The Quantified Veteran: Predicting Outcomes from Implantable Defibrillator Data – the Case of AF and Stroke

MINTU TURAKHIA, MD MAS

Director, Cardiac Electrophysiology
Core Investigator, Center for Implementation to Innovation
VA Palo Alto Health Care System
minang.turakhia@va.gov

Assistant Professor of Medicine
and (by courtesy) Health Research & Policy
Stanford University

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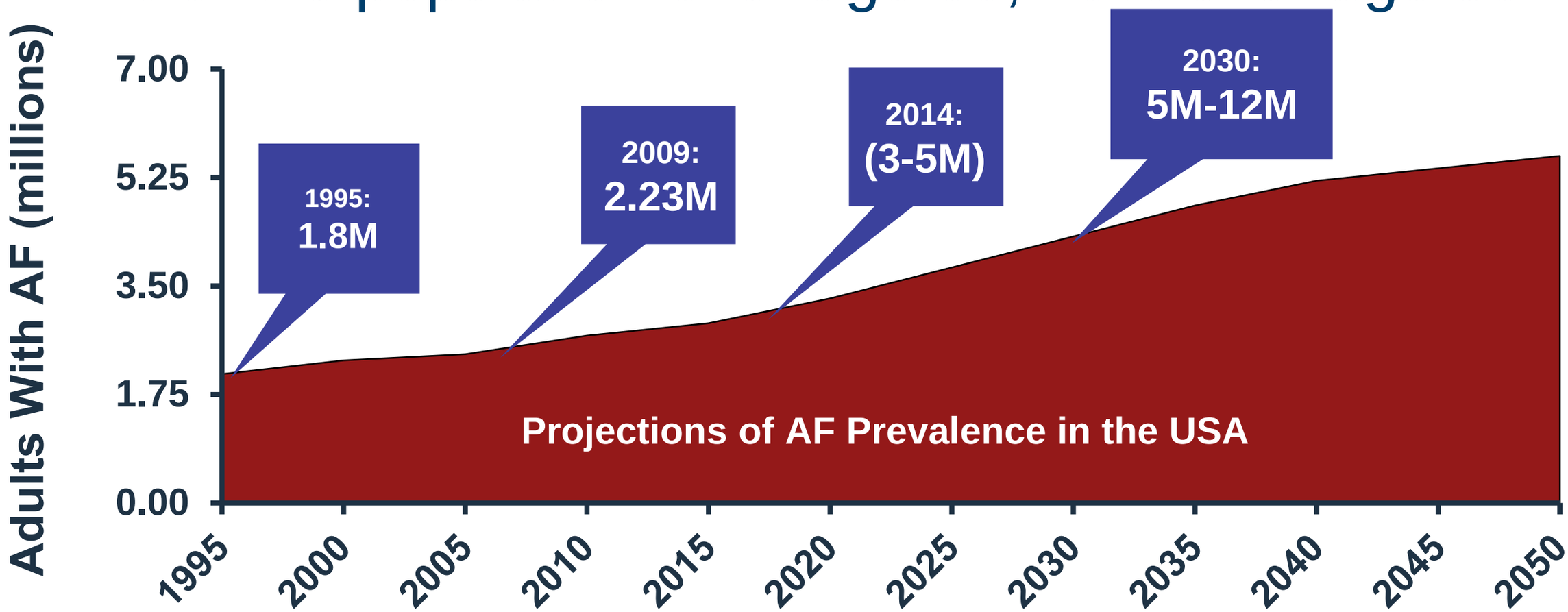
Questions we are tackling now…

- How much AF is needed to be at risk for stroke?
  - Reevaluation of causal inference
- What is temporal relationship of AF to stroke?
  - Can real-time AF detection be used to treat?
- Goal is to inform implementation of AF disease management strategies with wearable sensors

AF and stroke

Atrial Fibrillation

- Most common sustained arrhythmia in clinical practice
- 4% of the population over age 60; 10% over age 80



Adapted from Go. *JAMA.* 2001;285:2370.
Miyasaka Y. Circulation 2006;114:119-125

AF and stroke: the classical model

Physiology

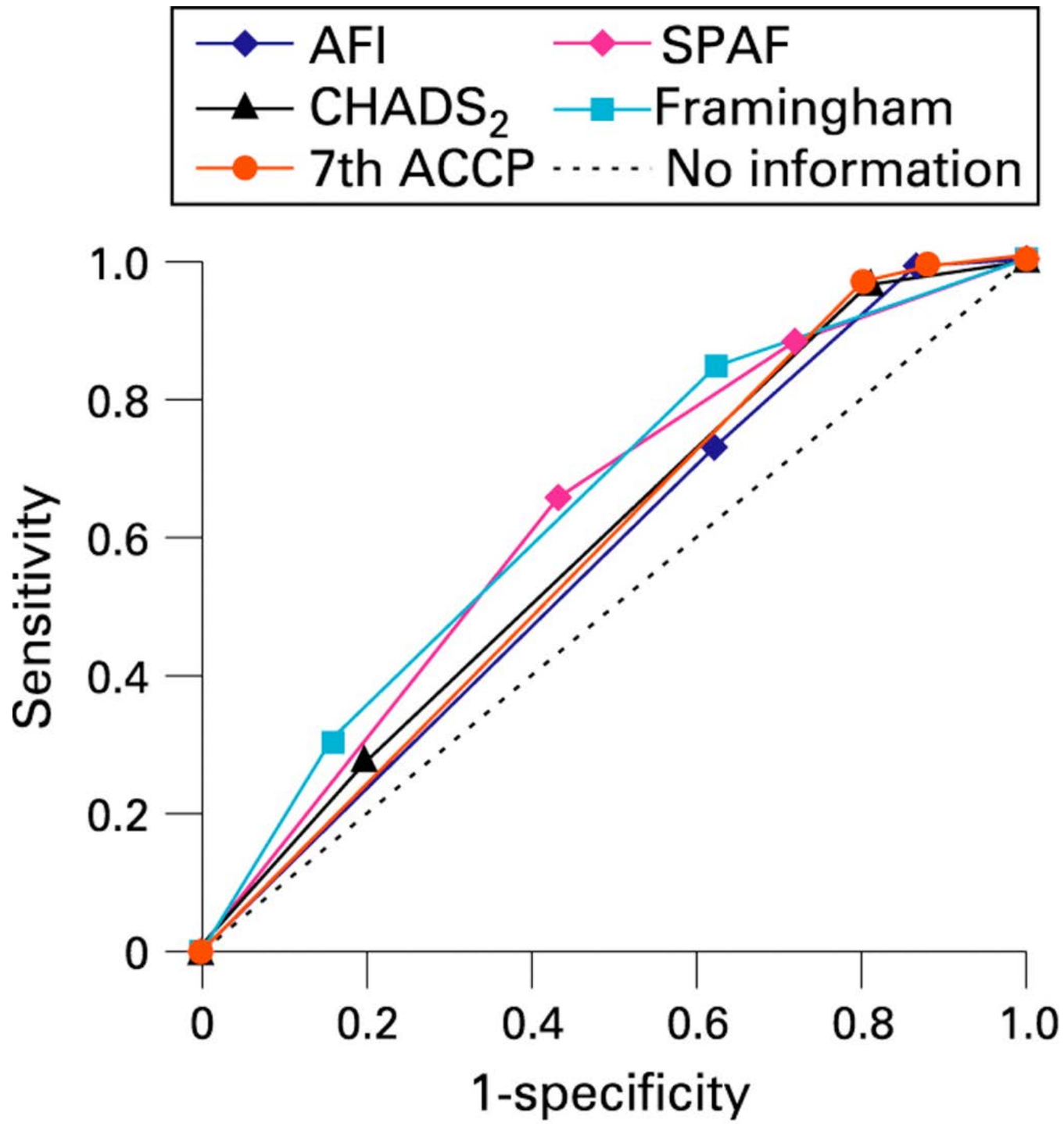
- Loss of coordinated electromechanical atrial activity
- Impaired emptying, stasis, hypercoagulability, blood clot formation (in left atrial appendage)

Implications for stroke risk

- 15% of 700,000 strokes/year in U.S.
- Risk if untreated: 3-12%/yr
- Stroke from AF has higher severity, disability and mortality (larger territory)

Therapies can prevent stroke in AF

How good are strokes risk scores?



- **c-statistic = 0.56-0.62**
- (0.50 = pure chance)
- Substantial misclassification
- Untreated "low risk" patients who get strokes
- Treated "high risk" patients who bleed

(Fang M, JACC 2006)

Then came CHA_2DS_2-VASc…

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(Lip GY, Chest 2010)

Weaknesses of CHA_2DS_2-VASc

- Goal to preserve sensitivity
- CHADS2 score gets reclassified upward
  - Age, CAD, female
- Few stroke events in derivation
- Nonrepresentative population distribution
- No validation from external authors

CHA_2	No.	Number of TE Events
0	103	0
1	162	1
2	184	3
3	203	8
4	205	4
5	95	3
6	57	3
7	25	3
8	9	1
9	1	1
Total	1,084	25

(Lip GY, Chest 2010)

Weaknesses of CHA_2DS_2-VASc

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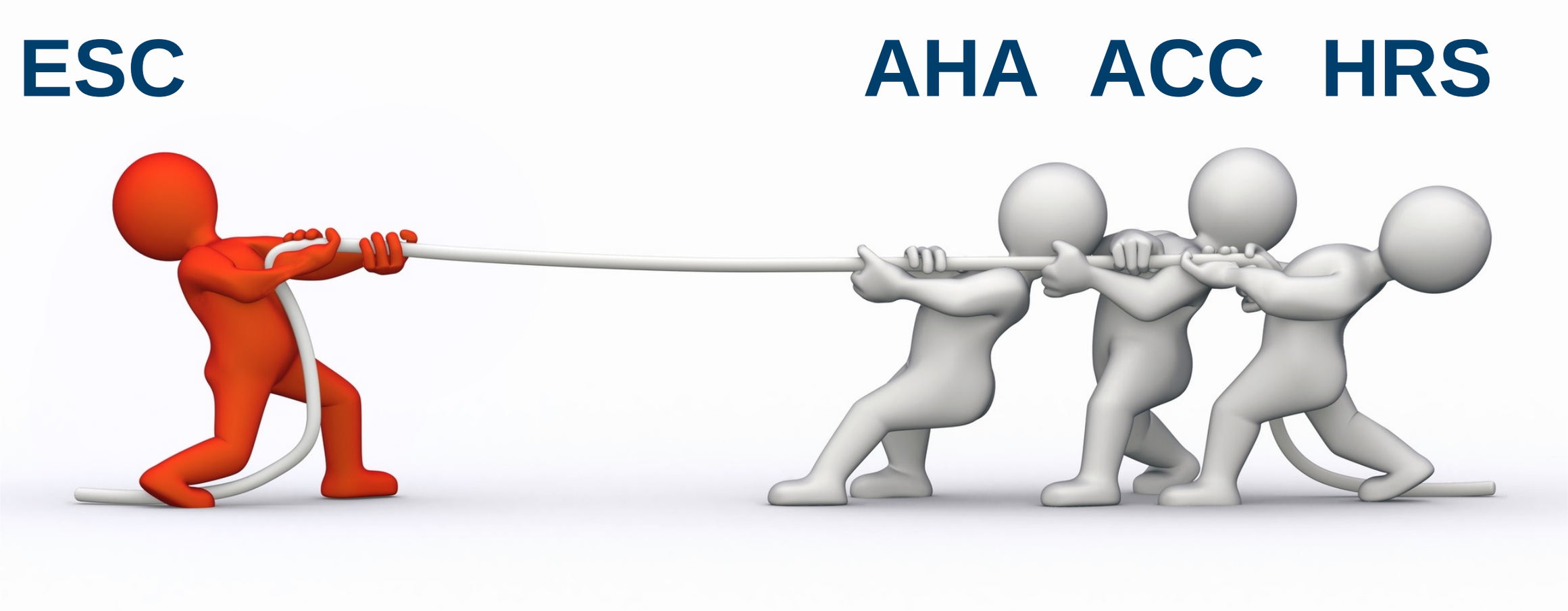
CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

(Lip GY, Chest 2010)

Guidelines

ESC

AHA ACC HRS



2011

CHA2DS2-VASC ≥ 2: OAC (I)

CHA2DS2-VASC = 1: OAC (IIa)

***Except if sole risk factor is sex**

CHA2DS2-VASC = 0: Nothing (I)

2006: CHADS2 ≥ 1

2014

CHA2DS2-VASC ≥ 2: OAC (I)

CHA2DS2-VASC = 0: Nothing (IIa)

CHA2DS2-VASC = 1: Anything (IIb)

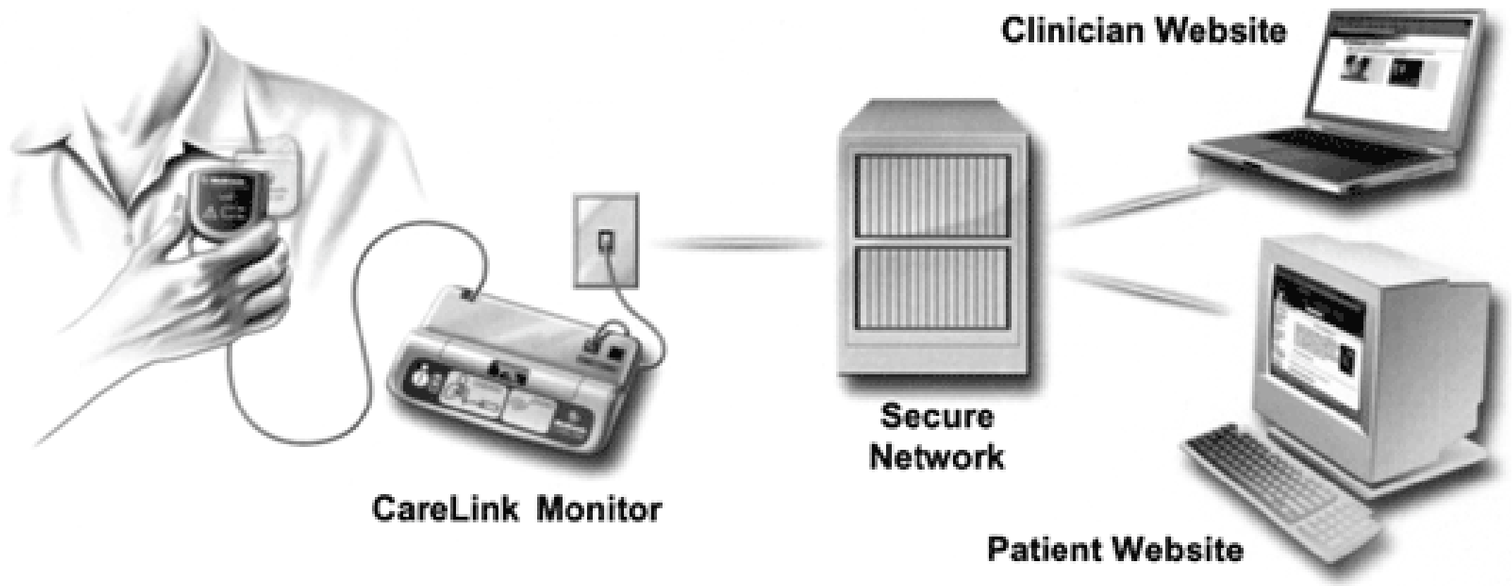
The biggest limitation of the scores is the diagnosis of AF itself

- AF defined by treatment, not disease
  - Hospital discharge with AF
  - Cardiology care
- Transient AF, lone AF, less sick patients not well represented
- No quantification of risk based on burden of AF, just whether identified as having AF as inpatient

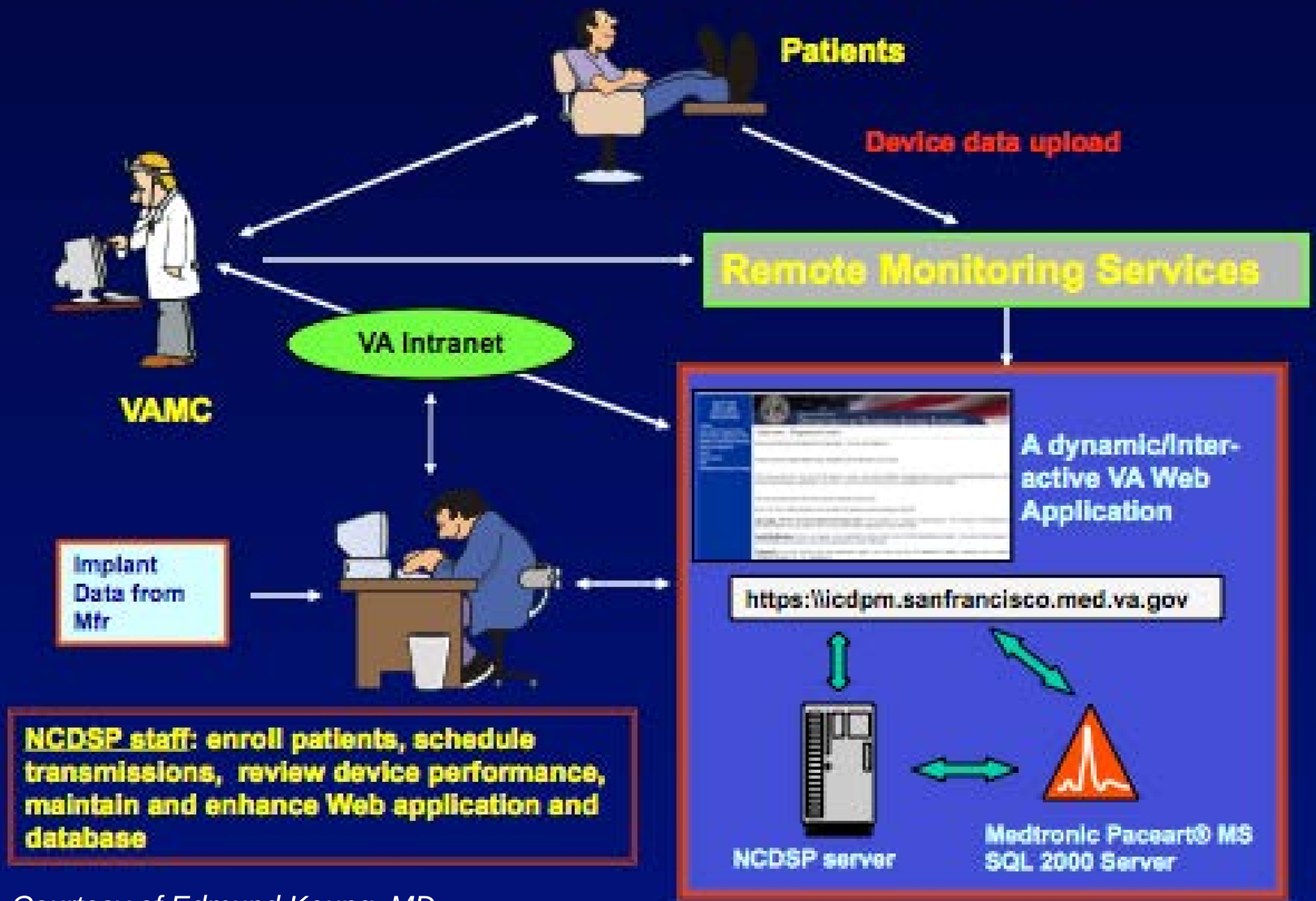
Daily AF burden and stroke

- How much AF is needed for stroke?
- What is relationship of timing of AF to presentation of stroke?
- Are some patterns of AF riskier than others?
- Can real-time AF detection be used to treat?

Remote monitoring for cardiac implantable electronic devices (CIED) is continuous



VA NCDSP I/O Operations



Courtesy of Edmund Keung, MD

ASSERT Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Subclinical Atrial Fibrillation and the Risk of Stroke

Jeff S. Healey, M.D., Stuart J. Connolly, M.D., Michael R. Gold, M.D.,
Carsten W. Israel, M.D., Isabelle C. Van Gelder, M.D.,
Alessandro Capucci, M.D., C.P. Lau, M.D., Eric Fain, M.D., Sean Yang, M.Sc.,
Christophe Bailleul, M.D., Carlos A. Morillo, M.D., Mark Carlson, M.D.,
Ellison Themeles, M.Sc., Elizabeth S. Kaufman, M.D.,
and Stefan H. Hohnloser, M.D., for the ASSERT Investigators*

METHODS

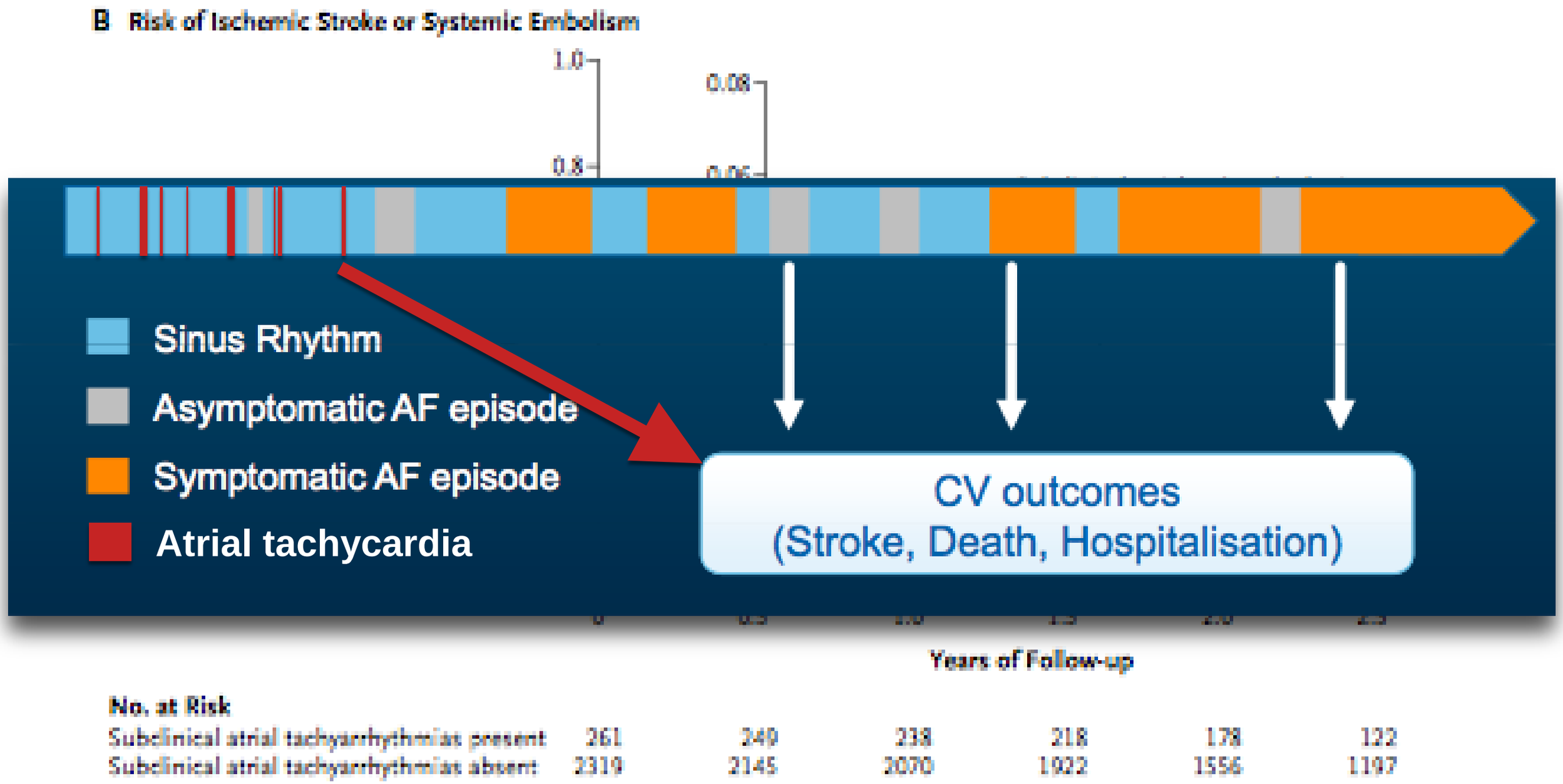
We enrolled 2580 patients, 65 years of age or older, with hypertension and no history of atrial fibrillation, in whom a pacemaker or defibrillator had recently been implanted. We monitored the patients for 3 months to detect subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes) and followed them for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. Patients with pacemakers were randomly assigned to receive or not to receive continuous atrial overdrive pacing.

(Healey JS, NEJM 2012)

ASSERT study results

- Subclinical atrial tachyarrhythmias (> 6 minutes) in 10% by 3 months
- AT associated with clinical AF
  - HR 5.56; 95% CI, 3.78-8.17
- AT associated with ischemic stroke/SE
  - HR 2.50; 95% CI, 1.28-4.89
- But, population attributable risk low: 13%

(Healey JS, NEJM 2012)



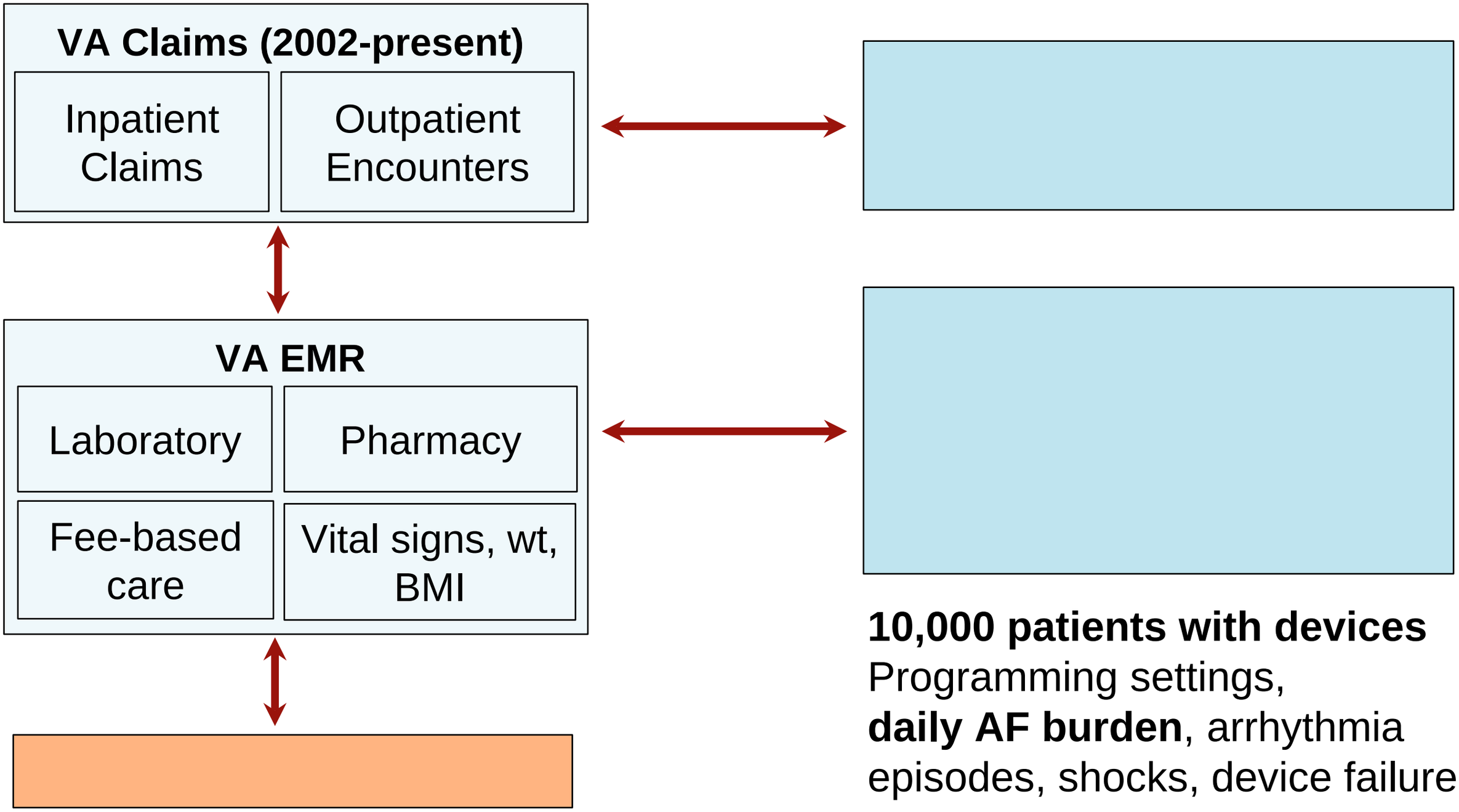
(Healey JS, NEJM 2012)

ASSERT stroke study

- Among 51 patients with stroke/SE
  - Only **1** had AT/AF at time of stroke
    - 25 (49%) had no AT/AF (including post-stroke)
    - Median time to AF was 339 days prior
    - 8 had AT/AF only after stroke

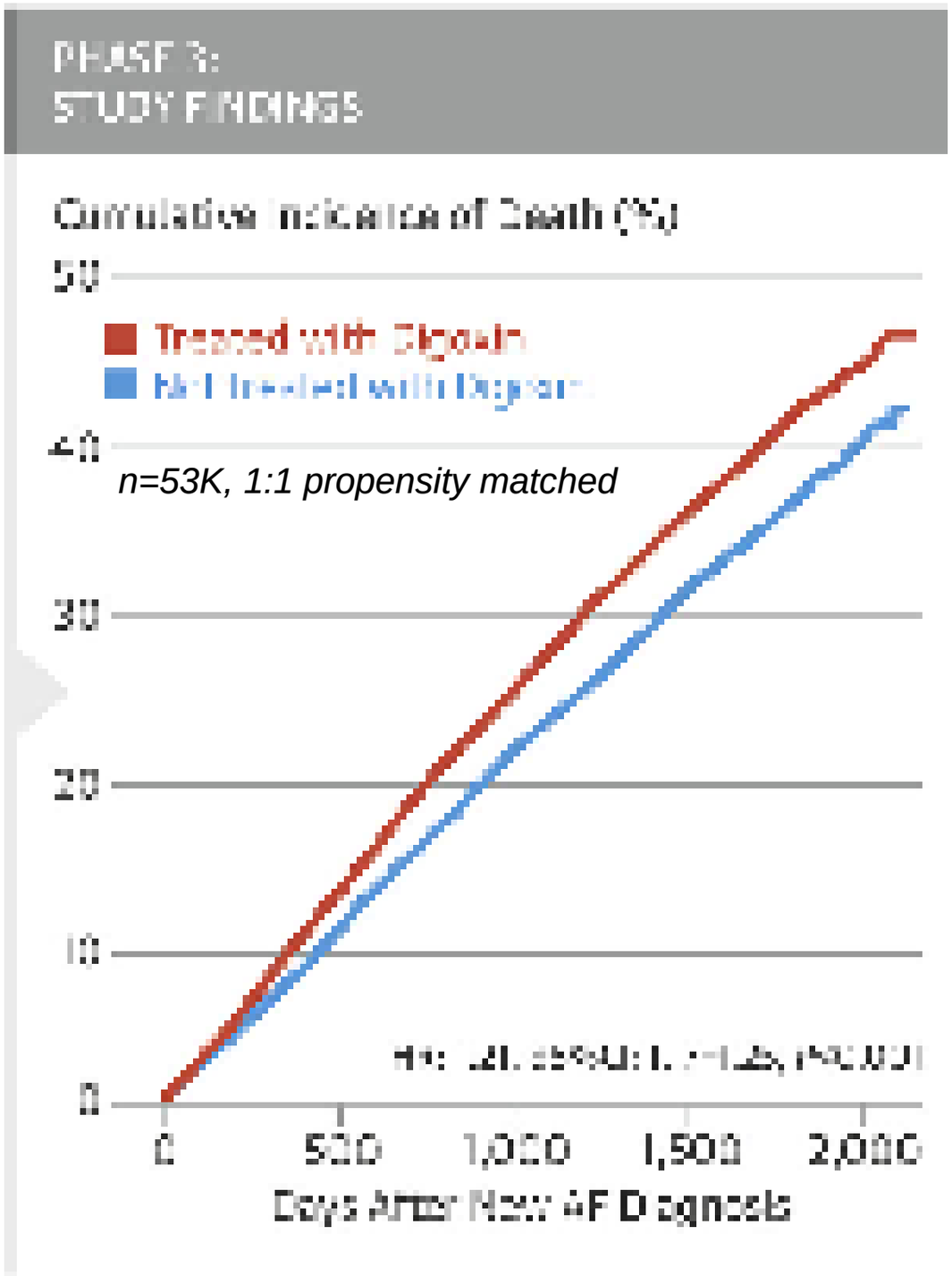
(Brambatti M, Circulation 2014)

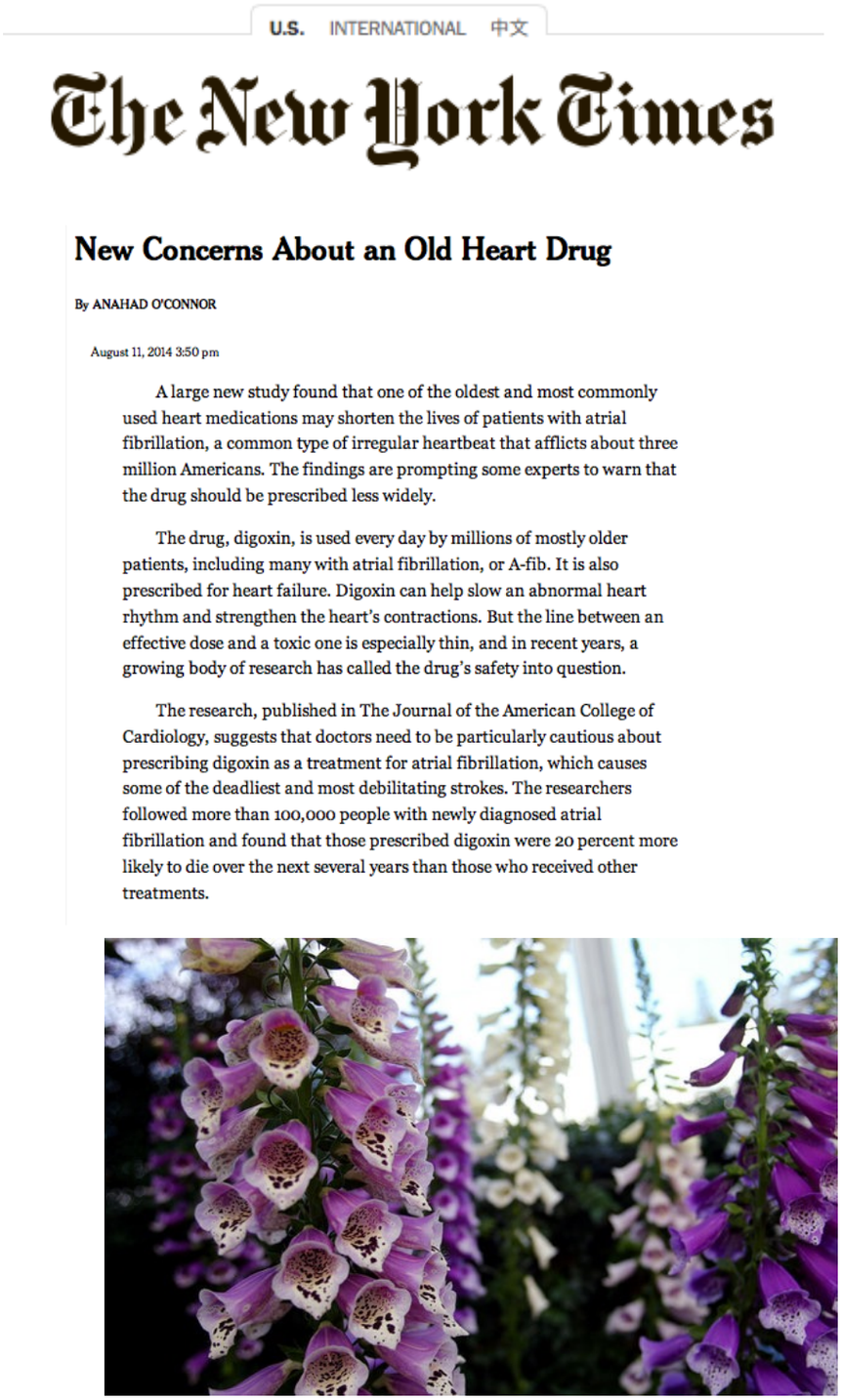
Daily AF burden and stroke: 500K AF pts
Integration with pacemaker/ICD data



(Turakhia M, JACC 2014; Turakhia M, HRS 2014)

TREAT-AF: ~200K patients w/new AF





U.S. INTERNATIONAL 中文

The New York Times

New Concerns About an Old Heart Drug

By ANAHAD O'CONNOR

August 11, 2014 3:50 pm

A large new study found that one of the oldest and most commonly used heart medications may shorten the lives of patients with atrial fibrillation, a common type of irregular heartbeat that afflicts about three million Americans. The findings are prompting some experts to warn that the drug should be prescribed less widely.

The drug, digoxin, is used every day by millions of mostly older patients, including many with atrial fibrillation, or A-fib. It is also prescribed for heart failure. Digoxin can help slow an abnormal heart rhythm and strengthen the heart's contractions. But the line between an effective dose and a toxic one is especially thin, and in recent years, a growing body of research has called the drug's safety into question.

The research, published in The Journal of the American College of Cardiology, suggests that doctors need to be particularly cautious about prescribing digoxin as a treatment for atrial fibrillation, which causes some of the deadliest and most debilitating strokes. The researchers followed more than 100,000 people with newly diagnosed atrial fibrillation and found that those prescribed digoxin were 20 percent more likely to die over the next several years than those who received other treatments.

(Turakhia M, et al. *JACC* 2014)

VA Carelink® study

- 10,000 patients with remote monitoring data from Medtronic
  - Medtronic data on back end provides daily measure of AF burden
    - 98% ICDs until recently
    - You cannot see this in PACEArt®
- 312 (3.2%) acute ischemic strokes
  - 187 with atrial lead and non-missing AF burden data up to 120d pre-stroke
    - 22,000 person-years
    - Event rate: 8.5 strokes/1,000 PYs

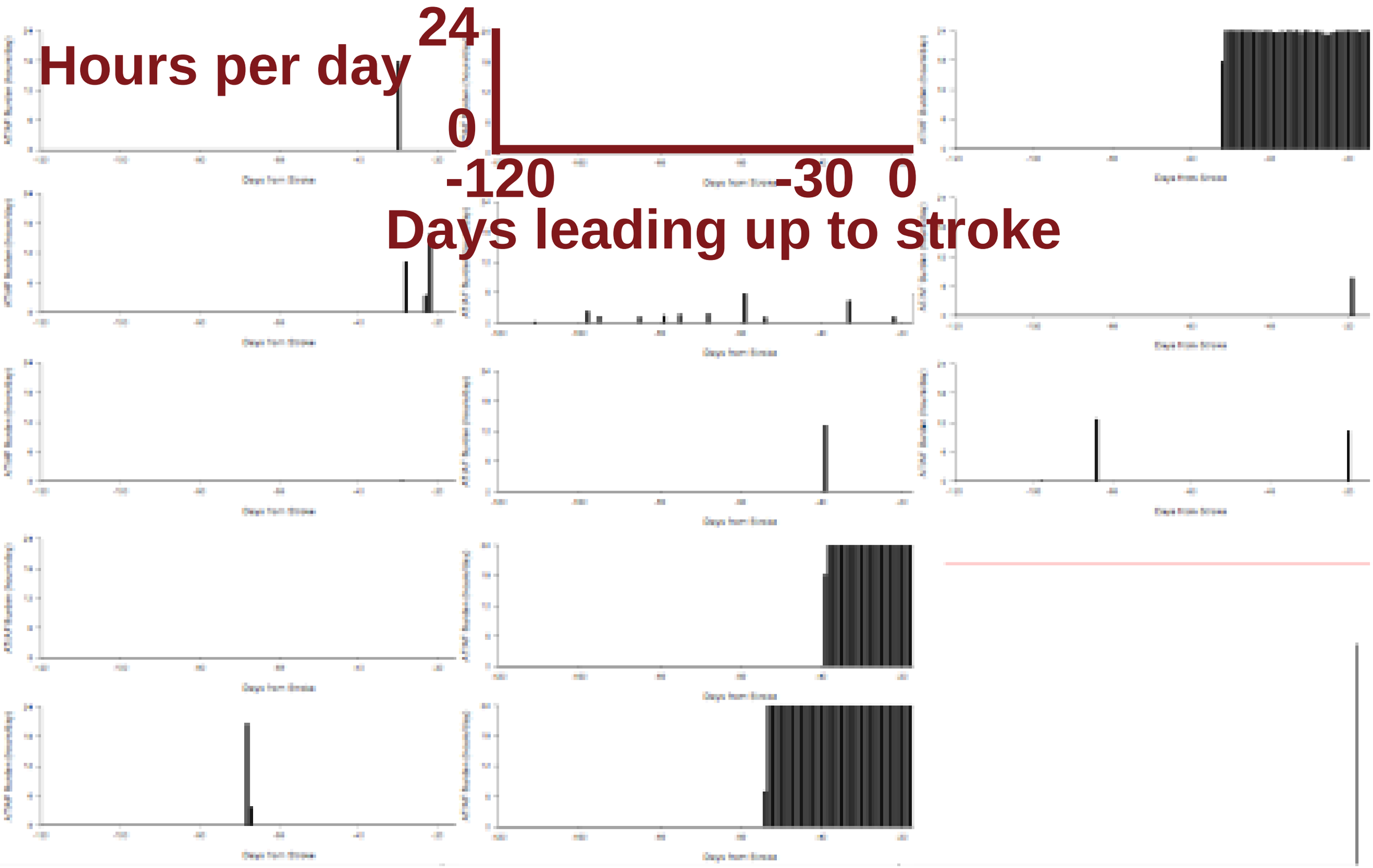
Baseline characteristics

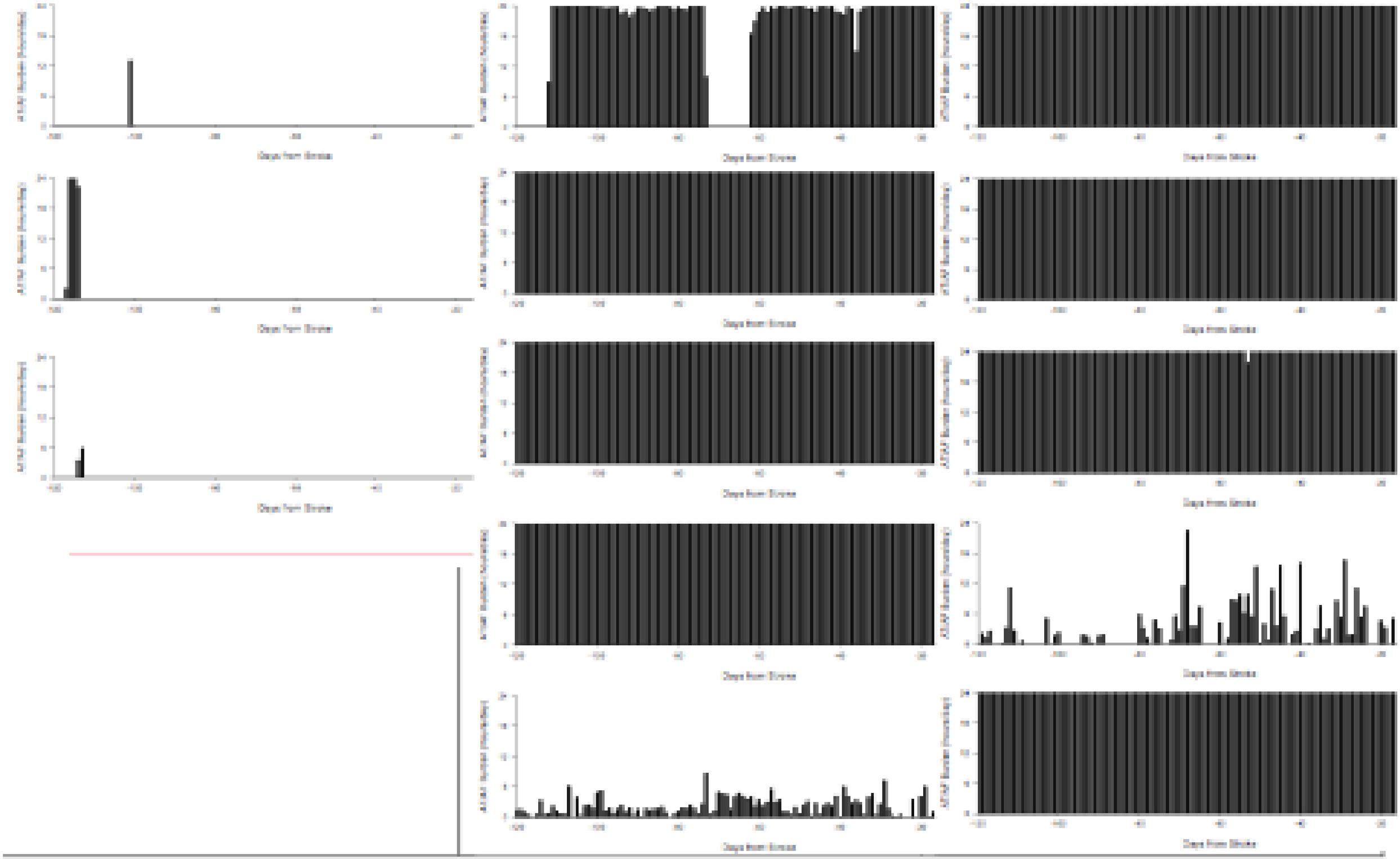
Age, mean ± SD	69 ± 8.4
Atrial Fibrillation, no. (%)	73 (39%)
Heart Failure, no. (%)	156 (83%)
Prior MI, no. (%)	26 (14%)
Coronary artery disease, no. (%)	168 (90%)
Chronic Obstructive Lung Disease	76 (41%)
Charlson Comorbidity Index, mean ± SD	3.8 ± 1.9
CHADS2 score, mean ± SD	3.2 ± 1.5

Results

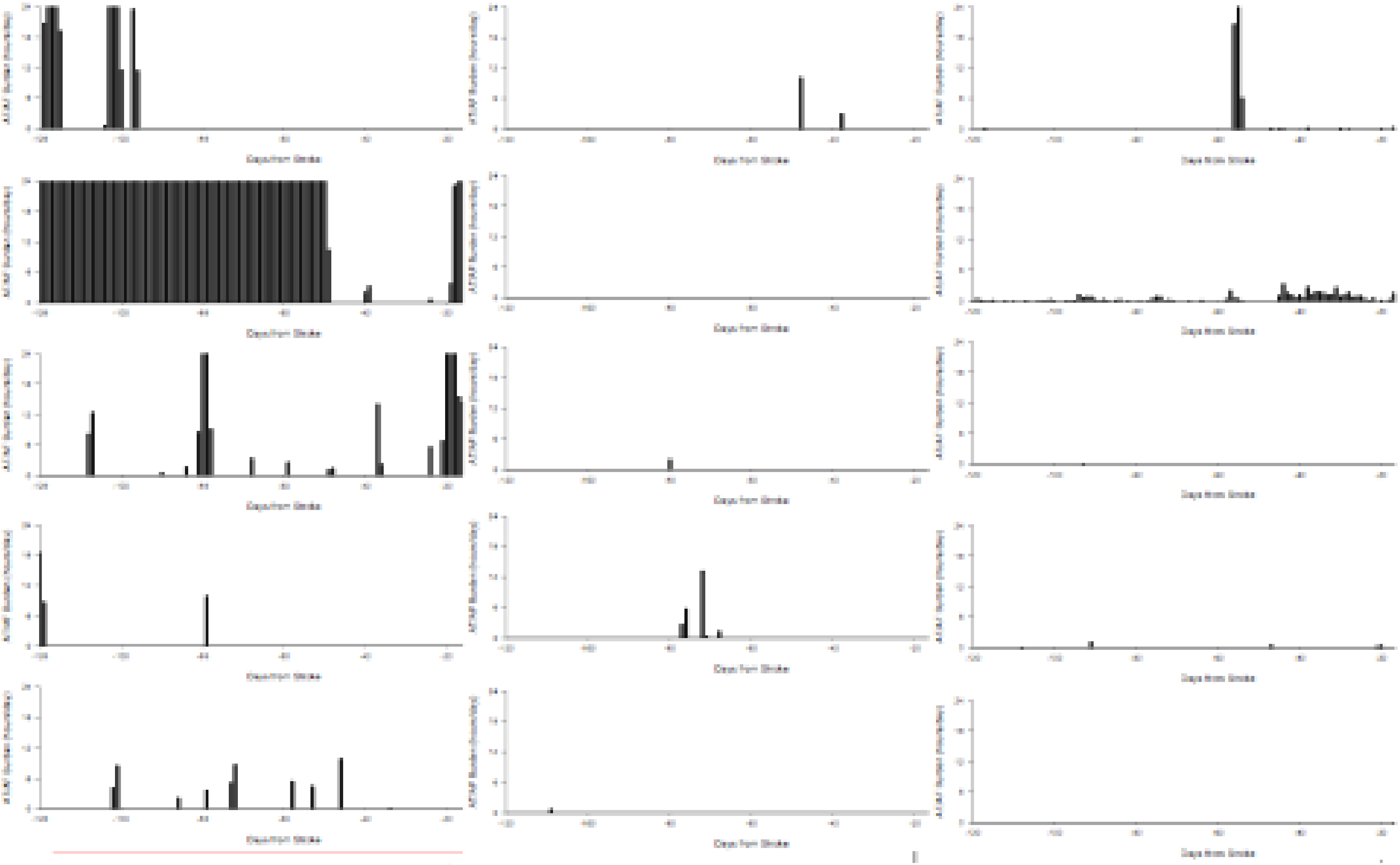
- 43/187 (23%) had AT/AF in 30d prior
  - 10 permanent; 10 paroxysmal
  - Mean burden in paroxysmals: 3.5±6.0h
- Comparing days 0-30 prior to days 90-120 prior (remote stroke-free interval)
  - 38% had new AT/AF
  - 34% had an increase in burden
  - 9% with decrease in burden
  - 19% permanent AF in both periods

(Turakhia M, HRS 2014)

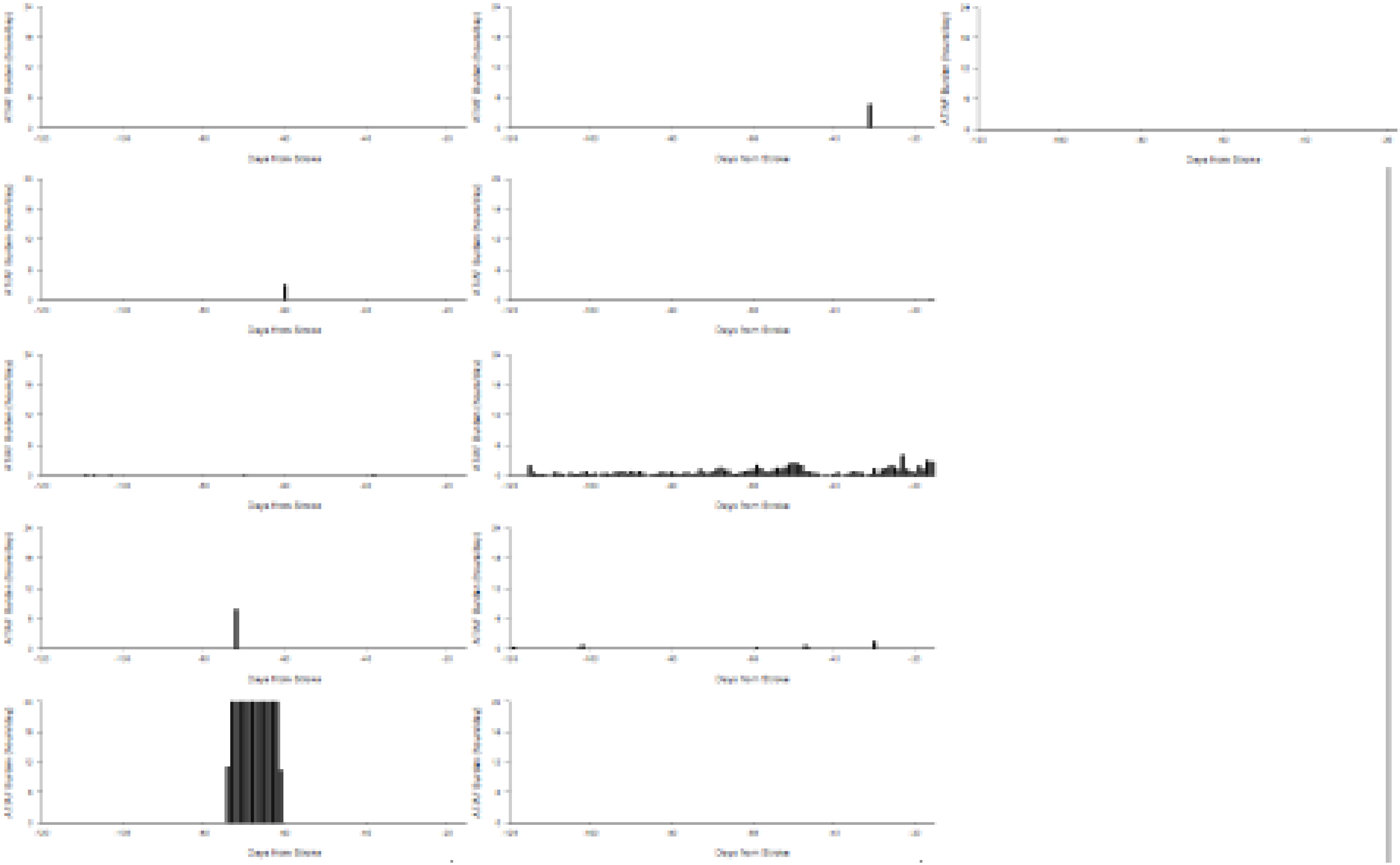

Hours per day
24
0
-120
-30
0
Days leading up to stroke



(Turakhia M, HRS 2014)



(Turakhia M, HRS 2014)



(Turakhia M, HRS 2014)

Results

- Among 43/187 patients with stroke and AT/AF preceding, 72% and AT/AF had new or increasing burden in 30d prior to stroke
- In patients with increasing AT/AF burden, burden increased by 1.9±3.4 hours/day
- Findings were similar when comparing with 180-210 days prior to stroke

(Turakhia M, HRS 2014)

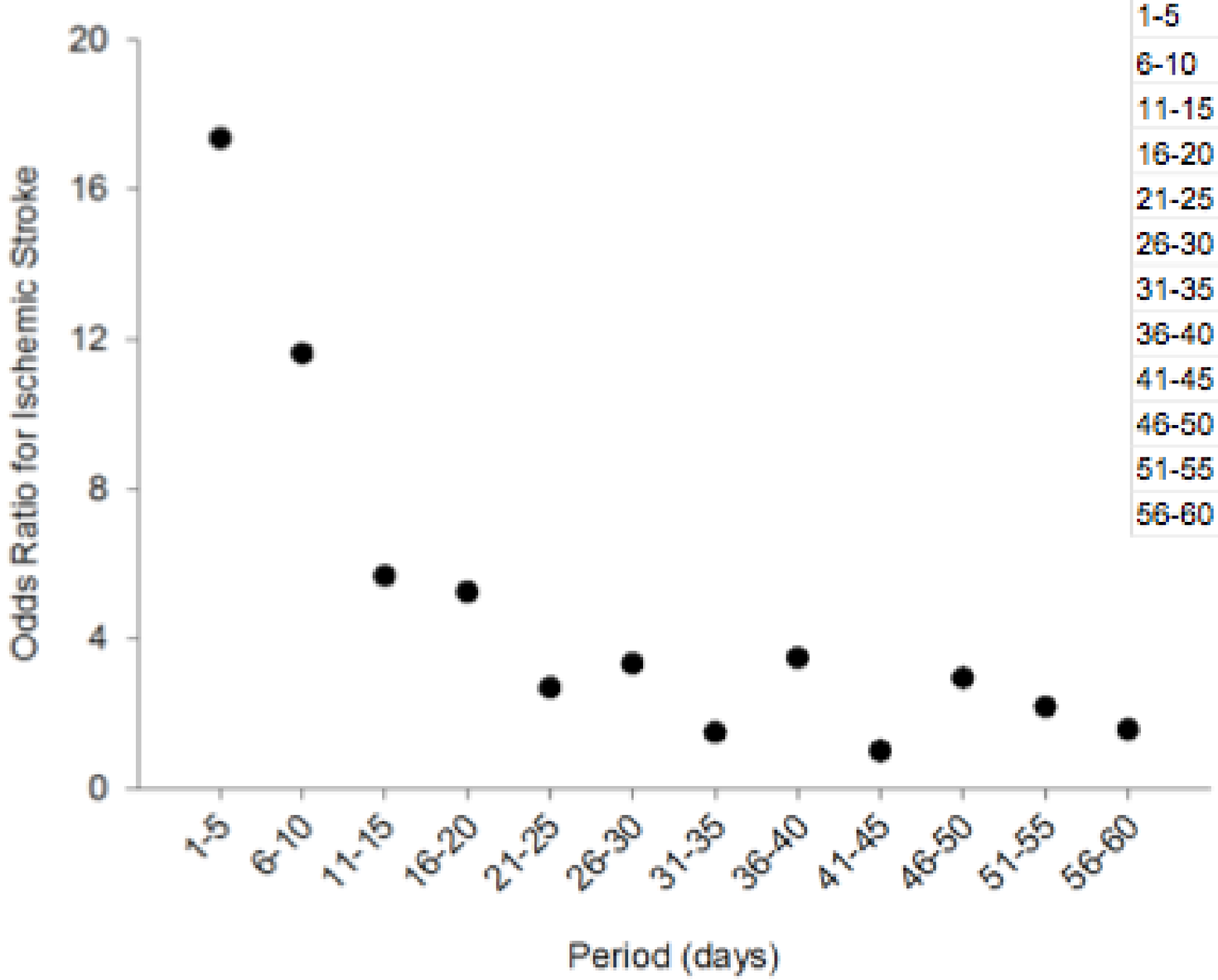
Case-Crossover Results

✦AF cutoff of ≥ 5.5 hours from TRENDS

Control Period Stroke Free Interval	Case Period 0-30 days prior to stroke: No AF	Case Period 0-30 days prior to stroke: AF
No AF	**156**	**13**
AF	**3**	**8**

- ✦ OR 13/3 = **4.33** (95% CI: 1.19, 23.71)
- ✦ After adjustment for warfarin use (discordance): **5.22** (95% CI: 1.22, 47.4)
- ✦ Results stable with AF cutoffs of 30 sec to 6 hrs

Exact timing of AF and risk



Period, days prior to stroke	Odds Ratio	95% Confidence Interval	P Value
1-5	17.4	5.39 - 73.1	<.0001
6-10	11.6	3.30 - 51.4	<.0001
11-15	5.66	1.65 - 20.5	0.0046
16-20	5.24	1.60 - 17.5	0.0053
21-25	2.68	0.689 - 9.63	0.1683
26-30	3.33	0.934 - 11.3	0.0647
31-35	1.49	0.296 - 6.06	0.7632
36-40	3.49	0.946 - 12.6	0.0615
41-45	1.00	0.160 - 4.68	1.0000
46-50	2.95	0.709 - 11.3	0.1476
51-55	2.18	0.470 - 8.52	0.3630
56-60	1.56	0.275 - 6.84	0.7445

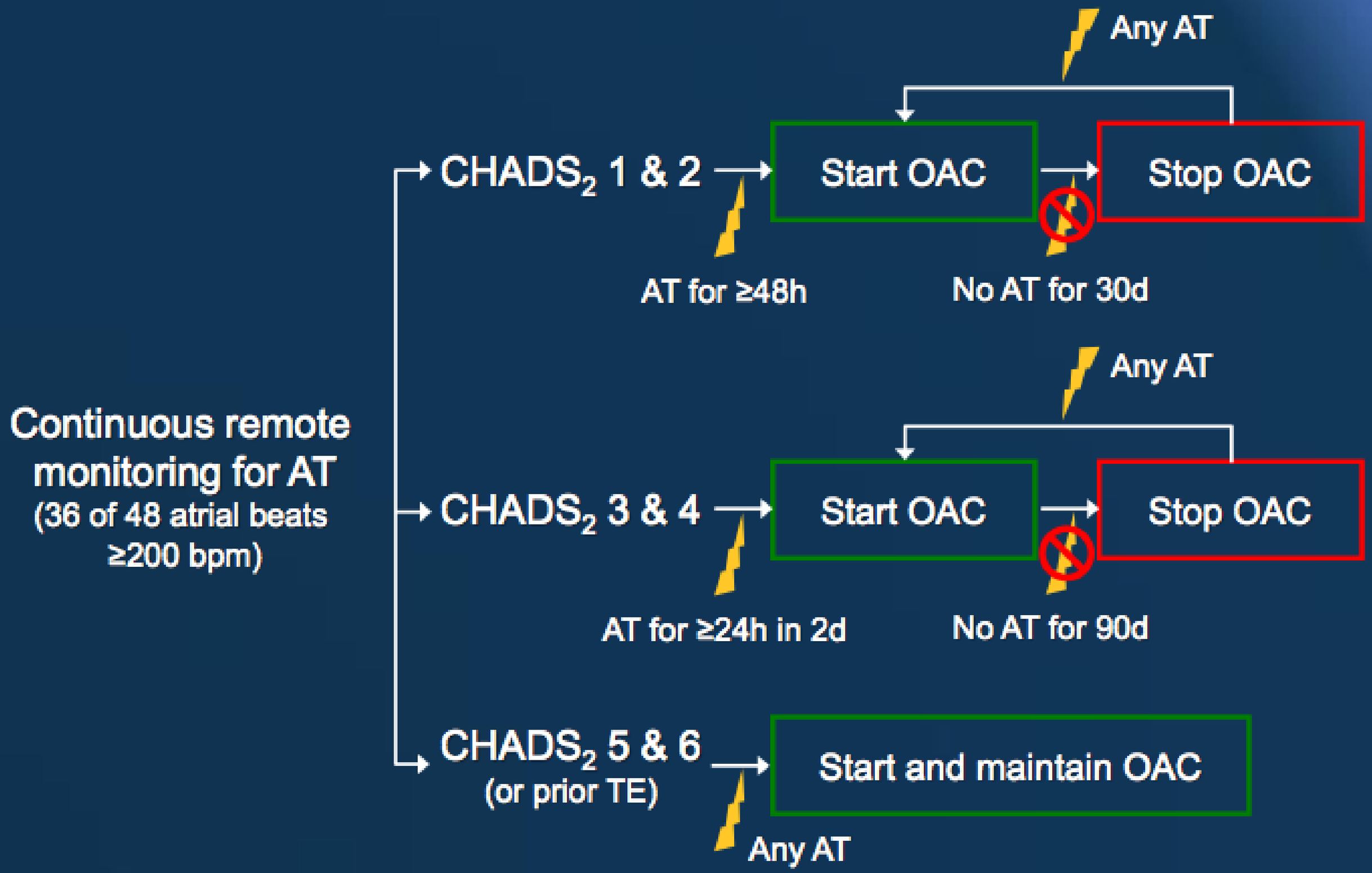
Singer DE…Turakhia M, ACC 2015

Is there a “dose” response?

- Varied threshold of AF on any given day in 30 days pre-stroke from 30 seconds to 6 hours
  - Unable to isolate an effect
  - 15 minutes, 30 minutes, 1 hour, 6 hours all similar
  - Large confidence intervals

Can anticoagulation therapy starts and stops based on AT/AF detection improve outcomes?

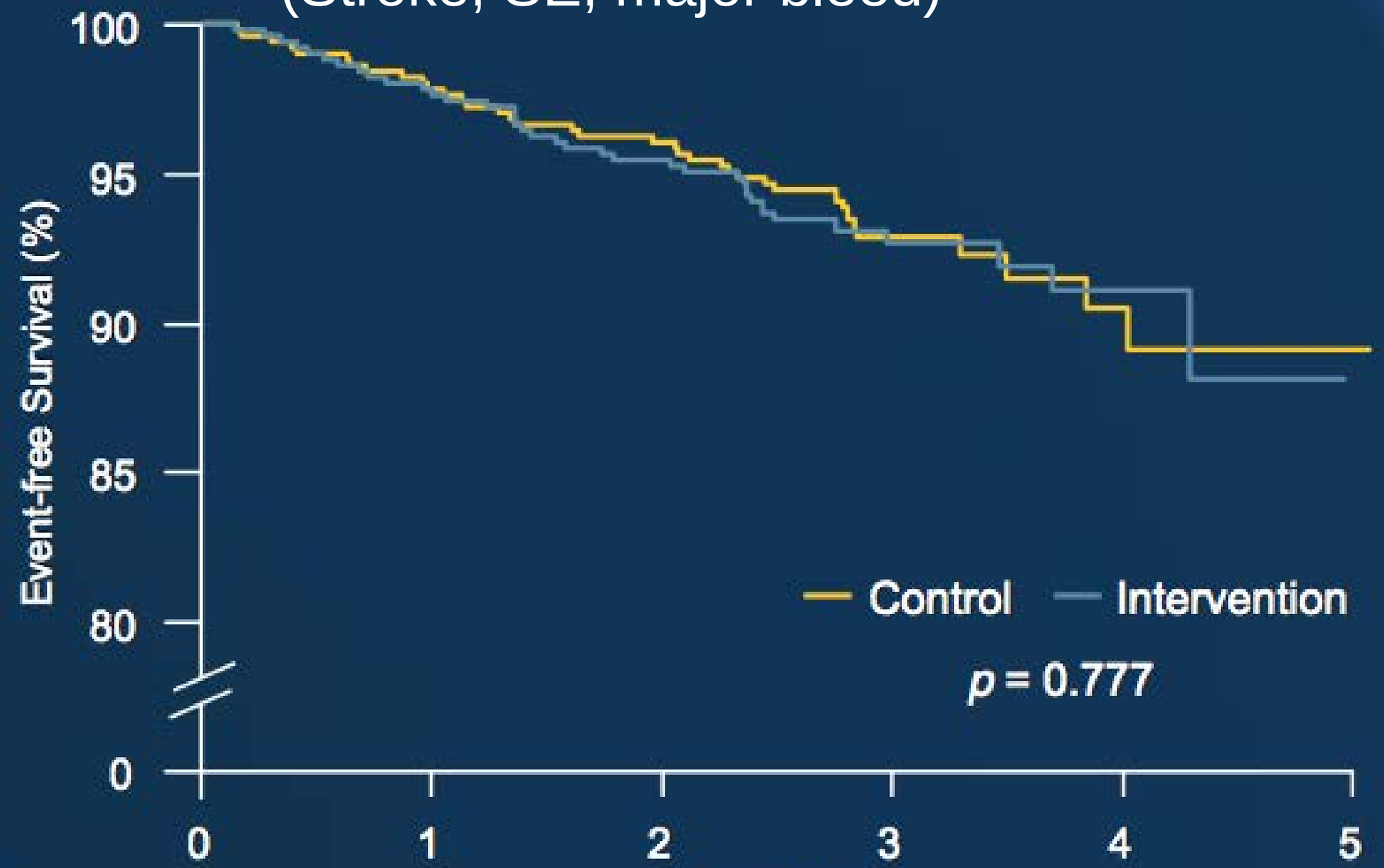
Anticoagulation Protocol Intervention Group



IMPACT

Primary Outcome Events

(Stroke, SE, major bleed)



N, Events						
Control	1361, 0	928, 27	543, 43	228, 57	75, 60	2, 61
Intervention	1357, 0	906, 28	538, 49	214, 59	66, 62	3, 63

What if we throw “big data tools” at the problem?

"OUR STATISTICIAN WILL DROP IN AND EXPLAIN WHY YOU HAVE NOTHING TO WORRY ABOUT."

“The thrombogenic atrium”

Atrial substrate may be more important than rhythm

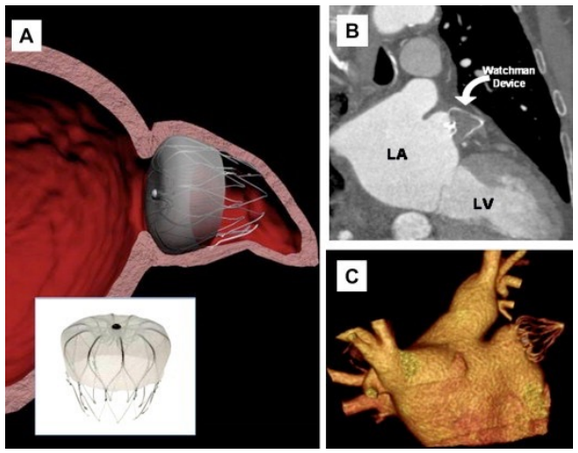
Risk prediction in the non-AF patient

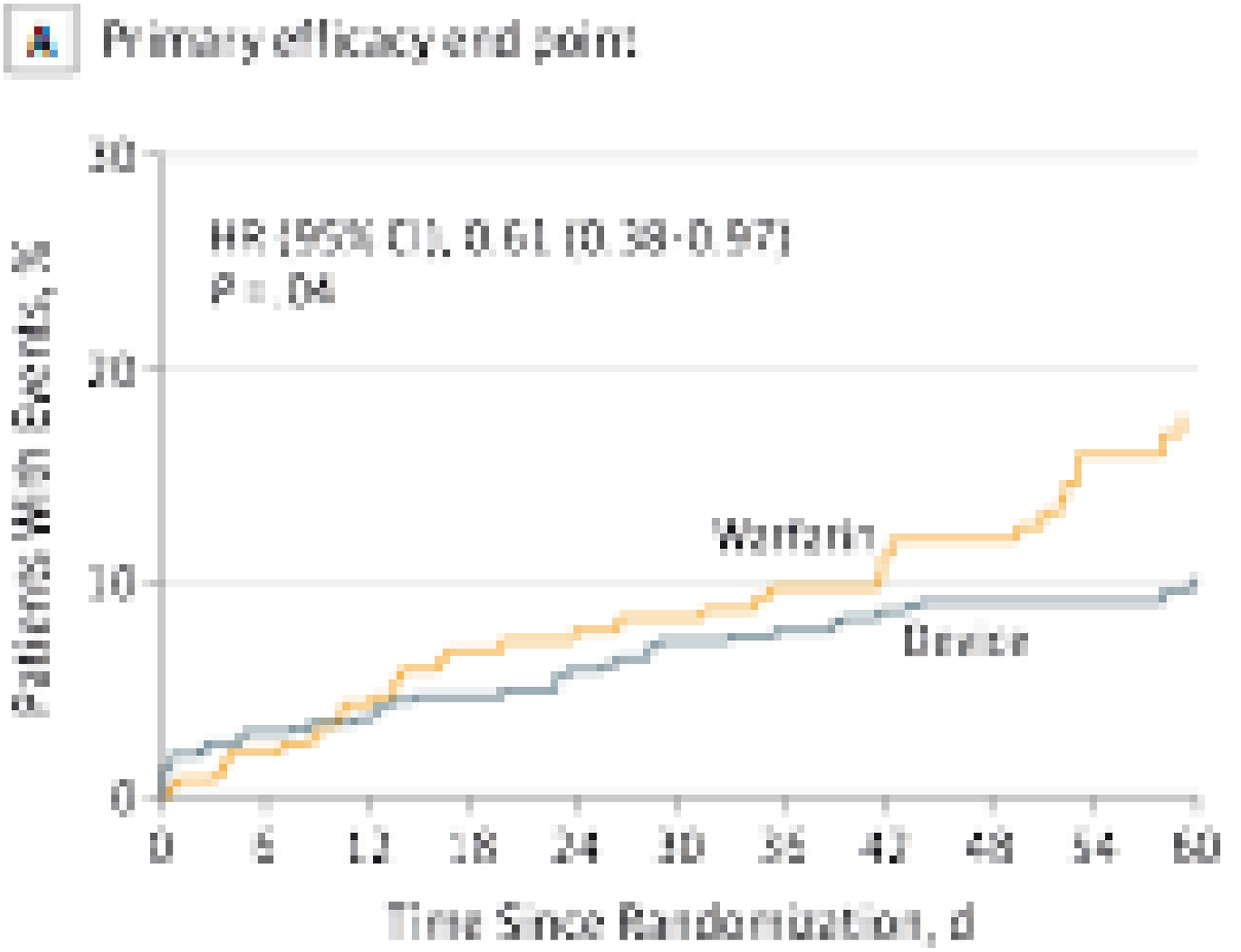
- 1024 patients w/stable CAD, no AF at baseline or follow-up
- c-statistic = 0.65 (same as NRAF)

CHADS2 score	Age-adjusted annual incidence % (95% CI) Arch Intern Med 2003;163:936–43	VA Heart & Soul Study
0	1.9 (1.2-3.0)	0.52 (0.19-1.41)
1	2.8 (2.0-3.8)	0.43 (0.20-0.90)
2	4.0 (3.1-5.1)	0.69 (0.36-1.3)
3	5.9 (4.6-7.3)	3.3 (1.8-5.9)
4	8.5 (6.3-11.1)	18.4 (9.9-34.1)
5	12.5 (8.2-17.5)	73.2 (17.3-309)

(Welles C, Turakhia M, Am Heart J 2011)

Watchman 4-year data





No. of patients

Device	463	398	382	370	360	345	337	327	317	285	196
Warfarin	244	230	218	210	200	188	173	158	147	121	87

(Reddy V, JAMA 2014)

LAFI predicts stroke/TIA in absence of AF

- 983 stable CAD patients without AF

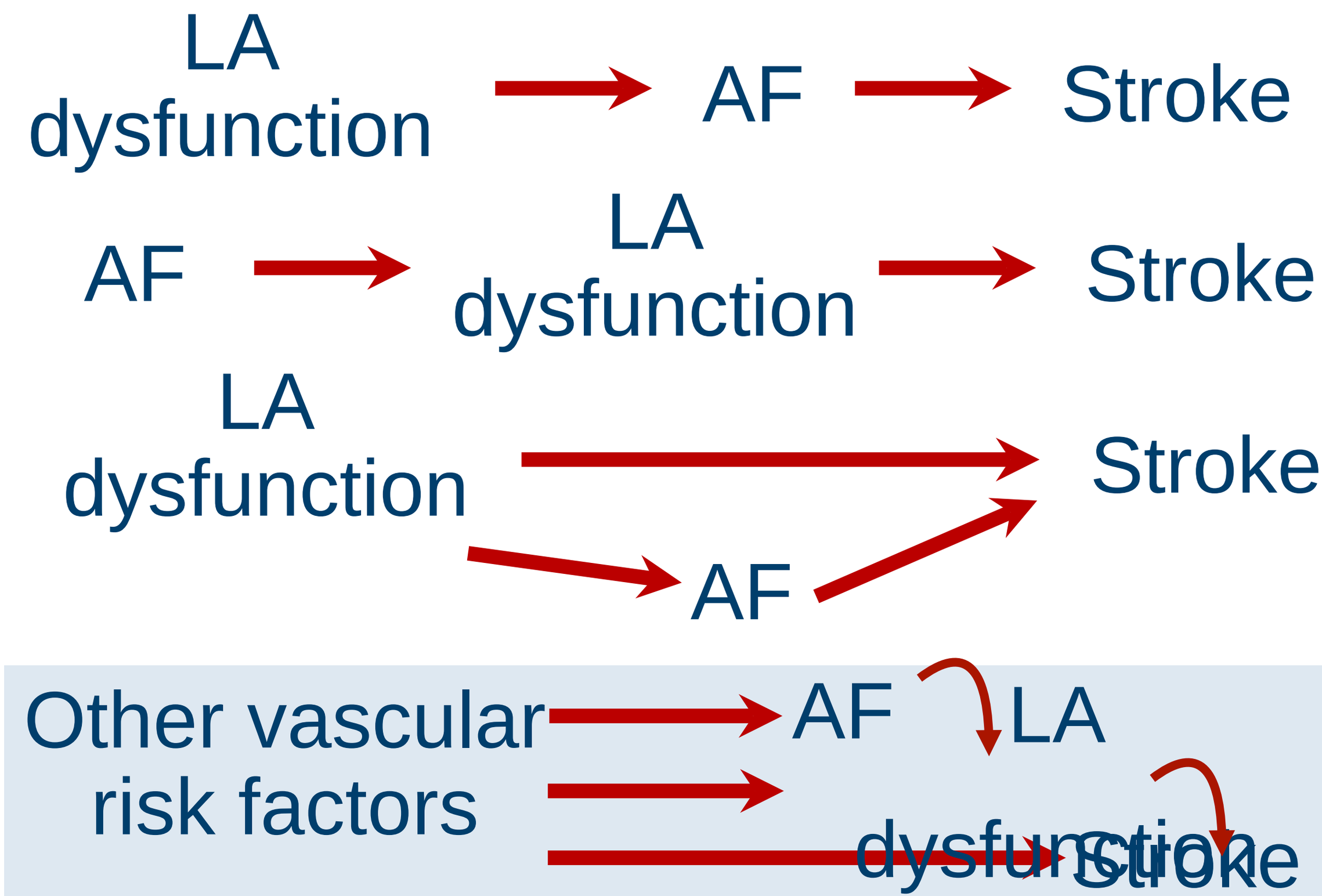
$$\text{LAFI} = \frac{\text{LA emptying fraction x LVOT VTI (cm}}{\text{LAESV indexed to BSA (cc/m}^2\text{)}}$$

Left Atrial Functional Index	Person-Time (Years)	Event Rate (per 1,000 Person-Years)	Age-adjusted HR (95% CI)	p Value
Quintile V (0-24.3 U)	1524	5.3	REF	REF
Quintile IV (24.3-34.2 U)	1440	9.0	1.7 (0.7-4.1)	0.23
Quintile III (34.2-43.1 U)	1460	2.7	0.5 (0.2-1.7)	0.29
Quintile II (43.1-54.6 U)	1345	10.4	1.9 (0.8-4.6)	0.14
Quintile I (54.6-160 U)	1222	15.6	2.6 (1.1-6.0)	0.03
Total	6991	8.3		

- LAFI superior to other LA indices
- **But** other studies have shown LA dysfunction associated with intracranial atherosclerosis

(Wong J, Turakhia M, Am J Cardiol, 2014)

What is the mechanism of stroke?



Summary

- Risk prediction schemes offer poor discrimination
  - Treatment geared toward sensitivity
- AF is causal in some patients but...
  - Most strokes not preceded by AF
  - CHADS2 predicts stroke well in non-AF
  - Rhythm-guided anticoagulation not effective
  - Optimal AF “dose” for risk is undefined
- Near-term stroke prediction from AF difficult
- May inform efforts for AF (and HF) disease management using wearable sensors

Conclusion

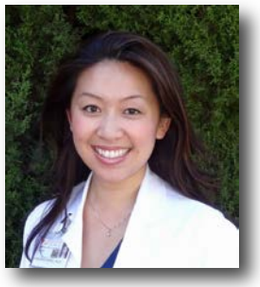
- Conceptual framework is shifting to think of AF as a marker of vascular risk, not just a cause of stroke
- Attributable risk of AF to stroke probably depends on competing risk from other comorbidities

Grant support

- VA Career Development Award
- AHA Scientist Development Grant
- VA MERIT # 09-092
- VA RRP #12-517
- Gilead Sciences CV Scholars Award
- Medtronic
- iRhythm
- VA QUERI LIP #51-040
- JT Stroke Shield Foundation
- Stanford METRICS
- Stanford WSDM

Research Group

- **Collaborators**
  - Paul Heidenreich, Michael Ho, Adam Rose, Ken Mahaffey, Bob Harrington, Russ Altman, Maarten Lansberg
- **Staff**
  - Jun Fan, Susan Schmitt, Aditya Ullal, Claire Than
- **Graduate Students**
  - Lichy Han
- **Residents**
  - Alex Perino, Andrew Chang, Jessica Hellyer
- **Postdocs/Fellows**
  - Daniel Kaiser, Celina Yong, Christo Swan, Farnaz Azarbal, Jared Miller, Nino Santangeli



Thank you !