Guardian® System for the Alerting of Patients to ST Segment Changes Indicative of Coronary Artery Occlusion

March 16, 2016
Angel Medical Systems, Inc.
FDA Circulatory System Devices Panel
Introduction

Tim Fischell, MD, FACC, FSCAI, FAHA
Medical Advisor
Angel Medical Systems, Inc.

Professor of Medicine
Michigan State University
Relying on Symptoms for Prompting Treatment for Heart Attacks Is Inadequate

Clinical Standard of Care

*Treatment for heart attacks requires the patient to have symptoms, recognize the symptoms, and then take action*

Problems:

- Presentation delay for patients suffering MI with symptoms, leading to heart muscle damage
- Symptoms are often atypical and go unrecognized
- Symptoms often do not occur at all (silent MIs)
Key Findings from ALERTS Study of the Guardian System

- Primary safety endpoint was met
- Primary efficacy endpoint was not met
- Secondary endpoints supporting proposed indication for use were met:
  - Significant reduction in late arrival for confirmed occlusive events
  - Significant reduction in time from occlusion-to-door for confirmed events
- Most of the confirmed events among Treatment patients were silent or presentation was before symptom onset
Proposed Indication for the Guardian System

The Guardian System is indicated to alert patients with prior acute coronary syndrome events to ST segment changes indicating acute coronary occlusion.

Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet Need for Earlier Treatment of Heart Attacks</td>
<td>David Holmes, MD</td>
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<tr>
<td></td>
<td>Professor of Medicine</td>
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<td></td>
<td>Mayo Clinic College of Medicine</td>
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<tr>
<td>Rationale for Continuous ST Segment Monitoring</td>
<td>Mitchell W. Krucoff, MD</td>
</tr>
<tr>
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<td>Professor of Medicine</td>
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<tr>
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<td>Duke University School of Medicine</td>
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<tr>
<td>AngelMed Guardian System</td>
<td>Tim Fischell, MD</td>
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<td>ALERTS Study Design</td>
<td>Christopher Mullin, MS</td>
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<td>Director, Product Development Strategy</td>
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<td>North American Science Associates</td>
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<tr>
<td>ALERTS Study Results</td>
<td>C. Michael Gibson, MD</td>
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<td>Professor of Medicine</td>
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<td>Harvard Medical School</td>
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<tr>
<td>Post-Approval Plans</td>
<td>David Fischell, PhD</td>
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<td>CEO, Angel Medical Systems, Inc.</td>
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<tr>
<td>Benefit-Risk Assessment</td>
<td>Mitchell W. Krucoff, MD</td>
</tr>
</tbody>
</table>
# Additional Experts

<table>
<thead>
<tr>
<th>Clinical Studies</th>
<th>David Keenan</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>VP, Clinical &amp; Regulatory Affairs</td>
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<td></td>
<td>Angel Medical Systems, Inc.</td>
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<tr>
<td>Human Factors</td>
<td>Chris Young, PhD</td>
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<tr>
<td></td>
<td>Senior Human Factors Engineer</td>
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<td></td>
<td>Angel Medical Systems, Inc.</td>
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</tbody>
</table>
Need for Earlier Treatment of Heart Attacks

David Holmes, MD, MACC, FSCAI, FAHA, FESC
Professor of Medicine
Mayo Clinic College of Medicine
Heart Attacks are a Major Source of Morbidity and Mortality in the U.S.

- Estimated 735,000 heart attacks per year\(^1\)
  - 210,000 recurrent heart attacks
- Death or debilitating HF more likely for recurrent events\(^2\)

1. AHA. *Circulation* 2015;131:e29-e322.
Approximately 1/3 of Heart Attacks Are Silent

<table>
<thead>
<tr>
<th>Study (Year) [Patient notes]</th>
<th>Number of MIs</th>
<th>% Silent MIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canto (2000)</td>
<td>434,877</td>
<td>33%</td>
</tr>
<tr>
<td>Males</td>
<td>180,922</td>
<td>29%</td>
</tr>
<tr>
<td>Females</td>
<td>253,954</td>
<td>39%</td>
</tr>
<tr>
<td>Reykjavik (1995, 1998)</td>
<td>878</td>
<td>34%</td>
</tr>
<tr>
<td>Framingham (1990)</td>
<td>363</td>
<td>30%</td>
</tr>
<tr>
<td>FIELD (2009) [diabetic]</td>
<td>730</td>
<td>37%</td>
</tr>
<tr>
<td>Leening (2010) [&gt;55 years of age]</td>
<td>6,305</td>
<td>48% (F=65%; M=37%)</td>
</tr>
<tr>
<td>McSweeny (2003) [females]</td>
<td>515</td>
<td>44%</td>
</tr>
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“Time is Muscle”: A Fundamental Tenet of Heart Attack Care

■ Reimer & Jennings (1979) showed a wave of necrosis spreads across heart as a function of time following coronary occlusion\(^1\)
  - Significant amounts of muscle could be salvaged in first 3 hours

■ Therapeutic importance of time in clinical outcomes:
  - Symptom-to-door time
  - Door-to-balloon (DTB) time
  - Door-to-needle (DTN) time

U.S. Healthcare System Has Been Changed to Accelerate Time-to-Treatment

- Impact of time-to-treatment on clinical outcomes has prompted:
  - Revisions to clinical treatment guidelines
  - National initiatives to reduce DTB time
  - Grading of hospitals on time metrics, rather than outcomes
- These efforts have led to considerable reductions in DTB and DTN times
- In the last 30 years, symptom-to-door times have not improved
Chest Pain is a Poor Prompt for Patients to Seek Treatment for a Heart Attack

- Not a sensitive prompt
  - More than one-third of heart attacks occur without chest pain

- Not a specific prompt
  - Only ~15-20% of patients presenting at an ER with chest pain are having an ACS or MI\textsuperscript{1,2}

- Not a timely prompt
  - Median time for arrival at a medical facility is several hours after onset of chest pain

- Symptom-to-door time does not improve after:
  - First heart attack\textsuperscript{3}
  - Patient education\textsuperscript{4}

\textsuperscript{2} Goodacre et al. \textit{Acad Emerg Med} 2002;9:203-8.
\textsuperscript{3} Gibson. Paper presented at \textit{Heart Rhythm Society} 2009.
Continuous Monitoring Would Significantly Reduce Patient-Related Delay

**Standard Paradigm**

- Median of 2 hours from symptom onset to 911

**Continuous Monitoring Paradigm**

- 2 minutes from coronary occlusion to 911

Represents “best-case” scenario where:

- Patient has symptoms
- Patient recognizes symptoms
- Symptoms start at onset of occlusion
- Very late arrivals are excluded

Independent of patient recognition of symptoms
Early Detection with Continuous Monitoring to Address Unmet Need

Asymptomatic

First Occlusion

Sustained Occlusion

Standard Paradigm

Symptoms + Patient Delay

Presentation

Continuous Monitoring Paradigm

Presentation

First Occlusion
Rationale for Continuous ST Segment Monitoring

Mitchell W. Krucoff, MD, FACC, FSCAI, FAHA
Professor, Medicine/Cardiology
Duke University Medical Center
Director, Cardiovascular Devices Unit
Director, eECG Core Laboratory
Duke Clinical Research Institute
Occluding a Coronary Artery Causes Rapidly Progressive ST Changes

Median time to 200uV: 22 seconds

ST Segment Elevation During Balloon Occlusion and Coronary Thrombosis

Acute ST Segment Changes Occur Quickly Following Total Coronary Occlusion

Rationale of Algorithm for AngelMed Guardian Emergency Alarms

- Rapidly progressive ST segment changes are highly specific for acute occlusion of a coronary artery supplying viable myocardium
- Diagnostic ST segment changes occur, on average, 22 seconds after coronary occlusion
- Intracardiac electrogram provides pragmatic, high-quality continuous ST monitoring
- These findings provide the pathophysiologic basis for the Guardian Emergency Alarms
AngelMed Guardian System

Tim Fischell, MD, FACC, FSCAI, FAHA
Medical Advisor
Angel Medical Systems, Inc.

Professor of Medicine
Michigan State University
Guardian System Designed to Alert Patients at the Time of Coronary Occlusion

**Implantable Medical Device (IMD)**
- Internal vibrational alert
- Implant procedure is identical to a single chamber pacemaker

**External Device (EXD)**
- Acoustic and visual alert
- Alarm silence button
Guardian Programmed to Patient-Specific
ST Segment Detection Thresholds

Guardian Programmer
- Programs ST segment change detection thresholds
- Retrieves data from before and after alarms
Guardian Provide Two Levels of Patient Alerting

**Emergency Alarms**
- ST changes indicating coronary occlusion
- Vibrates – Beeps – Red Light Flashes
- Patient should call 911

**“See Doctor” Alerts**
- Lower priority
- Indicate condition interfering with ST segment monitoring
Guardian Provides Continuous Monitoring Compared to Personalized Baseline

- Personalized normalized baseline
- Every 90 seconds, IMD records and analyzes 10 seconds of electrogram data
- Personalized baseline continuously updated based on last 24 hours of data
Emergency Alarm Algorithm Based on Pathophysiology of Acute Coronary Occlusion

- Rapidly progressive ST change > 3 SD from patient’s personalized baseline
- ST changes must occur during normal heart rate
- ST changes must persist for ≥ 2 minutes

![Diagram showing normal heart beat and occluded coronary with ST change highlighted](image-url)
Timely Evaluation of ST Segment Changes is Warranted in High-Risk Patients

- Not all presentations with Emergency Alarms will identify ongoing coronary occlusions
  - Coronary occlusion is a dynamic process
  - New onset bundle branch block can produce ST elevation
- Not all occlusive events will trigger an Emergency Alarm, such as:
  - Occlusion with collateral flow
  - Saphenous vein graft occlusion
ALERTS Study Design

Christopher Mullin, MS
Director, Product Development Strategy
North American Science Associates
Inclusion Criteria Used to Enroll Patients at High Risk

- Prior myocardial infarction, unstable angina, or previous and/or scheduled CABG
- One or more additional risk factors:
  - Type I or type II diabetes
  - Renal insufficiency
  - TIMI score $\geq 3$
Exclusion Criteria Minimize Interference with Guardian Diagnostics and Endpoint Adjudication

- Chronic arrhythmias, bundle branch block, and atrial fibrillation
- Cognitive inability to recognize and respond to alerts
- Physical inability to feel vibration in the left pectoral region
- LVEF < 35%
- Existing pacer or ICD implant
Follow-up Schedule During Randomized Period

- Enrollment from December 2008 to June 2013
- Patients randomized 1:1 after implant

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<thead>
<tr>
<th>Guardian Feature</th>
<th>Treatment</th>
<th>Control</th>
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<tbody>
<tr>
<td>Detection</td>
<td>ON</td>
<td>ON</td>
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<tr>
<td>Alerting</td>
<td>ON</td>
<td>OFF</td>
</tr>
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- Follow-up visits: 1, 3, and 6 months
- ECGs at pre-implant, randomization, and every follow-up visit
**High Rate of Patient Follow-up**

- **Enrolled (N=1020)**
  - Not implanted (N=110)
  - Implied (N=910)
    - Not randomized
      - Discontinued: 2
      - Death: 1
    - Randomized (N=907)
      - Treatment (N=451)
        - 6 months (N=437)
          - Death: 3
          - Withdrawal: 0
          - Discontinued: 10
          - Lost to follow-up: 1
      - Control (N=456)
        - 6 months (N=446)
          - Death: 3
          - Withdrawal: 1
          - Discontinued: 6
          - Lost to follow-up: 0

- 97% Follow-up Rate
Baseline Demographic Characteristics Were Well Balanced Between Groups

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<tr>
<th>Characteristic</th>
<th>Treatment Group (N=451)</th>
<th>Control Group (N=456)</th>
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<tr>
<td><strong>Age (years), Mean ± SD</strong></td>
<td>59 ± 11</td>
<td>60 ± 10</td>
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<td><strong>Sex (Female)</strong></td>
<td>30%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Ejection fraction (%), Mean ± SD</strong></td>
<td>54 ± 9</td>
<td>54 ± 9</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>46%</td>
<td>49%</td>
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<tr>
<td><strong>History of reperfusion/revascularization</strong></td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>History of renal insufficiency</strong></td>
<td>16%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Previous STEMI</strong></td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Previous NSTEMI</strong></td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>History of unstable angina</strong></td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Angina frequency: 3-6 times/month</strong></td>
<td>26%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Angina frequency: &gt;6 times/month</strong></td>
<td>24%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>TIMI risk score, Mean ± SD</strong></td>
<td>3.7 ± 1.0</td>
<td>3.6 ± 1.0</td>
</tr>
</tbody>
</table>
Definition of Occlusive Events and Positive Tests for Ischemia

- **Occlusive event**: Guardian-detected ST segment changes indicative of coronary occlusion
  - Treatment – emergency alarm
  - Control – data capture

- **Confirmatory positive tests**:  
  - 12-lead ECG changes indicative of ACS (per blinded ECG Core Lab)
  - Elevated cardiac enzymes (per SOC)
  - Angiographic evaluation (per blinded Angiographic Core Lab)
  - Stress test positive for ischemia
Definition of Confirmed Events

**Confirmed events** require:

1. Guardian-detected occlusive event
2. Confirmation by a positive test

- Used to determine time-to-door endpoints in ALERTS
- Adjudicated by independent AGEA committee
- If occlusion had multiple detections, first detection used for analysis
Definition of Maximum Time for Late Arrivals

- **Late arrival**: confirmed event with time from occlusion-to-door > 2 hours
- Maximum time for late arrival (look-back window)
  - 2008 (start of study): none specified
  - 2011: 7-day maximum specified
  - 2013: SAP amended to include up to 90-day maximum in response to new literature\(^1\)
- All revisions to maximum time for late arrival made prior to unblinding

Example Calculations of Time from Occlusion-to-Door

- Onset of Coronary Occlusion
- Treatment Patient
  - 2 min
  - 60 min Time-to-door
- Control Patient with Symptoms
  - 2 min
  - 90 min Symptom onset
  - 4.5 hours Time-to-door
- Control Patient without Symptoms
  - 2 min
  - 15 days Time-to-door
Definition of ACS Event

- **ACS event:**
  - Confirmed event, or
  - Site-identified positive ECG or angiographic tests

- Used for analyses not related to primary/secondary endpoints
Adaptive Sample Size Determination

- Bayesian adaptive design used to adjust sample size based on interim treatment effect
  - Interim looks planned every 300 patients after 600 randomized, up to maximum of 3,000 patients
  - Predictive model did not accurately assess new Q-wave at 6 months from earlier visits
Early Stopping of Enrollment in the ALERTS Study

- As result of modeling issues, AngelMed consulted with FDA to discuss early stopping of enrollment
  - All enrolled patients would continue to be followed
- FDA informed AngelMed that they would not approve or disapprove early stopping
- AngelMed stopped enrollment at 1,020 patients
  - Initial IDE-approved sample size
  - AngelMed did not request an increase
Early Stopping of Enrollment Did Not Bias Results in Favor of the Guardian

- Early stopping of enrollment was a major protocol violation
  - Decision made when sponsor was blinded
  - Rationale: adaptive sample size re-estimation was not reliable
  - Only information provided to sponsor was that model suggested enrollment continue
- Early stopping reduced power, lowering likelihood of finding significant results
- Does not impact data quality
ALERTS Protocol Omitted Two ECG Changes Indicative of ACS in Error

- ST depression and T-wave changes were adjudicated as positive tests
  - Omitted from protocol in error
  - Included in ECG Core Lab adjudication materials
- Both ST depression and T-wave changes are included in WHO definition of ACS and 2011 ACCF/AHA Guidelines\(^1,2\)

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Statistical Modeling in ALERTS

- Non-informative priors for statistical analysis
- Posterior probability: probability that Guardian is superior to Control
- Thresholds for statistical significance:
  - Primary safety endpoint: 0.954
  - Primary efficacy endpoint: 0.983
  - Secondary endpoints: multiplicity-controlled 0.975
ALERTS Study Results

C. Michael Gibson, MS, MD, FACC, FSCAI, FRCP, FAHA
Professor of Medicine
Harvard Medical School
Primary Safety Endpoint Definition

- All AEs reviewed and adjudicated by independent Adverse Events Committee
- Objective: demonstrate a > 90% freedom from system-related complications
## Description of 31 Primary Safety Events in 30 Patients

<table>
<thead>
<tr>
<th>Event</th>
<th># Events</th>
<th>% Subjects (N=910)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>Pain at or near pocket site</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Lead migration/dislodgment</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiac perforation</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Erosion</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Loss of sensing</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Visible bump where implanted in chest</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Other system-related complication*</td>
<td>5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Events include, lead adapter replacement, two early battery failures, subject request for removal due to discomfort, and skin erosion from the lead.
Primary Safety Objective Achieved

<table>
<thead>
<tr>
<th>Event-free patients</th>
<th>Primary Safety Endpoint (N=910)</th>
</tr>
</thead>
<tbody>
<tr>
<td>880</td>
<td></td>
</tr>
<tr>
<td>Patients with system-related complications</td>
<td>30</td>
</tr>
<tr>
<td>% Event-free</td>
<td>96.7%</td>
</tr>
<tr>
<td>Posterior probability</td>
<td>&gt; 0.9999</td>
</tr>
</tbody>
</table>

Note: Threshold for statistical significance = 0.954
Primary Efficacy Endpoint Definition

- Composite 6-month endpoint:
  1. Late arrival for confirmed event (>2 hours after first Guardian detection)
     - Pre-specified maximum for late arrivals of 7 to 90 days
  2. New Q-waves at 6 months
  3. Cardiac or unexplained death
Control Group Had Higher Frequency of Late Arrival for Confirmed Events

<table>
<thead>
<tr>
<th>Maximum Time for Late Arrival</th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-day Maximum</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>90-day Maximum</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>
Assessment of New Q-waves

- New pathological Q-waves identify new areas of permanent heart damage

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<thead>
<tr>
<th>Baseline at Randomization</th>
<th>New Q-waves Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Month Visit</td>
</tr>
<tr>
<td>-</td>
<td>X</td>
</tr>
<tr>
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</tbody>
</table>

- Single baseline serial over-read process showed: 10 Treatment vs. 14 Control new Q-waves
  - Consistent with ACC/ESC definition
Few Cardiac or Unknown Deaths; All Had Prior Guardian Detections

- 3 Treatment patients
  - 2 patients had multiple Emergency Alarms with no intervention due to absence of symptoms
  - 1 patient had high heart rate detection
- 1 Control patient
  - Guardian ST detection prior to death
Primary Efficacy Endpoint Results Impacted by Maximum Time for Late Arrivals

- Primary efficacy objective not met
- Higher posterior probability with 90-day maximum
  - Included 8 Control patients with >7-day delays in presentation

<table>
<thead>
<tr>
<th>Maximum Time for Late Arrivals</th>
<th>Treatment (N=423) n (%)</th>
<th>Control (N=428) n (%)</th>
<th>Treatment Difference [95% CrI]</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Days</td>
<td>16 (3.8%)</td>
<td>21 (4.9%)</td>
<td></td>
<td>0.786</td>
</tr>
<tr>
<td>90 Days</td>
<td>16 (3.8%)</td>
<td>29 (6.8%)</td>
<td></td>
<td>0.974</td>
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Threshold for statistical significance = 0.983
# ALERTS Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac or unexplained death</td>
<td>All patients</td>
</tr>
<tr>
<td>New Q-waves</td>
<td>All patients</td>
</tr>
<tr>
<td>Late arrival (&gt;2 hrs) for confirmed events</td>
<td>All patients</td>
</tr>
<tr>
<td>Average time from occlusion-to-door</td>
<td>All confirmed events</td>
</tr>
<tr>
<td>New Q-waves</td>
<td>Silent MI Risk Subgroup*</td>
</tr>
<tr>
<td>New Q-waves or late arrival</td>
<td>Silent MI Risk Subgroup*</td>
</tr>
</tbody>
</table>

*Silent MI Risk Subgroup: diabetics, women >65 years, prior silent MI
## Secondary Endpoints: Components of the Composite Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Treatment n/N (%)</th>
<th>Control n/N (%)</th>
<th>Treatment Difference [95% CrI]</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late arrival for confirmed event (90-day max)</td>
<td>4/439 (0.9%)</td>
<td>17/446 (3.8%)</td>
<td>0.9978</td>
<td></td>
</tr>
<tr>
<td>New Q-waves (single baseline)</td>
<td>10/420 (2.4%)</td>
<td>14/427 (3.3%)</td>
<td>0.7783</td>
<td></td>
</tr>
<tr>
<td>Cardiac or unexplained death</td>
<td>3/441 (0.7%)</td>
<td>1/447 (0.2%)</td>
<td>0.1830</td>
<td></td>
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Threshold for statistical significance = 0.975.
# Confirmatory Positive Tests by Group

<table>
<thead>
<tr>
<th># of Tests</th>
<th>Tests Confirming Event</th>
<th>Treatment (N=34)</th>
<th>Control (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzymes</td>
<td>ECG</td>
<td>Angio</td>
</tr>
<tr>
<td>4</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Adjudicated Confirmed Events Used to Evaluate Occlusion-to-Door Endpoints

- 94% of events confirmed by cardiac enzymes, ECG, or angiography; or multiple tests
- 52 confirmed events:
  - 34 events in Treatment group (27 pts)
  - 18 events in Control group (17 pts)
- Imbalance in number of confirmed events due to unrecognized silent ischemia in Control group
  - Nearly identical number of Guardian detections in both groups
## Secondary Endpoint: Time from Occlusion-to-Door for Confirmed Events

### Confirmed Events

<table>
<thead>
<tr>
<th>Time Range</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (Pts)</td>
<td>34 (27)</td>
<td>18 (17)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Median</td>
<td>51 minutes</td>
<td>22 days</td>
<td></td>
</tr>
</tbody>
</table>

### Time from First Guardian-Detected Occlusion to Presentation

- <2 hrs
- 2-6 hrs
- 6-24 hrs
- 24-48 hrs
- 2-7 days
- 7-30 days
- 30-50 days
- 50-70 days
- 70-90 days

---

**Note:** The chart compares the time from occlusion to presentation for confirmed events between the treatment and control groups. The median time for the treatment group is 51 minutes, and for the control group, it is 22 days, with a high posterior probability of >0.9999.
Several Factors Influenced Very Long Occlusion-to-Door Times in Control Group

- ALERTS is the first study to assess “occlusion-to-door” rather than “symptom-to-door”
- Control patients don’t present for silent events
- Coronary occlusion is a dynamic process
  - Vessels can repeatedly close and open
Guardian Prompted Patients to Seek Medical Attention for Silent Events or Before Symptom Onset

Guardian was able to prompt patients:
- For silent events
- Prior to onset of recognized symptoms

<table>
<thead>
<tr>
<th>% of Confirmed Events Without Symptoms</th>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>85%</td>
<td></td>
<td>28%</td>
</tr>
</tbody>
</table>

[Graph showing comparison between Treatment Group and Control Group with percentages for confirmed events without symptoms.]
### Secondary Endpoints in Silent MI Risk Subgroup

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment (N=222) n (%)</th>
<th>Control (N=243) n (%)</th>
<th>Treatment Difference [95% CrI]</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Q-waves</td>
<td>6 (2.7%)</td>
<td>12 (4.9%)</td>
<td></td>
<td>0.8867</td>
</tr>
<tr>
<td>New Q-waves or Late arrival for confirmed event</td>
<td>8 (3.6%)</td>
<td>17 (7.0%)</td>
<td></td>
<td>0.9446</td>
</tr>
</tbody>
</table>

- New Q-waves can identify new areas of permanent myocardial damage in silent MI patients who do not present emergently

Single ECG baseline analysis. Threshold for statistical significance = 0.975.
Post-Hoc Efficacy Analyses of ALERTS Study Data

- “Dual Baseline” analysis to correct for ECG artifacts
- Event-based analyses
ECG Artifacts Addressed with Dual Baseline Analysis

- Issue: pre-existing Q-waves missed at randomization
  - Some Q-waves didn’t appear on randomization ECG, but were present at pre-implant ECG
  - Fixed by dual baseline (required absence of Q-waves at screening and randomization)

<table>
<thead>
<tr>
<th>Pre-Implant Baseline</th>
<th>Randomization Baseline</th>
<th>1 Month Visit</th>
<th>3 Month Visit</th>
<th>6 Month Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>
Dual ECG Baseline Provides More Accurate Assessment of Primary Efficacy Endpoint

- Pre-specified analysis: single (randomization) baseline
- Post-hoc dual baseline analysis incorporated both pre-implant and randomization ECGs
  - Disqualifies 4 Q-waves that were not new

<table>
<thead>
<tr>
<th>ECG Baseline</th>
<th>Treatment (N=423) n (%)</th>
<th>Control (N=428) n (%)</th>
<th>Treatment Difference [95% CrI]</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>16 (3.8%)</td>
<td>29 (6.8%)</td>
<td></td>
<td>0.9740</td>
</tr>
<tr>
<td>Dual</td>
<td>13 (3.1%)</td>
<td>28 (6.5%)</td>
<td></td>
<td>0.9908</td>
</tr>
</tbody>
</table>

90-day maximum for late arrivals. Threshold for statistical significance = 0.983
Two Methods Used to Address FDA Request for Event-Based Analyses

- Patient-based analysis (primary analysis)
  - Each patient can only contribute 1 event
- Two event-based analyses:
  1. Endpoint-based analysis
     - Accounts for each primary endpoint event
  2. Detection-based analysis
     - Accounts for each primary endpoint event and Guardian-detected occlusion
Event-Based Analyses Provide Supportive Evidence Of Guardian Efficacy

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Rate Ratio [95% CrI]</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint-based analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>18</td>
<td>32</td>
<td></td>
<td>0.9779</td>
</tr>
<tr>
<td>Dual</td>
<td>15</td>
<td>31</td>
<td></td>
<td>0.9918</td>
</tr>
<tr>
<td>Detection-based analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>18</td>
<td>41</td>
<td></td>
<td>0.9989</td>
</tr>
<tr>
<td>Dual</td>
<td>15</td>
<td>40</td>
<td></td>
<td>0.9997</td>
</tr>
</tbody>
</table>

90-day maximum for late arrivals.
Threshold for statistical significance = 0.983
Device Performance

Diagnostic Accuracy of Emergency Alarms
Cardiac Catheterizations
STEMIs and Plaque Ruptures
Patient Acceptance
Treatments Group PPV for ACS Events

- Positive Predictive Value (PPV) analysis for ACS
  - Assesses accuracy of Emergency Alarms
  - Rules determined with FDA prior to unblinding
- True positive: confirmed positive alarm (CPA)
- False positive: non-confirmed positive alarm (NCPA)
- Confirmation of ACS by site or Core Lab
  - Site identification reflects clinical practice
  - Allows for reasonable comparison with published PPV for chest pain
- \[ \text{PPV} = \frac{\text{CPA}}{\text{CPA} + \text{NCPA}} \]
Summary of All Emergency Alarms in ALERTS Treatment Patients

- Treatment Alarms (N=179)
- Excluded Alarms (N=72)
- Evaluated Alarms (N=107)
- Aggregated Alarms (N=15) (i.e., no double-counting)
- PPV Analysis (N=92)
  - Confirmed Alarm (N=60)
  - Non-Confirmed Alarm (N=22)
  - Other Relevant Medical Conditions (N=10)

- Medical procedure induced (N=9)
- Inpatient alarm (N=18)
- Algorithm anomaly or programming error (N=18)
- Incomplete testing or non-compliance (N=27)

- Other Relevant Medical Conditions
  - Sleep apnea (N=1)
  - Vasospasm (N=5)
  - New bundle branch block (N=4)

34 AGEA-adjudicated events + 26 site-identified events
Rationale for Exclusion of Alarms from PPV Analysis

<table>
<thead>
<tr>
<th>Excluded Alarms (N=72)</th>
<th>N Alarms Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical procedure induced</td>
<td></td>
</tr>
<tr>
<td>• Cardiac cath / PCI / CABG</td>
<td>9</td>
</tr>
<tr>
<td>Inpatient alarm</td>
<td></td>
</tr>
<tr>
<td>• Patient was already in hospital</td>
<td>18</td>
</tr>
<tr>
<td>Programming error (n=17) / algorithm anomaly (n=1)</td>
<td></td>
</tr>
<tr>
<td>• Corrected early in the study</td>
<td>18</td>
</tr>
<tr>
<td>Incomplete testing (n=8) or non-compliance (n=19)</td>
<td></td>
</tr>
<tr>
<td>• Patient did not undergo timely protocol-specified standard of care tests</td>
<td>27</td>
</tr>
</tbody>
</table>
**PPV of Emergency Alarms for ACS Events Is Higher Than Chest Pain**

<table>
<thead>
<tr>
<th>Condition</th>
<th>PPV (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>65% (60/92)</td>
</tr>
<tr>
<td>ACS + Other Medically Relevant Conditions</td>
<td>77% (70/92)</td>
</tr>
<tr>
<td>Chest Pain (Bright et al.* (AMI))</td>
<td>16%</td>
</tr>
<tr>
<td>Chest Pain (Goodacre et al.* (AMI + ACS))</td>
<td>13%</td>
</tr>
</tbody>
</table>

ALERTS Emergency Department
Standard of Care Diagnostic Flow

Alarm

Alarm & Symptoms

ED Arrival

Serial ECG

Serial Enzymes

Positive

Negative or Inconclusive

Optionally Performed

Stress Test

Positive

Negative

Patient Discharge

SOC Chest Pain Protocol

SOC Outcome

Cardiac Cath
Cardiac Catheterizations in Patients Presenting with Alarms Highly Associated with Identified ACS

<table>
<thead>
<tr>
<th>Number of Cardiac Caths</th>
<th>Symptoms Only (N=33)</th>
<th>Alarm + Symptoms (N=19)</th>
<th>Alarm Only (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS Identified</td>
<td>23</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>No ACS Identified</td>
<td>10</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
Cardiac Catheterizations In Patients with Identified ACS Presenting Without Alarms

- 23 ACS identified for symptoms-only caths:
  - 4 Core Lab-confirmed thrombotic events
  - 19 were not thrombotic events, and would not be expected to trigger an Emergency Alarm:
    - 9 were progressive narrowing
    - 7 were <50% stenosis
    - 3 were pre-existing >50% stenosis not previously treated
- None of 23 events were associated with rapidly progressive, significant ST segment changes
Guardian Accurately Identified STEMIs and Plaque Ruptures

- All 5 STEMIs had an associated Guardian detection
- All 7 Core Lab-confirmed plaque ruptures occurring at normal heart rate had an associated Guardian detection
  - 1 plaque rupture missed due to high heart rate, which prevents ST shift detection
High Patient Acceptance of the Guardian System

- 175 subjects were eligible for IMD replacement at battery end of life
- 163 (93%) patients elected to receive a new Guardian device
Post-Approval Plans

David Fischell, PhD, FAIMBE
Chief Executive Officer
Angel Medical Systems, Inc.
AngelMed Proposes a Registry to Collect Additional Data on Events of Interest

- New registry study
  - Prospective, event-driven
  - Number of events required for registry closure to be discussed with FDA
  - Planned collaboration with ACC’s NCDR ACTION Registry
    - Allows for nested design and comparison to a control group without the Guardian
Proposed Post-Market Registry Endpoints

- 60 ACS events in 45/451 (10.0%) Treatment patients at only 6 months of follow-up
  - 3/4 of these patients were asymptomatic
- Proposed post-market registry endpoints:
  - Time from occlusion-to-door
  - Safety data
  - Emergency alarm compliance
  - PPV for qualified emergency alarms
  - Preservation of LVEF
  - New Q-waves
  - Long-term mortality
When commercially available, Guardian will provide valuable ECG diagnostic information:

- Electrograms from last 24 hours

Baseline Electrogram from 24 hrs before

Electrogram at Time of Alarm
Post-Market Training Program Will Tailor Education for Health Care Professionals

- Training program and education aimed at 3 groups of health care professionals:
  - EMTs and paramedics
  - Emergency department personnel
  - Coronary care practitioners and their support professionals
Controlled Distribution of the Guardian System Will Ensure Safe and Appropriate Use

- Initial distribution at ALERTS clinical sites
- As additional sites are trained, AngelMed will:
  - Distribute programmers at additional sites & local hospitals
  - Similar model used to support programmers for pacemakers and ICDs
Benefit-Risk Assessment

Mitchell W. Krucoff, MD, FACC, FSCAI, FAHA
Professor, Medicine/Cardiology
Duke University Medical Center
Director, Cardiovascular Devices Unit
Director, eECG Core Laboratory
Duke Clinical Research Institute
Rapid Progressive ST Elevation Indicates Coronary Artery Occlusion

- 30 years of advances in MI care:
  - Reperfusion therapies:
    - Thrombolytics
    - PCI
  - Organizational changes:
    - Brisk diagnostic recognition
    - Shortened door-to-balloon times
- Acute coronary occlusion is defined by pathologic ST segment elevation on ECG
Patient-Related Delay Has Not Improved Over 30 Years

- No progress in reducing:
  - 250,000 deaths before reaching hospital
  - Average 2-hour delay in presence of symptoms before calling 911
  - Silent MI
AngelMed Guardian: Addressing Patient Delay Among High-Risk Patients

- Alerts patients to acute coronary occlusions persistent for 2 minutes
- First technology to provide objective signal of coronary occlusion to high-risk patients
- Offers patients who suffer a silent MI their only chance for prompt treatment
Considerations for ALERTS Study

- Considerable care in design from AngelMed, FDA experts, cardiologists, and engineers
- Blinded Core Labs and independent committees
- 97% follow-up in randomized period
- Benefit-risk: totality of the data
  - Did not meet primary efficacy endpoint
  - Significant reduction in time from occlusion-to-door and late arrivals
  - Risk: implantation
  - 93% of ALERTS patients elected reimplantation
Guardian System is a Paradigm Shift in Treatment of Heart Attacks

<table>
<thead>
<tr>
<th>Old Paradigm</th>
<th>New Paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Reactive”</strong></td>
<td><strong>“Proactive”</strong></td>
</tr>
<tr>
<td>2 hours of symptoms</td>
<td>2 minutes of occlusion</td>
</tr>
<tr>
<td>Requires chest pain or atypical symptoms</td>
<td>Independent of symptoms</td>
</tr>
<tr>
<td>Sustained total occlusion of vessel</td>
<td>First occurrence of vessel occlusion</td>
</tr>
<tr>
<td>Treatment of MI</td>
<td>Prevention of MI</td>
</tr>
</tbody>
</table>

**Guardian System is a Paradigm Shift** in Treatment of Heart Attacks

**Best Case Scenario**

- 2 hours of symptoms
- Requires chest pain or atypical symptoms
- Sustained total occlusion of vessel
- Treatment of MI
Example of Coronary Occlusion Detection with the Guardian System

Patient at home

6:40 am

Guardian Baseline Electrogram

Emergency Alarm Electrogram

Fischell et al. *J Am Coll Cardiol* 2010;56:1089-98.
Example of Coronary Occlusion Detection with the Guardian System

Patient in ambulance

External Surface ECG

Guardian Electrogram

Example of Coronary Occlusion Detection with the Guardian System

Patient in emergency department

External Surface ECG

Guardian Electrogram

Fischell et al. *J Am Coll Cardiol* 2010;56:1089-98.
Example of Coronary Occlusion Detection with the Guardian System

Patient in cath lab

LCX – Occlusion  After Stent

Total time from occlusion to treatment in under 2 hours

Guardian System: Breakthrough Technology for High-Risk Patients

- Totality of the data from ALERTS
  - **Benefits**: accelerates time from occlusion-to-door among high-risk coronary patients; more accurate than chest pain
  - **Risks**: equivalent to single-chamber pacemaker

- Patients consistently wanted reimplantation
- Committed post-market study
- Guardian is the first solution to address patient-related delays for heart attacks
Guardian® System for the Alerting of Patients to ST Segment Changes Indicative of Coronary Artery Occlusion