Afib + Cryptogenic Stroke: A Neurologist View

American Heart Association | American Stroke Association
Learn and Live

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Center for Neurosciences

Tucson Medical Center

Center for NEUROSCIENCES
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Objectives

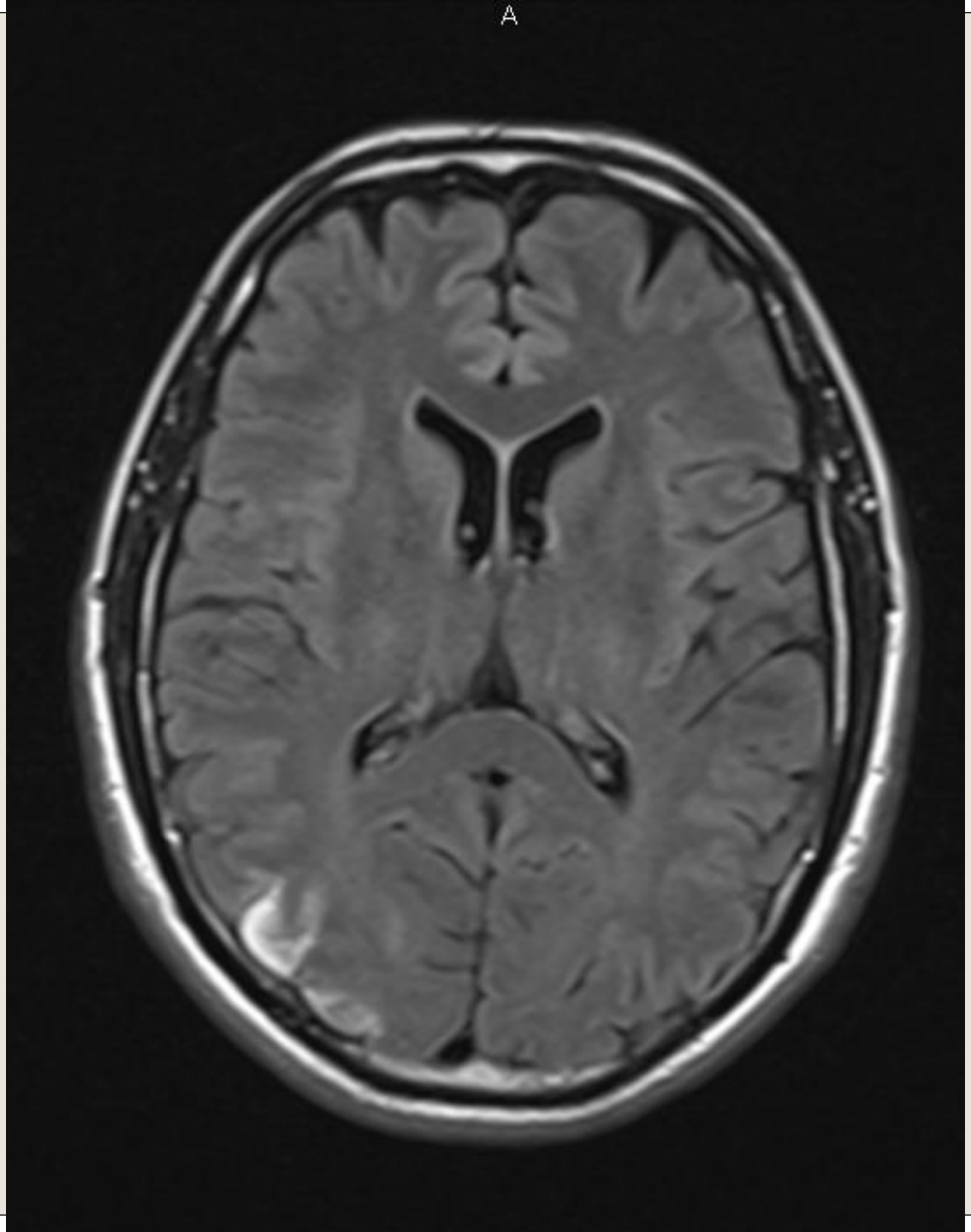
- Discuss the Risks of Cardioembolic Stroke
- Review Afib Related Stroke
- Review Prevention Strategies for Afib Related Stroke
- Review Approach to Evaluating Cryptogenic Stroke

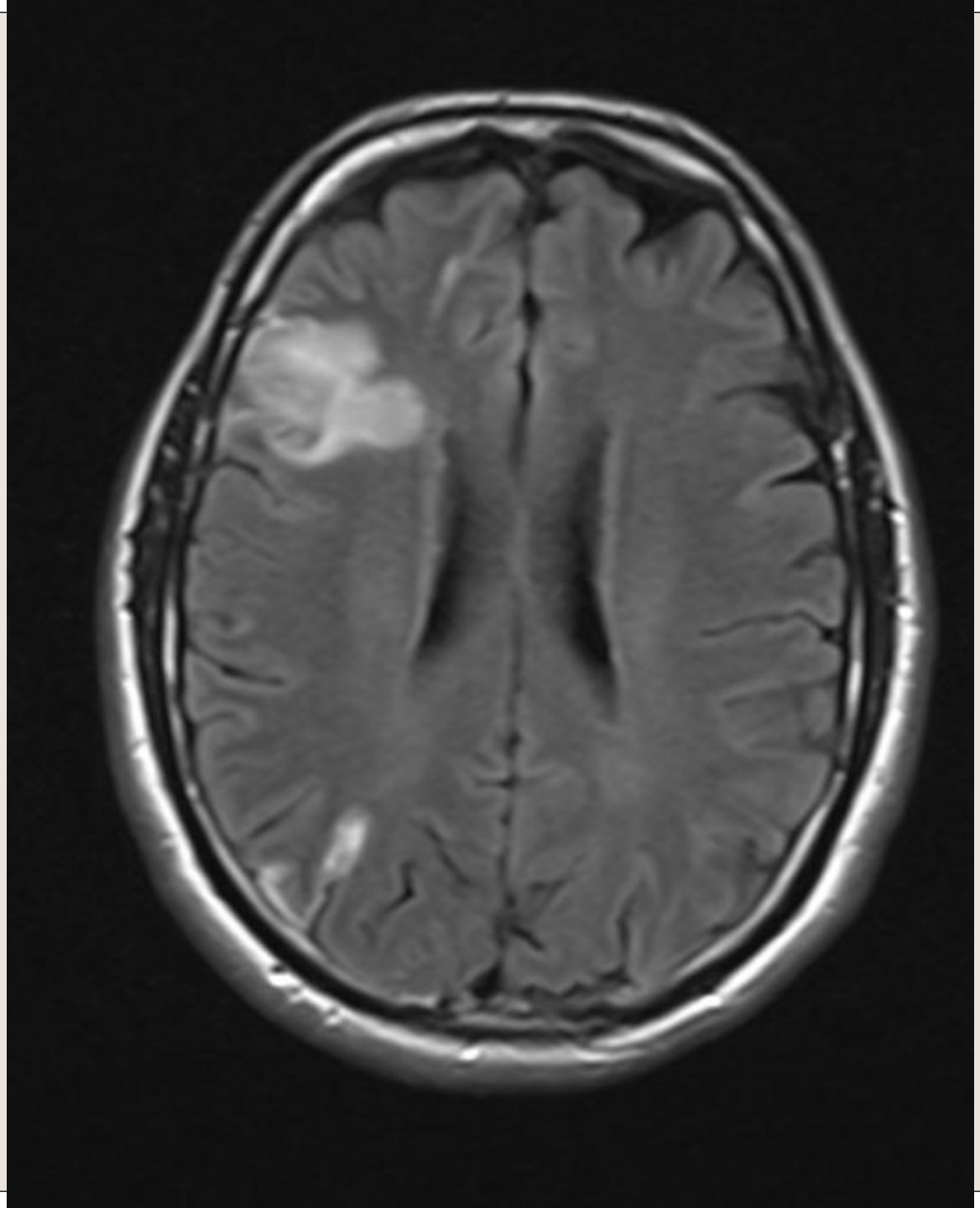
CASE

- 64 year old male
  - HPI:
    - Transient loss of vision on left side
  - PMH –
    - No medical issues
  - MEDS
    - None
  - SOCIAL:
    - Avid cyclist with over 100 miles week

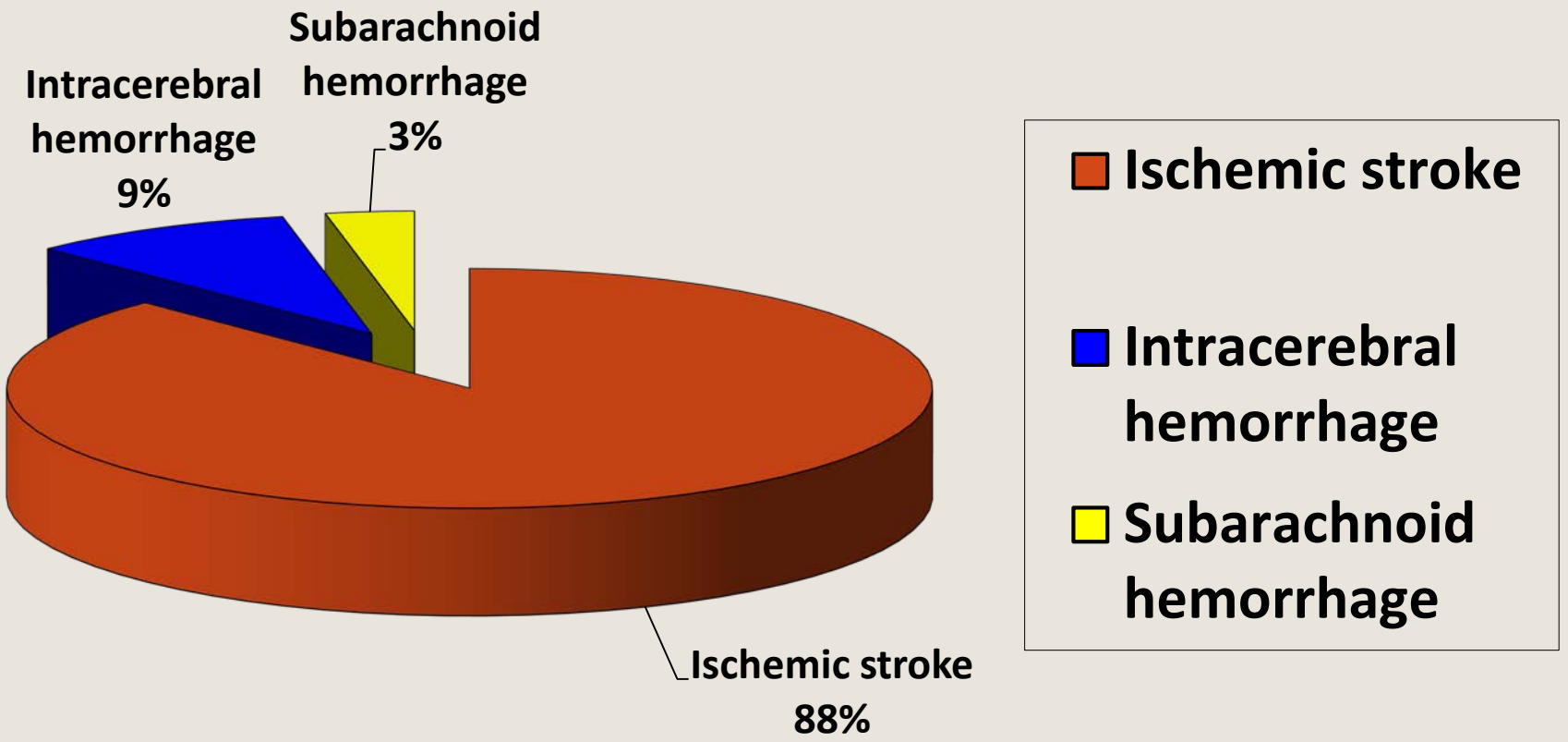
Case

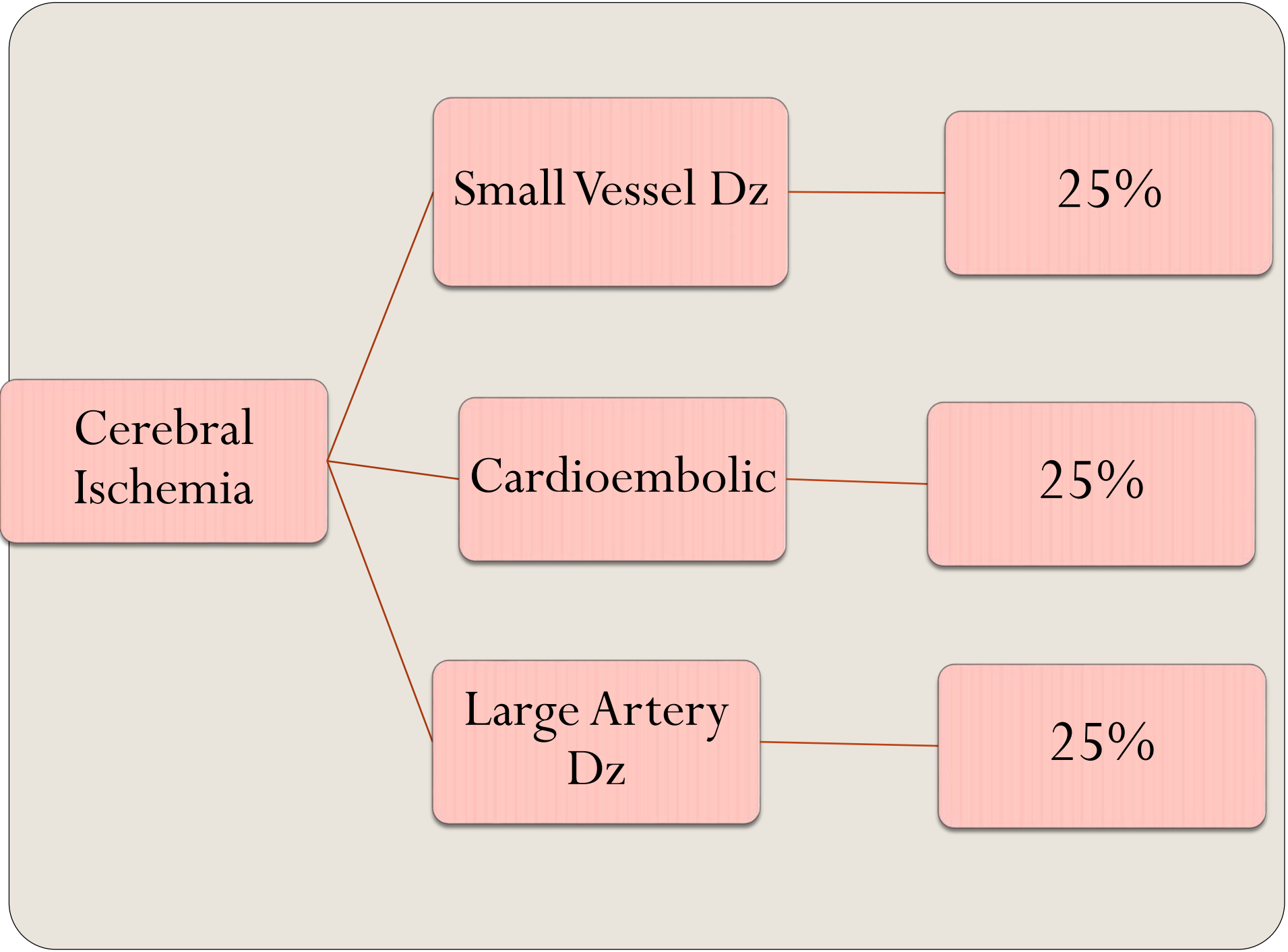
- July 2012
  - Referred to ophthalmologist – “Amaurosis Fugax”
  - Referred to neurologist
    - MRI


A



~795,000 Strokes Annually




Cerebral Ischemia
Small Vessel Dz
25%
Cardioembolic
25%
Large Artery Dz
25%

Cardioembolic Stroke

- Accounts for substantial proportion of overall stroke burden[1]
  - High prevalence
  - Greater severity of stroke
  - Less favorable prognosis
  - High recurrence risk

1. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27(10):1760Y1764.

Cardioembolic Causes

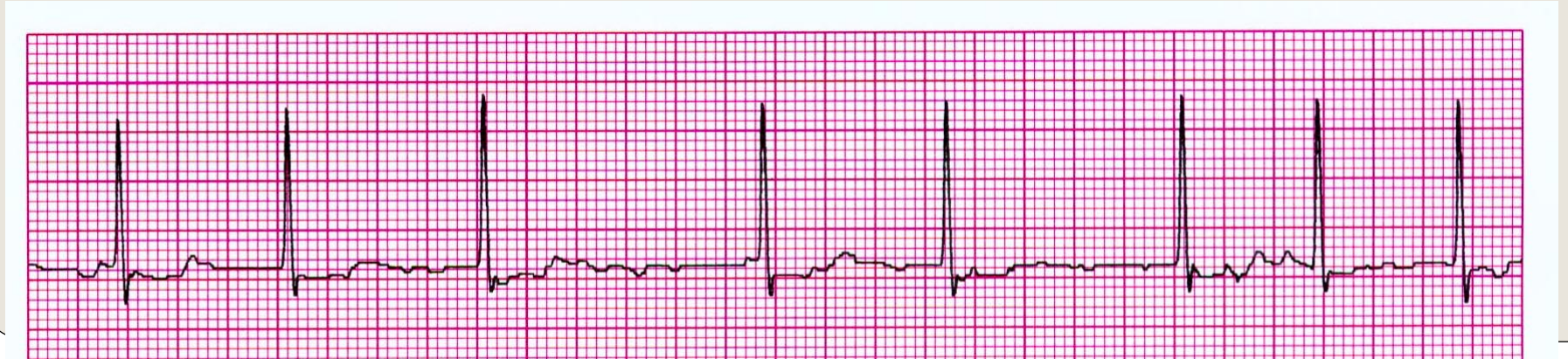
1. Atrial Fibrillation
2. Valvular disease
3. Heart Failure
4. Patent Foramen Ovale

Atrial Fibrillation (AF)

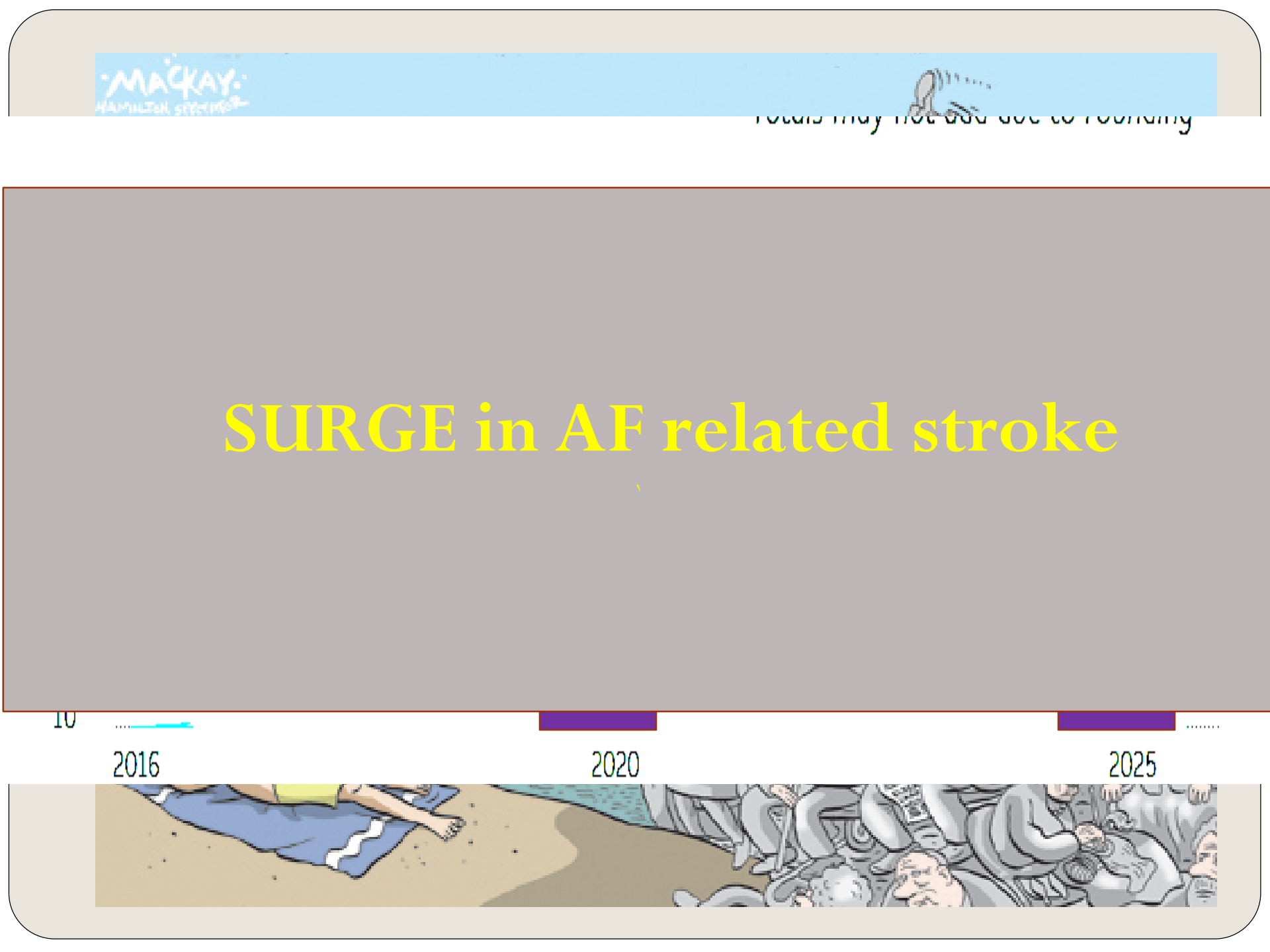
- >50% of cardioembolic strokes

- 2.7 million Americans
- 33 million worldwide
  - 2-3% at age 60
  - 8-10% at age 80

- Given increased risk of AF with age…



SURGE in AF related stroke



Afib

- Embolization from left atrial appendage and left atrium

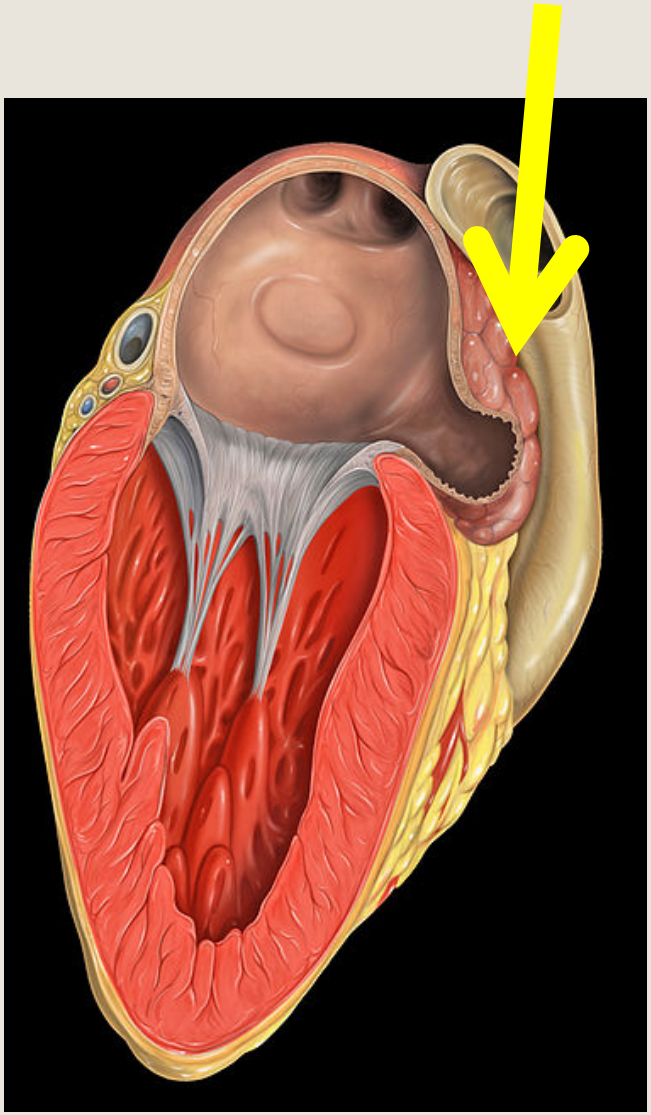
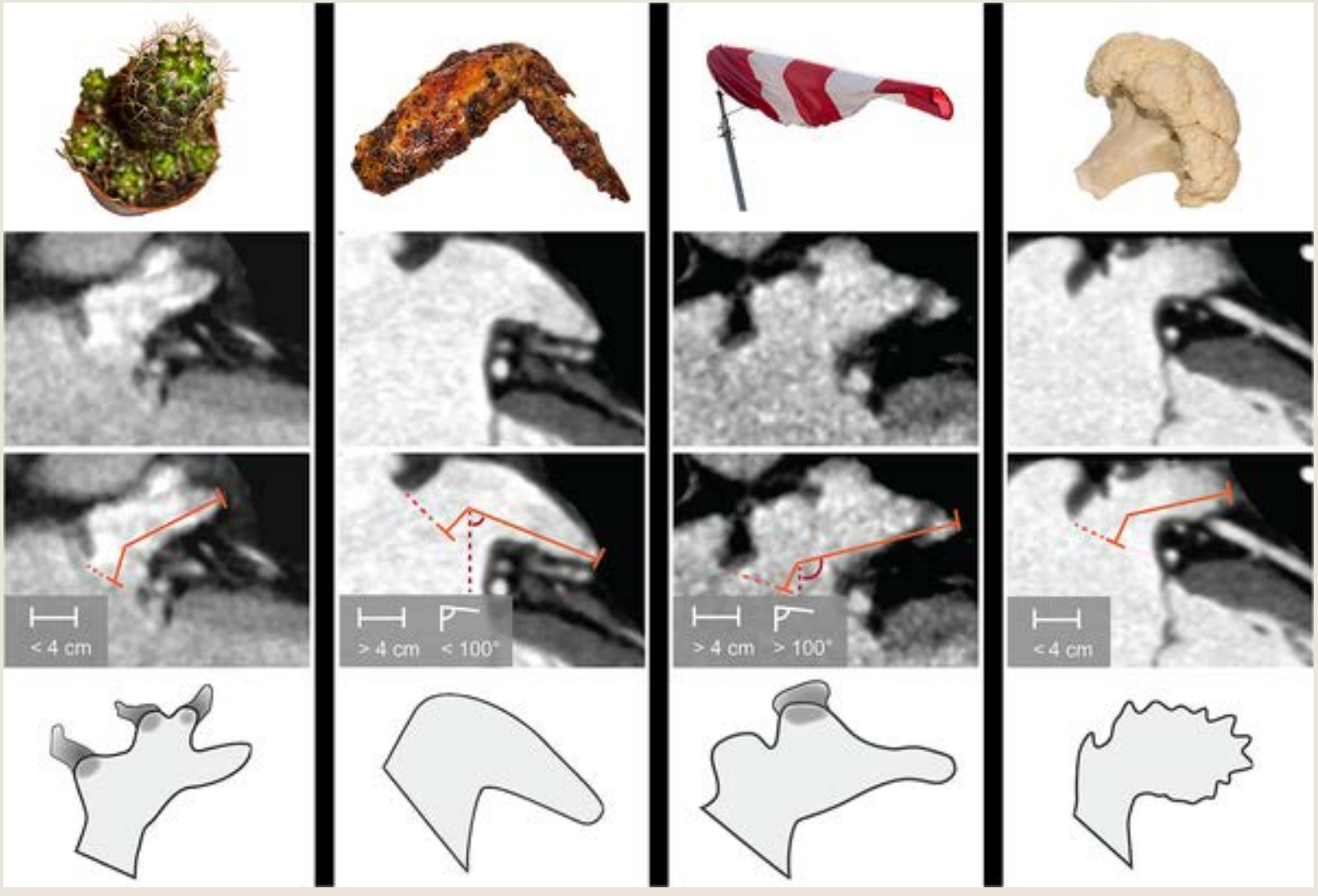


Fig 1. LAA morphology types based on Wang's classification with Kimura's quantitative limits.



Korhonen M, Muuronen A, Arponen O, Mustonen P, Hedman M, et al. (2015) Left Atrial Appendage Morphology in Patients with Suspected Cardiogenic Stroke without Known Atrial Fibrillation. PLoS ONE 10(3): e0118822. doi:10.1371/journal.pone.0118822
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0118822

PLOS | ONE

Afib

- Embolization from left atrial appendage and left atrium
- Risk same for paroxysmal vs persistent afib
  - How much afib is enough?

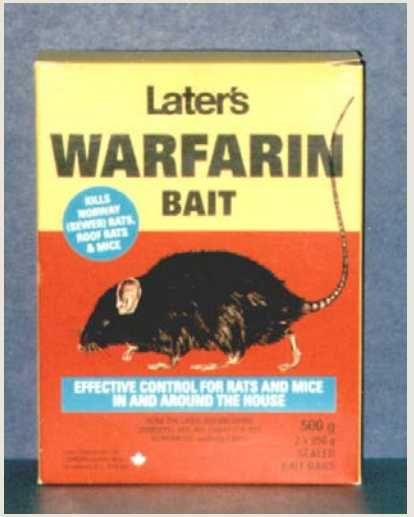
European Heart Journal (2014) **35**, 508–516
doi:10.1093/eurheartj/eht491

Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices)

Giuseppe Boriani[1]*, Taya V. Glotzer[2], Massimo Santini[3], Teena M. West[4], Mirko De Melis[4], Milan Sepsi[5], Maurizio Gasparini[6], Thorsten Lewalter[7], John A. Camm[8], and Daniel E. Singer[9]

1. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9
2. Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke prevention Strategies based on Atrial Fibrillation information from implanted devices). Eur Heart J 2014; 35: 508-16

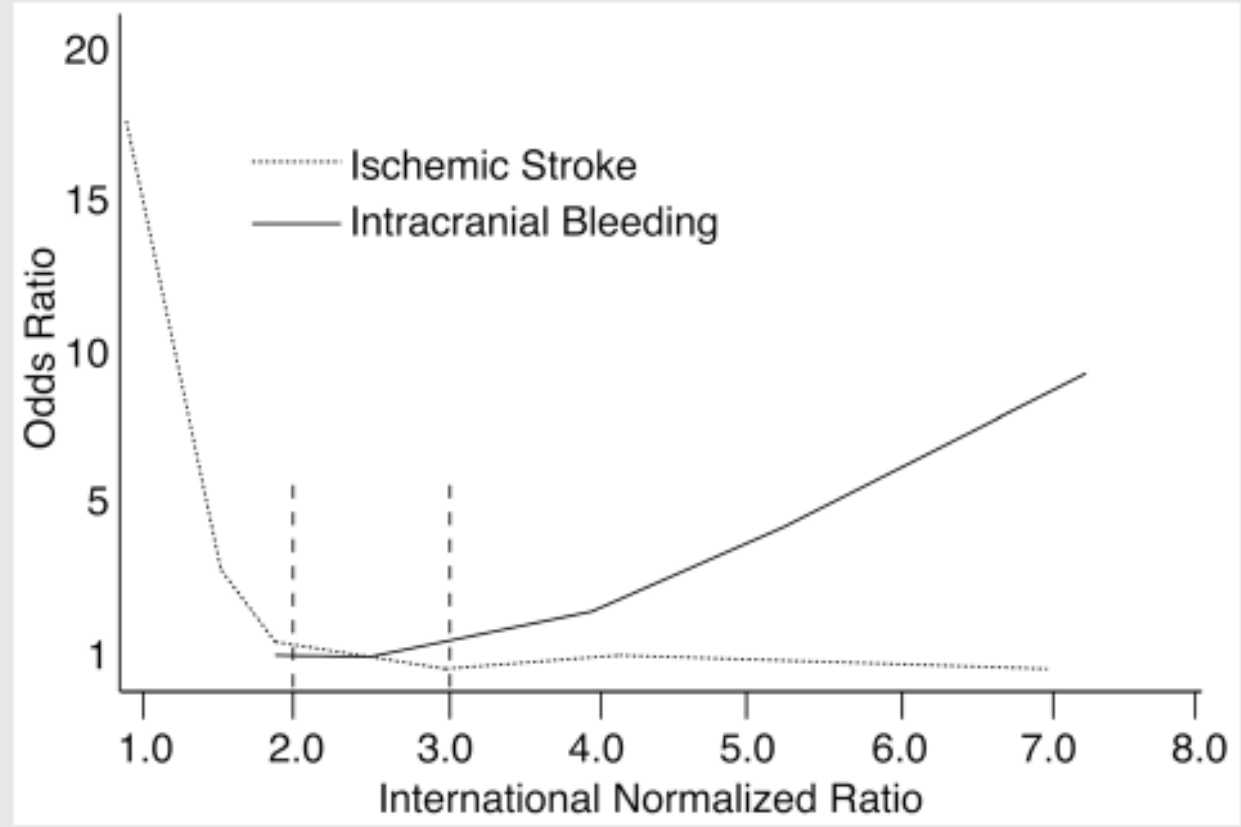
Treatment



- Aspirin
  - RR – 21%
- Warfarin
  - RR – 68%
  - Effectively reduces annual risk – 5% to 1.4%
- Aspirin + Clopidogrel
  - Better than Aspirin[1]
  - But not as good as warfarin[1]
  - Increased risk of bleed ~ similar to warfarin[1]

1. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360(20):2066Y2078

Treatment



1. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360(20):2066Y2078

Treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Afib

$CHADS_2$ Score	Annual Stroke Risk %	95% Confidence Interval	Recommendation
0	1.9	1.2–3.0	No antithrombotic
1	2.8	2.0–3.8	Antiplatelet or anticoagulation
2	4.0	3.1–5.1	Anticoagulation
3	5.9	4.6–7.3	Anticoagulation
4	8.5	6.3–11.1	Anticoagulation
5	12.5	8.2–17.5	Anticoagulation
6	18.2	10.5–27.4	Anticoagulation

1. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285(22):2864Y2870.

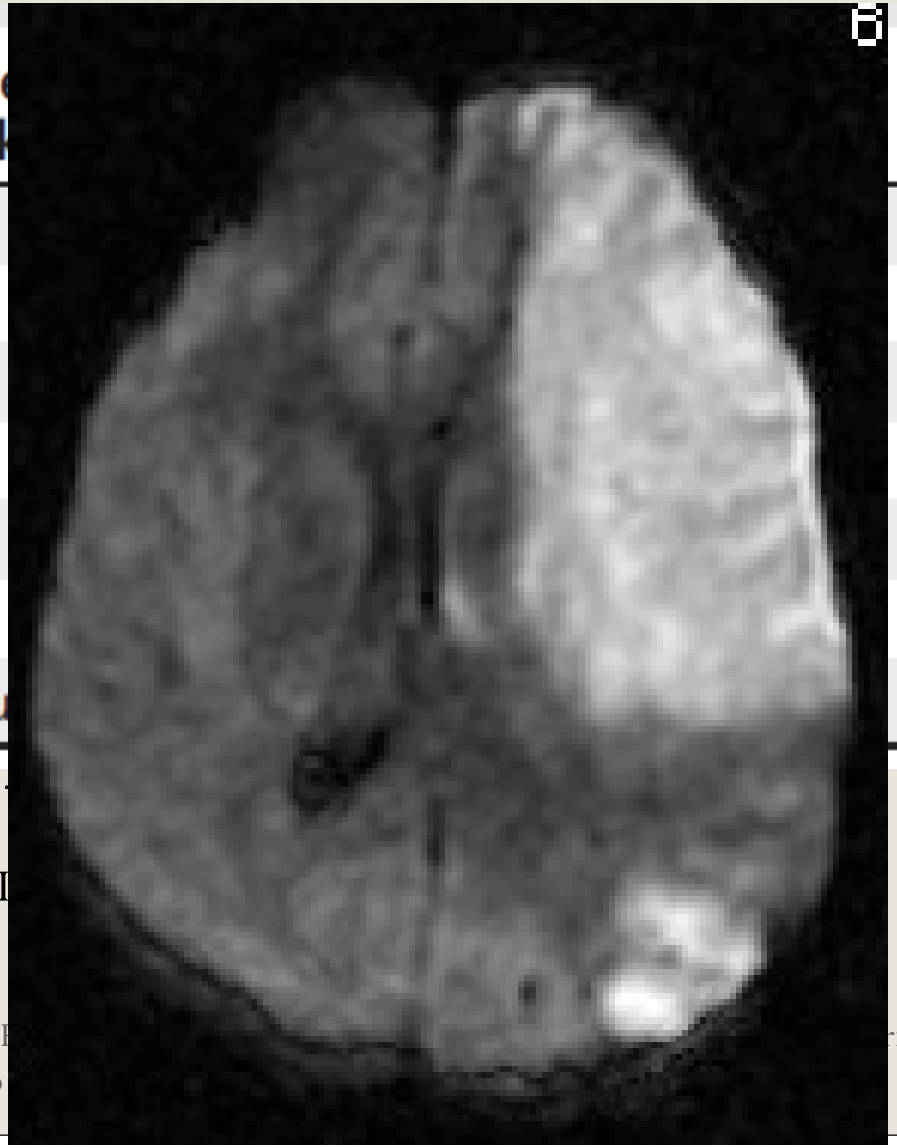
CHA_2DS_2-VASc Score	Annual Stroke Risk %	95% Confidence Interval	Recommendation
0	0.8	0.6–1.0	No antithrombotic
1	2.0	1.7–2.4	Antiplatelet or anticoagulation
2	3.7	3.4–4.1	Anticoagulation
3	5.9	5.5–6.3	Anticoagulation
4	9.3	8.7–9.9	Anticoagulation
5	15.3	14.3–16.2	Anticoagulation
6	19.7	18.2–21.4	Anticoagulation
7	21.5	18.8–24.6	Anticoagulation
8	22.4	16.3–30.8	Anticoagulation
9	23.6	10.6–52.6	Anticoagulation

[a] Data from Olesen JB, et al, BMJ.[6] *www.bmj.com/content/342/bmj.d124.*

1 Olesen JB, Lip GY, HansenML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.

Treatment

HAS-BLED Score	Bleed Risk	Recommendation
0	0.9	None
1	3.4	None
2	4.1	None
3	5.8	Caution warranted
4	8.9	Caution warranted
5	9.1	Caution warranted
≥6	Insu	Caution warranted



- Drugs
  - NSAI

1 point

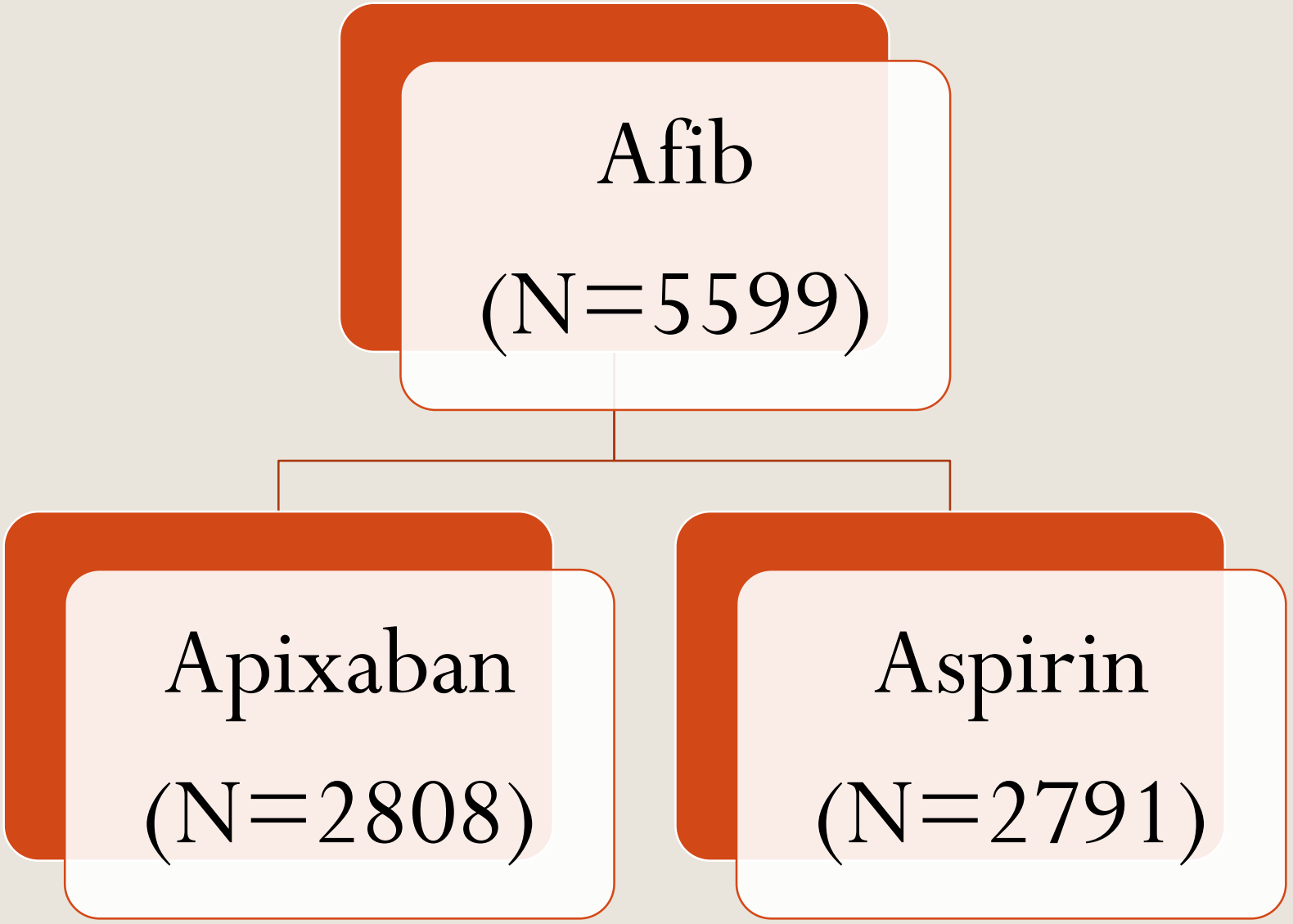
Pisters R, Lane DA, Nieuwlaat R ... risk of major bleeding in patients with atrial fibrillation: the Euro

The NEW ENGLAND JOURNAL of MEDICINE

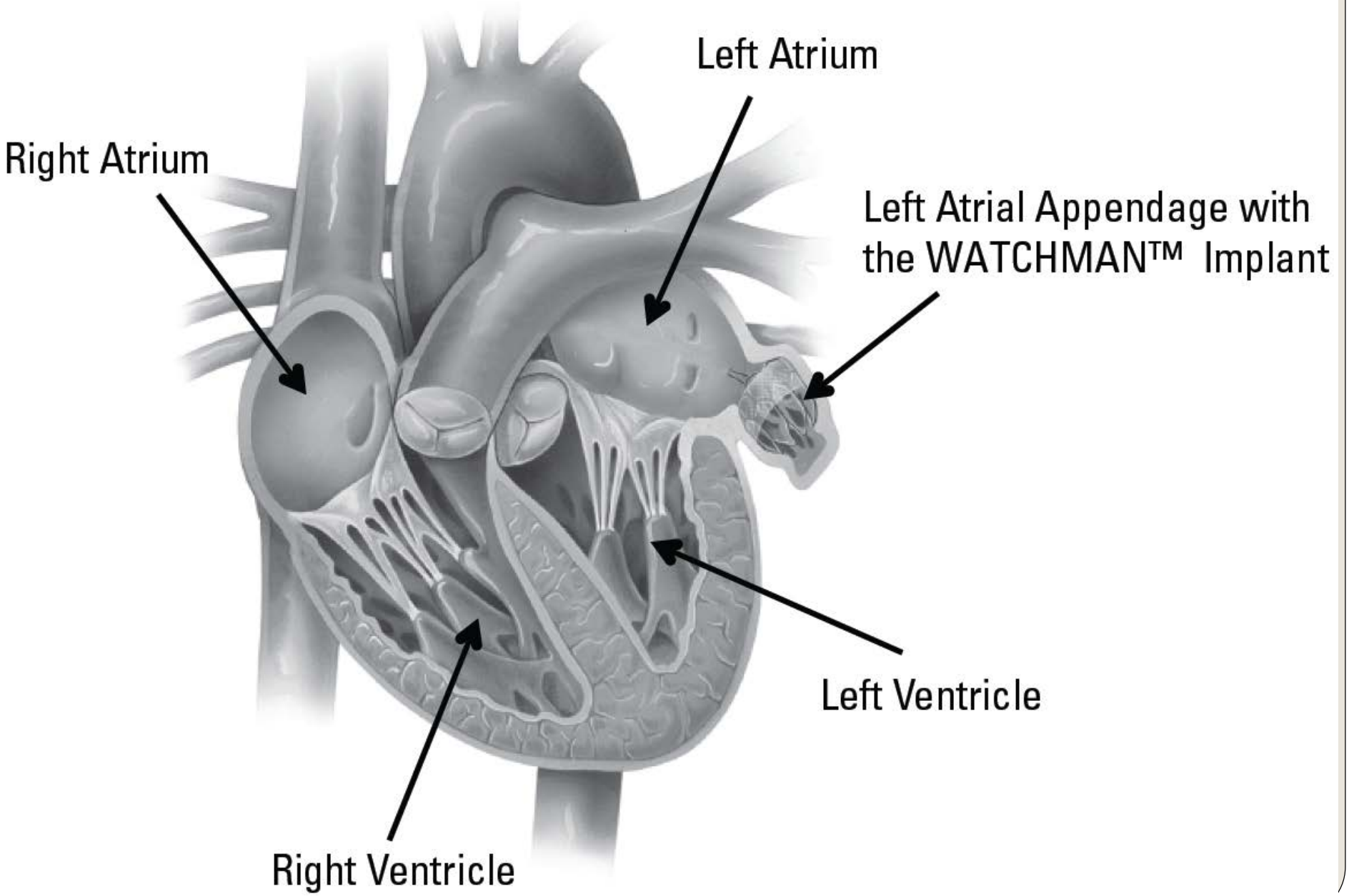
ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

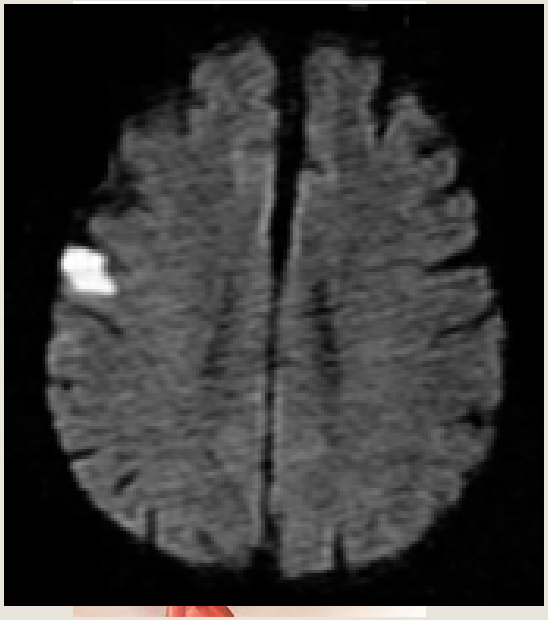
Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D.,


Afib
(N=5599)
Apixaban
(N=2808)
Aspirin
(N=2791)

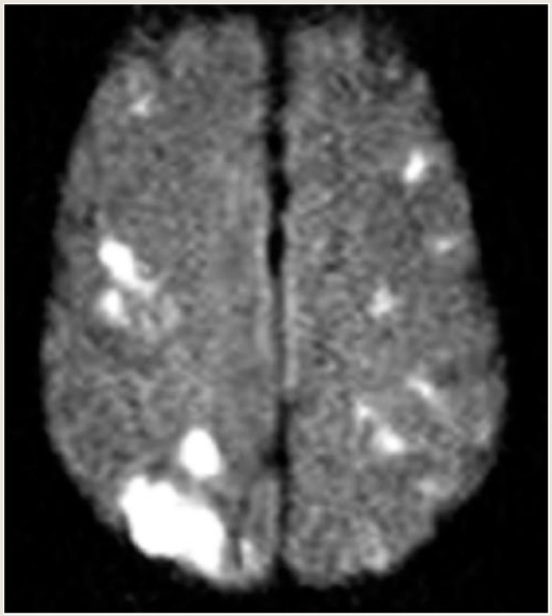
Major Bleed	Intracranial Bleed	Extracranial Bleed
Apixaban 1.4%/yr	Apixaban 0.4%/yr	Apixaban 1.1%/yr
Aspirin 1.2%/yr	Aspirin 0.4%/yr	Aspirin 0.9%/yr


Left Atrium
Right Atrium
Left Atrial Appendage with
the WATCHMAN™ Implant
Left Ventricle
Right Ventricle

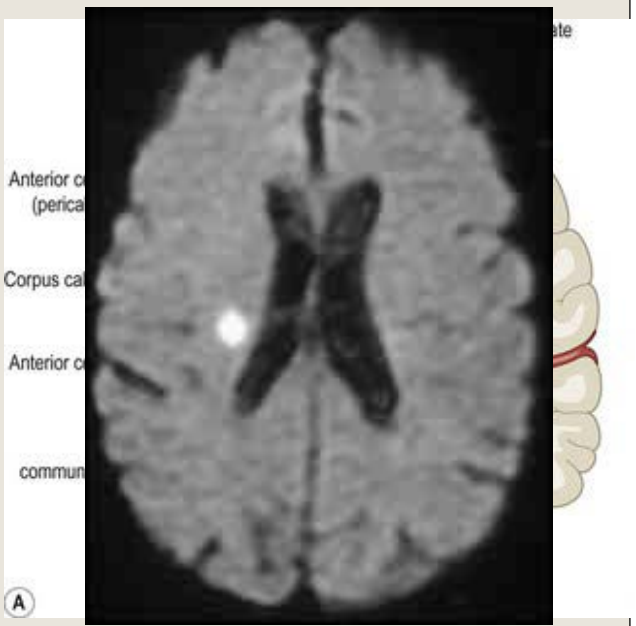
Large Artery
25%



Cardioembolic
25%



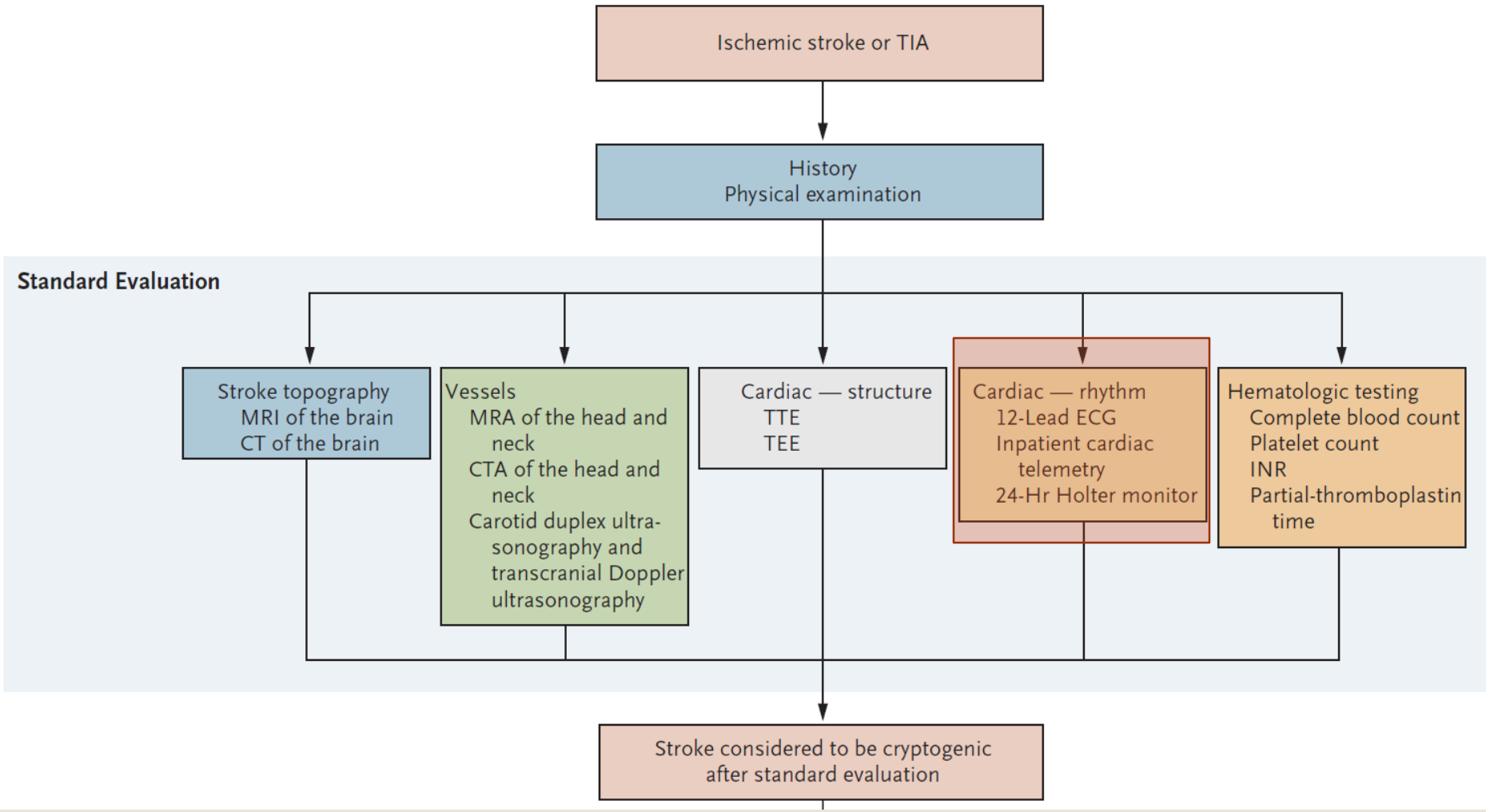
Small Vessel Dz
25%



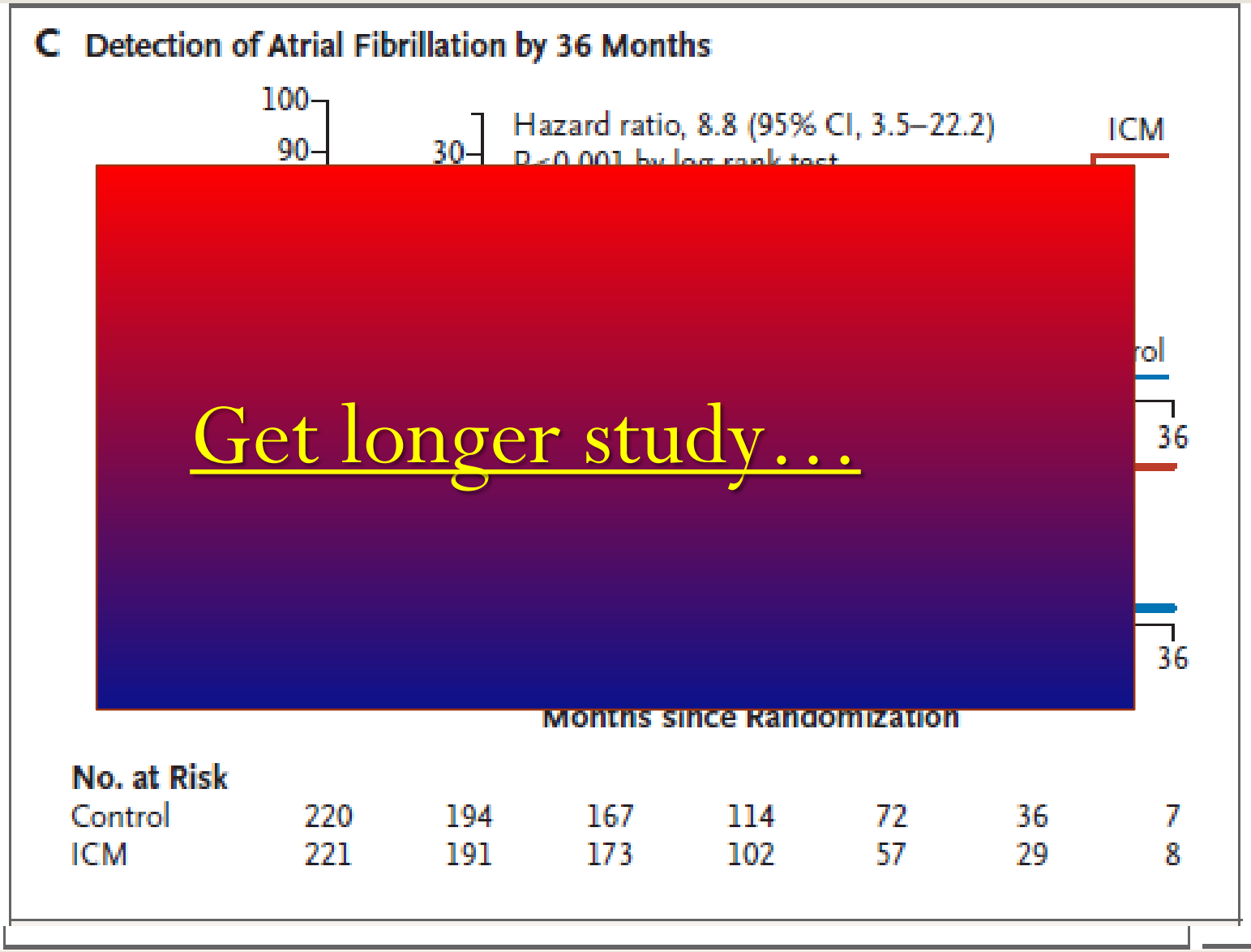
Cryptogenic Stroke

- 20-40% of all Strokes
- 120,000 to 180,00 patients per year
- Most are embolic…

Saver, J. Cryptogenic Stroke: NEJM 374;21



Saver, J. Cryptogenic Stroke: NEJM 374;21



Get longer study…

1. D. J. Gladstone, et all. Atrial Fibrillation in Patients with Cryptogenic Stroke N Engl J Med 2014 370:2467-2477
2. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-2486

AHA/ASA Guideline

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

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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)

Sequential Evaluation for afib

- Meta-anaylsis between 1980 – 2014
- 50 studies, > 11, 000 patients

- ER –EKG – 7.7%
- In hospital telemetry – 5.1%
- Ambulatory Holter (first 30 days) – 10.7%
- Second Ambulatory Evaluation (Insertable monitor) – 16.9%

- Overall Yield: 23.7%

Sposato LA, et all. Diagnosis of atrial fibrillation after stroke and TIA: A systemic review and meta-analysis. Lancet Neurol. 2015; 377-387

CARDIONET

Quick View - Aug 11, 2016

To: Pima Heart

BIOTRONIK
excellence for life

DOB: Sep 30, 1940
Phone: -

BioMonitor 2-AF (SN 91504486)
ICM implanted Jul 15, 2016

Last message: Aug 11, 2016
Last clinic follow-up: Jul 17, 2016

Device status	
Device status	OK
Battery status	OK (EOS, ERI, 50%, BOS)

Findings
Episode details received

Recordings memory	
Episodes	0 bin(s) available
Patient triggered recordings	4 bin(s) available

Sensing	
Sensing amplitude mean [mV]	0.57
Noise [% of day]	0.0

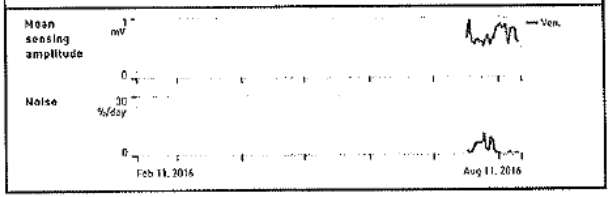
Detection settings	
Atrial fibrillation (AF)	Low
High ven. rate (HVR)	ON
Bradycardia	ON
Sudden rate drop	ON
Asystole duration [s]	3
Patient trigger	ON

Ven. arrhythmia since Jul 17, 2016	
High ven. rate episodes per day	0

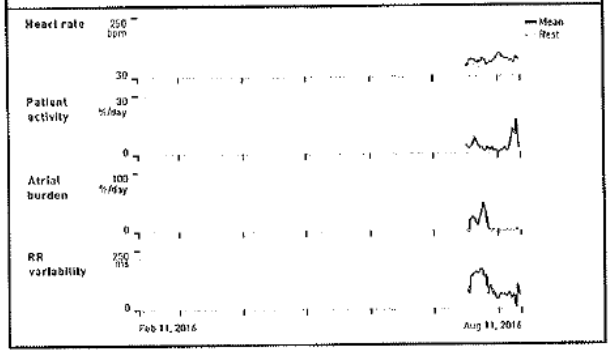
Atr. arrhythmia since Jul 17, 2016	
Atrial burden [% of day]	8.7
Atrial fibrillation episodes per day	5
Mean ven. heart rate during atr. burden [bpm]	91

Brady./Asyst. since Jul 17, 2016	
Bradycardia episodes per day	8
Sudden rate drop episodes per day	16
Asystole episodes per day	0
Patient triggered recordings per day	0

Sensing trends



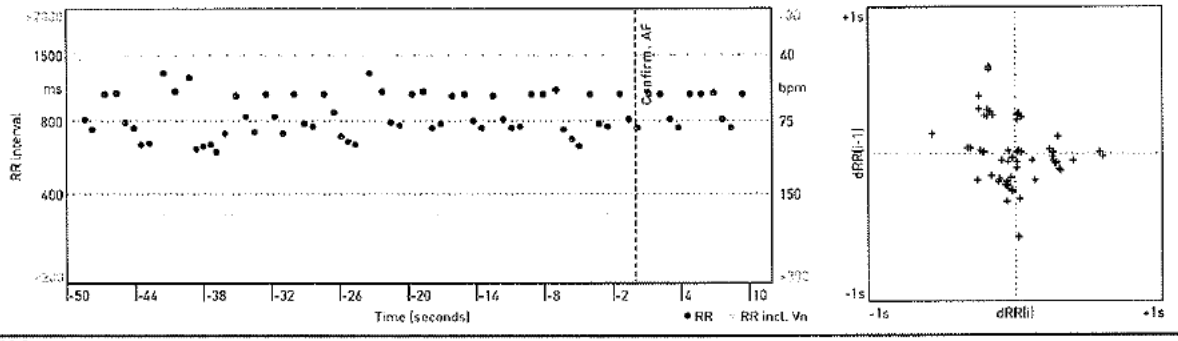
Long term trends



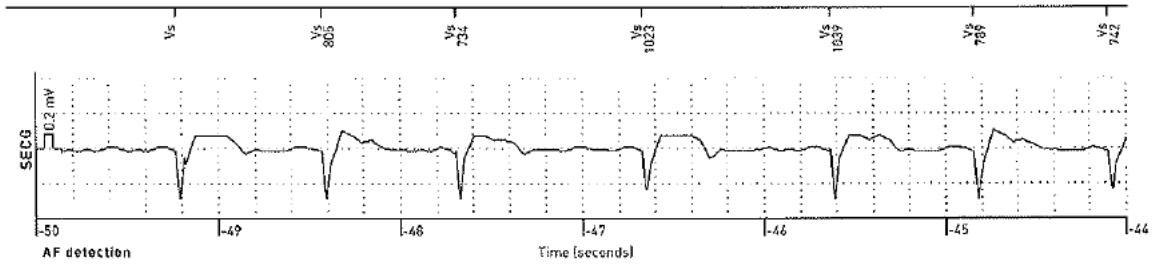
Recordings - Episode 81:

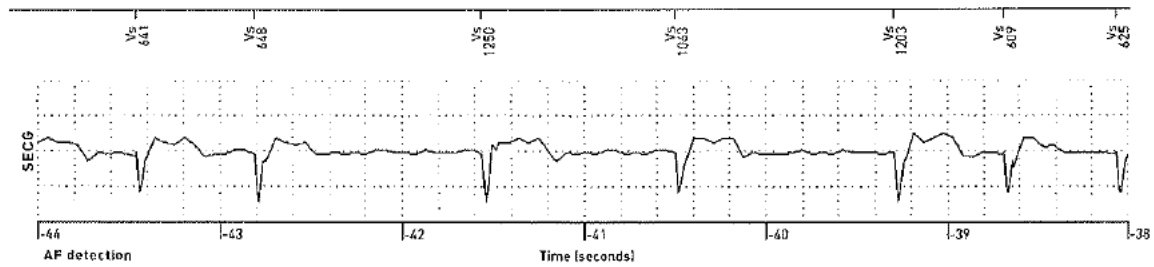
General	
Episode number	81
Episode type	AF
Detection	Aug 9, 2016 8:21:18 AM
Termination	Aug 9, 2016 8:52:54 AM
Duration	31min 36s
Device settings no.	3
Mean ven. rate / RR interval [ms]	896

Tachogram and Lorenz plot



SECG

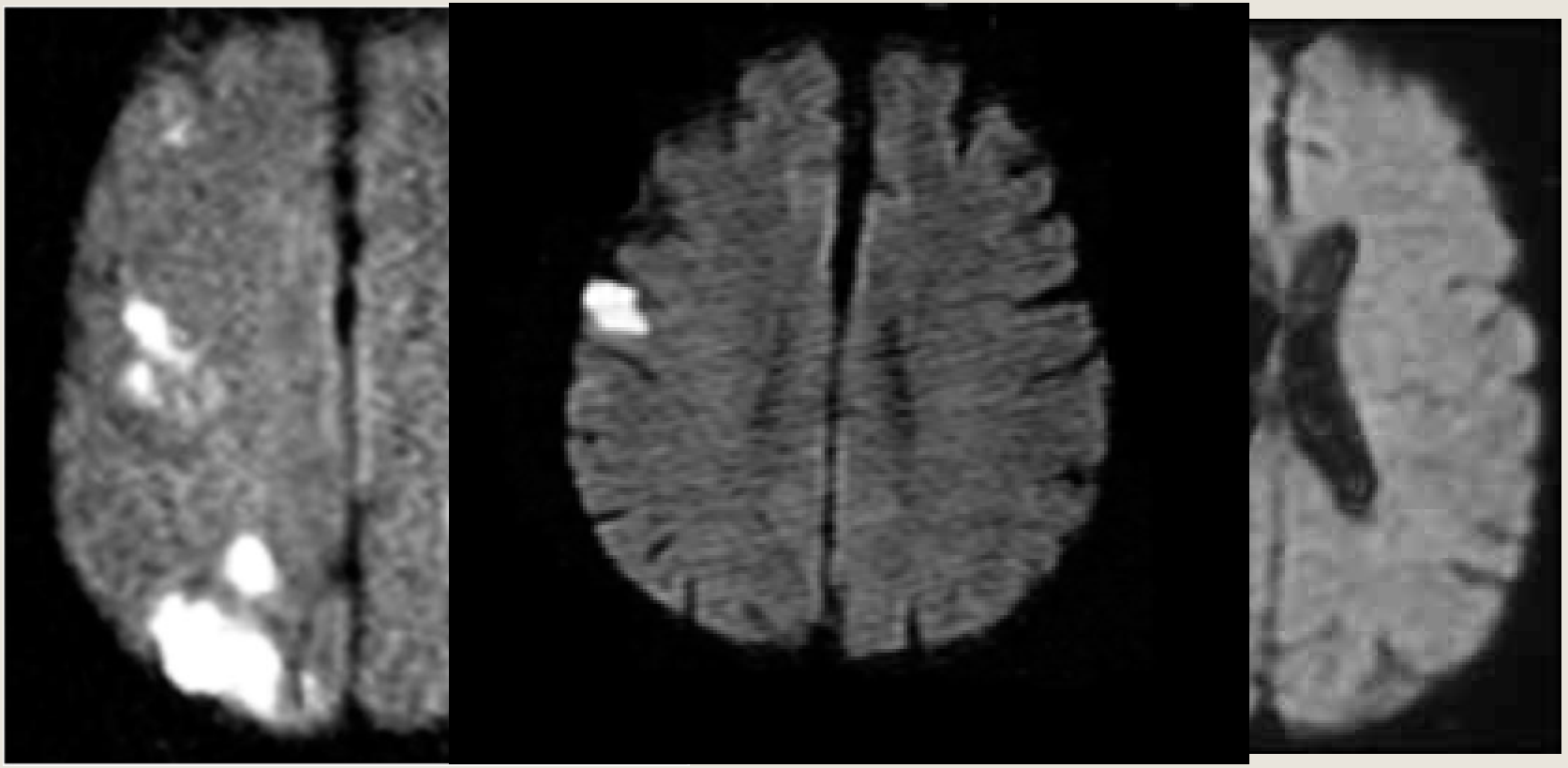




Who is at highest risk?

Higher Risk Patients

- Topographic pattern of stroke gives us insight



Higher Risk Patients

- Higher CHADs-VASc (2 or greater)

Saver, J. Cryptogenic Stroke: NEJM 374;21
Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9

Higher Risk Patients

- Higher CHADs-VASc (2 or greater)

Table 3. Risk of Ischemic Stroke or Systemic Embolism after the 3-Month Visit, According to Baseline $CHADS_2$ Score and According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.

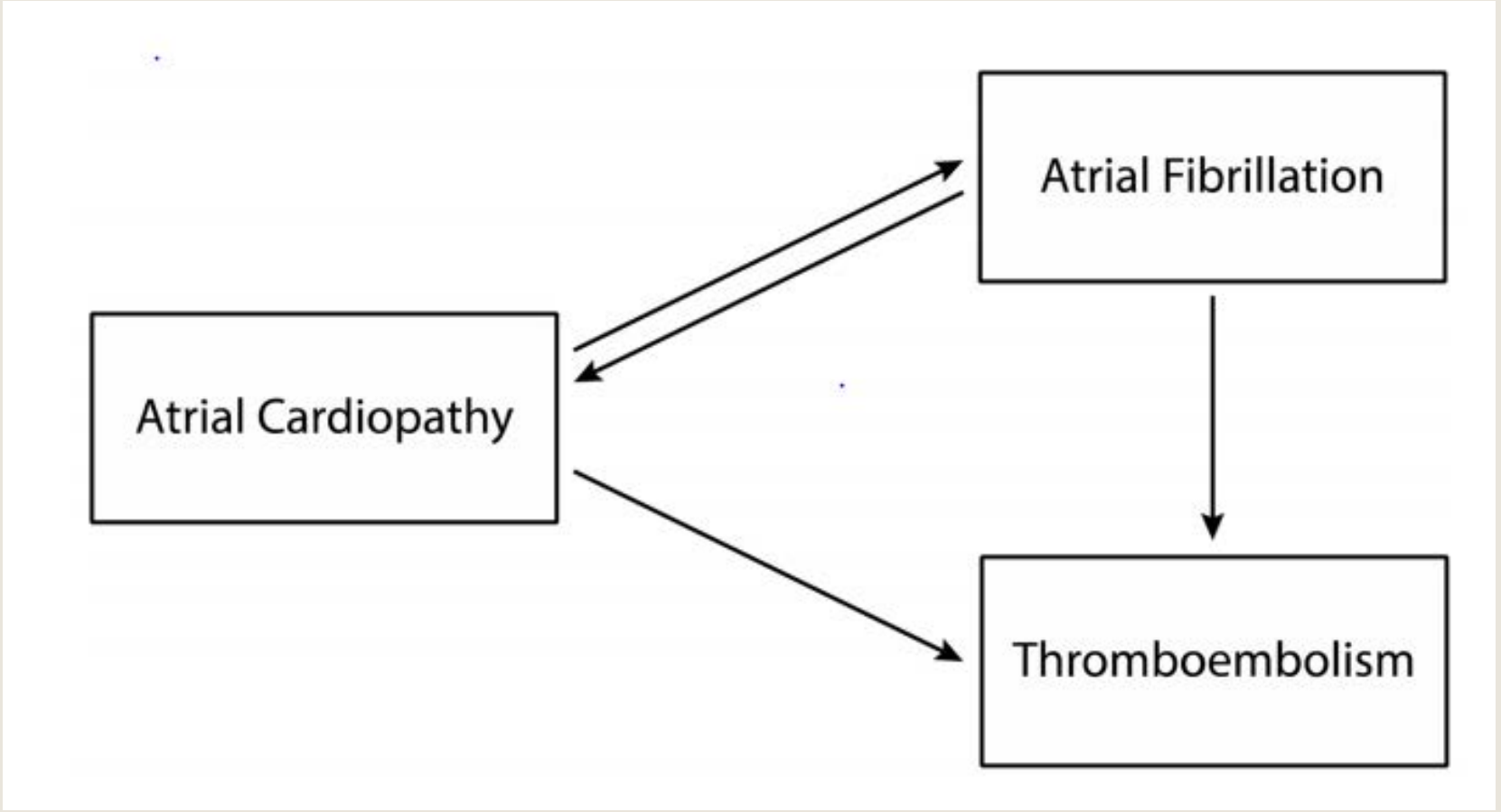
$CHADS_2$ Score	No. of Patients	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months						Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*
		Present			Absent			
		no. of patients	*no. of events*	*%/yr*	*no. of patients*	*no. of events*	*%/yr*	
1	600	68	1	0.56	532	4	0.28	2.11 (0.23–18.9)
2	1129	119	4	1.29	1010	18	0.70	1.83 (0.62–5.40)
>2	848	72	6	3.78	776	18	0.97	3.93 (1.55–9.95)

1. Saver, J. Cryptogenic Stroke: NEJM 374;21
2.Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9

Higher Risk Patients

- Infarct topographic features
- Higher CHADs-VASc (2 or greater)
- Older age (>60)
- Left Atrial Cardiopathy (dilatation, strain)

Saver, J. Cryptogenic Stroke: NEJM 374;21



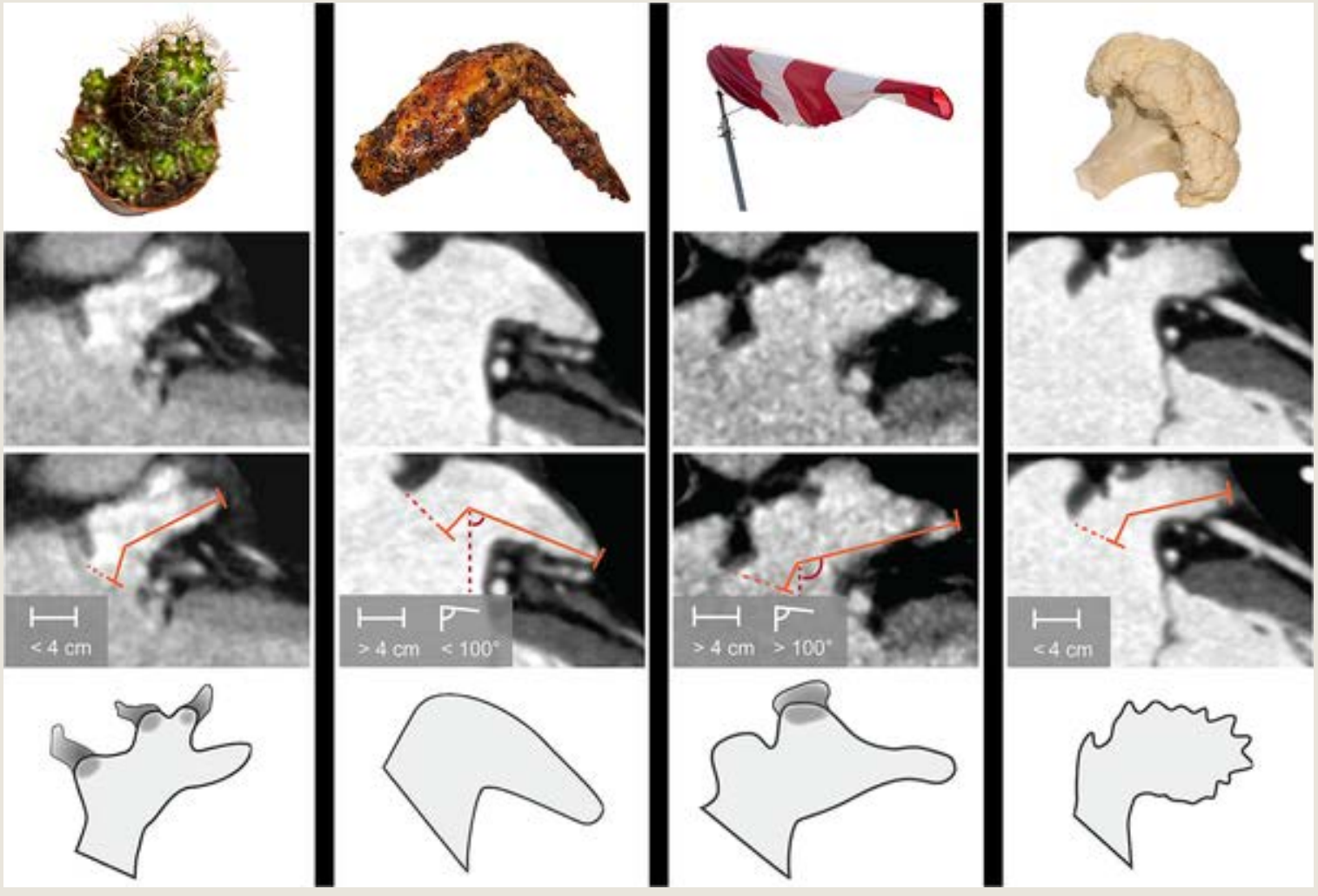
Kamel, et al. Atrial Cardiopathy: A Broadened Cause of Atrial Thromboembolism Beyond Atrial Fibrillation. Future Cardiol. 2015 May ; 11(3): 323–331

Higher Risk Patients

- Higher CHADs-VASc (2 or greater)
- Older age (>60)
- Infarct topographic features
- Left Atrial Cardiopathy (dilatation, strain)
- Morphological Features of Left Atrial Appendage

Saver, J. Cryptogenic Stroke: NEJM 374;21

Fig 1. LAA morphology types based on Wang's classification with Kimura's quantitative limits.



Korhonen M, Muuronen A, Arponen O, Mustonen P, Hedman M, et al. (2015) Left Atrial Appendage Morphology in Patients with Suspected Cardiogenic Stroke without Known Atrial Fibrillation. PLoS ONE 10(3): e0118822. doi:10.1371/journal.pone.0118822
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0118822

PLOS | ONE

What should we do?

Cryptogenic Stroke Treatment Algorithm

- Discharge on cardiac telemetry for at least 30 days
  - If multiple risk factors discharge on Oral Anticoagulation
  - If no risk factors discharge on oral antiplatelet is okay

Saver, J. Cryptogenic Stroke: NEJM 374;21

Cryptogenic Stroke Treatment Algorithm

- Initial 30 days of monitoring shows:
  - No evidence of pAF
    - Multiple risk factors
      - Subcutaneous loop monitor X 1-3 years
      - Continue OAC X 1 year then reconsider
    - No risk factors
      - Continue antiplatelet therapy

Saver, J. Cryptogenic Stroke: NEJM 374;21

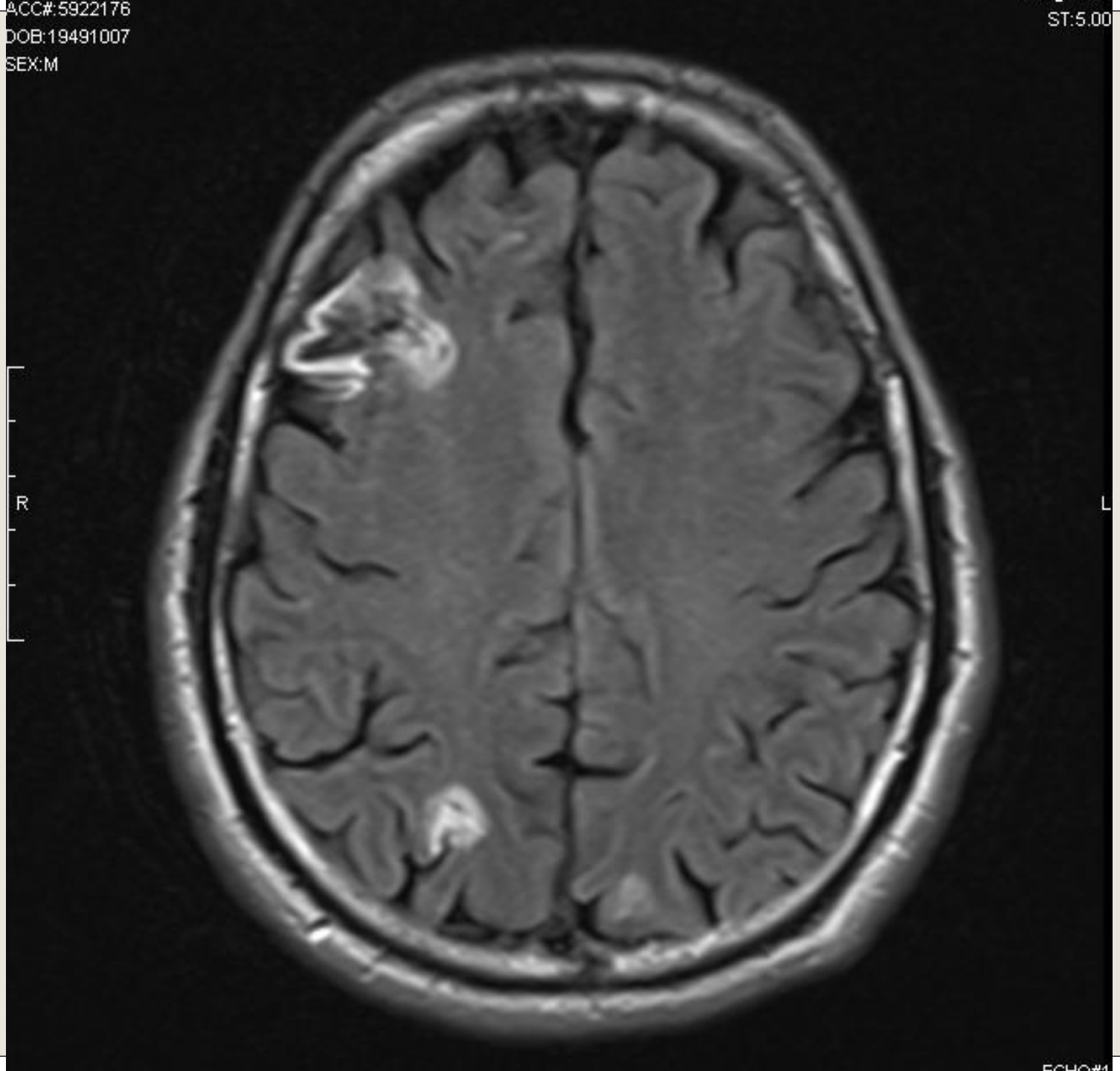
Treatment Algorithm

- Low Burden Afib (5-15 minutes/24 hours)
  - Multiple risk factors
    - Continue OAC
  - No risk factors
    - Subcutaneous loop recorder monitoring X 1-3 years
    - Switch to OAC for first year, then reconsider
- Higher burden (>15 minutes/24 hours)
  - Use OAC

Saver, J. Cryptogenic Stroke: NEJM 374;21

CASE 1

- 64 year old gentleman with recurrent strokes!!


ACC#:5922176
DOB:19491007
SEX:M
ST:5.00
R
L

Case 1

- Risk Factors:
  - Age > 60
  - Multiple territory strokes

Case 1

- Loop Monitor
- Oral Anticoagulation

Quick View - Aug 11, 2016

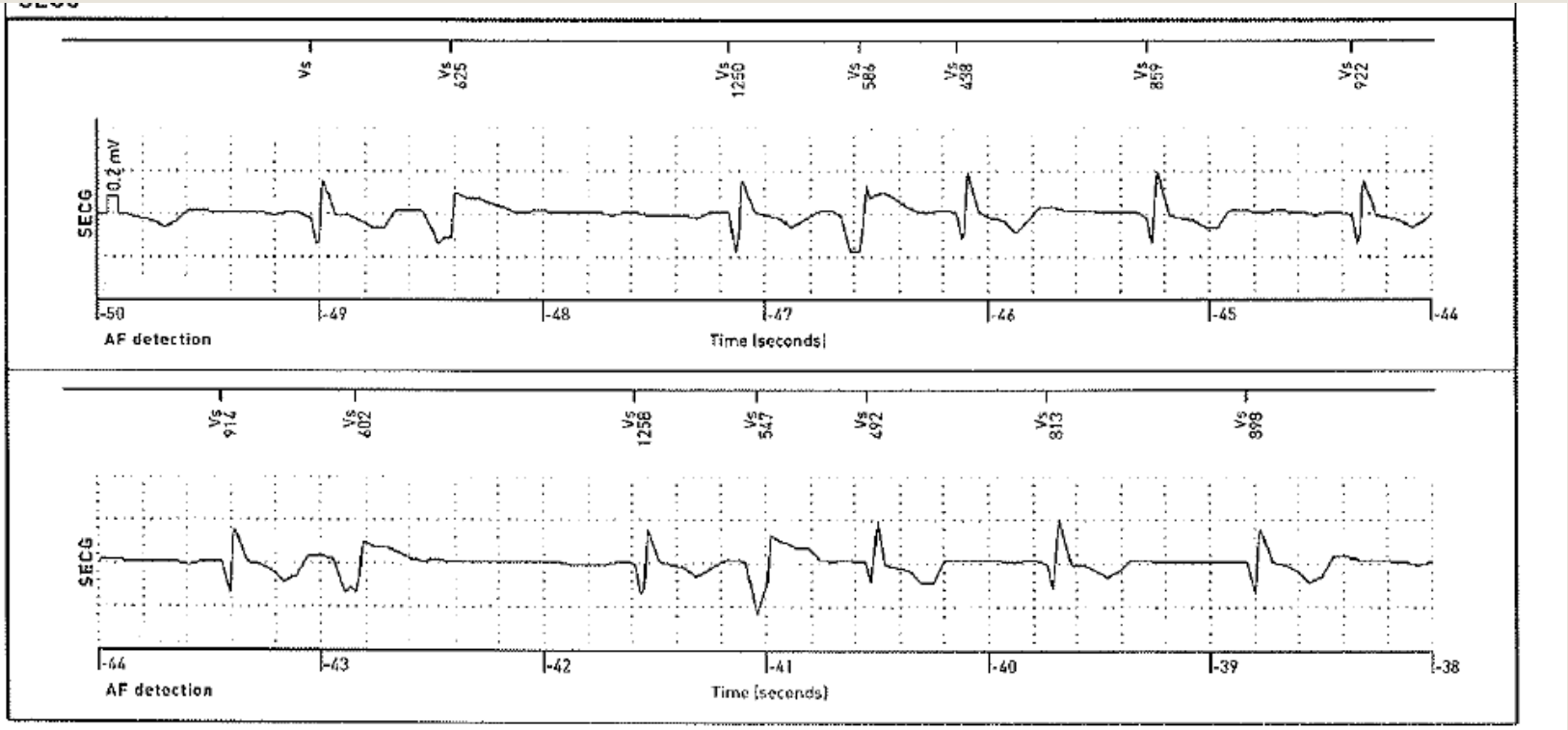
To: Pima Heart

BIOTRONIK
excellence for life

Name: -
Patient ID: [redacted]
DOB: Sep 30, 1940
Phone: -
BioMonitor 2-AF (SN 91504486)
ICM implanted Jul 15, 2016
Last message: Aug 11, 2016
Last clinic follow-up: Jul 17, 2016

Ven. arrhythmia since Aug 10, 2016	
High ven. rate episodes per day	0

Atr. arrhythmia since Aug 10, 2016	
Atrial burden [% of day]	0.8
Atrial fibrillation episodes per day	1
Mean ven. heart rate during atr. burden [bpm]	---


Vs
Vs 625
Vs 1250
Vs 586
Vs 438
Vs 859
Vs 922
SECG
0.2 mV
-50
-49
-48
-47
-46
-45
-44
AF detection
Time (seconds)
Vs 914
Vs 602
Vs 1256
Vs 547
Vs 492
Vs 813
Vs 998
SECG
-44
-43
-42
-41
-40
-39
-38
AF detection
Time (seconds)

Cardioembolic Strokes

- Account for large portion of stroke burden
- Afib we need to be aggressive about detection
  - Anticoagulation reduces risk of future ischemic stroke dramatically
  - CHADS and HAS-BLED
- **LOOK AGGRESSIVELY**

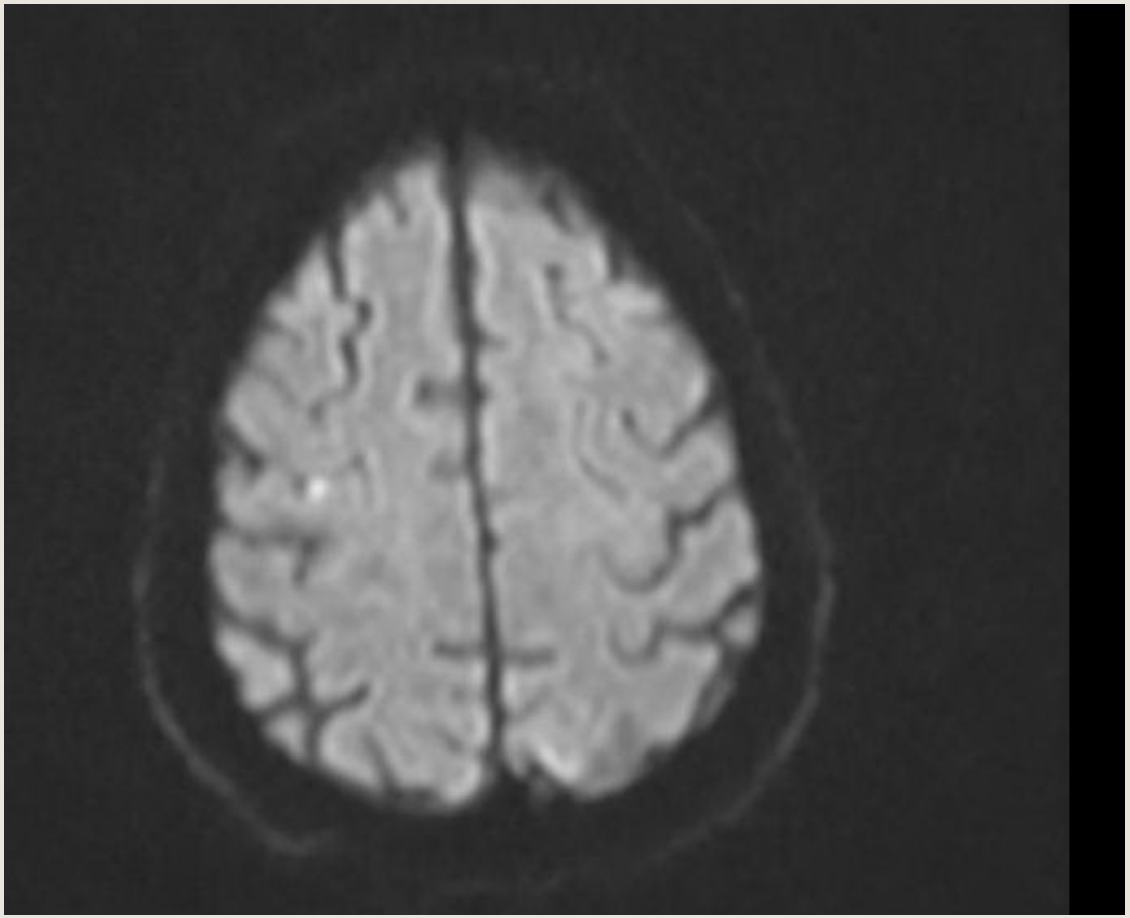
Case 2

- 73 year old
  - Transient episode of left hand clumsiness in shower

- PMH:
  - Atrial Flutter
  - HTN
  - Dyslipidemia

- MEDS:
  - Aspirin

Case 2



Case 2

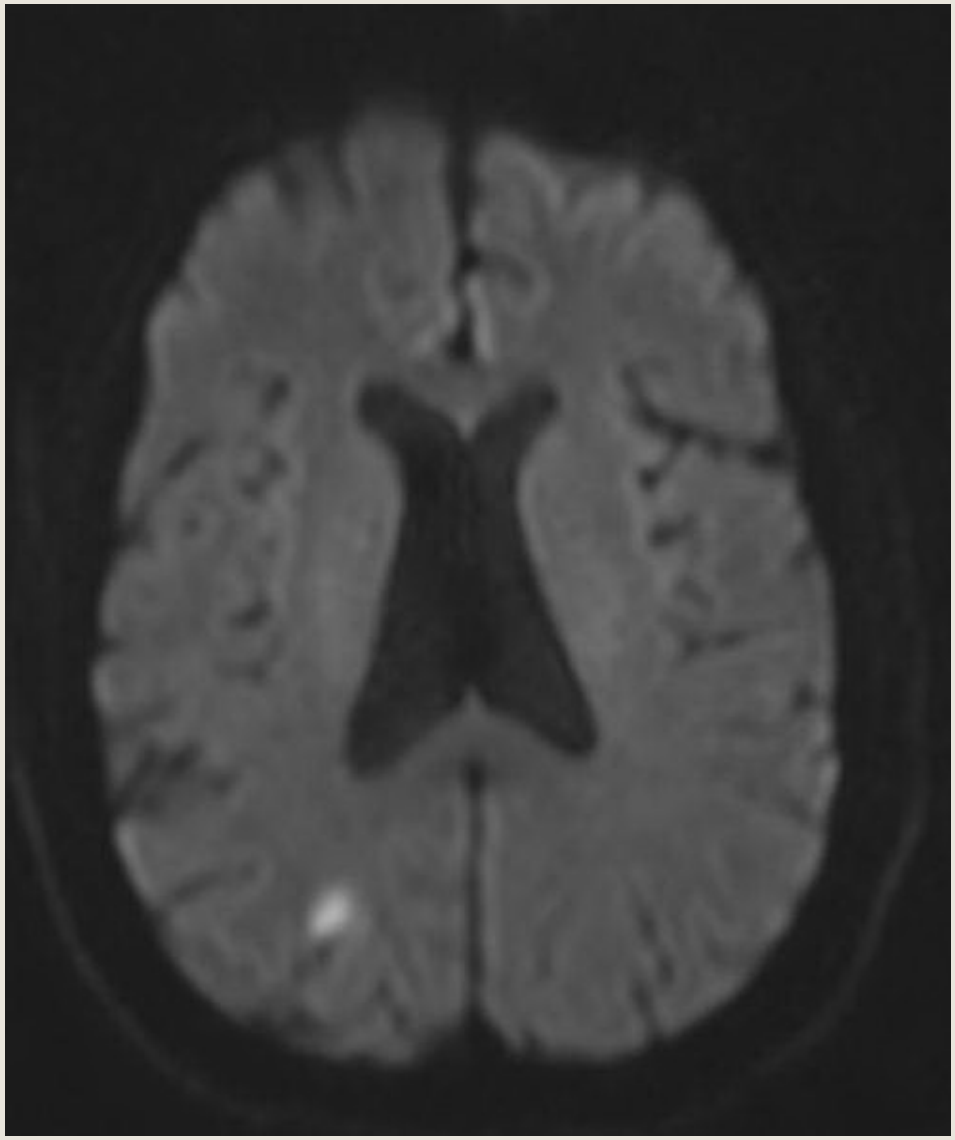
- Treatment?

- Started on Pradaxa 150mg bid

Case 2

- Returns to ER 18 months later
  - Again left hand clumsiness

Case 2



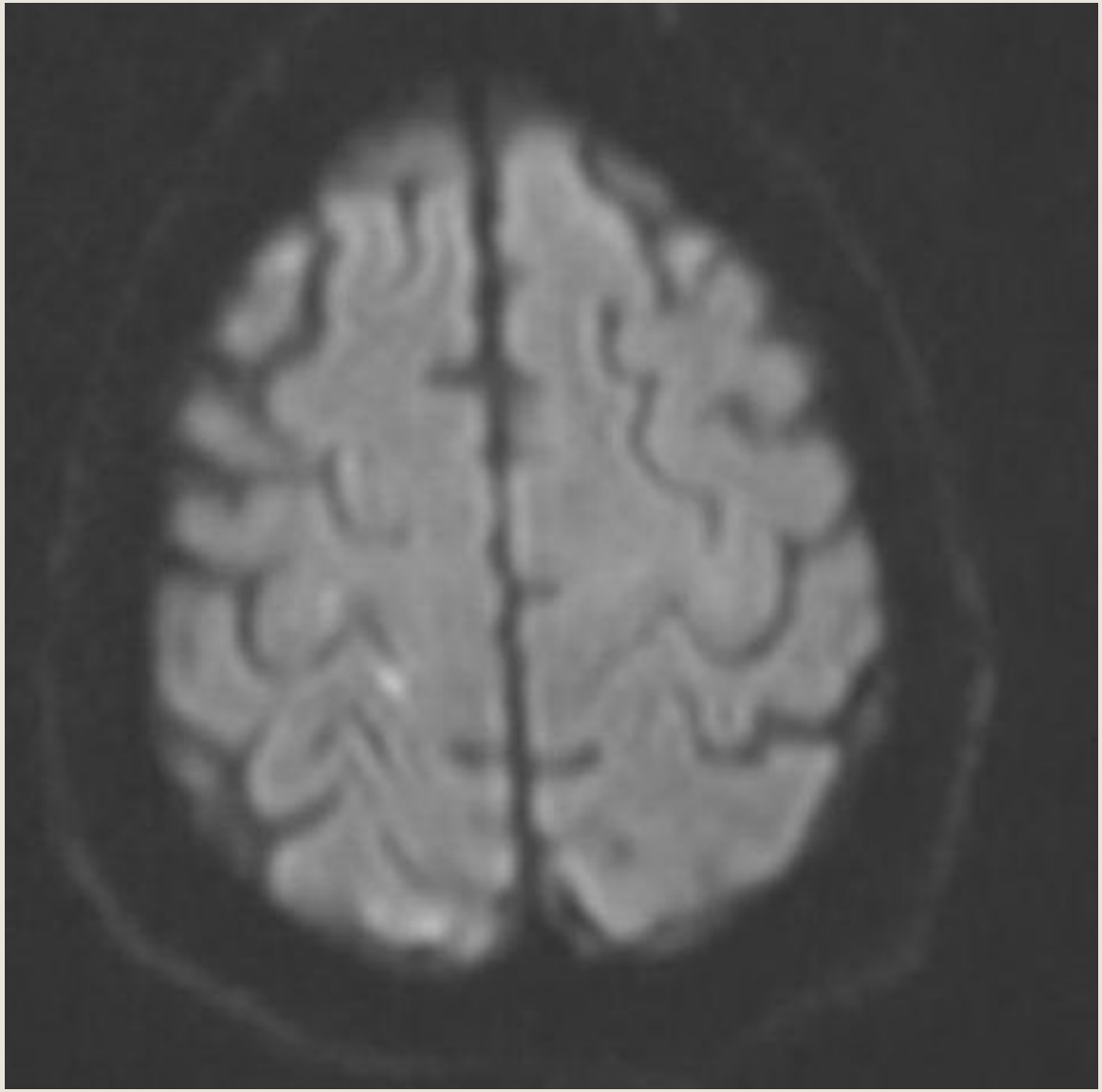
Case 2

- Treated as Pradaxa failure
  - Switched to warfarin

Case 2

- 6 months later
  - Returns to ER with left sided weakness
    - AGAIN??????

Case 2



Case 2