CRYSTAL AF

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ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

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•T. Sanna, ... J. Brachmann N Engl J Med;370:2478-86, 2014•

Background

- 30% of ischemic strokes are of unknown mechanism (cryptogenic stroke)
- Detection of AF usually prompts long term anticoagulation instead of antiplatelet therapy
- Optimal monitoring duration to detect AF is currently undetermined
- AF may be paroxysmal, occur rarely, and be asymptomatic, making detection with routine methods difficult

CRYptogenic STroke And underLying Atrial Fibrillation ("CRYSTAL AF")

- **Purpose**
- **To compare the continuous monitoring by Reveal XT to standard of care (SOC) in patients after diagnosis of cryptogenic stroke / TIA.**
- **Assess the incidence of AF in these subjects and aims to demonstrate the benefit of timely AF detection for patient care.**
- **Scope:**
- **Prospective, randomized, multi-center, global, post-market study**
- **Study subjects enrolled in Europe, US, & Canada**

•Sinha et al. Amer Heart Journal 2010;160, 36-41

Objectives of CRYSTAL-AF

- **Prospective, randomized, multi-center, global, post-market study**
- **To assess whether a long-term cardiac monitoring strategy with an implantable cardiac monitor (ICM) is superior to standard monitoring for the detection AF in patients with cryptogenic stroke.**
- **Determine the proportion of patients with cryptogenic stroke that have underlying AF.**
- **Determine actions taken after patient is diagnosed with AF**
- **Primary endpoint: Detection of AF at 6 months**

•T. Sanna…J.Brachmann; N Engl J Med;370:2478-86, 2014

CRYSTAL AF
Key Inclusion Criteria

- **Subjects must have had a cryptogenic stroke or TIA* within the previous 60 days**

- **As minimally defined by the American and European Stroke Guidelines and in conjunction with site-specific requirements a diagnosis of 'cryptogenic' must be established.**
  - **At a minimum the following tests are required:**
    - MRI or CT
    - 12-lead ECG
    - 24-hour ECG monitoring (e.g. Holter)
    - Transesophageal echocardiography (TEE)
    - CTA or MRA of head and neck to rule out arterial pathologies

- **Subject is 40 years of age or older**

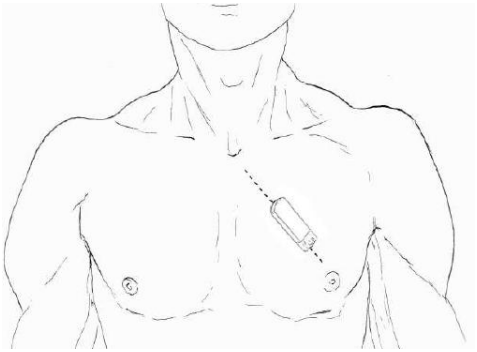
* *Inclusion of TIAs are limited to those with a visible lesion (MRI or CT) that fits the symptoms of the TIA with one of the following: speech problems, weakness of arm or leg, or hemianopsia*

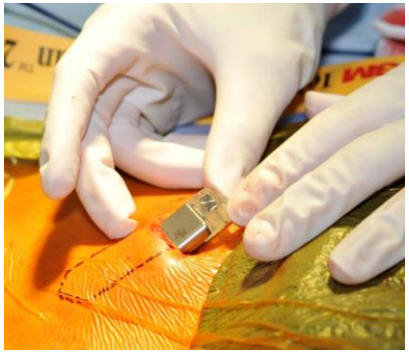
CRYSTAL AF
Key Exclusion Criteria

- **Known etiology of the stroke or TIA**
  - Large artery atherosclerosis,
  - acute small artery occlusion with lesion <1cm,
  - high risk cardiac or aortic arch source of embolism,
  - history of DVT
- **Untreated hyperthyroidism**
- **Myocardial infarction <1 month prior to stroke/TIA**
- **Coronary bypass grafting <1 month prior to stroke/TIA**
- **Valvular disease requiring immediate surgical intervention**
- **History of AF or atrial flutter**
- **Permanent indication for or contraindication for OAC at enrollment**
- **Life expectancy less than 1 year**
- **Indicated for implant with a pacemaker, ICD, CRT-device or an implantable hemodynamic monitoring system**

Comparison of Monitoring Strategies

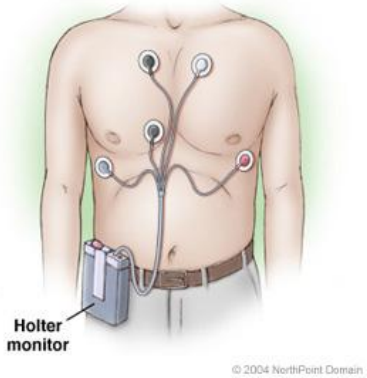
- Continuous Monitoring Arm:
- Insertion of REVEAL- XT





- **Minimally invasive outpatient procedure**
- **Local anesthetic and no leads or fluoroscopy**
- **15-30 minute procedure**
- **Device can be followed remotely**
- **MRI conditional**
- **3 year device longevity**
- **Automatic AF detection algorithm**

•Standard Monitoring Arm



- **Cardiac monitoring performed according**
- **to local standards, after mandated testing completed**

- **Symptoms consistent with AF were evaluated by study physicians**

Patient Follow-up

- **Patients in both arms received scheduled follow-up visits at:**
  - 1 month
  - 6 months
  - 12 months
  - Every 6 months thereafter until study closure

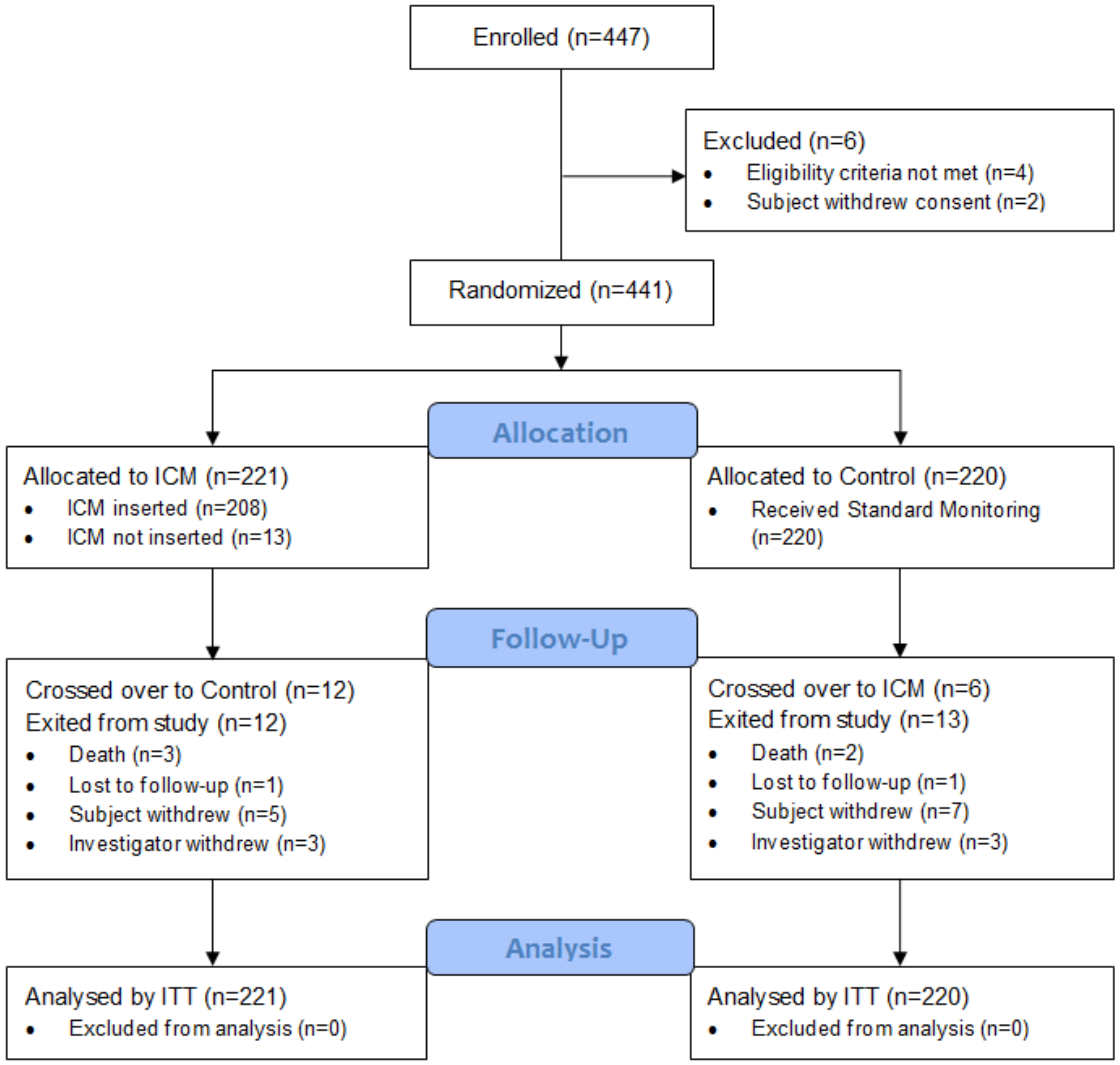
- **Follow-up visits recorded:**
  - Cardiac symptoms
  - Treatment modifications
  - Recurrence of stroke or TIA
  - Modified Rankin Scale
  - Health status (EQ-5D)

Methods

- AF defined as an episode of irregular heart rhythm, without detectable p waves, greater than 30 seconds

- AF episodes were identified by patient's physician and adjudicated by an independent committee

Patient Flow



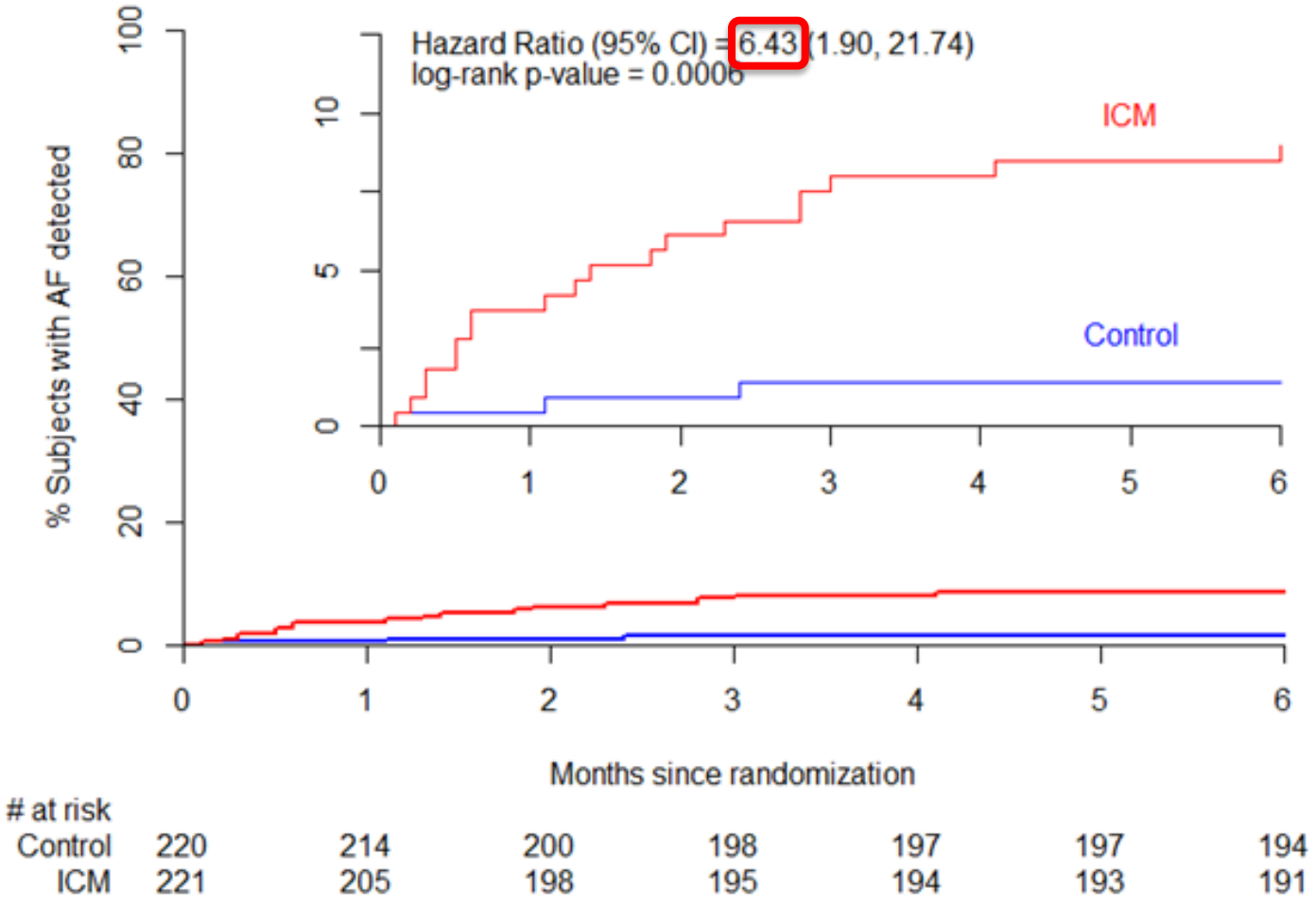
CRYSTAL-AF
Baseline Characteristics

	ICM	Control
Age	61.6 ± 11.4 years	61.4 ± 11.3 years
Gender - Male	142 (64.3%)	138 (62.7%)
Index Event – Stroke	200 (90.5%)	201 (91.4%)
Index Event – TIA	21 (9.5%)	19 (8.6%)
Pre-enrollment AF screening – Holter Monitoring	71.5% of patients Median of 23 hours (IQR 21-24)	70.9% of patients Median of 24 hours (IQR 22-24)
Pre-enrollment AF screening – Telemetry	29.9% of patients Median of 48 hours (IQR 36-96)	29.5% of patients Median of 72 hours (IQR 48-96)
Time between index event and randomization	36.6 ±28.2 days	39.6 ±26.9 days
Time to randomization and device insertion	8.7 ± 27.6 days	n/a

CRYSTAL-AF
Baseline Characteristics

Characteristic	Insertable Cardiac Monitor (N=221)	Control (N=220)	P Value
$CHADS_2$ score — no. (%)¶			0.17
2	69 (31.2)	81 (36.8)	
3	92 (41.6)	91 (41.4)	
4	50 (22.6)	34 (15.5)	
5	9 (4.1)	14 (6.4)	
6	1 (0.5)	0	
Hypercholesterolemia — no. (%)	125 (56.6)	128 (58.2)	0.77
Current smoker — no. (%)	43 (19.5)	44 (20.0)	0.91
Coronary artery disease — no. (%)	16 (7.2)	9 (4.1)	0.22
Use of antiplatelet agent — no. (%)	212 (95.9)	212 (96.4)	1.00

Primary Endpoint: DETECTION OF AF AT 6 MONTHS



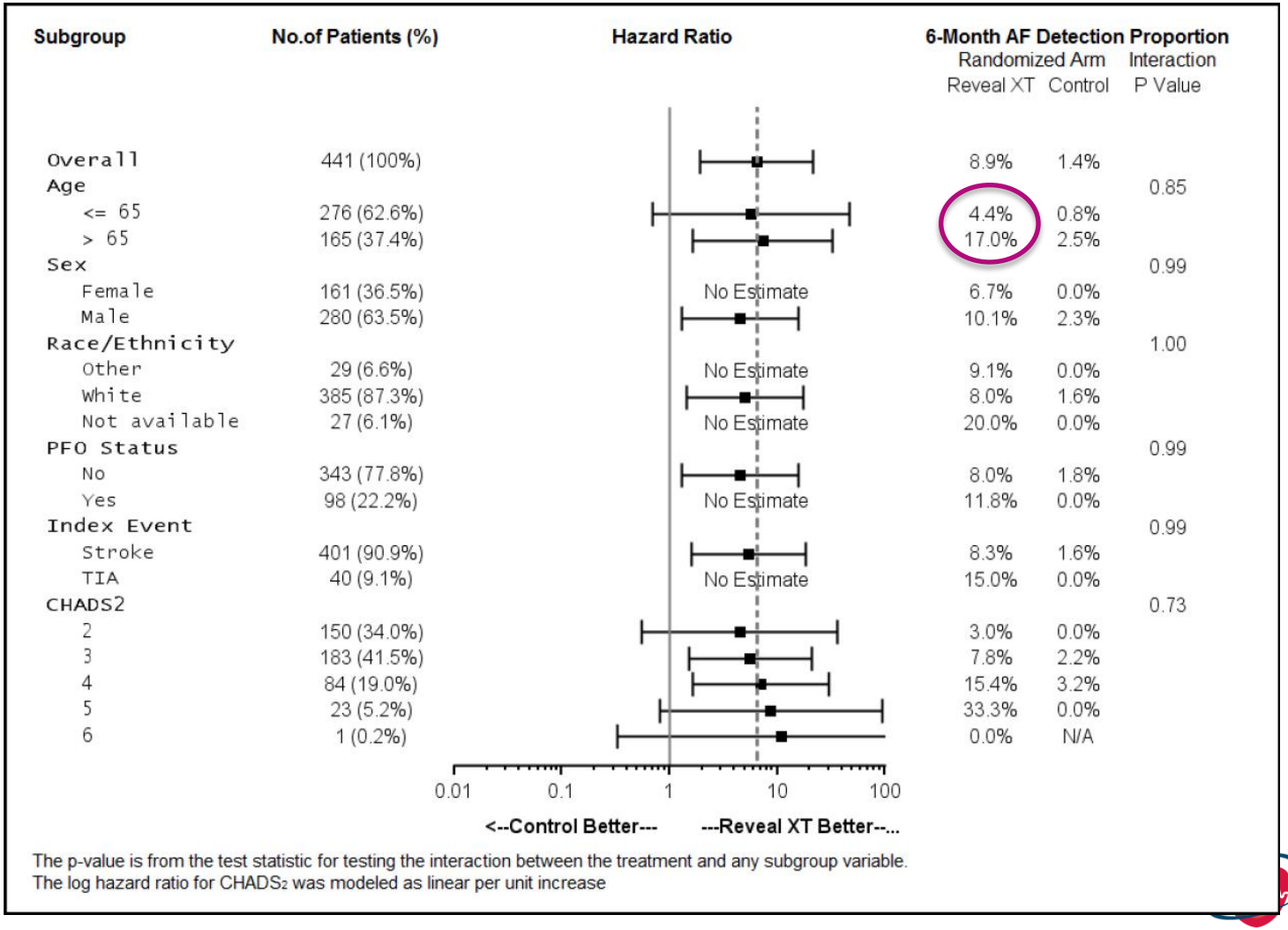
- **Rate of detection in ICM arm was 8.9% vs 1.4% in control arm**

- T. Sanna…J.Brachmann; N Engl J Med;370:2478-86, 2014

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

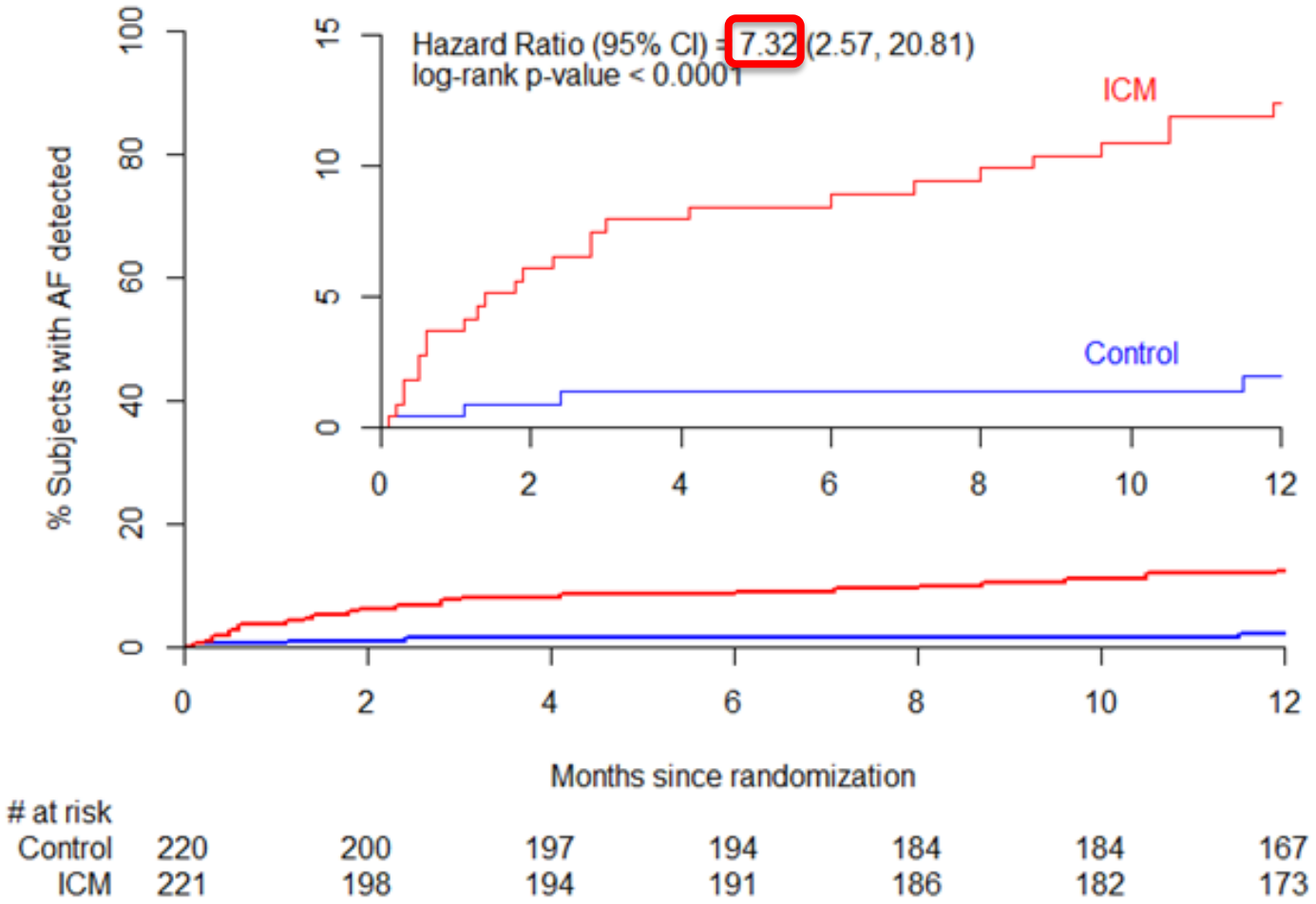
Subgroup Analysis



The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable.
The log hazard ratio for $CHADS_2$ was modeled as linear per unit increase

T. Sanna, J.Brachmann et al N Engl J Med;370:2478-86, 2014

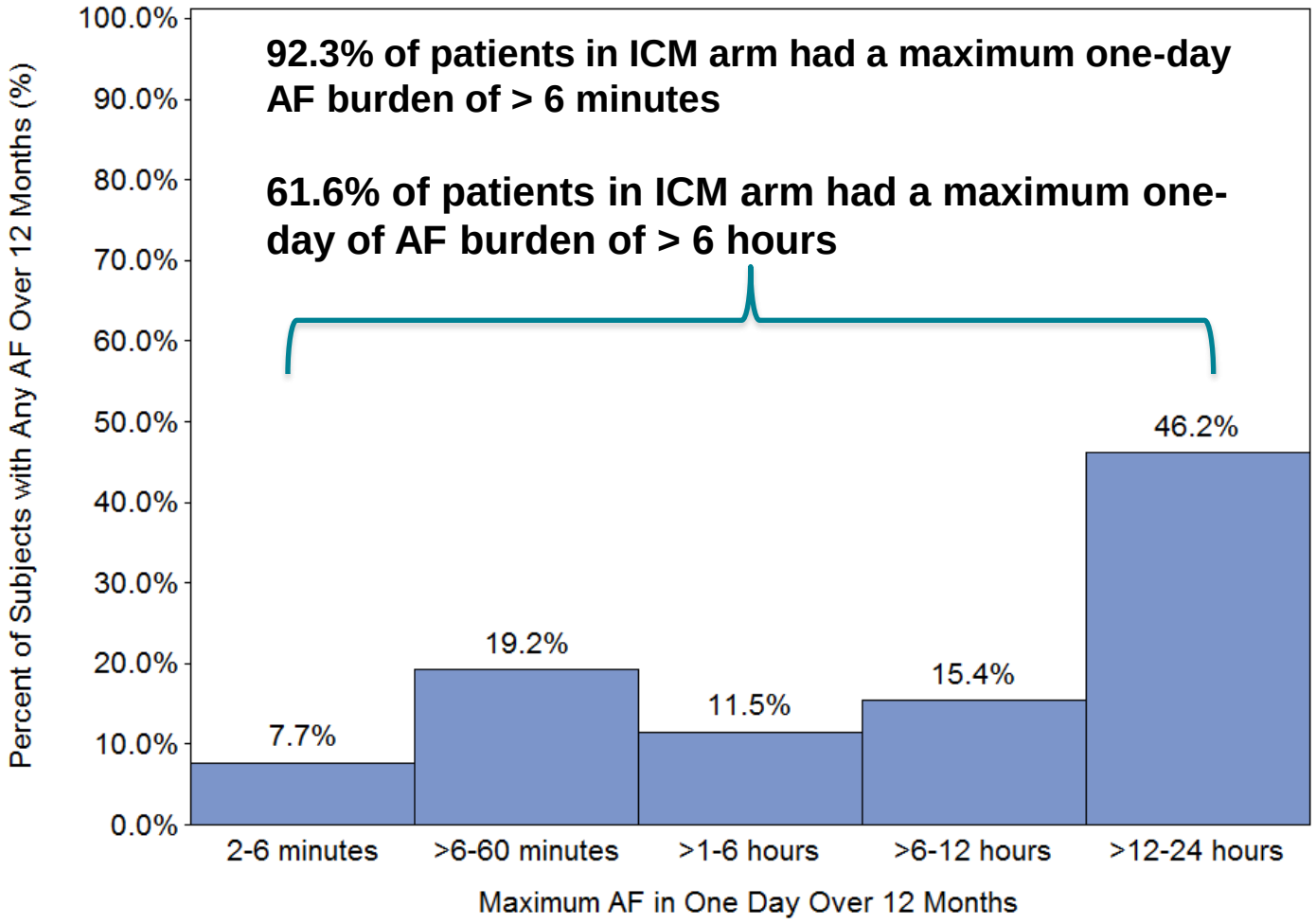
Secondary Endpoint: Detection of AF at 12 months



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

- T. Sanna…J.Brachmann; N Engl J Med;370:2478-86, 2014

Atrial Fibrillation Duration in ICM Arm at 12 Months (N=29)



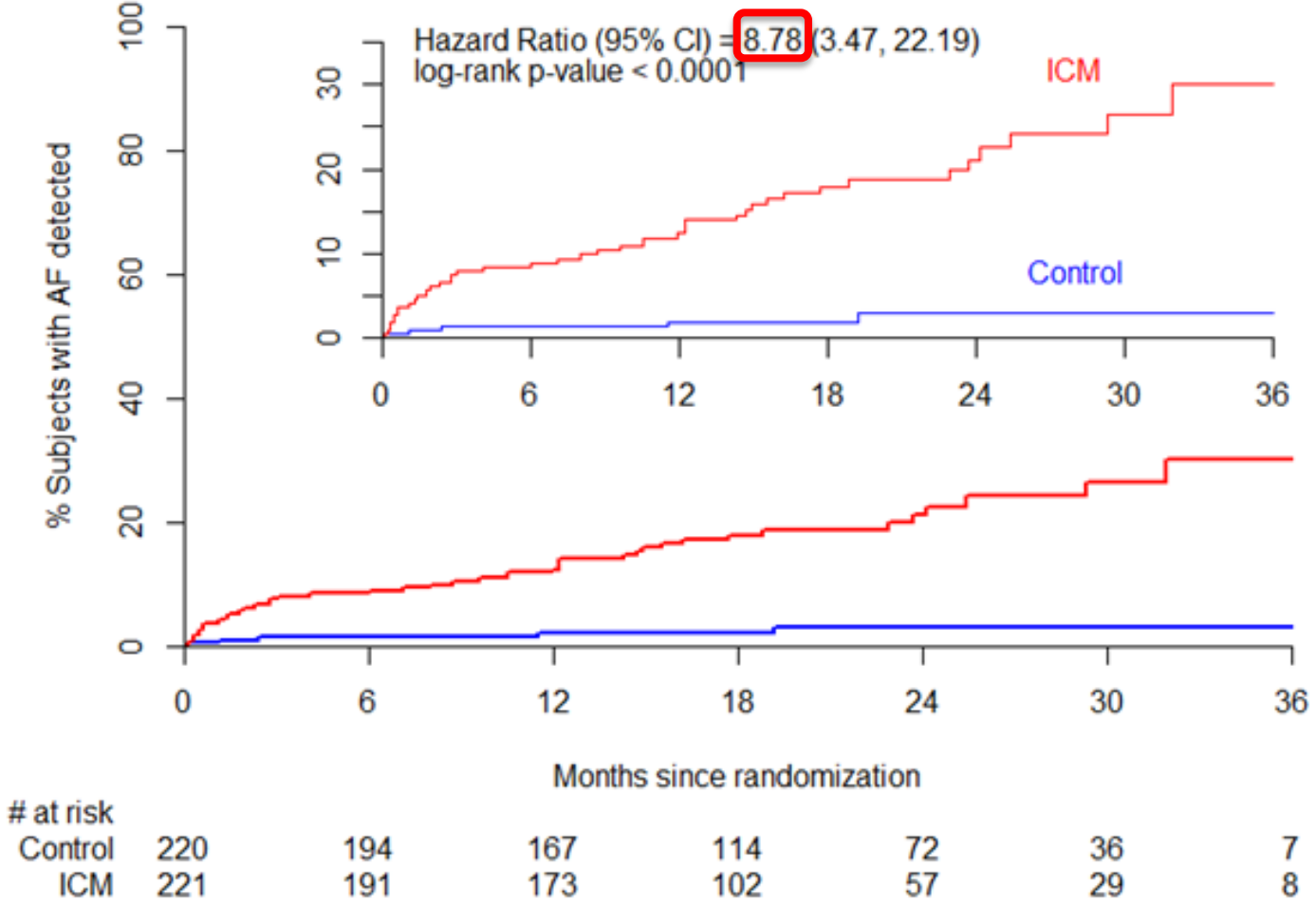
Tests Required for Detecting AF in the CRYSTAL-AF Study

12 Month Endpoints

	ICM	Control
Median Time from Randomization to AF Detection	84 days	52.5 days
Patients found to have AF	29	4
% Asymptomatic Episodes	79%	50%
Oral Anticoagulation Usage, overall	14.7%	6.0%
Tests required to find AF	Automatic AF detection	121 ECGs 32 24-hour Holters 1 Event Recorder
Complications	5 (2.4%) ICMs removed due to insertion site infection or pocket erosion	None

Detection of AF at 3 years

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



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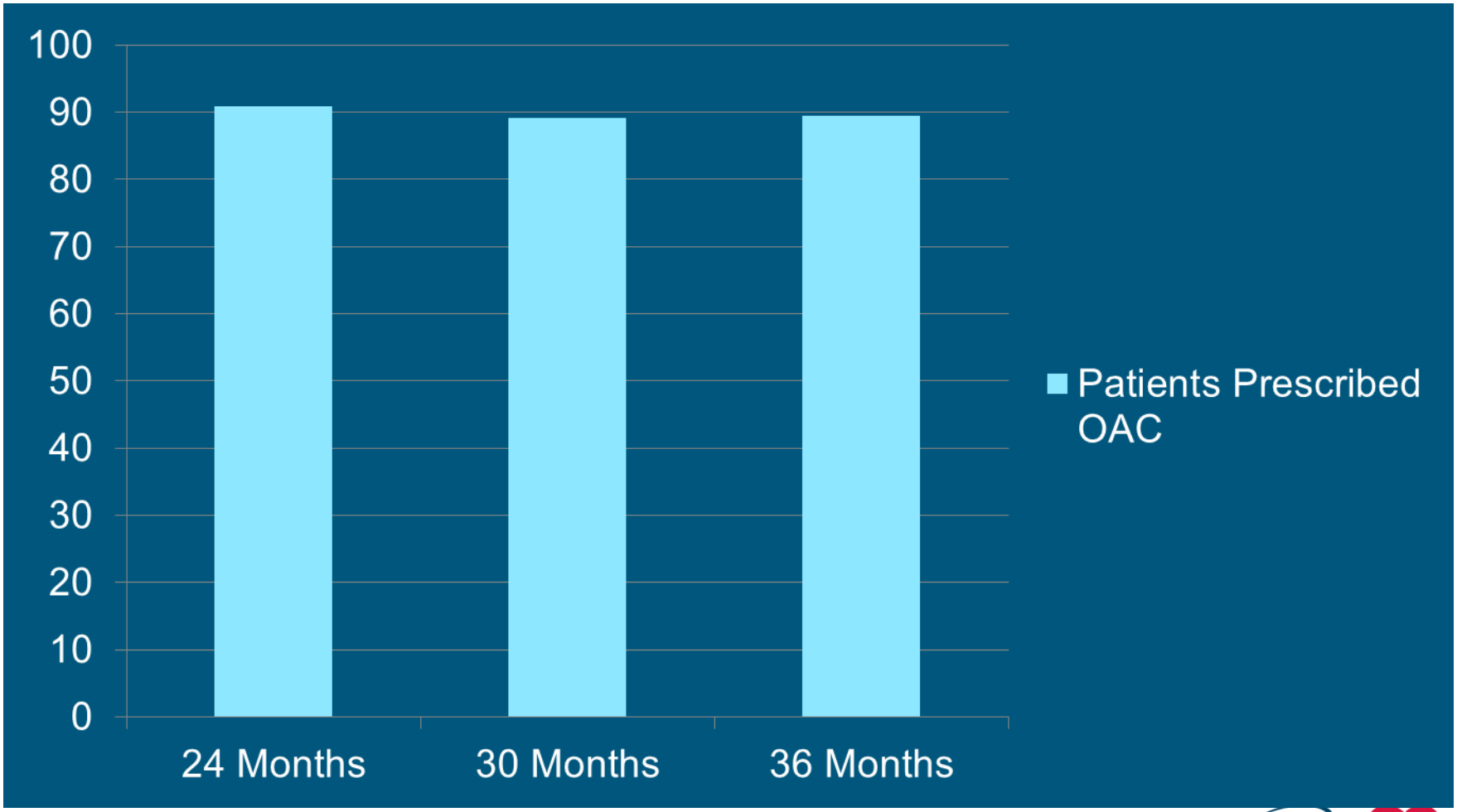
Clinical Decisions
OAC Usage in AF Patients: Both Arms



Approximately 90% of patients with AF were prescribed OAC

	ICM	Control
Median Time from Randomization to AF Detection	84 days	52.5 days
Patients found to have AF	29	4
% Asymptomatic Episodes	79%	50%
Oral Anticoagulation Usage, overall	14.7%	6.0%
OAC use in AF patients	96.6%	100%
Tests required to find AF	Automatic AF detection	121 ECGs 32 24-hour Holters 1 Event Recorder
Complications	5 (2.4%) ICMs removed due to insertion site infection or pocket erosion	None

Stroke Guidelines

- Until recently Stroke Guidelines recommended at least 24h Holter monitoring after a stroke of unknown cause[1]

- New in 2014 (AHA/ASA Guideline) :
- For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*. (New recommendation)[2]

1 Hacke W. Cerebrovascular Disease 2008; 25:457–507
2 Kernan WN. Stroke 2014, advance access published on May 1, 2014

Summary

- Insertable Cardiac Monitor (ICM) was 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

- In the ICM arm, AF was detected in 8.9%, 12.4%, and 30% of patients at 6 months, 12 months and 36 months, respectively

- More than 90% of patients with AF in the ICM arm had a day with greater than 6 minutes of AF, more than 60% of more than 6 hours

- Detection of AF changed management to oral anticoagulation in 90% of patients

Conclusions

- Atrial fibrillation is increasingly established as the leading cause of severe strokes.
- Longterm ECG monitoring has been proven to enhance the yield of silent AF in patients with cryptogenic stroke in a time-dependent fashion
- Long-term continuous monitoring should be performed in patients with cryptogenic stroke
- Additional studies are required to determine the clinical benefit of appropriate anticoagulation in this patients with cryptogenic stroke (ESUS)