Atrial Cardiopathy and Cryptogenic Stroke

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Disclosures

- Funding sources:
  - NIH/NINDS K23NS082367
  - NIH/NINDS R01NS097443
  - NIH/NINDS U01NS095869 (pending)
- Financial disclosures
  - Genentech (paid)
  - Medtronic (unpaid)
  - iRhythm (unpaid)

Cryptogenic stroke: a useful target

- Best to prevent stroke from occurring at all
- Remaining targets for improving stroke prevention?
  - One-third of ischemic strokes are cryptogenic
  - Uncovering causes may provide novel targets for stroke prevention

Sacco et al, *Ann Neurol*, 1989; Marnane et al, *Stroke*, 2010

Cryptogenic stroke = ESUS?

Personal View

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

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 mitral-disk 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.

Lancet Neurol 2014; 13: 429–38

See Comment page 344

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Causes of cryptogenic stroke?

- What are potentially undiscovered sources of embolism?

Causes of cryptogenic stroke?

- What are potentially undiscovered sources of embolism?
- Unrecognized large-artery atherosclerosis?

Gupta et al, *J Am Heart Assoc*, 2015; Gupta et al, *JACC Cardiovasc Imaging*, 2016

Causes of cryptogenic stroke?

- What are potentially undiscovered sources of embolism?
- Unrecognized cardiac embolism?

Occult atrial fibrillation?

- AF can be paroxysmal and asymptomatic
- Difficult to detect
  - Average burden: 1.8 hours/day
  - Any AF: <10% of days

Ziegler et al, *Stroke*, 2010

Occult atrial fibrillation?

- Delayed detection of AF is common
- Delayed detection may increase risk of recurrence
- Ambulatory heart-rhythm monitoring after stroke is cost-effective to diagnose AF
- Apixaban and dabigatran are cost-effective for prevention of recurrent stroke in AF
- Randomized trial of heart-rhythm monitoring after stroke is feasible

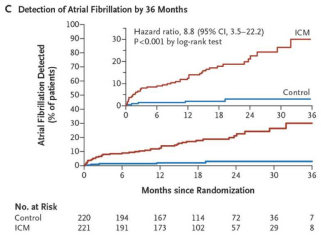
Kamel et al, *Stroke*, 2010; Kamel et al, *Stroke*, 2012; Kamel et al, *Neurology*, 2012; Kamel et al, *Stroke*, 2013

Occult atrial fibrillation?

- Observational studies: heart-rhythm monitoring establishes new diagnosis of AF in 10% of stroke patients
- Corroborated by two recent randomized clinical trials

Kishore et al, *Stroke*, 2014; Gladstone et al, *NEJM*, 2014; Sanna et al, *NEJM*, 2014

Occult atrial fibrillation?



Sanna et al, *NEJM*, 2014

Occult atrial fibrillation?

- 70% of cryptogenic stroke patients manifested no AF during 3 years of continuous heart-rhythm monitoring
- **Subclinical AF does not explain most cryptogenic strokes**

Kamel, *NEJM*, 2014

Other occult atrial disease?

- **Could some cryptogenic strokes arise from the left atrium in the absence of AF?**

Why is AF associated with stroke?

THE ARREST OF RECURRENT EMBOLISM DUE TO AURICULAR FIBRILLATION WITH MITRAL STENOSIS BY QUINIDINE–ANTICOAGULANT THERAPY*

By Howard Lackay, Lt. Col., M.C., U.S.A.F., and Edmund L. Housel, M.D., *Philadelphia, Pennsylvania*

A serious and often fatal complication of auricular fibrillation, especially when associated with mitral stenosis, is the production of intraauricular thrombosis and embolism. When embolism is recurrent, the condition is likely to be fatal unless normal auricular contractions are restored and the source of emboli is thereby eliminated. Although restoration of normal rhythm by quinidine ther-

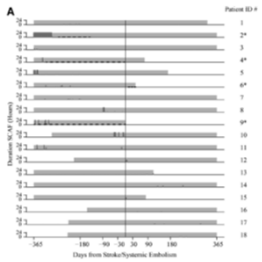
Why is AF associated with stroke?

- If dysrhythmia itself causes stroke, why is a single episode of **6 minutes of AF** associated with stroke months later?

Healey et al, *NEJM*, 2012

Poor temporal link b/w AF & stroke

- **Stroke may occur even before first manifestation of AF**
- 31% had no AF until after stroke



Brambatti et al, *Circulation*, 2014

Other atrial derangements in AF

- **AF is associated with many other atrial derangements besides dysrhythmia**
  - Endothelial dysfunction
  - Fibrosis
  - Impaired myocyte function
  - Chamber dilatation
- Dysrhythmia = marker for these derangements?

Cai et al, *Circulation*, 2002; Frustaci et al, *Circulation*, 1997; Mihm et al, *Circulation*, 2001; Vaziri et al, *Circulation*, 1994

Other atrial arrhythmias <> stroke

- Other atrial dysrhythmias are associated with stroke even in absence of AF:
  - Frequent PACs <> 2-fold higher risk of stroke

Binici et al, *Circulation*, 2010; Larsen et al, *J Am Coll Cardiol*, 2015

Other atrial arrhythmias <> stroke

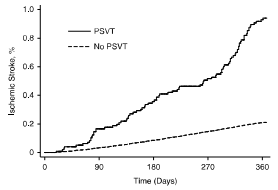


Figure. Cumulative rates of ischemic stroke are shown according to whether or not patients had a preexisting diagnosis of paroxysmal supraventricular tachycardia (PSVT).

Kamel et al, *Stroke*, 2013

What about self-limited AF?

- Perioperative AF assumed to be self-limited
- Not seen as long-term risk factor for ischemic stroke
- No recommendations for long-term follow-up or management
- But link with long-term stroke is unknown

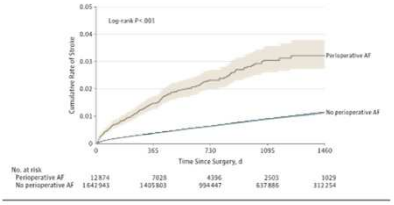
Epstein et al, *Chest*, 2005

What about self-limited AF?

- 1.7 million patients hospitalized for surgery across CA from 2007-2010
- Excluded those with AF before index hospitalization or stroke before or during index hospitalization
- Predictor variable: new-onset AF during index hospitalization
- Patients followed for up to 4 years for ischemic stroke

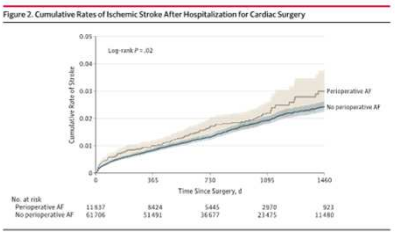
What about self-limited AF?

Figure 1. Cumulative Rates of Ischemic Stroke After Hospitalization for Noncardiac Surgery



What about self-limited AF?

Figure 2. Cumulative Rates of Ischemic Stroke After Hospitalization for Cardiac Surgery



What about self-limited AF?

Type of Surgery	Cumulative Rate of Stroke 1 Year After Hospitalization, % (95% CI)		Hazard Ratio (95% CI)
	Perioperative Atrial Fibrillation	No Perioperative Atrial Fibrillation	
Noncardiac	1.47 (1.24-1.75)	0.36 (0.35-0.37)	2.0 (1.7-2.3)
Cardiac	0.99 (0.81-1.20)	0.83 (0.76-0.91)	1.3 (1.1-1.6)

What about self-limited AF?

- Self-limited perioperative AF signifies a **long-term** increase in stroke risk
- Clinical implications:
  - Patients should be followed for AF recurrence
  - Anticoagulation?
- Research implications:
  - Is it all about the dysrhythmia?

Gialdini et al, *JAMA*, 2014

What about even earlier markers?

- Left atrial abnormality on 12-lead ECG is a marker of fibrosis, elevated filling pressures, and dilatation

Hancock et al, *JACC*, 2009

MESA cohort

- 6,741 participants without vascular disease in the Multi-Ethnic Study of Atherosclerosis
- Baseline digital measurements of P-wave area, duration, and terminal force in lead V_1 ($PTFV_1$)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke

MESA cohort

- $PTFV_1$ associated with incident stroke
  - HR per SD, 1.21; 95% CI, 1.02-1.44
- No change when adjusting for incident AF

Kamel et al, *Stroke*, 2014

CHS cohort

- Association of P-wave morphology with vascular brain injury in the Cardiovascular Health Study
- Predictor: $PTFV_1$
- Covariates: baseline confounders + incident AF
- MRI outcomes:
  - Infarcts
  - White matter grade

CHS cohort

- 3,129 participants with MRI data
- $PTFV_1$ associated with prevalent infarcts
  - RR per SD, 1.09; 95% CI, 1.04-1.16 (any infarcts)
  - RR per SD, 1.22; 95% CI, 1.08-1.38 (non-lacunar)
- No change when adjusting for incident AF

Kamel et al, *Stroke*, 2015

ARIC cohort

- 14,542 participants without AF in the Atherosclerosis Risk in Communities study
- Predictor: left atrial abnormality ($PTFV_1$ >4000)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke subtypes

ARIC cohort

- 14,542 participants without AF in the Atherosclerosis Risk in Communities study
- Predictor: left atrial abnormality ($PTFV_1$ >4000)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke subtypes
  - **Hypothesis: left atrial abnormality is more strongly associated with non-lacunar than lacunar stroke**

ARIC cohort

- Associations of left atrial abnormality with stroke:
  - Any ischemic stroke: HR, 1.3 (95% CI, 1.1-1.6)
  - Lacunar stroke: HR, 0.9 (95% CI, 0.6-1.4)
  - Non-lacunar stroke: HR, 1.5 (95% CI, 1.1-2.1)
- No change when adjusting for incident AF

Kamel et al, *Ann Neurol*, 2015

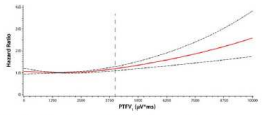


FIGURE 4: Relationship between P-wave terminal force in electrocardiogram lead V_1 ($PTFV_1$) and the risk of incident ischemic stroke. The plot displays the results of a restricted cubic spline model (see text for details). The dotted horizontal lines represent the 95% confidence interval, and the dotted vertical line represents the threshold of 4,000μV*ms that was used to define left atrial abnormality.

Kamel et al, *Ann Neurol*, 2015

NOMAS cohort

- Case-cohort comparison of 241 patients with ischemic stroke versus a random subcohort without stroke (N = 798)
- Predictor: $PTFV_1$ (measured by hand)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke subtypes

NOMAS cohort

- Case-cohort comparison of 241 patients with ischemic stroke versus a random subcohort without stroke (N = 798)
- Predictor: $PTFV_1$ (measured by hand)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke subtypes
  - **Hypothesis: left atrial abnormality is more strongly associated with cryptogenic or cardioembolic stroke subtypes**

NOMAS cohort

- Associations of left atrial abnormality with ischemic stroke:
  - Any stroke: HR per SD, 1.20 (95% CI, 1.03-1.39)
  - Non-cardioembolic stroke: HR per SD, 1.14 (95% CI, 0.92-1.40)
  - Cryptogenic/cardioembolic stroke: HR per SD, 1.31 (95% CI, 1.08-1.58)
- No change when adjusting for incident AF

Kamel et al, *Stroke*, 2015

Limitations

- No direct imaging of left atrial size/morphology
- Potential for residual confounding
- Cannot fully rule out subclinical AF as mediator

Summary

- A commonly used ECG measure of left atrial abnormality ($PTFV_1$) is associated with vascular brain injury independently of AF

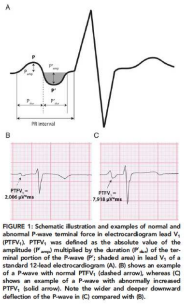
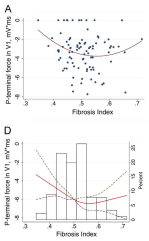


FIGURE 1: Schematic illustration and examples of normal and abnormal P-wave terminal force in electrocardiogram lead V_1 ($PTFV_1$). $PTFV_1$ was defined as the absolute value of the amplitude (P_{amp}) multiplied by the duration (P_{dur}) of the terminal portion of the P-wave (P_t; shaded area) in lead V_1 of a standard 12-lead electrocardiogram (A). (B) shows an example of a P-wave with normal $PTFV_1$ (dashed arrow), whereas (C) shows an example of a P-wave with abnormally increased $PTFV_1$ (solid arrow). Note the wider and deeper downward deflection of the P-wave in (C) compared with (B).

What does $PTFV_1$ represent?

Index	Per 1 mV*ms of PTF_{V1}	P
Maximum LA volume index (mL/m^2)	−1.6 (−2.8 to −0.4)	.010
Minimum LA volume index (mL/m^2)	−1.2 (−1.9 to −0.4)	.003
Global LAEF (%)	+1.1 (+0.1 to +2.1)	.026
LA reservoir function (%)	+7.2 (+1.1 to +13.3)	.021



Tiffany Win et al, *Heart Rhythm*, 2015

Evidence from other groups?

- **Left atrial size/function** and **NT-proBNP** have been associated with stroke and MRI-defined vascular brain injury independently of AF

Benjamin et al, *Circulation*, 1995; Folsom et al, *Stroke*, 2013; Russo et al, *JACC Cardiovasc Imaging*, 2013; Cushman et al, *Stroke*, 2014; Yaghi et al, *Stroke*, 2015

Updated hypothesis

- **Atrial cardiopathy can cause thromboembolism even in the absence of AF**
  - Dysrhythmia that defines AF is a common manifestation of atrial cardiopathy but is not necessary to cause thromboembolism

Comments and Opinions

Atrial Fibrillation and Mechanisms of Stroke
Time for a New Model

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

Received October 28, 2015; accepted December 4, 2015.
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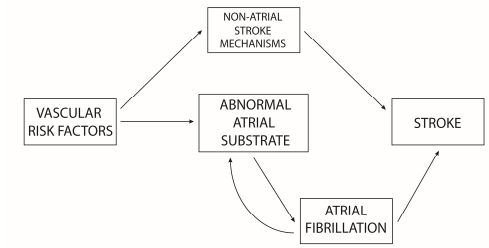
The opinions expressed in the article are not necessarily those of the editors or of the American Heart Association.
Guest Editor for this article was Seemant Chaturvedi, MD.
Correspondence to Hooman Kamel, MD, 407 E 61st St, New York, NY 10065. E-mail hok9010@med.cornell.edu
(*Stroke*. 2016;47:895-900. DOI: 10.1161/STROKEAHA.115.012004.)

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.115.012004



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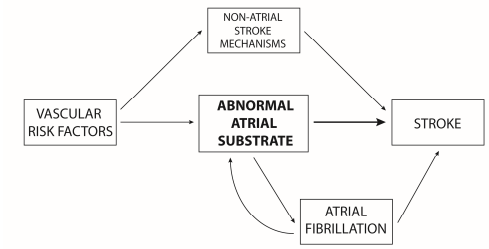

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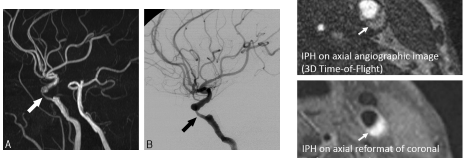
What about other embolic sources?

- Underlying sources of embolism are likely heterogeneous
- Besides atrial cardiopathy, another common cause is likely nonstenosing large-artery atherosclerosis



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LETTER TO THE EDITOR

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

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.

JACC: CARDIOVASCULAR IMAGING

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Therapeutic implications

- Heterogeneous mechanisms require personalized treatment
  - Given parallels to AF, atrial cardiopathy may benefit from anticoagulation
  - Less evidence for benefit of anticoagulation in large-vessel disease

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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

Stroke. 2013;44:714-719; originally published online January 22, 2013;
doi: 10.1161/STROKEAHA.112.675942
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

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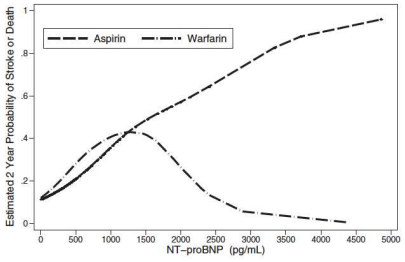

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Next steps

- Left atrial abnormality and racial differences in stroke risk (LANTERN)
- Proposed trial of anticoagulant versus antiplatelet therapy in patients with cryptogenic stroke and atrial cardiopathy (ARCADIA)
- Relationship between atrial cardiopathy and nonstenosing atherosclerotic plaque (ILLUMINATE)

AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA)

NIH StrokeNet Clinical Trial

PIs: Hooman Kamel, Mitchell Elkind, Will Longstreth, David Tirschwell
Study Statistician: Richard Kronmal
StrokeNet NCC PI: Joe Broderick
ARCADIA Data Core PI: Caitlyn Ellerbe

Study Cores:
Blood Laboratory: Eldad Hod
Echocardiography: Marco Di Tullio
ECG: Elsayed Soliman

Drug supply: BMS-Pfizer Partnership
Laboratory assay support: Roche

ARCADIA: Anticoagulation for Cryptogenic Stroke + Atrial Cardiopathy

- Primary hypothesis:
  - Apixaban superior to aspirin for preventing recurrent stroke in patients with cryptogenic stroke and atrial cardiopathy
- Atrial cardiopathy defined as ≥1 of following:
  - $PTFV_1$ >5000 µV*ms on 12-lead ECG
  - Left atrial size index ≥3 cm/mL^2 on echocardiogram (severe enlargement)
  - Serum NT-proBNP >250 pg/mL

Likely Benefits of ARCADIA

- Maximize chance of success by targeting the most biologically plausible group (i.e., those most similar to AF)
- Allow personalized treatment for preventing recurrent stroke
- Advance understanding of stroke pathogenesis
- Potentially set the stage for a primary prevention trial in patients with atrial cardiopathy

Acknowledgments

- NIH/NINDS
- Mitchell Elkind
- Will Longstreth
- David Tirschwell
- Richard Kronmal
- Costantino Iadecola
- Elsayed Soliman
- Richard Devereux
- Peter Okin

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