New Guidelines for Stroke Prevention in AF:
The Canadian Guidelines

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McMaster University, Canada
Venice Arrhythmia Meeting
Saturday October 17, 2015

October 16 - 18
14th EDITION 2015

MY CONFLICTS OF INTEREST ARE

Research Grants and Speaking Fees:

Medtronic, St. Jude Medical, Boston Scientific; Bristol-Meyers-Squibb, Bayer, Boehringer-Ingelheim

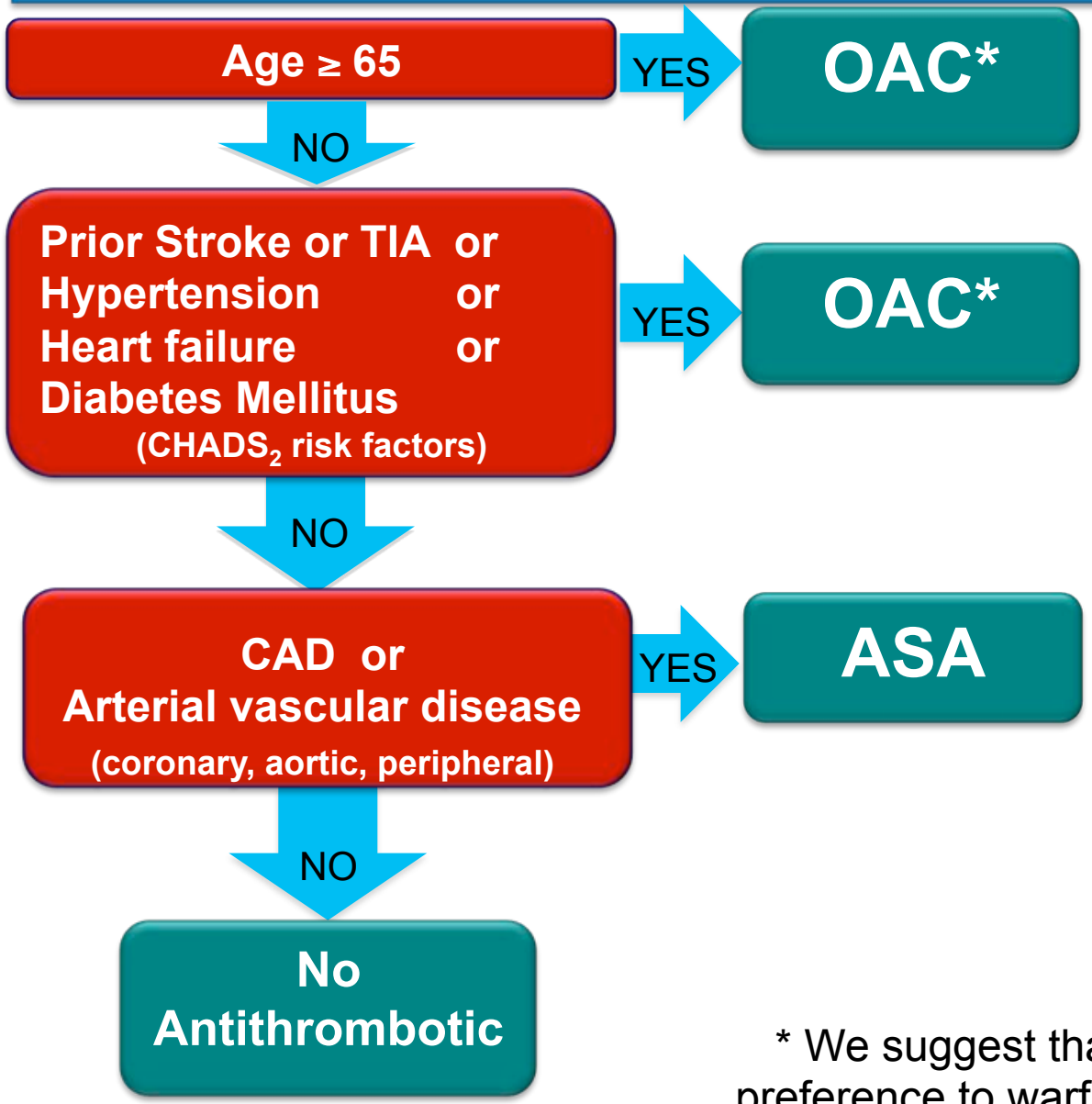
The Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines

- Evidence-based; expert panel
- Use "GRADE" format
- Include not only recommendations, but "practical tips" and "values and preferences"
- Disseminated via the web to physicians in Canada and abroad
- Highly cited and used

The CSS Guidelines – 2014 Update

- 1. Algorithm for OAC use in AF
- 2. Role of AF monitoring post-stroke
- 3. Sub-clinical AF
- 4. Role of LAA closure/removal

The "CCS Algorithm" for OAC Therapy in AF



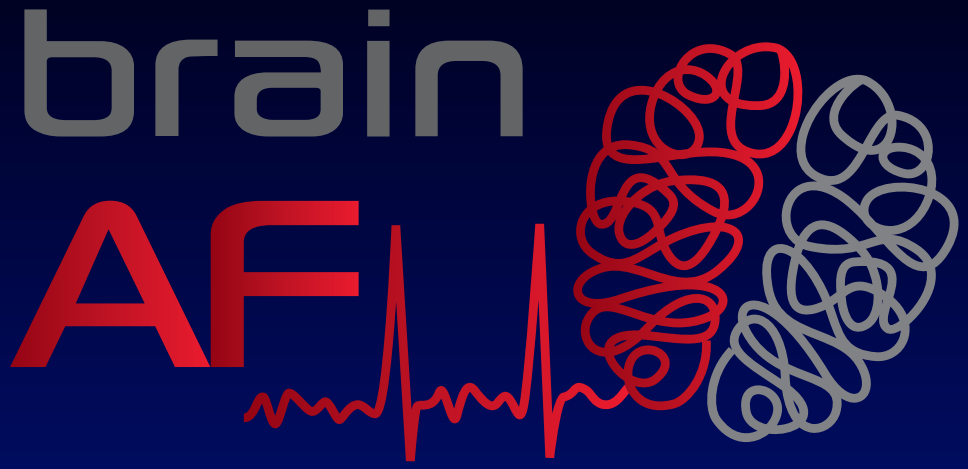
Consider and modify (if possible) all factors influencing risk of bleeding on OAC (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low eGFR, age ≥ 75, low body weight)**

****may require lower dosing**

* We suggest that a NOAC be used in preference to warfarin for non-valvular AF.

C-SPIN

Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute
MHICC



*B*linded *R*andomized trial of *A*nticoagulation to prevent *I*schemic stroke and *N*eurocognitive impairment in *A*trial *F*ibrillation:

Steering Committee:
Dr. L. Rivard, Dr. M. Talajic, Dr. P. Khairy, Dr. D. Johnson, Dr. S. Black, Dr. S. Nattel,
Dr. F. Massoud, Dr. M-C Guertin, Dr. S. Lanthier, Dr. J. Andrade, Dr. P. Dorian, Dr. J. Healey,
Dr. S. Kouz, Dr. I. Nault and Dr. D. Roy

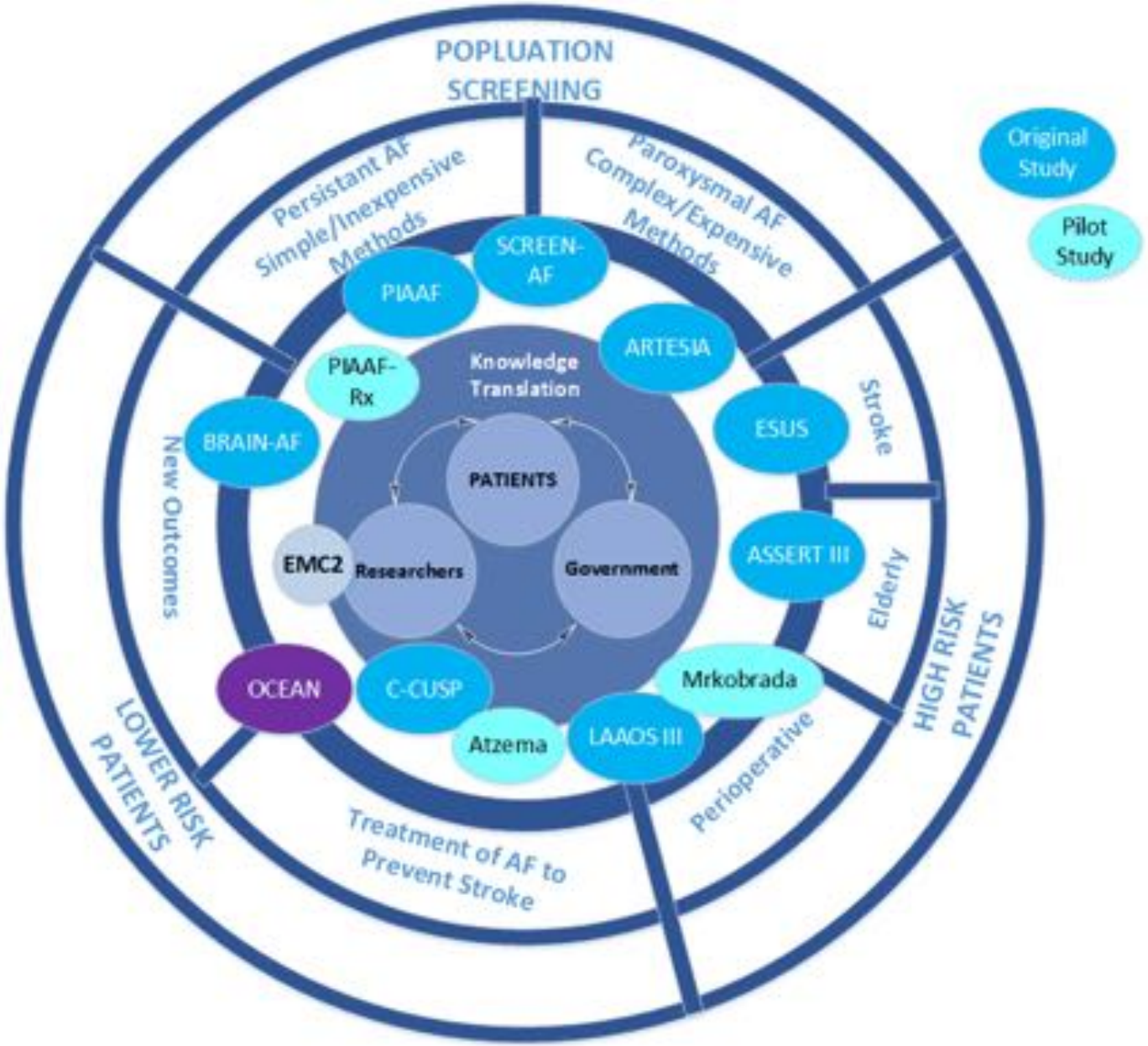
INSTITUT DE CARDIOLOGIE DE MONTRÉAL

C-SPIN

Canadian Stroke Prevention Intervention Network | Reseau Canadien pour la Prevention des Accidents Cerebrovasculaires

An ICRH Emerging Network

Network Studies



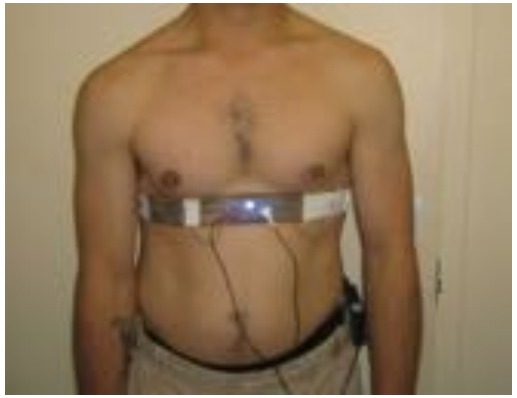
Post-stroke AF monitoring

- **Recommendation #8:** For patients being investigated for an acute embolic ischemic stroke or TIA, we recommend at least 24 hours of ECG monitoring to identify paroxysmal AF in potential candidates for OAC therapy. (Strong recommendation, Moderate Quality Evidence)

- **Recommendation #9:** For selected older patients with an acute, non-lacunar, embolic stroke of undetermined source for which AF is suspected but unproven, we suggest additional ambulatory monitoring (beyond 24 hrs) for AF detection, where available, if it is likely that OAC therapy would be prescribed if prolonged* AF is detected. (Conditional Recommendation, Moderate Quality Evidence)
- [*There are currently insufficient data to indicate what the
- minimum AF duration should be for OAC to be instituted, and expert opinion varies widely.]

EMBRACE: Study Intervention

- Event-triggered loop recorder
  (Braemar Inc., ER910AF)
  - automatically records AF
  - memory storage capacity: 30 minutes
  - programmed to record up to 11 events, max. 2.5 minutes per event

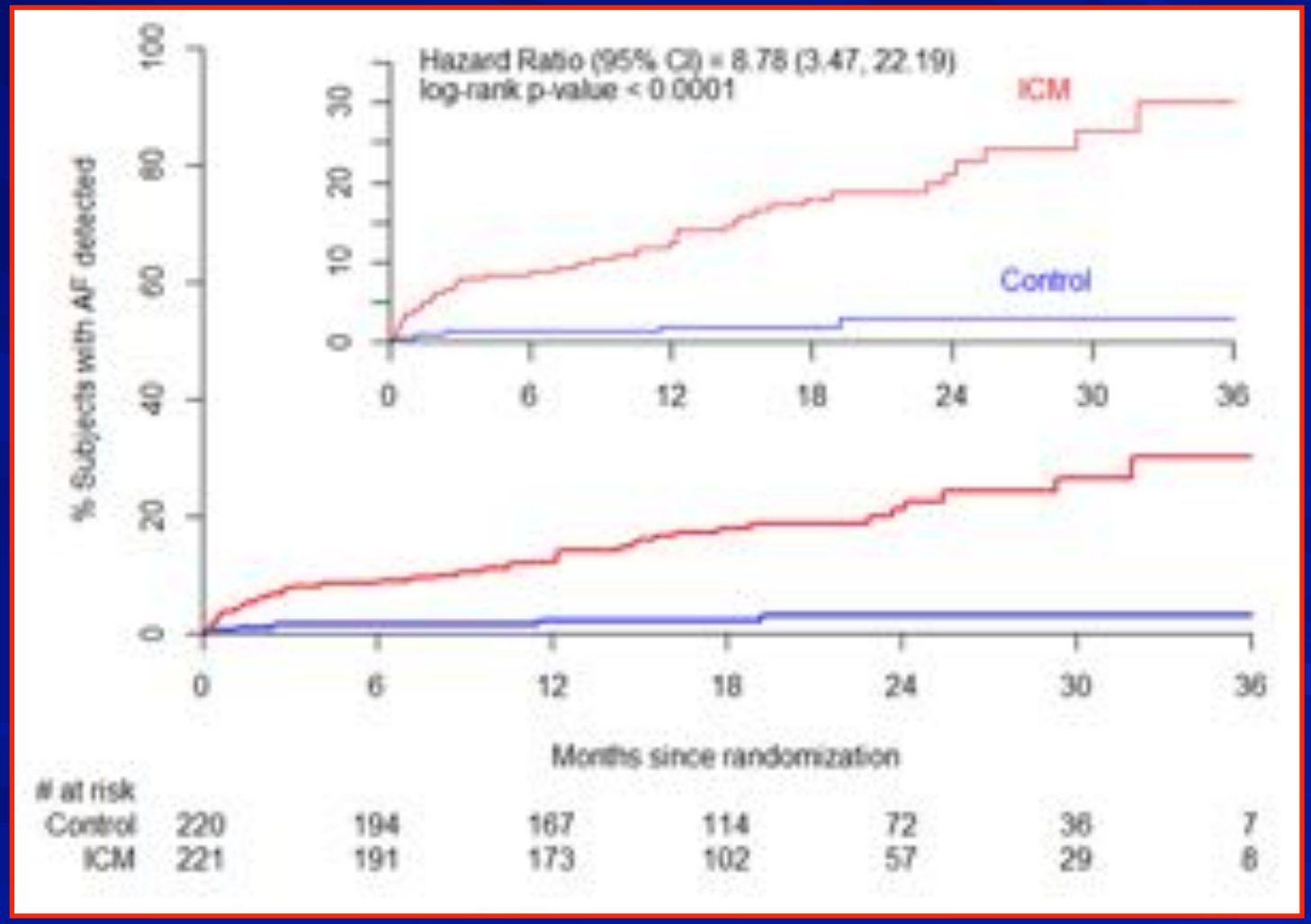


- Accuheart electrode belt
  (Cardiac Bio-Systems Inc.)
  - dry electrode technology (without adhesive skin-contact electrodes)
- Worn for 30 days or until AF detected
- Data handling
  - recorded data transmitted trans-telephonically to central station
  - ECG tracings of all events interpreted centrally by one physician blinded to clinical information
  - Results report sent to patient's study physician

EMBRACE: AF Detection at 90 Days

	Repeat Holter (n=285)	30-day Monitor (n=287)	p-value	Absolute Detection Difference (95% CI)	NNS
Primary Outcome					
AF ≥30 seconds	3%	16%	<0.001	13% (9%-18%)	8
AF ≥30 sec (study monitors only)	2%	15%	<0.001	13% (9%-18%)	8
Secondary Outcomes					
AF ≥2.5 min	2%	10%	<0.001	8% (4%-12%)	13
Any AF	4%	20%	<0.001	16% (10%-21%)	6

CRYSTAL-AF Trial: AF at 3 years
R. Bernstein 2014



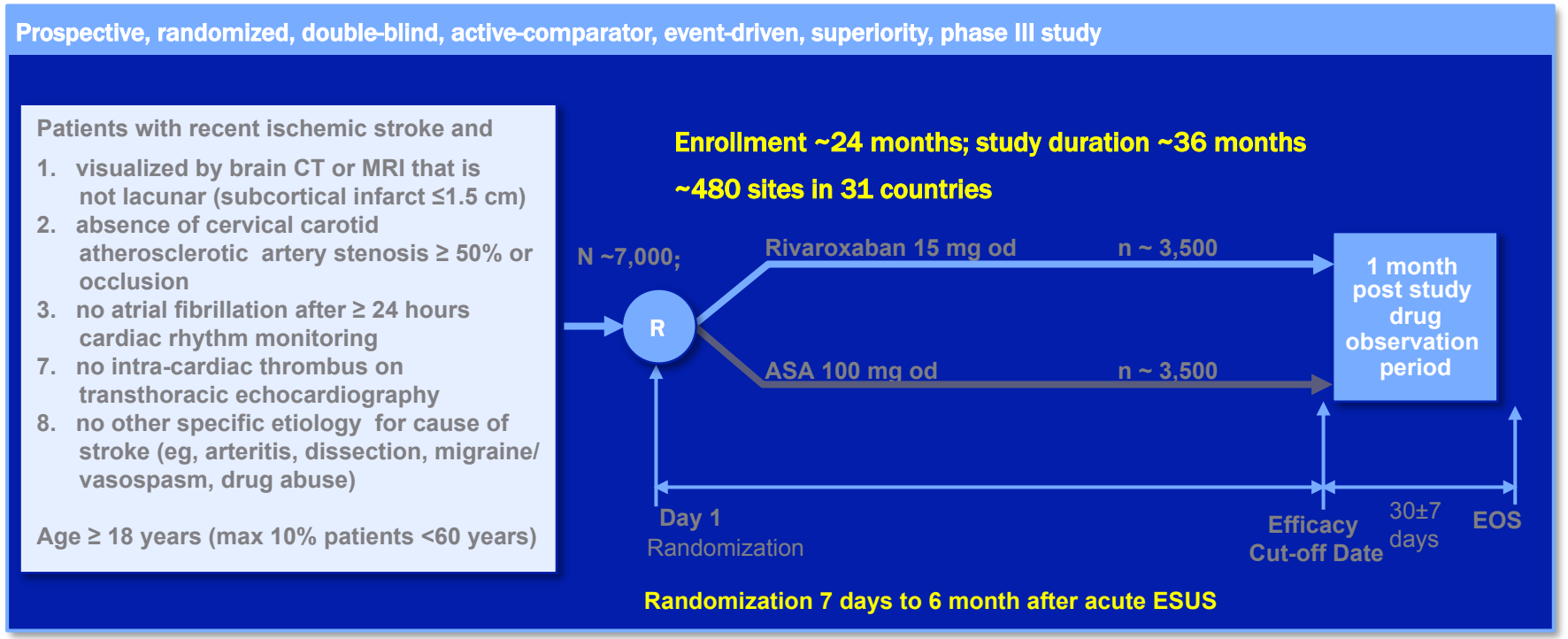
Rate of detection in ICM arm was 30.0% vs 3.0% in control arm

Embolic Stroke of Unknown Source: ESUS

- RCT of DOAC vs. ASA in patients with ESUS
- Exclude AF by 12-lead and a single 24 hour Holter
- Then, just treat empirically

- Dabigatran: C. Diener
- Rivaroxaban: R. Hart; S. Connolly

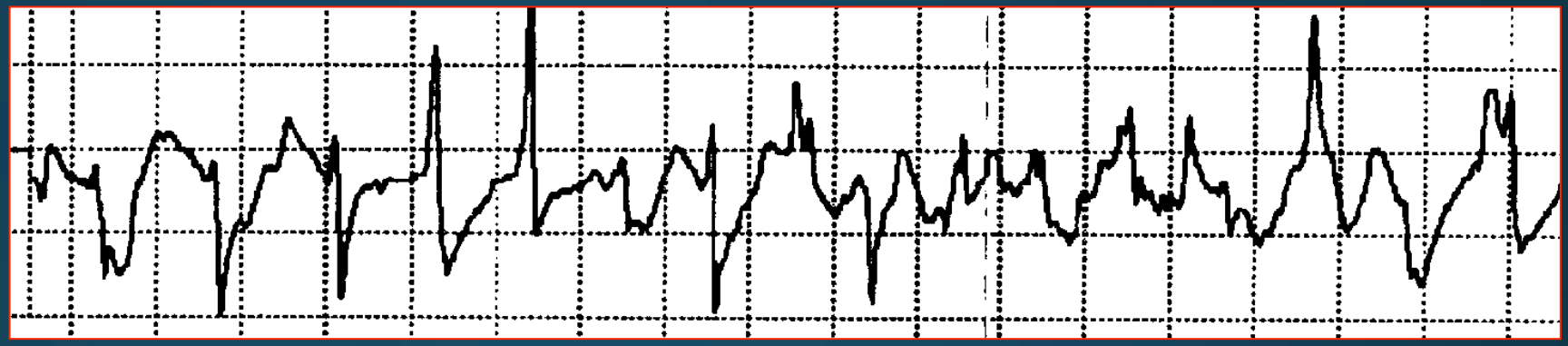
NAVIGATE-ESUS Trial Design



Two substudies:

- MRI substudy assessing covert strokes
- Biomarker / genetics substudy to identify biomarkers linked with ESUS, recurrent stroke and treatment response

Sub-Clinical Atrial Fibrillation



Recommendation #10: We suggest that it is reasonable to prescribe OAC therapy for patients with age ≥65 years or CHADS2 ≥1 ("CCS algorithm") who have episodes of SCAF lasting >24 hours, or for shorter episodes in high risk patients (such as those with a recent cryptogenic stroke). (Conditional Recommendation, Low Quality Evidence)

ASSERT: Clinical Outcomes

Healey JS, NEJM 2012

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

ASSERT: Time-Dependent Analysis

Duration of AT ≥ 190 Beats per Minute	Ischemic Stroke or Embolism: Atrial Tachyarrhythmia Present vs. Absent		
	RR	95% CI	P-Value
≥ 6 minutes	1.77	1.01-3.10	0.047
≥ 30 minutes	2.01	1.12-3.60	0.02
≥ 6 hours	2.99	1.55-5.77	0.001
≥ 24 hours	4.96	2.39-10.3	<0.001

Clinical Outcomes by $CHADS_2$

$CHADS_2$ Score	Total Pts.	Sub-clinical Atrial Tachyarrhythmia between enrollment and 3 months						Sub-clinical Atrial Tachyarrhythmia Present vs. absent		
		Present			Absent					
		Pts.	events	%/year	Pts.	events	%/year	HR	95% CI	P (trend)
1	600	68	1	0.56	532	4	0.28	2.11	0.23 – 18.9	
2	1129	119	4	1.29	1010	22	0.77	1.83	0.62 – 5.40	0.35
>2	848	72	6	3.78	776	18	0.97	3.93	1.55 – 9.95	

SCAF, Stroke Sub-Type and Severity in ASSERT

	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

ARTESiA Study

Patients with:
- SCAF (at least 1 episode ≥ 6 min but none > 24 hrs)
- CHA_2DS_2-VASc score ≥ 4
- No clinical AF, contraindication or requirement for anticoagulation

CONSENT and RANDOMIZE

The study will include 4000 patients from > 120 hospitals in Canada, USA and Europe

Target is 1-4 patients per month at each site

Double-blind, double-dummy design

Active aspirin 81mg OD + Placebo apixaban bid	Active apixaban 5mg or 2.5mg* bid + Placebo aspirin OD

* 2.5 mg for some patients requiring lower dose

Follow-up Visits at 1 month and every 6 months until 248 primary efficacy outcomes (est. avg 3 yrs)

<u>Primary Efficacy Outcomes:</u>
Stroke (including TIA with imaging)
Systemic Embolism

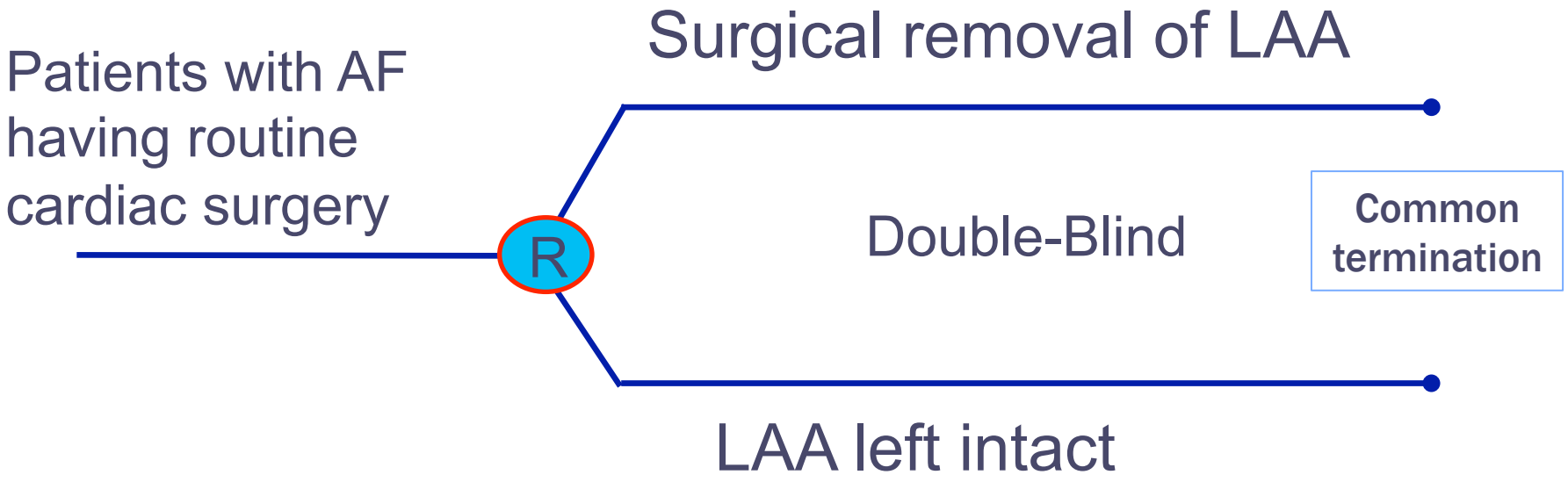
<u>Primary Safety Outcomes:</u>
Major Bleeding (ISTH)

Left Atrial Appendage Occlusion

- **Recommendation #11**: We suggest these non-approved LAA closure devices not be used, except in research protocols or in systematically-documented use protocols in patients at high
- risk of stroke (CHADS2≥2) for whom antithrombotic therapy is precluded. (Conditional Recommendation, Low Quality Evidence)

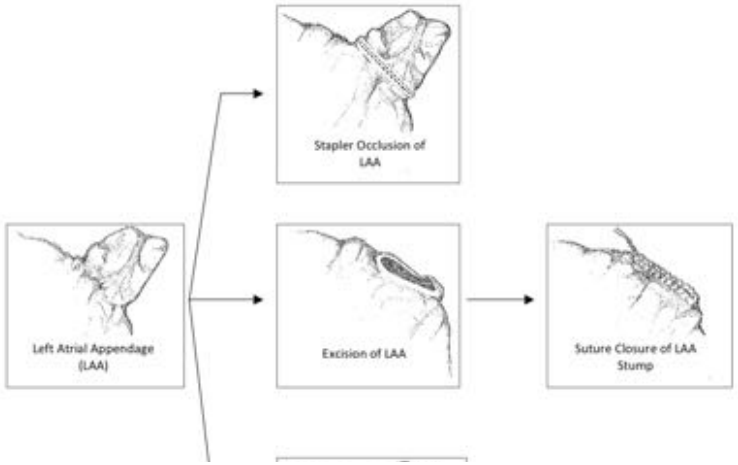
LAAOS III

4700 patients



Primary Outcome: Ischemic stroke or SE

LAAOS-III: Intervention



The following occlusion techniques are permitted:

- Amputation of the LAA and closure
  - Preferred technique
- Stapler closure of the LAA

Major Accomplishments/Activities

- 49 sites in 17 countries, 65 further sites confirmed
- 1206 patients recruited. 25% complete recruitment
- Average recruitment rate 1.4 pts/centre/month
- Compliance to treatment allocation 93.5%
- Presentation of network meta-analysis at ESC
- IRAS approval for UK sites!!!