# CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF)

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# Disclosures

**Richard Bernstein, MD, Ph.D:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted Bristol Myers Squibb/Pfizer, Boehringer Ingelheim Pharmaceuticals, personal fees from Medtronic, Inc., outside the CRYSTAL AF study

**Tommaso Sanna, MD:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted from Medtronic, Inc. outside the CRYSTAL AF study.

**Hans-Christoph Diener, MD, Ph.D:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work with Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daichii-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Thrombogenics, WebMD Global, Wyeth and Yamanouchi. Astra/Zeneca, GSK, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris.

**Rod S. Passman, MD:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted from Medtronic, Inc. outside the CRYSTAL AF study.

**Vincenzo Di Lazzaro, MD:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted from Medtronic, Inc. outside the CRYSTAL AF study.

**Carlos Morillo, MD:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted with Biotronik, Boston Scientific, Merck, Canadian Institutes of Health Research, TDR/WHO, St. Jude Medical.

Marilyn Rymer, MD: personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted from Medtronic, Inc. outside the CRYSTAL AF study.

Vincent Thijs, MD: personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted with Medtronic, Sygnis, Boehringer Ingelheim, Pfizer, Bayer.

**Johannes Brachmann, MD, PH.D:** personal fees from Medtronic, Inc. during the conduct of the CRYSTAL AF study. Other work conducted with Biotronik

# 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

# 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.
- **Primary endpoint: Detection of AF by six months**
- Determine the proportion of patients with cryptogenic stroke that have underlying AF.
- Determine actions taken after patient is diagnosed with AF

# Key Inclusion/Exclusion Criteria

**Inclusion:**

• ≥40 years of age

•Cryptogenic stroke (or clinical TIA), with infarct seen on MRI or CT, within the previous 90 days; and no mechanism (including AF) determined after:

- 12-lead ECG
- 24-hour ECG monitoring (e.g. Holter)
- Transesophageal echocardiography (TEE)
- CTA or MRA of head and neck to rule out arterial source
- Screening for hypercoagulable states in patients <55 years old

**Exclusion:**

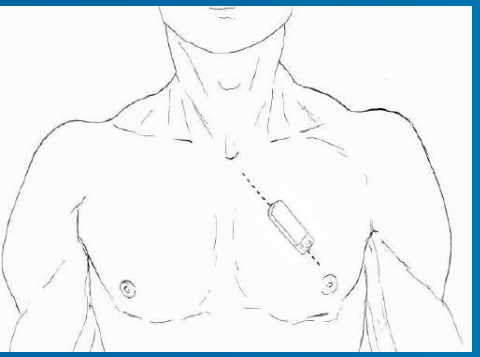
•History of AF or Atrial Flutter

•Permanent indication or contraindication for anticoagulation

•Indication for pacemaker or implantable cardioverter defibrillator

# 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

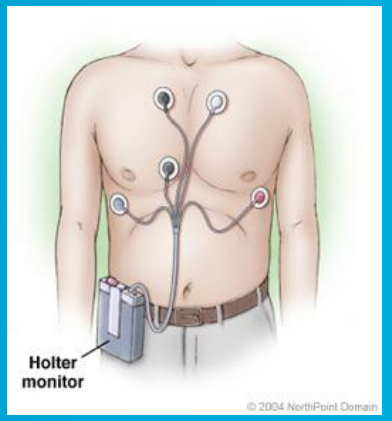
Device can be followed remotely

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

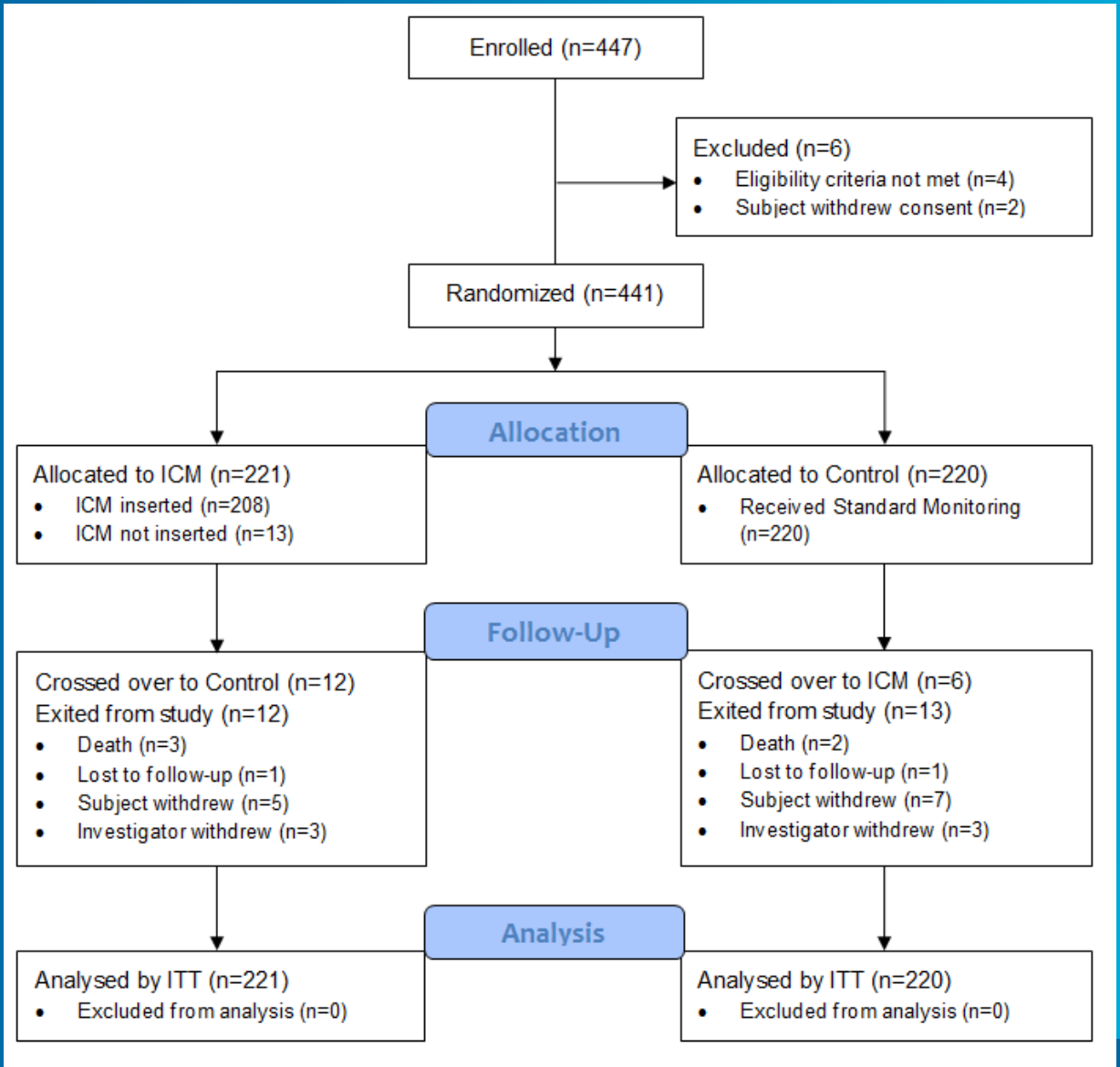
- Follow-up visits recorded:
  - Cardiac symptoms
  - Treatment modifications
  - Recurrence of stroke or TIA
  - Modified Rankin Scale
  - Health status (EQ-5D)

# 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



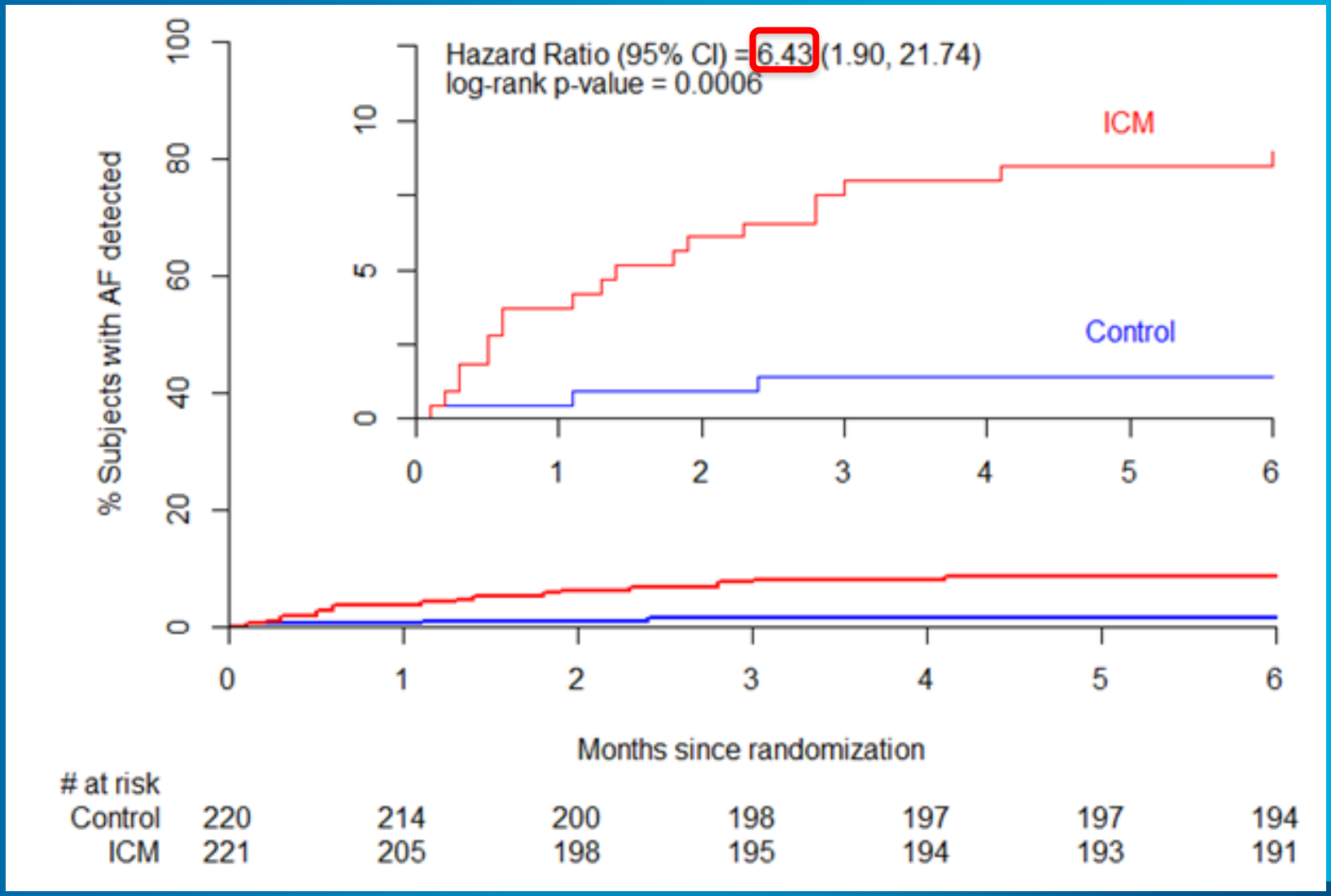
# Statistical Analysis

- Time to first documented AF episode within 6 months post-randomization was estimated by Kaplan-Meier Curves and compared between arms on an intention to treat using a log-rank test
- Cox proportional hazards regressions was used to estimate hazard ratios and for sub-group analyses, by performing a Wald test for interaction between the sub-group and randomized arm
- Time-to-event analysis methods used to analyze the primary endpoint were also used to analyze other time-to-event endpoints.
- Difference between arms in the proportion of subjects on OAC at follow-up was compared with Fisher's exact test

# 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<br>Median of 23 hours<br>(IQR 21-24) | 70.9% of patients<br>Median of 24 hours<br>(IQR 22-24) |
| Pre-enrollment AF screening – Telemetry | 29.9% of patients<br>Median of 48 hours<br>(IQR 36-96) | 29.5% of patients<br>Median of 72 hours<br>(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 |

# Primary Endpoint: DETECTION OF AF AT 6 MONTHS




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

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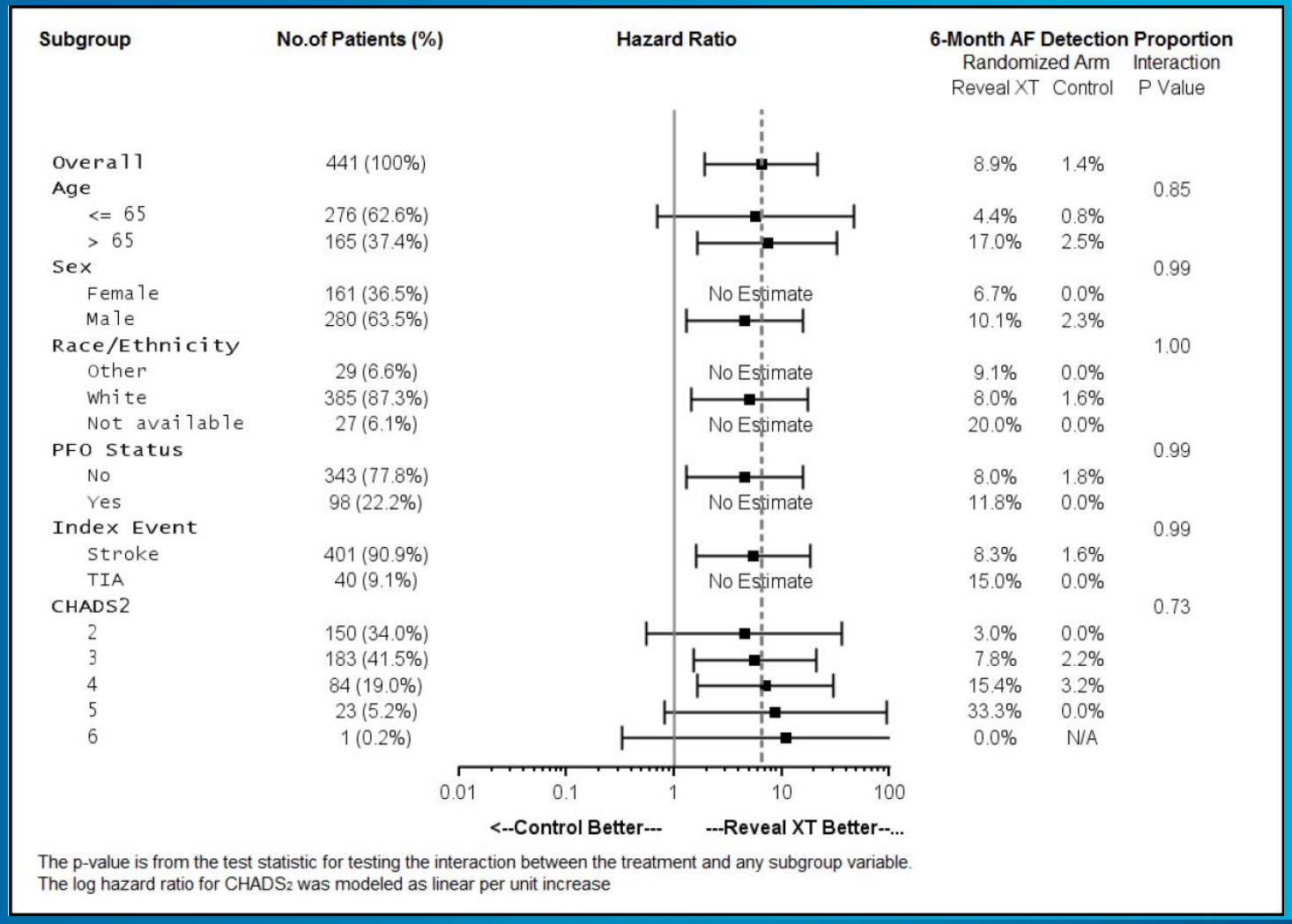
# 6 Month Endpoints

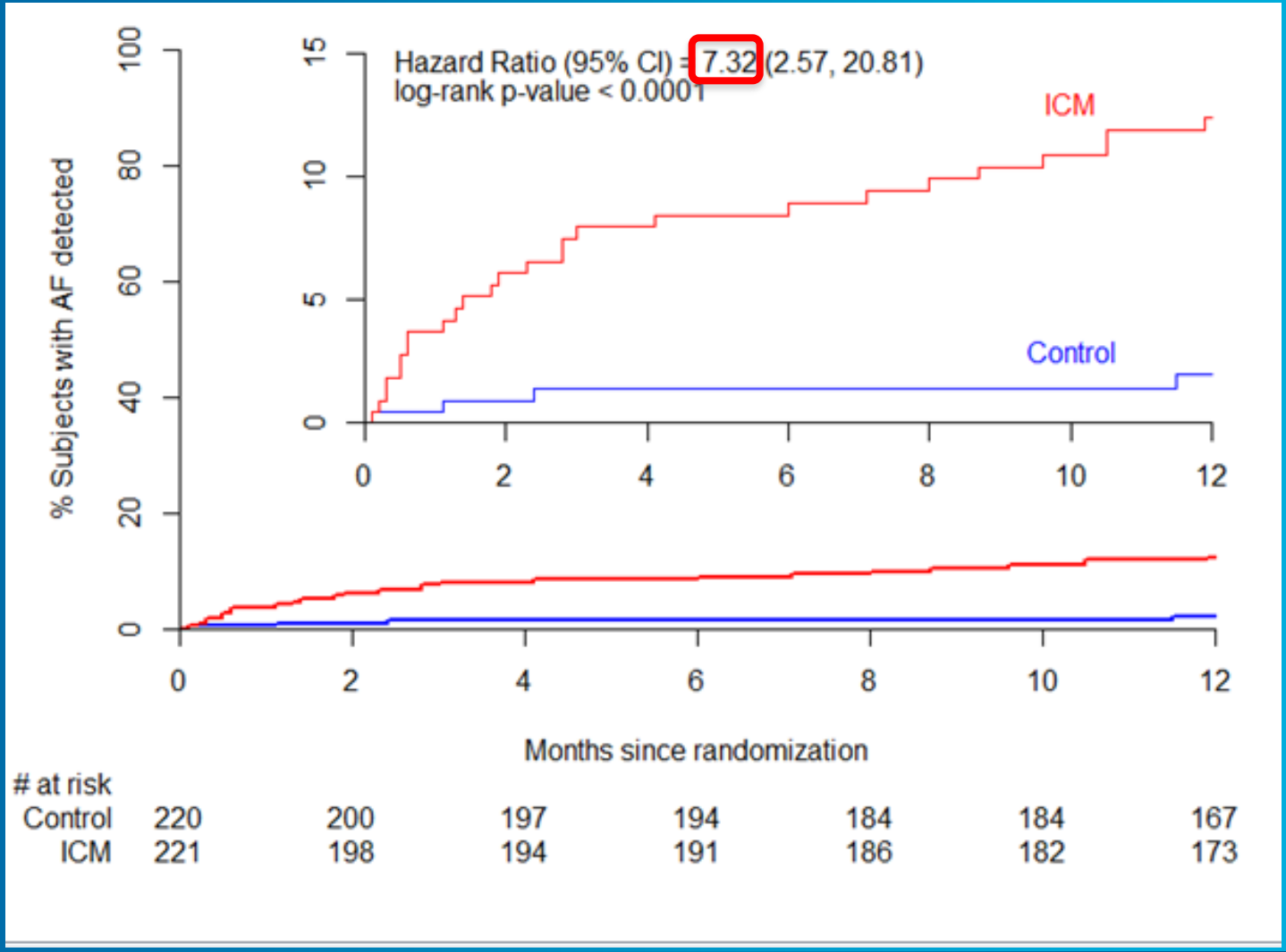
| | ICM | Control |
|---|---|---|
| Median Time from Randomization to AF Detection | 41 days | 32 days |
| Patients found to have AF | 19 | 3 |
| % Asymptomatic Episodes | 74% | 33% |
| Oral Anticoagulation Usage, overall | 10.1% | 4.6% |
| OAC use in patients with detected AF | 94.7% | 66.7% |
| Testing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

# Secondary Endpoint: Detection of AF at 12 months




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

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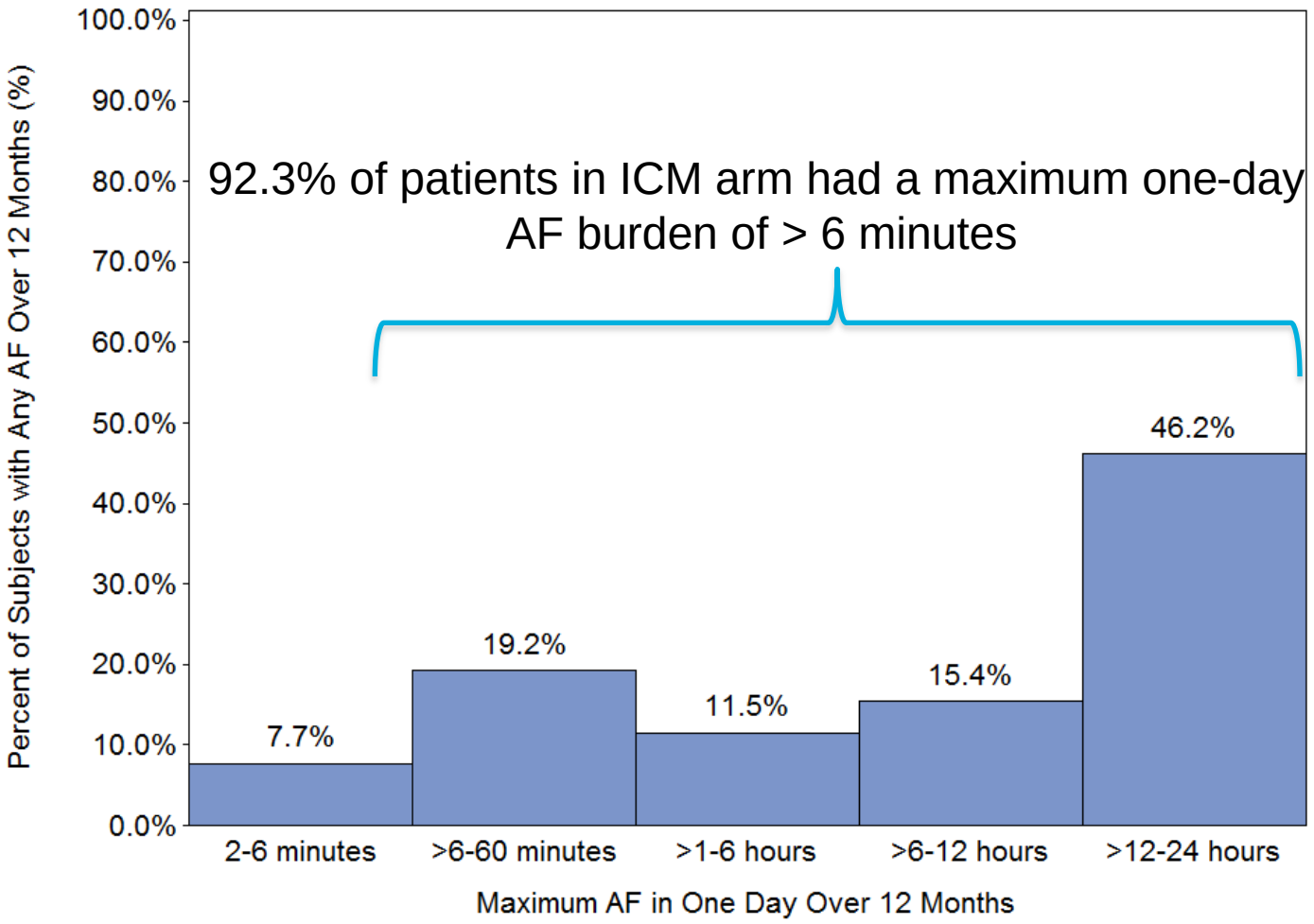
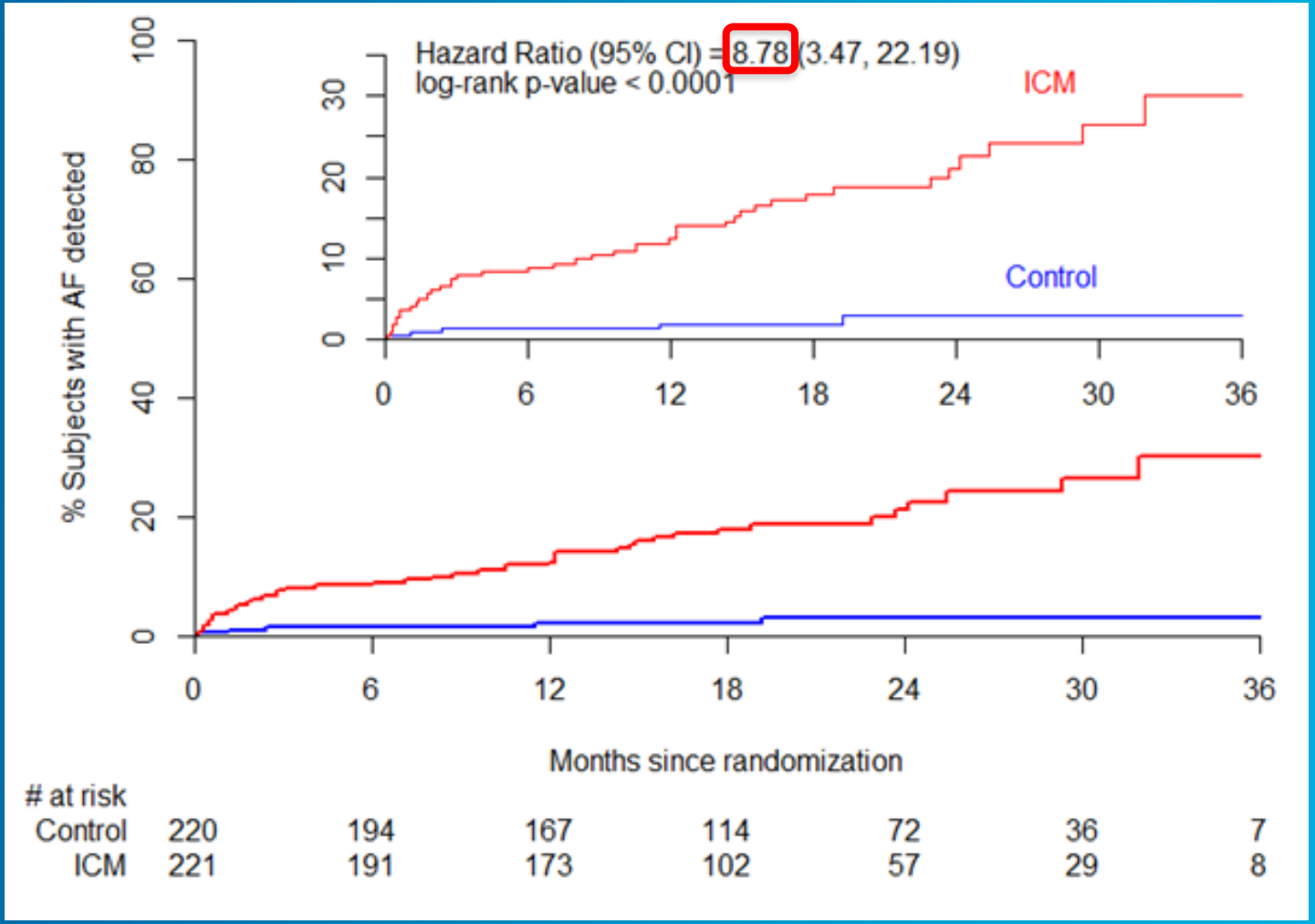
# 12 Month Endpoints

| | 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% |
| OAC use in AF patients | 96.6% | 100% |
| Tests required to find AF | Automatic AF detection | 121 ECGs<br>32 24-hour Holters<br>1 Event Recorder |
| Complications | 5 (2.4%) ICMs removed due to insertion site infection or pocket erosion | None |

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



# Detection of AF at 3 years




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

CRYSTAL AF

# Conclusions

- Insertable Cardiac Monitor (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
- In the ICM arm, AF was detected in 8.9%, 12.4%, and 30% of patients at 6 months, 12 months, and 36 months
- 92.3% of patients with AF in the ICM arm had a day with greater than 6 minutes of AF
- Detection of AF changed management to anticoagulation in 97% of patients
- Long-term continuous monitoring should be performed in patients with cryptogenic stroke

# Steering Committee Members

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