave deceleration time	1.01	0.99–1.03	0.26
Left atrial wall-motion velocity, e′-wave	1.13	0.93–1.39	0.24
Multivariate logistic regression models			
Model 1			
LAA wall-motion velocity, Apical wall, upward	1.42	1.10–1.96	0.02
Duration of AF	0.97	0.93–1.00	0.18
Model 2			
LAA wall-motion velocity, Apical wall, upward	1.45	1.10–2.12	0.02
LVEF	1.01	0.78–1.31	0.36
E-wave deceleration time	1.00	0.98–1.03	0.74
Left atrial wall-motion velocity, e′-wave	1.01	0.78–1.31	0.91

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Diastolic Dysfunction and Stroke Risk

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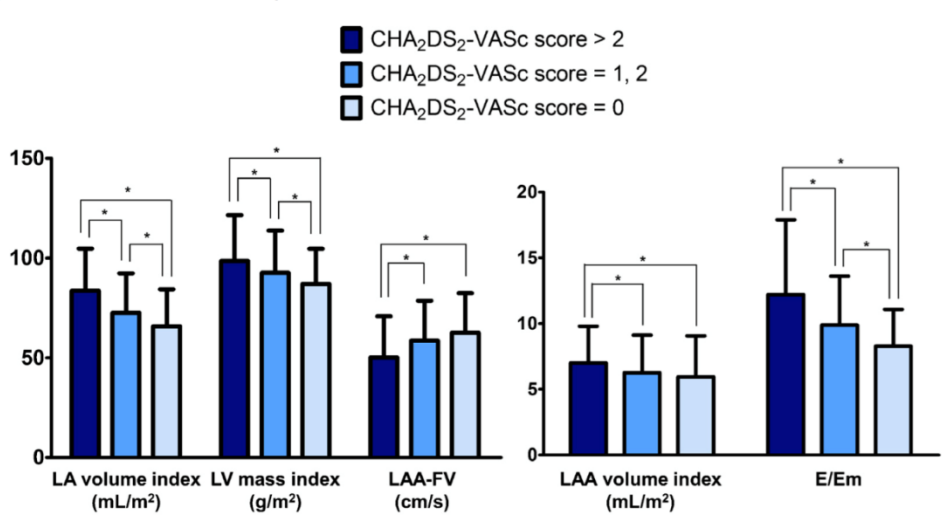
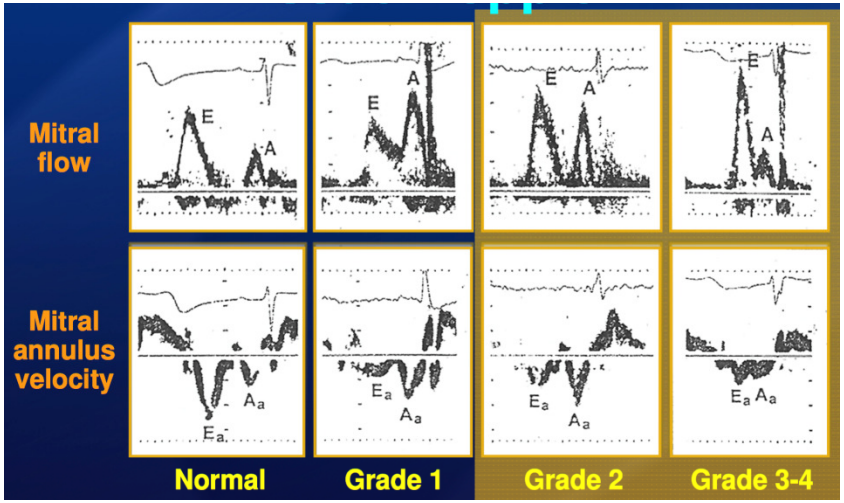
Original article

Left ventricular diastolic dysfunction is associated with atrial remodeling and risk or presence of stroke in patients with paroxysmal atrial fibrillation

Tae-Hoon Kim (MD), Chi Young Shim (MD, PhD), Jae Hyung Park (PhD), Chung Mo Nam (PhD), Jae-Sun Uhm (MD), Boyoung Joung (MD, PhD), Moon-Hyoung Lee (MD, PhD), Hui-Nam Pak (MD, PhD)*



*p<0.01

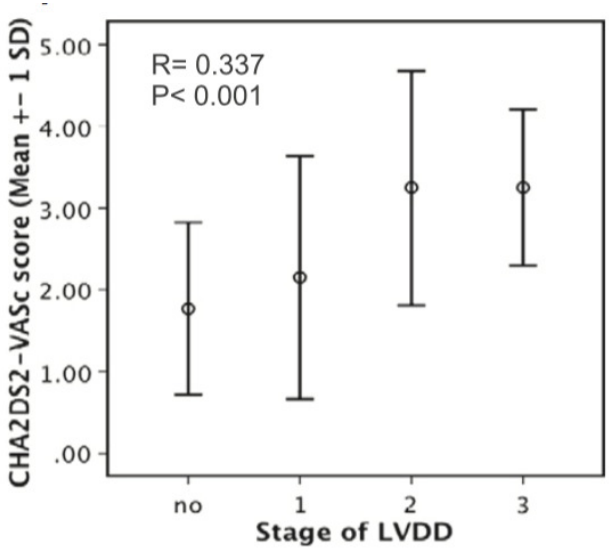


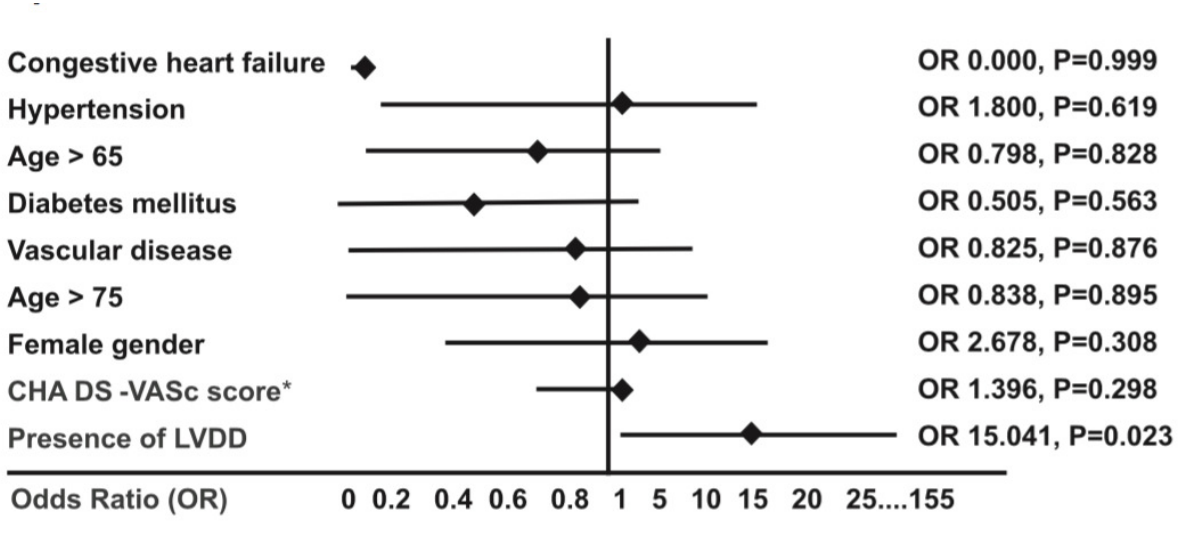
Stroke/TIA	Univariate analyses		
	OR	95% CI	*p*-value
Age (years)	1.056	1.035–1.077	**<0.001**
Female	1.275	0.832–1.953	0.264
Body surface area (m^2)	0.266	0.087–0.810	**0.020**
Body mass index (kg/m^2)	0.962	0.898–1.032	0.278
3D-CT			
LA volume index (mL/m^2)	1.023	1.012–1.034	**<0.001**
LAA volume index (mL/m^2)	1.112	1.039–1.190	**0.002**
TTE			
LA dimension (mm)	1.079	1.043–1.117	**<0.001**
LV mass index, (g/m^2)	1.006	0.997–1.016	0.180
LVEF (%)	0.980	0.959–1.003	0.082
E velocity (m/s)	1.013	0.767–1.336	0.929
Em velocity (cm/s)	0.899	0.825–0.980	**0.015**
Sm velocity (cm/s)	0.741	0.647–0.849	**<0.001**
E/Em	1.968	1.404–2.759	**<0.001**
TEE			
LAA-FV (cm/s)	0.968	0.957–0.980	**<0.001**
PV-FV Systolic/diastolic	0.782	0.468–1.306	0.348

Left ventricular diastolic dysfunction and thromboembolic risk in atrial fibrillation☆ Diastolic dysfunction and thromboembolic risk in AF

Jedrzej Kosiuk *, Ole Breithardt, Kerstin Bode, Jelena Kornej, Arash Arya, Thomas Gaspar, Gerhard Hindricks, Andreas Bollmann

Department of Electrophysiology, Heart Center Leipzig, Leipzig, Germany





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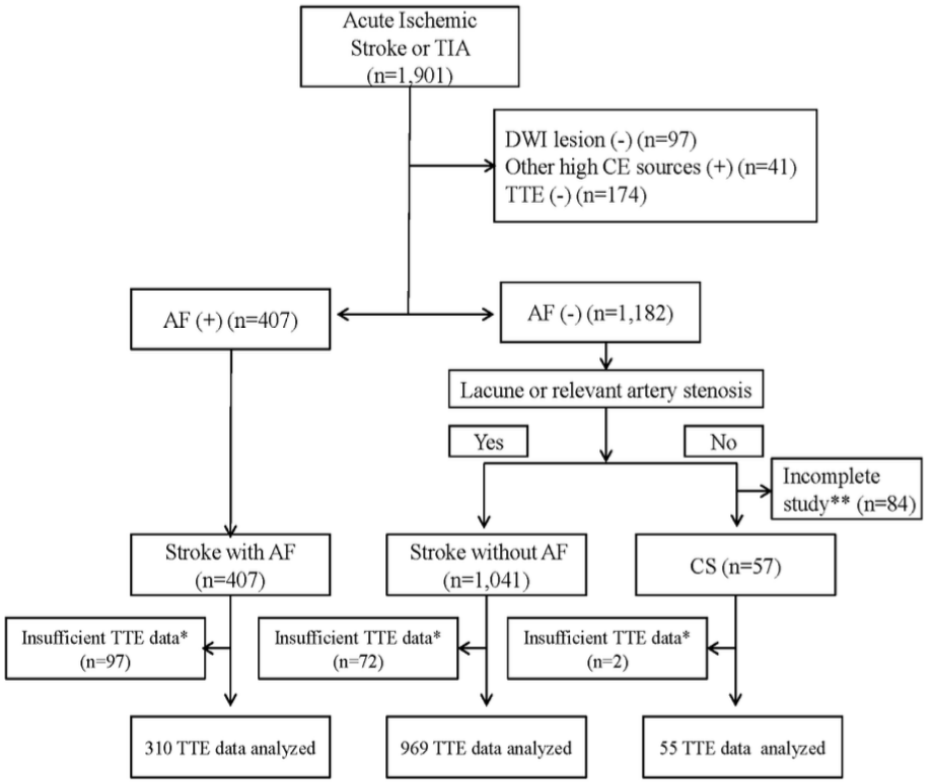
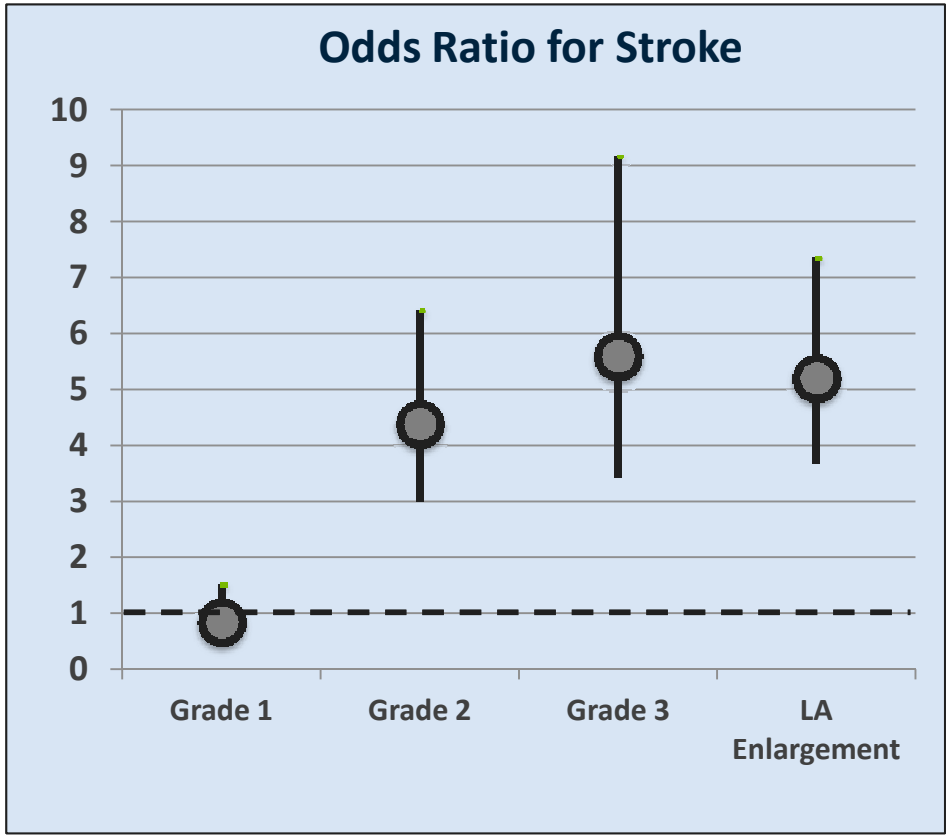
Implication of Left Ventricular Diastolic Dysfunction in Cryptogenic Ischemic Stroke

Jae-Young Seo, MD; Kyung Bok Lee, MD, PhD; Jung-Gon Lee, MD; Ji-Sun Kim, MD; Hakjae Roh, MD; Moo-Young Ahn, MD; Byoung Won Park, MD; Min Su Hyon, MD





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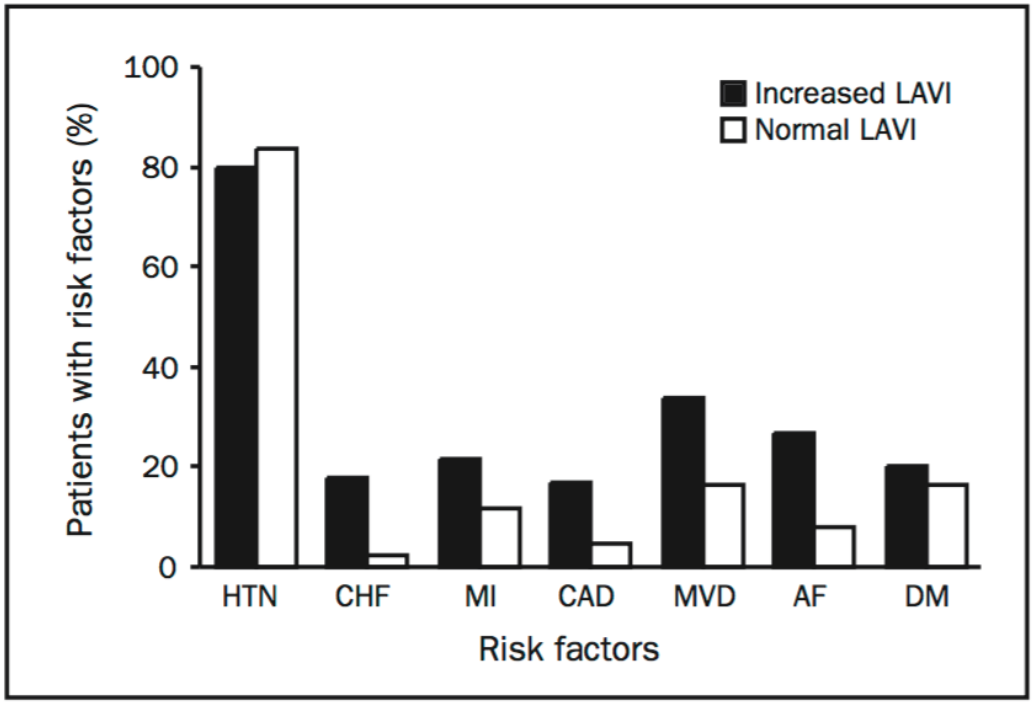
Left Atrial Volume Index and Stroke

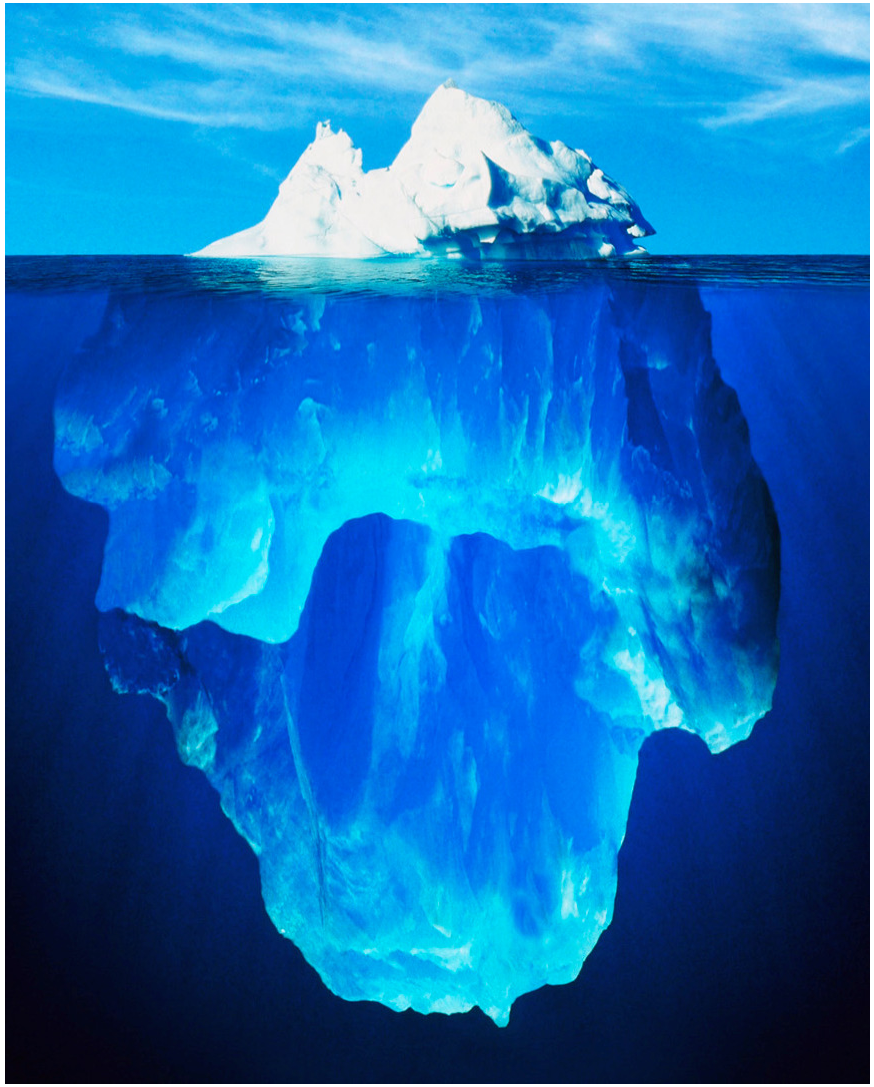
Increased Left Atrial Volume Index: Potent Biomarker for First-Ever Ischemic Stroke

KANIZ FATEMA, MBBS, PHD; KENT R. BAILEY, PHD; GEORGE W. PETTY, MD; IRENE MEISSNER, MD; MARTIN OSRANEK, MD; AHMED A. ALSAILEEK, MD; BIJOY K. KHANDHERIA, MD; TERESA S. TSANG, MD; AND JAMES B. SEWARD, MD



Characteristics	Patients (N=306)	Controls (N=397)	*P* value
Age (y), mean ± SD	75±12	68±11	<.001
Male	41	51	.01
History			
Congestive heart failure	14	5	<.001
Hypertension	81	48	<.001
Diabetes mellitus	19	10	.001
Transient ischemic attack	13	4	<.001
LAVI (mL/m^2), mean ± SD	42±21	32±24	<.001
LAVI ≥28 mL/m^2	75	52	<.001
$CHADS_2$ score, mean ± SD	1.9±1.2	0.9±1.0	<.001

of stroke (Table 4). When considered separately, both LAVI and $CHADS_2$ had significant associations with patient status. The odds ratio for stroke associated with a 1.5-fold increase in LAVI (eg, from 28 to 42 mL/m^2) was 1.66 (log likelihood ratio χ^2=27.9; P<.001), whereas the odds ratio associated with each point increase in $CHADS_2$ was 1.78 (χ^2=40.0; P<.001). When considered together in the same model, the adjusted odds ratios for LAVI and $CHADS_2$ were 1.52 per 1.5-fold increase in LAVI (P<.001) and 1.82 per unit increase in $CHADS_2$ (P<.001), respectively, with a model χ^2 of 63.6. When interactions between age and these 2 variables were considered, significant interactions were observed for each variable when separately



Atrial Fibrillation

Atrial Appendage
LA Volume/Size

Systemic Diseases

Hypertension
Obesity
Microvascular Dysfunction
Inactivity
Aging
Diabetes
Sleep Apnea

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Do We Want to Underestimated the Iceberg?

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If AF is a systemic disease, then are the results of PROTECT-AF Surprising?

Table 2. Intention-to-Treat Primary Efficacy and Safety Outcomes According to Treatment Group by Bayesian Model

Event	Device Group (n = 463)		Warfarin Group (n = 244)		Device/Warfarin Rate Ratio (95% Credible Interval)	Posterior Probabilities, %	
	Events/Patient-Years	Observed Rate[a]	Events/Patient-Years	Observed Rate[a]		Noninferiority	Superiority
Primary efficacy end point[b]	39/1720.2	2.3 (1.7-3.2)	34/900.8	3.8 (2.5-4.9)	0.60 (0.41-1.05)	>99	96
Stroke	26/1720.7	1.5 (1.0-2.2)	20/900.9	2.2 (1.3-3.1)	0.68 (0.42-1.37)	>99	83
Ischemic	24/1720.8	1.4 (0.9-2.1)	10/904.2	1.1 (0.5-1.7)	1.26 (0.72-3.28)	78	15
Hemorrhagic	3/1774.2	0.2 (0.0-0.4)	10/916.2	1.1 (0.5-1.8)	0.15 (0.03-0.49)	>99	99
Disabling[c]	8/1771.3	0.5 (0.2-0.8)	11/912.7	1.2 (0.6-1.9)	0.37 (0.15-1.00)	>99	98
Nondisabling[c]	18/1723.7	1.0 (0.7-1.7)	9/907.7	1.0 (0.4-1.7)	1.05 (0.54-2.80)	89	34
Systemic embolization	3/1773.6	0.2 (0.0-0.4)	0/919.5	0	NA		
Cardiovascular or unexplained death	17/1774.3	1.0 (0.6-1.5)	22/919.4	2.4 (1.4-3.4)	0.40 (0.23-0.82)	>99	99
Primary safety end point[d]	60/1666.2	3.6 (2.8-4.6)	27/878.2	3.1 (2.0-4.3)	1.17 (0.78-1.95)	98	20

- Mean 3.8 year follow-up
- Primary composite endpoint met criteria for both noninferiority and superiority **(Watchman + ASA)**
- This was primarily driven by a reduction in hemorrhagic stroke and CV or unexplained death

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of

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*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

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Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (25th, 75th %ile)	70 (63, 76)	70 (63, 76)
Women, %	35	35
Region, %		
North America	25	25
Latin America	19	19
Europe	40	40
Asia/Pacific	16	16
Warfarin naïve, %	43	43
CHADS score, mean (+/- SD)	2.1 (+/- 1.1)	2.1 (+/- 1.1)
1, %	34	34
2, %	36	36
≥ 3, %	30	30

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Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Qualifying risk factors, %		
Age ≥75 yrs	31	31
Prior stroke, TIA, or SE	19	20
Heart failure or reduced LV EF	35	36
Diabetes	25	25
Hypertension	87	88
Renal function (Cl_{Cr} ml/min), %		
Normal (>80)	41	41
Mild impairment (>50 – 80)	42	42
Moderate impairment (>30 – 50)	15	15
Severe impairment (≤ 30)	1.5	1.5

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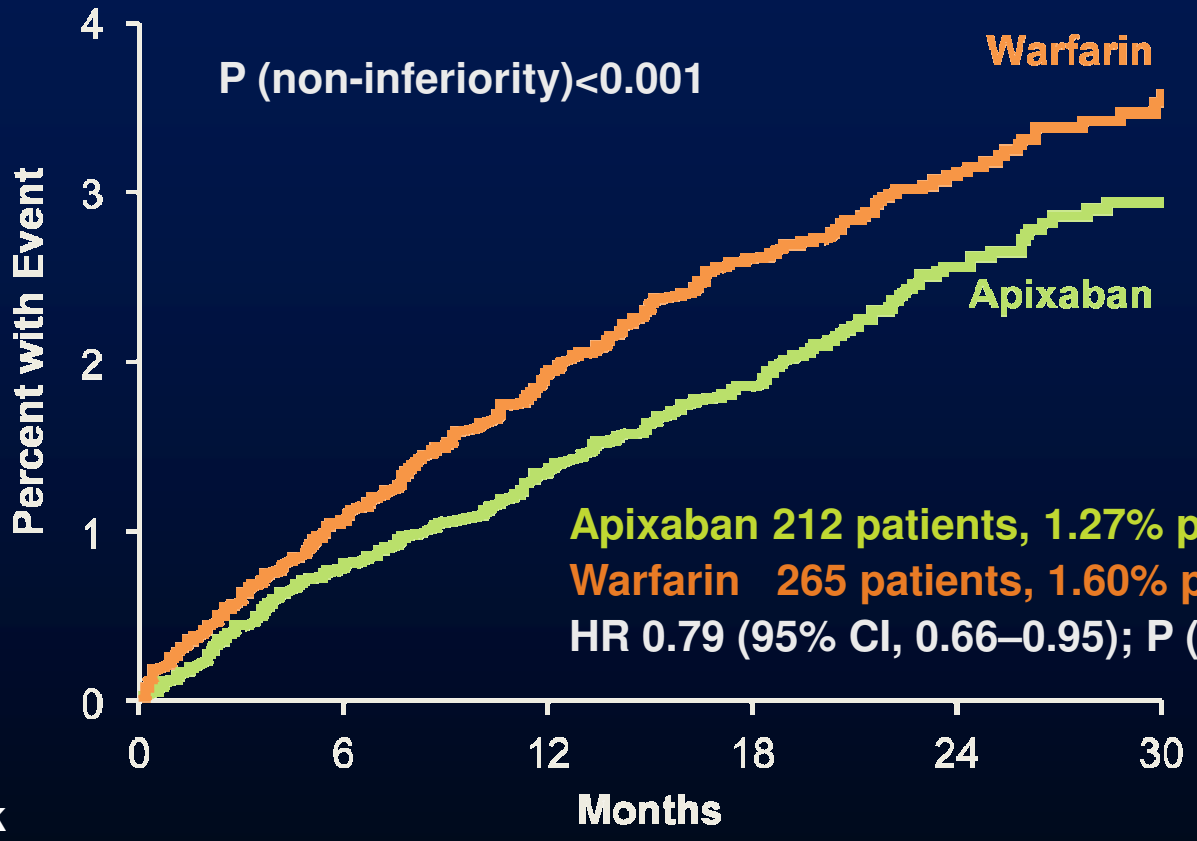
Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

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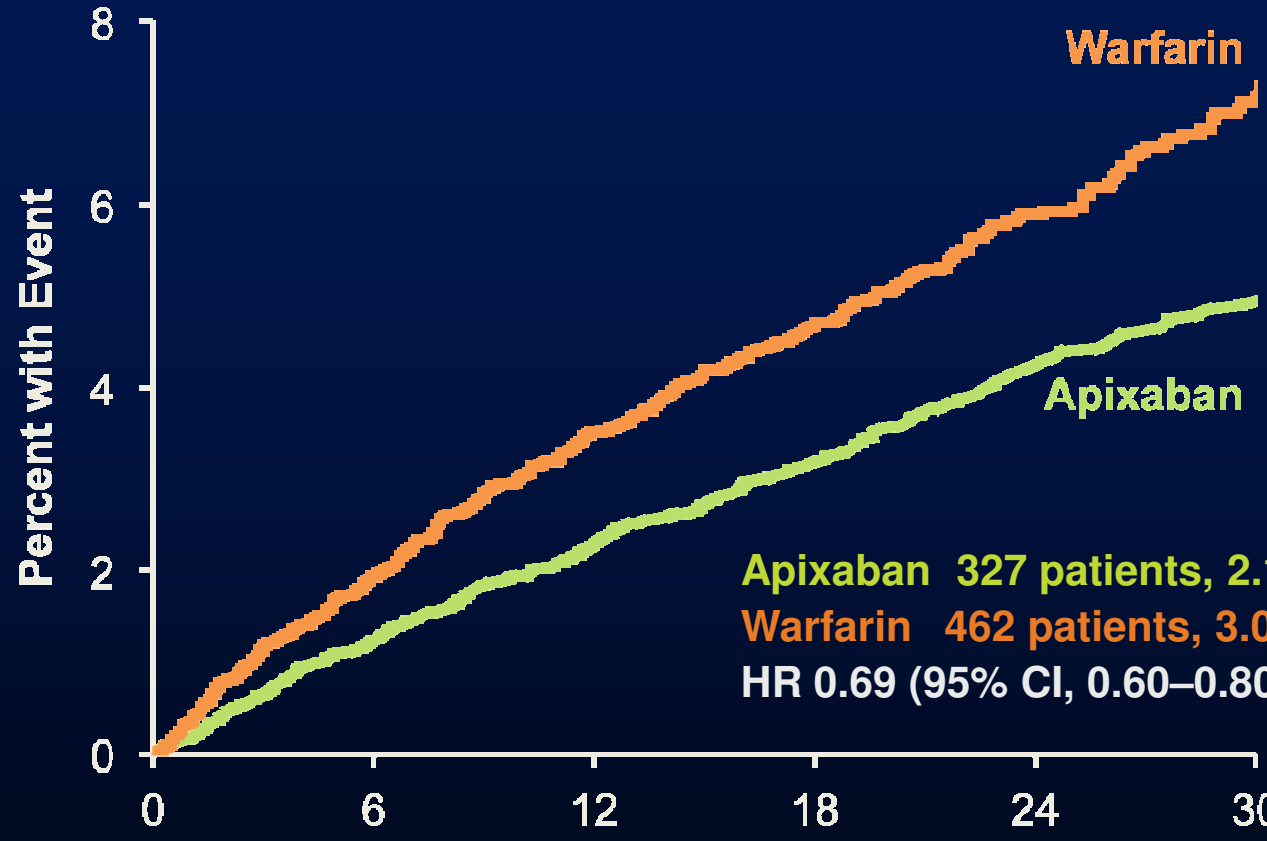
Major Bleeding

ISTH definition



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

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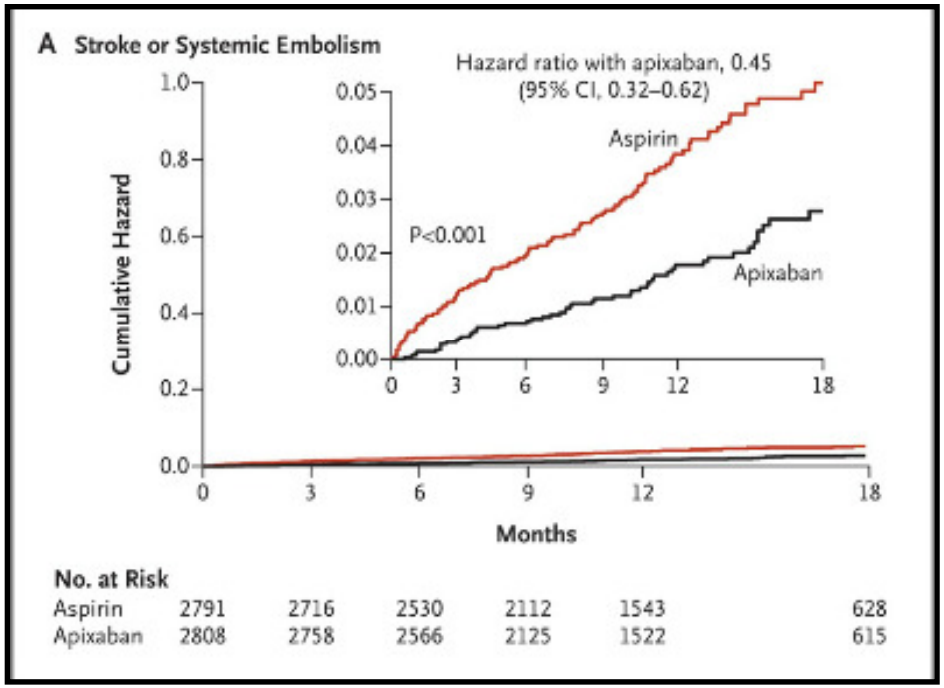
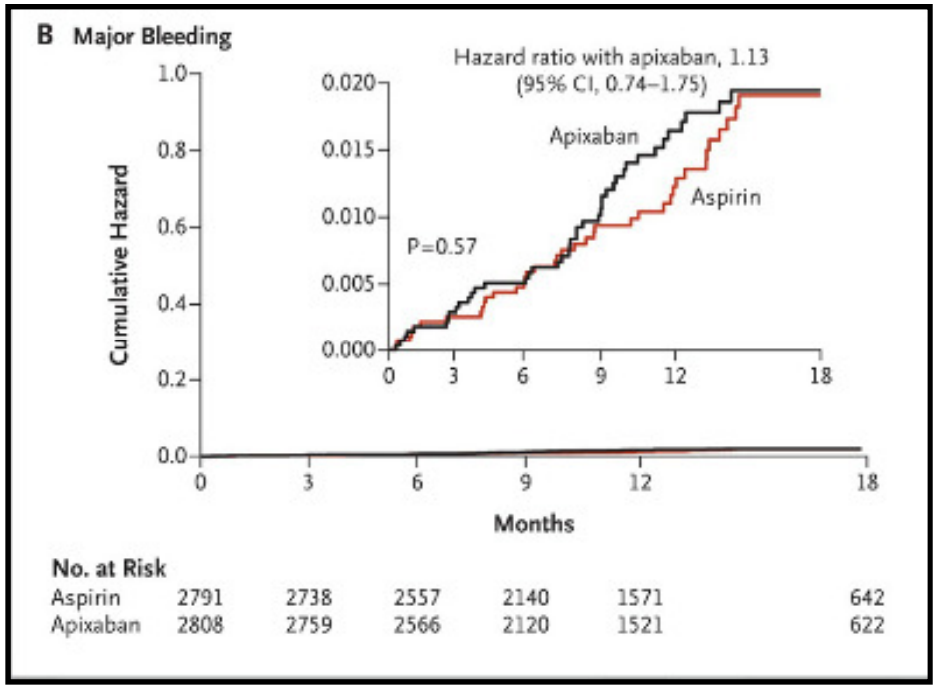
Apixaban Versus Aspirin

AVERROES Trial





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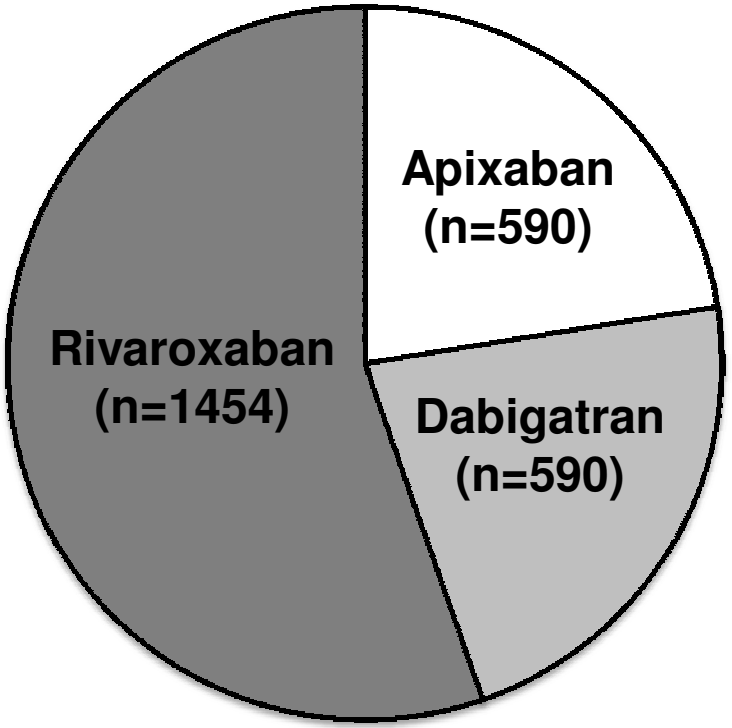
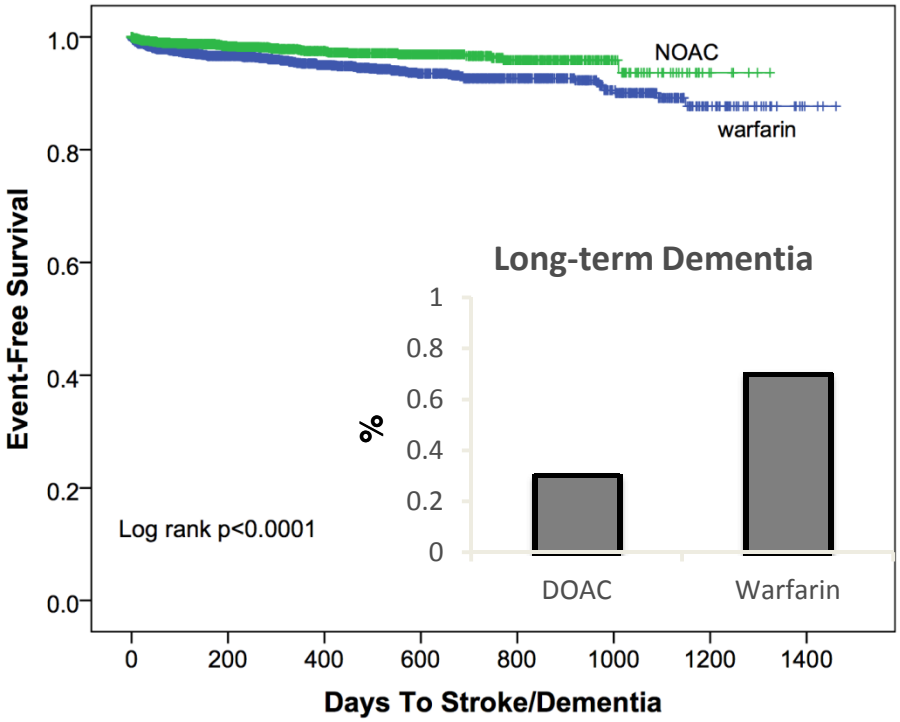
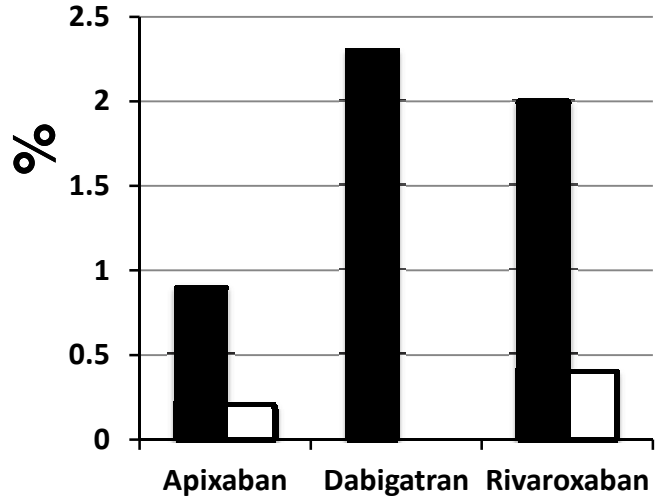
N Engl J Med 2011; 364:806-817

Direct Oral Anticoagulant Distribution



Propensity-Matched with a Warfarin Population (n=2,627)

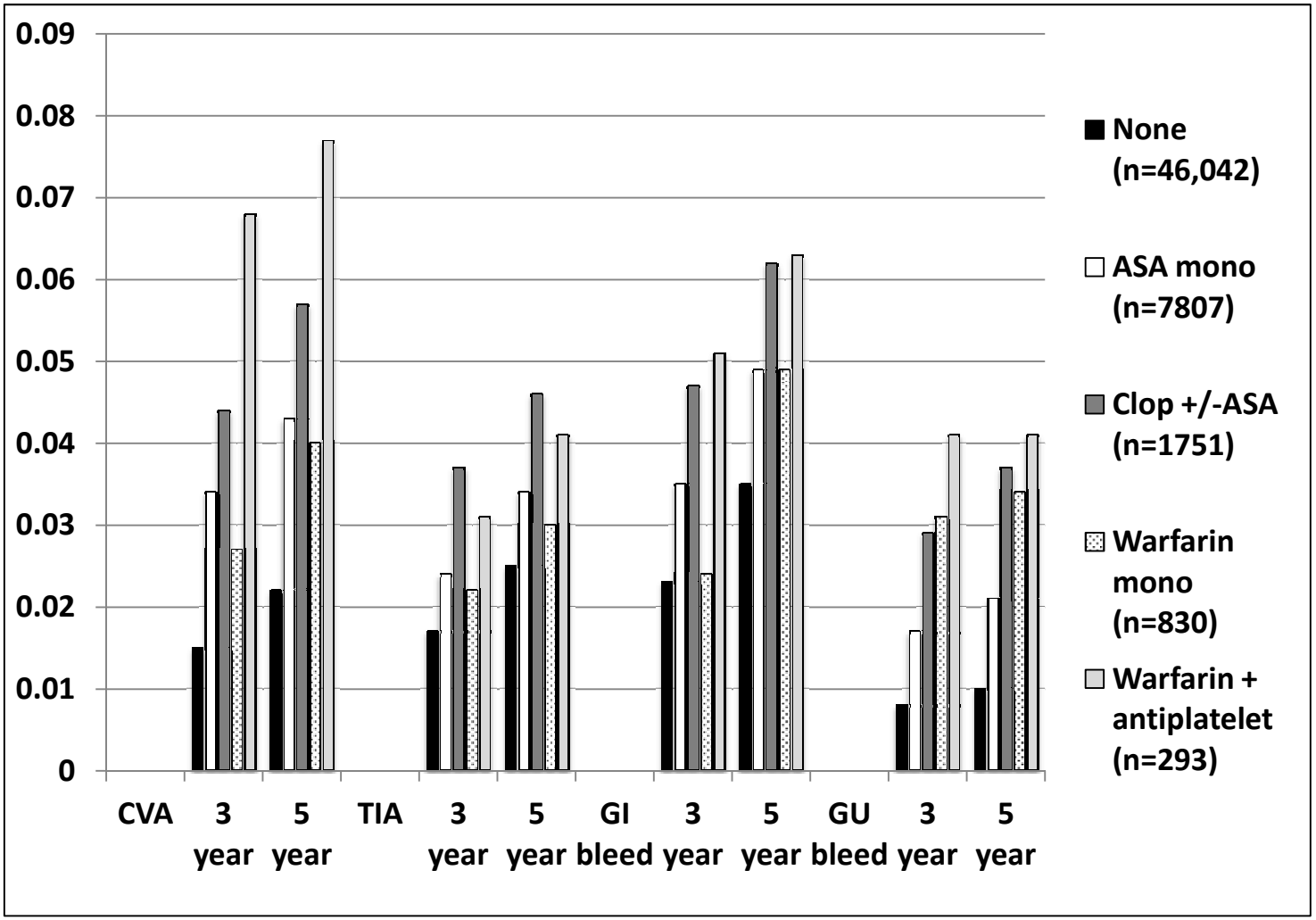




Long-Term Total Events

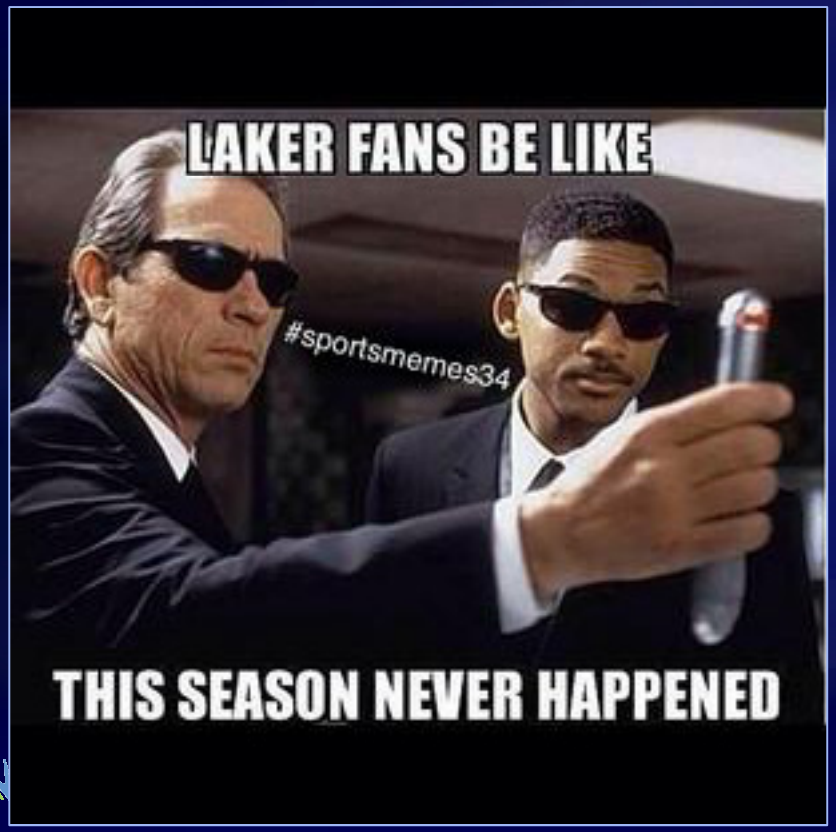
Follow-up for Dabigatran >1 yr Longer than other DOACs

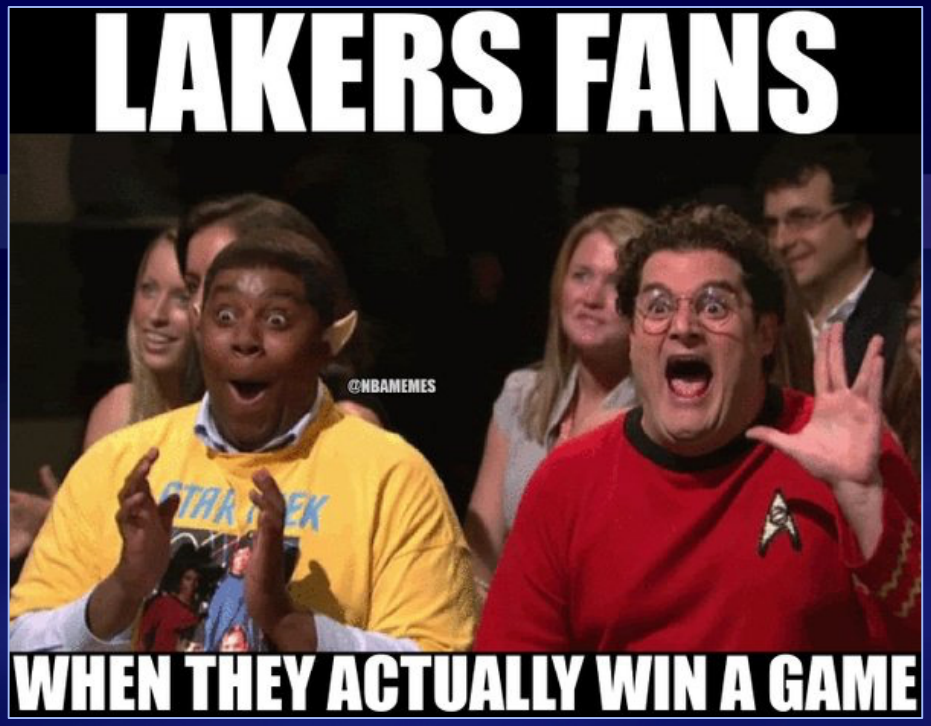
Is Aspirin a Safe and Effective Long-Term Drug for Prevention of CVA?



CHADS2 Vasc 0-2 Patients = Best Case Scenario for Risk

A Wish For Happiness to All – Even Dr. Doshi has Trials





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Conclusions

1. Until AF can be shown to be a focal disease of the atrium/appendage – consider appendage closure cautiously
2. Don't be fooled that lower large strokes mean the brain is not at risk
3. If AF is a systemic disease – only a systemic approach will work long-term, including for stroke prevention
4. If aspirin is still required post closure, we have a systemic anticoagulant that has similar long-term risks

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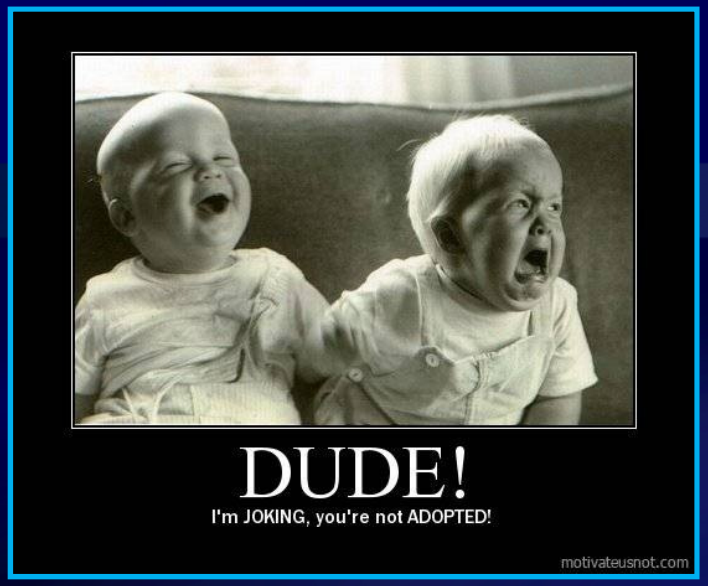
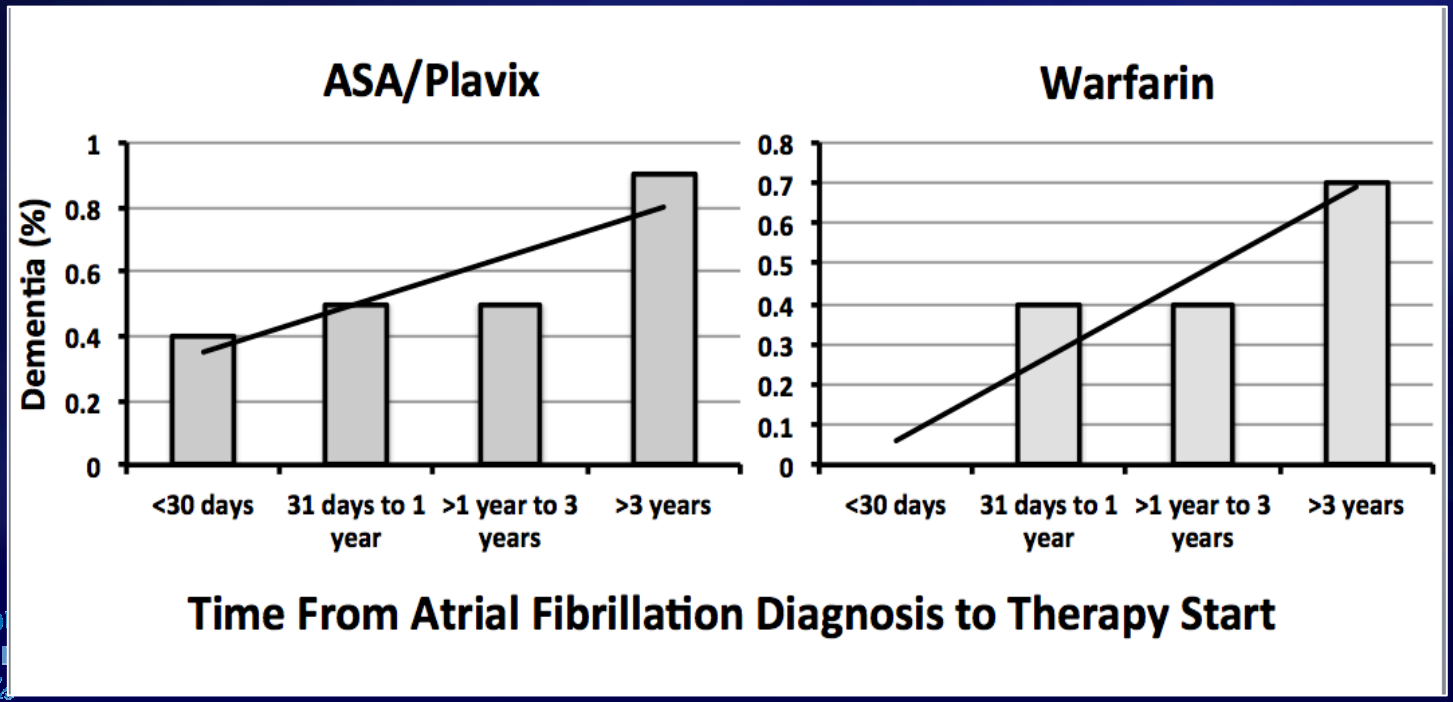
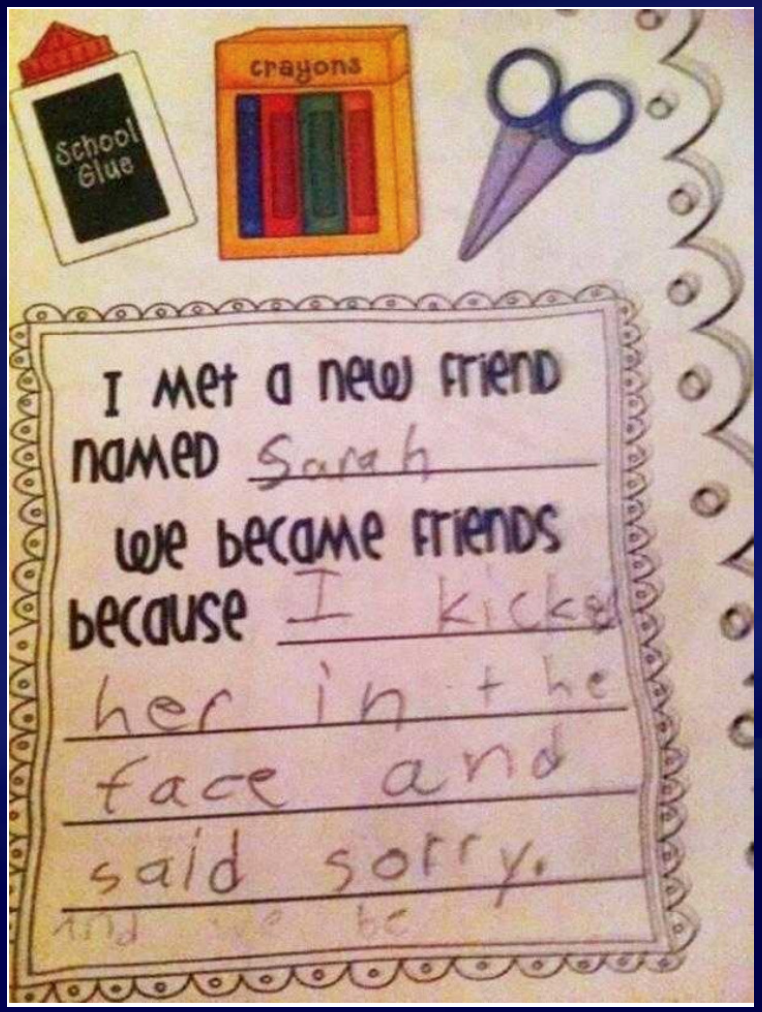


Making or LAA Closure Colleagues Happy

Never Too Late to Start Tx



Thank You



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