Relationship between AF burden and stroke: Is AF just a marker of increased thromboembolic risk?

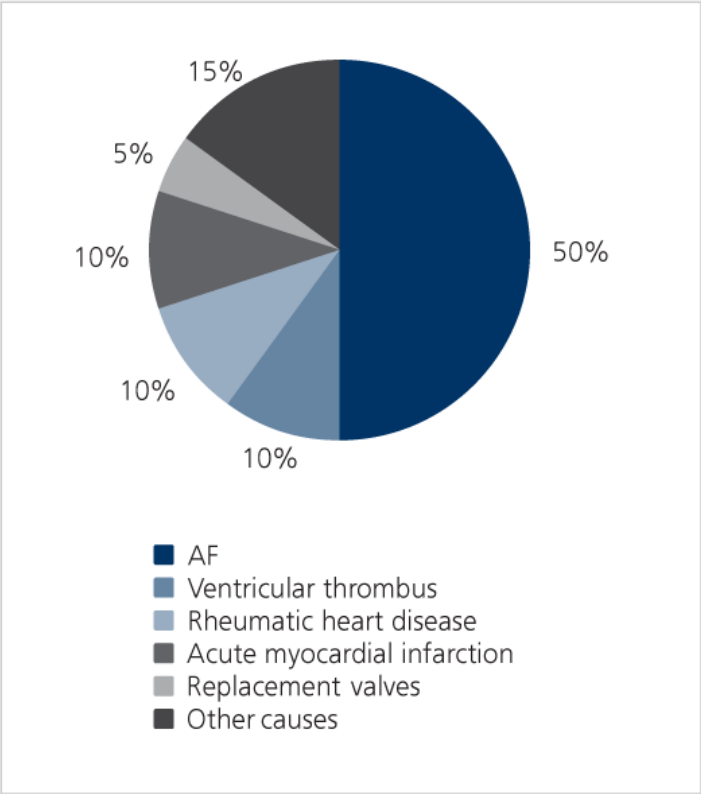
David J Fox
Consultant Cardiologist/Electrophysiologist
University Hospital of South Manchester
HRC October 2016

Setting the scene

- Multi-disciplinary audience
- AF and its role in stroke
- Risk assessment and stroke
- AF we know about
  - ECGS
- AF we don't know about
  - Devices
- Conclusions
  - Hopefully we can draw some ?!

Relationship between AF and stroke

AF causes 50% of all major embolic CVA



12 Months post stroke

Annual death Rate from AF		
YEAR	With AF	No AF
1	50	27
2	14	8
3	14	6
4	10	6
5	11	6
6	4	3
7	5	4
8	4	3

How do we currently assess AF stroke risk?

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 score	Patients (n = 1733)	Adjusted stroke rate %/ year
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

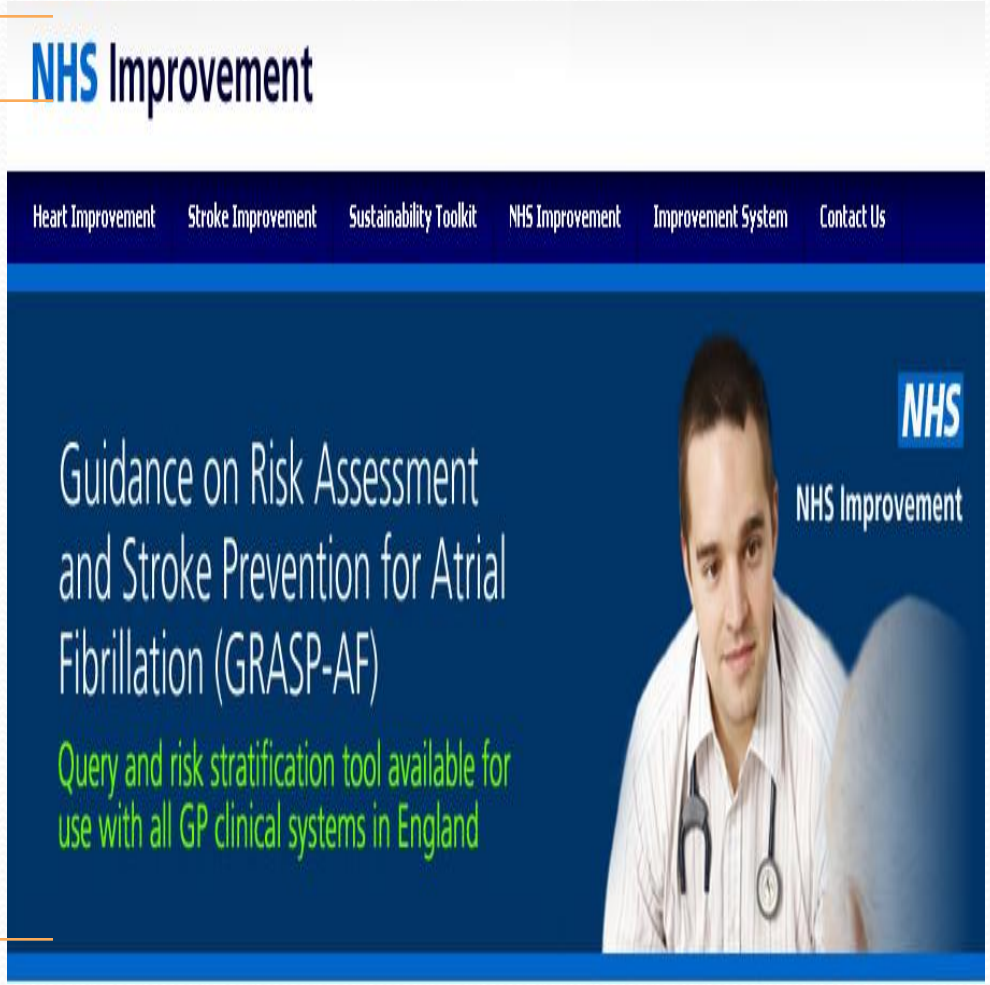
CHA2DS2-VASc score	Patients (n = 7329)	Adjusted stroke rate %/ year
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

From ESC AF Guidelines http://www.escardio.org/guidelines-surveillance/guidelines/Documents/guidelines-afib-FT.pdf

HASBLED Score also used to counter risk

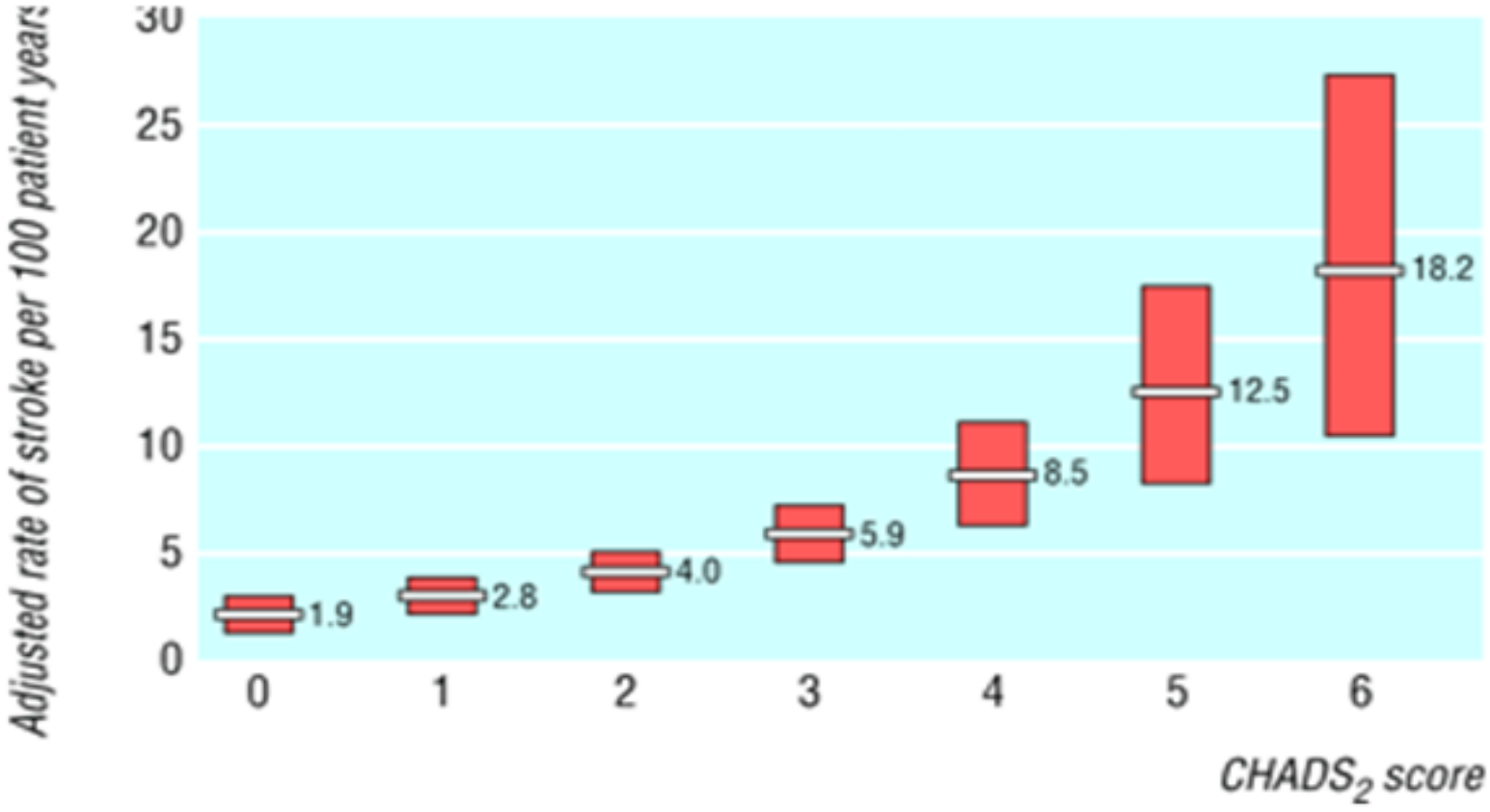
$CHADS_2$ and CHA_2DS_2-VASc both available in GRASP-AF

Risk factor	Points
Congestive heart failure/LV dysfunction	+1
Hypertension	+1
Age ≥75 years	+2
Diabetes mellitus	+1
Stroke/TIA/TE	+2
Vascular disease (MI, aortic plaque, PAD)*	+1
Age 65–74 years	+1
Sex category (female)	+1
Cumulative score	**Range 0–9**



http://www.improvement.nhs.uk/graspaf/- accessed 07/09/2012

Annual stroke risk by $CHADS_2$ score



WARFARIN / OAC REDUCES THESE RISKS BY APPROX 65-70%

AF Burden-What is it?

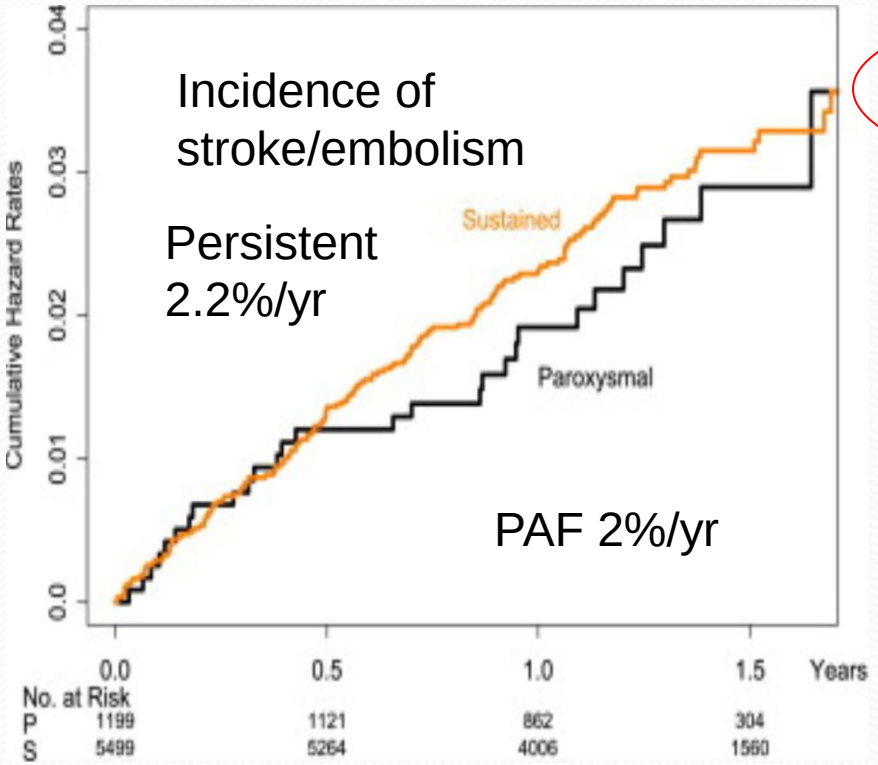
- ‘A measure of AF that is not dependent on the time to a recurrence or duration of time between recurrences and is more dependent on the *duration* of AF episodes’

- How much time spent in AF
- The longest episode spent in AF
- The longest episode of AF per unit time
- Proportion of days spent with an AF recording

Risk of stroke in Known PAF-ACTIVE W Study

6,697 pts (5499 persistent + 1199PAF)

Stroke/Systemic embolism



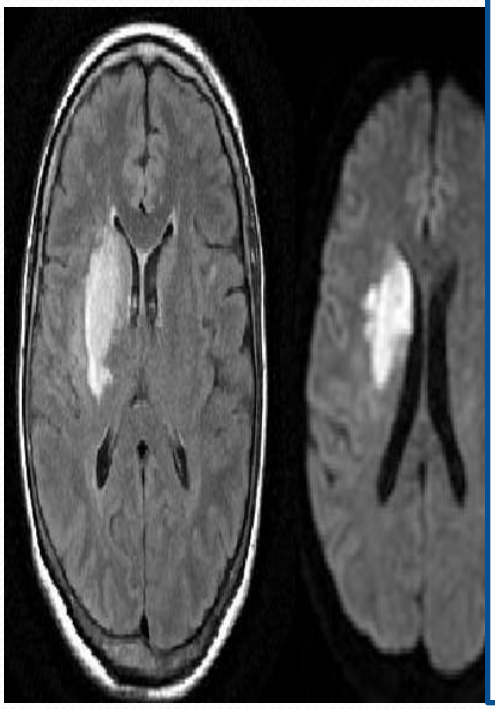
Population-CHADS 2

Risk F	Persist	PAF	P Value
>75yrs	2004	338	<0.001
HTN	4450 (81%)	999 (83%)	n/s
Stroke/ TIA	996 (18%)	170 (14%)	n/s
LV Dysfunction	996 (18%)	125 (10%)	<0.001
CHADS Score	2.04+/- 1.12	1.79+/- 1.03	<0.001

Hohnloser S et al JACC 2007:50:2056-63

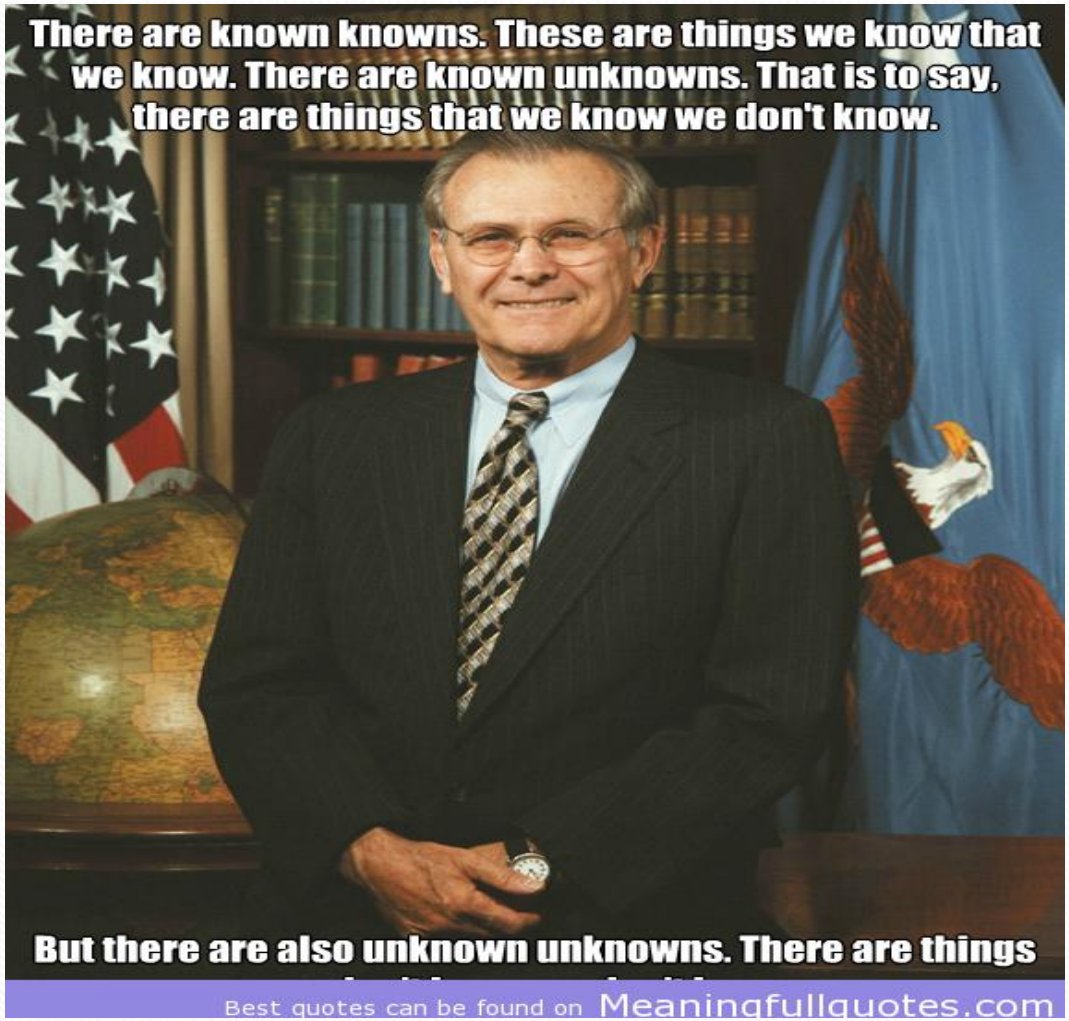
Known PAF vs NSR -stroke rates?

- Yamanouchi
  - Autopsy specimens >70y with PAF
  - 54% stroke vs 22% age matched non AF control

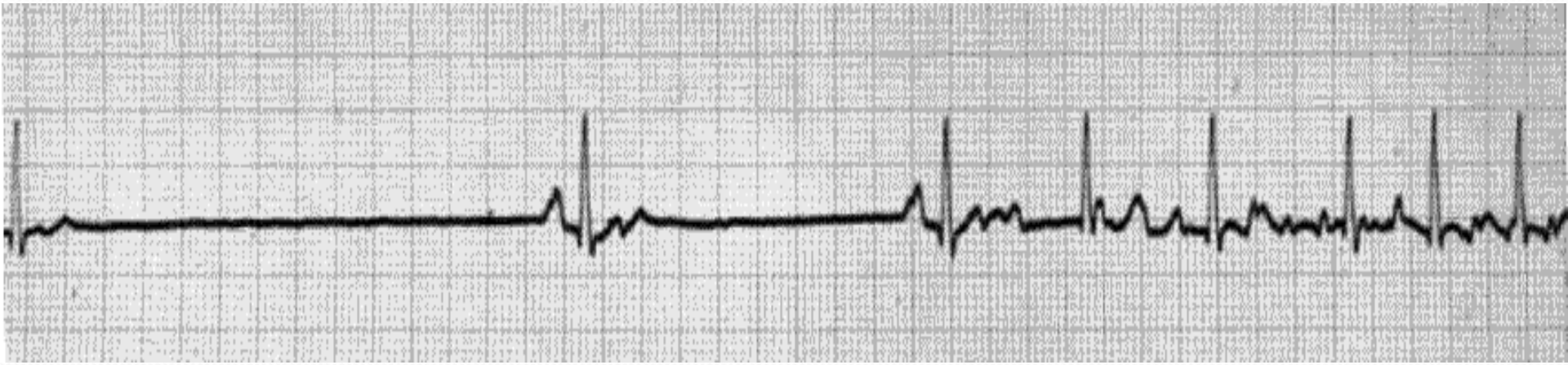


Yamanouchi H, Mizutani T, et al. Paroxysmal atrial fibrillation: high frequency of embolic brain infarction in elderly autopsy patients. Neurology1997; 49:1691–4

What about the AF we don't know about?.....Ask Donald



AF detected on Pacemakers and Implanted devices



AF Burden and CIED

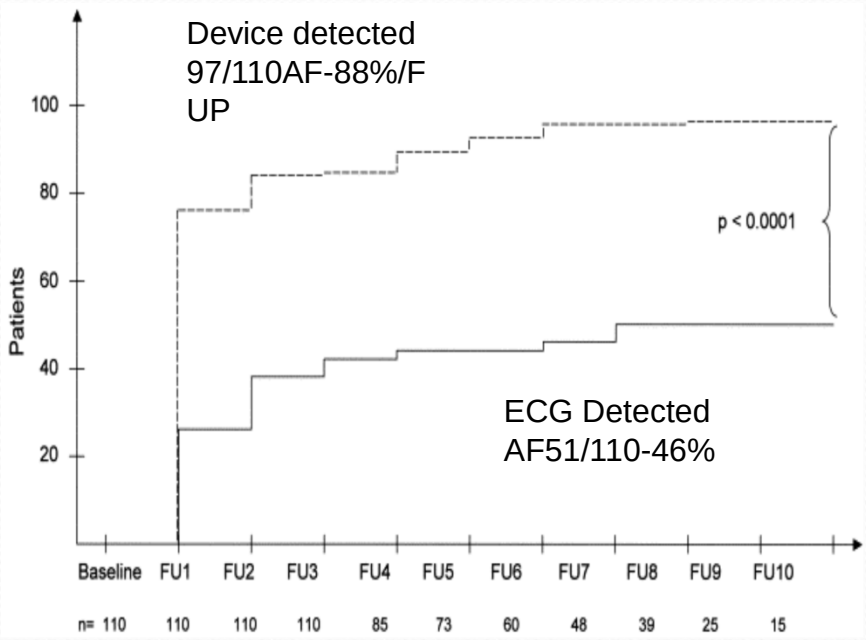
Table 3 Studies in the literature that analysed the relationship between AHRE or AF burden, as detected by an implanted CIEDs (a pacemaker or an ICD)

Author, year, reference	No. of patients	AF burden associated with stroke	HR (95% CI) for stroke p-value	Other findings
Glotzer et al., 2003 (26)	312 (patients with sinus node dysfunction)	≥ 5 min	2.79 (1.51–5.15) p = 0.0011	
Capucci et al., 2005 (27)	725 (patients with bradyarrhythmias and history of PAF)	> 24 h	3.1 (1.1–10.5) p = 0.044	
Botto et al., 2008 (13)	568 (patients with bradyarrhythmias and history of PAF)	> 5 min		Combining AF burden and $CHADS_2$ make it possible to distinguish a subgroup at low and high risk of stroke
Glotzer et al., 2009 (28)	2486 (patients with ≥ 1 stroke risk factor implanted with a pacemaker or an ICD)	≥ 5.5 h	2.20 (0.96–5.05) p = 0.06	
Ziegler et al., 2010 (29)	163 (previous thromboembolic event, no PAF)	≥ 5 min		73% of new AF patients with previous TE experienced episodes of AF < 10% of follow-up days
Boriani et al., 2011 (30)	568 (patients with bradyarrhythmias and history of PAF)	> 5 min		Combining AF burden and $CHADS_2$ or CHA_2DS_2-VASc improves prediction of stroke, reaching C-statistics of 0.713 and 0.910, respectively
Healey et al., 2012 (31)	2580 (≥ 65 years, hypertension, no history of PAF)	> 6 min	2.49 (1.28–4.85) p = 0.007	
Shanmugam et al., 2012 (32)	560 (heart failure patients treated with CRT)	≥ 3.8 h	9.4 (1.8–47.0) p = 0.006	40% of the study population had at least 1 day with AF burden > 14 min
Boriani et al. 2013 (33)	10,016 patients with a CIED, without permanent AF, median age 70 years (pooled analysis of three studies)	≥ 1 h	2.11 (1.22–3.64) p = 0.008	

PAF, paroxysmal atrial fibrillation; CIED, cardiac implantable electrical device; HR, hazard ratio; CI, confidence intervals.

Do we see all AF ?

Cumulative detection of AF by either Device (hatched) ECG (Solid)

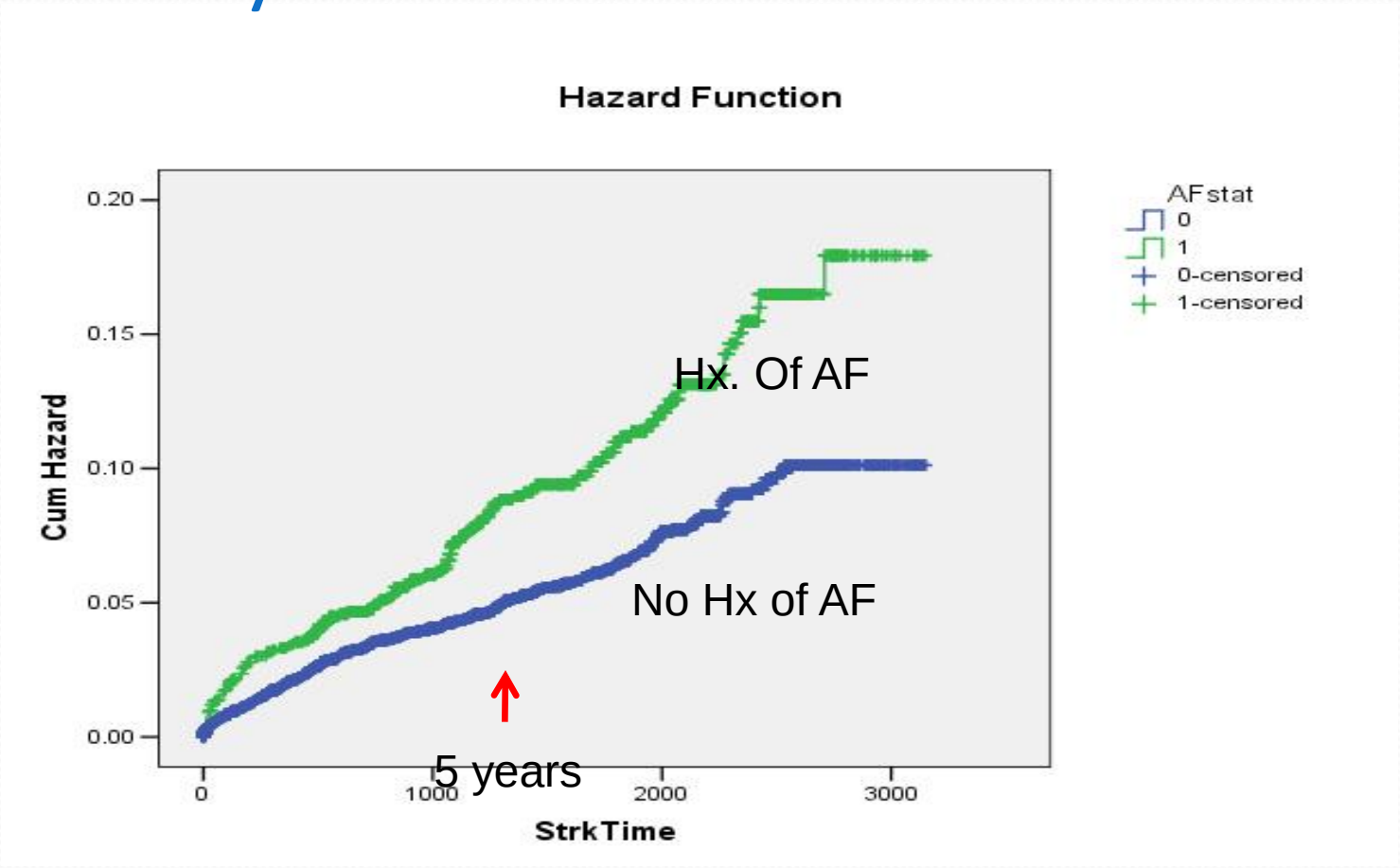


Study observations

- Known AF pts with a device
- Endpoints looked for AF >48hrs
- Much higher pick up of AF when combining device 'e grams' plus clinic ECG
- 19 pts had AF >48 hrs on device traces and where asymptomatic

Israel CW et al JACC 2004;43:47-52

Stroke risk in pacemaker patients by history of AF



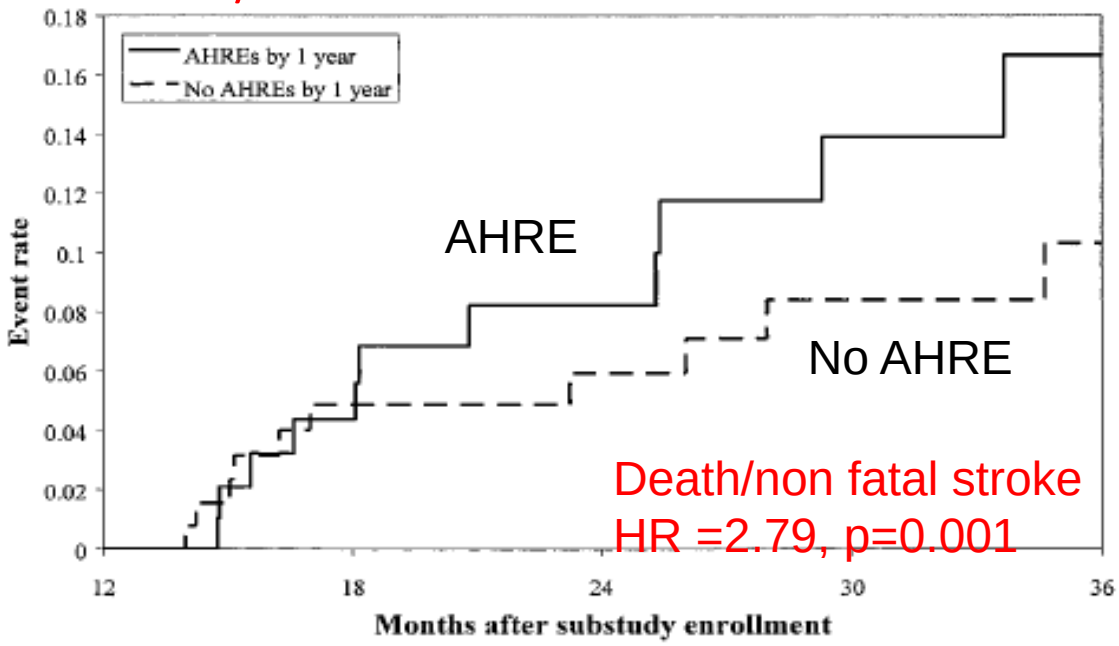
Healey et et Circulation 2006

Atrial High Rates and risk of stroke/death-post hoc analysis from MOST Study

Ancillary MOST Study

312 pts

Event logged if
AR>220/10beats or more



ATRIAL HIGH RATES PREDICT:

Inc mortality

Death/non fatal CVA

AF

Figure 2. Kaplan-Meier plot of death or non-fatal stroke after 1 year of ancillary study follow-up in patients with AHREs vs those without AHREs; $P=0.001$. MOST indicates Mode Selection Trial; AHRE, atrial high rate episodes.

Glotzer TV et al Circulation 2003;1614-9

TRENDS STUDY

2486 PTS-Longest total duration of AT/AF in hrs on any given day in a 30 day rolling window

Question:

Is there a critical value of daily atrial tachyarrhythmia

From device diagnostics that predict stroke risk

Over 65y group with one risk factor for stroke needing a device

GROUP (Atrial arrhyt)	Risk	CVA/ TIA	HR	95% CI	P
Zero Burden	1.1%	0.5%	-	-	-
Low (<5.5hr)	1.1%	1.1%	0.98	0.34 - 2.82	0.97
High (>5.5hr)	2.4%	1.8%	2.2	0.96 - 5.05	0.06

Glotzer TV et al Circ Arrhythmia EP 2009:2:474-80

TRENDS Study

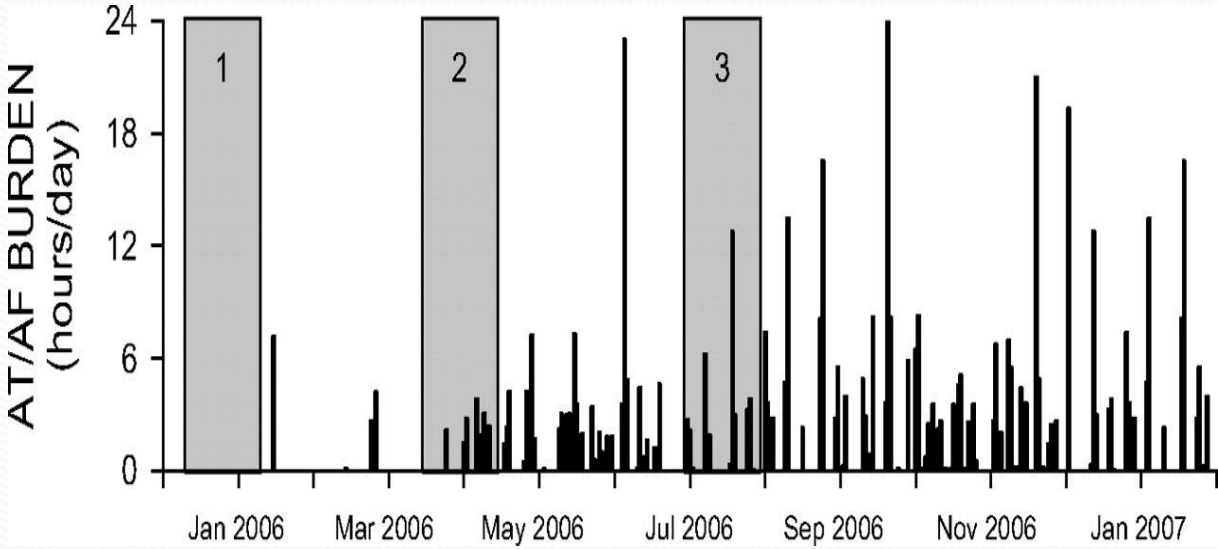
2486 patients

AF/AT Burden- longest TOTAL duration of AF/AT in hours on any given day- 30 day rolling window

Suggestion that more/longer period of AF (NOT just the diagnosis of AF) increase the TE risk

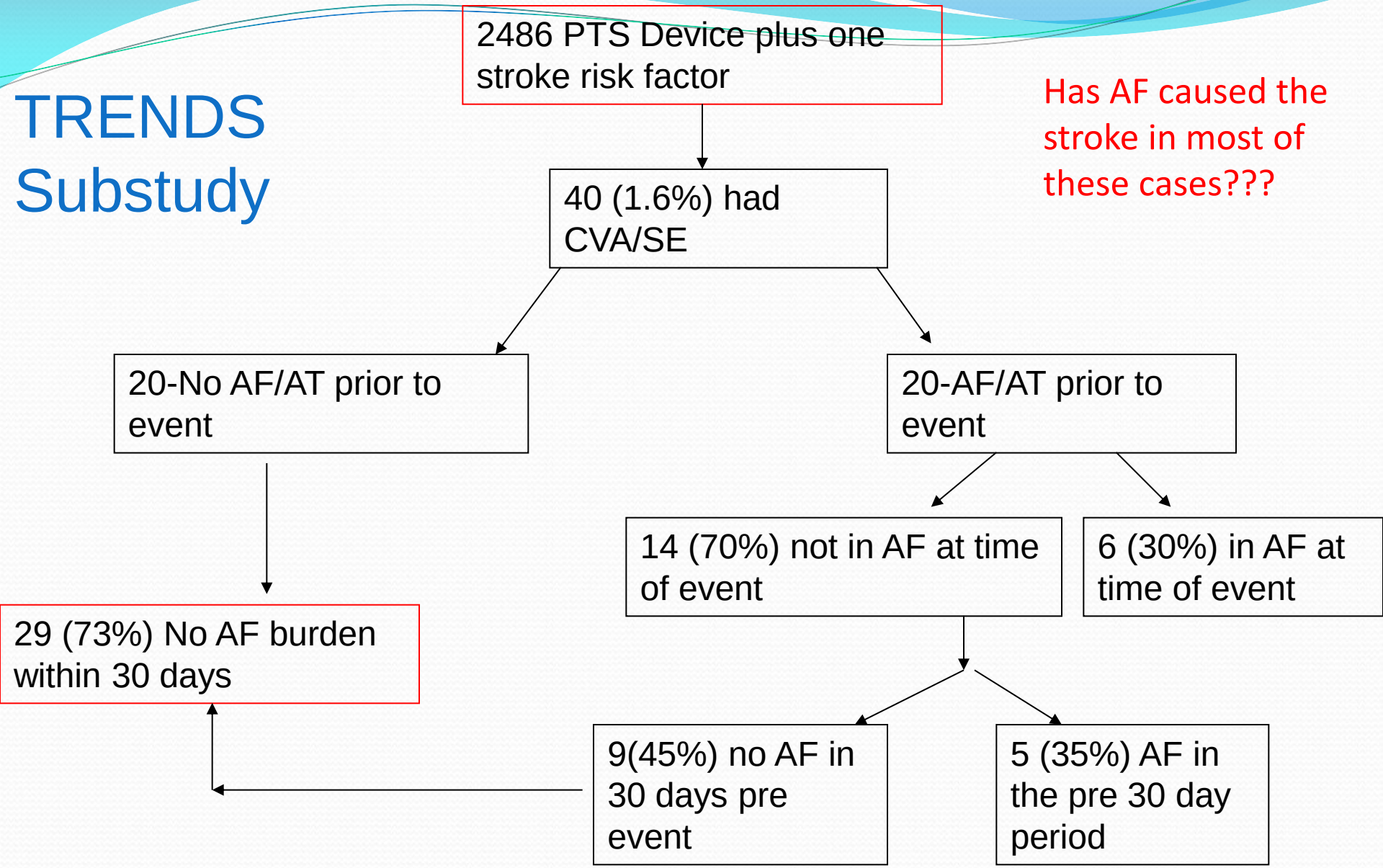
AT/AF burden ≥5.5 hours on any of 30 prior days appeared to double TE risk.

Example of 30-day windows assessing AT/AF burden from data collected from device diagnostics.



Glotzer TV et al Circ Arrhythmia EP 2009:2:474-80

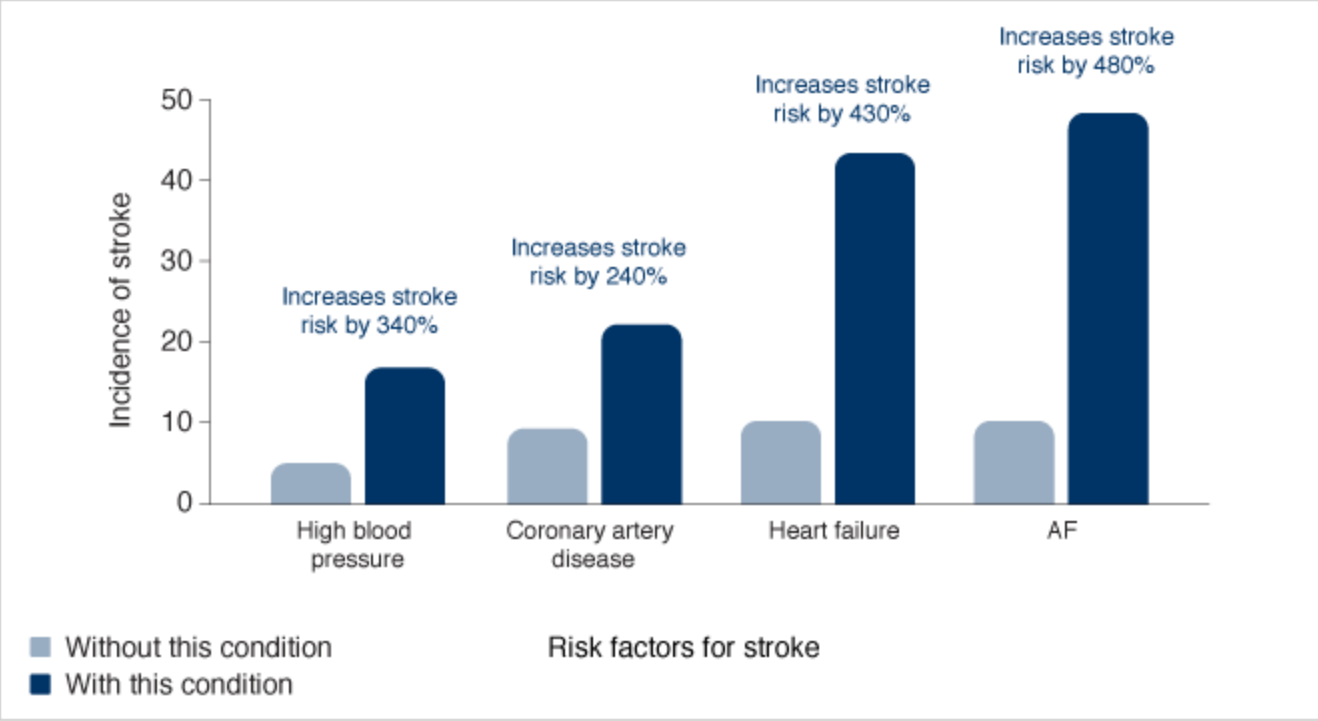
TRENDS Substudy



Has AF caused the stroke in most of these cases???

Daoud E et al 2011, Heart Rhythm;8: 1415-23

Is AF a surrogate marker for stroke in this complex group??



CHADSVasc Hypertensive scores a point, but if extreme hypertension plus smoking????.....

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)

- Pooled data from 22,433 patients from 3 large studies
  - Trends
  - PANORAMA
  - Italian Clinical Service Study

  - 10,016 Eligible
    - Exclusions:
    - Short follow up
    - Single Chamber VVI system
    - Incomplete Follow up
    - Permanent AF

Boriani G et al Eur Heart J 2014: 21;35:508-16

Pooled Analysis from prospective studies-SOS AF Study

OBJECTIVE:

The aim of this study was to assess the association between maximum daily atrial fibrillation (AF) burden and risk of ischaemic stroke.

- 43% of the 10,016 pts had at least one episode of AF OF >5min in the 24mth follow up period
- Threshold of >5min was statistically associated with increased risk of stroke
- Highest point was for a threshold of >1hr

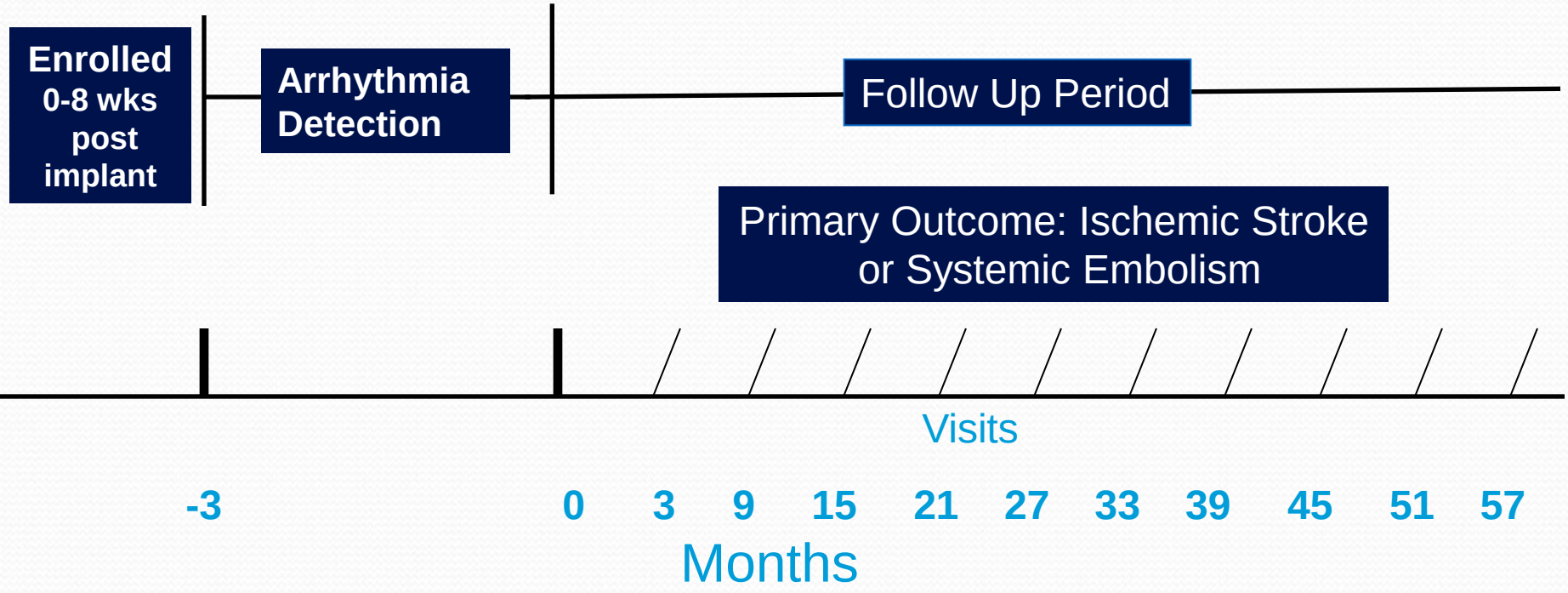
CONCLUSIONS:

Device-detected AF burden is associated with an increased risk of ischaemic stroke in a relatively unselected population of CIEDs patients. This finding may add to clinically appropriate decision-making on anticoagulation treatment.

Study Design

Prospective Cohort Design
To determine if device-detected atrial tachyarrhythmias are associated with an increased risk of stroke or embolism?

Mininum Follow up	**1.75 yrs**
Maxmum Follow Up	**5 yrs**
Mean Follow Up	**2.8 yrs**



Healey J et al NEJM 2012;366:120-129

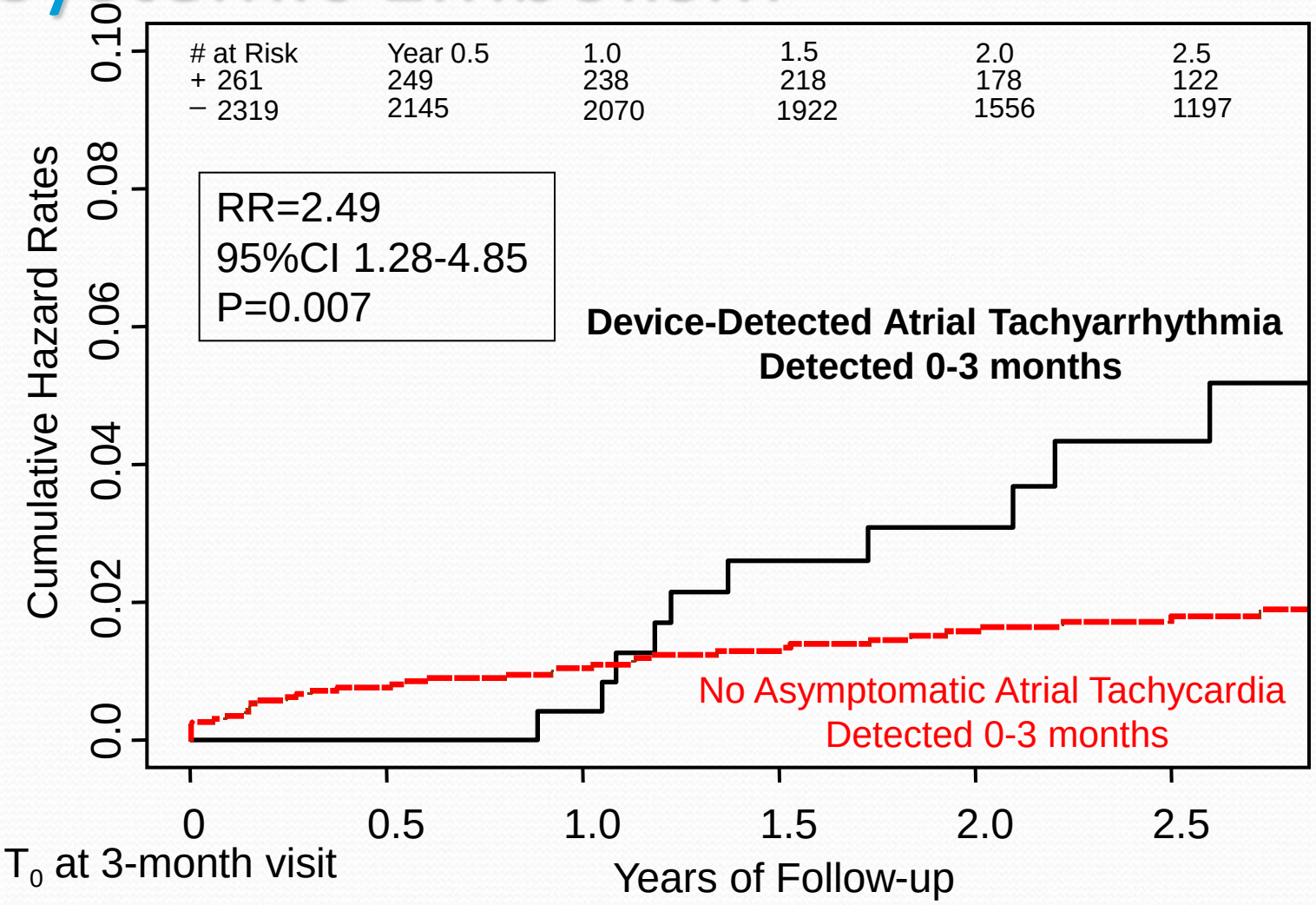
ASSERT: Study Design

- Patient Eligibility
  - Enrolled after new dual-chamber pacemaker or ICD
  - Age ≥ 65 years
  - History of hypertension
  - Excluded if any history of AF
  - Excluded if on Vitamin K antagonist
  - Pre-specified primary analysis:
    - Monitor from enrolment to 3 month visit for atrial tachyarrhythmia defined *as >6 minutes and an atrial rate of >190 bpm*
    - Prospective follow up for ischemic stroke or systemic embolism from 3 month visit onwards
- Statistical power to detect ≥ 1% per year increase in primary outcome

ASSERT: Study Results

- 2580 patients enrolled following implant of first pacemaker or ICD (St. Jude Medical)
  - 2451 pacemaker, 129 ICD patients
- Mean follow up 2.8 yrs
- 36% of patients had at least one device-detected atrial tachyarrhythmia
  - >6 min, >190 bpm; at mean FU of 2.8 years
- Cumulative rate of VKA use <2% per year

ASSERT: Ischaemic Stroke or Systemic Embolism



Are all AHRE real? AWARE Trial (N=1642)

- Appropriate: 73%
  - AF – 42%
  - Aflutter – 27%
  - Atrial Tachycardia – 4%
- Inappropriate: 27%
  - RNRVAS – 17%
  - Noise – 5%
  - Farfield R-wave oversensing – 3%
  - Sinus tachycardia – 2%

Clinical Outcomes Adjusted for Baseline Risk of Stroke

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Tachyarrhythmia Present vs. absent		
	Absent N= 2319		Present N= 261				
	events	%/ year	events	%/year	RR	95% CI	p
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.50	1.28 – 4.89	0.008
Vascular Death	153	2.62	19	2.92	1.14	0.71 – 1.84	0.59
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.27	0.86 – 1.88	0.23
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.75	3.89 – 8.47	<0.001

Conclusions-ASSERT Trial

- Over 2.8 years mean follow up, device-detected atrial tachyarrhythmias (>6 min, >190 bpm) are present in 36% of pacemaker patients with hypertension; but no prior history of AF

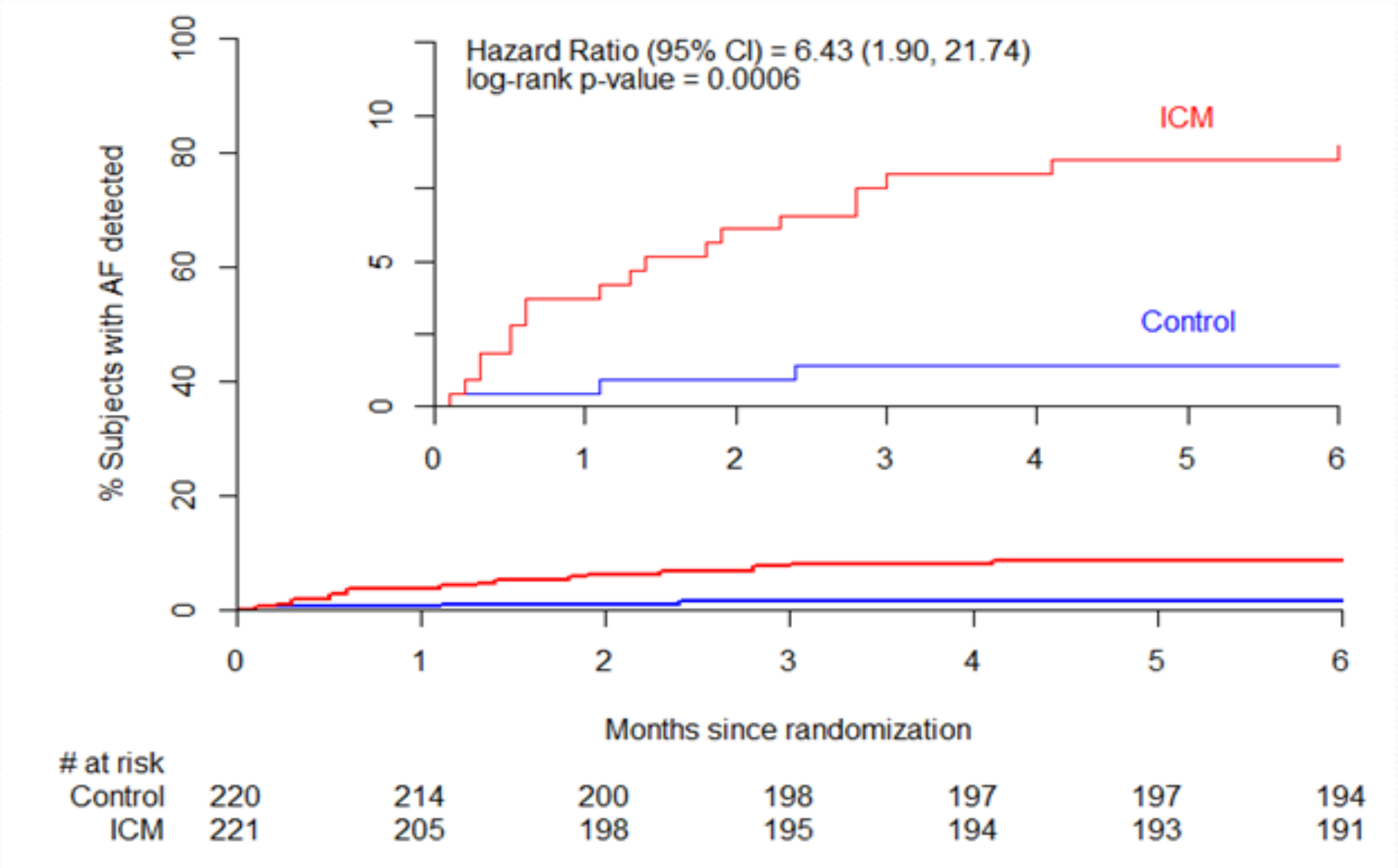
- Device-detected atrial tachyarrhythmias are associated with a 2.5-fold increased risk of ischemic stroke or systemic embolism

- In patients with $CHADS_2$ score > 2, device-detected atrial tachyarrhythmias increase the absolute risk of stroke or systemic embolism to 4% per year

AF detected from Non Pacemaker /ICD devices

- CRYSTAL AF (and EMBRACE) Trials
- Inclusion:
  - Recent cryptogenic stroke, TIA
- Primary Outcome:
  - Time to first documented episode of AF
- Rationale
  - Lot of asymptomatic AF

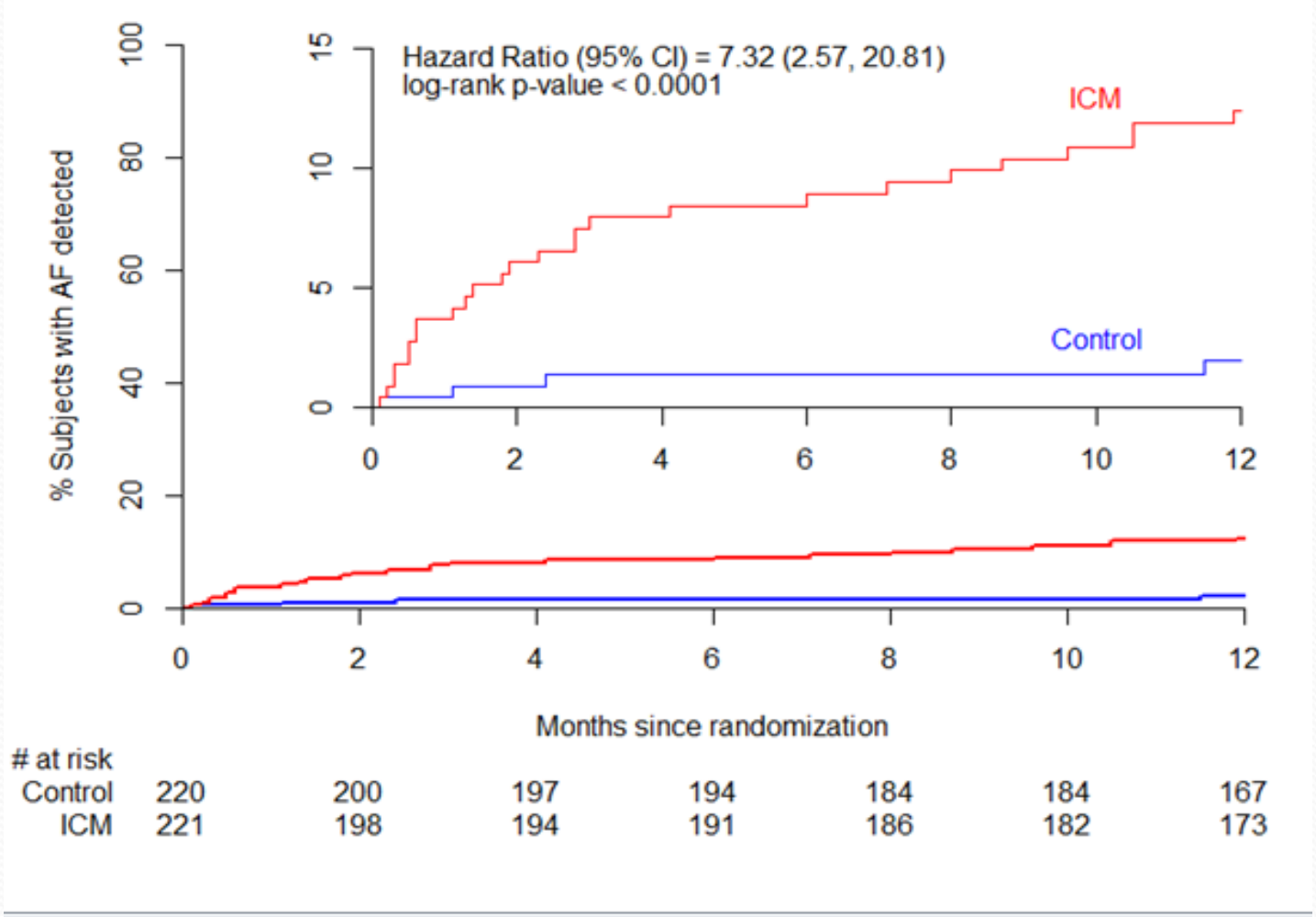
Primary Endpoint: DETECTION OF AF AT 6 MONTHS-CRYSTAL AF



6 Month Endpoints

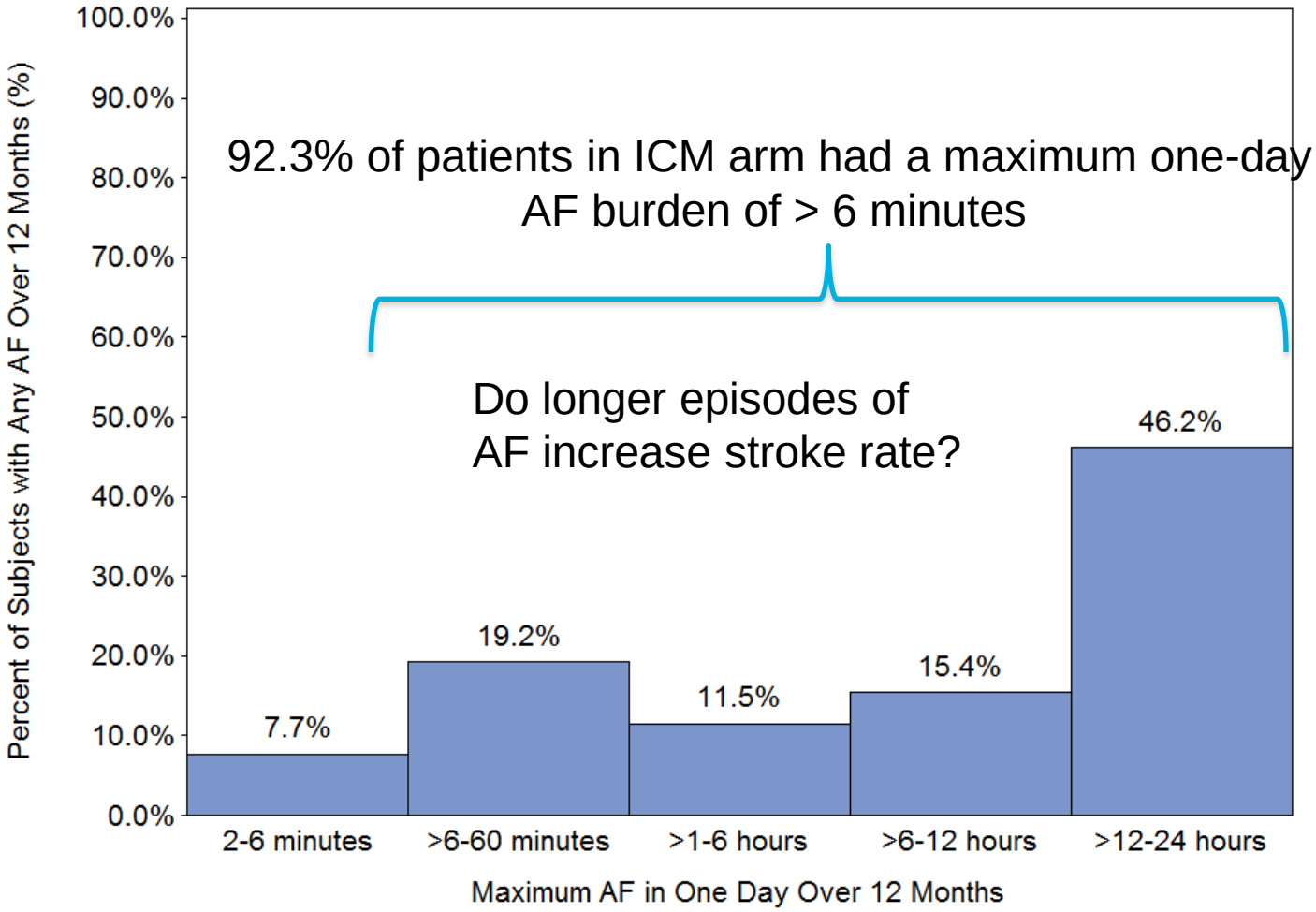
	ICM	Control
Median Time from Randomization to AF Detection	41 days	32 days
Patients found to have AF	19	3
% Asymptomatic Episodes	74%	33%
Oral Anticoagulation Usage, overall	10.1%	4.6%
OAC use in patients with detected AF	94.7%	66.7%
Testing required to detect AF	Automatic AF detection	88 ECGs 20 24-hour Holters 1 event recorder

Secondary Endpoint: Detection of AF at 12 months



Rate of detection in ICM arm was 12.4% vs 2.0% in control arm

Atrial Fibrillation Duration in REVEAL® XT arm at 12 months (N=29)



Conclusions

- ICM is superior to standard monitoring in detection of AF at 6 months (HR = 6.43), 12 months (HR=7.32), and 36 months (HR=8.78) in patients with cryptogenic stroke
- AF was detection rises month on month
- 92.3% of patients with AF in the ICM arm had a day with greater than 6 minutes of AF
- Should we consider long-term continuous monitoring in patients with cryptogenic stroke?

EMBRACE Study – also published in NEJM

- Canadian Study
- N = 572
- Subjects were ≥55 years old
- Two arms
  - 30 day event-triggered recorder
  - Standard care (24 hour Holter)
- Primary Outcome
  - AF episodes of 30 seconds or longer within 90 days
- Secondary Outcomes
  - AF episodes of 2.5 minutes or longer within 90 days
  - Anticoagulation status at 90 days

Table 1 Comparison of the EMBRACE and CRYSTAL-AF trials

Table 1 | Comparison of the EMBRACE[1] and CRYSTAL-AF[2] trials

Study	Investigation group	*n*	Onset of monitoring after stroke (days)	Duration of monitoring (days)	Proportion with AF (%)
EMBRACE[1]	Usual* Intensive‡	285 286	75.1 ± 38.6	90	3.2 16.1
CRYSTAL-AF[2]	Usual* Intensive§	220 221	38.1 ± 27.6	~180	1.4 8.9

*12-lead ECG and Holter ECG monitoring for 24–48 h. ‡Continuous surface ECG for 4 weeks. §Subcutaneous ECG monitoring with an implanted device for up to 3 years. Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram.

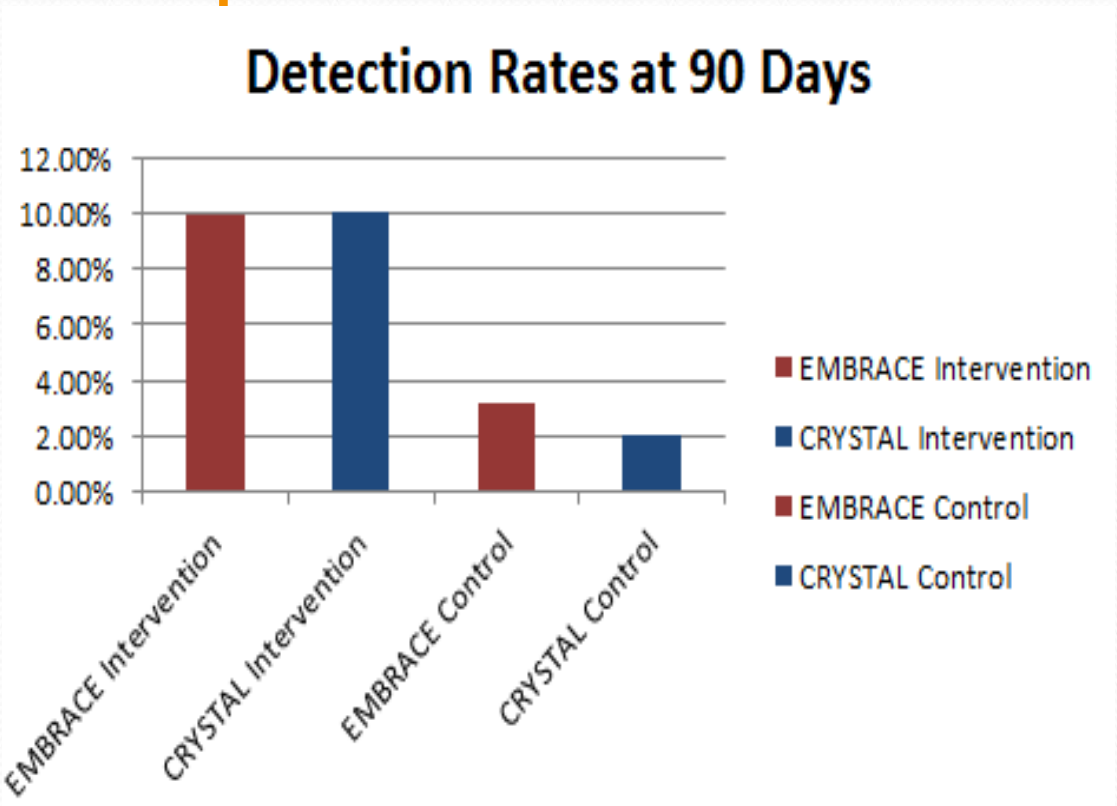
Embrace: More AF BUT work up pre study less, older pts, shorter burst AF considered ie 30s vs 2min

Camm, A. J. (2014) Cryptogenic stroke—can we abandon this apologetic diagnosis?
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2014.111

nature REVIEWS CARDIOLOGY

Creating a Similar Comparison

- Age ≥ 55 years
- 2-2.5 minute definition of AF in intervention arm
- 30 second definition of AF in control arm
- 90 days of follow-up



Using similar age criteria and AF definitions results in similar findings

Conclusions

- PAF is not benign
- AHRE appear to suggest increased risk of stroke/SE/AF
  - Consider closer follow up
- AHRE noted on device interrogation should be scrutinised before deciding on anticoagulation
  - They are not all AF
  - Very brief ones not the same as AF
- Increasing burden/periods of AF appears to increase risk
  - Seconds likely less problematic than hours

Conclusions

- AF likely to be a marker of risk
  - Athero-emboli from aorta/carotids
- Complex association between AF and stroke- Having AF may be a surrogate marker for increasing stroke risk
  - Stress/BP surges/Alcohol/CAD/IHD/lipids
- Cryptogenic stroke patients
  - Consider prolonged cardiac monitoring