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 from 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 conducted from 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, Syngis, 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

Enrolled (n=447)

Excluded (n=6)
- Eligibility criteria not met (n=4)
- Subject withdrew consent (n=2)

Randomized (n=441)

Allocated to ICM (n=221)
- ICM inserted (n=208)
- ICM not inserted (n=13)

Allocated to Control (n=220)
- Received Standard Monitoring (n=220)

Follow-Up

Crossed over to Control (n=12)
Exited from study (n=12)
- Death (n=3)
- Lost to follow-up (n=1)
- Subject withdrew (n=5)
- Investigator withdrew (n=3)

Crossed over to ICM (n=8)
Exited from study (n=13)
- Death (n=2)
- Lost to follow-up (n=1)
- Subject withdrew (n=7)
- Investigator withdrew (n=3)

Analysis

Analysed by ITT (n=221)
- Excluded from analysis (n=0)

Analysed by ITT (n=220)
- Excluded from analysis (n=0)
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:

<table>
<thead>
<tr>
<th></th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61.6 ± 11.4 years</td>
<td>61.4 ± 11.3 years</td>
</tr>
<tr>
<td><strong>Gender - Male</strong></td>
<td>142 (64.3%)</td>
<td>138 (62.7%)</td>
</tr>
<tr>
<td><strong>Index Event – Stroke</strong></td>
<td>200 (90.5%)</td>
<td>201 (91.4%)</td>
</tr>
<tr>
<td><strong>Index Event – TIA</strong></td>
<td>21 (9.5%)</td>
<td>19 (8.6%)</td>
</tr>
<tr>
<td><strong>Pre-enrollment AF screening – Holter Monitoring</strong></td>
<td>71.5% of patients Median of 23 hours (IQR 21-24)</td>
<td>70.9% of patients Median of 24 hours (IQR 22-24)</td>
</tr>
<tr>
<td><strong>Pre-enrollment AF screening – Telemetry</strong></td>
<td>29.9% of patients Median of 48 hours (IQR 36-96)</td>
<td>29.5% of patients Median of 72 hours (IQR 48-96)</td>
</tr>
<tr>
<td><strong>Time between index event and randomization</strong></td>
<td>36.6 ± 28.2 days</td>
<td>39.6 ± 26.9 days</td>
</tr>
<tr>
<td><strong>Time to randomization and device insertion</strong></td>
<td>8.7 ± 27.6 days</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Primary Endpoint: DETECTION OF AF AT 6 MONTHS

Rate of detection in ICM arm was 8.9% vs 1.4% in control arm
## 6 Month Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time from Randomization to AF Detection</td>
<td>41 days</td>
<td>32 days</td>
</tr>
<tr>
<td>Patients found to have AF</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>% Asymptomatic Episodes</td>
<td>74%</td>
<td>33%</td>
</tr>
<tr>
<td>Oral Anticoagulation Usage, overall</td>
<td>10.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>OAC use in patients with detected AF</td>
<td>94.7%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Testing required to detect AF</td>
<td>Automatic AF detection</td>
<td>88 ECGs 20 24-hour Holters 1 event recorder</td>
</tr>
</tbody>
</table>
## Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Hazard Ratio</th>
<th>6-Month AF Detection Proportion</th>
<th>Interaction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>441 (100%)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 65</td>
<td>276 (62.6%)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>&gt; 65</td>
<td>165 (37.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>161 (36.5%)</td>
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</tr>
<tr>
<td>Male</td>
<td>280 (63.5%)</td>
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<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>29 (6.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>385 (87.3%)</td>
<td></td>
<td></td>
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<tr>
<td>Not available</td>
<td>27 (6.1%)</td>
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<tr>
<td><strong>PFO Status</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>343 (77.8%)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98 (22.2%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Index Event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>401 (90.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>40 (9.1%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>CHADS2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>150 (34.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>183 (41.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>64 (19.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>23 (5.2%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>1 (0.2%)</td>
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</tbody>
</table>

The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable. The log hazard ratio for CHADS2 was modeled as linear per unit increase.

CRYS

![Graph showing subgroup analysis results](image)
Secondary Endpoint: Detection of AF at 12 months

Rate of detection in ICM arm was 12.4% vs 2.0% in control arm
## 12 Month Endpoints

<table>
<thead>
<tr>
<th>Metric</th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time from Randomization to AF Detection</td>
<td>84 days</td>
<td>52.5 days</td>
</tr>
<tr>
<td>Patients found to have AF</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>% Asymptomatic Episodes</td>
<td>79%</td>
<td>50%</td>
</tr>
<tr>
<td>Oral Anticoagulation Usage, overall</td>
<td>14.7%</td>
<td>6.0%</td>
</tr>
<tr>
<td>OAC use in AF patients</td>
<td>96.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Tests required to find AF</td>
<td>Automatic AF detection</td>
<td>121 ECGs 32 24-hour Holters 1 Event Recorder</td>
</tr>
<tr>
<td>Complications</td>
<td>5 (2.4%) ICMs removed due to insertion site infection or pocket erosion</td>
<td>None</td>
</tr>
</tbody>
</table>
Atrial Fibrillation Duration in ICM Arm at 12 months (N=29)

92.3% of patients in ICM arm had a maximum one-day AF burden of > 6 minutes
Detection of AF at 3 years

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