Treatment of Sub-Clinical Atrial Fibrillation

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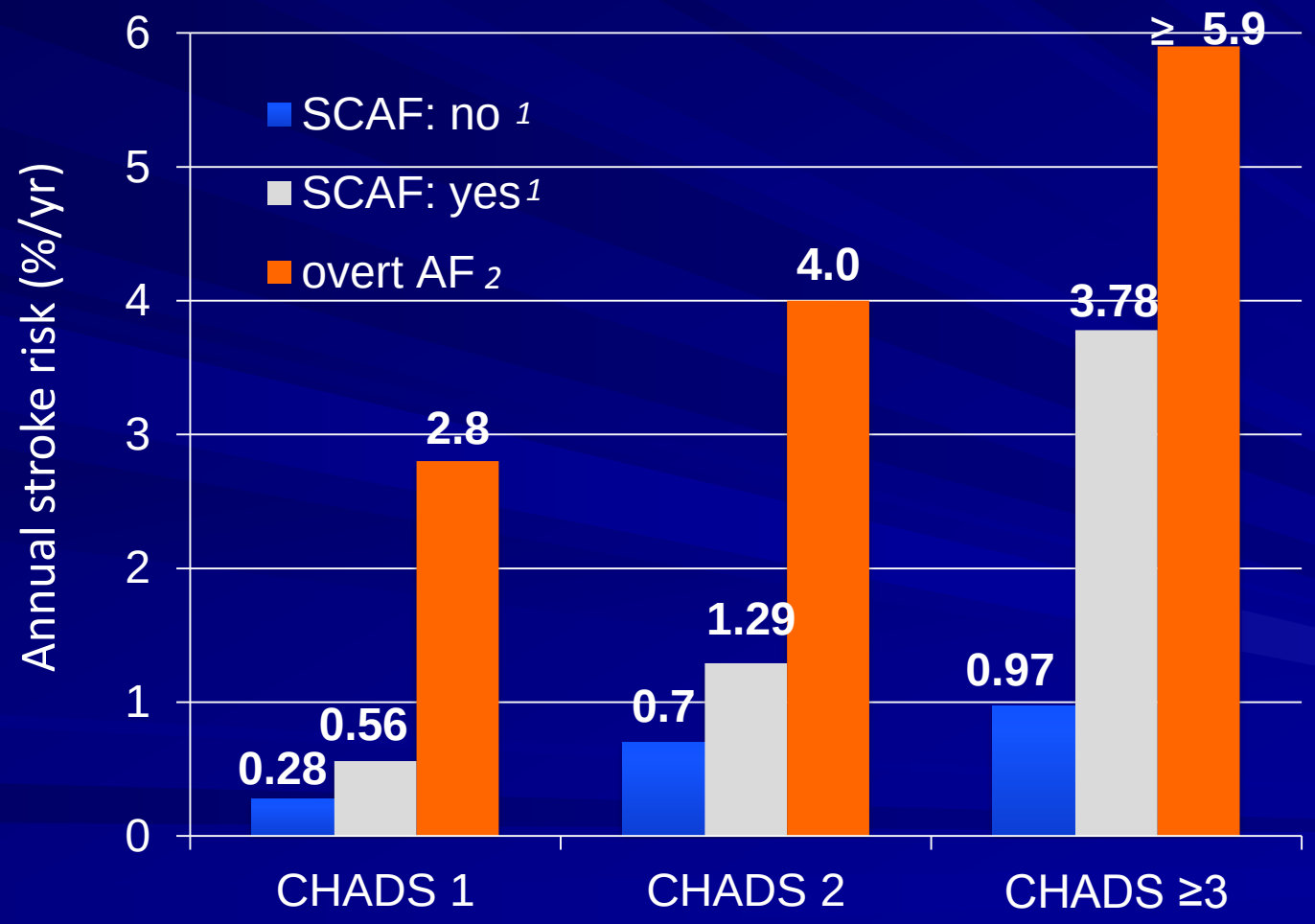
ASSERT: Clinical Outcomes

Healey JS, NEJM 2012

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

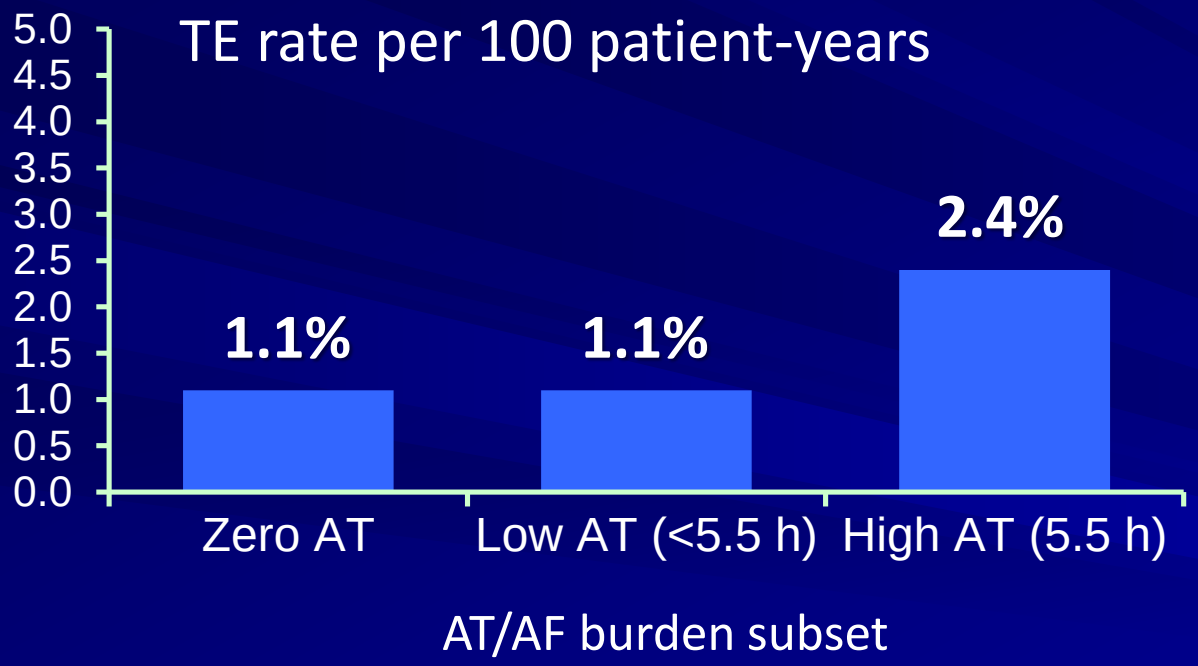
Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N=2319		Present N= 261				
	events	%/year	events	%/ year	RR	95% CI	p
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.49	1.28 – 4.85	0.007
Vascular Death	153	2.62	19	2.92	1.11	0.69 – 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

Stroke Risk for SCAF is Lower than AF



[1]Healey JS et al. N Engl J Med. 2012;366:120–9
[2]Gage BF et al. JAMA. 2001;285:2864–70

TRENDS: SCAF burden and stroke?

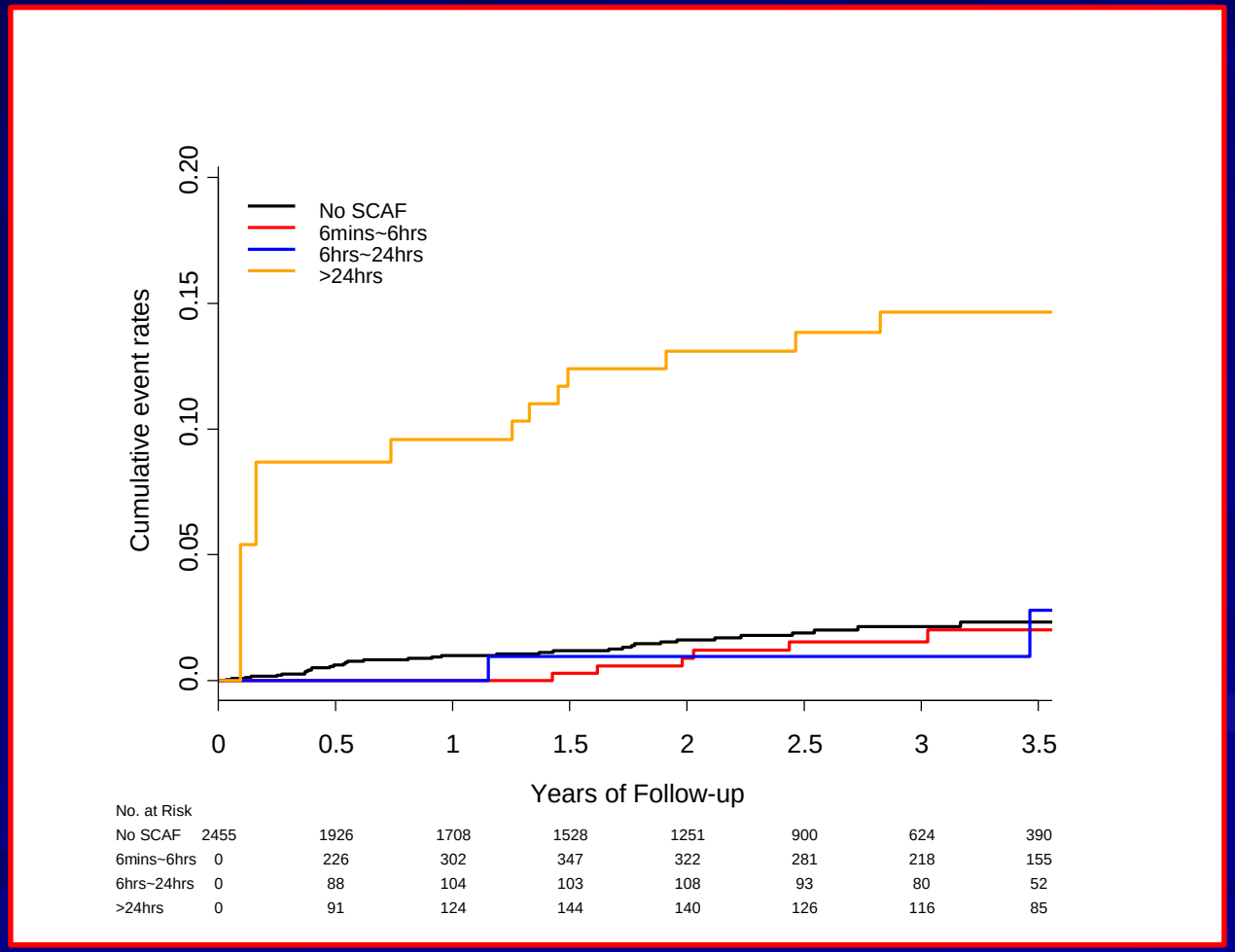


AT/AF burden	**HR** for TE high vs zero burden
Low <5.5 h	**0.98** [0.34, 2.82]
High ≥5.5 h	**2.20** [0.96, 5.05]

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



No. at Risk								
No SCAF	2455	1926	1708	1528	1251	900	624	390
6mins~6hrs	0	226	302	347	322	281	218	155
6hrs~24hrs	0	88	104	103	108	93	80	52
>24hrs	0	91	124	144	140	126	116	85

ASSERT; van Gelder IC, Eur Heart J 2017

Meta-Analysis of SCAF Duration and Stroke Risk: Rahimi Eur Heart J 2017

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

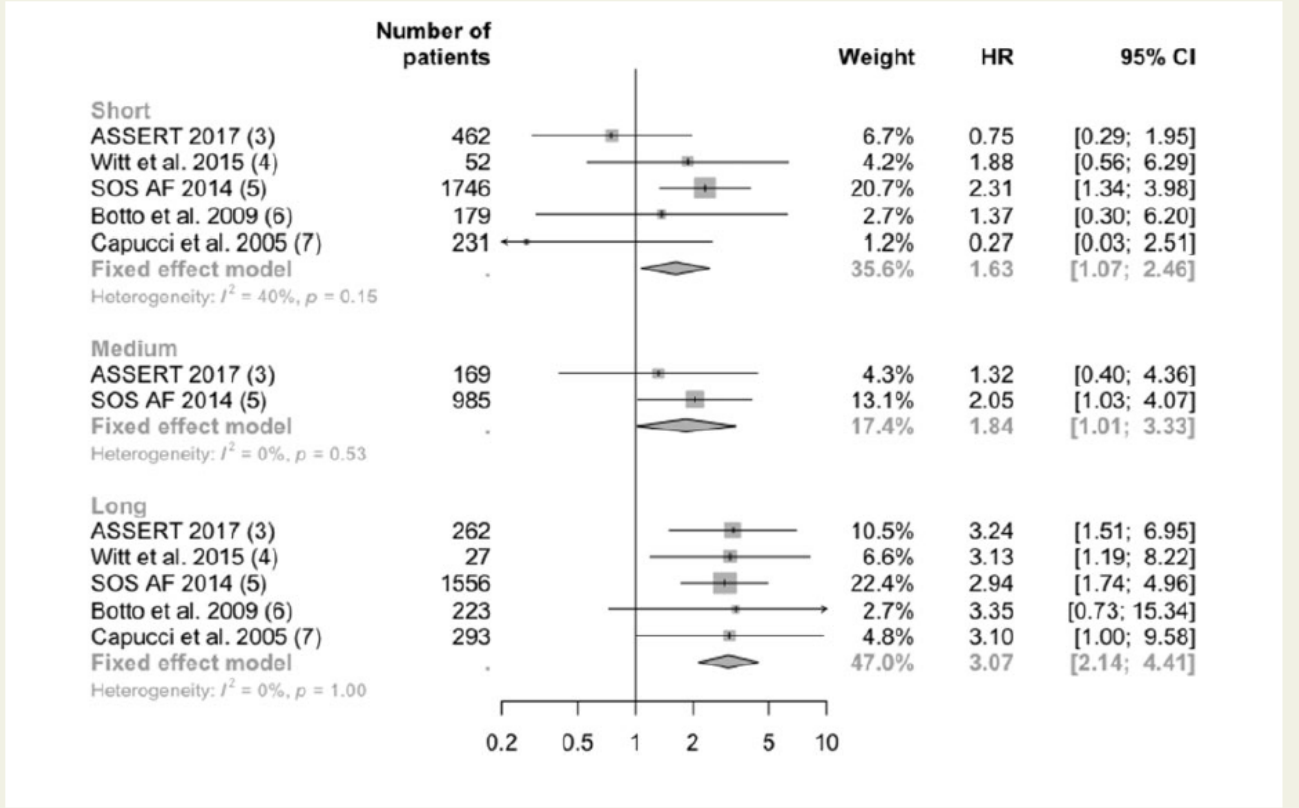


Figure 1 Association of risk of stroke and embolism by categories of duration of subclinical atrial fibrillation (AF). Inclusion criteria for patients were: Witt *et al.*, implantable cardioverter defibrillator (ICD) and no clinical AF; SOS AF, implantable devices and no clinical AF; Botto *et al.*, 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.

Age and Major Bleeding Risk: AVERROES

KH Ng; Age and Aging 2016

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

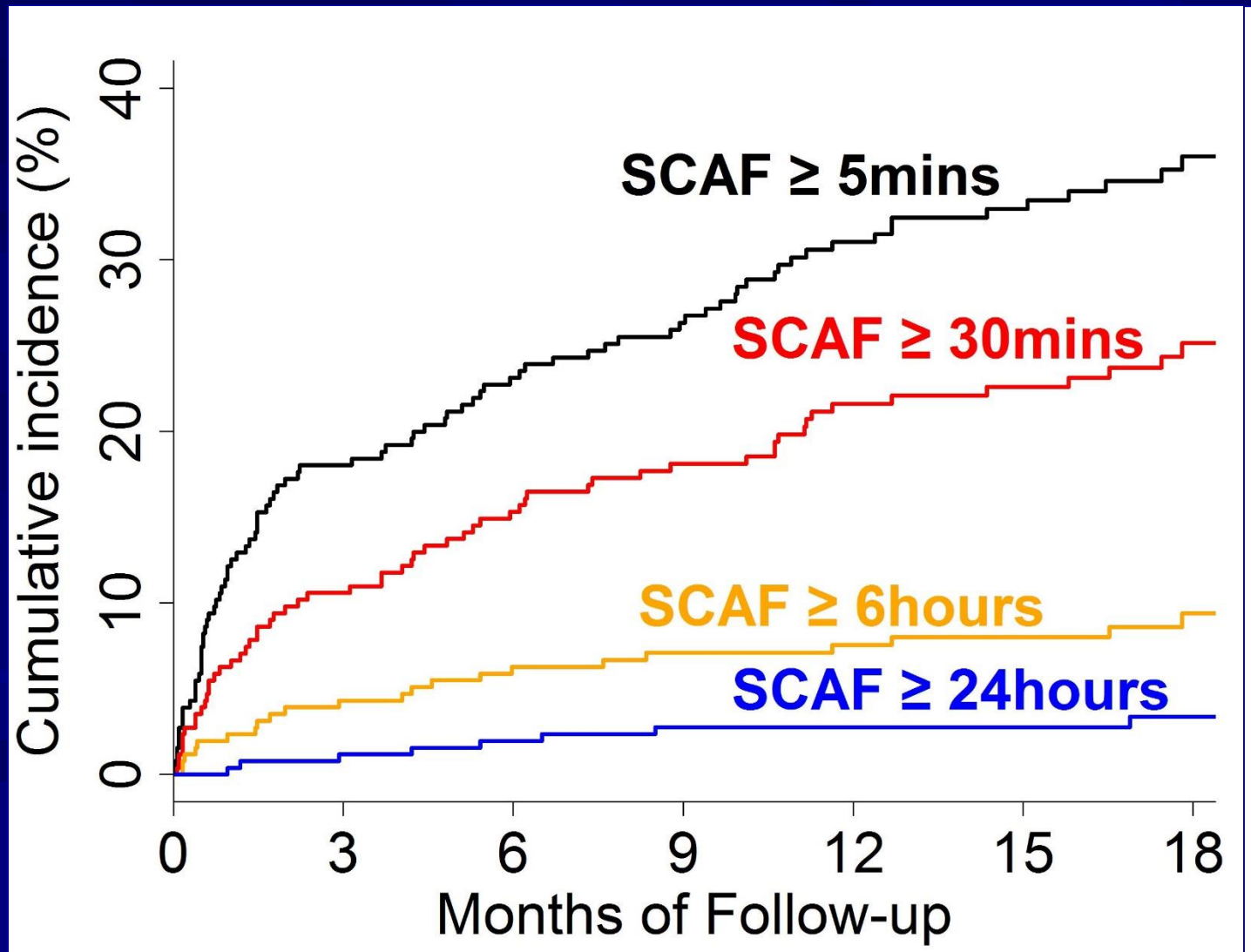
AF Screening with Continuous Monitoring

Study	Size	Device	Inclusion	Rate of AF Detection
ASSERT-II	250	SJM Confirm	Age>65, AND CHADS-VASc≥2, or OSA, or BMI> 30; AND LA> 58mL, or NT-ProBNP > 290 pg/mL	≥ 5 min 34.4% at one year
GRAF	200	MDT REVEAL-XT	Age ≥ 18 CHADS-VASc≥4	Pending
REVEAL-AF	450	MDT REVEAL-XT	Age ≥ 18 CHADS≥3, or CKD/COPD/OSA/CAD	29.3% at 18 months
PREDATE-AF	245	REVEAL-LINQ	Age>18, AND CHADS-VASc≥2	≥ 6 min 22.4% at 451 days
DANISH LOOP	6000	REVEAL-LINQ (1500)	Age > 70 One of HTN, DM, HF or stroke	Pending

Patient Characteristics (N=256)

Age, mean±SD	73.85±6.24
Female, n(%)	88 (34.4)
Caucasian, n(%)	246 (96.1)
History of Hypertension, n(%)	188 (73.4)
Heart failure, n(%)	22 (8.6)
Diabetes, n(%)	64 (25.0)
Prior stroke, TIA or SE, n(%)	123 (48.0)
Sleep Apnea, n(%)	29 (11.3)
BMI	28.69±4.64
Valvular Heart Disease, n(%)	37 (14.5)
CHA_2DS_2-VASc, mean±SD	4.14±1.36
LA diameter (cm), mean±SD	4.74±0.79
LA volume (ml), mean±SD	76.53±20.61

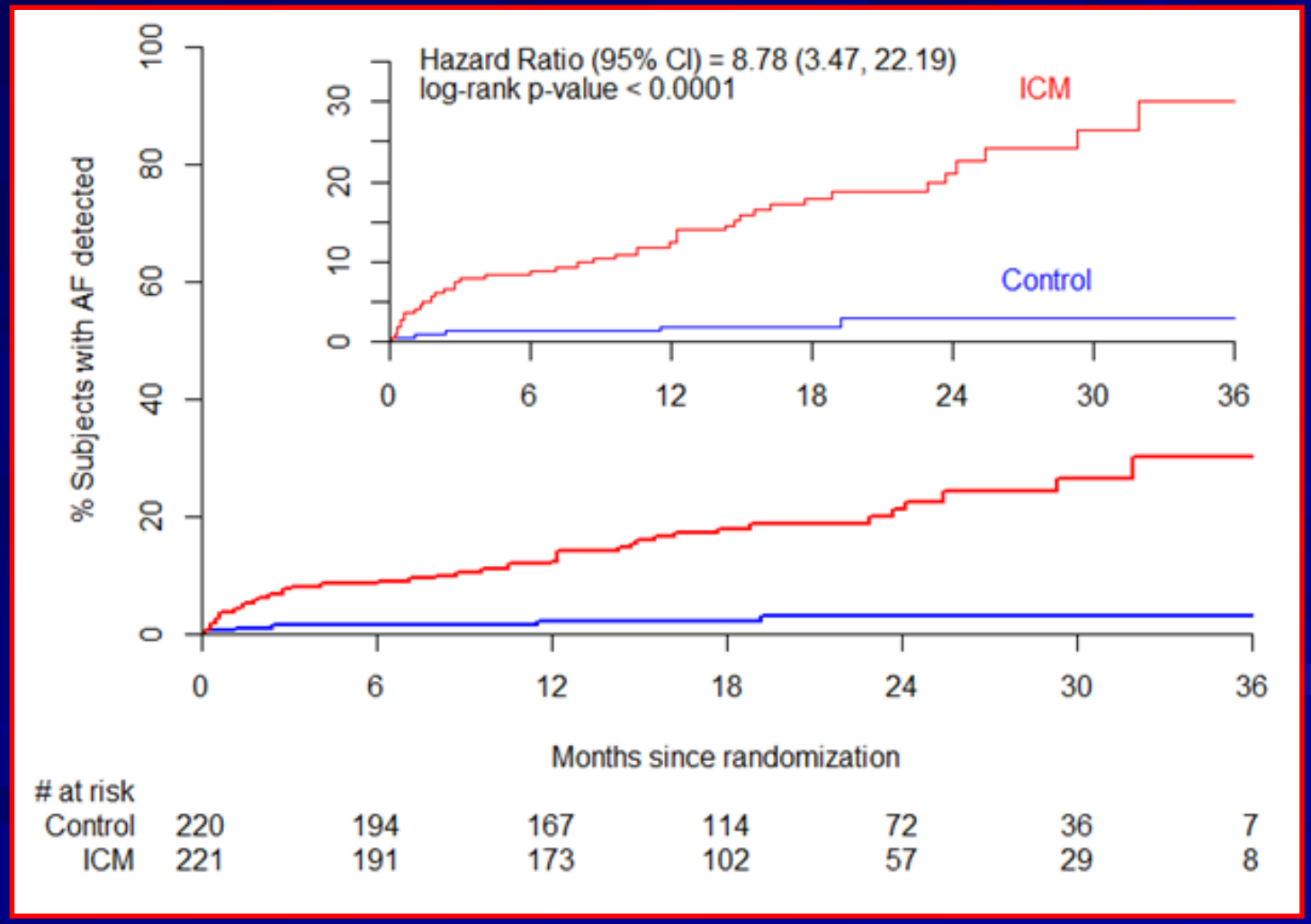
Incidence of SCAF



Rate per year (95% CI)
34.4% (27.7% – 42.3%)
21.8% (16.7% – 27.8%)
7.1% (4.5% – 10.6%)
2.7% (1.2% – 5.0%)

CRYPTOGENIC STROKE: CRYSTAL-AF Trial: AF

R. Bernstein NEJM 2014



Rate of detection in ICM arm was 30.0% vs 3.0% in control arm

7000 patients at 460 sites in 31 countries; 450 primary events; expected event rate 3.8%/yr

NAVIGATE-ESUS Trial Design

Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

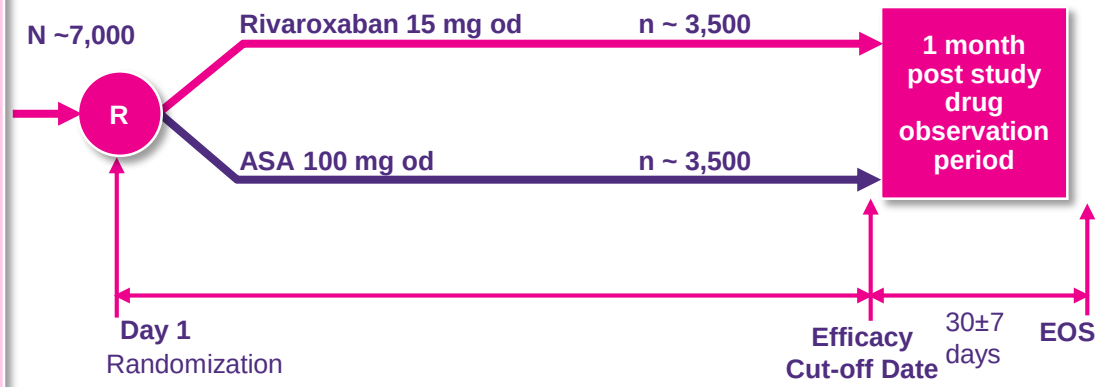
Patients with recent ischemic stroke and

1. visualized by brain CT or MRI that is not lacunar (subcortical infarct ≤1.5 cm)
2. absence of cervical carotid atherosclerotic artery stenosis > 50% or occlusion
3. no atrial fibrillation after ≥ 24 hours cardiac rhythm monitoring
4. no intra-cardiac thrombus on transthoracic echocardiography
5. no other specific etiology for cause of stroke (eg, arteritis, dissection, migraine/ vasospasm, drug abuse)

Age ≥ 50 years

~460 sites in 31 countries

Target RRR 30%; superiority w/ 90% power α=0.05
Enrollment ~24 months; minimum treatment ~6 months; study duration ~36 months
Estimated mean treatment duration 6 - 24 months;



Randomization 7 days to 6 month after acute ESUS

October 2017: Study stopped early for futility

- **Comparable efficacy between rivaroxaban and aspirin**
- **Increased bleeding in rivaroxaban arm (though overall rates were low)**

NAVIGATE ESUS

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.

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)**
  - **Age ≥ 65 with 2 additional CHADS-VASc factors or ≥ 55 with 3 additional 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

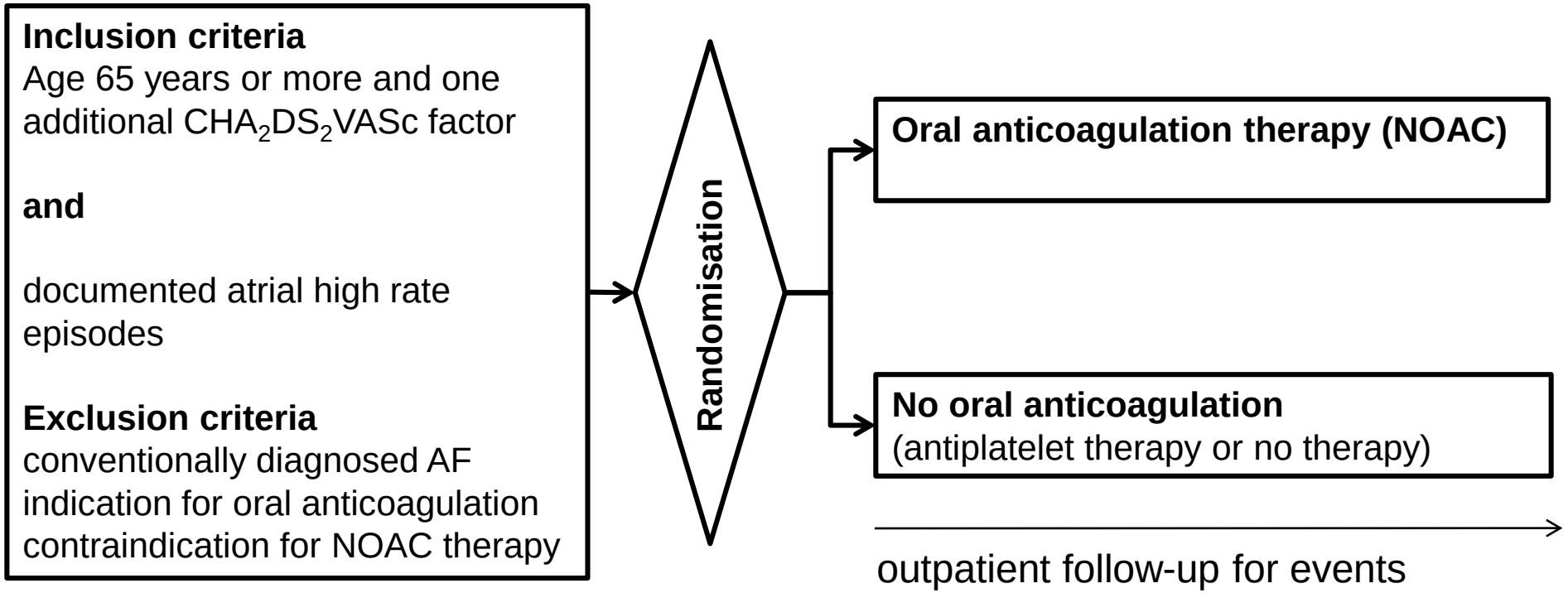
(+ placebo apixaban)

Follow-up Visits: 1 month and every 6 months (avg 3 yrs follow up)

1° Efficacy Outcomes:	1° Safety Outcome:
Stroke (including TIA with imaging), Systemic Embolism	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

Flow chart of NOAH – AFNET 6



NOAC non-vitamin K antagonist oral anticoagulant

In a double-blind design, we will determine established indications in the inclusion criteria for antiplatelet therapy, and provide blind aspirin or blind placebo for the patients not receiving anticoagulation. Patients randomized to NOAC will not receive aspirin in addition.
Minimal FU 9 months (all patients to be followed until end of trial)
NOAC: edoxaban 60 mg OD (reduced to 30 mg OD as per EU Label)

https://clinicaltrials.gov/ct2/show/NCT02618577?term=NOAH&rank=1, NCT02618577

Kirchhof P, et al Am Heart J. 2017;190:12-8.