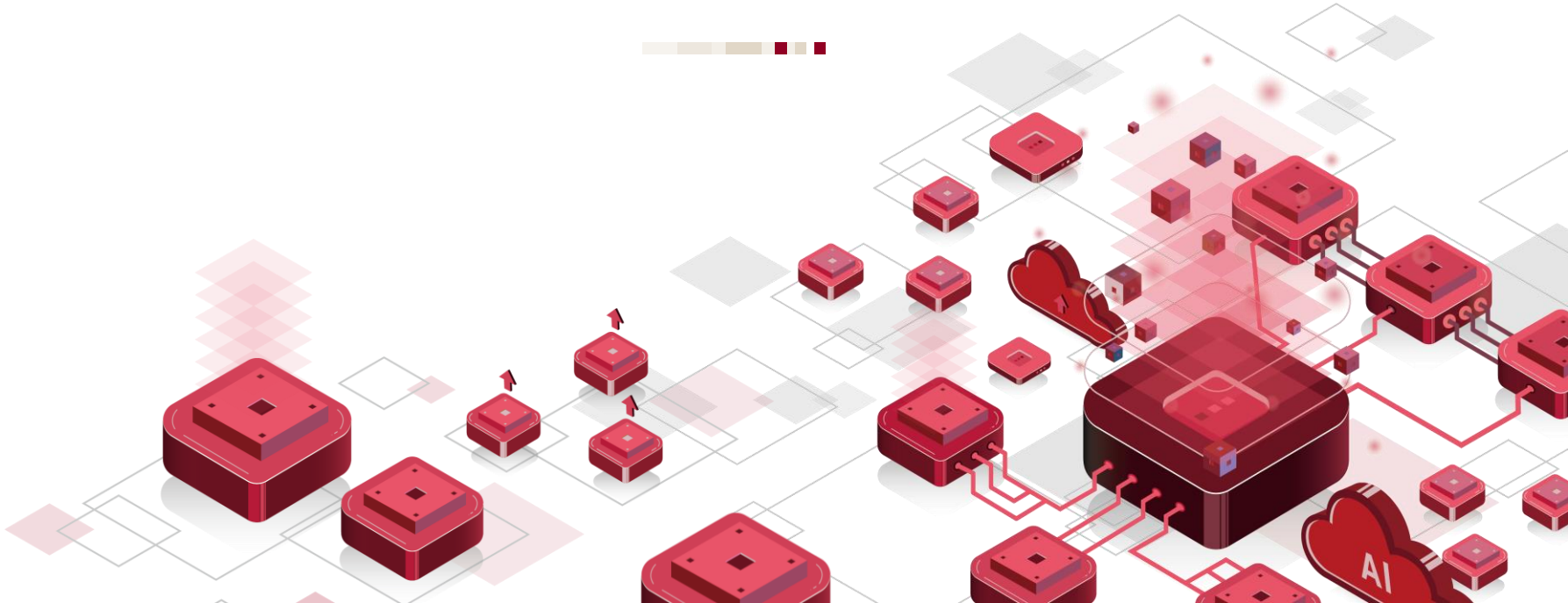
Multimodality Imaging Approach to LA Remodeling in Subclinical AF

고대 구로병원 이대인



고려대학교구로병원
KOREA UNIVERSITY GURO HOSPITAL

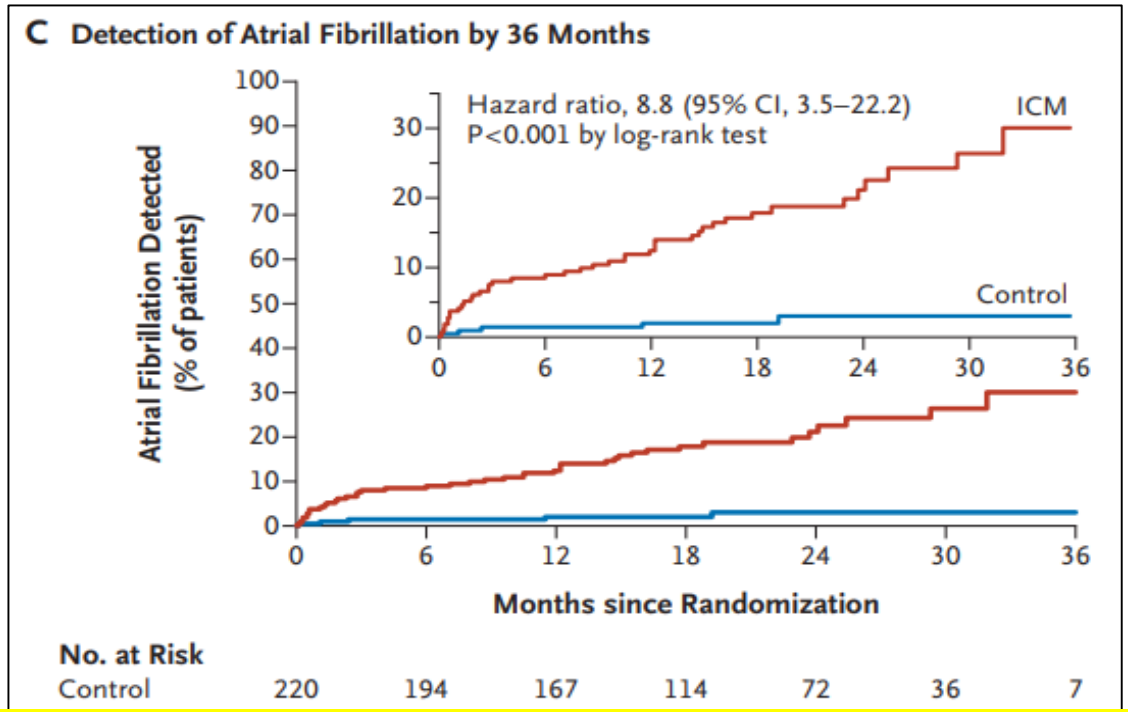
고려대학교
KOREA UNIVERSITY

Cryptogenic stroke and underlying AF (CRYSTAL AF)

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*



Attractive hypothesis

An occult paroxysmal AF is believed to be the cause for a significant number of cryptogenic stroke, especially ESUS.

Subclinical atrial fibrillation (SCAF)

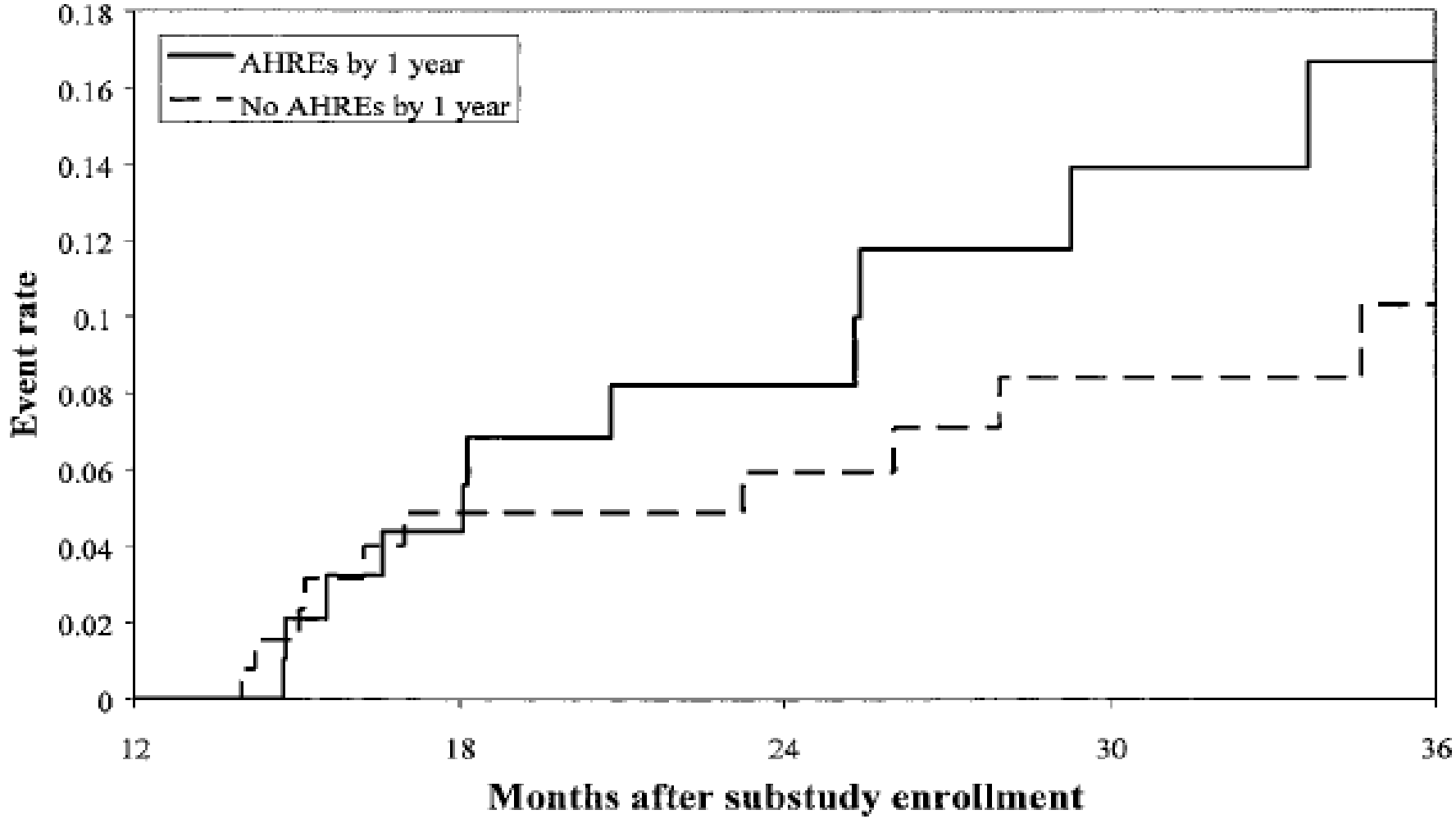
Atrial High Rate Episodes Detected by Pacemaker Diagnostics Predict Death and Stroke

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

Circulation.2003;107:1614-1619

- **VVIR (VDIR) vs. DDDR** : 6-year cohort study in patients with SSS, **AF occurrence rate**
- **Atrial high rate events (AHREs)** > 220 bpm in pacemaker device
- CPI (Guidant) Discovery DR, Medtronic Thera DR, Medtronic, Prodigy DR, Medtronic Kappa, Medtronic 7271
- Median f/up = 33 months

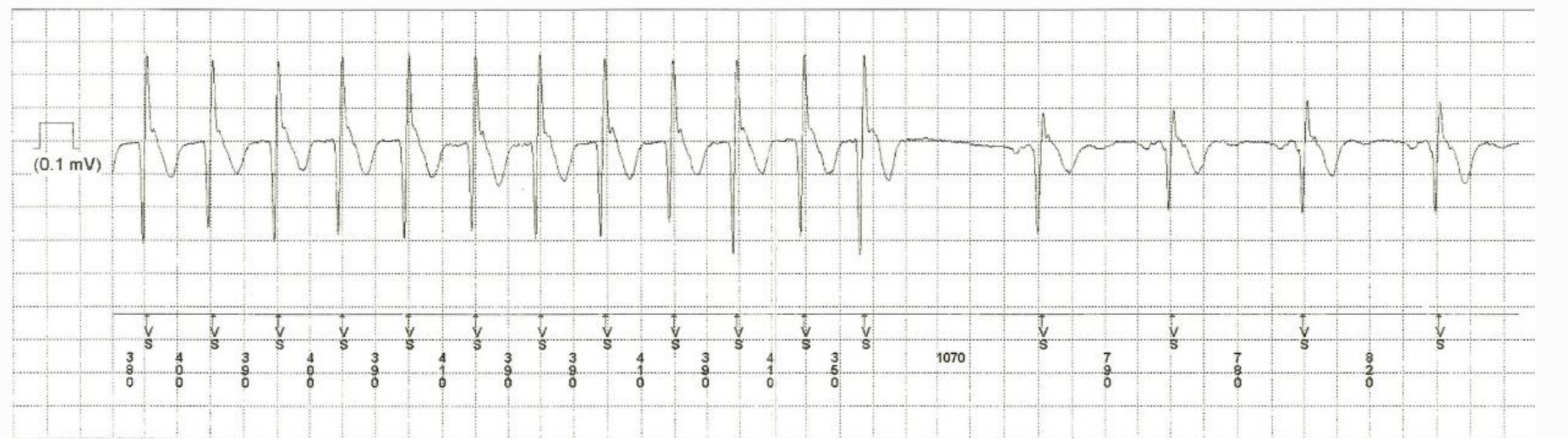
Natural history of AHREs in CIED



AHREs : strokes (X2.5), all-cause mortality (X2.8)

Definition of SCAF

- Subclinical atrial fibrillation (SCAF) : asymptomatic AF detected on cardiac implantable electronic devices (CIEDs) and external monitoring without history of AF.



An anticoagulation treatment is beneficial in patients with subclinical AF (AHREs on CIED) ?

Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial

Renato D. Lopes, MD, MHS, PhD,[a] Marco Alings, MD, PhD,[b] Stuart J. Connolly, MD,[c] Heather Beresh, MSc,[c] Christopher B. Granger, MD,[a] Juan Benezet Mazuecos, MD,[d] Giuseppe Boriani, MD, PhD,[e] Jens C. Nielsen, MD, DMSc,[f] David Conen, MD, MPH,[c,g] Stefan H. Hohnloser, MD,[h] Georges H. Mairesse, MD,[i] Philippe Mabo, MD,[j] A. John Camm, MD,[k] and Jeffrey S. Healey, MD, MSc[c] *Durham, NC; Utrecht, the Netherlands; Hamilton, Canada; Madrid, Spain; Modena, Italy; Aarhus, Denmark; Basel, Switzerland; Frankfurt, Germany; Arlon, Belgium; Rennes, France; and London, United Kingdom*

2017

Gap in knowledge in threshold of AHREs duration

Study	>30 s	>1 min	>2 min	>5 min	>6 min	>1 h	>6 h	<24 h	>24 h
Chen et al. (2021) [36]	HR 1.584 CI 1.009-2.487, p=0.046	HR 1.841 CI 1.178–2.879, p=0.007	HR 2.105 CI 1.370-3.235, p=0.001	HR 2.030 CI 1.334–3.089, p=0.001			HR 1.870 CI 1.160–3.014, p=0.010		HR 1.822 CI 1.059–3.137, p=0.030
Lu et al. (2021) [37]			HR 13.406 CI 2.959–60.743, p=0.001	HR 5.725 CI 1.960–16.720, p=0.001					HR 2.950 CI 1.008–8.634, p=0.048
Chen et al. (2021) [38]					HR 1.679 CI 1.147–2.457, p=0.008		HR 1.739 CI 1.120–2.701, p=0.014		
Zakeri et al. (2020) [39]					HR 3.35 CI 1.15–9.77, p=0.027				
Lu et al. (2021) [40]				HR 5.252 CI 2.575-10.715, p<0.001			HR 2.548 CI 1.284–5.058, p=0.007		
Boriani et al. (2014) [48]				HR 1.76 CI 1.02–3.02, p=0.041		HR 2.11 CI 1.22–3.64, p=0.008			
Ishigushi et al. (2021) [41]									HR 2.2 CI 1.1–4.4, p<0.01
Pastori et al. (2020) [43]				HR 1.788 CI 1.247–2.562, p=0.002					HR 2.390 CI 1.481–3.857, p<0.001
Park et al. (2021) [44]								OR 1.13 CI 1.08–1.19, p<0.001	OR 20.1 CI 7.60–52.7, p<0.001
Witt et al. (2015) [45]									HR 3.13 CI 1.16–8.39, p=0.023
van Gelder et al. (2017) [47]									HR 3.24 CI 1.51–6.95, p=0.003

Clinical Research in Cardiology (2022) 111:994–1009

The different threshold of AHREs duration according to CHAS2 score

Journal of Cardiovascular Electrophysiology / Volume 20, Issue 3 / p. 241-248

Full Access

Presence and Duration of Atrial Fibrillation Detected by Continuous Monitoring: Crucial Implications for the Risk of Thromboembolic Events

GIOVANNI L. BOTTO M.D., LUIGI PADELETTI M.D., MASSIMO SANTINI M.D., ALESSANDRO CAPUCCI M.D., MICHELE GULIZIA M.D., FRANCESCO ZOLEZZI M.D., STEFANO FAVALE M.D. ... See all authors

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https://doi.org/10.1111/j.1540-8167.2008.01320.x

Stroke rates[b] per AHRE burden and CHA_2DS_2VASc category
(*n* = 21 768 device patients not taking OAC)[1466]

	Baseline maximum daily burden		
CHA_2DS_2-VASc score	No AF	AF 6 min–23.5 h	AF >23.5 h
0	0.33%	0.52%	0.86%
1	0.62%	0.32%	0.50%
2	0.70%	0.62%	1.52%
3-4	0.83%	1.28%	1.77%
≥5	1.79%	2.21%	1.68%

- $CHADS_2$ score 0 – 1: AHREs duration was >24 hours increased stroke risk
- $CHADS_2$ score ≥2, episodes lasing >6 minutes increased risk

There is likely a complex interplay between predisposing risk factors, AF duration/burden, and propensity of ischemic stroke.

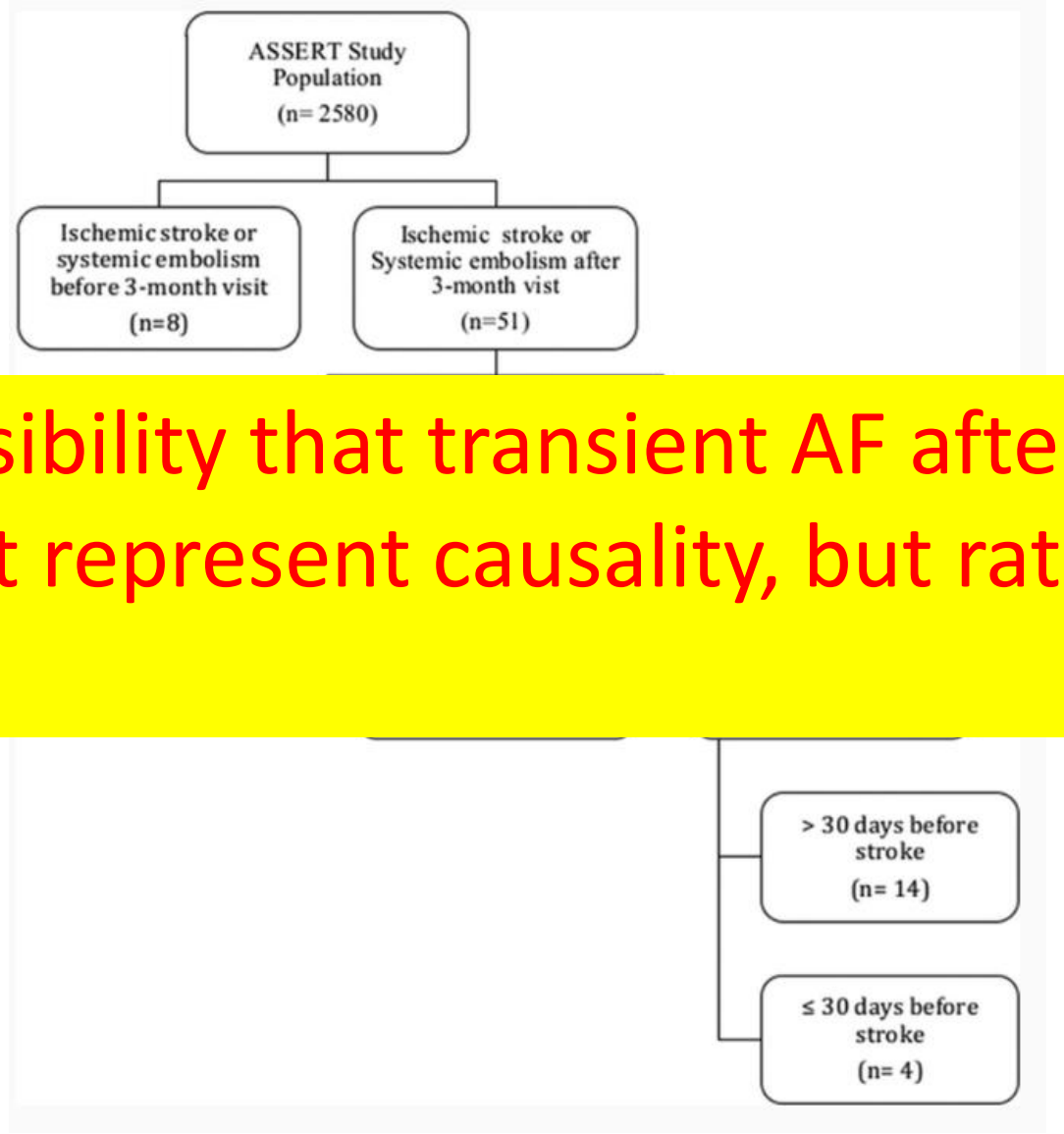
Temporal mismatch between subclinical AF and embolic events

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

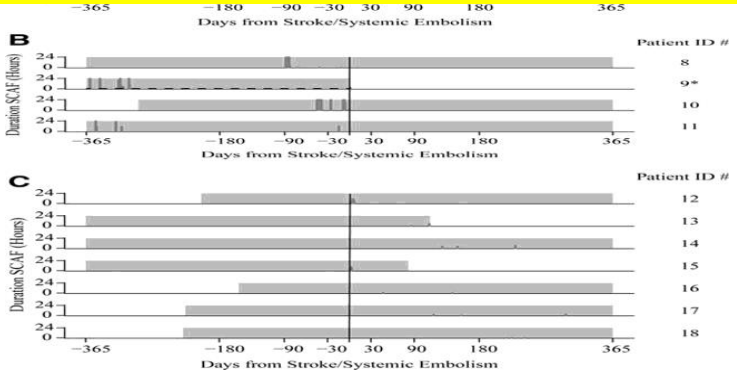
American Heart Association.

Temporal Relationship between Subclinical Atrial Fibrillation and Embolic Events

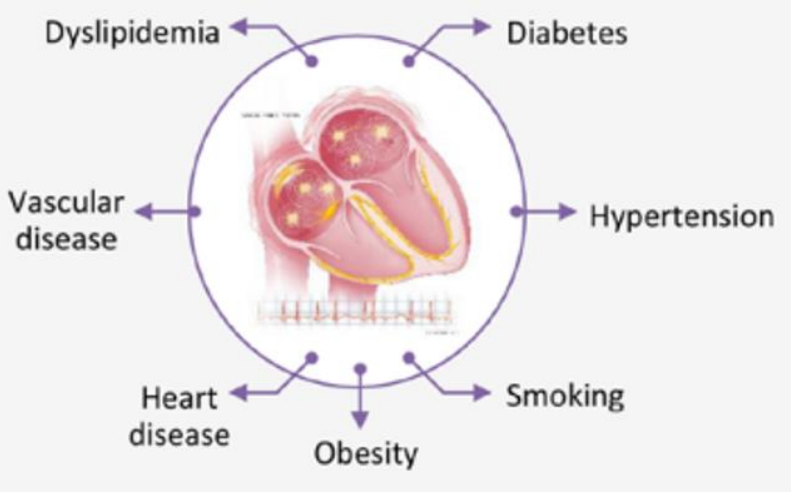
Michela Brambatti, Stuart J. Connolly, Michael R. Gold, Carlos A. Morillo, Alessandro Capucci, Carmine Muto, Chu Lau, Isabelle C. Van Gelder, Stefan H. Hohnloser, Mark Carlson, Eric Fain, Juliet Nakamya, Georges H. Mairesse, Marta Halytska, Wei Q. Deng, Carsten W. Israel and Jeff S. Healey
on behalf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



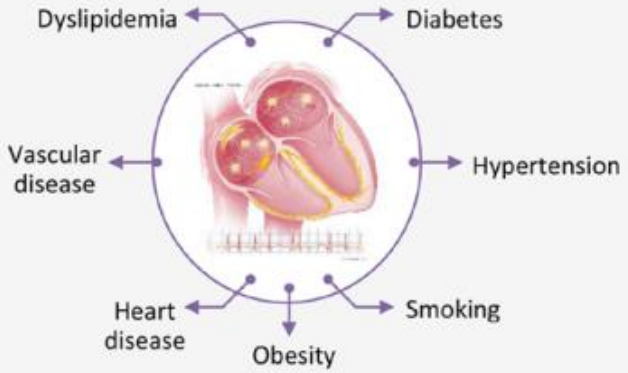
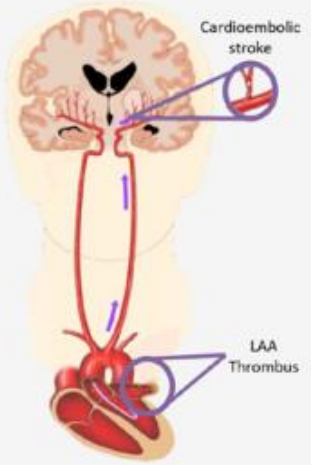
These findings raise the possibility that transient AF after cryptogenic stroke might not represent causality, but rather an association.



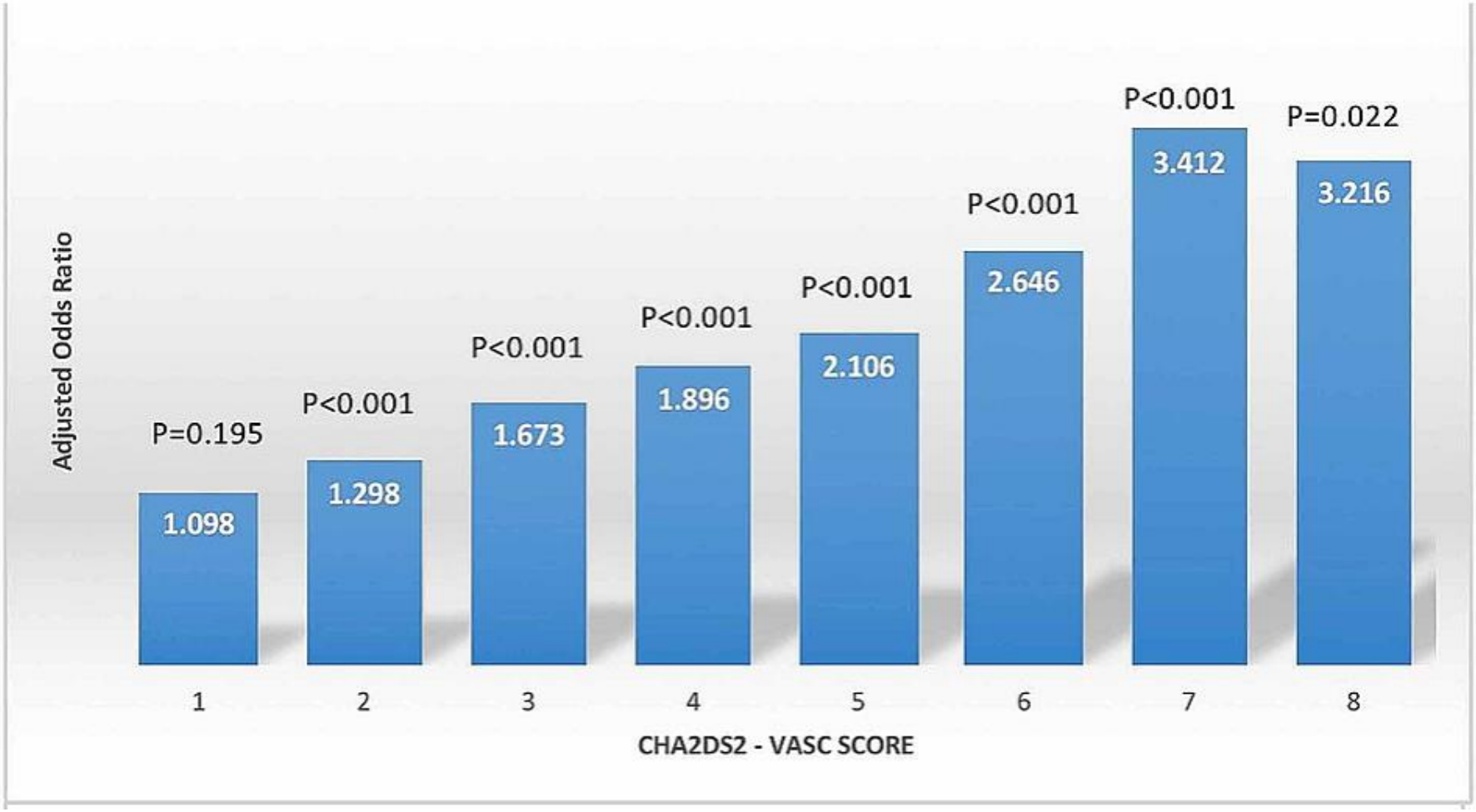
Subclinical AF's role for stroke: surrogate marker vs. direct cause ??



AF shares pathophysiological mechanisms with stroke.

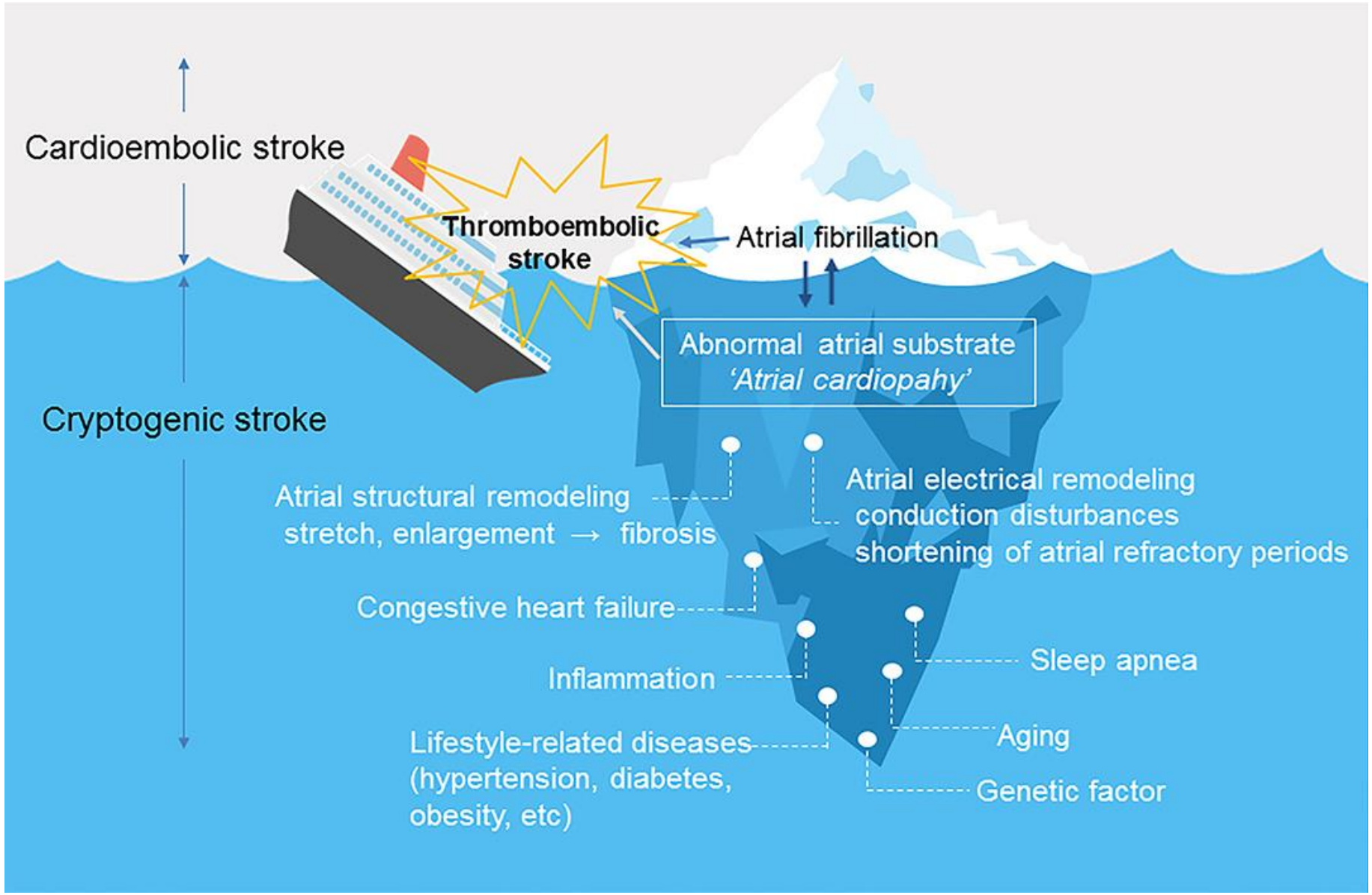
	AF as a Risk Marker	AF as a Direct Cause
Concept	 • AF is a stroke risk marker that is epidemiologically associated with stroke, not necessarily always causative	AF directly leads to LAA thrombus formation and risk of cardioembolic stroke 
Implications for the definition of a critical AF threshold	• Need to determine sufficient burden/duration of AF that associates with risk	• How much AF is needed to promote LAA thrombus formation? • Need to determine temporal relationships, burden, etc.
Therapeutic implications	• AF burden less important • Treat AF along with other risk factors • Minimal role for rhythm control as a stroke reduction strategy • Anticoagulation should not be stopped post ablation	• Role for "pill in the pocket" anticoagulation? • Role for rhythm control as a strategy for stroke reduction? • Role for continuous monitoring/tracking of PAF burden?

Revisit of CHA2DS2-VASc score



This indicates that AF by itself is unlikely to be the sole driver for LA thrombogenesis.

Atrial cardiomyopathy: a mediator between risk factors and stroke



Research

JAMA Cardiology | Original Investigation

Association of Left Atrial Strain With Ischemic Stroke Risk in Older Adults

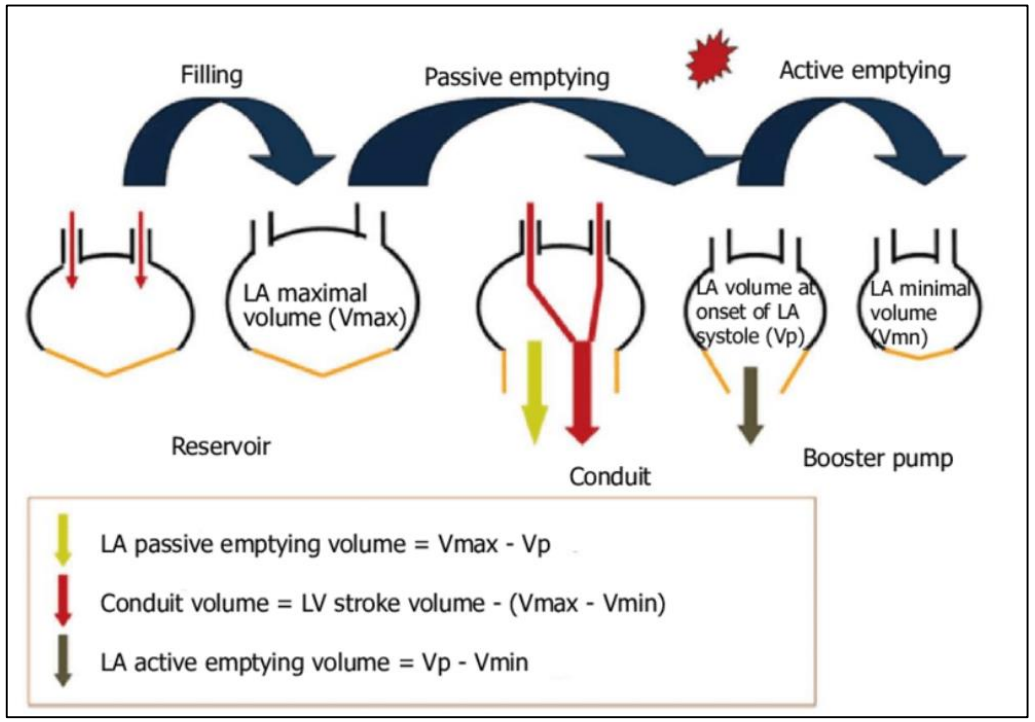
Carlo Mannina, MD; Kazato Ito, MD; Zhezhen Jin, PhD; Yuriko Yoshida, MD; Kenji Matsumoto, MD; Sofia Shames, MD; Cesare Russo, MD; Mitchell S. V. Elkind, MS, MD; Tatjana Rundek, MS, MD, PhD; Mitsuhiro Yoshita, MD; Charles DeCarli, MD; Clinton B. Wright, MD; Shunichi Homma, MD; Ralph L. Sacco, MS, MD; Marco R. Di Tullio, MD

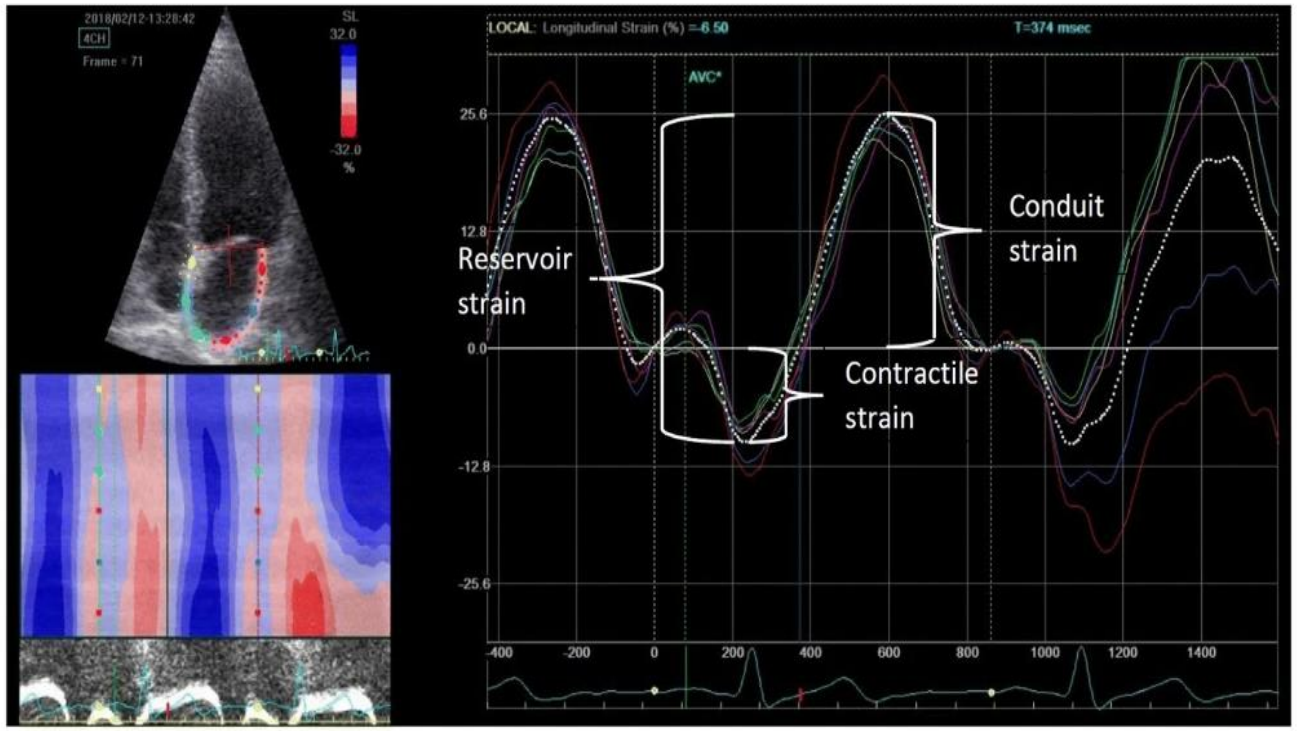
JAMA Cardiol. 2023;8(4):317-325

Hypothesis generation

- The ischemic stroke is higher among patients with LA enlargement
- Atrial dysfunction, accessed by LA strain, precedes LA enragement
- In normal LA size, LA strain can predict the ischemic stroke risk?

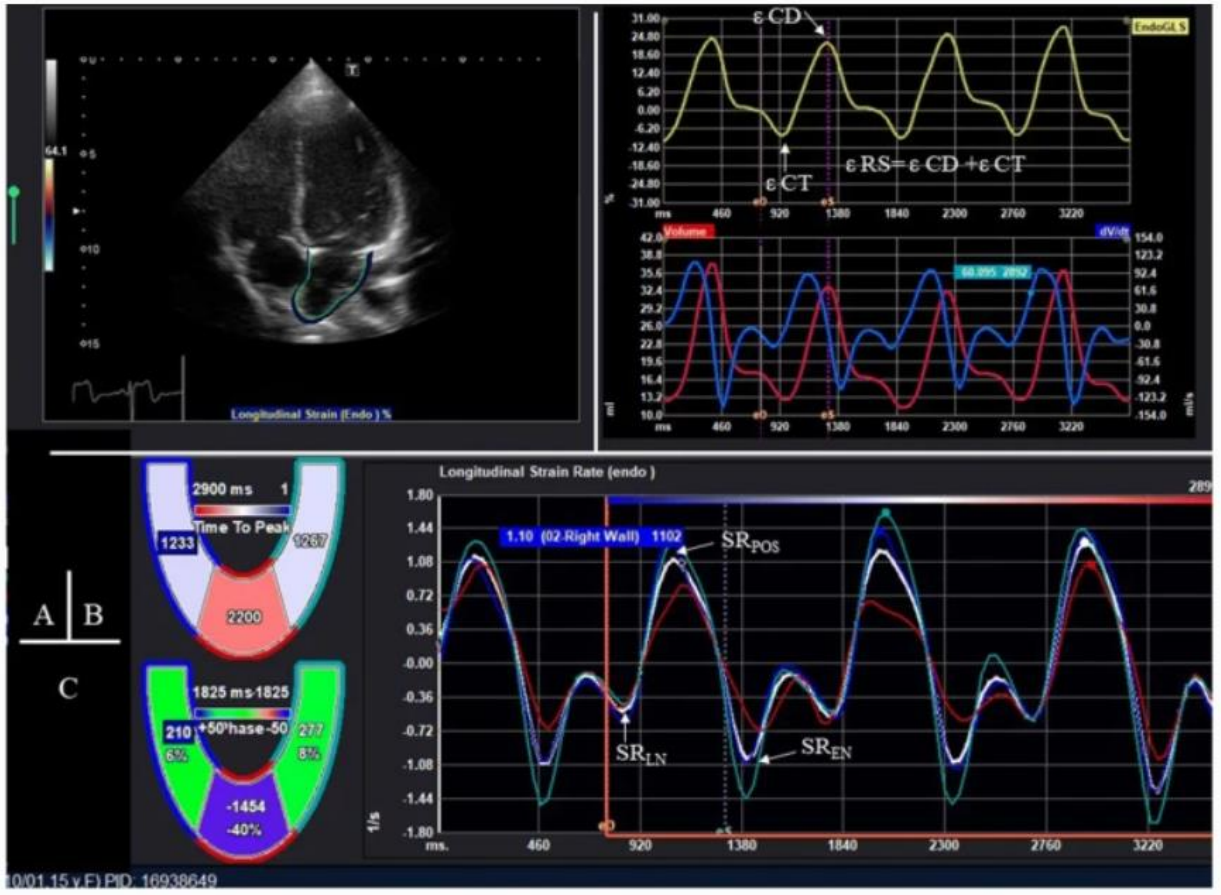
Atrial function





- LA reservoir function, expressed as global peak positive longitudinal LAε
- LA conduit function: peak negative longitudinal LASR during early ventricular diastole
- LA pump function, expressed as global peak negative longitudinal LASR during LA contraction

Left atrial longitudinal strain (LAGS)



- LAGS was accessed using the 2D speckle tracking method obtained from an apical four-chamber view.
- Three-points (septal and lateral corners of MA and LA roof) was manually plotted and followed by automatic tracing (TOMTEC software).
- LV global longitudinal strains = the mean of LA reservoir function at six segments
- Abnormal GLS = -14.7%

Study design

- Retrospective study
- Cardiovascular Abnormalities and Brain Lesions (CABL) study cohort derived from Northern Manhattan Study (NOMAS) prospective cohort
- 806 participants (>40 years olds) without AF diagnosis
- TTE and brain MRI in 2003-2008
- f/up by active hospital surveillance of admission and checked up for ischemic stroke (TOAST classification) based on ICD-9 codes

- new-onset ischemic stroke occurred in 53 participants (7%)

Table 4. Association of LAε and LASR With Incident Ischemic Stroke

	Univariable model		Multivariable model[a]	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Positive longitudinal LAε	3.33 (1.91-5.79)	<.001	3.12 (1.56-6.24)	.001
Positive longitudinal LASR during ventricular systole	2.12 (1.19-3.78)	.01	1.24 (0.59-2.60)	.57
Negative longitudinal LASR during early ventricular diastole	1.93 (1.06-3.52)	.03	1.52 (0.73-3.15)	.26
Negative longitudinal LASR during LA contraction	3.23 (1.86-5.59)	<.001	2.89 (1.44-5.80)	.003

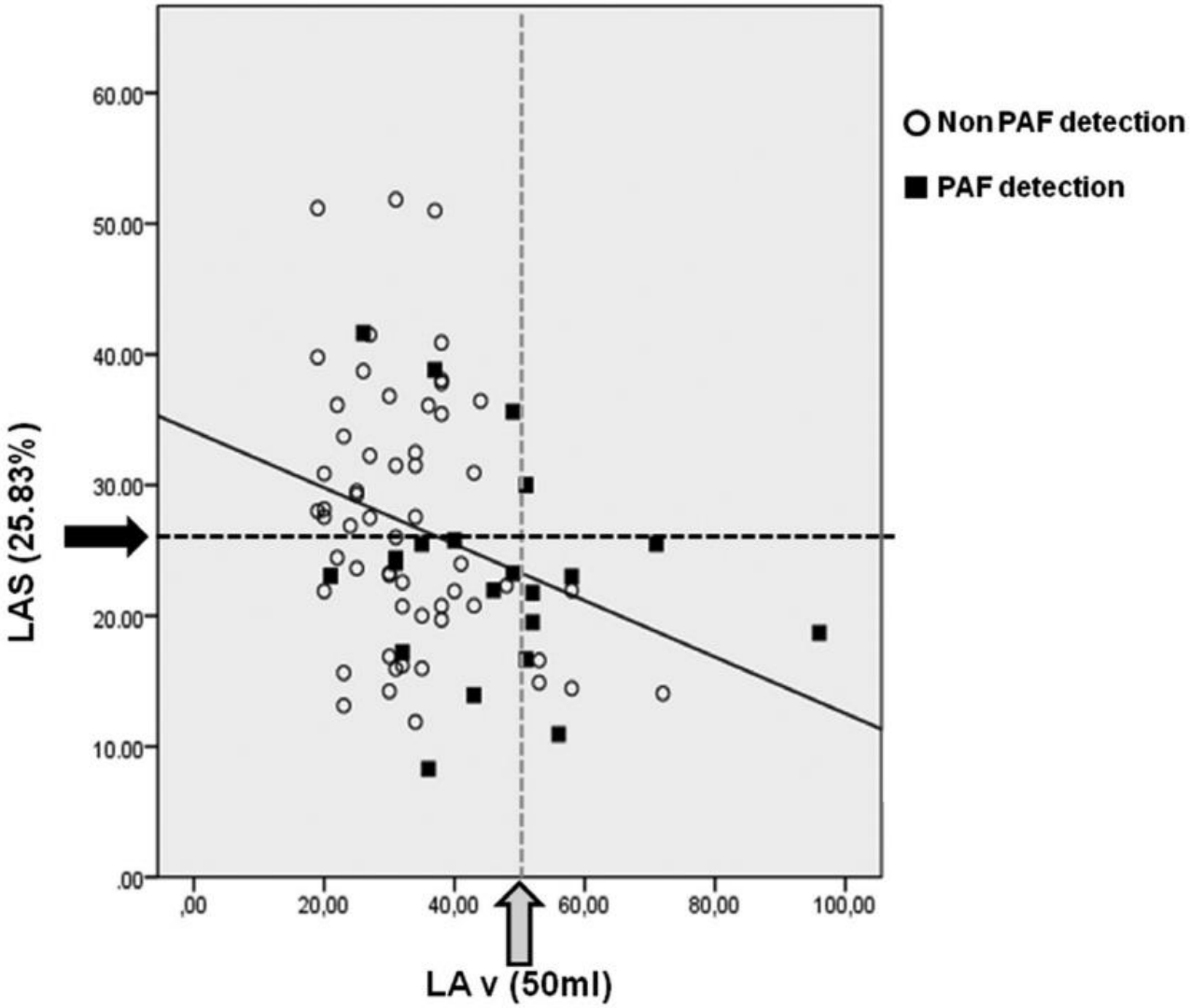
Abbreviations: HR, hazard ratio; LAε, left atrial strain; LASR, left atrial strain rate.

[a] Adjusted for age, hypertension, systolic blood pressure, white matter hyperintensities, mitral regurgitation greater than mild, hypertension medications, left ventricular ejection fraction, left ventricular mass, β-blocker use, left atrial minimum volume index, left atrial emptying volume index, abnormal left ventricular global longitudinal strain; and new-onset atrial fibrillation during follow-up. The values are comparing the lowest (worst) quintile with all other quintiles.

LA Strain is a predictor for incident AF

Left Atria Strain Is a Surrogate Marker for Detection of Atrial Fibrillation in Cryptogenic Strokes

Jorge Pagola, MD; Teresa González-Alujas, MD; Alan Flores, MD; Marian Muchada, MD; David Rodriguez-Luna, MD; Laia Seró, MD; Marta Rubiera, MD; Sandra Boned, MD; Marc Ribó, MD; José Álvarez-Sabin, MD; Arturo Evangelista, MD; Carlos A. Molina, MD



Atrial fibrosis in sinus rhythm

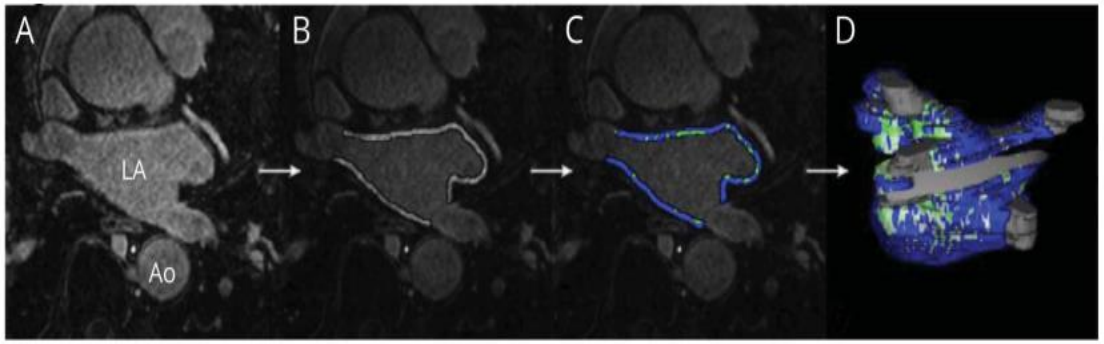
ARTICLE

Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation

Karman Tandon, MD, MPH, David Tirschwell, MD, MSc, W.T. Longstreth, Jr., MD, MPH, Bryn Smith, MS, and Nazem Akoum, MD, MS

Correspondence
Dr. Akoum
nakoum@
cardiology.washington.edu

Neurology® 2019;93:e381-e387. doi:10.1212/WNL.0000000000007827



Neurology® 2019;93:e381-e387.

Hypothesis

atrial fibrosis and associated atrial cardiopathy

may be in the causal pathway of cardioembolic stroke

independently of atrial fibrillation (AF)

Table 2 Means and SDs of LA fibrosis, LA surface area, and LA volume indexed to body surface area for the 3 study groups

	ESUS (n = 10)	Controls (n = 10)	AF (n = 10)
LA fibrosis, %	16.8 ± 5.7[a]	10.6 ± 5.7	17.8 ± 4.8[a]
LA surface area, cm^2	120.1 ± 28.2	108.5 ± 30.3	128.9 ± 40.9
LA volume index, mL/m^2	37.9 ± 12.9	34.6 ± 13.2	62.5 ± 51.0

Abbreviations: AF = atrial fibrillation; ESUS = embolic stroke of undetermined source; LA = left atrial.
[a] $p < 0.05$ compared to controls by pairwise comparisons.

P-wave terminal force in lead V1 (PTFV1)

Electrocardiographic Left Atrial Abnormality and Risk of Stroke

Northern Manhattan Study

Hooman Kamel, MD; Madeleine Hunter; Yeseon P. Moon, MS; Shadi Yaghi, MD; Ken Cheung, PhD; Marco R. Di Tullio, MD; Peter M. Okin, MD; Ralph L. Sacco, MD; Elsayed Z. Soliman, MD, MSc, MS; Mitchell S.V. Elkind, MD, MS

Stroke. 2015;46:3208-3212

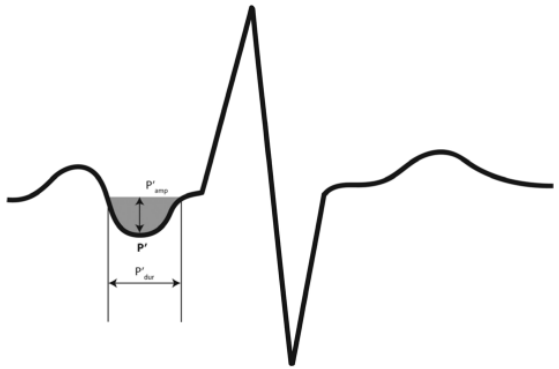


Figure. Schematic illustration of P-wave terminal force in lead V_1. P-wave terminal force in lead V_1 was defined as the absolute value of the amplitude (P'_{amp}) multiplied by the duration (P'_{dur}) of the downward portion of the P-wave (P′, shaded area) in lead V_1 of a standard 12-lead ECG.

Table 2. Associations Between P-Wave Terminal Force in ECG Lead V1 and Incident Ischemic Stroke Subtypes

Outcome*	Model 1†	Model 2‡	Model 3§
Any ischemic stroke	1.24 (1.07–1.42)	1.21 (1.04–1.39)	1.20 (1.03–1.39)
Ischemic stroke subtypes			
Cryptogenic or cardioembolic	1.31 (1.10–1.55)	1.28 (1.07–1.53)	1.31 (1.08–1.58)
Cryptogenic	1.29 (0.99–1.68)	1.25 (0.95–1.65)	1.29 (0.96–1.72)
Cardioembolic	1.32 (1.07–1.62)	1.30 (1.05–1.62)	1.23 (0.97–1.56)
Noncardioembolic	1.14 (0.94–1.40)	1.12 (0.92–1.37)	1.14 (0.92–1.40)

- P-wave terminal force in lead V_1

= Integral between P wave duration and P wave Amplitude at P wave-terminals force

Results are reported as the hazard ratio (95% confidence inte
each
1-SD increase in P-wave terminal force in lead V

1.

Summary

- When SCAF is documented in CIEDs, AF by itself is unlikely to be the sole driver for LA thrombogenesis.
- There is likely a complex interplay between predisposing risk factors, AF duration/burden, and propensity of ischemic stroke.
- Moreover, atrial cardiomyopathy rather than occult AF (SCAF) can one of main drivers for ischemic stroke.
- Left atrial size (volumes) on various imaging modalities, LA longitudinal strain, PTFV1 can reflect left atrial remodeling and are associated with ischemic stroke, in patients without history of AF.
- To estimate the risk of ischemic stroke in patients with SCAF, the sophisticated prediction model reflecting the complex interplay between the duration SCAF, multiple predisposing risk factors, and atrial structural substrates is warranted.

감사합니다!

Q&A