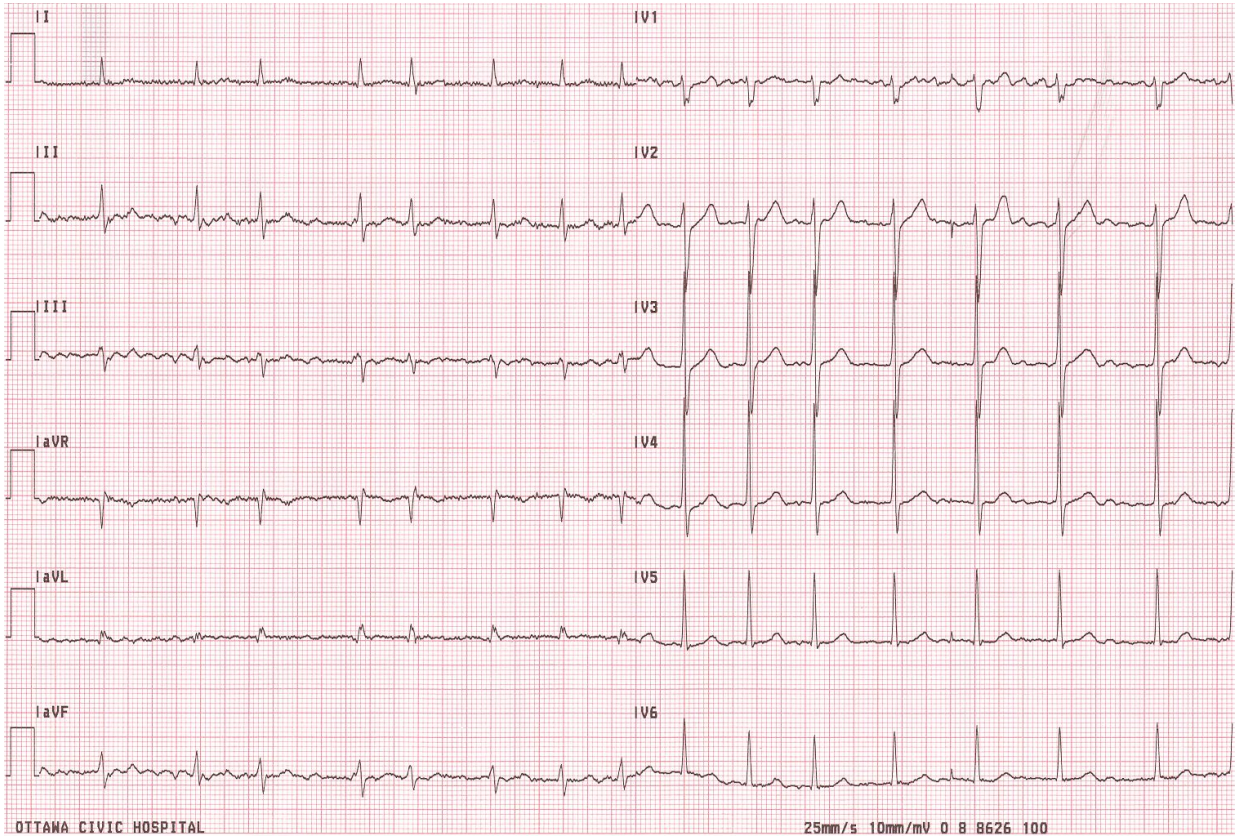
Apixaban for the Reduction of Thrombo-Embolism in Device-Detected Sub-Clinical Atrial Fibrillation

ARTESiA

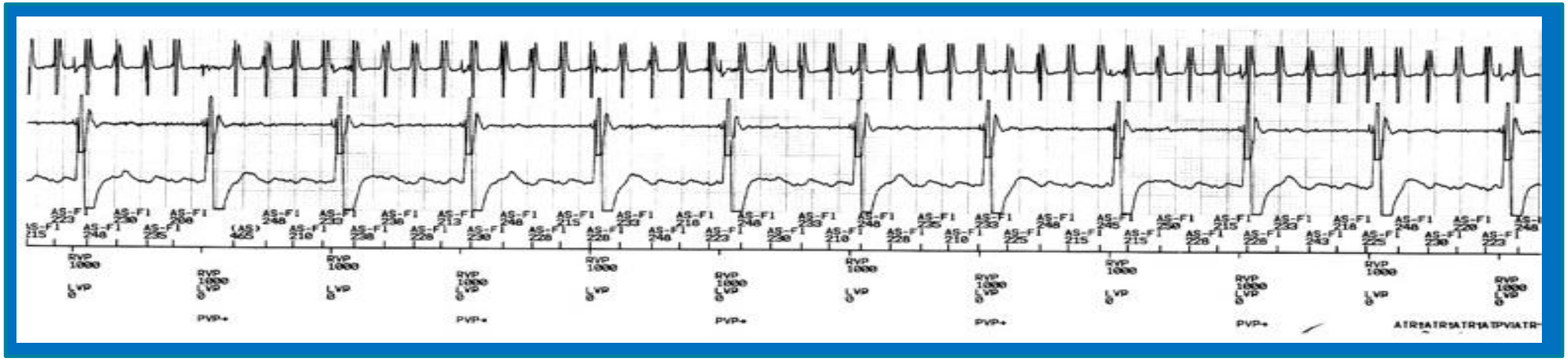
Scientific Rationale: Management of SCAF

What is Atrial Fibrillation?



- Cohort studies such as Framingham performed 12-lead ECG 1-2/year
- 70-80% of patients in RCTs of anticoagulation had persistent or permanent AF (those with paroxysmal had to have high burden)

SCAF Detected by Cardiac Devices



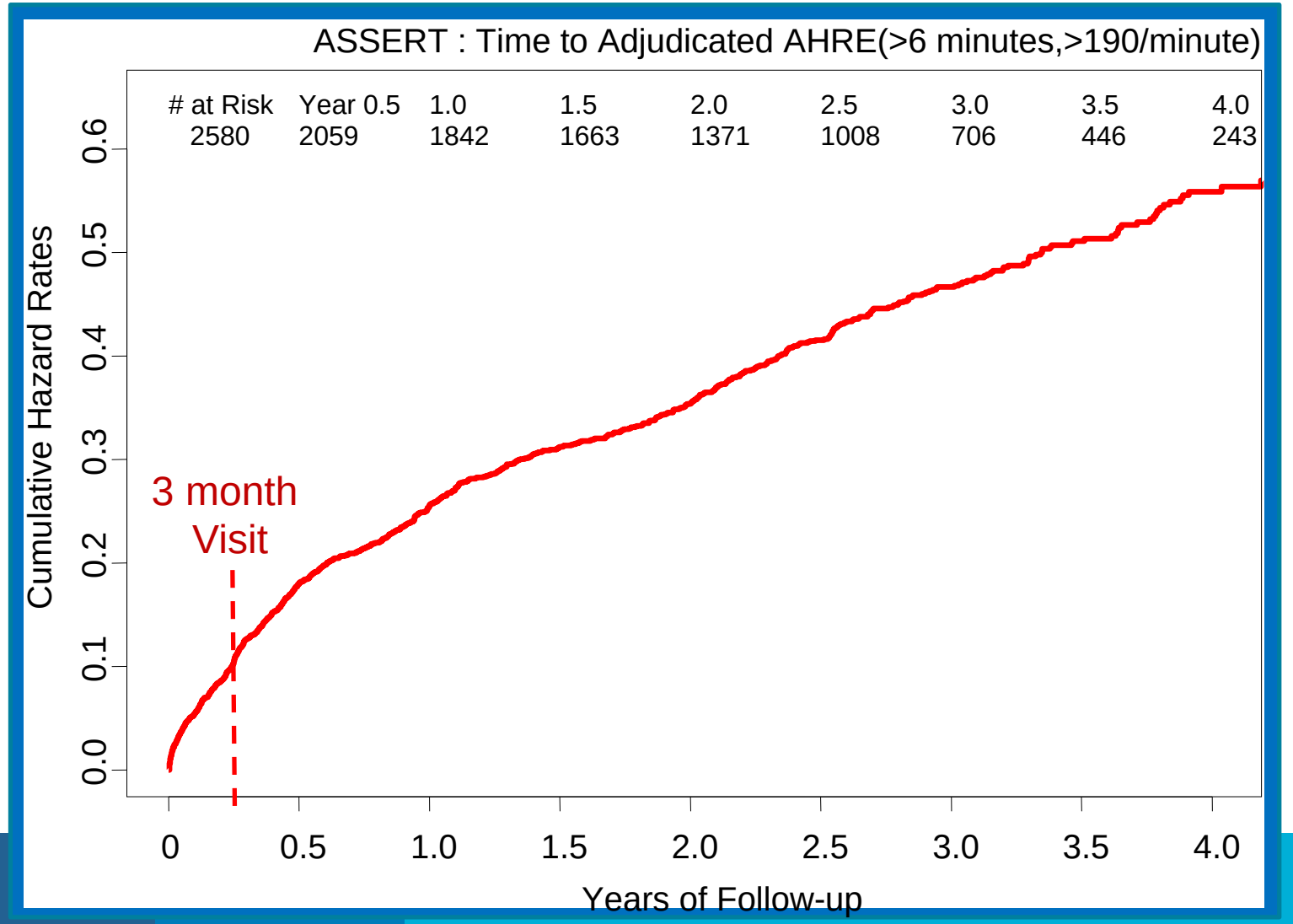
SCAF is a variant of clinical AF but differs in that SCAF:

- would not be detected by means other than an implanted device with <u>continuous (24/7) long-term recording</u>
- is often asymptomatic; episodes short in duration (minutes to hours)

ASSERT, NEJM 2012

Atrial Tachyarrhythmia > 6 min, >190 bpm

SCAF is VERY Common in the Pacemaker/ICD Populations



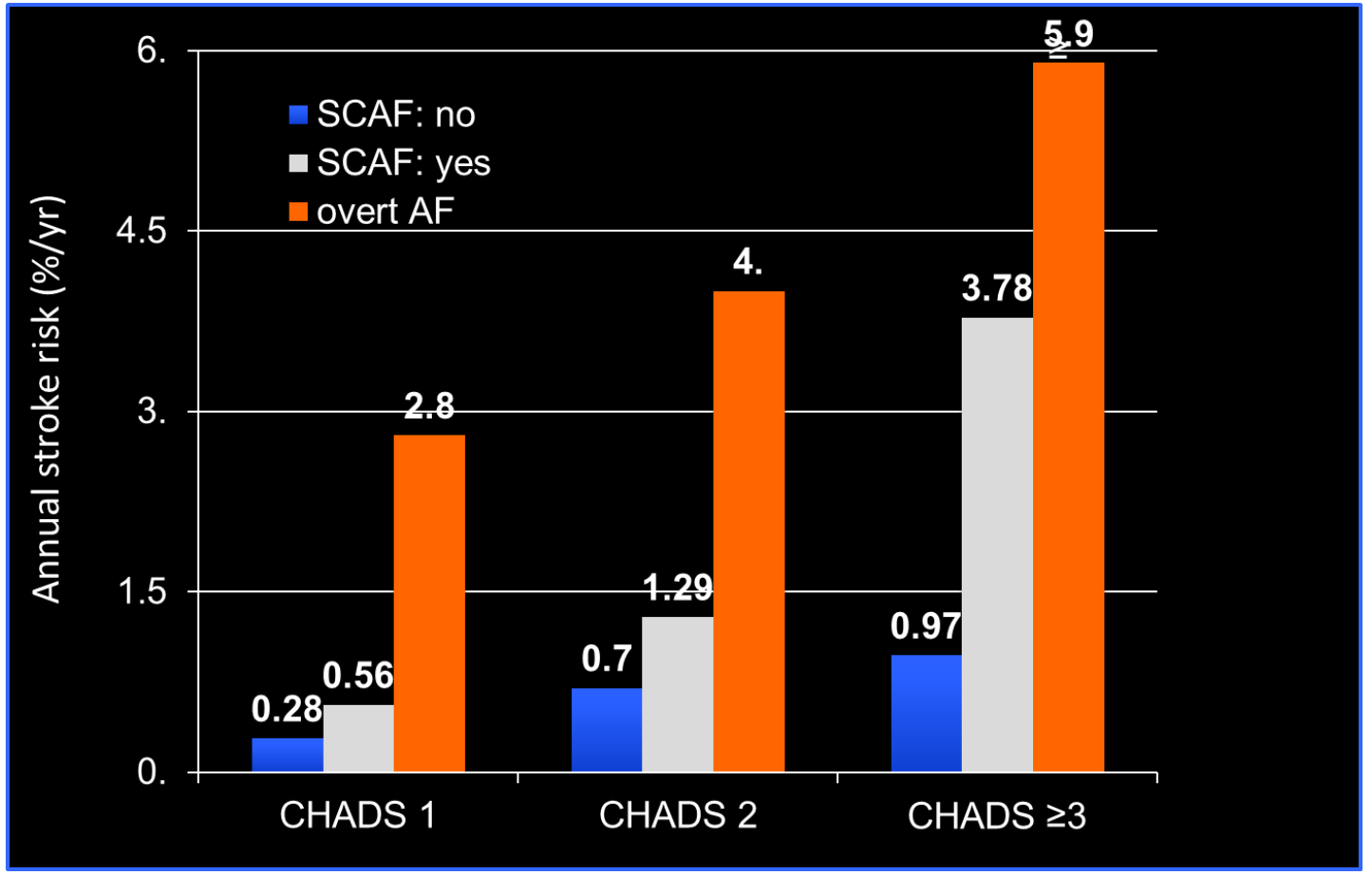
ASSERT: Clinical Outcomes

Both absolute and relative risks of stroke with SCAF are lower than with clinical AF

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial 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	2.49	1.28 – 4.85	0.007
Vascular Death	153	2.62	19	2.92	1.11	0.69 – 1.79	0.67
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.25	0.85 – 1.84	0.27
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.56	3.78 – 8.17	<0.001

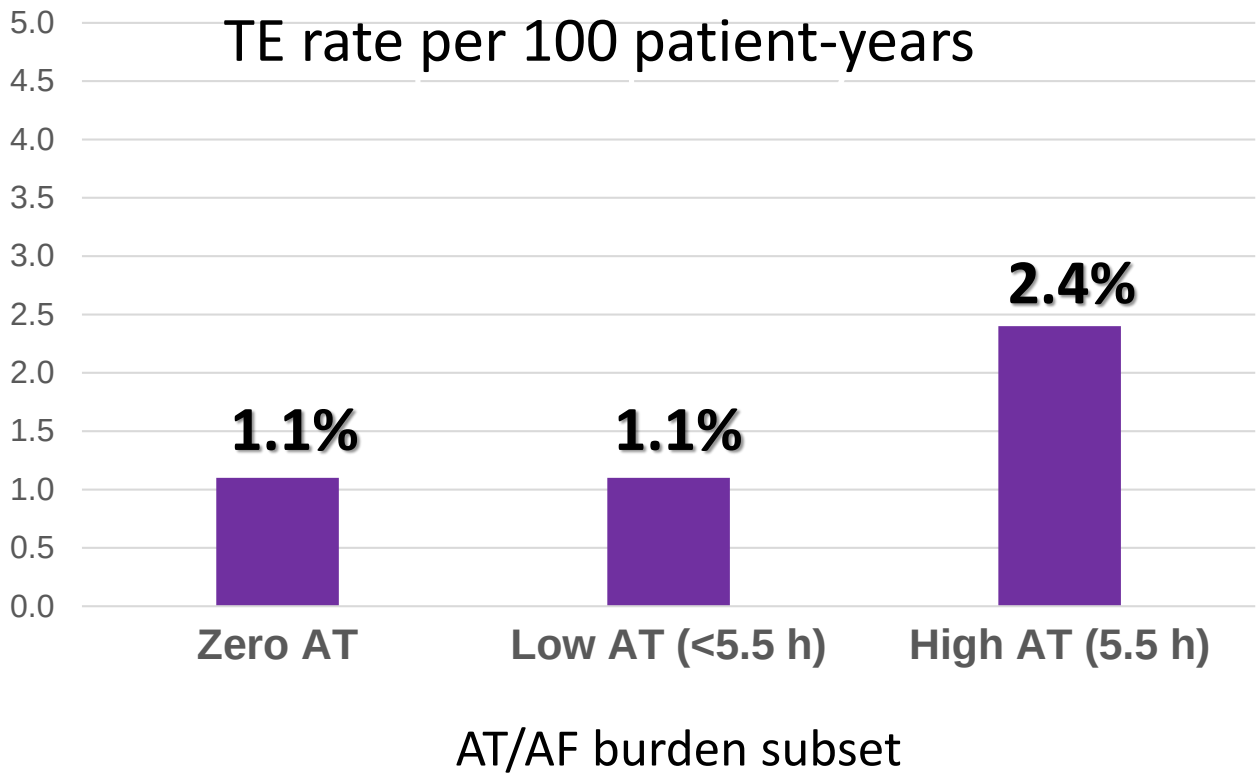
Healey JS, NEJM 2012

Stroke Risk for SCAF is Lower than AF



Healey JS et al. N Engl J Med. 2012;366:120
Gage BF et al. JAMA. 2001;285:2864.

TRENDS: SCAF burden and stroke?

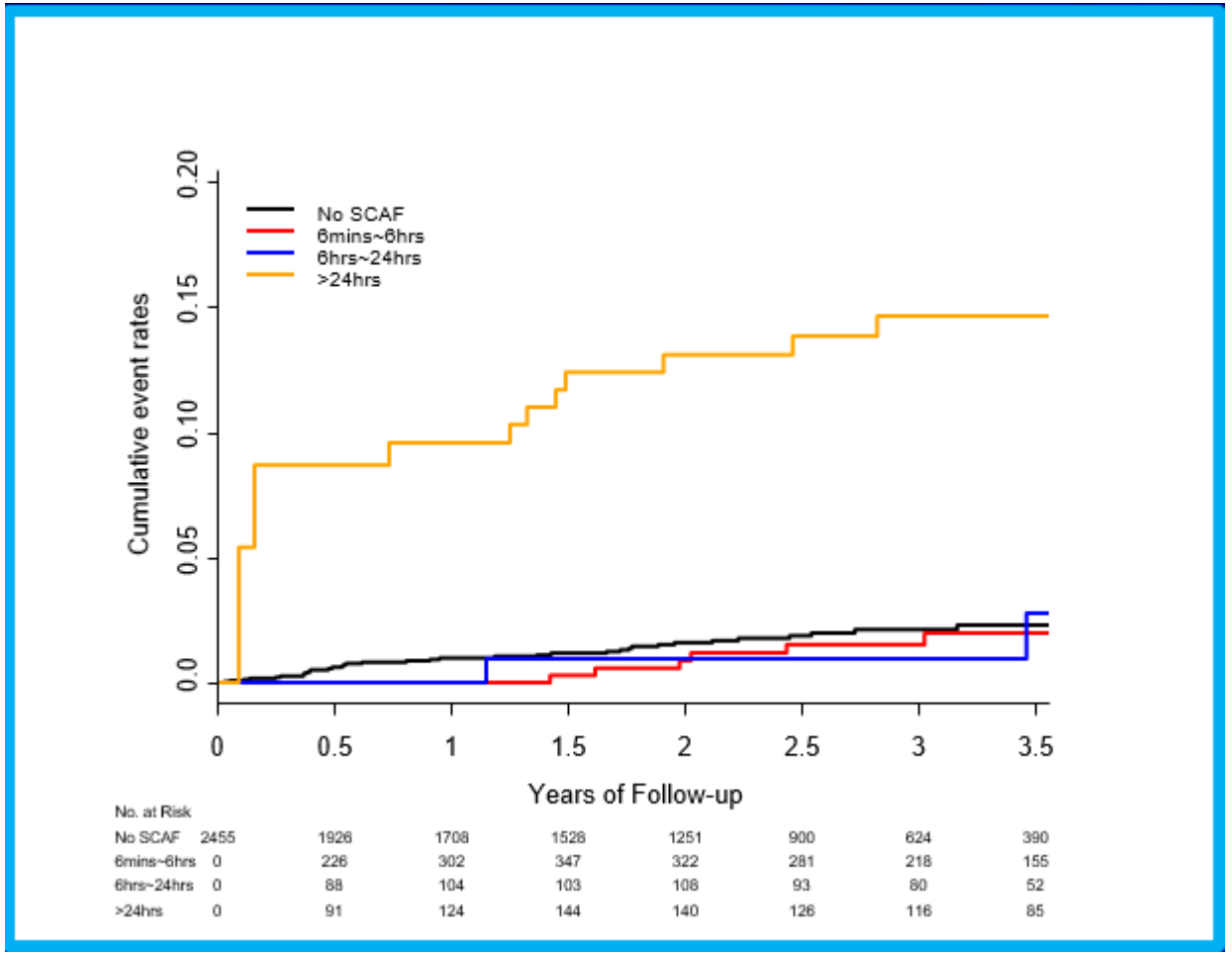


AT/AF burden	HR for TE high vs zero burden
Low <5.5 h	0.98 [0.34, 2.82]
High ≥5.5 h	2.20 [0.96, 5.05]

Glötzer TV et al. Circulation Arrhyth Electrophys 2009;2:474–80.

Risk of Stroke/SE According to Duration of SCAF

Stroke risk in ASSERT is seen mostly for patients with SCAF lasting >24 hours. In them, the risk is approx. 5% per year – similar to clinical AF.



ASSERT; van Gelder IC, Eur Heart J 2017

Meta Analysis of SCAF Duration and Stroke Risk

Unclear, and low risk of stroke for SCAF of short and medium duration

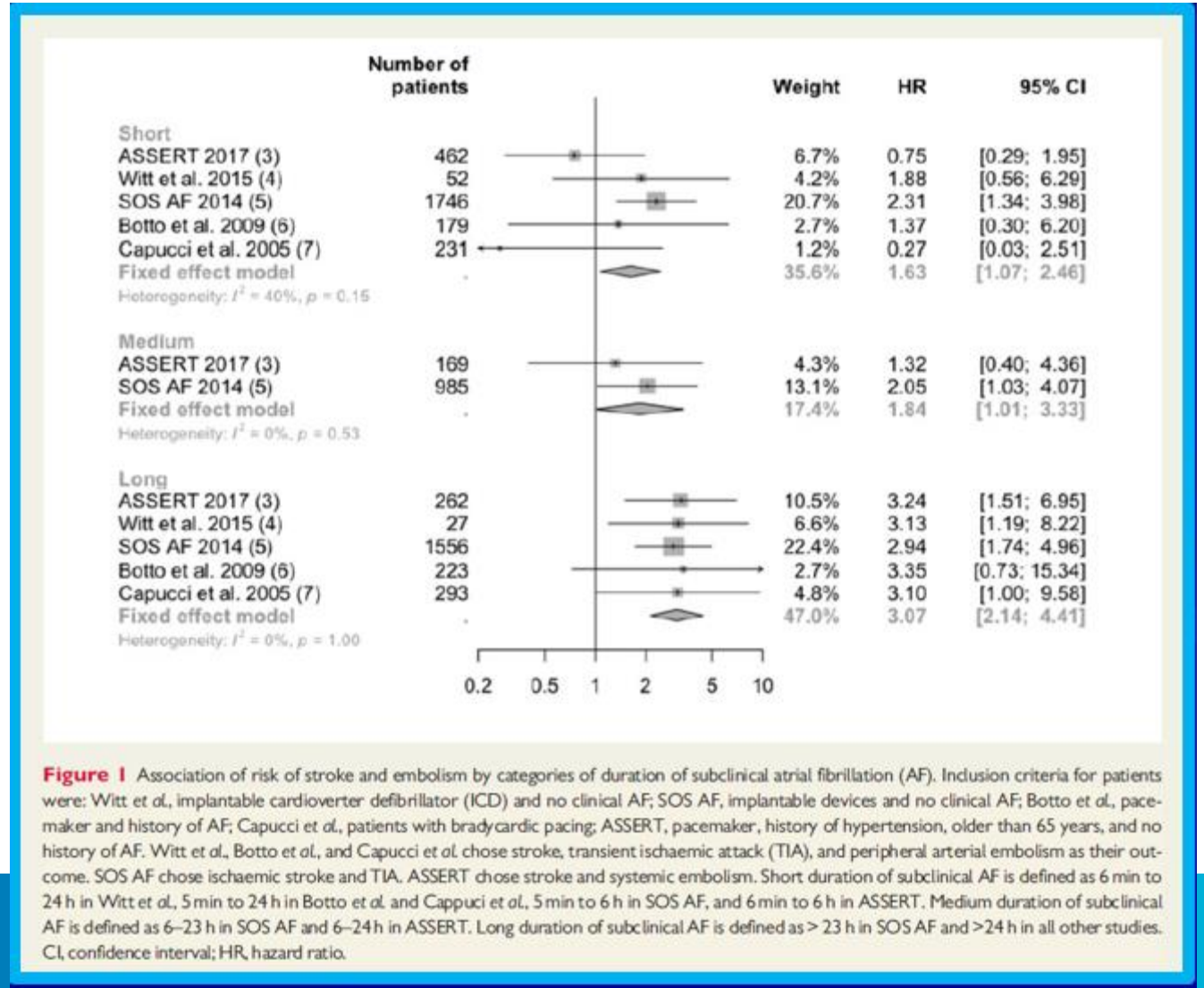


Figure 1 Association of risk of stroke and embolism by categories of duration of subclinical atrial fibrillation (AF). Inclusion criteria for patients were: Witt *et al.*, implantable cardioverter defibrillator (ICD) and no clinical AF; SOS AF, implantable devices and no clinical AF; Botto *et al.*, pacemaker and history of AF; Capucci *et al.*, patients with bradycardic pacing; ASSERT, pacemaker, history of hypertension, older than 65 years, and no history of AF. Witt *et al.*, Botto *et al.*, and Capucci *et al.* chose stroke, transient ischaemic attack (TIA), and peripheral arterial embolism as their outcome. SOS AF chose ischaemic stroke and TIA. ASSERT chose stroke and systemic embolism. Short duration of subclinical AF is defined as 6 min to 24 h in Witt *et al.*, 5 min to 24 h in Botto *et al.* and Cappuci *et al.*, 5 min to 6 h in SOS AF, and 6 min to 6 h in ASSERT. Medium duration of subclinical AF is defined as 6–23 h in SOS AF and 6–24 h in ASSERT. Long duration of subclinical AF is defined as > 23 h in SOS AF and >24 h in all other studies. CI, confidence interval; HR, hazard ratio.

Rahimi Eur Heart J 2017

Only longer-lasting, higher-burden sub-clinical AF appears to increase stroke risk

Age and Major Bleeding Risk: AVERROES

	Age < 75 years	Age ≥ 75 years
ASA	0.7%/year	2.2%/year
Apixaban	0.8%/year	2.6%/year

KH, Ng Age and Aging, 2016

SCAF and Stroke: The Decision to Treat

- **Must weigh risks and benefits of NOAC therapy**
  - Absolute stroke risk is lower than with AF
  - Risk of bleeding is higher in elderly patients

- **Must assume that the Relative Risk Reduction for NOAC therapy is the same as for AF**
  - This may or may not be true
  - Not all strokes in AF or SCAF are preventable with OAC

SCAF, Stroke Sub-type and Severity in ASSERT

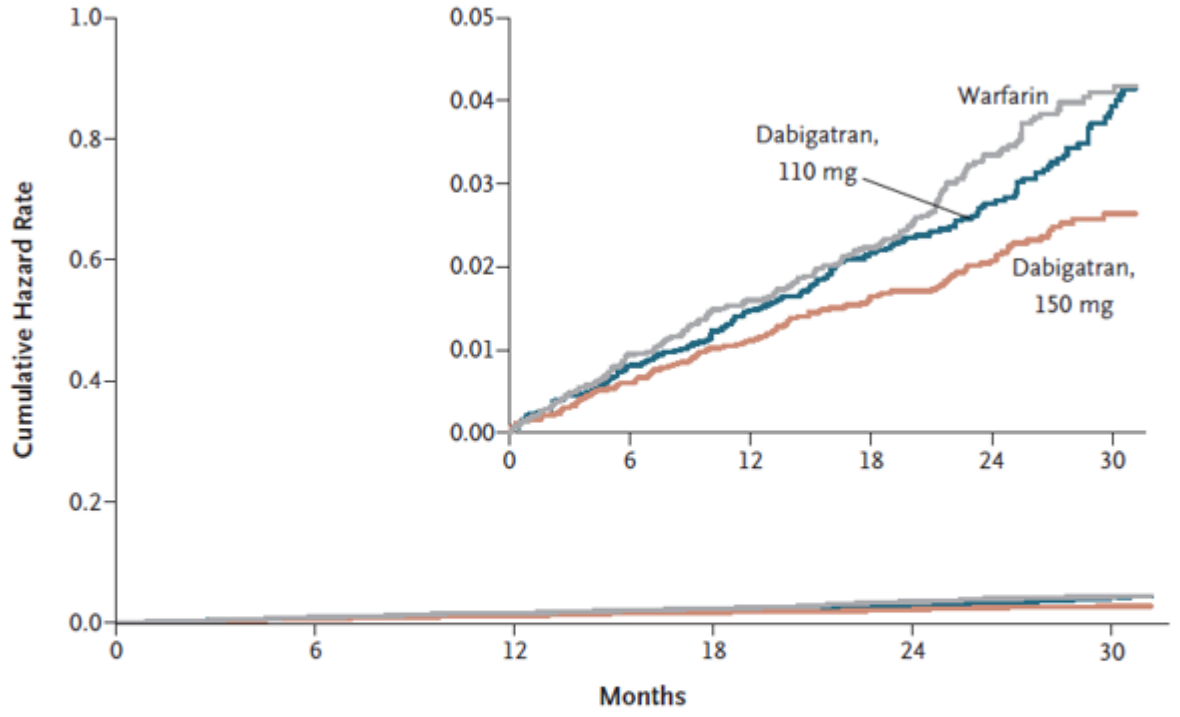
Patients with SCAF have stroke from a variety of mechanisms – many of which are not embolic

	NO AHRE (N=25)	AHRE (N=19)	P Value
Stroke Subtype			
Cardio-embolic, n(%)	2 (8.0)	5 (26.3)	0.210
Large artery disease, n(%)	0 (0.0)	1 (5.3)	0.432
Lacuna, n(%)	7 (28.0)	5 (26.3)	0.901
Uncertain, n(%)	16 (64.0)	8 (42.1)	0.149
Localization			
Cortical, n(%)	9 (36.0)	10 (52.6)	0.270
Subcortical, n(%)	12 (48.0)	7 (36.8)	0.459
Uncertain, n(%)	4 (16.0)	2 (10.5)	0.684
7-Day RANKIN score, mean±SD	3.2 ± 1.8	3.4 ± 1.9	0.642
30-Day RANKIN score, mean±SD	2.5 ± 1.9	2.9 ± 1.7	0.518

K Perera AHJ, 2018

Stroke in Anticoagulated Patients

Even with anticoagulation patients with AF still have stroke (1% per year on Dabi 150 BID)

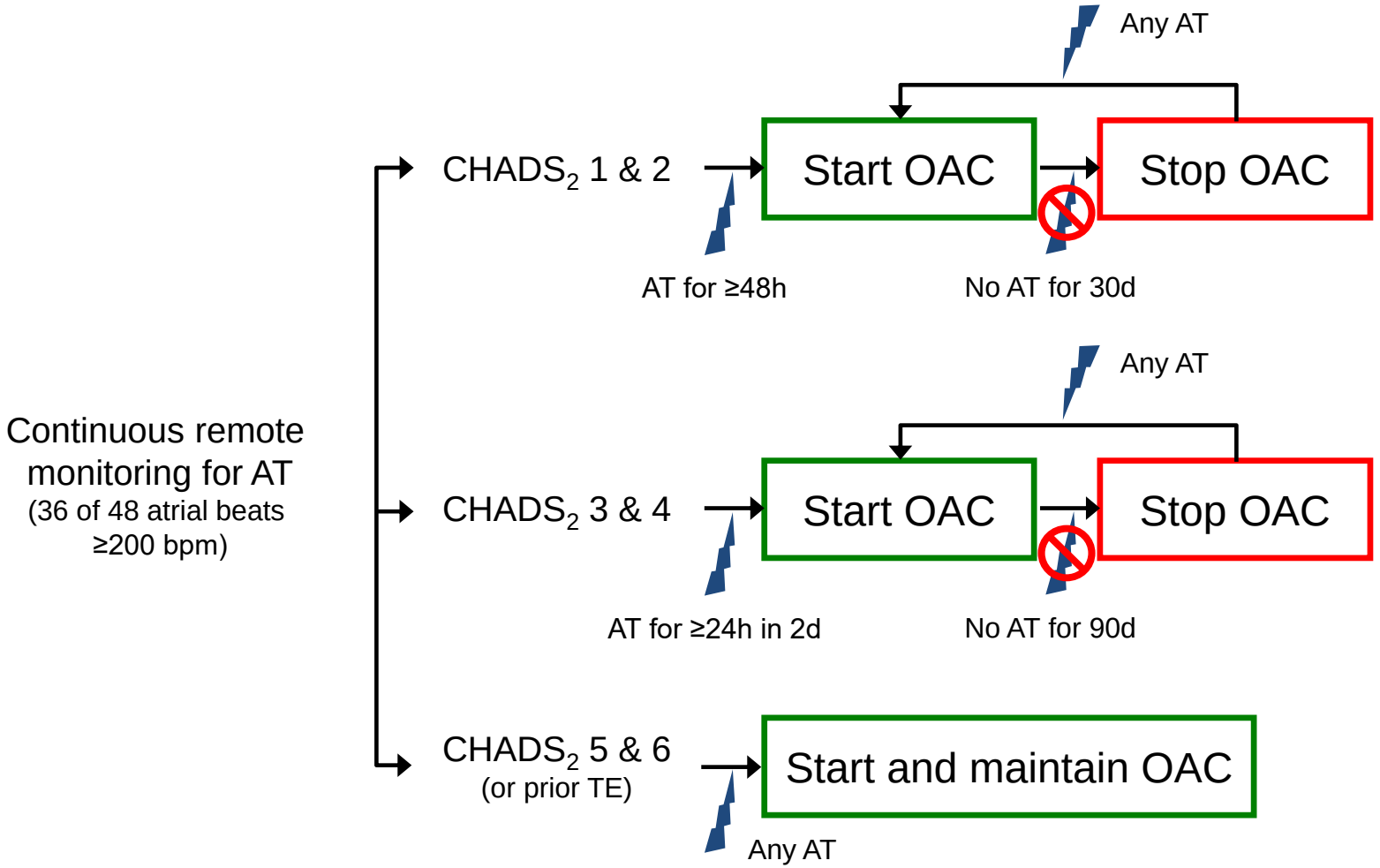


No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

RELY, Connolly SJ, NEJM 2009

IMPACT Study: Anticoagulation Protocol Intervention Group



IMPACT: Clinical Outcomes

No Observed Benefit!

	Control Group N = 1,361		Intervention Group N = 1,357		Hazard Ratio	*p*
	N	rate	N	rate		
Primary endpoint	61	2.3	63	2.4	1.06	0.732
Mortality	140	5.1	147	5.4	1.07	0.662
Thromboembolism	37	1.4	32	1.2	0.88	0.586
Ischemic stroke	28	1.0	22	0.8	0.79	0.417
Systemic embolism	2		0		-	0.969
TIA	8		10		1.27	0.619
Hemorrhagic stroke	3	0.1	3	0.1	1.03	0.973
Other major bleed	32	1.2	43	1.6	1.39	0.145

Rates are expressed as the number of events per 100 patient-years.

Study Design

ARTESiA Study Design

Patients with:
- **SCAF 6 min to 24 hrs**
- **Risk factors for stroke (age ≥ 75, previous stroke/ TIA/ SE or multiple risk factors)**
- **No clinical AF/not on OAC, no contraindication**

CONSENT and RANDOMIZE

4000 patients from ~250 hospitals in Canada, USA and Europe

Double-blind, double-dummy design

Apixaban Arm:
5mg or 2.5mg bid

(+ placebo aspirin)

Aspirin Arm:
81 mg OD

(+ placebo apixaban)

Follow-up Visits: 1 month and every 6 months
1° Efficacy Outcomes – Stroke (including TIA with imaging), SE
1° Efficacy Outcomes – Major Bleed

Rationale and the design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. Lopes et al. AHJ, Vol. 189, p. 137-145

Study Population: Inclusion Criteria

- Permanent pacemaker or defibrillator (with or without resynchronization) or insertable cardiac monitor capable of detecting SCAF.
- At least 1 episode of device-detected atrial high rate ≥ 6 min but < 24 hrs in duration, with average 175 bpm
  - SCAF can be at any time prior to enrolment
  - No distinction made between Atrial Fibrillation & Atrial Flutter
- Age ≥ 55 years

Study Population: Inclusion Criteria

- Risk Factors for Stroke (ANY of the following):
  - Previous stroke, TIA or SE
  - Age ≥ 75 years
  - 65-74 years with at least **2** other **risk factors**
  - 55-64 years with at least **3** other **risk factors**

Other risk factors:

-Hypertension -Female

-Heart failure -Vascular disease (i.e. CAD, PAD or Aortic Plaque)

-Diabetes

Guidance for Stroke Risk Factors:

Stroke or TIA	Any clinical history of stroke (signs or symptoms ≥ 24 hours) or TIA (signs or symptoms < 24 hours) OR CT or MRI evidence of prior silent infarction (with or without symptoms)
Systemic Arterial Embolism	Any clinical history of systemic arterial embolism
Hypertension	Any history of hypertension requiring antihypertensive treatment OR two blood pressure readings > 140/90 (either value) on separate days taken after 5 minutes rest and which would, in the opinion of the treating physician, require treatment with antihypertensive therapy
Heart Failure	Clinical heart failure diagnosed at any time OR a left ventricular ejection fraction <50%
Diabetes	Known history of diabetes OR currently taking insulin or any oral diabetic medication OR HbA1c > 8% OR fasting blood sugar > 14 mmol/L
Vascular disease	Evidence of atherosclerosis on coronary angiogram, nuclear testing or stress testing; or evidence of aortic or peripheral arterial disease using ultrasound, CT or MRI imaging. Vascular disease need only be present, not necessarily flow-limiting or symptomatic.

Study Population: Exclusion Criteria

- Clinical atrial fibrillation documented by surface ECG (12 lead ECG, Telemetry, Holter)
- Mechanical valve prosthesis, recent (within past 6 months) DVT or PE or other condition requiring treatment with OAC
- Allergy to aspirin or apixaban
- Severe renal insufficiency (serum creatinine > 2.5 mg/dL [221 µmol/L] or a calculated creatinine clearance < 25 ml/min)
- Serious bleeding in the last 6 months or at high risk of bleeding
  (this includes, but is not limited to: prior intracranial hemorrhage, active peptic ulcer disease, clinically significant thrombocytopenia or anemia, recent stroke within past 10 days, documented hemorrhagic tendencies or blood dyscrasias)
- Moderate to severe hepatic impairment
- Ongoing need for combination therapy with aspirin and clopidogrel (or other combination of two platelet inhibitors)

Study Population: Exclusion Criteria (2)

- Meets criteria for requiring lower dose of apixaban AND also has ongoing need for strong inhibitors of both CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, ritonavir or clarithromycin)
- Ongoing need for strong dual inducers of both CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)
- Received an investigational drug in the past 30 days
- Participants considered by the investigator to be unsuitable for the study (e.g. non-compliant with treatment or follow-up or with life expectancy < 2 years due to concomitant disease.
- Women who are pregnant, breast-feeding or of child-bearing potential without an acceptable form of contraception in place

Primary Outcomes (centrally adjudicated)

Primary Efficacy:

Stroke (including TIA with DWI)

(rapid onset of neuro symptoms with no other readily identifiable cause, confirmation of diagnosis e.g., specialist consult or imaging)

Systemic Arterial Embolism

(clinical signs and symptoms plus at least one objective measure)

Primary Safety:

ISTH Major Bleeding

(fatal, symptomatic in critical area or organ, Hg drop ≥ 2 g/dL or transfusion ≥ 2 units blood)

Secondary and Other Outcomes

Secondary Outcomes:

- Ischemic Stroke
- Myocardial Infarction
- Vascular death
- Total death (vascular and non-vascular)
- Composite of stroke, MI, SE and total Death
- Composite of stroke, MI, SE, total death and major bleeding

Other Study Outcomes: (common in this population)

- Clinical AF
- Hospitalization for Heart Failure
- Cardioversion or ablation for AF