REVEAL™ ICM
CLINICAL EVIDENCE GUIDE

Cardiac Rhythm & Heart Failure (CRHF) Diagnostics & Monitoring
TABLE OF CONTENTS

- Reveal LINQ™ ICM Procedure Data
- Reveal Sensing & Algorithm Performance
- Syncope
- Palpitations
- Unexplained Falls
- Cryptogenic Stroke
- AF Management
- Primary Prevention: Suspected AF
CARDIAC RHYTHM MONITORING OPTIONS

- Multiple monitoring options are available

- Choice of technology is based on:
  - Frequency of arrhythmias and symptoms
  - Indication
  - Patient and physician preference

<table>
<thead>
<tr>
<th>SHORT-TERM/INTERMITTENT MONITORING</th>
<th>LONG-TERM MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter Monitor</td>
<td>Insertable Cardiac Monitor (ICM)</td>
</tr>
<tr>
<td>Traditional Holter</td>
<td>SEEQ™ MCT/ECM</td>
</tr>
<tr>
<td>Extended Holter</td>
<td>Mobile Cardiac Telemetry</td>
</tr>
<tr>
<td>Records every heartbeat</td>
<td>Traditional MCT</td>
</tr>
<tr>
<td>Records over itself; saves events only</td>
<td>External Loop Event Recorder (ELR)</td>
</tr>
<tr>
<td>Short-term wear and send in</td>
<td></td>
</tr>
<tr>
<td>Records every heartbeat; 24/7 monitor</td>
<td></td>
</tr>
<tr>
<td>Saves events only; automatically transmits arrhythmic ECG; 24/7 monitor</td>
<td></td>
</tr>
</tbody>
</table>
CARDIAC RHYTHM MONITORING OPTIONS

- Time to diagnosis varies based on technology employed, indication and study design
- Important considerations when evaluating time to diagnosis:
  - Both time to diagnosis AND yield are important
  - “The more you look, the more you will find”
    - i.e. if you only monitor for 7 days, you will never have a time to diagnosis longer than one week
15+ YEARS OF REVEAL™ ICM LONG-TERM CARDIAC MONITORING

- 1998: Reveal ILR FDA approval — manual trigger only
- 2000: Reveal Plus FDA approval — automated arrhythmia detection
- 2007: Reveal DX FDA approval — automated brady, tachy, asystole detection
- 2009: ICM indications position paper (EHRA)
- 2010: ICM in Syncope Guidelines (ESC)
- 2011: ICM in Syncope Guidelines (NICE)
- 2013: Palpitation Mgmt position paper (EHRA)
- 2014: Dx Testing Guidelines (ESC)
- 2016: Reveal LINQ FDA approval

- 1998-2016
  - Syncope: 400+ publications*
  - ICM indications in the Guidelines
  - Palpitations: 40+ publications*
  - ICM indications in the Guidelines
  - Cryptogenic Stroke: 40+ publications*
  - ICM in the AF Guidelines
  - AF Management: 200+ publications*
  - High Risk AF*

*Abstracts and manuscripts
The majority of abstracts and manuscripts are Reveal ICM
REVEAL
LINQ™ ICM
PROCEDURE
DATA
REAL-WORLD PROCEDURE EXPERIENCE WITH REVEAL LINQ™ ICM
REVEAL LINQ ICM REGISTRY: MITTAL, WSA POSTER 2015 (BEIJING, CHINA)1

- Ongoing prospective, global, multi-center registry evaluating real-world performance of Reveal LINQ™ ICM
- N=203 patients enrolled at centers in the US (8), Europe (4) and the Middle East (1) at ≥ 1 month post-insertion
- 52% female, age: 61 ± 17 y
- All insertions were successful
- 1 procedure-related AE (0.49%) and 2 SAEs (0.98%):  
  - 2 infections (0.98%) (1 AE and 1 SAE requiring explant)
  - 1 insertion pain SAE (requiring explant)

Reveal LINQ ICM can be inserted easily and safely in a variety of settings within the hospital

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=203</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Primary Indications for ICM (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>85 (42%)</td>
</tr>
<tr>
<td>Suspected AF/AF Management</td>
<td>57 (28%)</td>
</tr>
<tr>
<td>AF Ablation Monitoring</td>
<td>26 (13%)</td>
</tr>
<tr>
<td><strong>Main Referring Physicians</strong></td>
<td></td>
</tr>
<tr>
<td>Electrophysiologist/Implanting Cardiologist</td>
<td>98 (48%)</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>80 (39%)</td>
</tr>
<tr>
<td>General Practitioner</td>
<td>11 (5%)</td>
</tr>
<tr>
<td><strong>Main Implanting Physicians</strong></td>
<td></td>
</tr>
<tr>
<td>Electrophysiologist</td>
<td>190 (94%)</td>
</tr>
<tr>
<td>Interventional Cardiologist</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Pre-procedural Antibiotics</td>
<td>99 (49%)</td>
</tr>
<tr>
<td>Post-procedural Antibiotics</td>
<td>10 (5%)</td>
</tr>
<tr>
<td><strong>Location of Procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Electrophysiology Lab</td>
<td>118 (58%)</td>
</tr>
<tr>
<td>Clean Room</td>
<td>50 (25%)</td>
</tr>
<tr>
<td>Catheterization Lab</td>
<td>31 (15%)</td>
</tr>
<tr>
<td>Electrophysiology Lab Holding Area</td>
<td>4 (2%)</td>
</tr>
<tr>
<td><strong>Anesthesia</strong></td>
<td></td>
</tr>
<tr>
<td>Local Anesthetic</td>
<td>165 (81%)</td>
</tr>
<tr>
<td>Moderate Intravenous Sedation</td>
<td>36 (18%)</td>
</tr>
<tr>
<td>General</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>None</td>
<td>6 (3%)</td>
</tr>
<tr>
<td><strong>Wound Closure Method</strong></td>
<td></td>
</tr>
<tr>
<td>Steri-strips</td>
<td>141 (70%)</td>
</tr>
<tr>
<td>Staples</td>
<td>57 (28%)</td>
</tr>
<tr>
<td>Suture(s)</td>
<td>49 (24%)</td>
</tr>
<tr>
<td>Surgical Glue</td>
<td>35 (17%)</td>
</tr>
</tbody>
</table>

1. Mittal et al. Real-world procedure experience with the Reveal LINQ™ insertable cardiac monitoring system: A global multicenter registry. WSA congress 2015, Beijing, China
REVEAL LINQ™ ICM SAFETY PROFILE: RESULTS FROM TWO TRIALS
REVEAL LINQ ICM USABILITY AND REGISTRY: MITTAL, PACE 2015

- Procedure-related events from a controlled clinical trial (Reveal LINQ™ ICM Usability study) and a real-world Registry (Reveal LINQ ICM Registry)
- N=273 patients
  - 151 Reveal LINQ ICM Usability patients (followed for 1 month) – 16 centers
  - 122 Reveal LINQ ICM Registry patients (all events reported upon occurrence) – 7 centers
- Infection rates were low in both studies: Reveal LINQ ICM Usability (n=2; 1.3%); Reveal LINQ ICM Registry (n=2; 1.6%)
- Total procedure-related SAEs were low (n=3; 1.1%)

Reveal LINQ ICM can be inserted with minimal associated adverse events

<table>
<thead>
<tr>
<th>Procedure Characteristics</th>
<th>Usability (n=151)</th>
<th>Registry (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheterization or electrophysiology lab</td>
<td>130 (86.1%)</td>
<td>94 (77.0%)</td>
</tr>
<tr>
<td>Clean room</td>
<td>15 (9.9%)</td>
<td>28 (23.0%)</td>
</tr>
<tr>
<td>Operating room</td>
<td>2 (1.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Practice office</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local anesthetic</td>
<td>150 (99.3%)</td>
<td>98 (80.0%)</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>4 (2.6%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Moderate intravenous sedation</td>
<td>None</td>
<td>24 (19.7%)</td>
</tr>
<tr>
<td>None</td>
<td>1 (0.7%)</td>
<td>4 (3.3%)</td>
</tr>
<tr>
<td>Preprocedural antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>73 (48.3%)</td>
<td>51 (41.6%)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>60 (39.7%)</td>
<td>NR</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>Other</td>
<td>70 (51.7%)</td>
<td>NR</td>
</tr>
<tr>
<td>Incision site preparation prior to insertion</td>
<td>0 (0.0%)</td>
<td>98 (77.2%)</td>
</tr>
<tr>
<td>No</td>
<td>0 (0.0%)</td>
<td>98 (77.2%)</td>
</tr>
<tr>
<td>Yes</td>
<td>150 (99.3%)</td>
<td>NR</td>
</tr>
<tr>
<td>Betadine</td>
<td>48 (31.8%)</td>
<td>NR</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>73 (48.3%)</td>
<td>NR</td>
</tr>
<tr>
<td>Isoniazid (antibacterial)</td>
<td>17 (11.9%)</td>
<td>NR</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>11 (7.3%)</td>
<td>NR</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0%)</td>
<td>NR</td>
</tr>
<tr>
<td>Use of provided incision tool</td>
<td>151 (100%)</td>
<td>78 (62.2%)</td>
</tr>
<tr>
<td>Use of provided insertion tool</td>
<td>145 (95.7%)</td>
<td>NR</td>
</tr>
<tr>
<td>Thoracic anatomical location</td>
<td></td>
<td>111 (91.0%)</td>
</tr>
<tr>
<td>Sewt</td>
<td>139 (92.1%)</td>
<td>88 (72.7%)</td>
</tr>
<tr>
<td>Good</td>
<td>9 (6.0%)</td>
<td>8 (6.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.0%)</td>
<td>20 (17.5%)</td>
</tr>
<tr>
<td>Device fixation with sutures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (14.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>No</td>
<td>129 (85.4%)</td>
<td>112 (91.8%)</td>
</tr>
<tr>
<td>Not specified</td>
<td>0 (0.0%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Wound closure method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suture</td>
<td>64 (42.4%)</td>
<td>20 (16.4%)</td>
</tr>
<tr>
<td>Staples</td>
<td>None</td>
<td>31 (25.4%)</td>
</tr>
<tr>
<td>Surgical glue</td>
<td>14 (9.3%)</td>
<td>29 (23.6%)</td>
</tr>
<tr>
<td>Adhesive strips</td>
<td>60 (39.7%)</td>
<td>55 (45.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (8.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Suture and adhesive strips or glue</td>
<td>11 (7.3%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

1. Mittal et al. Safety profile of a miniaturized insertable cardiac monitor: results from two prospective trials. PACE 2015; 38:1464-1469
REVEAL LINQ™ ICM INSERTIONS IN CATH LAB VS RECOVERY ROOM
HARRINGTON, HRS POSTER 2015¹

- N=83 patients were inserted with Reveal LINQ™ ICM and follow for 172 ± 105 days:
  - 44 in cardiac catheterization lab
  - 39 in sterile recovery room
- Optional use of peri-procedural IV Cephazolin
- No infections were observed
- 2 complications resulting in explant:
  - 1 extrusion due to physical exertion 62 days post-insertion (recovery room group)
  - 1 extrusion due to traumatic injury 21 days post-insertion (cath lab group)

### Insertion of Reveal LINQ ICM outside of the cath lab yet within the walls of the hospital is feasible

<table>
<thead>
<tr>
<th></th>
<th>Catheterization Laboratory (n = 44)</th>
<th>Recovery Room (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57 ± 14</td>
<td>57 ± 17</td>
<td>0.952</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>29 (66%)</td>
<td>25 (64%)</td>
<td>0.863</td>
</tr>
<tr>
<td>BMI, (kg/m²)</td>
<td>28 ± 5</td>
<td>29 ± 5</td>
<td>0.322</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>26 (59%)</td>
<td>23 (59%)</td>
<td>0.996</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3 (7%)</td>
<td>5 (13%)</td>
<td>0.352</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>3 (7%)</td>
<td>3 (8%)</td>
<td>0.875</td>
</tr>
<tr>
<td>Strokes/TIA, n (%)</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>0.812</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td>1 (2.2%)</td>
<td>1 (2.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Peri-procedural antibiotics, n (%)</td>
<td>10 (23%)</td>
<td>8 (21%)</td>
<td>0.204</td>
</tr>
</tbody>
</table>

¹ Harrington et al. Feasibility and safety of Reveal LINQ insertion in sterile recovery room versus cardiac catheterization laboratory environment. Heart Rhythm 2015 12 Suppl 1 (S328-S329)
N=489 patients from the ongoing Reveal LINQ™ ICM Registry had device insertion:
- In-lab (Cath/EP lab/OR) (n=304)
- Out-of-lab (clean/procedure room or EP lab holding area (n=185)

There was no difference in procedure-related adverse events (1.3% in-lab vs 1.6% out-of-lab)

Of 489 procedures, only one resulted in a serious infection requiring explant
  - Overall infection rate: 0.8%
    - 2 (0.7%) In-lab; 1 serious
    - 2 (1.1%) Out-of-lab: both minor

Other adverse events: 2 erosions and 1 migration

While significant procedure differences were observed between in-lab vs. out-of lab, this had no apparent effect on the occurrence of infections or other adverse events

<table>
<thead>
<tr>
<th>Procedure Characteristics</th>
<th>In-lab (304)</th>
<th>Out-of Lab (185)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthesia</td>
<td>252 (82.9%)</td>
<td>184 (99.5%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Moderate IV sedation</td>
<td>61 (20.1%)</td>
<td>1 (0.5%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pre-operative abx</td>
<td>121 (39.8%)</td>
<td>8 (4.3%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Post-operative abx</td>
<td>46 (15.1%)</td>
<td>3 (1.6%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Use incision of tool</td>
<td>225 (74%)</td>
<td>70 (37.8%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Use of insertion tool</td>
<td>234 (77%)</td>
<td>168 (90.8%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Device fixation</td>
<td>21 (6.9%)</td>
<td>1 (0.5%)</td>
<td>&lt; 0.0002</td>
</tr>
<tr>
<td>Wound closure: Suture</td>
<td>10 (3.3%)</td>
<td>27 (14.6%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Staples</td>
<td>112 (36.8%)</td>
<td>103 (55.7%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adhesive strips</td>
<td>183 (60.2%)</td>
<td>103 (55.7%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Real-world use of antibiotics (abx) in Reveal LINQ™ ICM insertion procedures (Reveal LINQ ICM Registry)

- N=375 patients from 14 US centers
- 66.4% of patients did not receive pre-procedural abx
- Overall infection rate: 1.1% (n=4)
  - Group without abx (n=249): 0.8% (n=2)
  - Group with abx (n=126): 1.6% (n=2)
- 60.5% of procedures were performed in the cath/EP lab; the rest out of the lab but within hospital

Real-world insertions of Reveal LINQ ICM in the US were mainly performed without the use of prophylactic antibiotics and are associated with a low infection rate

COST COMPARISON: PROCEDURE ROOM vs. EP/CATH LAB
KANTERS, EUROPACE

- Cost comparison of Reveal LINQ™ ICM insertion in a procedure room vs. Reveal™ XT in cath or EP lab
- Bottom-up costing analysis using data from Netherlands, France and the UK
- Reveal LINQ ICM procedure:
  - Shorter waiting time between decision and implant
  - Shorter room occupancy (55 min)
  - Shorter procedure time (9.4 min; 5-10 min shorter)
  - May be performed by less qualified personnel
  - No antibiotics needed
  - Decrease of disposable materials due to insertion kit
- Procedure room savings in the UK: €662

Miniaturization of technology saves hospital resources and improves patient care pathway

<table>
<thead>
<tr>
<th></th>
<th>Reveal XT in cath lab</th>
<th>Reveal LINQ in procedure room</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure-related costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labor</td>
<td>€104</td>
<td>€42</td>
<td>-€63</td>
</tr>
<tr>
<td>Medication</td>
<td>€6</td>
<td>€2</td>
<td>-€4</td>
</tr>
<tr>
<td>Materials</td>
<td>€23</td>
<td>€20</td>
<td>-€3</td>
</tr>
<tr>
<td>Room-related costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labor</td>
<td>€8</td>
<td>€7</td>
<td>-€1</td>
</tr>
<tr>
<td>Instruments/equipment</td>
<td>€100</td>
<td>€5</td>
<td>-€95</td>
</tr>
<tr>
<td>Cleaning</td>
<td>€57</td>
<td>€4</td>
<td>-€53</td>
</tr>
<tr>
<td>Overhead costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overhead costs</td>
<td>€197</td>
<td>€30</td>
<td>-€167</td>
</tr>
<tr>
<td>Hospital admission costs</td>
<td></td>
<td>€276</td>
<td>-€276</td>
</tr>
<tr>
<td>Total costs difference</td>
<td></td>
<td></td>
<td>-€662</td>
</tr>
</tbody>
</table>

The net cost impact for hospital depends on the cost difference between the two devices.

Reveal LINQ™ ICM can be inserted easily and safely, in a variety of settings\(^1\)\(^-\)\(^4\).

Moving the Reveal LINQ ICM insertion procedure to clean rooms/EP lab holding areas within the hospital appears feasible without compromising safety\(^4\).

Most Reveal LINQ ICM insertions in the US were performed without the use of prophylactic antibiotics and are associated with a low infection rate\(^5\).

Insertion of Reveal LINQ ICM outside the cath/EP lab is more cost-effective than Reveal™ XT ICM inserted in cath/EP lab\(^6\).

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1. Mittal et al. Real-world procedure experience with the Reveal LINQ™ insertable cardiac monitoring system: a global multicenter registry. WSA congress 2015, Beijing, China (not published)
2. Mittal et al. Safety profile of a miniaturized insertable cardiac monitor: results from two prospective trials. PACE 2015;00:1-6
REVEAL™ ICM SENSING & ALGORITHM PERFORMANCE
Phase 1 of the Reveal LINQ™ ICM Usability study (to assess sensing and wireless capabilities)

- N=30; 1 month follow-up
- Automatic transmissions were successful 79.5% of the time; transmission failures were followed by successful automated or manual transmissions on a subsequent day
- 217 arrhythmic episodes stored in devices during follow-up
- All implants were successful
- No serious procedure- or system- related adverse events occurred during follow-up

Reveal LINQ ICM supports arrhythmia detection and monitoring, achieving adequate sensing performance

- R-wave amplitudes were 584 ± 325 µV at implant and 596 ± 336 µV at 1 month (P=0.8) (benchmark ≥ 200 µV)

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REVEAL LINQ™ ICM SENSING PERFORMANCE
REVEAL LINQ ICM USABILITY: PÜRERFELLNER, ACC POSTER 2015

- N=151 at 1 month follow-up
- All insertions were successful
- Implant location: “Best”: 92%; “Good”: 6%; Other: 2%
- Sensing: R-wave amplitudes:
  - At implant: 0.543 ± 0.295 mV
  - At one month: 0.599 ± 0.314 mV

Reveal LINQ™ ICM supports arrhythmia detection with a simplified procedure, achieving stable sensing performance.

1. Pürerfellner et al. The miniaturized Reveal LINQ™ insertable cardiac monitoring system: a description of the procedure experience. JACC 2015; 65(10_S)
REVEAL LINQ™ ICM SENSING IN DIFFERENT BODY TYPES
REVEAL LINQ ICM USABILITY: DEKKER, ESC POSTER 2015

- N=151 patients at 1-month follow-up
- Wide range of BMI (18.2 – 42.1)
- High BMI was associated with reduced R-wave values at insertion ($p = 0.002$) and 1 month follow-up ($p = 0.001$)
- However, sensing was over the minimum 0.2mV at implant (97.3%) and 1 month follow-up (96.6%)
- No device migration was detected
AF ALGORITHM PERFORMANCE OF REVEAL™ XT
XPECT: HINDRICKS, CIRC ARRHYTHM EP 2010¹

- Prospective, multi center study evaluating detection performance of the AF algorithm
- N=247 patients with Reveal™ XT ICM
- Patients with paroxysmal AF
- 98.5% AF detection accuracy

AF Burden (% time in AF) was accurately measured in the large majority of patients

### Sensitivity and Specificity

<table>
<thead>
<tr>
<th></th>
<th>Pts w/AF</th>
<th>Pts w/o AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>XT detected</td>
<td>73</td>
<td>19</td>
</tr>
<tr>
<td>XT non-detected</td>
<td>3</td>
<td>111</td>
</tr>
</tbody>
</table>

- Sensitivity: 96.1%
- Specificity: 85.4%

AF ALGORITHM IMPROVEMENT IN REVEAL LINQ™ ICM
PÜRERFELLNER, HEART RHYTHM 2014¹

- Validation of new algorithm in Reveal LINQ™ ICM, designed to reduce inappropriate AF detection by identifying a single P-wave between 2 R waves

- Holter and ICM data from 206 patients (XPECT trial)

The improved algorithm reduced inappropriately detected episodes (by 46%) and duration (by 55%) with minimal reduction in sensitivity

Reveal LINQ™ ICM Usability Study: N=151 patients

24h-Holter data were compared to ICM data at 1 month follow-up

38 subjects had 112 true AF episodes

The overall accuracy of the ICM was 99.4%

High correlation between AF burden measured with the ICM and the Holter (Pearson Coefficient = 0.995)

Reveal LINQ ICM reliably detects the presence or absence of AF compared with Holter

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-based results</strong></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97.4</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.0</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>92.5</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>99.0</td>
</tr>
<tr>
<td>Accuracy</td>
<td>97.1</td>
</tr>
<tr>
<td><strong>Main Implanting Physicians</strong></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98.4</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.5</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>97.2</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>99.7</td>
</tr>
<tr>
<td>Accuracy</td>
<td>99.4</td>
</tr>
<tr>
<td><strong>Episode-based results</strong></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97.1 (97.1-97.2)</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>90.4 (97.6-96.2)</td>
</tr>
</tbody>
</table>

REAL-WORLD PERFORMANCE OF REVEAL LINQ™ ICM AF ALGORITHM
MITTAL, HEART RHYTHM

- PPV depends on 3 things:
  - Incidence of AF in population
  - Duration of the episode
  - Sensitivity programming

- N=3759 patients from Discovery™Link database with at least 3 mo follow-up

- True positive rate by population:

<table>
<thead>
<tr>
<th>Reason for Monitoring</th>
<th>Device Programming AF Detection Parameters</th>
<th>Optimization Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope 3.4% (n = 1604)</td>
<td>AF-only</td>
<td>Least</td>
</tr>
<tr>
<td>Cryptogenic Stroke 28% (n = 1106)</td>
<td>AF-only</td>
<td>Balanced</td>
</tr>
<tr>
<td>AF Ablation/ Management 28% (n = 1049)</td>
<td>AF-only</td>
<td>Nominal</td>
</tr>
</tbody>
</table>

- False positive rate by population:

<table>
<thead>
<tr>
<th>Reason for Monitoring</th>
<th>True Positive Rate</th>
<th>False Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope 3.4% (n = 1604)</td>
<td>0.23</td>
<td>0.05</td>
</tr>
<tr>
<td>Cryptogenic Stroke 28% (n = 1106)</td>
<td>3.8</td>
<td>0.65</td>
</tr>
</tbody>
</table>

- False positive rate is manageable for clinical review in all populations

SENSING AND ALGORITHM PERFORMANCE - EVIDENCE SUMMARY
REVEAL™ ICM

- Reveal LINQ™ ICM achieves clinically required sensing performance
  1-3

- AF algorithm in Reveal™ XT ICM and Reveal LINQ ICM accurately detects AF burden in the majority of patients
  4-5

- Improved AF algorithm in Reveal LINQ ICM reduces inappropriately detected episodes and duration compared to its predecessor
  5

- Reveal LINQ ICM accurately detects AF compared with Holter
  6

- Positive predictive value for the AF algorithm is dependent on incidence of AF with in the population, duration of episodes and sensitivity programming
  6

2. Pürerfellner et al. The miniaturized REVEAL LINQ™ insertable cardiac monitoring system: a description of the procedure experience. JACC 2015; 65(10_S)
**SYNCOPE**

*Syncope*, the medical term for *fainting* or *passing out*, is defined as a transient loss of consciousness (TLOC) and postural tone characterized by rapid onset, short duration, and spontaneous recovery, due to global cerebral hypoperfusion (low blood flow to the brain) that most often results from hypotension (low blood pressure).
BACKGROUND: SYNCOPE

**Magnitude**
- 40% of the population will have at least one syncope event

**Inpatient Challenge**
- Approximately half of patients admitted to hospital leave without a diagnosis

**Patient’s Frustration**
- In reaching a diagnosis, patients see 3 different specialists, undergo 13 tests, and 1/3 have significant associated trauma

**Cardiac Causes**
- Cardiac syncope is common, doubles the risk of death, and is associated with a 6-month mortality rate greater than 10%

3. Edvardsson N et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. Europace 2011;13:262-9
SYNCOPE: OCCURRENCE & IMPACT

- Syncope accounts for 3-5% of emergency department visits and 1-3% of all hospital admissions\(^1,2\)
- Cardiac syncope carries a 6-month mortality rate of greater than 10% and doubles the risk of death\(^3\)

---

2. Silverstein MD et al. Patients with syncope admitted to medical intensive care units. JAMA 1982;248:1185-1189
Prior to ICM implant, only 12% of patients had tests within current guideline recommendations (mean: £710); up to 10% of patients had tests exceeding £3540

The early use of specialized tests and the repetition of tests can be reduced

ICMs should be implanted earlier in the care pathway, in accordance to guidelines

---

1. Edvardsson N, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry Europace 2011;13:262-269
USE OF ICM IN SYNCOPE PATHWAY REMAINS INEFFICIENT
EHRA SURVEY, EUROPACE 2014

- 42 European centers evaluated use of ICM in clinical practice
- Less than 20% of patients with unexplained syncope received an ICM in accordance with guidelines
- Reveal LINQ™ ICM was the most used ICM (57% of centers)

There is poor adherence to guidelines regarding use of ICM in unexplained syncope

Review of 2,106 patients presenting with syncope at the ER and admitted to a hospital

In nearly half of the patients, a diagnosis or etiology remained unknown despite extensive testing

“Perhaps the finding in this study that causes the most concern is the extent to which unhelpful, and presumably unnecessary, testing in the evaluation of syncope continues to be performed.”

<table>
<thead>
<tr>
<th>Test</th>
<th># of Tests Performed</th>
<th>Helped Determine Etiology</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head CT Scan</td>
<td>1,327</td>
<td>7 (0.5%)</td>
<td>$696,675</td>
</tr>
<tr>
<td>Carotid Ultrasonography</td>
<td>267</td>
<td>2 (1.0%)</td>
<td>$117,480</td>
</tr>
<tr>
<td>EEG</td>
<td>174</td>
<td>1 (0.6%)</td>
<td>$65,946</td>
</tr>
<tr>
<td>Head MRI</td>
<td>154</td>
<td>3 (2.0%)</td>
<td>$173,558</td>
</tr>
<tr>
<td>Total Cost</td>
<td></td>
<td></td>
<td>$1,053,659</td>
</tr>
</tbody>
</table>

## SYNCOPE DIAGNOSIS
### TESTING OPTIONS AND THEIR DIAGNOSTIC YIELDS

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>2-11%(^1)</td>
</tr>
<tr>
<td>Holter Monitoring</td>
<td>2%(^2)</td>
</tr>
<tr>
<td>External Loop Recorder</td>
<td>20%(^3)</td>
</tr>
<tr>
<td>Tilt Table</td>
<td>11-87%(^4,5)</td>
</tr>
<tr>
<td>EP Study without structural heart disease</td>
<td>11%(^6)</td>
</tr>
<tr>
<td>Neurological (CT scan, carotid doppler)</td>
<td>0-4%(^5)</td>
</tr>
<tr>
<td>Reveal ICM</td>
<td>43-88%(^3,7,8)</td>
</tr>
</tbody>
</table>

Patients with unexplained syncope (N=60)

Randomized to Reveal™ ICM or conventional testing (Holter + tilt table + EP testing)

Over 1-year follow-up, Reveal ICM provided superior diagnostic yield (52% vs 20%, p=0.012)

Bradycardia was the most frequent cause of syncope (90%)

Patient flow diagram shows higher diagnostic yield with Reveal ICM monitoring

Patients with unexplained syncope and without a pacing indication following basic clinical work-up, tilt-test and 24-h Holter

Randomized to Reveal™ Plus (n=103) or conventional testing (n=98)

Median follow-up: 17 months

More ICM patients received an ECG diagnosis than by conventional testing (43% vs 6%; HR 6.53 [95% CI 3.73-11.4]; p<0.001)

Time to ECG directed therapy was 6.5x quicker for ILR group (P<0.001)

SUPERIOR DIAGNOSTIC YIELD THAN CONVENTIONAL TESTS
DA COSTA, ARCH CARDIOVASC DIS 2013¹

- Multi-center, randomized to Reveal ICM (n=41) or conventional follow-up (n=37)
- Patients with bundle branch block, unexplained syncope and negative EPS
- During 2.5-y follow-up, more recurrent significant arrhythmias were detected in the ICM group (37% vs 11%; p=0.01)
- ICM time to diagnosis: 6 mo (IQR 1-23 mo)
- AV Block was the mechanism for syncope recurrence in 75% of patients
- 24% of all patients received an IPG/ICD


ICM strategy was largely superior in detecting recurrent arrhythmic events

Table 2: Comparison between the ILR and conventional groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 41)</th>
<th>Group 2 (n = 37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>15 (36.6)</td>
<td>4 (10.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>AV block III</td>
<td>11 (26.8)</td>
<td>3 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>5 (7.3)</td>
<td>1 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or number (%).
AV: atrioventricular; BBB: bundle branch block; HV: His to ventricular; ILR: implantable loop recorder; LVEF: left ventricular ejection fraction.
N=78 patients randomized 1:1 to Reveal/Reveal Plus ICM or conventional evaluation (CONV)

Follow-up: 14 months

ICM provided superior diagnostic yield than CONV: 46% vs. 5%, p<0.001

ICM patients had lower healthcare-related costs:

- Shorter hospitalization
- Received fewer advanced cardiology tests

9x more ICM patients diagnosed

<table>
<thead>
<tr>
<th>Cause of syncope</th>
<th>ILR (n = 39)</th>
<th>CONV (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasovagal</td>
<td>4 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV block</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>1.0</td>
</tr>
<tr>
<td>SN disease</td>
<td>4 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychogenic</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-syncopal (epilepsy)</td>
<td>1 (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Supposed 8 (20)

Data are number (%).
AV: atrioventricular; CONV: conventional evaluation; ILR: implantable loop recorder; SN: sinus node.

ICM GUIDES EFFECTIVE PACEMAKER THERAPY
ISSUE 3: BRIGNOLE, CIRCULATION 2012

- N=511 patients with neurally mediated syncope (NMS) received an ICM to screen for asystolic neurally mediated syncope
- 89 patients had asystolic syncope identified by ICM within 12 months
  - 77 patients were randomized (1:1) and received IPG (ON vs OFF)
- 2-year syncope recurrence rate was:
  - 57% with IPG OFF
  - 25% with IPG ON (HR 57%, p=0.039)
- ICM is effective in stratifying patients, driving specific interventions that improve outcomes in neurally mediated syncope

32% absolute reduction in syncope recurrence with IPG therapy

PICTURE STUDY: OVERVIEW

- **PICTURE** was a prospective, multi-center, observational study conducted from November 2006 to October 2009.

- **PICTURE** aimed to:
  - Collect information on the use of the Reveal™ ICM in the syncope patient care pathway.
  - Investigate Reveal ICM’s effectiveness in the diagnosis of unexplained recurrent syncope in everyday clinical practice.

- 71 sites from 11 European and Middle Eastern countries.

PICTURE STUDY: METHODS & CHARACTERISTICS\(^1\)

**Methods**

- Patients were eligible if they had recurrent unexplained syncope or pre-syncope
- Patients were followed until the first recurrence of a syncopal event leading to a diagnosis, or for at least 1 year
- 570 of 650 enrolled subjects had available follow-up visit data and were included in the analysis

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>(570 (100%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>306 (54%)</td>
</tr>
<tr>
<td>Age +/- SD</td>
<td>61 +/- 17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>277 (49%)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>84 (15%)</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>57 (10%)</td>
</tr>
<tr>
<td>Age at first syncope</td>
<td>55 +/- 20</td>
</tr>
<tr>
<td>Previous syncopal events (median)</td>
<td>4</td>
</tr>
</tbody>
</table>

1. Edvardsson N, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry Europace 2011;13:262-269
PICTURE STUDY RESULTS: PATIENT EXPERIENCE

- 70% of patients had been hospitalized at least once for syncope
- 36% of patients had experienced significant trauma in association with a syncopal episode
- Overall, patients had seen an average of 3 different specialists for their syncope

PICTURE STUDY RESULTS\(^1\)
DIAGNOSTIC TESTS PERFORMED BEFORE REVEAL™ ICM IMPLANT

The median number of tests performed per patient was 13
(inter-quartile range 9 - 20)

<table>
<thead>
<tr>
<th>Test</th>
<th>Total recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard ECG</td>
<td>556 (98%)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>490 (86%)</td>
</tr>
<tr>
<td>Basic laboratory tests</td>
<td>488 (86%)</td>
</tr>
<tr>
<td>Ambulatory ECG monitoring</td>
<td>382 (67%)</td>
</tr>
<tr>
<td>In-hospital ECG monitoring</td>
<td>311 (55%)</td>
</tr>
<tr>
<td>Exercise testing</td>
<td>297 (52%)</td>
</tr>
<tr>
<td>Orthostatic blood pressure measurements</td>
<td>275 (48%)</td>
</tr>
<tr>
<td>MRI/CT scan</td>
<td>267 (47%)</td>
</tr>
<tr>
<td>Neurological or psychiatric evaluation</td>
<td>270 (47%)</td>
</tr>
<tr>
<td>EEG</td>
<td>222 (39%)</td>
</tr>
<tr>
<td>Carotid sinus massage</td>
<td>205 (36%)</td>
</tr>
<tr>
<td>Tilt test</td>
<td>201 (35%)</td>
</tr>
<tr>
<td>Electrophysiology testing</td>
<td>144 (25%)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>133 (23%)</td>
</tr>
<tr>
<td>External loop recording</td>
<td>67 (12%)</td>
</tr>
<tr>
<td>ATP test</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>Other tests</td>
<td>52 (9%)</td>
</tr>
<tr>
<td>No tests performed</td>
<td>1 (0%)</td>
</tr>
</tbody>
</table>

1. Edvardsson N, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry Europace 2011;13:262-269
PICTURE STUDY RESULTS¹
SYNCOPE RECURRENCE AND DIAGNOSTIC YIELD

- During follow-up, 38% of patients had a recurrence of syncope within 1 year

- Reveal™ ICMs guided diagnosis in 78% of patients with recurrence

¹ Edvardsson N, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry Europace 2011;13:262-269
PICTURE STUDY¹
TREATMENT DECISIONS MADE IN RELATION TO SYNCOPE DIAGNOSIS

Of the 170 Reveal ICM-guided diagnoses, 75% were cardiac-related

¹ Edvardsson N, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry Europace 2011;13:262-269
REduced time to diagnosis and treatment
DRAK-HERNANDEZ, REV ESP CARDIOL 2013¹

- N=109 patients inserted with Reveal™ DX/XT for unexplained syncope
- Retrospective assessment of patients followed with CareLink™ Network or conventional on-site follow-up
- Remote monitoring reduced:
  - Time to diagnosis (56 days vs. 260 days, p<0.001)
  - Time to initiation of specific treatment (73 days vs. 260 days, p<0.001)

Remote monitoring of ICM reduced time to treatment by 187 days

ICMS ARE A COST-EFFECTIVE DIAGNOSTIC TOOL
RAST: KRAHN, J AM COLL CARDIOL 2003

- N=60 patients with unexplained syncope were randomized (1:1) to:
  - Conventional testing (2-4 week ELR + tilt table + EP testing) (n=30)
  - 1-year ICM monitoring with Reveal (n=30)
  - ICM monitoring as a primary strategy yielded more diagnoses than conventional testing (47% vs. 20%, p=0.029)
  - ICM strategy was more cost-effective and efficient than conventional testing

Primary monitoring with ICM reduced cost by $2,016 (p=0.002)

ICMS ARE A COST-EFFECTIVE DIAGNOSTIC TOOL
EASYAS: FARWELL, EUROPEAN HEART J 2004¹

- N=201 patients with unexplained syncope were randomized (1:1) to conventional testing or ICM (Reveal Plus) and followed for 6 months
- ICM monitoring yielded more ECG diagnoses than conventional testing (33% vs. 4%, HR 7.9 [95% CI [2.8-22.3]; p<0.0001)
- ICM patients had fewer post-randomization investigations and hospital days, resulting in cost savings

### Significant decrease in costs in ICM patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Reveal</th>
<th>Control</th>
<th>Difference in cost (£) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography head</td>
<td>4</td>
<td>8</td>
<td>-5.30 (-13.86 to 1.29)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>1</td>
<td>1</td>
<td>-0.05 (-3.06 to 2.91)</td>
</tr>
<tr>
<td>Electroencephalogram</td>
<td>0</td>
<td>2</td>
<td>-2.04 (-4.80 to 0.72)</td>
</tr>
<tr>
<td>Carotid doppler</td>
<td>3</td>
<td>5</td>
<td>-2.19 (-8.14 to 2.89)</td>
</tr>
<tr>
<td>Echo</td>
<td>12</td>
<td>15</td>
<td>-8.54 (-25.31 to 6.54)</td>
</tr>
<tr>
<td>24-hr Holter</td>
<td>4</td>
<td>11</td>
<td>-7.34 (-15.08 to -0.37)</td>
</tr>
<tr>
<td>ELR “R Test”</td>
<td>5</td>
<td>28</td>
<td>-29.84 (-43.49 to -18.04)</td>
</tr>
<tr>
<td>Electrophysiologic study</td>
<td>0</td>
<td>1</td>
<td>-6.12 (-17.90 to 5.65)</td>
</tr>
<tr>
<td>Investigations</td>
<td>£34.0</td>
<td>£95.4</td>
<td>-£61.43 (-£92.92 to -£35.16)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>£379</td>
<td>£1,090</td>
<td>-£747.30 (-£2,728.48 to £72.75)</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td><strong>£406</strong></td>
<td><strong>£1,210</strong></td>
<td>-£808.72 (-£2,766.22 to -£123.42)</td>
</tr>
</tbody>
</table>

ICMS ARE A COST-EFFECTIVE DIAGNOSTIC TOOL

DAVIS, EUROPACE 2012¹

- Patients with unexplained or suspected arrhythmic syncope after initial and specialist cardiovascular assessment

- ICM monitoring resulted in cost savings by reducing recurrent arrhythmias and in QALY gains (quality-adjusted life years)

- The ICER (incremental cost-effectiveness ratio) was below the £20,000-30,000 willingness-to-pay UK threshold (£17,400 per QALY gained)

- Model developed to inform NICE guidance for ICM monitoring

---

1. Davis S, et al. Implantable loop recorders are cost-effective when used to investigate transient loss of consciousness which is either suspected to be arrhythmic or remains unexplained. Europace. 2012;14:402-409
ICMS ARE A COST-EFFECTIVE DIAGNOSTIC TOOL
PROVIDENCIA, BMC CARDIOVASC DIS 2014¹

- Markov model to estimate the financial impact of early referral for ICMs vs. conventional testing (CONV) in the context of Portugal
- N=197 patients with unexplained syncope
- Over 3 years, the costs of hospital admissions for ICM group were 23% lower than CONV
- The use of ICMs leads to earlier diagnosis and fewer hospital admissions/tests, allowing significant cost savings over lifetime

Lifetime savings for ICM group: €1563-€4940 per patient

ESC SYNCOPE GUIDELINES, *EUROPEAN HEART JOURNAL* 2009
RECOMMENDATIONS FOR THE USE OF ICM MONITORING

| Class I ICM Guidelines | - Indicated in early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high risk criteria and a high likelihood of recurrence within battery longevity of the device
|                        | - Indicated in high risk individuals in whom comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment
| Class IIa ICM Guidelines | Consider to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain reflex syncope presenting with frequent or traumatic syncopal episodes |

**NICE CLINICAL SYNCOPE GUIDELINE CG109, 2010**

DIAGNOSTIC TESTING ACCORDING TO FREQUENCY OF SYMPTOMS

“For people with a suspected cardiac arrhythmic cause of syncope, offer an ambulatory ECG. Do not offer a tilt test as a first-line investigation”

<table>
<thead>
<tr>
<th>Frequency of syncope</th>
<th>Suggested ECG monitoring technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several times a week</td>
<td>24-48h Holter monitoring</td>
</tr>
<tr>
<td>Every 1-2 weeks</td>
<td>External loop recorder</td>
</tr>
<tr>
<td>Less than once per month</td>
<td>Implantable loop recorder</td>
</tr>
</tbody>
</table>

## ESC GUIDELINES ON CARDIAC PACING AND CRT, *EUR HEART J* 2013

### DIAGNOSTIC TESTING ACCORDING TO FREQUENCY OF SYMPTOMS

<table>
<thead>
<tr>
<th>Frequency of symptoms</th>
<th>Suggested ECG monitoring technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>24 h Holter, in-hospital telemetric monitoring</td>
</tr>
<tr>
<td>Every 2–3 days</td>
<td>48–72 h Holter, in-hospital telemetric monitoring</td>
</tr>
<tr>
<td>Every week</td>
<td>7 day Holter or external loop recorder</td>
</tr>
<tr>
<td>Every month</td>
<td>14–30 days external loop recorder</td>
</tr>
<tr>
<td>Less than once per month</td>
<td>Implantable loop recorder</td>
</tr>
</tbody>
</table>

*ECG = electrocardiogram*

---

### EVIDENCE SUMMARY

**ICMS FOR UNEXPLAINED SYNCOPE**

- Syncope care pathway remains inefficient, despite guidelines. With high detection sensitivity, ICMs should be implanted earlier in evaluation as supported by guidelines\(^1\)-\(^4\)

- In unexplained syncope, ICMs provide superior diagnostic yield (37-52%) compared to conventional tests (6-20%), increasing rate of guideline directed therapy\(^5\)-\(^8\)

- In neurally-mediated syncope ICM guides pacemaker therapy, resulting in 57% reduced risk of recurrent syncope\(^9\)

- ICM with remote monitoring reduces time to diagnosis and targeted treatment\(^10\)

- ICMs are cost-effective \(^5\), \(^11\)-\(^13\)

---

2. Edvardsson N et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. Europace 2011;13:262-9269
12. Davis S, et al. Implantable loop recorders are cost-effective when used to investigate transient loss of consciousness which is either suspected to be arrhythmic or remains unexplained. Europace. 2012;14:402-409
PALPITATIONS
BACKGROUND: PALPITATIONS

- Palpitations account for 16% of symptoms that prompt patients to visit a general practitioner\(^1\)
- It is the second most common complaint for specialist cardiologic evaluation (1\(^{st}\): chest pain)\(^2\)

- Symptom with broad range of causes; usually benign but some are life threatening
- Generally transitory, patients are often asymptomatic during evaluation

- Even after extensive testing, it is not always possible to establish a definite cause
- Frequent and recurrent palpitations can impair QoL\(^1\)

- Tachyarrhythmias, structural heart disease, bradyarrhythmias

DIAGNOSIS OF UNEXPLAINED PALPITATIONS
TESTING OPTIONS AND THEIR DIAGNOSTIC YIELDS

Wide range of diagnostic yield is mainly due to differences in the frequency of symptoms

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter Monitoring</td>
<td>0¹-57%²</td>
</tr>
<tr>
<td>External Loop Recorder</td>
<td>19¹-36%³</td>
</tr>
<tr>
<td>Reveal™ ICM</td>
<td>73⁴-81%⁵</td>
</tr>
</tbody>
</table>

ICM HAS HIGHER DIAGNOSTIC YIELD AND IS MORE COST-EFFECTIVE THAN CONVENTIONAL TESTS
RUP: GIADA, J AM COLL CARDIOL 2007¹

- N=50 patients with infrequent palpitations (≤1 episode/month)
- After negative complete initial evaluation, randomized (1:1):
  - 1-year ICM monitoring
  - Conventional strategy (24h Holter + 4-week ELR + EP study)
- Cost per diagnosis was lower in the ICM group, despite higher initial cost
- ICM is a safe and more cost-effective diagnostic approach in patients with infrequent palpitations

Diagnostic Outcome

<table>
<thead>
<tr>
<th>Diagnosis, n (%)</th>
<th>Conventional Diagnostic Strategy (n = 24)</th>
<th>Implantable Loop Recorder (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular tachycardia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Paroxysmal AV block</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No diagnosis, n (%)</td>
<td>19 (79)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>No palpitation recurrence during monitoring</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Patient error in activating</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Recorder malfunctioning</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Negative EPS</td>
<td>19</td>
<td>—</td>
</tr>
</tbody>
</table>

REVEAL ICM GUIDES PHYSICIANS TO RULE OUT OR IDENTIFY ARRHYTHMIAS IN PATIENTS WITH PALPITATIONS
FABER, EUR HEART J. ESC POSTER 2015¹

- N=68 patients with unexplained palpitations received a Reveal™ XT and were followed for 15 months
- Arrhythmias were identified or ruled out in 94% of patients:
  - 55 patients (81%) had detected arrhythmia(s)
  - 9 patients (13%) experienced symptoms without detected arrhythmias (ruled out)
- This resulted in significant therapeutic and clinical actions

ICM identified arrhythmias in the majority of patients with unexplained palpitations

ICMs are indicated in:

- Monthly to yearly palpitations associated with hemodynamic compromise
- When all the other examinations prove inconclusive
- Non-compliant patients without hemodynamic compromise when a clinically significant arrhythmic cause is likely or must be ruled out


* Indicated only in selected cases
§ Refers to ECG–symptom correlation available
ICM provides superior diagnostic yield (73%) compared to conventional tests (21%), and is more cost-effective\(^1\)

ICM guides physicians to rule out or identify arrhythmias in patients with unexplained palpitations\(^2\)

---

REVEAL™ ICM IN DIAGNOSIS OF UNEXPLAINED FALLS
BHANGU, HEART 2016¹

- Prospective single-center study of recurrent fallers with ≥2 unexplained falls presenting to the ER
- 70 patients (mean age 70) received a Reveal™ DX ICM or Reveal™ XT ICM with daily monitoring (CareLink™ Network) and followed 9 months
- 71% (n=50) had a cardiac arrhythmia (mean time to detection: 47 days)
  - 20% (n=14) had a simultaneous fall
  - 51% (n=36) had a cardiac arrhythmia independent of fall
  - 34% (n=24) had ICM-guided treatment
- Patients who had an arrhythmia were more likely to fall during follow-up (p=0.0012)

Cardiac arrhythmias have a high prevalence in older unexplained fallers

<table>
<thead>
<tr>
<th>Fall risk factor at baseline</th>
<th>Fall during follow-up N = 36</th>
<th>No fall during follow-up N = 34</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.2 (10.80)</td>
<td>70.2 (8.96)</td>
<td>0.40</td>
</tr>
<tr>
<td>TUG (mean ± SD)</td>
<td>11.39 ± 1.56</td>
<td>10.60 ± 1.24</td>
<td>0.42</td>
</tr>
<tr>
<td>MMSE (mean ± SD)</td>
<td>28.27 ± 0.60</td>
<td>28.08 ± 0.60</td>
<td>0.65</td>
</tr>
<tr>
<td>CES-D (mean ± SD)</td>
<td>12.47 ± 2.18</td>
<td>8.79 ± 2.58</td>
<td>0.06</td>
</tr>
<tr>
<td>POMA (mean ± SD)</td>
<td>24.41 ± 1.604</td>
<td>25.09 ± 1.12</td>
<td>0.49</td>
</tr>
<tr>
<td>FES (mean ± SD)</td>
<td>25.5 ± 8.19</td>
<td>19.35 ± 6.85</td>
<td>0.25</td>
</tr>
<tr>
<td>Arrhythmia detected during follow-up</td>
<td>36 (100%)</td>
<td>6 (18%)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Denotes significance at p < 0.05

CES-D: Centre for Epidemiologic Studies Depression Scale; FES: Falls Efficacy Scale; ILR: implantable loop recorder; MMSE: mini-mental state examination; POMA: performance oriented mobility assessment; TUG: timed up and go test.

¹Bhangu, et al. Long-term cardiac monitoring in older adults with unexplained falls and syncope. Heart 2016; 0:1-6
CRYPTOGENIC STROKE
BACKGROUND: CRYPTOGENIC STROKE

- 15 million people suffer a stroke each year worldwide, 80% of which are ischemic in origin\(^1\)
- 25% of ischemic strokes are considered cryptogenic despite intense work-up\(^2\)

- At least 1/3 of patients with AF are asymptomatic\(^3\)
- Paroxysmal AF may be the cause of cryptogenic stroke but is also an important risk factor for recurrent stroke

- Cardioembolism caused by AF accounts for at least 15-20% of all ischemic strokes\(^4\)

- Detection of AF in stroke patients informs treatment decisions on changing from antiplatelet agents to OAC\(^5\)

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On average every 40 seconds someone has a stroke in the US;
  - 77% are first-ever attacks and 23% are recurrent
  - Recurrent stroke is devastating and carries a high morbidity and mortality

**Proportion of patients with recurrent stroke in 5 years after first stroke (US)**

Chart source: Pooled data from the Framingham Heart Study, Atherosclerosis Risk in Communities study, and Cardiovascular Health Study of the National Heart, Lung, and Blood Institute.

---

AF DETECTION RATES DEPEND ON SEVERAL FACTORS

- Patient characteristics
  - Age
  - Other risk factors for AF
  - Rigor of stroke work-up
  - Severity of index stroke
- Definition of AF
  - Duration threshold
  - Episode adjudication
- How long you look
- Compliance to monitoring technology

For these reasons, it may be difficult to compare AF detection rates across studies.
HOW SHOULD WE DETERMINE IF AF IS PRESENT FOLLOWING CRYPTOGENIC STROKE?

Method #1: Wait for the patient to tell you

But symptoms are a poor marker for AF burden

### Asymptomatic AF → Low Sensitivity

<table>
<thead>
<tr>
<th>Study</th>
<th>AF Definition</th>
<th>Method of Monitoring</th>
<th>% Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Page, et al. 1997¹</td>
<td>≥ 30 seconds</td>
<td>External monitors: 1 day/week (5x)</td>
<td>92.3% of episodes</td>
</tr>
<tr>
<td>Strickberger, et al. 2005²</td>
<td>≥ 24 V. beats (~ 20-30 seconds)</td>
<td>Implantable pacemakers</td>
<td>94% of episodes</td>
</tr>
<tr>
<td>Quirino, et al. 2009³</td>
<td>≥ 30 seconds</td>
<td>Implantable pacemakers</td>
<td>81% of episodes</td>
</tr>
<tr>
<td>Orlov, et al. 2007⁴</td>
<td>≥ 1 minute</td>
<td>Implantable pacemakers</td>
<td>94.7% of episodes</td>
</tr>
<tr>
<td>Verma, et al. 2013⁵</td>
<td>≥ 2 minutes</td>
<td>Implantable loop recorders</td>
<td>79% of episodes</td>
</tr>
</tbody>
</table>

INTERMITTENT MONITORING IS HIGHLY INACCURATE
ZIEGLER, HEART RHYTHM 2006

- N = 574 pacemaker patients
- All known to have AF
- 12-month retrospective analysis
- Intermittent monitoring was simulated at randomly selected days

Intermittent and symptom-based monitoring is highly inaccurate for identifying patients with any or long-duration AT/AF and for assessing AT/AF burden

MONITORING SENSITIVITY IS HIGHLY DEPENDENT ON PATIENT POPULATION

Known AF Patient Population

EXAMPLE: Quarterly Holter recording detects AF in 54% of the patients with AF, and is correct only 29% of the time in ruling out AF in patients.

LIMITATIONS OF SHORT-TERM MONITORING

- N = 163 patients with previous ischemic stroke/ TIA, no known AF, implanted with a pacemaker or ICD
- Newly detected AT/AF (NDAF) ≥ 5 minute was found in 28% patients during 1 year follow-up
- 73% of patients experienced episodes of AT/AF on <10% of follow-up days

Most episodes would not have been detected by standard monitoring

CRYPTOGENIC STROKE POPULATION

**CHOE, *AM J CARDIOL* 2015¹**

Sensitivity (%)

Negative Predictive Value

**all p < 0.001 vs. Continuous Monitoring**

**Monitoring Method**

## SUMMARY OF REVEAL™ ICM STUDIES IN CRYPTOGENIC STROKE

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of monitoring (months)*</th>
<th>Definition of AF</th>
<th>Time to diagnose (days)*</th>
<th>AF detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRYS-TAL AF&lt;sup&gt;1&lt;/sup&gt; (ICM arm)</td>
<td>6</td>
<td>&gt; 2 minutes</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>84</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td></td>
<td>252</td>
<td>30</td>
</tr>
<tr>
<td>Ziegler&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6</td>
<td>2 minutes</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>SURPRISE&lt;sup&gt;3&lt;/sup&gt;</td>
<td>19</td>
<td>&gt; 2 minutes</td>
<td>109</td>
<td>16</td>
</tr>
<tr>
<td>Ritter&lt;sup&gt;4&lt;/sup&gt;</td>
<td>10</td>
<td>&gt; 30 seconds</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>Cotter&lt;sup&gt;5&lt;/sup&gt;</td>
<td>8</td>
<td>2 minutes</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>Etgen&lt;sup&gt;6&lt;/sup&gt;</td>
<td>12</td>
<td>&gt; 6 minutes</td>
<td>152</td>
<td>27</td>
</tr>
<tr>
<td>Rojo-Martinez&lt;sup&gt;7&lt;/sup&gt;</td>
<td>9</td>
<td>2 minutes</td>
<td>102</td>
<td>33</td>
</tr>
<tr>
<td>Poli&lt;sup&gt;8&lt;/sup&gt;</td>
<td>12</td>
<td>&gt; 2 minutes</td>
<td>105</td>
<td>33</td>
</tr>
<tr>
<td>Jorfida&lt;sup&gt;9&lt;/sup&gt;</td>
<td>14.5</td>
<td>&gt; 5 minutes</td>
<td>162</td>
<td>46</td>
</tr>
</tbody>
</table>

*Mean or median depending on study

ICM DETECTS LOW BURDEN / ASYMPTOMATIC AF
SURPRISE: CHRISTENSEN, EUR J NEUROL 2014¹

- N=85 cryptogenic stroke patients
- Standard cryptogenic stroke workup
- Inserted with Reveal™ XT ICM and monitored by 7-day ECG
- Mean follow-up: 569 days
- AF detected in 16.1% of patients
- AF was asymptomatic in all cases and occurred at low burden (1-4 h)
- Average time to AF detection post-stroke was 109 days

HIGHER DIAGNOSTIC YIELD THAN SHORT-TERM MONITORING
RITTER, STROKE 2013¹

- N=60 cryptogenic stroke patients
- Standard cryptogenic stroke workup
- Inserted with Reveal™ ICM and monitored by 7-day ECG
- Median follow-up: 382 days
- AF detected by ICM in 10 patients (17%) vs 7-day ECG in 1 (1.7%)
- Average time to AF detection post-stroke was 64 days

Most patients were diagnosed with AF within 90 days after ICM insertion

ICM DETECTS AF IN CRYPTOGENIC STROKE PATIENTS
COTTER, NEUROLOGY 2013

- N=52 cryptogenic stroke patients
- Standard cryptogenic stroke workup
- Inserted with Reveal™ XT ICM
- Median follow-up: 229 days
- AF detected in 13/51 patients (25.5%)
- Median time to AF detection: 48 days
- Median duration of first AF episode: 6 minutes

ICM identified AF in 25% of cryptogenic stroke patients ~48 days after insertion

---

ICM DETECTS AF IN CRYPTOGENIC STROKE PATIENTS
ETGEN, STROKE 2013¹

- N=22 cryptogenic stroke patients
- Standard cryptogenic stroke workup
- Inserted with Reveal™ XT ICM
- 1 year follow-up
- AF definition: episode ≥ 6 minutes
- AF detected in 6/22 patients (27.3%)
- Median time to AF detection: 161 days
- 4/6 patients were asymptomatic

ICM identified AF in ≈ 25% of cryptogenic stroke patients 5 months after insertion

ICM DETECTS AF IN CRYPTOGENIC STROKE PATIENTS
ROJO-MARTINEZ, REV NEUROL 2013

- N=101 cryptogenic stroke patients
- Standard cryptogenic stroke workup
- Inserted with Reveal™ XT ICM
- Mean follow-up: 281 days
- AF detected in 34% of patients
- Median time to AF detection: 102 days

In 25% of patients, the first AF episode was detected more than 6 months after stroke

SURVIVAL FUNCTION

REVEAL™ ICM IDENTIFIES ASYMPTOMATIC AF FOLLOWING CRYPTOGENIC STROKE
JORFIDA, J CARDIOVASC MED 2014¹

- N=54 cryptogenic stroke patients with at least 1 AF risk factor

- Inserted with Reveal™ XT ICM

- All patients had CHA₂DS₂-VASc ≥3

- AF detected in 46% of patients over median follow-up of 14.5 months

- Median time to AF detection: 5.4 months

- Majority of episodes were paroxysmal (96%) and asymptomatic (76%)

- Duration of AF episodes
  - 24% had AF episodes of 5 min – 1 hour
  - 52% had AF episodes of up to 1 day
  - 24% had AF episodes of > 1 day

ICM DETECTS AF FOLLOWING CRYPTOGENIC STROKE
POLI, EUR J NEUROL 2016¹

- N=74 patients with cryptogenic stroke/TIA and at least one AF risk factor:
  - CHA₂DS₂-VASc score ≥4
  - Presence of atrial runs
  - LA size > 45 mm
  - LAA flow < 0.2 m/s or spontaneous echo contrast

- Inserted with Reveal™ XT ICM (n=36) or Reveal LINQ™ ICM (n=38)
- Median CHA₂DS₂-VASc score=5 (IQR 4–6)
- AF detected in 28% at 6 months and 33.3% at 12 months
- Mean time to AF detection: 105 days
- Presence of atrial runs and LA size >45 mm were independent predictors of AF

When ICM candidates are selected by AF risk factors after cryptogenic stroke, the detection rate of AF is 1/3 at 1 year

Objectives:

- Assess ICM vs. standard care for detection of AF in cryptogenic stroke patients
  - 6 month endpoint (primary)
  - 12 month endpoint (secondary)
- Determine proportion of patients with underlying AF
- Record actions taken after AF diagnosis

Patient inclusion criteria:

- ≥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

---

CRystal AF Study: Primary & Secondary Endpoints

Detection of AF at 6 months
ICM finds 6x more patients with AF

![Graph showing % Subjects with AF detected over months since randomization for ICM and Control groups.]

- Hazard Ratio (95% CI) = 6.43 (1.90, 21.74)
- Log-rank p-value = 0.0006
- % Subjects with AF detected: ICM 8.4%, Control 1.4%

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>ICM</td>
</tr>
<tr>
<td>220</td>
<td>221</td>
</tr>
<tr>
<td>214</td>
<td>205</td>
</tr>
<tr>
<td>200</td>
<td>198</td>
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<td>190</td>
<td>186</td>
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<td>184</td>
<td>182</td>
</tr>
<tr>
<td>184</td>
<td>173</td>
</tr>
</tbody>
</table>

Detection of AF at 12 months
ICM finds 7x more patients with AF

![Graph showing % Subjects with AF detected over months since randomization for ICM and Control groups.]

- Hazard Ratio (95% CI) = 7.32 (2.57, 20.81)
- Log-rank p-value < 0.0001
- % Subjects with AF detected: ICM 12.4%, Control 2.8%

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>ICM</td>
</tr>
<tr>
<td>220</td>
<td>221</td>
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<tr>
<td>200</td>
<td>194</td>
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<td>197</td>
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<td>181</td>
<td>170</td>
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<tr>
<td>180</td>
<td>167</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time 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>Tests required to detect AF</td>
<td>Auto AF detection</td>
<td>88 ECGs, 20 24-hr Holters, 1 Event Recorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRYSTAL AF STUDY: 36 MONTHS
8.8x more AF detected than standard follow-up arm

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Control</th>
<th>ICM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>220</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td>194</td>
<td>191</td>
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<td>167</td>
<td>173</td>
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<td></td>
<td>114</td>
<td>102</td>
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<tr>
<td></td>
<td>72</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

- Hazard Ratio (95% CI) = 8.78 (3.47, 22.19)
- log-rank p-value < 0.0001

<table>
<thead>
<tr>
<th></th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to AF Detection</td>
<td>252 days</td>
<td>72 days</td>
</tr>
<tr>
<td>Patients found to have AF</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>% Asymptomatic Episodes</td>
<td>81%</td>
<td>40%</td>
</tr>
<tr>
<td>Tests required to detect AF</td>
<td>Auto AF detection</td>
<td>202 ECGs, 52 24-hr Holters, 1 Event Recorder</td>
</tr>
</tbody>
</table>

LONG MEDIAN TIME TO AF DIAGNOSIS
CRYSTAL AF SUB-ANALYSIS: BRACHMANN, CIRC ARRHYTHM EP 2016¹

- At 36 months, median time from randomization to AF detection was 8 months

- Rate of AF detection increased progressively in ICM arm: 3.7% at 1 month vs. 30% at 36 months

- Median maximum AF burden (time in AF in a single day): 10.5 hours (Q1-Q3: 2.9-23.8)
  - 94.9% (n=37) of patients with AF had a maximum burden of >6 minutes

- 94.7% (n=42) of patients with ICM-detected AF were prescribed OAC therapy

8x more ICM-detected AF by 36 months compared with 1 month

---

RISK FACTORS FOR AF OFFER ONLY MODERATE PREDICTIVE ABILITY
CRYSTAL AF SUB-ANALYSIS: THIJS, NEUROLOGY 2016

Parameters tested:
- Age, sex, race
- BMI
- Type and severity of index event
- CHADS₂ score
- PR-interval
- Diabetes, hypertension
- Congestive heart failure
- Patent foramen ovale
- Premature atrial contractions

Increasing age and a prolonged PR-interval offered moderate predictive ability in identifying cryptogenic stroke patients with AF

1. Thijs et al. Predictors for atrial fibrillation detection after cryptogenic stroke: results from CRYSTAL AF. Neurology 2016,19:261-269
NO ASSOCIATION BETWEEN INFARCT TOPOGRAPHY AND AF CRYSTAL AF SUB-ANALYSIS: BERNSTEIN, CEREBROVASC DIS 2015¹

Long-term monitoring should be considered in all cryptogenic stroke patients, regardless of brain imaging findings

- Retrospective analysis of brain images from Reveal™ ICM patients (N=212)
- No significant associations found between AF detection and infarct type, size or arterial distribution

```
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AF Detection (With)</th>
<th>AF Detection Rate (Without)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lesion Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td>14.0%</td>
<td>8.9%</td>
<td>1.6 [0.7-3.6]</td>
<td>0.26</td>
</tr>
<tr>
<td>Subcortical</td>
<td>13.1%</td>
<td>10.8%</td>
<td>1.4 [0.5-3.5]</td>
<td>0.50</td>
</tr>
<tr>
<td>Cortical and Subcortical</td>
<td>17.4%</td>
<td>9.3%</td>
<td>2.1 [0.9-4.8]</td>
<td>0.08</td>
</tr>
<tr>
<td>Internal Border Zone</td>
<td>0.0%</td>
<td>11.4%</td>
<td>0.0 [0.0-n/a]</td>
<td>0.60</td>
</tr>
<tr>
<td>Lacunar</td>
<td>5.7%</td>
<td>13.4%</td>
<td>0.4 [0.1-1.3]</td>
<td>0.10</td>
</tr>
<tr>
<td>Posterior Circulation</td>
<td>25.0%</td>
<td>10.0%</td>
<td>2.5 [0.9-7.4]</td>
<td>0.08</td>
</tr>
<tr>
<td>Acute Lesion Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Lesion &lt; 5 mm</td>
<td>15.1%</td>
<td>9.5%</td>
<td>1.7 [0.7-3.8]</td>
<td>0.23</td>
</tr>
<tr>
<td>Any Lesion ≥ 5 mm</td>
<td>12.0%</td>
<td>8.5%</td>
<td>1.7 [0.5-5.6]</td>
<td>0.40</td>
</tr>
<tr>
<td>Acute Arterial Distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Cerebral Artery</td>
<td>9.9%</td>
<td>14.7%</td>
<td>0.65 [0.3-1.4]</td>
<td>0.28</td>
</tr>
<tr>
<td>Anterior Cerebral Artery</td>
<td>14.3%</td>
<td>11.6%</td>
<td>1.1 [0.15-8.4]</td>
<td>0.90</td>
</tr>
<tr>
<td>Posterior Cerebral Artery</td>
<td>18.6%</td>
<td>10.0%</td>
<td>2.1 [0.9-5.0]</td>
<td>0.07</td>
</tr>
<tr>
<td>Brainstem</td>
<td>16.7%</td>
<td>11.5%</td>
<td>1.4 [0.2-10.3]</td>
<td>0.74</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>23.5%</td>
<td>10.5%</td>
<td>2.2 [0.75-6.5]</td>
<td>0.14</td>
</tr>
</tbody>
</table>
```

¹ Bernstein et al. Infarct topography and detection of atrial fibrillation in cryptogenic stroke patients: Results from CRYSTAL AF. Cerebrovasc Dis. 2015;40:91-6
CONTINUOUS MONITORING IS SUPERIOR TO INTERMITTENT
CRYSTAL AF SUB-ANALYSIS: CHOE, AM J CARDIOL 2015

- Simulated intermittent monitoring was compared to continuous rhythm monitoring in 168 Reveal™ ICM patients

<table>
<thead>
<tr>
<th>Short-term Monitoring</th>
<th>Periodic Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour</td>
<td>Quarterly 24-hour Holters</td>
</tr>
<tr>
<td>48-hour</td>
<td>Quarterly 48-hour Holters</td>
</tr>
<tr>
<td>7-day Holter</td>
<td>Quarterly 7-day Holters</td>
</tr>
<tr>
<td>21-day Event Recorder</td>
<td>Monthly 24-hour Holters</td>
</tr>
<tr>
<td>30-day Event Recorders</td>
<td>Monthly 24-hour Holters</td>
</tr>
</tbody>
</table>

- Low sensitivity: 1.3-22.8%
- Negative predictive value: 82.3-85.6%

Intermittent rhythm monitoring would have failed to identify previously undiagnosed AF in the vast majority of cryptogenic stroke patients.

>30 DAYS OF CONTINUOUS MONITORING ARE NEEDED
ZIEGLER, CEREBROVASC DIS 2015¹

- N=1247 real-world cryptogenic stroke (CS) patients monitored by Reveal LINQ™ ICM
- DiscoveryLink database analysis
- CS diagnosis: physician’s discretion
- Follow-up: 6 months
- Diagnostic yield at 6 months: 12.2% (n=147)
- Median time to detection: 58 days
- Continuous monitoring for periods longer than the current guideline recommendation of 30 days may be warranted in CS patients

Monitoring for only 30 days misses 62% of patients with AF at 6 months

Analysis supports CRYSTAL AF results and confirms that ICM should be strongly considered in CS patients

1. Ziegler et al. Real-world experience with insertable cardiac monitors to find atrial fibrillation in cryptogenic stroke, Cerebrovascular Diseases, 2015; 40:175-81
>30 DAYS OF CONTINUOUS MONITORING ARE NEEDED
ROGERS, ANN ORAL 2016

- N=1247 real-world cryptogenic stroke (CS) patients monitored by Reveal LINQ™ ICM
- DiscoveryLink database analysis
- CS diagnosis: physician’s discretion
- Follow-up: 326 ± 85 days
- Diagnostic yield at 12 months: 16.3% (n=203)

12-month, real-world analysis supports CRYS\_TAL AF results and confirms that ICM should be strongly considered in CS patients

---

1. Rogers et al. Incidence of atrial fibrillation within one year of cryptogenic stroke among a large, real-world population with insertable cardiac monitors, Neurology 2016;86:16 SUPPL 1
ICMs ARE A COST-EFFECTIVE DIAGNOSTIC TOOL
DIAMANTOPOULOS, INT J STROKE 2016¹

ICMs are cost-effective for the prevention of recurrent stroke in cryptogenic stroke patients

- Lifetime Markov model estimating cost-effectiveness of ICMs (UK)
- Monitoring with ICM was associated with fewer recurrent strokes and increased QALYs (quality-adjusted life years) compared to SoC
- Stroke-related costs were reduced in ICM patients, but overall costs were higher
- The ICER (incremental cost-effectiveness ratio) was below the £20,000-30,000 willingness-to-pay threshold (£17,175 per QALY gained)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Ischemic Stroke</th>
<th>QALYs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SoC</td>
<td>0.447</td>
<td>7.216</td>
<td>£17,045</td>
</tr>
<tr>
<td>ICM</td>
<td>0.404</td>
<td>7.367</td>
<td>£19,631</td>
</tr>
<tr>
<td>Incremental</td>
<td>-0.044</td>
<td>0.151</td>
<td>£2,587</td>
</tr>
<tr>
<td>ICER GBP</td>
<td>UK Threshold = £30,000</td>
<td></td>
<td>£17,175</td>
</tr>
<tr>
<td>ICER USD</td>
<td>US Threshold = $50,000</td>
<td></td>
<td>$28,308</td>
</tr>
<tr>
<td>NNI* to avoid stroke</td>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

GUIDELINES ARE EVOLVING TO INCORPORATE ICM FOR AF SCREENING IN STROKE SURVIVORS

AHA/ASA Guideline 2014

Class IIa – Level of Evidence C

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

ESC Guideline 2016

Class IIa – Level of Evidence B

In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation

2016 EUROPEAN SOCIETY OF CARDIOLOGY
ATRIAL FIBRILLATION GUIDELINES

- Updated guidelines on the diagnosis and management of AF
- ESC Task Force with representation from the European Heart Rhythm Association (EHRA), and EACTS as well as by the European Stroke Organization (ESO)
- For the first time, incorporate ICM’s into post-stroke monitoring recommendations

### Classes of Recommendations

<table>
<thead>
<tr>
<th>Classes of recommendations</th>
<th>Definition</th>
<th>Suggested wording to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/is indicated</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td></td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
<td>Should be considered</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
<td>May be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective; and in some cases may be harmful.</td>
<td>Is not recommended</td>
</tr>
</tbody>
</table>

### Levels of Evidence

<table>
<thead>
<tr>
<th>Level of evidence A</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>

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A NUMBER OF STUDIES HAVE DOCUMENTED BENEFIT OF REVEAL™ ICM IN CRYPTOGENIC STROKE PATIENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Time between index event and monitoring (days)*</th>
<th>ICM monitoring (months)*</th>
<th>Definition of AF</th>
<th>Time to diagnosis (days)*</th>
<th>AF detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etgen ‘13 &lt;sup&gt;1&lt;/sup&gt;</td>
<td>8.5</td>
<td>12</td>
<td>&gt;6 minutes</td>
<td>152</td>
<td>27</td>
</tr>
<tr>
<td>Ritter ‘13 &lt;sup&gt;2&lt;/sup&gt;</td>
<td>13</td>
<td>10</td>
<td>&gt;30 seconds</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>Poli ‘15 &lt;sup&gt;3&lt;/sup&gt;</td>
<td>27</td>
<td>12</td>
<td>&gt;2 minutes</td>
<td>105</td>
<td>33</td>
</tr>
<tr>
<td>CRYSTAL AF’14 &lt;sup&gt;4&lt;/sup&gt;(ICMarm)</td>
<td>38 to randomization + 6 d before ICM insertion</td>
<td>6</td>
<td>&gt;30 seconds</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>SURPRISE ‘14 &lt;sup&gt;5&lt;/sup&gt;</td>
<td>69</td>
<td>19</td>
<td>&gt;2 minutes</td>
<td>109</td>
<td>16</td>
</tr>
<tr>
<td>Jorfida ‘15 &lt;sup&gt;6&lt;/sup&gt;</td>
<td>108</td>
<td>14.5</td>
<td>&gt;5 minutes</td>
<td>162</td>
<td>46</td>
</tr>
<tr>
<td>Cotter ‘13 &lt;sup&gt;7&lt;/sup&gt;</td>
<td>174</td>
<td>8</td>
<td>2 minutes</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>Ziegler ‘15 &lt;sup&gt;8&lt;/sup&gt;</td>
<td>n/a</td>
<td>6</td>
<td>2 minutes</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Rojo-Martinez ‘19 &lt;sup&gt;9&lt;/sup&gt;</td>
<td>n/a</td>
<td>9</td>
<td>2 minutes</td>
<td>102</td>
<td>33</td>
</tr>
<tr>
<td>Müller ‘16 &lt;sup&gt;10&lt;/sup&gt;</td>
<td>unknown</td>
<td>11</td>
<td>≥30 seconds</td>
<td>30</td>
<td>18</td>
</tr>
</tbody>
</table>

+3 meta-analyses
- Sposato <sup>11</sup>
- Afzal <sup>11</sup>
- Dussault <sup>13</sup>

*Mean or median depending on study

---

13. Dussault et al. Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2015; 8:263-289
EVIDENCE SUMMARY
ICMs for AF DETECTION IN CRYPTOGENIC STROKE

- ICM detects low burden/asymptomatic AF in cryptogenic stroke patients
- ICM offers higher diagnostic yield than standard monitoring, 7-day Holter, and intermittent monitoring
- Infarct topography and predictors of AF offer only moderate predictive ability
- Long-term monitoring with ICMs should be considered in CS patients
- ICM is a cost-effective diagnostic tool for the prevention of recurrent stroke in cryptogenic stroke patients

12. Thijs et al. Predictors for atrial fibrillation detection after cryptogenic stroke: results from CRYSTAL AF. Neurology 2016;19:261-269
14. Rogers et al. Incidence of atrial fibrillation within one year of cryptogenic stroke among a large, real-world population with insertable cardiac monitors. Neurology 2016;86:16 SUPPL 1
### BACKGROUND: AF MANAGEMENT

<table>
<thead>
<tr>
<th>Magnitude</th>
<th>Atrial Fibrillation affects 1-2% of the general population¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AF ablation is indicated to alleviate symptomatic AF²</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal AF burden is variable and often asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Short-term monitoring is suboptimal for understanding burden</td>
</tr>
<tr>
<td></td>
<td>Cardioembolism caused by AF accounts for at least 15-20% of all ischemic stroke³</td>
</tr>
<tr>
<td></td>
<td>Management of AF can reduce stroke risk and improve quality of life²</td>
</tr>
</tbody>
</table>

¹ Camm, Guidelines for the management of atrial fibrillation. EurHeart J. 2010, 31:2369-2429
² January, 2014 AHA/ACC/HRS Guidelines for the management of patients with atrial fibrillation. Circulation 2014; 64:e1-e76
POST-ABLATION REVEAL™ ICM MONITORING EVIDENCE

- Multiple studies using Reveal™ ICM to monitor AF burden post ablation
  - 60+ Manuscripts
  - 90+ Abstracts

- The majority focus on true AF burden after different ablation techniques
  - Positive results for detecting AF post ablation – occurs at low rates and is mostly asymptomatic
ATRIAL FIBRILLATION IS OFTEN ASYMPTOMATIC POST-ABLATION
DISCERN AF: VERMA, JAMA INTERN MED 2013\(^1\)

- Multicenter, prospective clinical trial
  - N= 50; Reveal™ XT
  - Follow up : 3mo pre-ablation; 18 mo post-ablation
- 86% reduction in AT/AF burden via catheter ablation
- 56% of all episodes recorded were asymptomatic (pre/post ablation)
  - Ratio of asymptomatic to symptomatic episodes increased from 1.1 to 3.7 post-ablation
- 12% of patients were completely asymptomatic post ablation

\(^1\) Verma et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF). JAMA Intern Med 2013; 173:149-156
ATRIAL FIBRILLATION IS OFTEN ASYMPTOMATIC POST-ABLAATION

PEDROTE, J CARDIOVASC ELECTROPHYSIOL 2013¹

- N=35; Reveal™ XT ICM
- Follow up: 3mo pre-ablation; 12mo post-catheter ablation
- AF burden dropped from 2.5% (1-5%) to 0% (0-0.25%) post ablation
- Ratio of asymptomatic to symptomatic episodes increased from 1.1 to 3.7 post-ablation

AF monitoring provides information on the true reduction of AF burden following catheter ablation

SYMPTOM – ARRHYTHMIA CORRELATION FOR AF IS POOR
TONDO, J CARDIOVASC ELECTROPHYSIOL 2014

- Single center; prospective study
- N= 143; Reveal™ XT ICM
- 14 mo follow up post 1st PVI catheter ablation
- 45/98 (46%) of patients with at least 1 AF recurrence (≥6 min) were asymptomatic
- 13/45 (29%) of patients with no recurring AF reported symptoms

Symptom–arrhythmia correlation improves as episode duration increases; however, relying on symptoms to monitor for AF recurrence is not ideal

<table>
<thead>
<tr>
<th>OVERALL FOLLOW-UP PERIOD</th>
<th>Total</th>
<th>Symptomatic Patients</th>
<th>Asymptomatic Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with any AF recurrence ≥ 6 minutes</td>
<td>98 (69%)</td>
<td>53 (54%)</td>
<td>45 (46%)</td>
</tr>
<tr>
<td>Patients without AF recurrence</td>
<td>45 (31%)</td>
<td>13 (29%)</td>
<td>32 (71%)</td>
</tr>
<tr>
<td>Based on duration of AF recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with AF &gt; 6 minutes &lt; 1 hour</td>
<td>24 (17%)</td>
<td>9 (38%)</td>
<td>15 (62%)</td>
</tr>
<tr>
<td>Patients with AF &gt; 1 hour &lt; 12 hours</td>
<td>31 (22%)</td>
<td>16 (52%)</td>
<td>15 (48%)</td>
</tr>
<tr>
<td>Patients with AF &gt; 12 hours &lt; 24 hours</td>
<td>19 (13%)</td>
<td>13 (68%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Patients with AF ≥ 24 hours</td>
<td>24 (17%)</td>
<td>15 (63%)</td>
<td>9 (37%)</td>
</tr>
</tbody>
</table>

ICM-GUIDED RE-ABLATION IS MORE EFFECTIVE THAN ANTI-ARRHYTHMIA DRUG MANAGEMENT FOR RECURRENT PAF

POKUSHALOV, CIRCAE 2011 & 2013 (REVEAL™ XT ICM)\(^1\)-\(^2\)

ICM monitoring during 3 month “Blanking period” post-ablation guides optimal therapy via re-ablation

Two studies using ICM detected AF burden to guide re-ablation decision making

1. Pokushalov et al. Use of an implantable monitor to detect arrhythmia recurrences and select patients for repeat catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011; 4:823-31;

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1. Pokushalov et al. Use of an implantable monitor to detect arrhythmia recurrences and select patients for repeat catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011; 4:823-31;
REVEAL™ ICM MONITORING PRE- AND POST-ABLATION ASSISTS PATIENT MANAGEMENT
OUDEMAN, EUR J CARDIOThorAC SURG 2015

- N= 20; Reveal™ XT ICM
- Follow up: 4 weeks pre-ablation; 12 months post-ablation
- 2 ablation procedures were postponed due to not reaching AF burden threshold of 10% via ICM monitoring
- 66% reduction in AF burden 12 months post surgical ablation
- 12/15 (80%) at 12 months were free from AF and anti-arrhythmic drugs (AADs)

Monitoring for AF pre-ablation can be used to determine if ablation is necessary by documenting true burden

ANTI-ARRHYTHMIC DRUGS POST-ABALATION CAN BE EFFECTIVELY TITRATED WITH LONG-TERM MONITORING

ABASCUS: KAPPA, *J CARDIOVASC ELECTROPHYSIO*, 2013\(^1\)

- **N= 44 AF ablation patients**
  - 12-month follow-up via ICM (Reveal™ XT ICM) or conventional monitoring (30-day transtelephonic monitors at baseline, and at 5 & 11 months post-ablation)

- Reveal XT ICM found AF recurrence in 18 vs. 7 pts with conventional monitoring

- Long-term monitoring led to more actionable events than conventional monitoring
  - 71% vs. 44% of patients (ICM versus conventional monitoring) removed from AAD
  - 60% vs. 39% of patients discontinued rate control medication

ICM continuous monitoring has a higher diagnostic rate for post-ablation recurring AF and can guide medical therapy decisions better than conventional monitoring

MONITORING PATIENTS POST-ABLATION CAN AID IN MEDICAL MANAGEMENT FOR HIGH RISK PATIENTS

ZUERN, PACE 2015¹

Long-term cardiac monitoring was used to manage patients off OACs in low-to-moderate stroke risk post-ablation without adverse events

- N=65 AF ablation patients inserted with Reveal™ XT ICM
- 32 month mean follow up
- CHADS₂ 1-3; no AF recurrence after 3 months; post-ablation discontinued OACs
- 63% (41) of patients remained off OACs at end of follow-up
  - Re-initiation of OACs was due to:
    - 21 (32%) AF burden > 1 hr
    - 2 deep vein thrombosis
    - 1 pulmonary embolism
- No strokes or TIAs

¹ Zuern et al. Anticoagulation after catheter ablation of atrial fibrillation guided by implantable cardiac monitors. PACE; 2015 38:688-693
MANAGING LOW STROKE RISK (CHADS2 <2) PATIENTS OFF ANTICOAGULATION
PASSMAN (REACT.COM), J CARDIOVASC ELECTROPHYSIOLOG 2016
(Additional studies are required to show safety and effectiveness)

- N=50; Reveal™ XT ICM
- 41 patients with previous ablation
- 465 day mean follow up
- Low stroke risk patients (CHADS$_2$ 1-2); AF free for 60 days – discontinued OACs

- 94% reduction of time on anticoagulation
- 18 (31%) patients required re-initiation of anticoagulation (AF burden ≥1 hr)

- No strokes or deaths occurred in patients
- 2 potential and 1 confirmed TIA – patients on aspirin w/CHADS$_2$ = 1
- 3 traumatic bleeds in patients on aspirin

Long-term cardiac monitoring was effective in managing low-stroke-risk patients off OACs with low-AF burden

1. Passman et al. Targeted anticoagulation for atrial fibrillation guided by continuous rhythm assessment with an insertable cardiac monitor: the rhythm evaluation for anticoagulation with continuous monitoring (REACT.COM) pilot study. PACE 2016; 27:264-70
MANAGING PATIENTS OFF ANTICOAGULATION WHO ARE AT RISK FOR BLEEDING COMPLICATIONS
MASCARENHAS, EUROPACE
(Additional studies are required to show safety and effectiveness)

- N=70; Reveal™ XT ICM or Reveal LINQ™ ICM
- Post-cardioversion; mean follow-up: 23 months
- Higher stroke and bleed risk patients (CHADS$_2$ ≥ 2 and HAS-BLED ≥3)
- 90% (18/20) patients with variable (1-50%) AF burden reduced burden to <1% titrating AADs based on ICM data
- 76% patients discontinued anticoagulation therapy (with <1% AF burden & patient consent)
  - No strokes or TIsAs occurred
  - 24 vs 0% of patients on OACs vs off had major bleeds

Long-term cardiac monitoring was effectively used to manage high-risk stroke and bleed-risk patients off anticoagulation and to optimize rhythm control

ICM are not specifically in the guidelines; however they can accurately provide the following required data:

<table>
<thead>
<tr>
<th>PRE-ABLATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>• “Prior to undergoing a catheter ablation procedure, it is important to confirm that a patient’s symptoms result from AF and to determine whether a patient has paroxysmal or persistent AF”</td>
</tr>
<tr>
<td>• “This is of importance as the ablation technique, procedure outcome, anticoagulation strategies employed, and the need for TEE prior to the procedure may be impacted by the accurate characterization of the AF type and burden”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POST-ABLATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>• “ECGs should be obtained at all follow-up visits. More intense monitoring should be mainly driven by the clinical impact of AF detection with strict monitoring being necessary (e.g., in patients with thromboembolic risk factors for determining the adequate anticoagulation approach)”</td>
</tr>
<tr>
<td>• “Patients in whom discontinuation of systemic anticoagulation is being considered should consider undergoing continuous ECG monitoring to screen for asymptomatic AF/AFL/AT”</td>
</tr>
</tbody>
</table>

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EVIDENCE SUMMARY
ICMS FOR AF MANAGEMENT

- Paroxysmal AF can be asymptomatic, particularly after AF ablation procedures\(^1-3\)

- ICM monitoring can be used to manage AF pre- and post-ablation
  - Determine if patient meets threshold of AF burden for ablation procedure\(^4\)
  - Determine need to re-ablate based on burden\(^5-6\)

- Small studies suggest that anti-arrhythmic medication can be managed based on AF burden\(^7-8\)

- Small studies suggest that oral anticoagulation medication can be managed based on AF burden\(^8-10^*\)

\(^*\)Additional studies are required to show safety and effectiveness

1. Verma et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF). JAMA Intern Med 2013; 173:149-156
5. Pokushalov et al. Use of an implantable monitor to detect arrhythmia recurrences and select patients for repeat catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011; 4:823-31
PRIMARY PREVENTION: SUSPECTED AF
### BACKGROUND: PRIMARY PREVENTION

**Magnitude**
- Atrial Fibrillation affects 1-2% of the general population\(^1\)

**Inpatient Challenge**
- Paroxysmal AF is difficult to detect as it is often asymptomatic and varies in onset and duration\(^2\)

**Patient’s Frustration**
- Cardioembolism caused by AF accounts for at least 15-20% of all ischemic stroke\(^3\)

**Cardiac Causes**
- Detection and management of AF can reduce risk for stroke\(^4\)

---

2. Liao, Noninvasive cardiac monitoring for detection paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. Stroke 2007; 38:2935-40
# SYMPTOMS ARE NOT A GOOD INDICATOR OF AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Monitoring</th>
<th>% Asymptomatic AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Page, et al. 1994¹</td>
<td>External Monitors: 1 day/week</td>
<td>92.3% of episodes</td>
</tr>
<tr>
<td></td>
<td>(5x)</td>
<td></td>
</tr>
<tr>
<td>Strickberger, et al. 2005²</td>
<td>Implantable Pacemakers</td>
<td>94% of episodes</td>
</tr>
<tr>
<td>Quirino, et al. 2009³</td>
<td>Implantable Pacemakers</td>
<td>81% of episodes</td>
</tr>
<tr>
<td>Orlov, et al. 2007⁴</td>
<td>Implantable Pacemakers</td>
<td>94.7% of episodes</td>
</tr>
<tr>
<td>Verma, et al. 2013⁵</td>
<td>Implantable Loop Recorders</td>
<td>79% of episodes</td>
</tr>
</tbody>
</table>

5. Verma et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF). JAMA Intern Med 2013; 173:149-156
POOR CORRELATION WITH PATIENT SYMPTOMS

STRICKERBERGER, HEART RHYTHM 2005¹

- N=48 patients with history of AF¹
- 95% of AT episodes were asymptomatic
- AF symptoms are accurate only 15% of the time
- 45% of patients reported symptoms without recorded AT event
- Page, et al identified a 12:1 ratio of asymptomatic: symptomatic AT²

AS AF BURDEN INCREASES, SO DOES STROKE RISK
TRENDS: GLOTZER, CIRC ARR EP 2009¹

- N=2486; PM, ICD, CRT
  - Medical history: ≥1 stroke risk factors, w/o persistent AT/AF
  - 1.4 years follow-up
- Mean CHADS₂ score: 2.2±1.2
- Device detected AT/AF in 24% of patients
- Annualized thromboembolic event (TE) rate was 1.2% (40 patients)
- High AT/AF burden (≥5.5 hr) within 30-days was associated with increased risk of TE event in patients with therapeutic devices

>5.5 h AT/AF burden increases risk of thromboembolic events 2.2x

<table>
<thead>
<tr>
<th>AT/AF Burden Subset</th>
<th>Annualized TE Rate (95% CI), %</th>
<th>Annualized TE Rate Excluding TIA (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero AT/AF burden</td>
<td>1.1 (0.8 – 1.6)</td>
<td>0.5 (0.3 – 0.9)</td>
</tr>
<tr>
<td>Low AT/AF burden (&lt; 5.5 h)</td>
<td>1.1 (0.4 – 2.8)</td>
<td>1.1 (0.4 – 2.8)</td>
</tr>
<tr>
<td>High AT/AF burden (≥ 5.5 h)</td>
<td>2.4 (1.2 – 4.5)</td>
<td>1.8 (0.9 – 3.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Hazard Ratio (95% CI) *</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT/AF burden</td>
<td>Low burden vs. zero burden</td>
<td>0.98 (0.34, 2.82)</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>High burden vs. zero burden</td>
<td>2.20 (0.96, 5.05)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

IDENTIFYING SUBCLINICAL (ASYMPTOMATIC) AF IS VALUABLE

ASSERT: HEALEY, N ENGL J MED 2012¹

- N=2580; PM or ICD
  - Hypertensive w/ no history of AF
  - 2.5 years mean follow-up

- Subclinical AT/AF (>190 bpm for >6 min) detected in 10 % of patients within first 3 months

- Patients with subclinical AT/AF were:
  - 5.6x more likely to develop clinical AF
  - 2.5x more likely to have an ischemic stroke or systemic embolism

Patients with no known AF and high CHADS$_2$ scores are at elevated risk for stroke/TIA. Identifying AF in high risk patients could lead to improved stroke prevention therapy with OACs.

- Multi-center, prospective cohort study
- N= 916
  - No history of AF; not on anticoagulation; stable coronary heart disease
  - Median follow-up: 6.4 years
- Mean CHADS$_2$ Score: 1.7
- Stroke/TIA risk compared to CHADS$_2$ Score 0-1
  - CHADS2 Score 2-3 = 2.7X
  - CHADS2 Score 4-6 = 4.6X

1. Welles et al. The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among patients with coronary heart disease: data from the heart and soul study. Am Heart J. 2011; 162:555-61
IDENTIFYING PATIENTS AT HIGH RISK FOR AF
FRONTERA, PACE 2015

- Retrospective analysis, patients with ICM for syncope and/or palpitations
- N=200 (90% Reveal™ XT ICM; 10% Confirm)
- 42 (21%) patients had detected paroxysmal AF
  - Only 62% of these (26/42) were symptomatic
- PAF patients differed significantly from non-PAF patients:
  - Age (older), more smokers, higher cholesterol, decreased eGFR, larger LA volume, longer PR intervals and incomplete RBBB
  - Higher median CHA₂DS₂-VASc score: 3.5 vs 2
- Smoking and incomplete RBBB were significant predictors of paroxysmal AF

Patients with PAF have a higher risk for stroke than non-AF patients based on CHA₂DS₂-VASc Score
Continuous monitoring via ICM is important as symptoms to not correlate well with arrhythmia

1. Frontera et al. Demographic and clinical characteristics to predict paroxysmal atrial fibrillations: insights from an implantable loop recorder population. PACE 2015;38: 1217-22
ICM MONITORING IN HIGH RISK PATIENTS
PREDATE INTERIM ANALYSIS: NASIR, HRS ORAL 2016

- Patients: CHA$_2$DS$_2$-VASc ≥2
- No AF/AFI (atrial flutter) at baseline
- 1º endpoint: incidence of AF/AFI >6min

Results:
- N=245; age: 74 (mean); 41% female
- CHA$_2$DS$_2$-VASc 4.6 ± 1.5
- 12 mo follow-up for interim analysis
- 22% AF/AFI detection rate
  - AF detection was not affected by either prior stroke or CHA$_2$DS$_2$-VASc <5 vs ≥5
  - Females had significantly less AF than males (p=0.011)
- 136.4 ± 135.8 days mean time to AF/AFI detection
  - 27% (15/54) detected in first 30 days
- Medical management decisions:
  - 16.6% elected rhythm control
    - 7AAD, 1 ablation, 1 cardioversion
  - 65.5% started NOAC/warfarin

22% of a patient population at high risk was found to have >6min of AF within 12 months

These data highlight the utility of Reveal™ ICMs to identify AF in a high risk, largely asymptomatic population

1. Nasir et al. Predicting atrial fibrillation for flutter (predate-AF) study: interim analysis, Heart Rhythm 2016 13:5 SUPPL.
EVIDENCE SUMMARY
ICMs FOR PRIMARY PREVENTION OF STROKE

- Symptoms are not a good indicator for presence of AF\textsuperscript{1-5}
- Device detected AT/AF\textsuperscript{6} and asymptomatic AF\textsuperscript{7-8} increase the risk of ischemic stroke
- Continuous monitoring with ICMs can identify AF in patients at high risk\textsuperscript{9-10}

BRIEF STATEMENT
MEDTRONIC REVEAL LINQ™ LNQ11 INSERTABLE CARDIAC MONITOR AND PATIENT ASSISTANT

Indications
REVEAL LINQ™ LNQ11 Insertable Cardiac Monitor
The Reveal LINQ Insertable Cardiac Monitor is an implantable patient-activated and automatically-activated monitoring system that records subcutaneous ECG and is indicated in the following cases:

- patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- patients who experience transient symptoms such as dizziness, palpitation, syncope and chest pain, that may suggest a cardiac arrhythmia.

This device has not been tested specifically for pediatric use.

Patient Assistant
The Patient Assistant is intended for unsupervised patient use away from a hospital or clinic. The Patient Assistant activates the data management feature in the Reveal Insertable Cardiac Monitor to initiate recording of cardiac event data in the implanted device memory.

Contraindications
There are no known contraindications for the implant of the Reveal LINQ Insertable Cardiac Monitor. However, the patient’s particular medical condition may dictate whether or not a subcutaneous, chronically implanted device can be tolerated.

Warnings/Precautions
REVEAL LINQ™ LNQ11 Insertable Cardiac Monitor
Patients with the Reveal LINQ Insertable Cardiac Monitor should avoid sources of diathermy, high sources of radiation, electrosurgical cautery, external defibrillation, lithotripsy, therapeutic ultrasound and radiofrequency ablation to avoid electrical reset of the device, and/or inappropriate sensing as described in the Medical procedure and EMI precautions manual. MRI scans should be performed only in a specified MR environment under specified conditions as described in the Reveal LINQ MRI Technical Manual.

Patient Assistant
Operation of the Patient Assistant near sources of electromagnetic interference, such as cellular phones, computer monitors, etc., may adversely affect the performance of this device.

Potential Complications
Potential complications include, but are not limited to, device rejection phenomena (including local tissue reaction), device migration, infection, and erosion through the skin.

See the device manual for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please call Medtronic at 1-800-328-2518 and/or consult Medtronic’s website at www.medtronic.com.

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.
BRIEF STATEMENT
MEDTRONIC MYCARELINK™ PATIENT MONITOR, MEDTRONIC CARELINK™ NETWORK AND CARELINK™ MOBILE APPLICATION

The Medtronic MyCareLink Patient Monitor and the Medtronic CareLink Network are indicated for use in the transfer of patient data from Medtronic implantable cardiac devices. These products are not a substitute for appropriate medical attention in the event of an emergency. Data availability and alert notifications are subject to Internet connectivity and access, and service availability. The MyCareLink Patient Monitor must be on and in range of the device. Alert notifications are not intended to be used as the sole basis for making decisions about patient medical care.

Intended Use
The Medtronic MyCareLink Patient Monitor and CareLink® Network are indicated for use in the transfer of patient data from some Medtronic implantable cardiac devices based on physician instructions and as described in the product manual. The CareLink Mobile Application is intended to provide current CareLink Network customers access to CareLink Network data via a mobile device for their convenience. The CareLink Mobile Application is not replacing the full workstation, but can be used to review patient data when a physician does not have access to a workstation. These products are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. CareLink Network availability and mobile device accessibility may be unavailable at times due to maintenance or updates, or due to coverage being unavailable in your area. Mobile device access to the Internet is required and subject to coverage availability. Standard text message rates apply.

Contraindications
There are no known contraindications.

Warnings and Precautions
The MyCareLink Patient Monitor must only be used for interrogating compatible Medtronic implantable devices.

See the device manual for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please call Medtronic at 1 (800) 328-2518 and/or consult Medtronic’s website at www.medtronic.com.

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