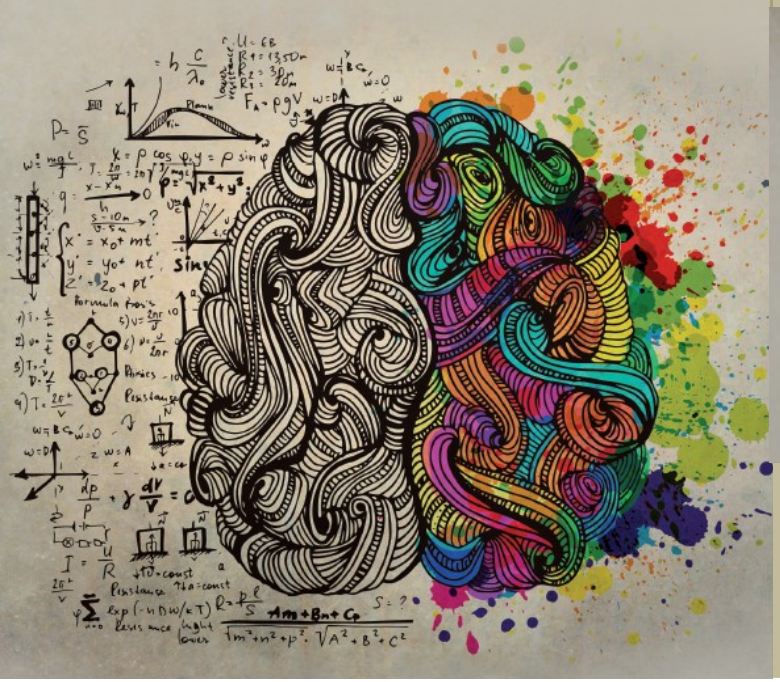
XXVI CONGRESSO NAZIONALE

Società Italiana Interdisciplinare NeuroVascolare



SINERGIE INTERDISCIPLINARI NEL PAZIENTE NEUROLOGICO CRITICO

Lecce, 1-2 dicembre 2017

Protocolli operativi per la gestione dell'ictus criptogenetico

Fabio Bandini
S.C. Neurologia
Ospedale San Paolo - Savona

Asl2
Sistema Sanitario Regione Liguria

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Stroke. 1993;24:35-41

American Heart Association | American Stroke Association

Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment.

H P Adams, Jr, B H Bendixen, L J Kappelle, J Biller, B B Love, D L Gordon and E E Marsh, 3rd

TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

An Evidence-Based Causative Classification System for Acute Ischemic Stroke

Hakan Ay, MD,[1,2] Karen L. Furie, MD,[2] Aneesh Singhal, MD,[2] Wade S. Smith, MD, PhD,[3] A. Gregory Sorensen, MD,[1] and Walter J. Koroshetz, MD[2]

Table 1. Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) Classification Criteria to Determine Causative Subtypes of Acute Ischemic Stroke

Stroke Mechanism	Level of Confidence	Criteria
Undetermined causes	Unknown (no "evident" or "possible" criteria for the causes (above)	Cryptogenic embolism: 1. Angiographic evidence of abrupt cutoff consistent with a blood clot within otherwise angiographically normal looking intracranial arteries, *or* 2. Imaging evidence of complete recanalization of previously occluded artery, *or* 3. Presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels[16,28] Other cryptogenic: those not fulfilling the criteria for cryptogenic embolism Incomplete evaluation: absence of diagnostic tests that, up to the examiner's judgment, would have been essential to uncover the underlying cause
	Unclassified	The presence of more than one evident mechanism where there is either probable evidence for each or no probable evidence to be able to establish a single cause

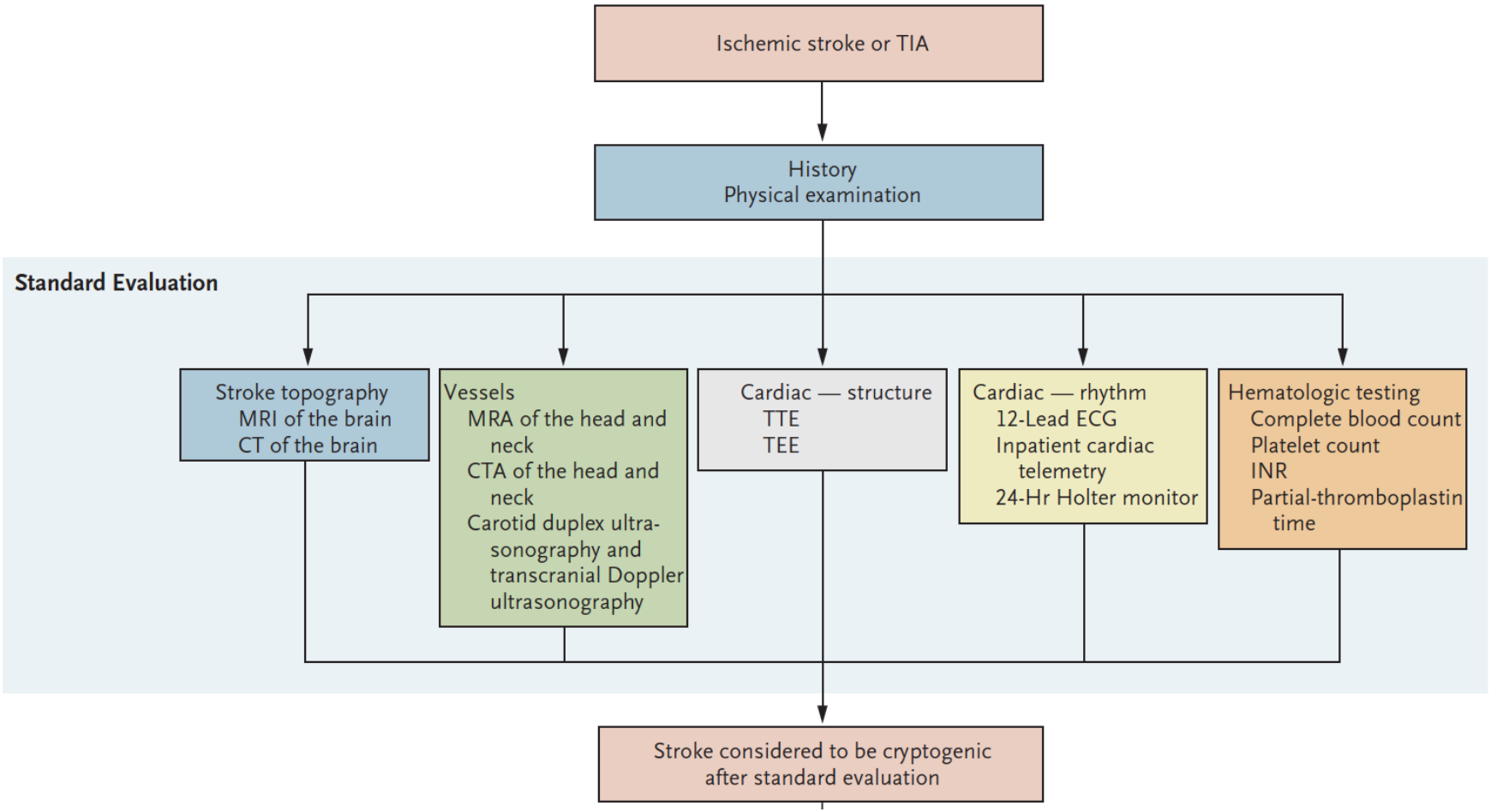
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Cryptogenic Stroke

Jeffrey L. Saver, M.D.



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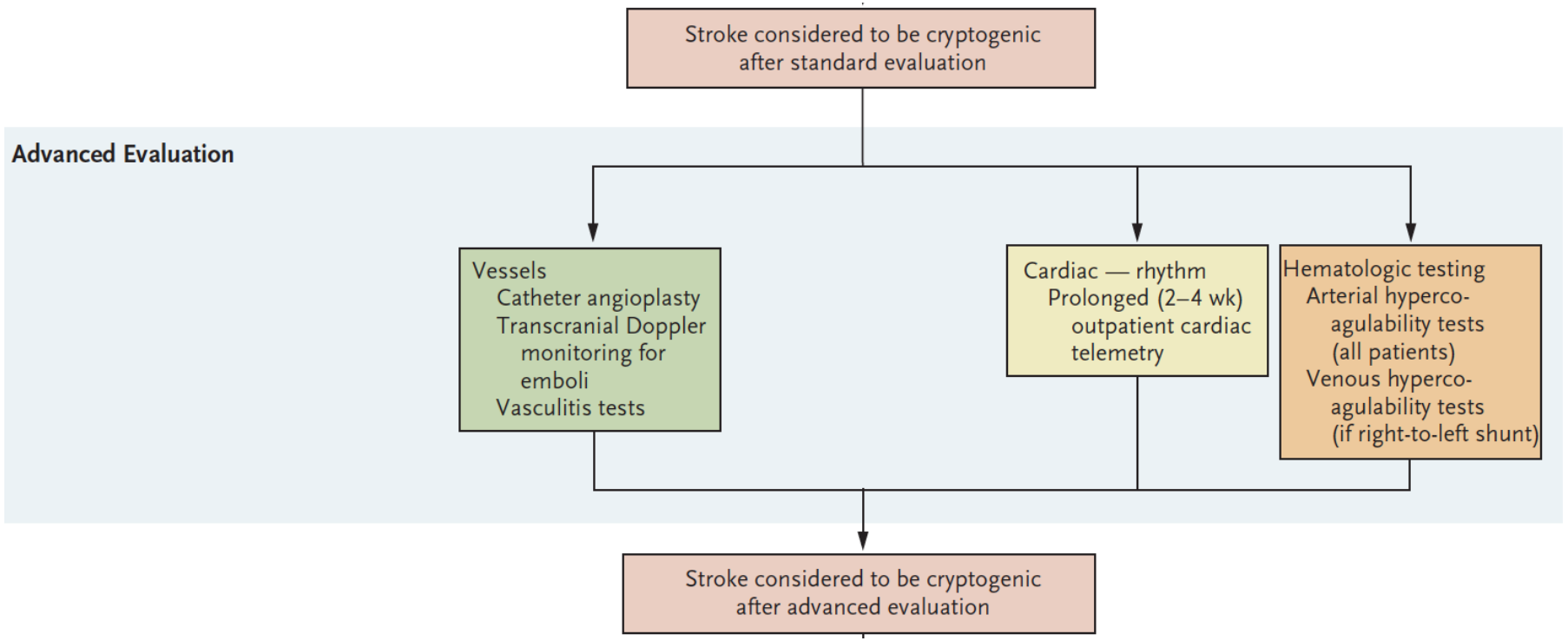

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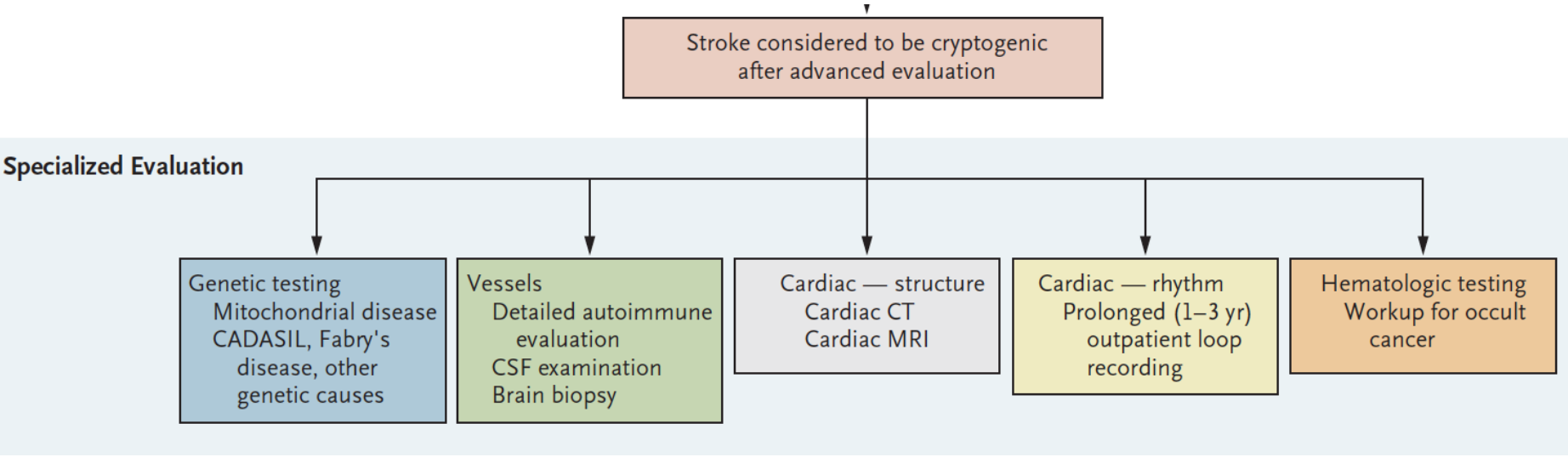


The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 374;21 NEJM.ORG MAY 26, 2016

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Cryptogenic Stroke

Jeffrey L. Saver, M.D.

KEY CLINICAL POINTS

CRYPTOGENIC STROKE

- One quarter of patients with ischemic stroke have no probable cause found after standard workup, including echocardiography, inpatient cardiac telemetry or 24-hour Holter monitoring, magnetic resonance imaging or computed tomographic (CT) imaging of topographic features of the infarct in the brain, and magnetic resonance or CT angiographic assessment of neck and brain arteries. Additional investigation identifies a likely mechanism in more than half these patients.
- Most cryptogenic ischemic strokes are embolic in origin, arising from proximal arterial sources, the heart, or venous sources (with right-to-left shunts).
- Investigation in patients with cryptogenic stroke typically includes evaluation for atherosclerotic and nonatherosclerotic arteriopathies, cardiac sources of embolism (structural and rhythm abnormalities), and disturbances of coagulation.
- Patent foramen ovale is found in up to half of young adults with cryptogenic stroke but is also found in one quarter of healthy persons.
- Occult, low-burden, paroxysmal atrial fibrillation is increasingly recognized as a source of cryptogenic stroke, especially in older patients.

Embolic strokes of undetermined source: the case for a new clinical construct

Lancet Neurol 2014; 13: 429–38

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Cryptogenic (of unknown cause) ischaemic strokes are now thought to comprise about 25% of all ischaemic strokes. Advances in imaging techniques and improved understanding of stroke pathophysiology have prompted a reassessment of cryptogenic stroke. There is persuasive evidence that most cryptogenic strokes are thromboembolic. The thrombus is thought to originate from any of several well established potential embolic sources, including minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. Accordingly, we propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, with a clear indication for anticoagulation. Because emboli consist mainly of thrombus, anticoagulants are likely to reduce recurrent brain ischaemia more effectively than are antiplatelet drugs. Randomised trials testing direct-acting oral anticoagulants for secondary prevention of embolic strokes of undetermined source are warranted.

Embolic strokes of undetermined source: the case for a new clinical construct

Lancet Neurol 2014; 13: 429–38

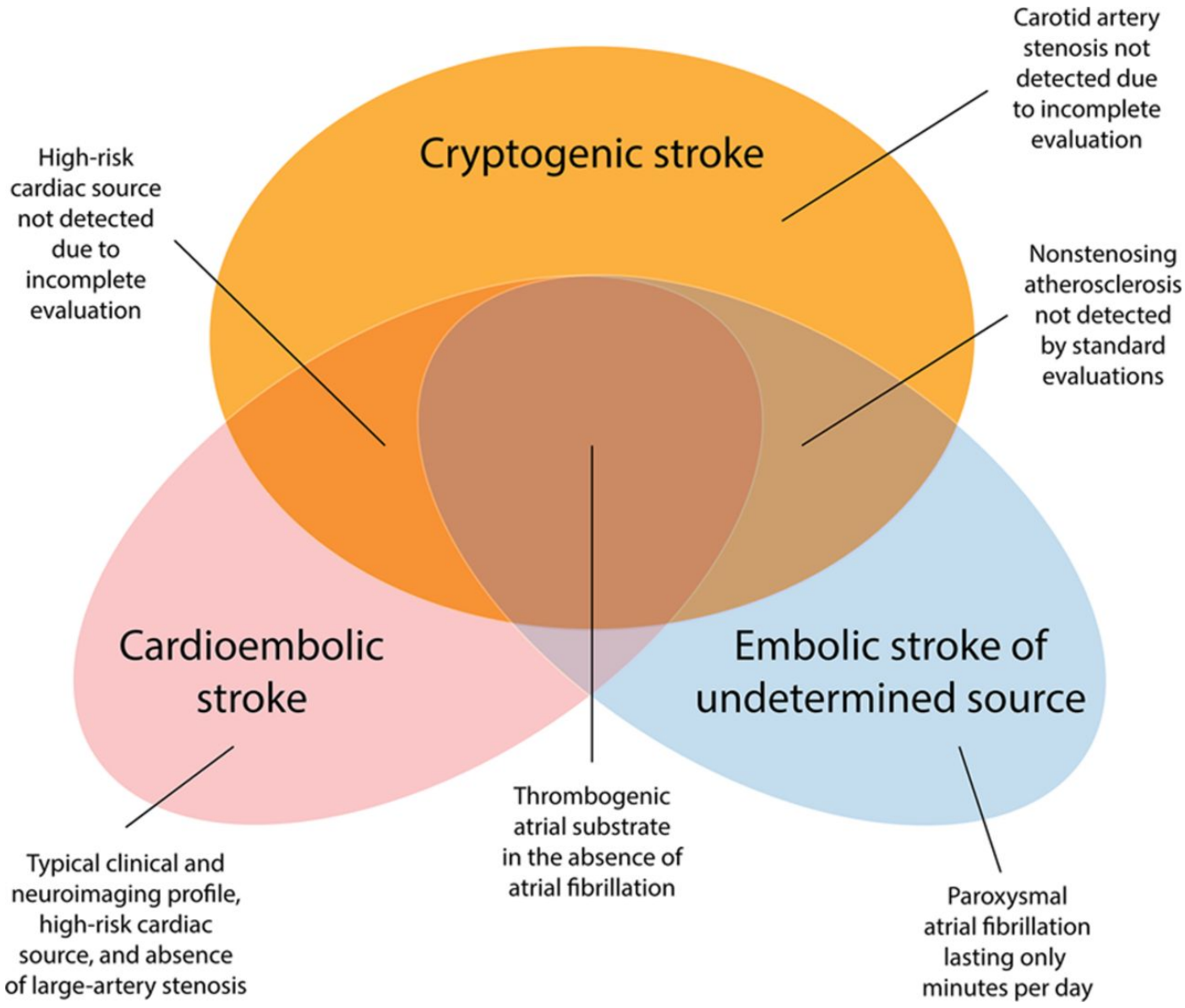
Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)


Cryptogenic stroke
Carotid artery stenosis not detected due to incomplete evaluation
High-risk cardiac source not detected due to incomplete evaluation
Nonstenosing atherosclerosis not detected by standard evaluations
Cardioembolic stroke
Embolic stroke of undetermined source
Typical clinical and neuroimaging profile, high-risk cardiac source, and absence of large-artery stenosis
Thrombogenic atrial substrate in the absence of atrial fibrillation
Paroxysmal atrial fibrillation lasting only minutes per day

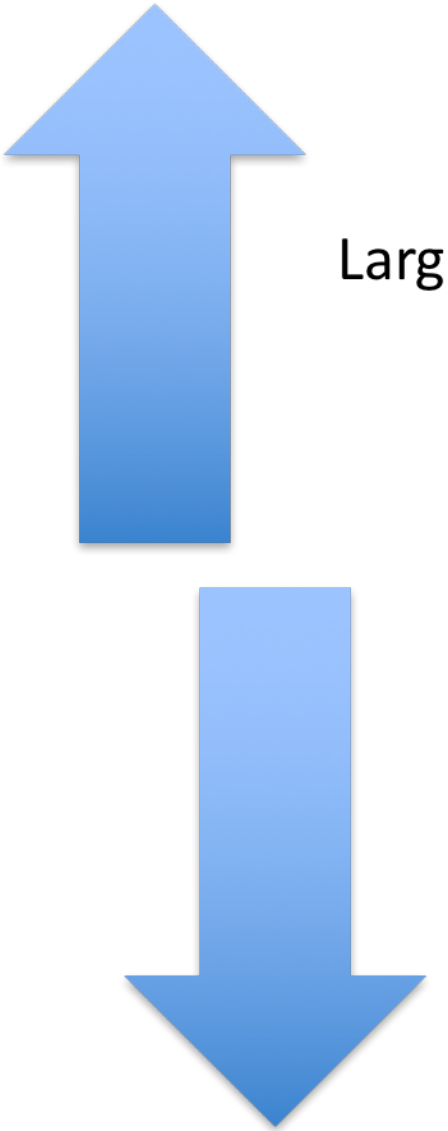
Cryptogenic stroke and Risk factors prevalence

- Substantially similar to patients with stroke of known causes

- Demographic factors: NOMASS (2002) younger patients (55% < 45yrs vs 42% > 45yrs). Not confirmed by other studies

- Hypertension: lower in cryptogenic stroke
- Diabetes and hyperlipemia: similar
- Smoking: inverse association

Cryptogenic stroke and risk of stroke recurrence



Large artery atherosclerosis

Cryptogenic Stroke

Small artery disease

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Stroke. 2016;47:2278-2285

Risk Stratification for Recurrence and Mortality in Embolic Stroke of Undetermined Source

George Ntaios, Konstantinos Vemmos, Gregory Y.H. Lip, Eleni Koroboki, Efstathios Manios, Anastasia Vemmou, Ana Rodríguez-Campello, Elisa Cuadrado-Godia, Eva Giralt-Steinhauer, Valentina Arnao, Valeria Caso, Maurizio Paciaroni, Exuperio Diez-Tejedor, Blanca Fuentes, Josefa Pérez Lucas, Antonio Arauz, Sebastian F. Ameriso, Maximiliano A. Hawkes, Lucía Pertierra, Maia Gómez-Schneider, Fabio Bandini, Beatriz Chavarria Cano, Ana Maria Iglesias Mohedano, Andrés García Pastor, Antonio Gil-Núñez, Jukka Putaala, Turgut Tatlisumak, Miguel A. Barboza, George Athanasakis, Konstantinos Makaritsis and Vasileios Papavasileiou

Background and Purpose—The risk of stroke recurrence in patients with Embolic Stroke of Undetermined Source (ESUS) is high, and the optimal antithrombotic strategy for secondary prevention is unclear. We investigated whether congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or transient ischemic attack (TIA; $CHADS_2$) and CHA_2DS_2-VASc scores can stratify the long-term risk of ischemic stroke/TIA recurrence and death in ESUS.

Methods—We pooled data sets of 11 stroke registries from Europe and America. ESUS was defined according to the Cryptogenic Stroke/ESUS International Working Group. Cox regression analyses were performed to investigate if prestroke $CHADS_2$ and congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category (CHA_2DS_2-VASc) scores were independently associated with the risk of ischemic stroke/TIA recurrence or death. The Kaplan–Meier product limit method was used to estimate the cumulative probability of ischemic stroke/TIA recurrence and death in different strata of the $CHADS_2$ and CHA_2DS_2-VASc scores.

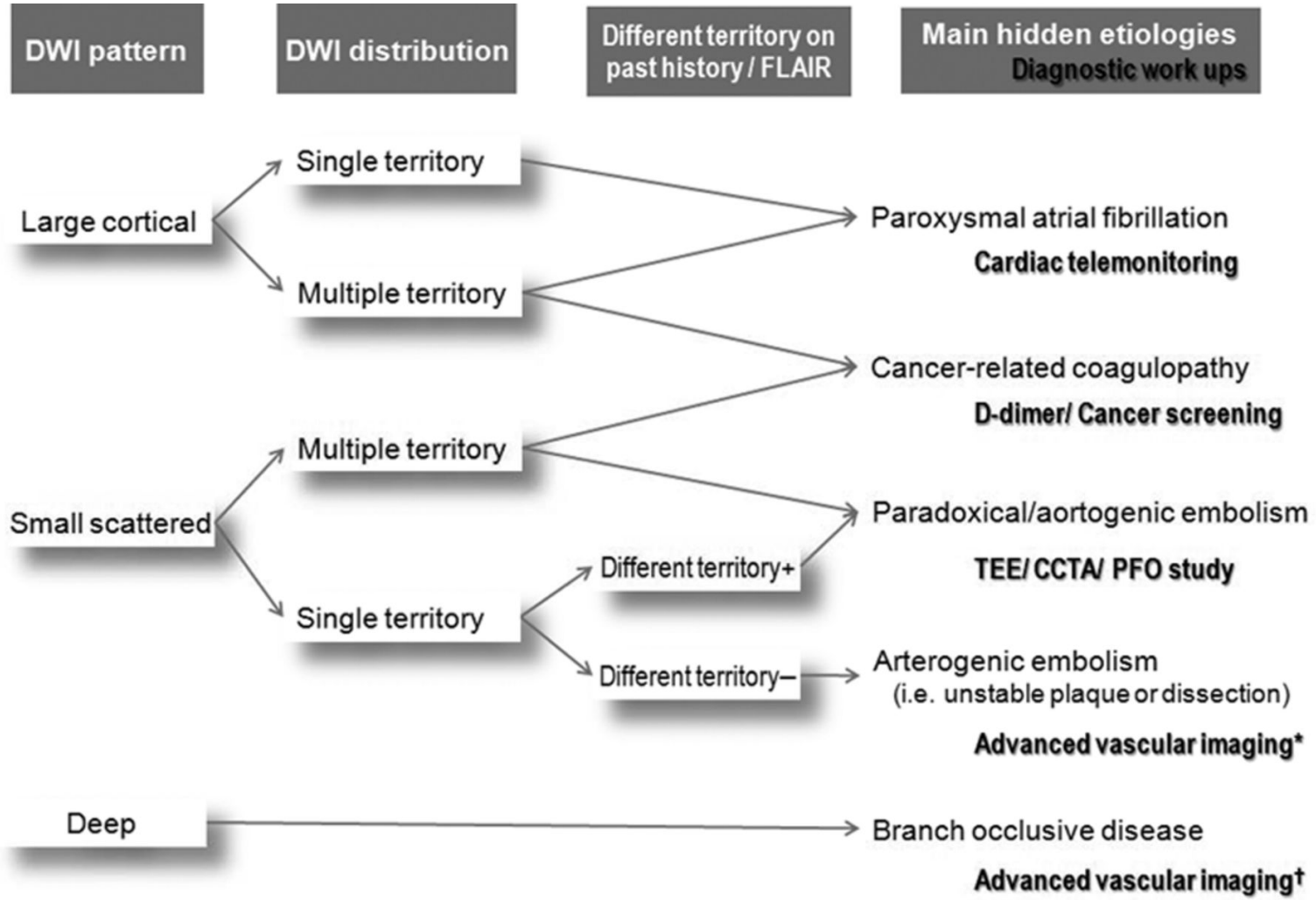
Results—One hundred fifty-nine (5.6% per year) ischemic stroke/TIA recurrences and 148 (5.2% per year) deaths occurred in 1095 patients (median age, 68 years) followed-up for a median of 31 months. Compared with $CHADS_2$ score 0, patients with $CHADS_2$ score 1 and $CHADS_2$ score >1 had higher risk of ischemic stroke/TIA recurrence (hazard ratio [HR], 2.38; 95% confidence interval [CI], 1.41–4.00 and HR, 2.72; 95% CI, 1.68–4.40, respectively) and death (HR, 3.58; 95% CI, 1.80–7.12, and HR, 5.45; 95% CI, 2.86–10.40, respectively). Compared with low-risk CHA_2DS_2-VASc score, patients with high-risk CHA_2DS_2-VASc score had higher risk of ischemic stroke/TIA recurrence (HR, 3.35; 95% CI, 1.94–5.80) and death (HR, 13.0; 95% CI, 4.7–35.4).

Conclusions—The risk of recurrent ischemic stroke/TIA and death in ESUS is reliably stratified by $CHADS_2$ and CHA_2DS_2-VASc scores. Compared with the low-risk group, patients in the high-risk CHA_2DS_2-VASc group have much higher risk of ischemic stroke recurrence/TIA and death, approximately 3-fold and 13-fold, respectively. (***Stroke*. 2016;47:2278-2285.**

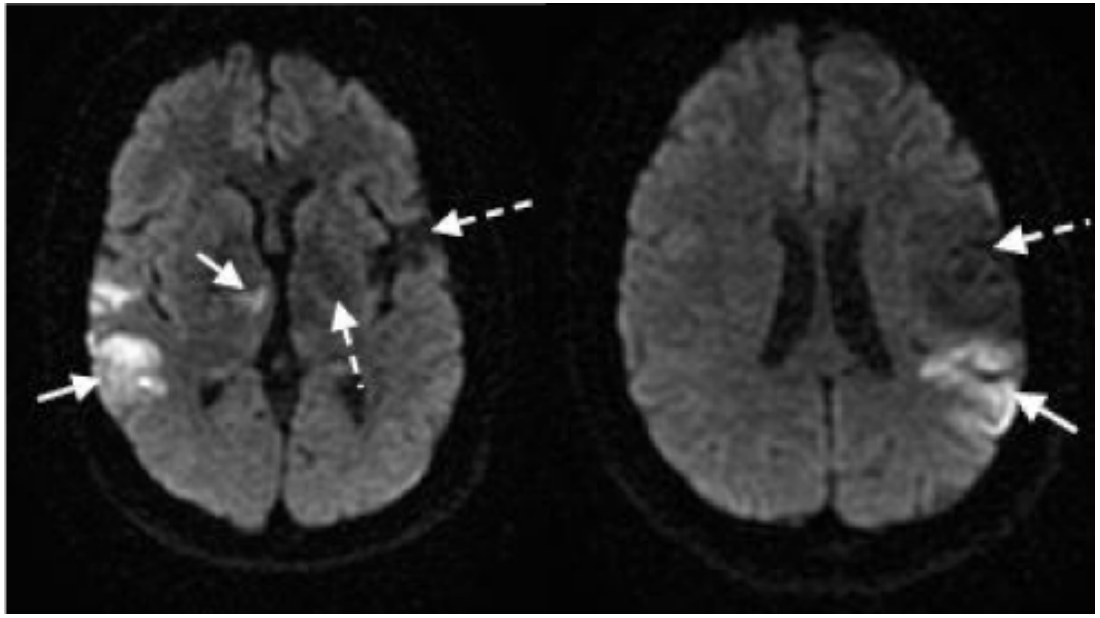
Diagnostic workup

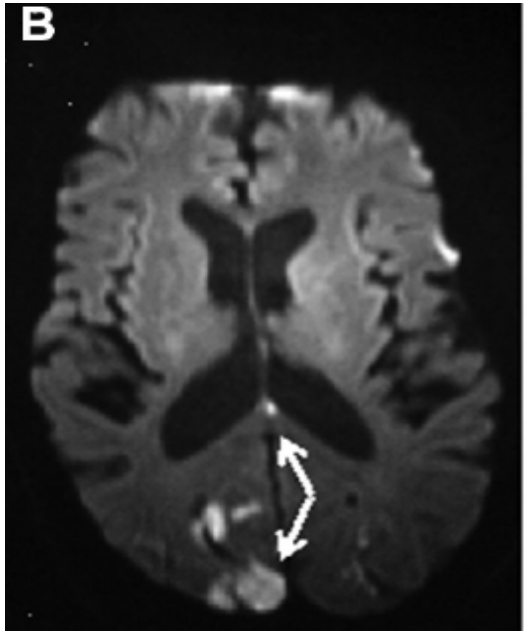
- Neuroimaging
- Vascular Imaging
- Cardiac Evaluation
  - Cardiac Monitoring
  - Cardiac Imaging
- Hypercoagulable Testing
- Evaluation for Malignancy

Diagnostic workup - Neuroimaging



Bang et al. Stroke. 2014

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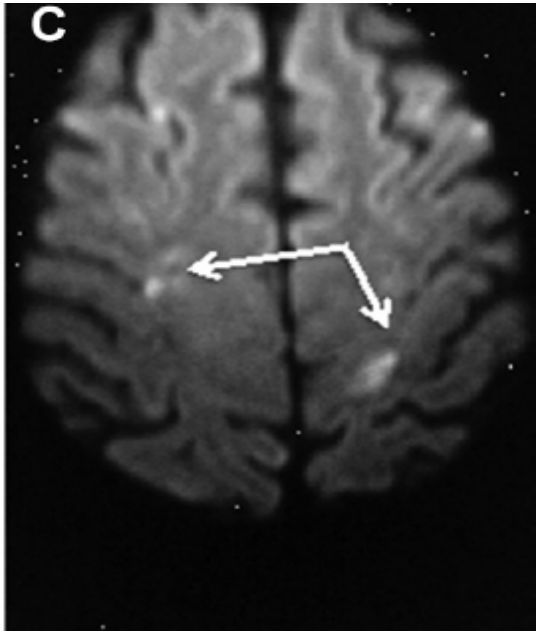
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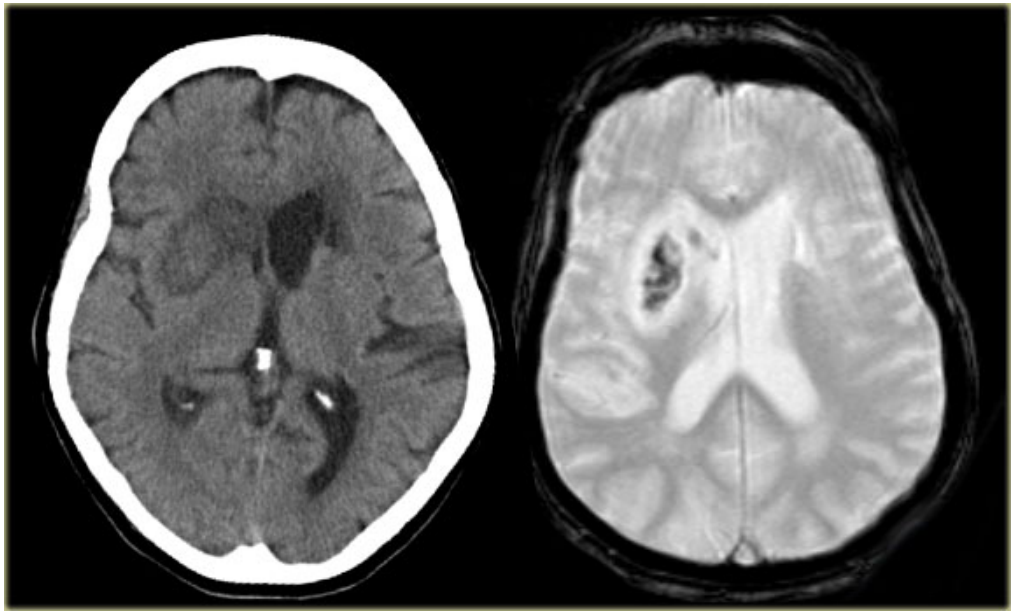

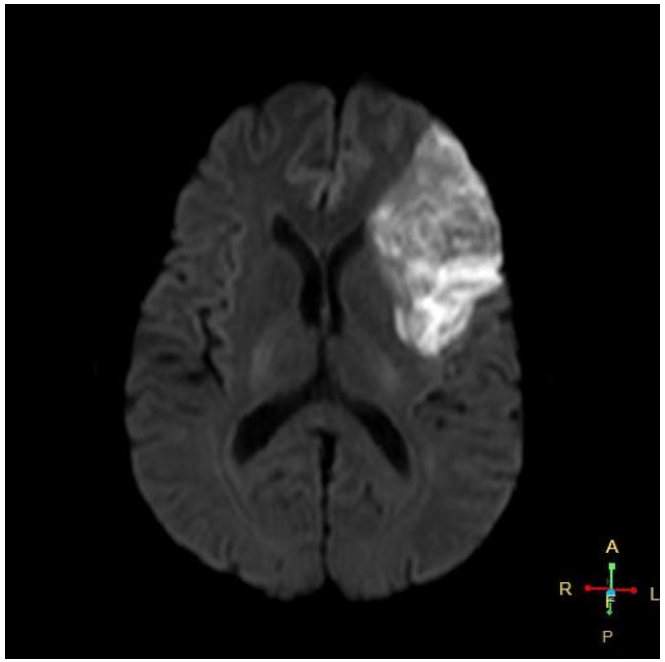
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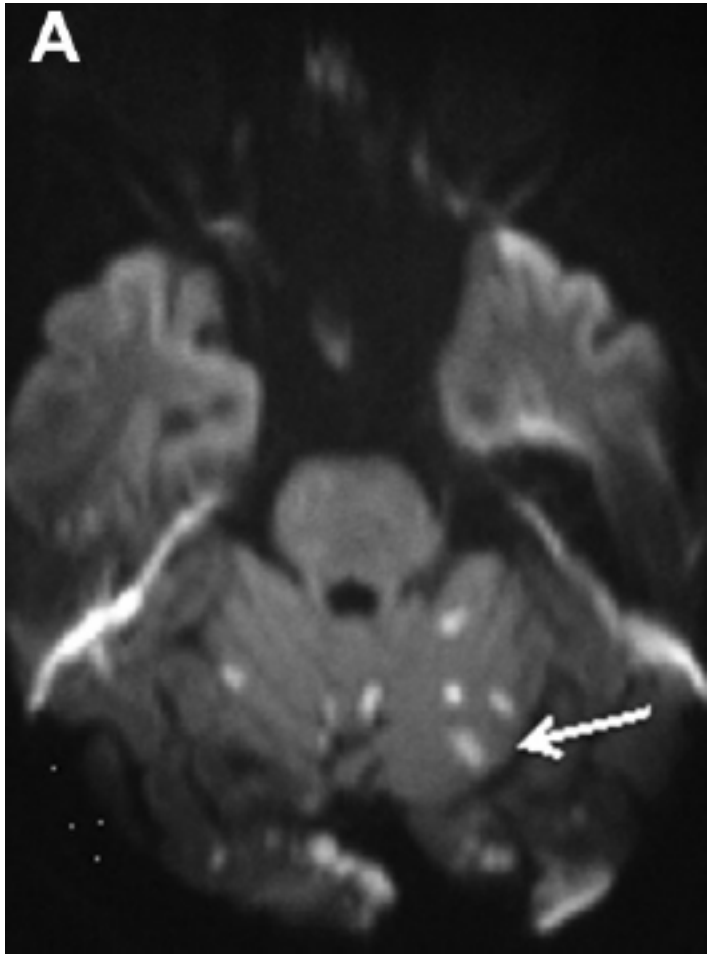
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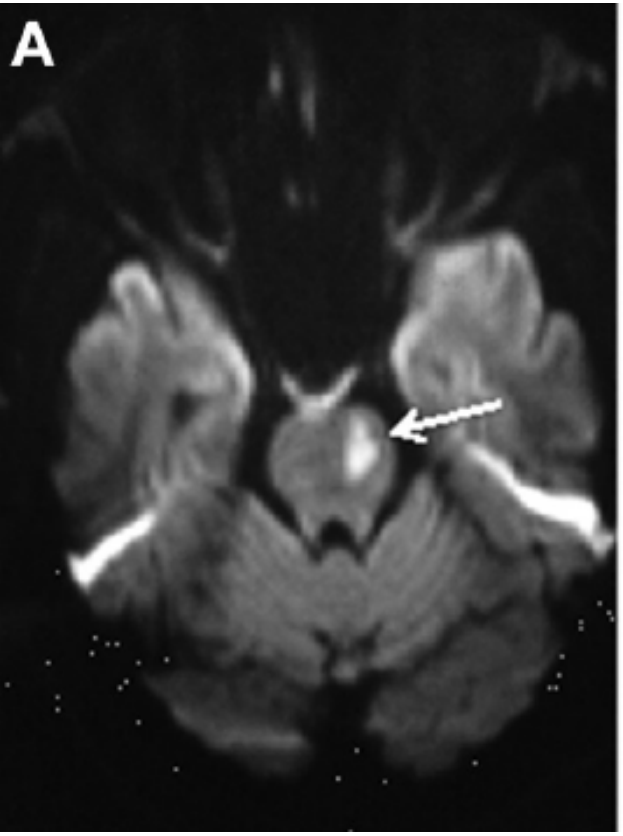
Diagnostic workup – Vascular Imaging

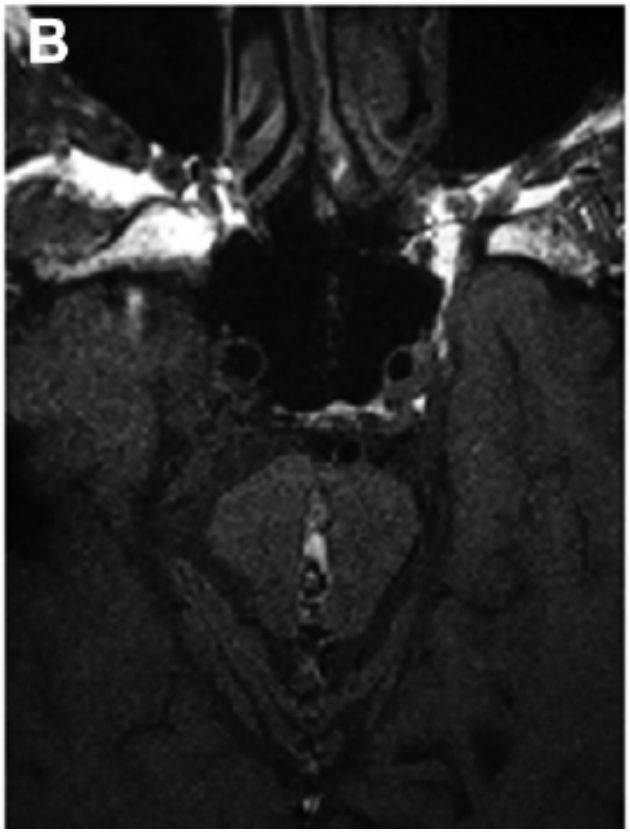
	Carotid Stenosis 70-99%				
	Angiography	**Angio-CT**	**MRA**	**US**	**TC-US**
Sensibility		76-85%	90%	90%	-
Specificity		93%	90%	80%	-

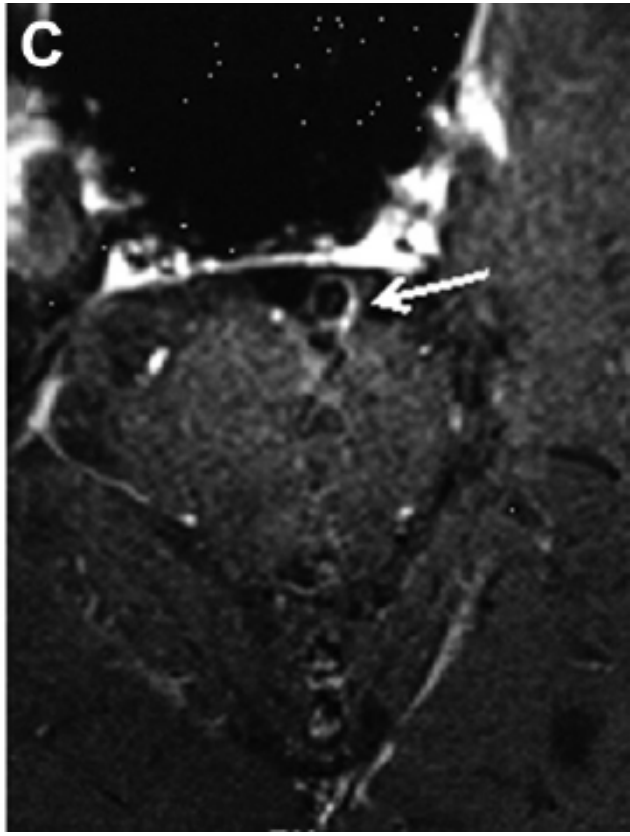
	Intracranial artery stenosis				
	Angiography	**Angio-CT**	**MRA**	**US**	**TC-US**
Sensibility		78-100%	60-90%	-	Limited data
Specificity		82-100%	90%	-	Limited data

Koelemay et al., Stroke 2004; Wardlaw et al., Lancet 2006; Latchaw et al., Stroke 2009; Debrey et al., Stroke 2008

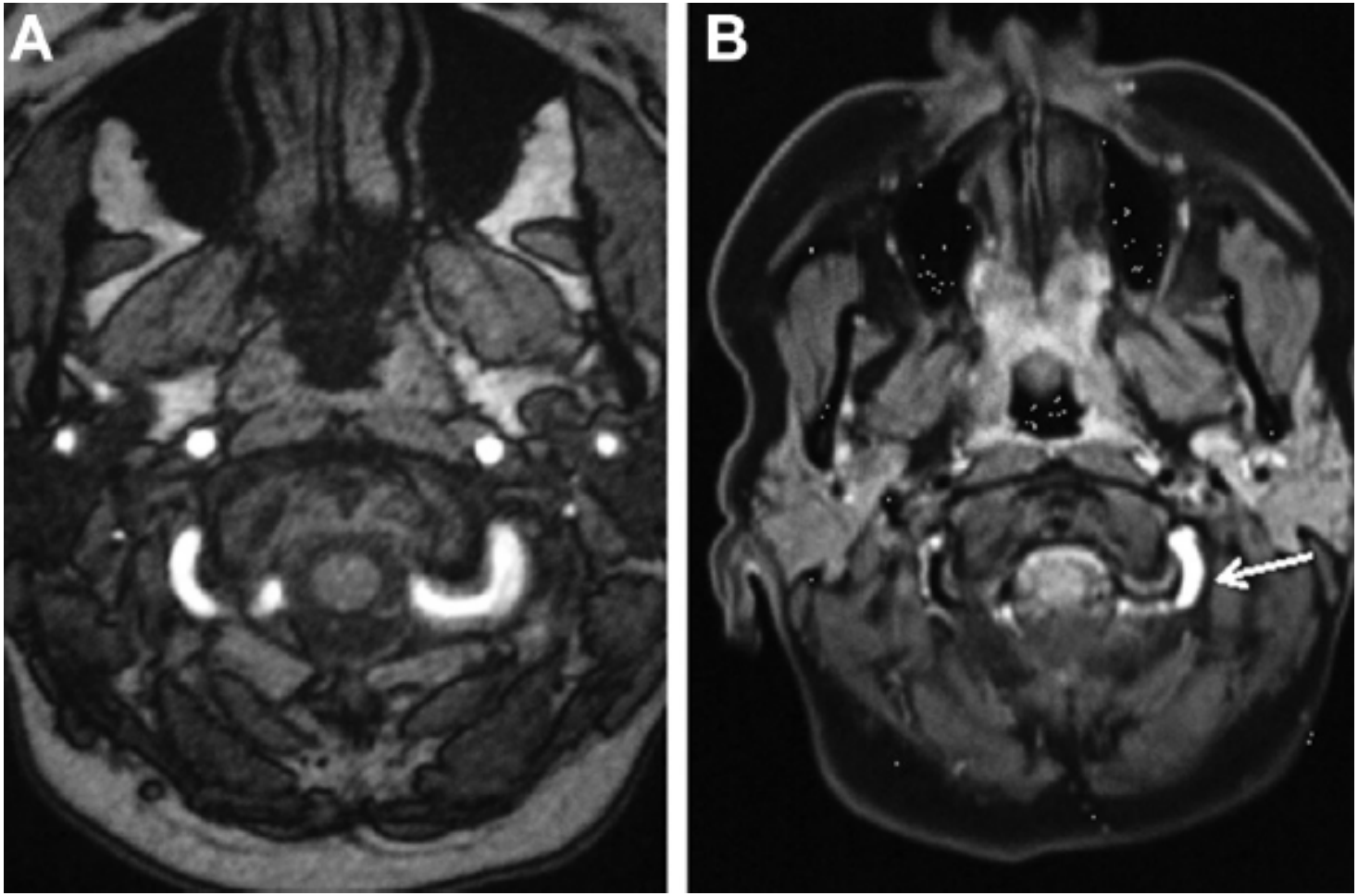
MRA







MRA



Diagnostic workup – Cardiac Monitoring

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

Seek and Ye Shall Find Fibrillations
David Z. Rose, Daniel Falcao and Ryan C. Martin

Stroke. 2016;47:1969-1971; originally published online July 12, 2016;

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

Underutilization of Ambulatory ECG Monitoring After Stroke and Transient Ischemic Attack: Missed Opportunities for Atrial Fibrillation Detection
Jodi D. Edwards, Moira K. Kapral, Jiming Fang, Gustavo Saposnik and David J. Gladstone
Investigators of the Registry of the Canadian Stroke Network

Medscape EDUCATION

theheart.org from WebMD

Hidden in Plain Sight

Connecting the Dots Between Cryptogenic Stroke and Atrial Fibrillation

Moderator

Elaine M. Hylek, MD, MPH

Professor of Medicine
Associate Director, Education and Training Division Clinical and Translational Science Institute
Boston University
Boston, Massachusetts

Panelist

Philip B. Gorelick, MD, MPH

Professor of Translational Science and Molecular Medicine
Michigan State University, College of Human Medicine
Medical Director, Mercy Health Hauenstein Neurosciences
Grand Rapids, Michigan

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

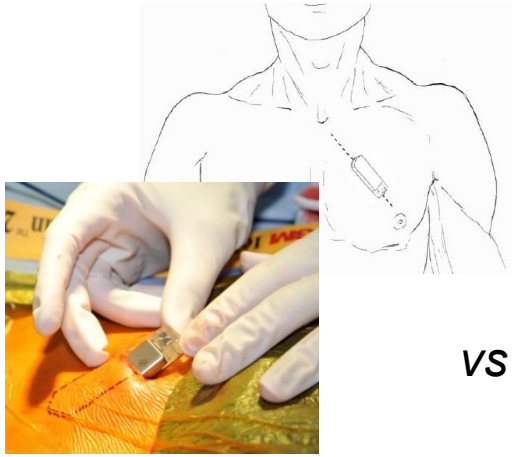
Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and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

RESULTS

By 6 months, atrial fibrillation had been detected in 8.9% of patients in the ICM group (19 patients) versus 1.4% of patients in the control group (3 patients) (hazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; P<0.001). By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ICM group (29 patients) versus 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; 95% CI, 2.6 to 20.8; P<0.001).

CONCLUSIONS

ECG monitoring with an ICM was superior to conventional follow-up for detecting atrial fibrillation after cryptogenic stroke. (Funded by Medtronic; CRYSTAL AF ClinicalTrials.gov number, NCT00924638.)



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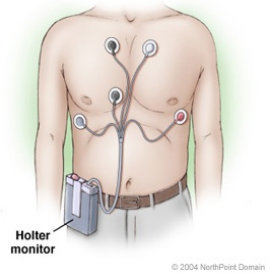


REVEAL® XT, Medtronic *vs* **standard follow-up**

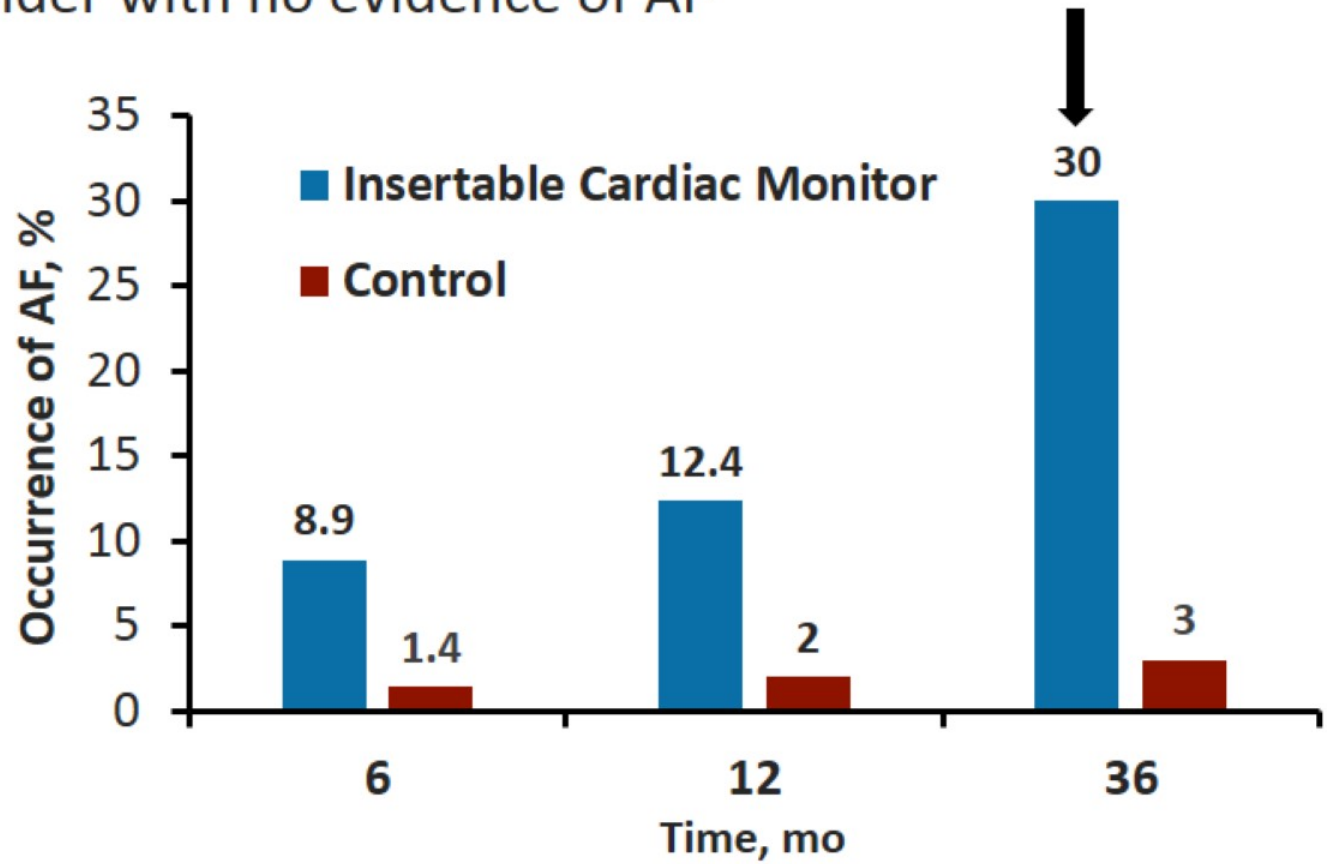
FA (%) 6 mesi	8.9	vs	1.4
12 mesi	12.4	vs	2

CRYSTAL-AF

CRYSTAL AF

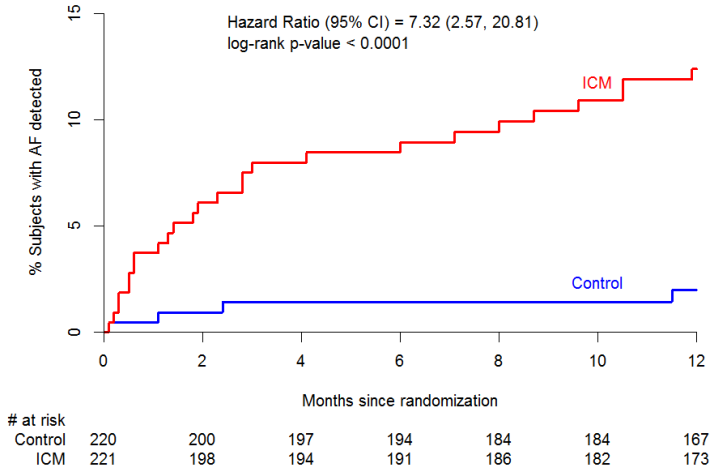
Results at 36 Months

- N = 441 patients with cryptogenic stroke aged 40 years or older with no evidence of AF

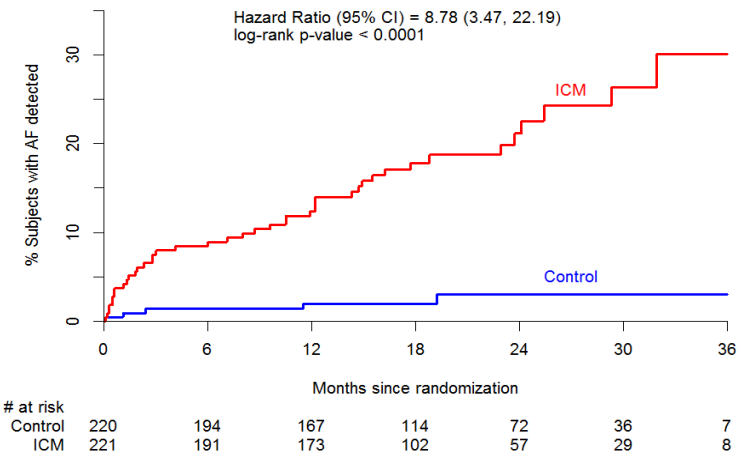


Brachmann J, et al. *Circ Arrhthm Electrophysiol*. 2016;9:e003333.

Detection of AF at 12 Months



Detection of AAF at 36 months



CRYSTAL-AF

75% were aymptomatic

EMBRACE

The NEW ENGLAND JOURNAL of MEDICINE

Detection of Atrial Fibrillation in the Two Monitoring Groups

Table 2. Detection of Atrial Fibrillation in the Two Monitoring Groups.

Outcome	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	number/total number (percent)		*percentage points*		
Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days†	45/280 (16.1)	9/277 (3.2)	12.9 (8.0–17.6)	<0.001	8 (5.7–12.5)
Secondary outcomes‡					
Detection of atrial fibrillation with duration ≥30 sec	44/284 (15.5)	7/277 (2.5)	13.0 (8.4–17.6)	<0.001	8 (5.7–11.9)
Detection of atrial fibrillation with duration ≥2.5 min	28/284 (9.9)	7/277 (2.5)	7.4 (3.4–11.3)	<0.001	14 (8.8–29.4)
Detection of atrial fibrillation of any duration	56/284 (19.7)	13/277 (4.7)	15.0 (9.8–20.3)	<0.001	7 (4.9–10.2)

* The number of patients needed to screen was defined as the number of patients who would need to be screened in order to detect atrial fibrillation in one additional patient (with a 30-day monitoring strategy vs. repeat 24-hour Holter monitoring).

† The primary analysis included all the patients who underwent randomization for whom outcome data were available (i.e., patients who underwent any amount of cardiac monitoring or 90-day follow-up in whom the status of atrial fibrillation could be determined). In the primary analysis, atrial fibrillation was detected either clinically or by means of study monitoring.

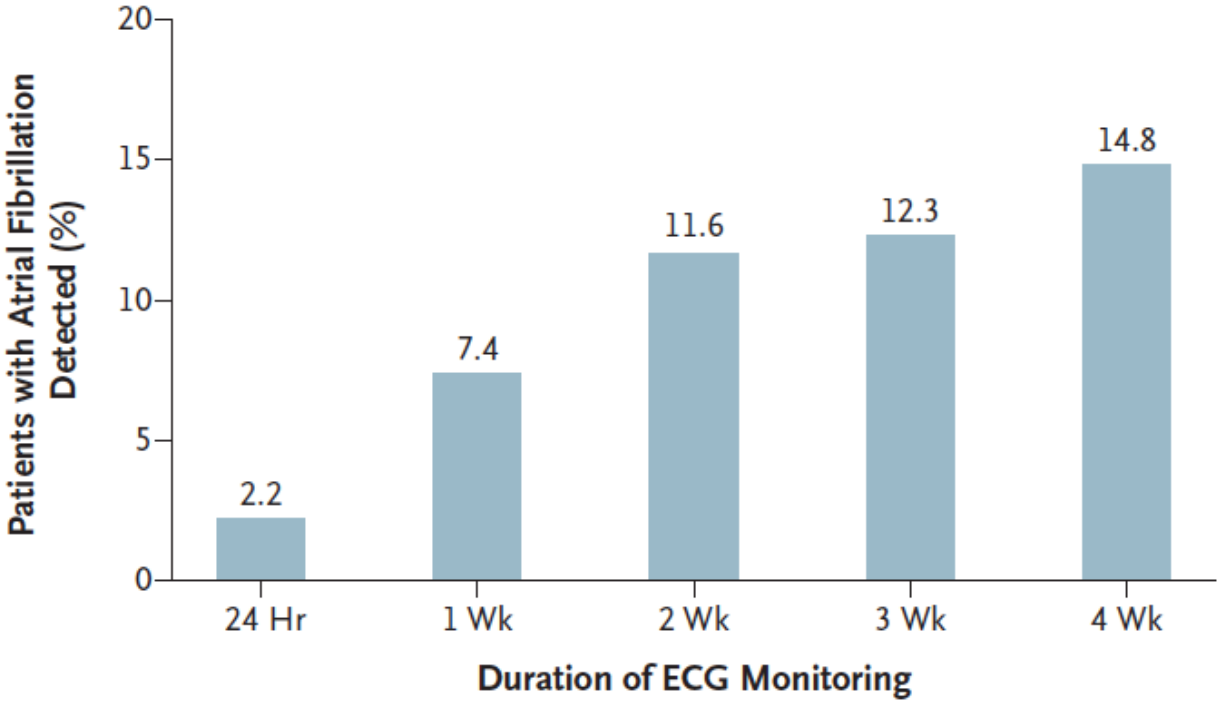
‡ The secondary analyses included all the patients who underwent randomization and any amount of cardiac monitoring. The detection of atrial fibrillation in the secondary analyses was by means of the study monitors.

Gladstone DJ et al. N Engl J Med 2014;370:2467-2477

EMBRACE

Results

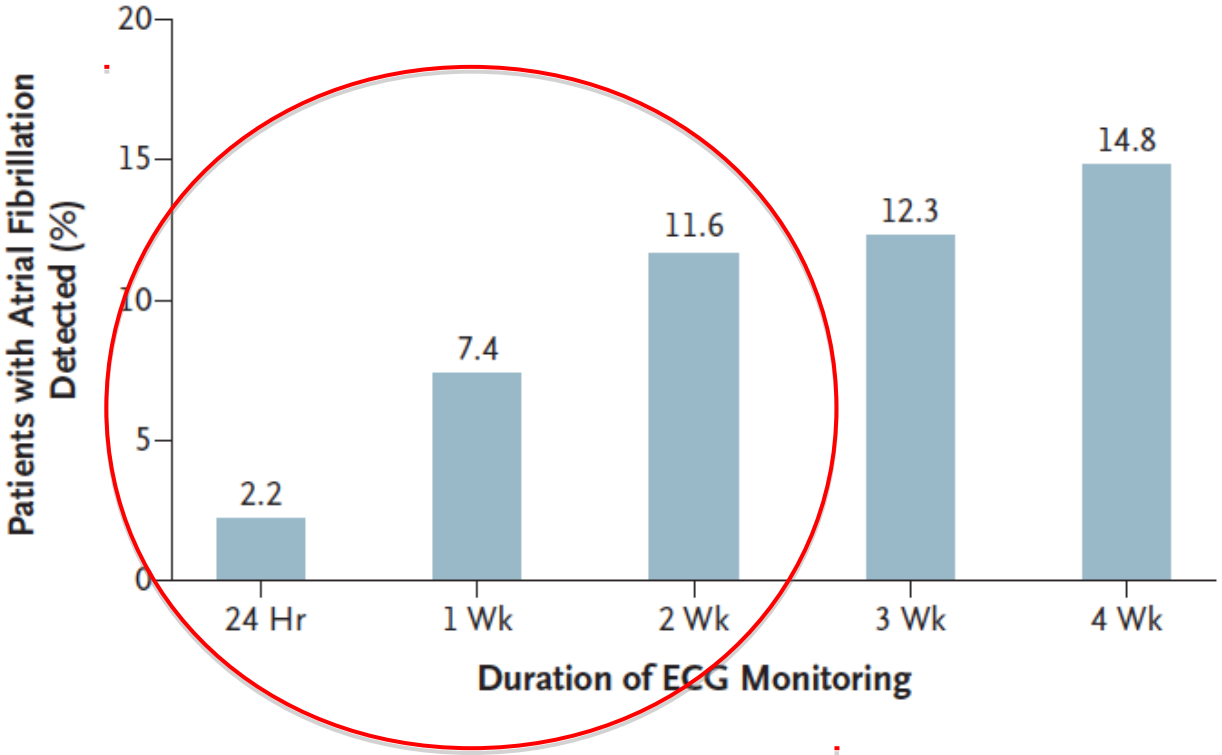
- N = 572 patients with cryptogenic stroke aged 55 or older with no evidence of AF



Gladstone DJ et al. N Engl J Med 2014;370:2467-2477

EMBRACE TIMING

- N = 572 patients with cryptogenic stroke aged 55 or older with no evidence of AF



Gladstone DJ et al. N Engl J Med 2014;370:2467-2477

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
(*Stroke*. 2016;47:2380-2385.
American Heart Association | American Stroke Association

Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke

Jean Hai Ein Yong, Kednapa Thavorn, Jeffrey S. Hoch, Muhammad Mamdani, Kevin E. Thorpe, Paul Dorian, Mike Sharma, Andreas Laupacis and David J. Gladstone
on behalf of the EMBRACE Steering Committee

Background and Purpose—Prolonged ambulatory ECG monitoring after cryptogenic stroke improves detection of covert atrial fibrillation, but its long-term cost-effectiveness is uncertain.

Methods—We estimated the cost-effectiveness of noninvasive ECG monitoring in patients aged ≥55 years after a recent cryptogenic stroke and negative 24-hour ECG. A Markov model used observed rates of atrial fibrillation detection and anticoagulation from a randomized controlled trial (EMBRACE) and the published literature to predict lifetime costs and effectiveness (ischemic strokes, hemorrhages, life-years, and quality-adjusted life-years [QALYs]) for 30-day ECG (primary analysis) and 7-day or 14-day ECG (secondary analysis), when compared with a repeat 24-hour ECG.

Results—Prolonged ECG monitoring (7, 14, or 30 days) was predicted to prevent more ischemic strokes, decrease mortality, and improve QALYs. If anticoagulation reduced stroke risk by 50%, 30-day ECG (at a cost of USD $447) would be highly cost-effective ($2000 per QALY gained) for patients with a 4.5% annual ischemic stroke recurrence risk. Cost-effectiveness was sensitive to stroke recurrence risk and anticoagulant effectiveness, which remain uncertain, especially at higher costs of monitoring. Shorter duration (7 or 14 days) monitoring was cost saving and more effective than an additional 24-hour ECG; its cost-effectiveness was less sensitive to changes in ischemic stroke risk and treatment effect.

Conclusions—After a cryptogenic stroke, 30-day ECG monitoring is likely cost-effective for preventing recurrent strokes; 14-day monitoring is an attractive value alternative, especially for lower risk patients. These results strengthen emerging recommendations for prolonged ECG monitoring in secondary stroke prevention. Cost-effectiveness in practice will

Research

International Journal of Stroke
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Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke

Alex Diamantopoulos[1], Laura M. Sawyer[1], Gregory YH Lip[2,3,4], Klaus K Witte[5], Matthew R Reynolds[6], Laurent Fauchier[7], Vincent Thijs[8], Ben Brown[9], Maria E Quiroz Angulo[10] and Hans-Christoph Diener[11]

Abstract

Background and aims: Documentation of atrial fibrillation is required to initiate oral anticoagulation therapy for recurrent stroke prevention. Atrial fibrillation often goes undetected with traditional electrocardiogram monitoring techniques. We evaluated whether atrial fibrillation detection using continuous long-term monitoring with an insertable cardiac monitor is cost-effective for preventing recurrent stroke in patients with cryptogenic stroke, in comparison to the standard of care.

Methods: A lifetime Markov model was developed to estimate the cost-effectiveness of insertable cardiac monitors from a UK National Health Service perspective using data from the randomized CRYSTAL-AF trial and other published literature. We also conducted scenario analyses ($CHADS_2$ score) and probabilistic sensitivity analyses. All costs and benefits were discounted at 3.5%.

Results: Monitoring cryptogenic stroke patients with an insertable cardiac monitor was associated with fewer recurrent strokes and increased quality-adjusted life years compared to the standard of care (7.37 vs 7.22). Stroke-related costs were reduced in insertable cardiac monitor patients, but overall costs remained higher than the standard of care (£19,631 vs £17,045). The incremental cost-effectiveness ratio was £17,175 per quality-adjusted life years gained, compared to standard of care in the base-case scenario, which is below established quality-adjusted life years willingness-to-pay thresholds. When warfarin replaced non-vitamin-K oral anticoagulants as the main anticoagulation therapy, the incremental cost-effectiveness ratio was £13,296 per quality-adjusted life years gained.

Conclusion: Insertable cardiac monitors are a cost-effective diagnostic tool for the prevention of recurrent stroke in patients with cryptogenic stroke. The cost-effectiveness results have relevance for the UK and across value-based healthcare systems that assess costs relative to outcomes.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

(*Stroke*. 2014;45:2160-2236.)

American Heart Association | American Stroke Association

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

AF Recommendations

1. For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*. (New recommendation)

Beyond AF
Atrial cardiopathy

HHS Public Access
Author manuscript
Future Cardiol. Author manuscript; available in PMC 2016 May 16.

Atrial Cardiopathy: A Broadened Concept of Left Atrial Thromboembolism Beyond Atrial Fibrillation

Hooman Kamel, MD[1], **Peter M. Okin, MD**[2], **W. T. Longstreth Jr., MD, MPH**[3], **Mitchell S.V. Elkind, MD, MS**[4], and **Elsayed Z. Soliman, MD, MSc, MS**[5]

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Future Cardiol. Author manuscript; available in PMC 2016 May 16.

Atrial Cardiopathy: A Broadened Concept of Left Atrial Thromboembolism Beyond Atrial Fibrillation

Hooman Kamel, MD[1], **Peter M. Okin, MD**[2], **W. T. Longstreth Jr., MD, MPH**[3], **Mitchell S.V. Elkind, MD, MS**[4], and **Elsayed Z. Soliman, MD, MSc, MS**[5]

Atrial fibrillation (AF) has long been associated with a heightened risk of ischemic stroke and systemic thromboembolism, but recent data require a re-evaluation of our understanding of the nature of this relationship. New findings about the temporal connection between AF and stroke, alongside evidence linking markers of left atrial abnormalities with stroke in the absence of apparent AF, suggest that left atrial thromboembolism may occur even without AF. These observations undermine the hypothesis that the dysrhythmia that defines AF is necessary and sufficient to cause thromboembolism. In this commentary, we instead suggest that the substrate for thromboembolism may often be the anatomic and physiological atrial derangements associated with AF. Therefore, our understanding of cardioembolic stroke may be more complete if we shift our representation of its origin from AF to the concept of atrial cardiopathy.

Stroke
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Left Atrial Enlargement and Stroke Recurrence: The Northern Manhattan Stroke Study

Shadi Yaghi, Yeseon P. Moon, Consuelo Mora-McLaughlin, Joshua Z. Willey, Ken Cheung, Marco R. Di Tullio, Shunichi Homma, Hooman Kamel, Ralph L. Sacco and Mitchell S.V. Elkind

Stroke. 2015;46:1488-1493; originally published online April 23, 2015;

Background and Purpose—Although left atrial enlargement (LAE) increases incident stroke risk, the association with recurrent stroke is less clear. Our aim was to determine the association of LAE with recurrent stroke most likely related to embolism (cryptogenic and cardioembolic) and all ischemic stroke recurrences.

Methods—We followed 655 first ischemic stroke patients in the Northern Manhattan Stroke Study for ≤5 years. LA size from 2D echocardiography was categorized as normal LAE (52.7%), mild LAE (31.6%), and moderate–severe LAE (15.7%). We used Cox proportional hazard models to calculate the hazard ratios and 95% confidence intervals for the association of LA size and LAE with recurrent cryptogenic/cardioembolic and total recurrent ischemic stroke.

Results—LA size was available in 529 (81%) patients. Mean age at enrollment was 69±13 years; 45.8% were male, 54.0% Hispanic, and 18.5% had atrial fibrillation. Over a median of 4 years, there were 65 recurrent ischemic strokes (29 were cardioembolic or cryptogenic). In multivariable models adjusted for confounders, including atrial fibrillation and heart failure, moderate–severe LAE compared with normal LA size was associated with greater risk of recurrent cardioembolic/cryptogenic stroke (adjusted hazard ratio 2.83, 95% confidence interval 1.03–7.81), but not total ischemic stroke (adjusted hazard ratio 1.06, 95% confidence interval, 0.48–2.30). Mild LAE was not associated with recurrent stroke.

Conclusion—Moderate to severe LAE was an independent marker of recurrent cardioembolic or cryptogenic stroke in a multiethnic cohort of ischemic stroke patients. Further research is needed to determine whether anticoagulant use may reduce risk of recurrence in ischemic stroke patients with moderate to severe LAE. (***Stroke*. 2015;46:1488-1493. DOI: 10.1161/STROKEAHA.115.008711.**)

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Electrocardiographic Left Atrial Abnormality and Risk of Stroke: Northern Manhattan Study

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

Background and Purpose—Electrocardiographic left atrial abnormality has been associated with stroke independently of atrial fibrillation (AF), suggesting that atrial thromboembolism may occur in the absence of AF. If true, we would expect an association with cryptogenic or cardioembolic stroke rather than noncardioembolic stroke.

Methods—We conducted a case-cohort analysis in the Northern Manhattan Study, a prospective cohort study of stroke risk factors. P-wave terminal force in lead V_1 was manually measured from baseline ECGs of participants in sinus rhythm who subsequently had ischemic stroke (n=241) and a randomly selected subcohort without stroke (n=798). Weighted Cox proportional hazard models were used to examine the association between P-wave terminal force in lead V_1 and stroke etiologic subtypes while adjusting for baseline demographic characteristics, history of AF, heart failure, diabetes mellitus, hypertension, tobacco use, and lipid levels.

Results—Mean P-wave terminal force in lead V_1 was 4452 (±3368) μV*ms among stroke cases and 3934 (±2541) μV*ms in the subcohort. P-wave terminal force in lead V_1 was associated with ischemic stroke (adjusted hazard ratio per SD, 1.20; 95% confidence interval, 1.03–1.39) and the composite of cryptogenic or cardioembolic stroke (adjusted hazard ratio per SD, 1.31; 95% confidence interval, 1.08–1.58). There was no definite association with noncardioembolic stroke subtypes (adjusted hazard ratio per SD, 1.14; 95% confidence interval, 0.92–1.40). Results were similar after excluding participants with a history of AF at baseline or new AF during follow-up.

Conclusions—ECG-defined left atrial abnormality was associated with incident cryptogenic or cardioembolic stroke independently of the presence of AF, suggesting atrial thromboembolism may occur without recognized AF.

Stroke
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Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke: Results From the EMBRACE Trial

David J. Gladstone, Paul Dorian, Melanie Spring, Val Panzov, Muhammad Mamdani, Jeff S. Healey and Kevin E. Thorpe
for the EMBRACE Steering Committee and Investigators*

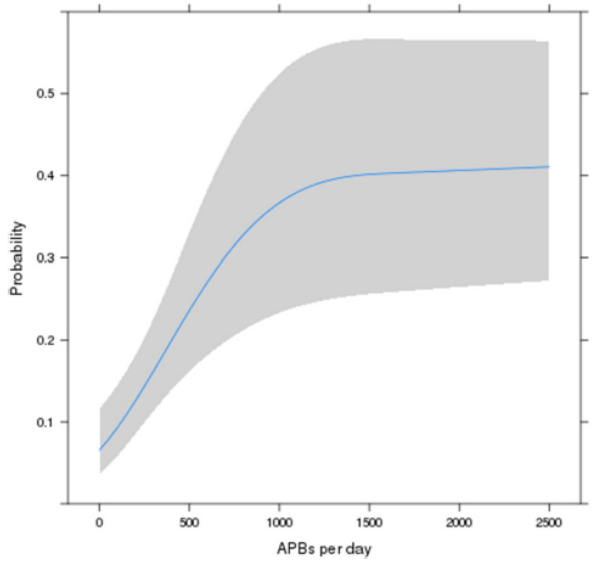
Stroke. 2015;46:936-941; originally published online February 19, 2015;

Background and Purpose—Many ischemic strokes or transient ischemic attacks are labeled cryptogenic but may have undetected atrial fibrillation (AF). We sought to identify those most likely to have subclinical AF.

Methods—We prospectively studied patients with cryptogenic stroke or transient ischemic attack aged ≥55 years in sinus rhythm, without known AF, enrolled in the intervention arm of the 30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial. Participants underwent baseline 24-hour Holter ECG poststroke; if AF was not detected, they were randomly assigned to 30-day ECG monitoring with an AF auto-detect external loop recorder. Multivariable logistic regression assessed the association between baseline variables (Holter-detected atrial premature beats [APBs], runs of atrial tachycardia, age, and left atrial enlargement) and subsequent AF detection.

Results—Among 237 participants, the median baseline Holter APB count/24 h was 629 (interquartile range, 142–1973) among those who subsequently had AF detected versus 45 (interquartile range, 14–250) in those without AF ($P<0.001$). APB count was the only significant predictor of AF detection by 30-day ECG ($P<0.0001$), and at 90 days ($P=0.0017$) and 2 years ($P=0.0027$). Compared with the 16% overall 90-day AF detection rate, the probability of AF increased from <9% among patients with <100 APBs/24 h to 9% to 24% in those with 100 to 499 APBs/24 h, 25% to 37% with 500 to 999 APBs/24 h, 37% to 40% with 1000 to 1499 APBs/24 h, and 40% beyond 1500 APBs/24 h.

Conclusions—Among older cryptogenic stroke or transient ischemic attack patients, the number of APBs on a routine 24-hour Holter ECG was a strong dose-dependent independent predictor of prevalent subclinical AF. Those with frequent APBs have a high probability of AF and represent ideal candidates for prolonged ECG monitoring for AF detection.



Cardiac Imaging

TTE

- Noninvasive
- Less expensive
- Widely available

TEE

- Better views
  - LA
  - LAA
  - Aortic arch
  - Cardiac shunts

Most cardiac sources identified by TEE (cardiac shunts and aortic plaques) do not necessarily lead to a change in management ***(Yaghi et al., Circulation 2017)***

Cardiac Imaging

Potential cardiac source	TTE	TEE
LA cavity thrombus	0	1 (1%)
LAA thrombus	1 (1%)	38 (16%)
PFO	3(1%)	12 (5%)
Atrial septal aneurysm	5 (2%)	8 (3%)
Aorthic plaques	1 (1%)	69 (30%)
Valvulopathies	16 (7%)	16 (7%)

Adapted from: De Bruijn et al., Stroke 2006

Cardiac Imaging

Stroke
Journal of the American Heart Association

Stroke. 2006;37:2531-2534

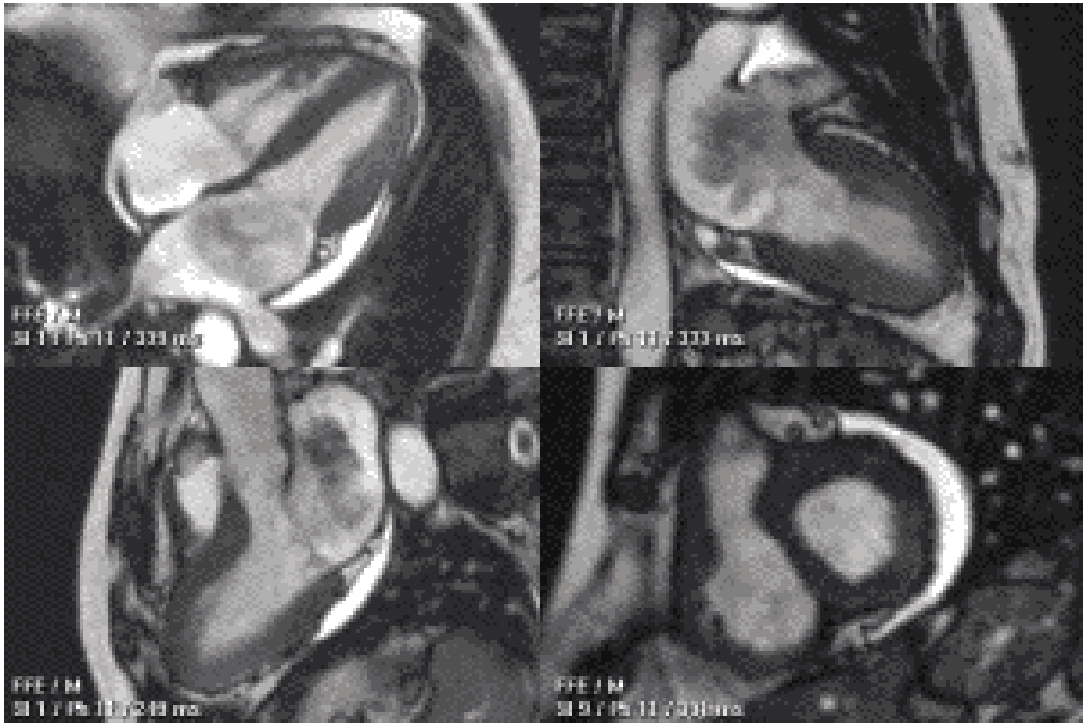
American Heart Association | American Stroke Association

Transesophageal Echocardiography Is Superior to Transthoracic Echocardiography in Management of Patients of Any Age With Transient Ischemic Attack or Stroke

Sebastiaan F.T.M. de Bruijn, Willem R.P. Agema, Gert Jan Lammers, Ernst E. van der Wall, Ron Wolterbeek, Eduard R. Holman, Edward L.E.M. Bollen and Jeroen J. Bax

	TTE(+) & TEE(+)	TTE(+) & TEE(−)	TTE(−) & TEE(+)	TTE(−) & TEE(−)
All 231 patients				
Cardiac source	16% (37/231)	0	39% (90/231)	45% (104/231)
Major risk factor	3% (8/231)	0	16% (38/231)	80% (185/231)
192 patients >45 years				
Cardiac source	18% (34/192)	0	42% (80/192)	41% (78/192)
Major risk factor	4% (8/192)	0	17% (33/192)	79% (151/192)
39 patients ≤45 years				
Cardiac source	8% (3/39)	0	26% (10/39)	67% (26/39)
Major risk factor	0	0	13% (5/39)	87% (34/39)

Cardiac MRI



Gold standard noninvasive test for several cardiovascular parameters (ie, cardiac tumors, left atrial volume, cardiomyopathies, cardiac amyloidosis)

Original Paper

Cerebrovasc Dis 2014;37:277–284
DOI: 10.1159/000360073

Received: September 21, 2013
Accepted: January 27, 2014
Published online: May 7, 2014

Cerebrovascular Diseases

Cardiac MRI Improves Identification of Etiology of Acute Ischemic Stroke

Alex Baher[a, b] Ashkan Mowla[c, e] Santhisri Kodali[b] Venkateshwar R. Polsani[d]
Faisal Nabi[d] Sherif F. Nagueh[d] John J. Volpi[c] Dipan J. Shah[d]

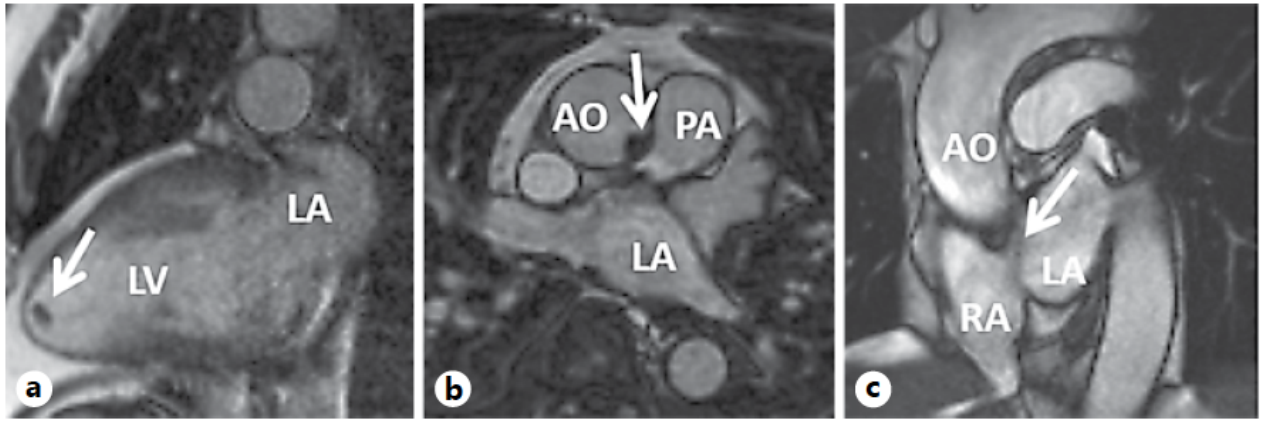


Fig. 1. Cardiovascular sources of embolism detected by CMR in patients with cryptogenic stroke. **a** Apical thrombus (arrow) using the thrombus imaging technique (TI-600) in two-chamber view. **b** Axial image of the thoracic aorta representing a thrombus in the ascending aorta (arrow). **c** An SSFP still frame of the oblique sagittal view showing a patent foramen ovale. TI = Time to inversion; LV = left ventricle; LA = left atrium; AO = aorta; RA = right atrium; PA = pulmonary artery.

Results: RDW detected cardioaortic embolism (CAE) stroke in 32 (37.6%) patients and cryptogenic stroke in 23 patients (27.1%). Addition of CMR resulted in a 26.1% reduction in the rate of cryptogenic strokes (6 patients).

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Cardiac magnetic resonance imaging has limited additional yield in cryptogenic stroke evaluation after transesophageal echocardiography

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Abstract

Background: The use of cardiac magnetic resonance imaging is increasing, but its role in the diagnostic work-up following ischemic stroke has received limited study. We aimed to explore the added yield of cardiac magnetic resonance imaging to identify cardio-aortic sources not detected by transesophageal echocardiography among patients with cryptogenic stroke.

Methods: A retrospective single-center cohort study was performed from 01 January 2009 to 01 March 2013. Consecutive patients who had both a stroke protocol cardiac magnetic resonance imaging and a transesophageal echocardiography preformed during a single hospitalization were included. All cardiac magnetic resonance imaging studies underwent independent, blinded review by two investigators. We applied the causative classification system for ischemic stroke to all patients, first blinded to cardiac magnetic resonance imaging results; we then reapplied the causative classification system using cardiac magnetic resonance imaging. Standard statistical tests to evaluate stroke subtype reclassification rates were used.

Results: Ninety-three patients were included in the final analysis; 68.8% were classified as cryptogenic stroke after initial diagnostic evaluation. Among patients with cryptogenic stroke, five (7.8%) were reclassified due to cardiac magnetic resonance imaging findings: one was reclassified as "cardio-aortic embolism evident" due to the presence of a patent foramen ovale and focal cardiac infarct and four were reclassified as "cardio-aortic embolism possible" due to mitral valve thickening (n = 1) or hypertensive cardiomyopathy (n = 3). Overall, findings on cardiac magnetic resonance imaging reduced the percentage of patients with cryptogenic stroke by slightly more than 1%.

Conclusion: Our stroke subtype reclassification rate after the addition of cardiac magnetic resonance imaging results to a diagnostic work-up which includes transesophageal echocardiography was very low. Prospective studies evaluating the role of cardiac magnetic resonance imaging and transesophageal echocardiography among patients with cryptogenic stroke should be considered.

Journal of the American College of Cardiology
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Does the Left Atrial Appendage Morphology Correlate With the Risk of Stroke in Patients With Atrial Fibrillation?

Results From a Multicenter Study

Luigi Di Biase, MD, PHD,*†‡ Pasquale Santangeli, MD,*‡ Matteo Anselmino, MD, PHD,§ Prasant Mohanty, MBBS, MPH,* Ilaria Salvetti, MD,§ Sebastiano Gili, MD,§ Rodney Horton, MD,* Javier E. Sanchez, MD,* Rong Bai, MD,* Sanghamitra Mohanty, MD,* Agnes Pump, MD,* Mauricio Cereceda Brantes, MD,* G. Joseph Gallinghouse, MD,* J. David Burkhardt, MD,* Federico Cesarani, MD,‖ Marco Scaglione, MD,¶ Andrea Natale, MD,*† Fiorenzo Gaita, MD§

Austin, Texas; and Foggia, Turin, and Asti, Italy

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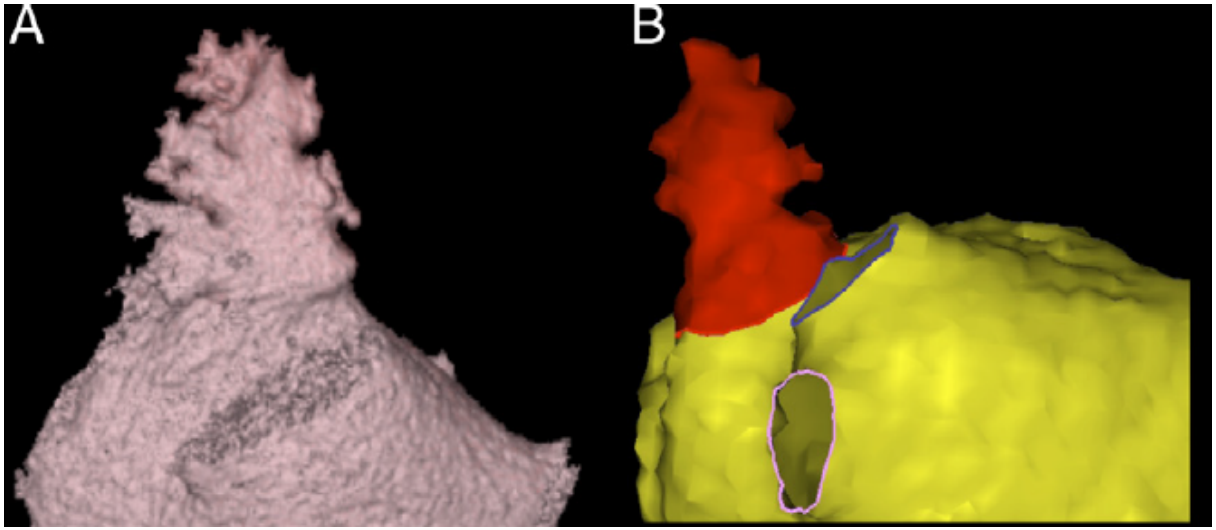
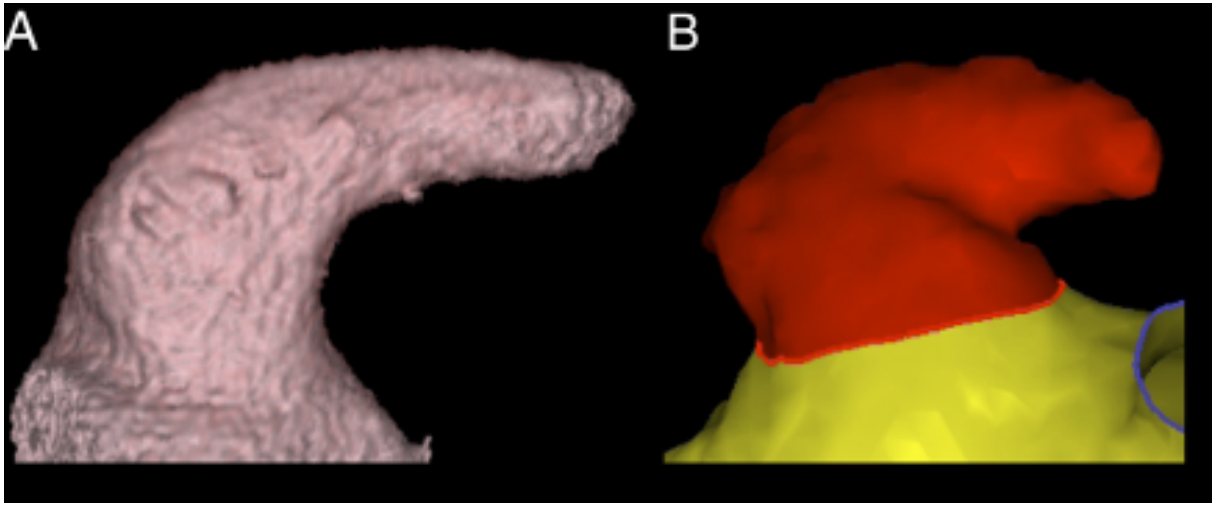


Cactus 30%



Cicken wing 48%

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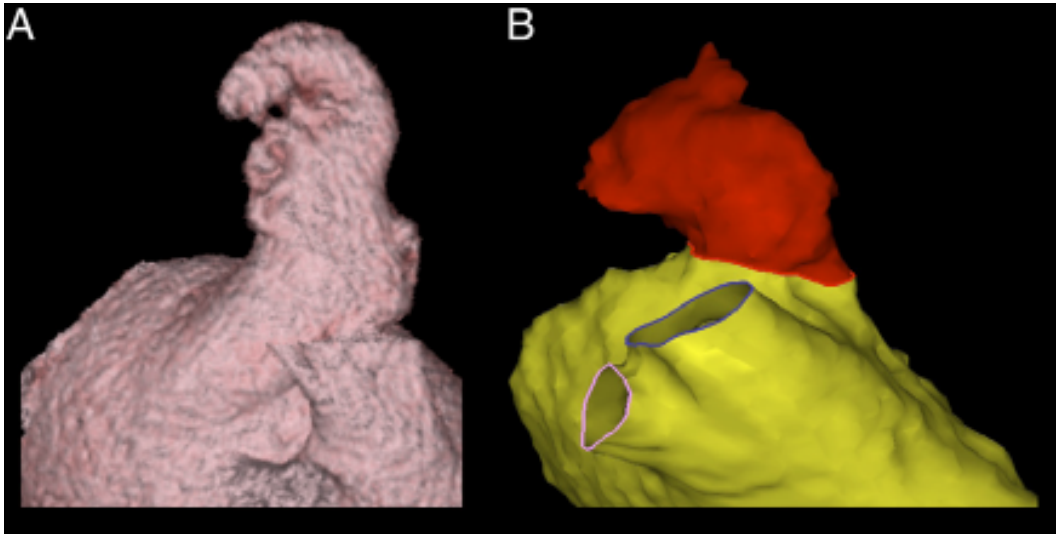
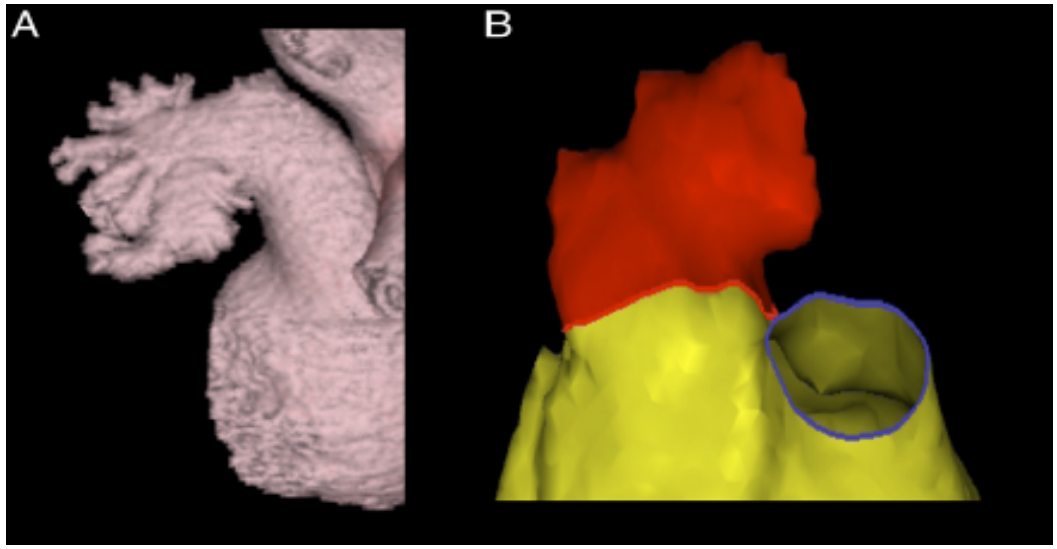


Windsock 19%



Cauliflower 3%

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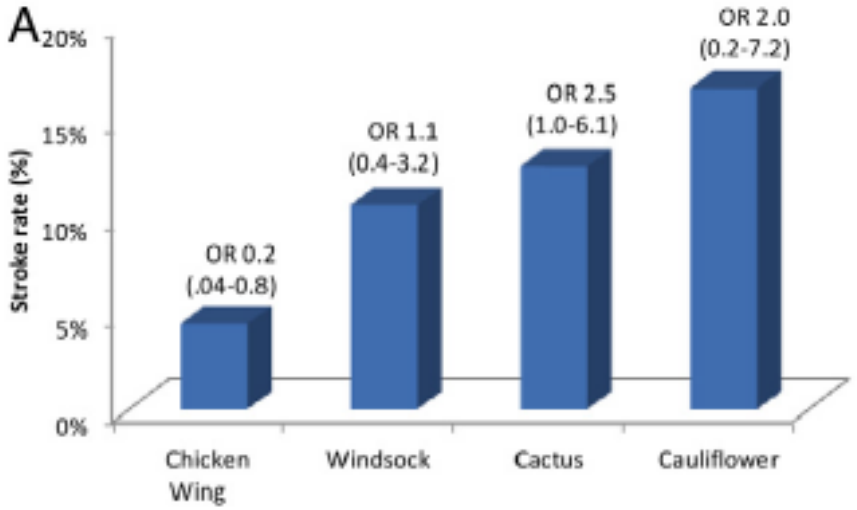

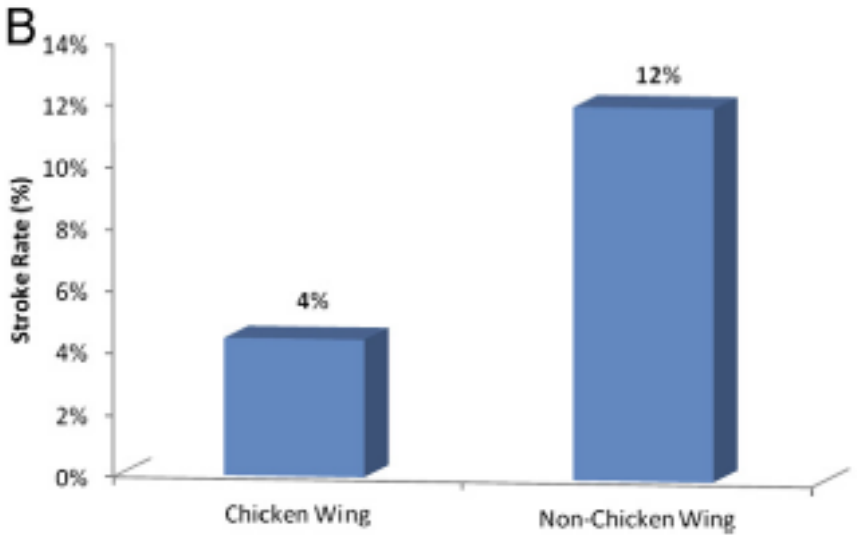

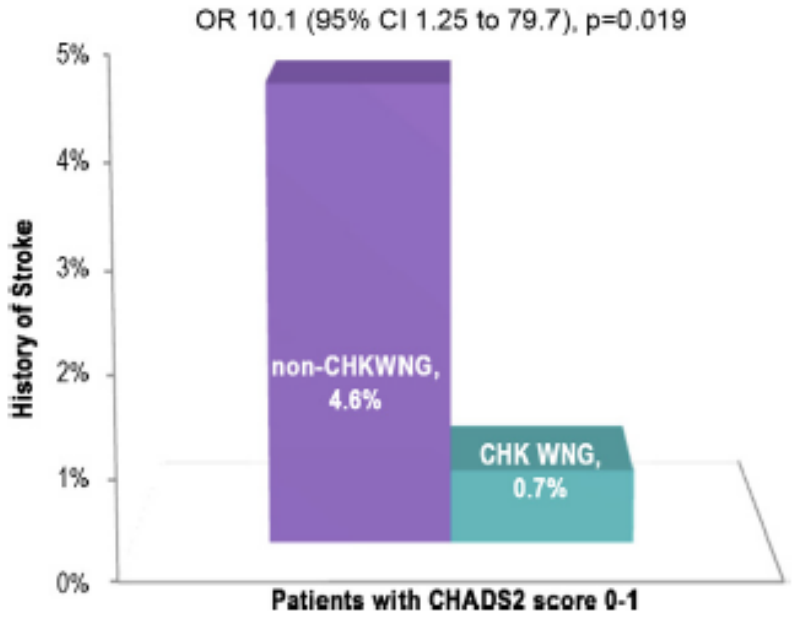

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Results From a Multicenter Study

Luigi Di Biase, MD, PHD,*†‡ Pasquale Santangeli, MD,*‡ Matteo Anselmino, MD, PHD,§ Prasant Mohanty, MBBS, MPH,* Ilaria Salvetti, MD,§ Sebastiano Gili, MD,§ Rodney Horton, MD,* Javier E. Sanchez, MD,* Rong Bai, MD,* Sanghamitra Mohanty, MD,* Agnes Pump, MD,* Mauricio Cereceda Brantes, MD,* G. Joseph Gallinghouse, MD,* J. David Burkhardt, MD,* Federico Cesarani, MD,‖ Marco Scaglione, MD,¶ Andrea Natale, MD,*† Fiorenzo Gaita, MD§

Austin, Texas; and Foggia, Turin, and Asti, Italy

Background LAA represents one of the major sources of cardiac thrombus formation responsible for TIA/stroke in patients with atrial fibrillation (AF).

Methods We studied 932 patients with drug-refractory AF who were planning to undergo catheter ablation. All patients underwent cardiac CT or MRI of the LAA and were screened for history of TIA/stroke. Four different morphologies were used to categorize LAA: Cactus, Chicken Wing, Windsock, and Cauliflower.

Results CT scans of 499 patients and MRI scans of 433 patients were analyzed (age 59 ± 10 years, 79% were male, and 14% had $CHADS_2$ [Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack] score ≥2). The distribution of different LAA morphologies was Cactus (278 [30%]), Chicken Wing (451 [48%]), Windsock (179 [19%]), and Cauliflower (24 [3%]). Of the 932 patients, 78 (8%) had a history of ischemic stroke or TIA. The prevalence of pre-procedure stroke/TIA in Cactus, Chicken Wing, Windsock, and Cauliflower morphologies was 12%, 4%, 10%, and 18%, respectively ($p = 0.003$). After controlling for $CHADS_2$ score, gender, and AF types in a multivariable logistic model, Chicken Wing morphology was found to be 79% less likely to have a stroke/TIA history (odd ratio: 0.21, 95% confidence interval: 0.05 to 0.91, $p = 0.036$). In a separate multivariate model, we entered Chicken Wing as the reference group and assessed the likelihood of stroke in other groups in relation to reference. Compared with Chicken Wing, Cactus was 4.08 times ($p = 0.046$), Windsock was 4.5 times ($p = 0.038$), and Cauliflower was 8.0 times ($p = 0.056$) more likely to have had a stroke/TIA.

Conclusions Patients with Chicken Wing LAA morphology are less likely to have an embolic event even after controlling for comorbidities and $CHADS_2$ score. If confirmed, these results could have a relevant impact on the anticoagulation management of patients with a low-intermediate risk for stroke/TIA. (J Am Coll Cardiol 2012;60:531–8)

Europace (2015) **17**, 539–545
doi:10.1093/europace/euu347

CLINICAL RESEARCH
Atrial fibrillation

Left atrial appendage morphology is closely associated with specific echocardiographic flow pattern in patients with atrial fibrillation

Margot Petersen[1], Adalbert Roehrich[1], Jan Balzer[1], Dong-In Shin[1], Christian Meyer[1,2], Malte Kelm[1], and Eva S. Kehmeier[1]*

European Heart Journal - Cardiovascular Imaging Advance Access published May 5, 2015

European Heart Journal – Cardiovascular Imaging
doi:10.1093/ehjci/jev117

Correlation between left atrial appendage morphology and flow velocity in patients with paroxysmal atrial fibrillation

Keiko Fukushima[1†*], Noritoshi Fukushima[1,2†], Ken Kato[1†], Koichiro Ejima[1], Hiroki Sato[2], Kenji Fukushima[3], Chihiro Saito[1], Keiko Hayashi[1], Kotaro Arai[1], Tetsuyuki Manaka[1], Kyomi Ashihara[1], Morio Shoda[1], and Nobuhisa Hagiwara[1]

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Stroke. 2015;46:3554-3559

American Heart Association | American Stroke Association

Left Atrial Appendage Function and Stroke Risk

Shadi Yaghi, Christopher Song, William A. Gray, Karen L. Furie, Mitchell S.V. Elkind and Hooman Kamel

LAA Dysfunction in Cryptogenic Stroke

Few data exists on the relationship between LAA dysfunction and cryptogenic stroke specifically, and patients with cryptogenic stroke do not routinely undergo detailed assessment of the LAA. However, the considerations above support further investigation of the LAA as a cause of many currently cryptogenic strokes. Measurements of LAA function can be performed by TTE, which is widely available, noninvasive, and used in the evaluation of most patients with cryptogenic stroke. Including these measurements in the diagnostic evaluation of patients with cryptogenic stroke may help understand the recurrent stroke risk and potentially improve stroke prevention strategies.

Conclusions

The left atrium is increasingly implicated in the pathogenesis of cryptogenic stroke, and the LAA serves as the most common site of thrombus formation in the left atrium. Given the substantial benefit of anticoagulant therapy in patients with atrial disease in the form of AF, such therapy may ultimately prove beneficial for patients without AF but compelling evidence of LAA dysfunction. Future research is needed to identify optimal methods to assess patients for LAA dysfunction and to test the benefit of anticoagulant therapy in stroke prevention in these patients.

WARCEF

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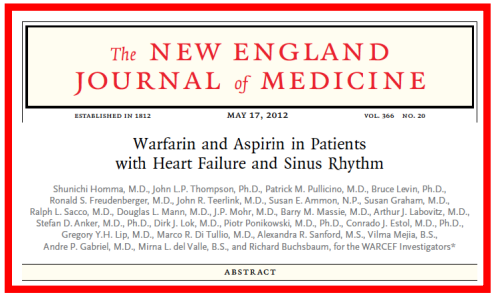
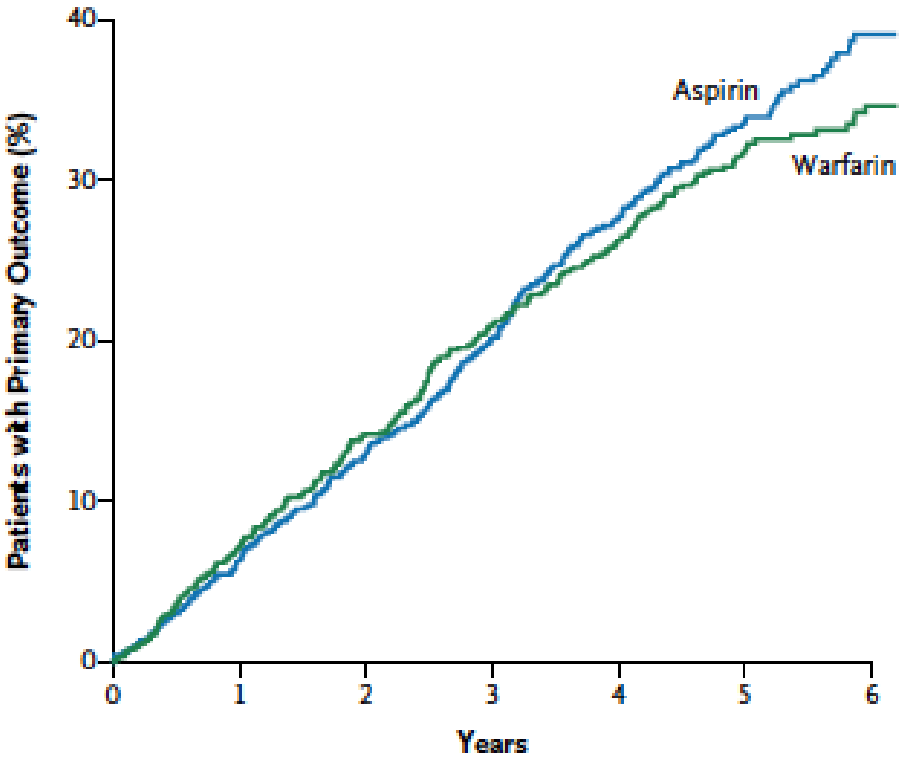
Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

Shunichi Homma, M.D., John L.P. Thompson, Ph.D., Patrick M. Pullicino, M.D., Bruce Levin, Ph.D., Ronald S. Freudenberger, M.D., John R. Teerlink, M.D., Susan E. Ammon, N.P., Susan Graham, M.D., Ralph L. Sacco, M.D., Douglas L. Mann, M.D., J.P. Mohr, M.D., Barry M. Massie, M.D., Arthur J. Labovitz, M.D., Stefan D. Anker, M.D., Ph.D., Dirk J. Lok, M.D., Piotr Ponikowski, M.D., Ph.D., Conrado J. Estol, M.D., Ph.D., Gregory Y.H. Lip, M.D., Marco R. Di Tullio, M.D., Alexandra R. Sanford, M.S., Vilma Mejia, B.S., Andre P. Gabriel, M.D., Mirna L. del Valle, B.S., and Richard Buchsbaum, for the WARCEF Investigators*

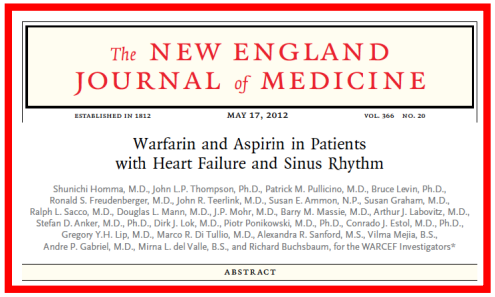
ABSTRACT



WARCEF



No. at Risk							
Aspirin	1163	1073	860	658	508	329	94
Warfarin	1142	1049	852	653	525	363	115



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2012 VOL. 366 NO. 20

Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

Shunichi Homma, M.D., John L.P. Thompson, Ph.D., Patrick M. Pullicino, M.D., Bruce Levin, Ph.D., Ronald S. Freudenberger, M.D., John R. Teerlink, M.D., Susan E. Ammon, N.P., Susan Graham, M.D., Ralph L. Sacco, M.D., Douglas L. Mann, M.D., J.P. Mohr, M.D., Barry M. Massie, M.D., Arthur J. Labovitz, M.D., Stefan D. Anker, M.D., Ph.D., Dirk J. Lok, M.D., Piotr Ponikowski, M.D., Ph.D., Conrado J. Estol, M.D., Ph.D., Gregory Y.H. Lip, M.D., Marco R. Di Tullio, M.D., Alexandra R. Sanford, M.S., Vilma Mejia, B.S., Andre P. Gabriel, M.D., Mirna L. del Valle, B.S., and Richard Buchsbaum, for the WARCEF Investigators*

ABSTRACT

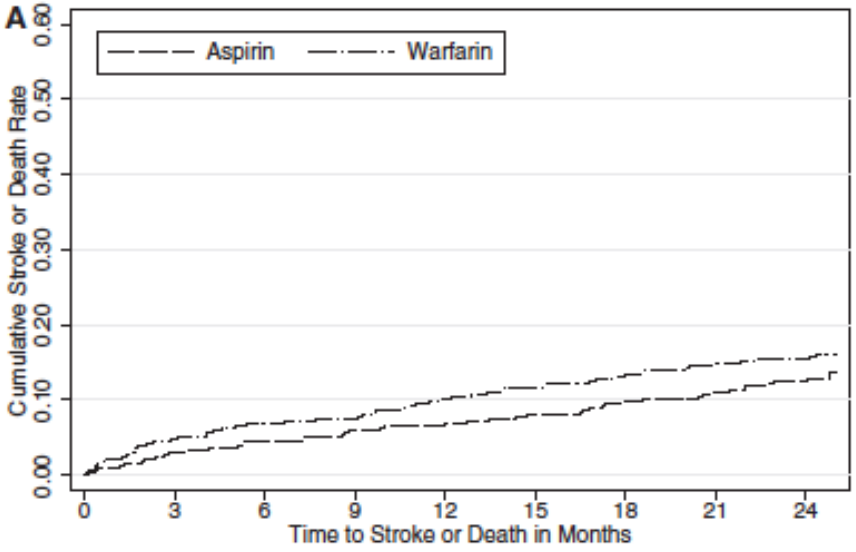
WARCEF

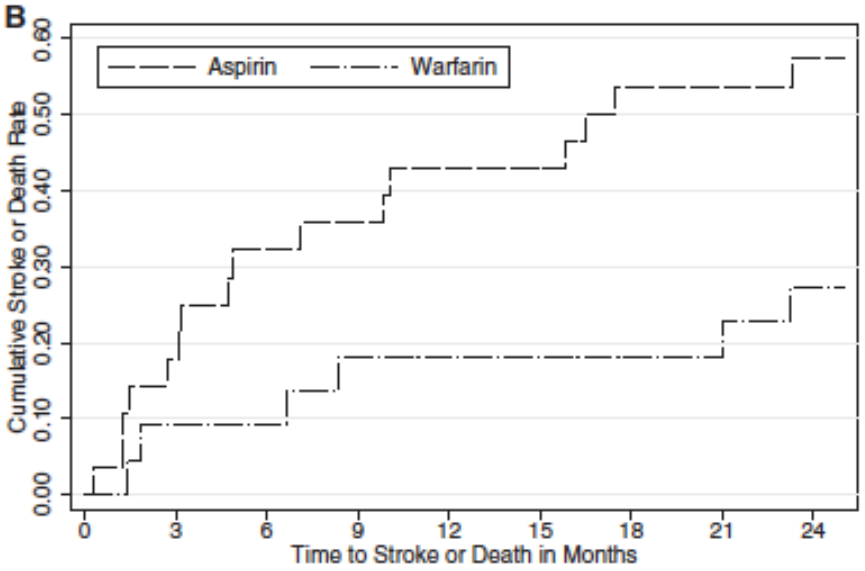
Outcome	Warfarin (N = 1142)		Aspirin (N = 1163)		Hazard Ratio (95% CI)†	P Value
	no. of patients (%)	*unadjusted rate of events/100 patient-yr*	*no. of patients (%)*	*unadjusted rate of events/100 patient-yr*		
Primary outcome: death, ischemic stroke, or intracerebral hemorrhage						
Composite	302 (26.4)	7.47	320 (27.5)	7.93	0.93 (0.79–1.10)	0.40
Components						
Death	268 (23.5)	6.63	263 (22.6)	6.52	1.01 (0.85–1.20)	0.91
Ischemic stroke	29 (2.5)	0.72	55 (4.7)	1.36	0.52 (0.33–0.82)	0.005
Intracerebral hemorrhage	5 (0.4)	0.12	2 (0.2)	0.05	2.22 (0.43–11.66)	0.35
Safety outcome: death, ischemic stroke, intracerebral hemorrhage, or intracranial hemorrhage‡	307 (26.9)	7.61	323 (27.8)	8.02	0.94 (0.80–1.10)	0.44
Main secondary outcome: death, ischemic stroke, intracerebral hemorrhage, myocardial infarction, or hospitalization for heart failure						
Composite	447 (39.1)	12.70	435 (37.4)	12.15	1.07 (0.93–1.23)	0.33
Components§						
Death	156 (13.7)	4.43	158 (13.6)	4.41	1.03 (0.81–1.30)	0.83
Ischemic stroke	20 (1.8)	0.57	41 (3.5)	1.14	0.55 (0.32–0.96)	0.03
Intracerebral hemorrhage	4 (0.4)	0.11	2 (0.2)	0.06	1.77 (0.32–9.88)	0.51
Myocardial infarction	28 (2.5)	0.80	31 (2.7)	0.87	0.98 (0.58–1.64)	0.93
Hospitalization for heart failure	239 (20.9)	6.79	203 (17.5)	5.67	1.21 (0.998–1.47)	0.053

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
(*Stroke*. 2013;44:714-719.)
American Heart Association | American Stroke Association

Amino Terminal Pro–B-Type Natriuretic Peptide, Secondary Stroke Prevention, and Choice of Antithrombotic Therapy

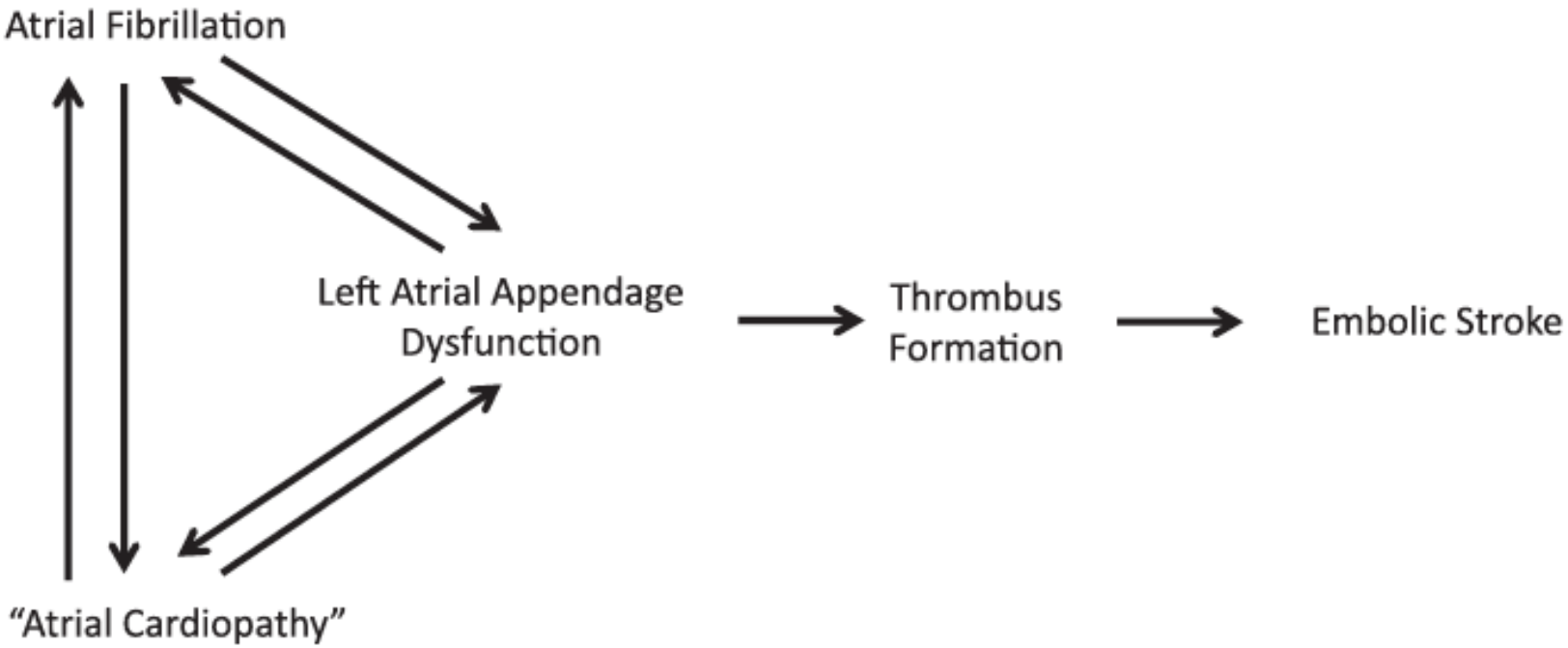
W.T. Longstreth, Jr, Richard A. Kronmal, John L.P. Thompson, Robert H. Christenson, Steven R. Levine, Rebecca Gross, Robin L. Brey, Richard Buchsbaum, Mitchell S.V. Elkind, David L. Tirschwell, Stephen L. Seliger, J.P. Mohr and Christopher R. deFilippi





Post hoc analysis from the WARSS study

Atrial Cardiopathy



Atrial cardiopathy: evidence of markers of atrial dysfunction such as elevated N-terminal proBNP, evidence of p-wave dispersion on ECG, increased left atrial size, and paroxysmal supraventricular tachycardia.

Diagnostic workup – Hypercoagulability

- Inherited and acquired hypercoagulable states are associated with venous thrombosis, but their association with arterial cerebral infarction is uncertain
- Young women with ischemic stroke have a higher prevalence of aPL
- The relationship between PFO and thrombophilia deserves further studies

Diagnostic workup – Malignancy

- Cancer produces
  - Alteration of the homeostatic cascade
  - Damage to the endothelium integrity
  - Changes in platelet funtion
  - Cryptogenic stroke most common stroke subtype with reduced survival

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Stroke. 2014;45:2292-2297
American Heart Association | American Stroke Association

Cryptogenic Subtype Predicts Reduced Survival Among Cancer Patients With Ischemic Stroke

Babak B. Navi, Samuel Singer, Alexander E. Merkler, Natalie T. Cheng, Jacqueline B. Stone, Hooman Kamel, Costantino Iadecola, Mitchell S.V. Elkind and Lisa M. DeAngelis

Background and Purpose—Cryptogenic stroke is common in patients with cancer. Autopsy studies suggest that many of these cases may be because of marantic endocarditis, which is closely linked to cancer activity. We, therefore, hypothesized that among patients with cancer and ischemic stroke, those with cryptogenic stroke would have shorter survival.

Methods—We retrospectively analyzed all adult patients with active systemic cancer diagnosed with acute ischemic stroke at a tertiary care cancer center from 2005 through 2009. Two neurologists determined stroke mechanisms by consensus. Patients were diagnosed with cryptogenic stroke if no specific mechanism could be determined. The diagnosis of marantic endocarditis was restricted to patients with cardiac vegetations on echocardiography or autopsy and negative blood cultures. Patients were followed until July 31, 2012, for the primary outcome of death. Kaplan–Meier statistics and the log-rank test were used to compare survival between patients with cryptogenic stroke and patients with known stroke mechanisms. Multivariate Cox proportional hazard analysis evaluated the association between cryptogenic stroke and death after adjusting for potential confounders.

Results—Among 263 patients with cancer and ischemic stroke, 133 (51%) were cryptogenic. Median survival in patients with cryptogenic stroke was 55 days (interquartile range, 21–240) versus 147 days (interquartile range, 33–735) in patients with known stroke mechanisms ($P<0.01$). Cryptogenic stroke was independently associated with death (hazard ratio, 1.64; 95% confidence interval, 1.25–2.14) after adjusting for age, systemic metastases, adenocarcinoma histology, and functional status.

Conclusions—Cryptogenic stroke is independently associated with reduced survival in patients with active cancer and ischemic stroke. (***Stroke*. 2014;45:2292-2297.**)

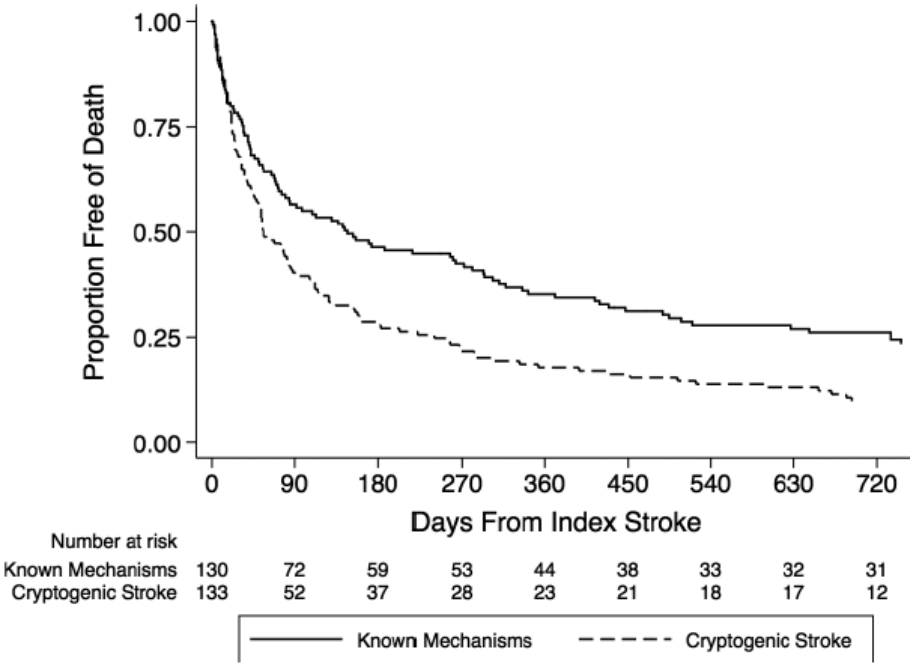
Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

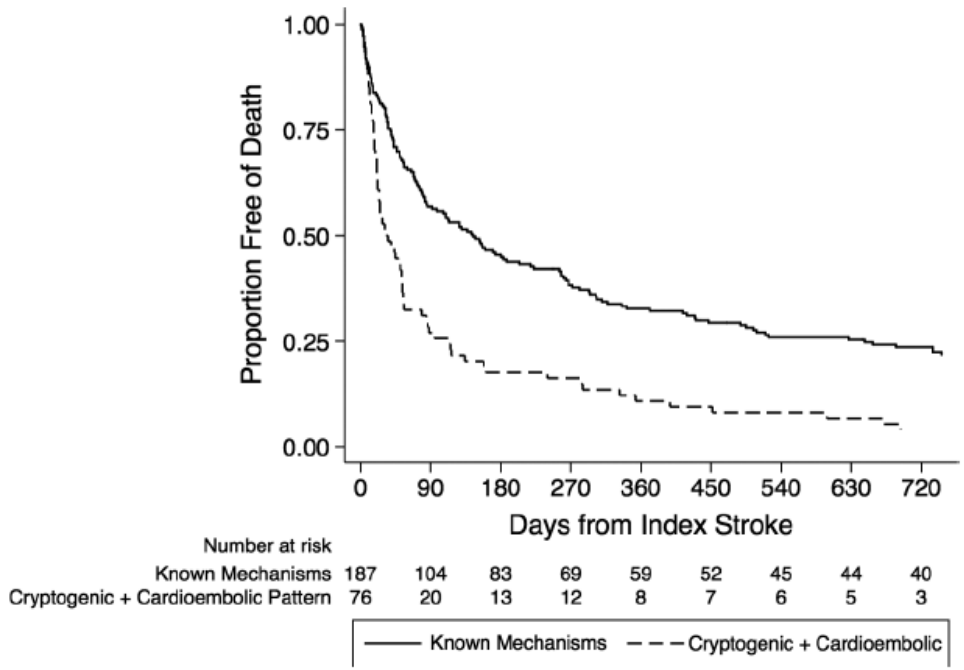
Stroke. 2014;45:2292-2297

American Heart Association | American Stroke Association

Cryptogenic Subtype Predicts Reduced Survival Among Cancer Patients With Ischemic Stroke

Babak B. Navi, Samuel Singer, Alexander E. Merkler, Natalie T. Cheng, Jacqueline B. Stone, Hooman Kamel, Costantino Iadecola, Mitchell S.V. Elkind and Lisa M. DeAngelis





Patent Foramen Ovale

- Weak association between PFO and cryptogenic stroke
  (Di Tullio et al., 2007; Alsheikh-Ali et al., 2009; Kent et al., 2013)
- Risk of Paradoxical Embolism (ROPE) score
- Investigation for venous thrombi
- PFO treatment

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

Neurology® 2013;81:619-625

Kent DM et al. Neurology 2013; 81:619-625

Table 4 RoPE score calculator

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

Neurology® 2013;81:619-625

Kent DM et al. Neurology 2013; 81:619-625

Table 5 PFO prevalence, attributable fraction, and estimated 2-year risk of stroke/TIA by point score strata, using control rate of 25%

	Cryptogenic stroke (n = 3,023)			CS patients with PFO (n = 1,324)	
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)[a]	PFO-attributable fraction, % (95% CI)[a]	No. of CS patients with PFO[a]	Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)
0-3	613	23 (19-26)	0 (0-4)	108	20 (12-28)
4	511	35 (31-39)	38 (25-48)	148	12 (6-18)
5	516	34 (30-38)	34 (21-45)	186	7 (3-11)
6	482	47 (42-51)	62 (54-68)	236	8 (4-12)
7	434	54 (49-59)	72 (66-76)	263	6 (2-10)
8	287	67 (62-73)	84 (79-87)	233	6 (2-10)
9-10	180	73 (66-79)	88 (83-91)	150	2 (0-4)

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

Neurology® 2013;81:619-625

Kent DM et al. Neurology 2013; 81:619-625

ABSTRACT

Objective: We aimed to create an index to stratify cryptogenic stroke (CS) patients with patent foramen ovale (PFO) by their likelihood that the stroke was related to their PFO.

Methods: Using data from 12 component studies, we used generalized linear mixed models to predict the presence of PFO among patients with CS, and derive a simple index to stratify patients with CS. We estimated the stratum-specific PFO-attributable fraction and stratum-specific stroke/TIA recurrence rates.

Results: Variables associated with a PFO in CS patients included younger age, the presence of a cortical stroke on neuroimaging, and the absence of these factors: diabetes, hypertension, smoking, and prior stroke or TIA. The 10-point Risk of Paradoxical Embolism score is calculated from these variables so that the youngest patients with superficial strokes and without vascular risk factors have the highest score. PFO prevalence increased from 23% (95% confidence interval [CI]: 19%–26%) in those with 0 to 3 points to 73% (95% CI: 66%–79%) in those with 9 or 10 points, corresponding to attributable fraction estimates of approximately 0% to 90%. Kaplan-Meier estimated stroke/TIA 2-year recurrence rates decreased from 20% (95% CI: 12%–28%) in the lowest Risk of Paradoxical Embolism score stratum to 2% (95% CI: 0%–4%) in the highest.

Conclusion: Clinical characteristics identify CS patients who vary markedly in PFO prevalence, reflecting clinically important variation in the probability that a discovered PFO is likely to be stroke-related vs incidental. Patients in strata more likely to have stroke-related PFOs have lower recurrence risk. *Neurology*® 2013;81:619–625

PFO – Investigating venous thrombi

- 10-22% is the reported frequency of deep venous thrombosis (DVT) detection in patients with PFO and stroke ***(Lethen et al., 1997; Cramer et al., 2004; Liberman et al., 2014)***

- 80% of detected DVT were asymptomatic ***(Lethen et al., 1997)***

- Use of MRI venography for pelvic DVTs (8-20% of suspected DVT) ***(Cramer et al., 2004; Liberman et al., 2014)***

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Stroke. 2014;45:2324-2329

American Heart Association | American Stroke Association

Diagnostic Yield of Pelvic Magnetic Resonance Venography in Patients With Cryptogenic Stroke and Patent Foramen Ovale

Ava L. Liberman, Vistasp J. Daruwalla, Jeremy D. Collins, Matthew B. Maas, Marcos Paulo Ferreira Botelho, Jad Bou Ayache, James Carr, Ilana Ruff, Richard A. Bernstein, Marc J. Alberts and Shyam Prabhakaran

Background and Purpose—Paradoxical embolization is frequently posited as a mechanism of ischemic stroke in patients with patent foramen ovale. Several studies have suggested that the deep lower extremity and pelvic veins might be an embolic source in cryptogenic stroke (CS) patients with patent foramen ovale.

Methods—Consecutive adult patients with ischemic stroke or transient ischemic attack and a patent foramen ovale who underwent pelvic magnetic resonance venography as part of an inpatient diagnostic evaluation were included in this single-center retrospective observational study to determine pelvic and lower extremity (LE) deep venous thrombosis (DVT) prevalence in CS versus non-CS stroke subtypes.

Results—Of 131 patients who met inclusion criteria, 126 (96.2%) also had LE duplex ultrasound data. DVT prevalence overall was 7.6% (95% confidence interval, 4.1–13.6), pelvic DVT 1.5% (95% confidence interval, 0.1–5.8), and LE DVT 7.1% (95% confidence interval, 3.6–13.2). One patient with a pelvic DVT also had a LE DVT. Comparing patients with CS (n=98) with non-CS subtypes (n=33), there was no significant difference in the prevalence of pelvic DVT (2.1% versus 0%, P=1), LE DVT (6.2% versus 10.3%, P=0.43), or any DVT (7.2% versus 9.1%, P=0.71).

Conclusions—Among patients with ischemic stroke/transient ischemic attack and patent foramen ovale, the majority of detected DVTs were in LE veins rather than the pelvic veins and did not differ by stroke subtype. The routine inclusion of pelvic magnetic resonance venography in the diagnostic evaluation of CS warrants further prospective investigation. (***Stroke*. 2014;45:2324-2329.**)

PFO - Medical Treatment

- Multiple nonrandomized, prospective follow-up studies have suggested that there is no benefit associated with AO over antiplatelet therapy ***(Shariat et al., 2013; Kernan et al., 2014; Kent et al., 2015)***

- PICSS study ***(Homma et al., 2002)*** is the only randomized controlled trial comparing ASA to Warfarin as therapy for PFO-associated stroke:
  - 2-year recurrent stroke/TIA rates were similar in the two cohorts (16.5% vs 13.2%; P = .65)

CLOSURE I

ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

ABSTRACT

CLOSURE I

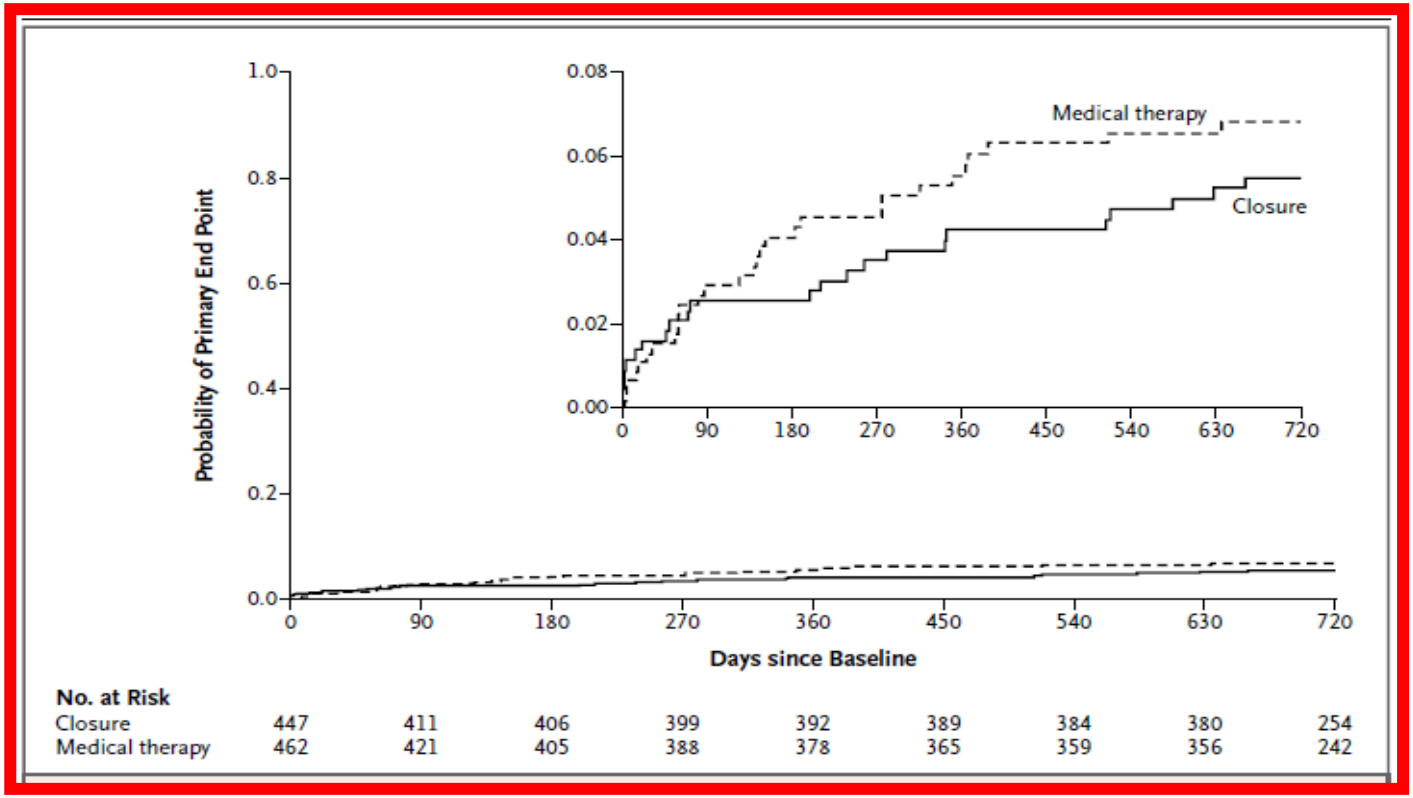
- Multicenter, randomized, open label trial comparing percutaneous PFO closure to medical therapy

- Cryptogenic stroke or transient ischemic attack (TIA) in patients 18-60 y/o

- Primary Endpoint- Stoke/TIA during 2 year followup, death from any cause during first 30 days, neurologic death to two years

- 909 patients enrolled
  - 447 underwent closure with StarFlex, then treated with Clopidogrel (75 mg daily x 6 months) and Aspirin (81 or 325 mg x 2 years)
  - 462 patients received medical therapy alone: Warfarin (target INR 2-3), aspirin 325 or both at the discretion of the operator

Results



Primary Endpoint- 5.5% in device closure group
6.8% in medical therapy group
P=0.37

RESPECT

ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

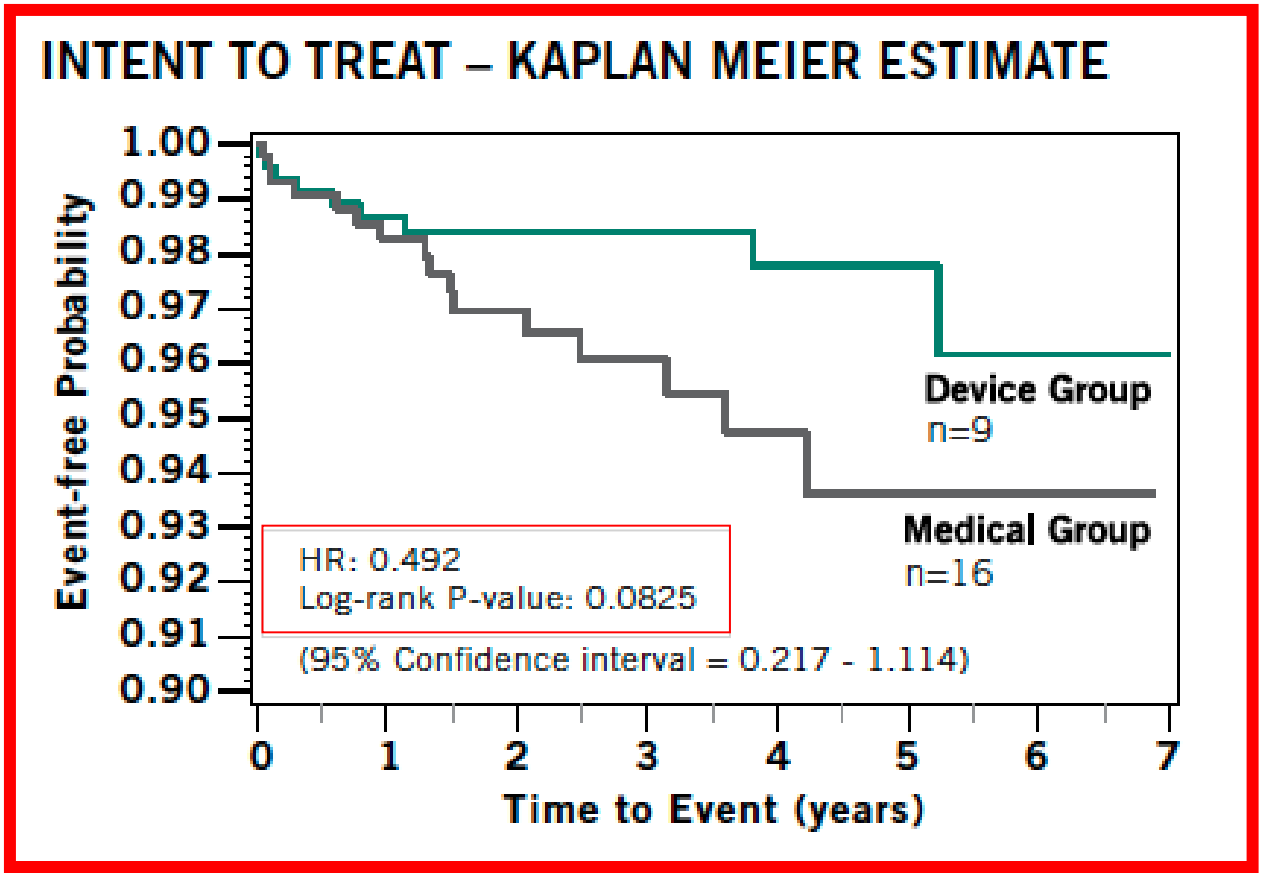
ABSTRACT

RESPECT
CLINICAL TRIAL

- Multicenter: 69 Sites (62 US, 7 Canada)
  - Prospective, 1:1 Randomized
    - Closure with the AGA AMPLATZER™ PFO Occluder plus medical therapy
    - Medical Treatment Regimens: Aspirin, Warfarin, Clopidogrel, Aspirin + Dipyridamole, Aspirin + Clopidogrel (removed from protocol in 2006)
- 980 patients enrolled with clinical stroke confirmed by CT/MRI imaging age 18-60 within 9 months
- TEE documented PFO

RESPECT
CLINICAL TRIAL

Results



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

CONCLUSIONS

Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up. (Funded by St. Jude Medical; RESPECT Clinical-Trials.gov number, NCT00465270.)

N Engl J Med 2017;377:1033-42.

REDUCE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

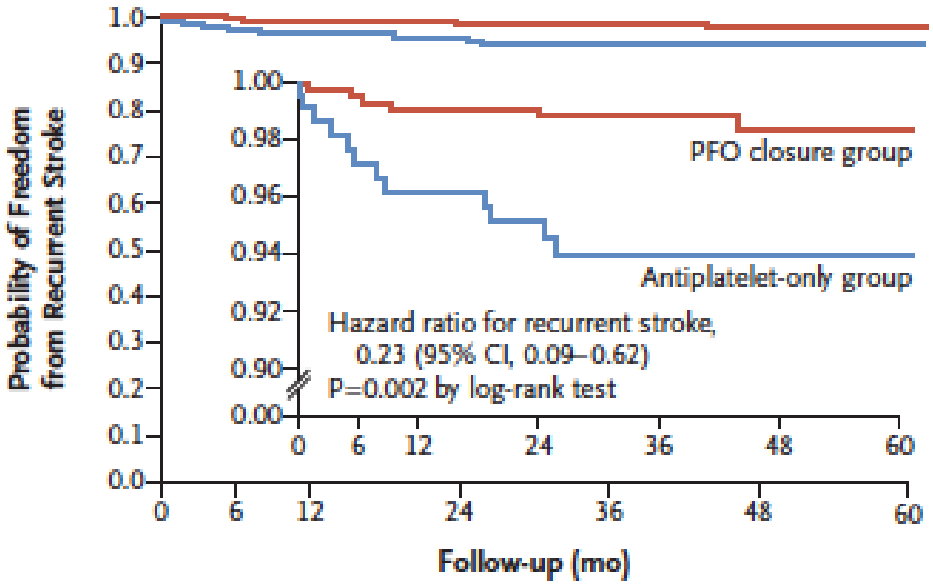
ABSTRACT

N Engl J Med 2017;377:1033-42.

REDUCE

Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

End Point	PFO Closure Group	Antiplatelet-Only Group	Effect Size	P Value
	no. of patients/total no. (%)			
Clinical ischemic stroke†	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)‡	0.002§
New brain infarction¶	22/383 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)‖	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/177 (6.8)	0.19 (0.07–0.54)‖	0.005**
Silent brain infarction only	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)‖	0.97**



N Engl J Med 2017;377:1033-42.

REDUCE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

ABSTRACT

CONCLUSIONS

Among patients with a PFO who had had a cryptogenic stroke, the risk of subsequent ischemic stroke was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone; however, PFO closure was associated with higher rates of device complications and atrial fibrillation. (Funded

CLOSE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

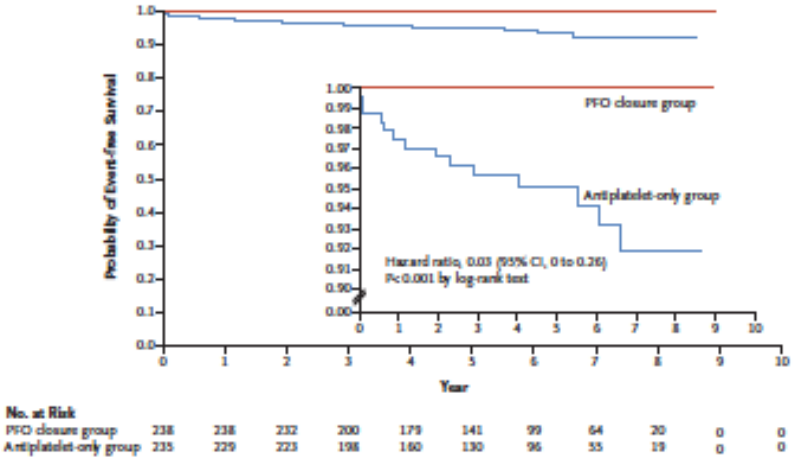
J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

ABSTRACT

CLOSE

Table 2. Efficacy Outcomes.*

Outcome	Randomization Groups 1 and 2			
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	Hazard Ratio (95% CI)†	P Value
Primary efficacy outcome				
Stroke in the intention-to-treat population — no. of patients	0	14§	0.03 (0.00–0.26)	<0.001
Stroke in the per-protocol population — no./total no. of patients	0/217	14/223§	0.04 (0.00–0.27)	<0.001
Secondary efficacy outcomes‖				
Disabling stroke**	0	1	0.33 (0.00–6.18)	0.63
Cerebral hemorrhage	0	0	NA	NA
Ischemic stroke, transient ischemic attack, or systemic embolism	8	21	0.39 (0.16–0.82)	0.01
Transient ischemic attack	8	8	0.97 (0.37–2.56)	0.96
Systemic embolism	0	0	NA	NA
Death from any cause	0	0	NA	NA
Success of device implantation — no./total no. (%)‡‡	234/235 (99.6)	NA	NA	NA
Success of PFO closure — no./total no. (%)§§	202/228 (88.6)	NA	NA	NA



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The NEW ENGLAND JOURNAL of MEDICINE

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Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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ABSTRACT

CONCLUSIONS

Among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. (Funded by the French Ministry of Health; CLOSE ClinicalTrials.gov number, NCT00562289.)

Aortic Arch Atherosclerosis

- Aortic arch plaques (thickness > 4mm) are an independent predictor of ischemic stroke risk ***(NEJM, 1996).***
- Patients with aortic plaques > 4 mm in thickness are at higher risk of:
  - Ischemic stroke ***(Amarenco et al, 1994; Jones et al., 1995)***
  - Recurrent ischemic stroke (11,9% > 4mm vs 2.8% < 1mm)
- Plaque ulceration and plaque mobility are also associated with risk of ischemic stroke

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

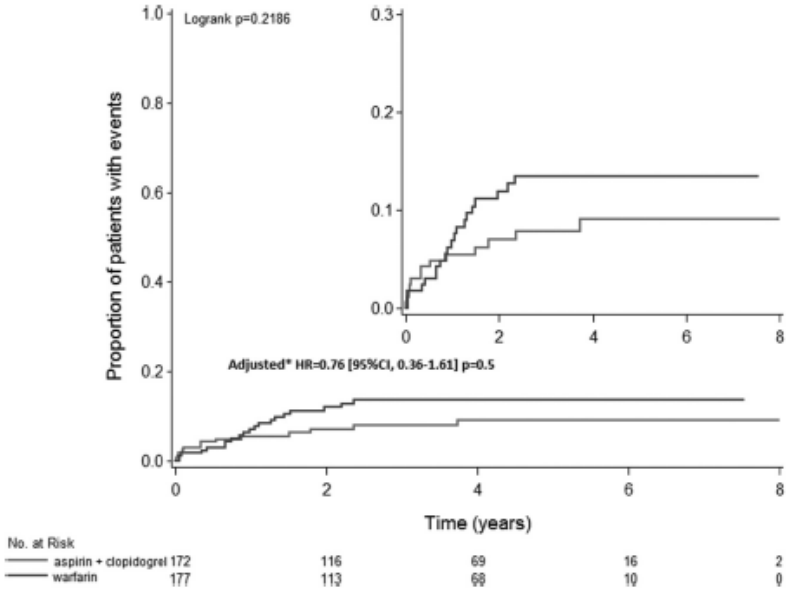
Stroke. 2014;45:1248-1257

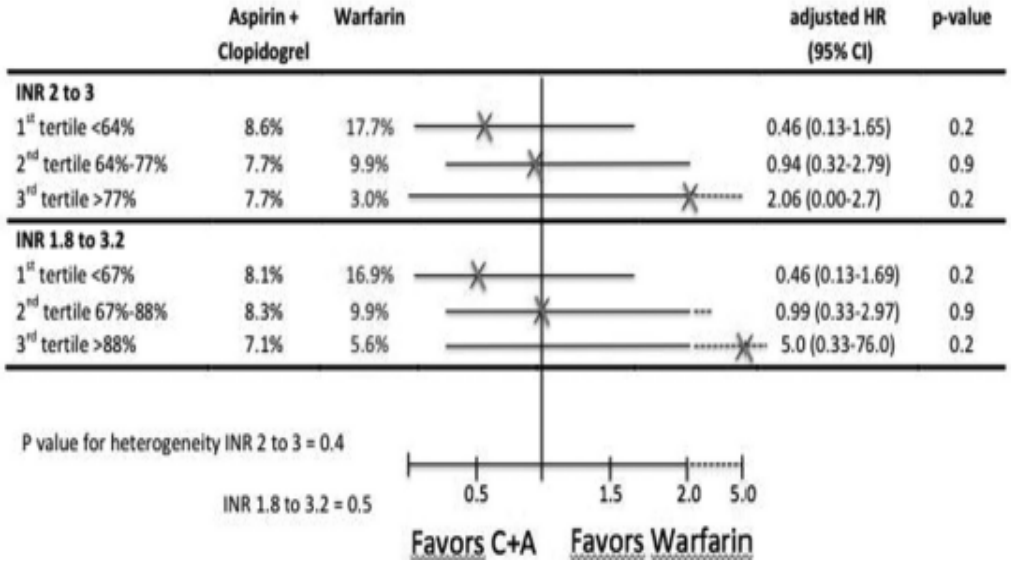
American Heart Association | American Stroke Association

Clopidogrel Plus Aspirin Versus Warfarin in Patients With Stroke and Aortic Arch Plaques

Pierre Amarenco, Stephen Davis, Elizabeth F. Jones, Ariel A. Cohen, Wolf-Dieter Heiss, Markku Kaste, Cédric Laouénan, Dennis Young, Malcolm Macleod and Geoffrey A. Donnan
The Aortic Arch Related Cerebral Hazard Trial Investigators

Amarenco et al





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LETTER TO THE EDITOR

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Association Between Nonstenosing Carotid Artery Plaque on MR Angiography and Acute Ischemic Stroke

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TABLE 1 Carotid Artery Characteristics Ipsilateral and Contralateral to This Side of Cerebral Infarction

	ICA Ipsilateral to Stroke	ICA Contralateral to Stroke	p Value*
Overall (N = 109)			
Prevalence of IHIS	22/109	9/109	0.0124
Median carotid stenosis	0 (0 to 47.5; 0)	0 (0 to 49; 0)	0.6694
TOAST stroke subtype			
Cryptogenic (n = 50)			
Prevalence of IHIS	11/50	0/50	0.0009
Median carotid stenosis	0 (0 to 47.5; 15.6)	0 (0 to 49; 5.6)	0.4896
Cardioembolic (n = 37)			
Prevalence of IHIS	7/37	6/37	0.7630
Median carotid stenosis	0 (0 to 41; 0)	0 (0 to 34.8; 0)	0.4360
Small vessel occlusion (n = 22)			
Prevalence of IHIS	4/22	3/22	0.6547
Median carotid stenosis	0 (0 to 17.4; 0)	0 (0 to 39.1; 0)	0.1250

Values are n/N or % (range; IQR). *p value by McNemar's test for correlated proportions or Wilcoxon signed rank sum test, as appropriate. Carotid stenosis calculated using standard North American Symptomatic Carotid Endarterectomy Trial criteria.

ICA = internal carotid artery; IHIS = intraplaque high intensity signal; IQR = interquartile range; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

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Cryptogenic Stroke and Nonstenosing Intracranial Calcified Atherosclerosis

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Objective: Because some cryptogenic strokes may result from large-artery atherosclerosis that goes unrecognized as it causes <50% luminal stenosis, we compared the prevalence of nonstenosing intracranial atherosclerotic plaques ipsilateral to cryptogenic cerebral infarcts versus the unaffected side using imaging biomarkers of calcium burden. *Methods:* In a prospective stroke registry, we identified patients with cerebral infarction limited to the territory of one internal carotid artery (ICA). We included patients with stroke of undetermined etiology and, as controls, patients with cardioembolic stroke. We used noncontrast computed tomography to measure calcification in both intracranial ICAs, including qualitative calcium scoring and quantitative scoring utilizing the Agatston–Janowitz (AJ) calcium scoring. Within subjects, the Wilcoxon signed-rank sum test for nonparametric paired data was used to compare the calcium burden in the ICA upstream of the infarction versus the ICA on the unaffected side. *Results:* We obtained 440 calcium measures from 110 ICAs in 55 patients. Among 34 patients with stroke of undetermined etiology, we found greater calcium in the ICA *ipsilateral* to the infarction (mean Modified Woodcock Visual Scale score, 6.7 ± 4.6) compared with the *contralateral* side (5.4 ± 4.1) ($P = .005$). Among 21 patients with cardioembolic stroke, we found no difference in calcium burden ipsilateral to the infarction (6.7 ± 5.9) versus the contralateral side (7.3 ± 6.3) ($P = .13$). The results were similar using quantitative calcium measurements, including the AJ calcium scores. *Conclusion:* In patients with strokes of undetermined etiology, the burden of calcified intracranial large-artery plaque was associated with downstream cerebral infarction. **Key Words:** Cryptogenic stroke—intracranial atherosclerosis—CT scan—calcium—stroke etiology.