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

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

Additional Experts

Clinical Studies	**David Keenan** VP, Clinical & Regulatory Affairs Angel Medical Systems, Inc.
Human Factors	**Chris Young, PhD** Senior Human Factors Engineer Angel Medical Systems, Inc.

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.
2 Thune et al. *Eur J Heart Fail* 2011;13:148-53.

Approximately 1/3 of Heart Attacks Are Silent

Study (Year) [Patient notes]	Number of MIs	% Silent MIs
Canto (2000)	434,877	33%
Males	180,922	29%
Females	253,954	39%
Reykjavik (1995, 1998)	878	34%
Framingham (1990)	363	30%
FIELD (2009) [diabetic]	730	37%
Leening (2010) [>55 years of age]	6,305	48% (F=65%; M=37%)
McSweeny (2003) [females]	515	44%

"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

1 Reimer & Jennings. *Lab Invest* 1979;40:633-44.

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[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[3]
  - Patient education[4]

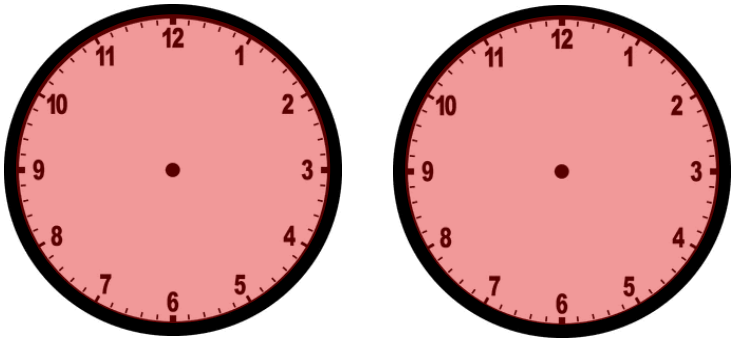
1 Bright & Pocock. *Can J Emerg Med* 2002;4:212-4.
2 Goodacre et al. *Acad Emerg Med* 2002;9:203-8.
3 Gibson. Paper presented at *Heart Rhythm Society* 2009.
4 Luepker et al. *JAMA* 2000;284:60-67.

Continuous Monitoring Would Significantly Reduce Patient-Related Delay

Standard Paradigm

Median of 2 hours

from symptom onset to 911



Represents “best-case” scenario where:

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

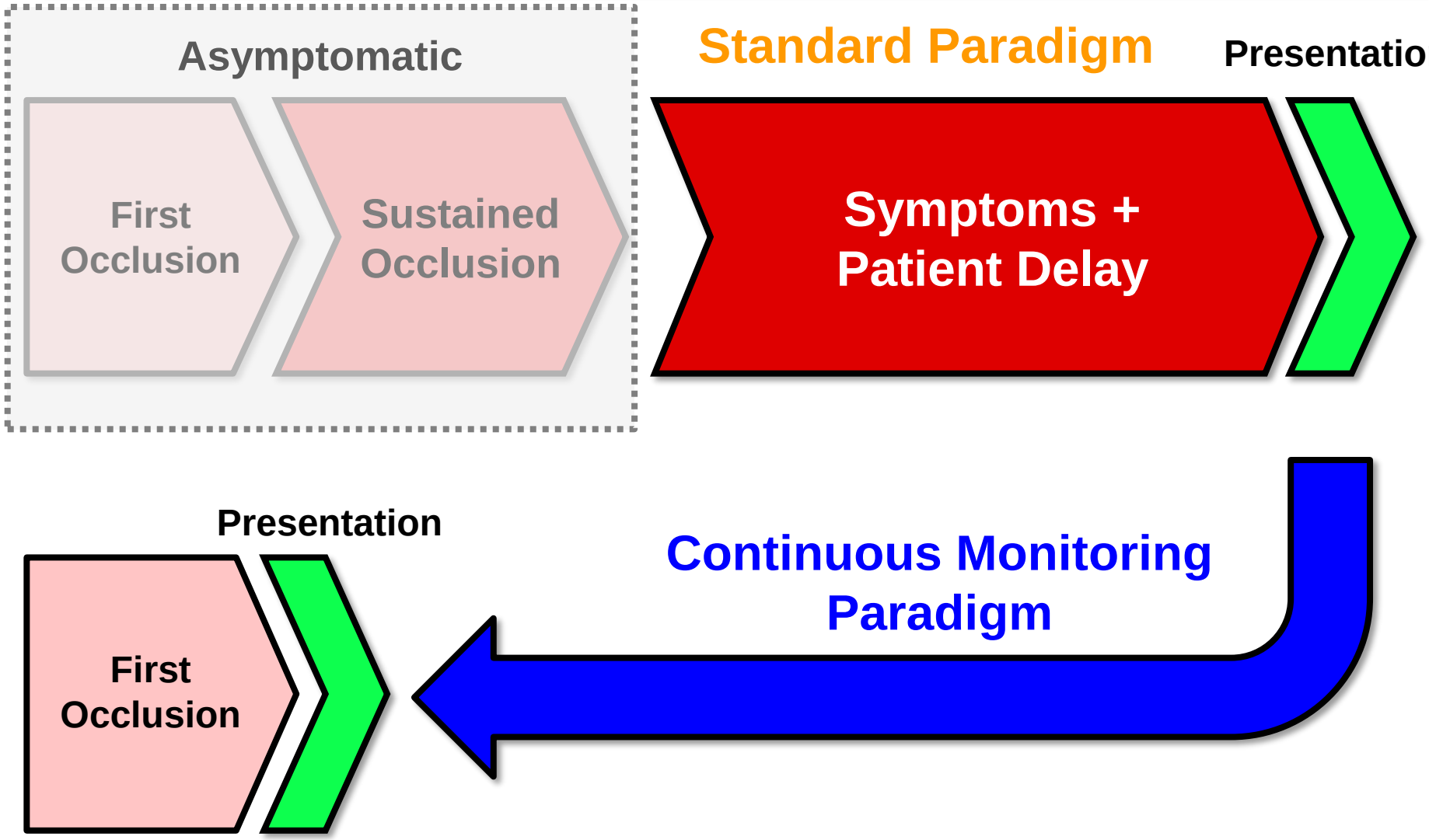
Continuous Monitoring Paradigm

2 minutes

from coronary occlusion to 911

Independent of patient recognition of symptoms

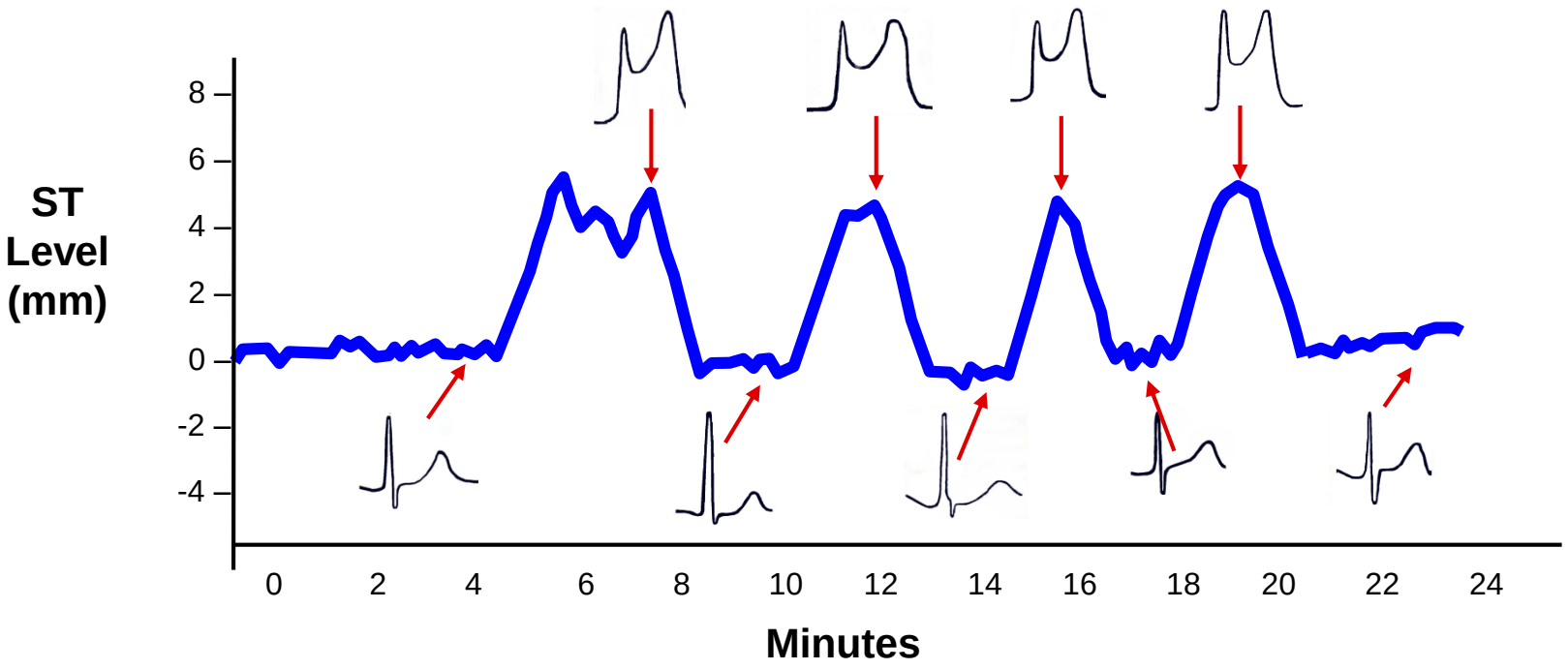
Early Detection with Continuous Monitoring to Address Unmet Need



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

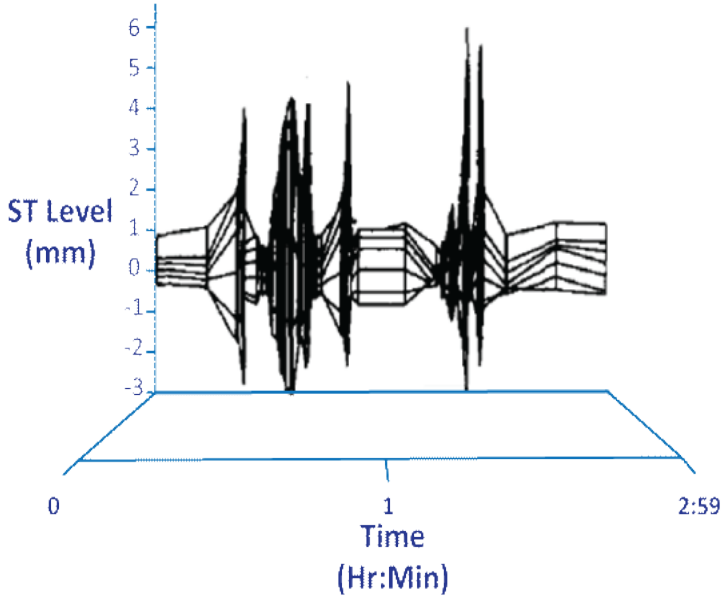


Median time to 200uV: 22 seconds

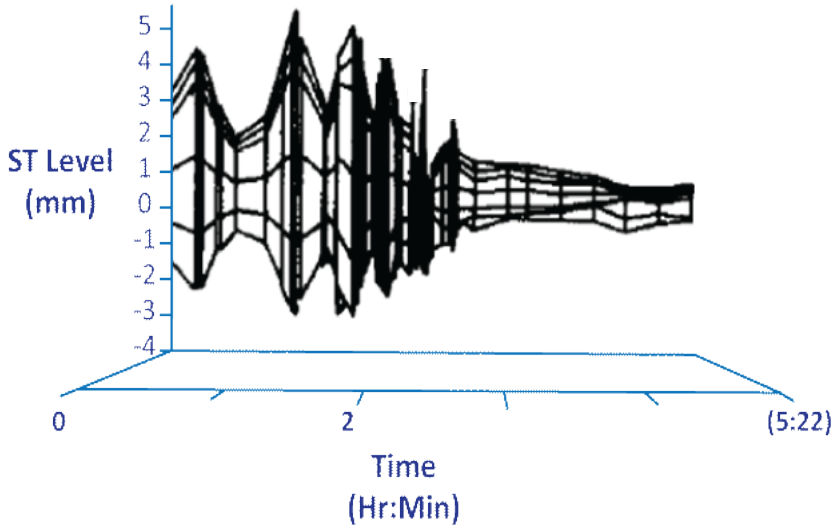
Krucoff et al. *J Electrocardiography* 1987;20 Suppl:15-21.

ST Segment Elevation During Balloon Occlusion and Coronary Thrombosis

PTCA



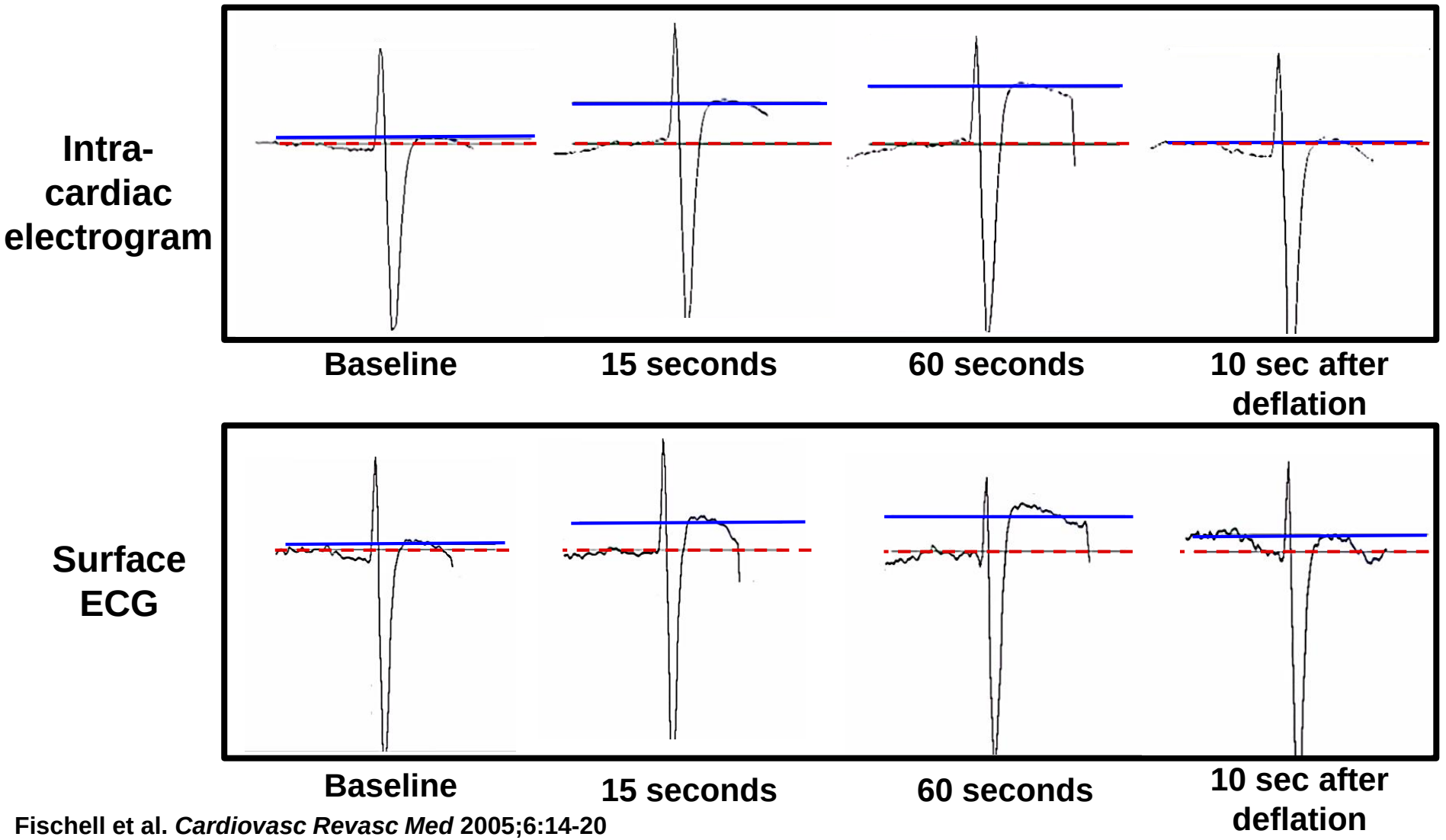
STEMI + PTCA



90 degree Views

Krucoff et al. *Am J Cardiol* 1993;71:145-51.

Acute ST Segment Changes Occur Quickly Following Total Coronary Occlusion



Fischell et al. *Cardiovasc Revasc Med* 2005;6:14-20

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
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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

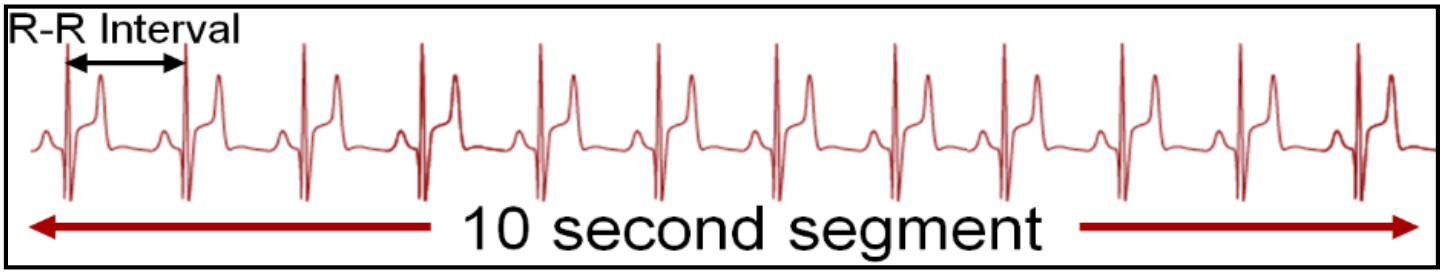
- ST changes indicating coronary occlusion
- Vibrates – Beeps – Red Light Flashes
- Patient should call 911

"See Doctor" Alerts

- Lower priority
- Indicate condition interfering with ST segment monitoring

Guardian Provides Continuous Monitoring Compared to Personalized Baseline

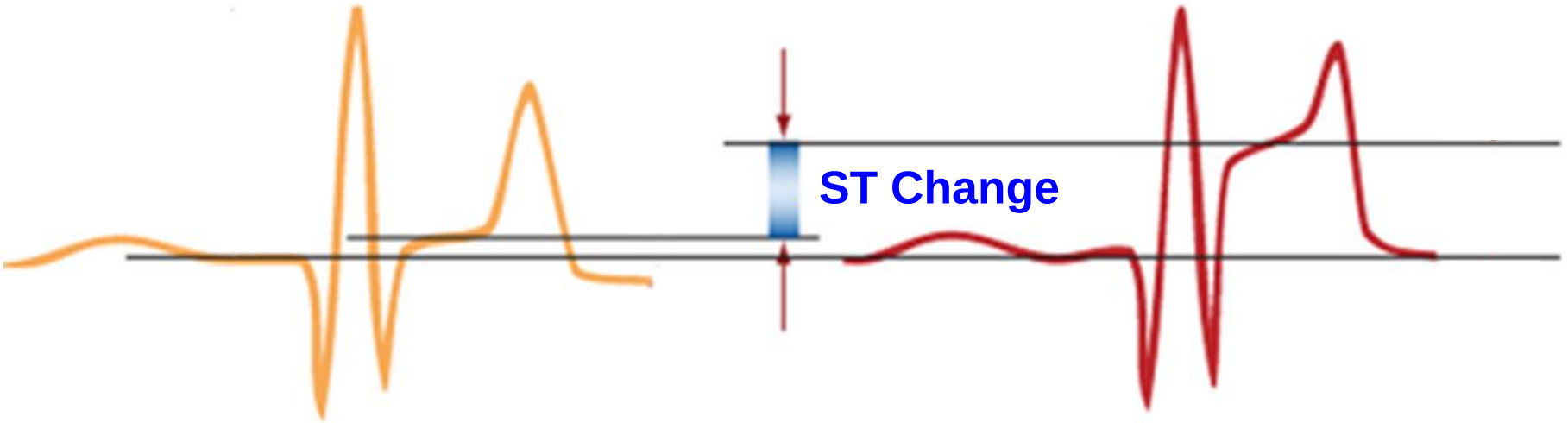
- Personalized normalized baseline
- Every 90 seconds, IMD records and analyzes 10 seconds of electrogram data



- 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



Normal Heart Beat **Occluded Coronary**

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 ≥ 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

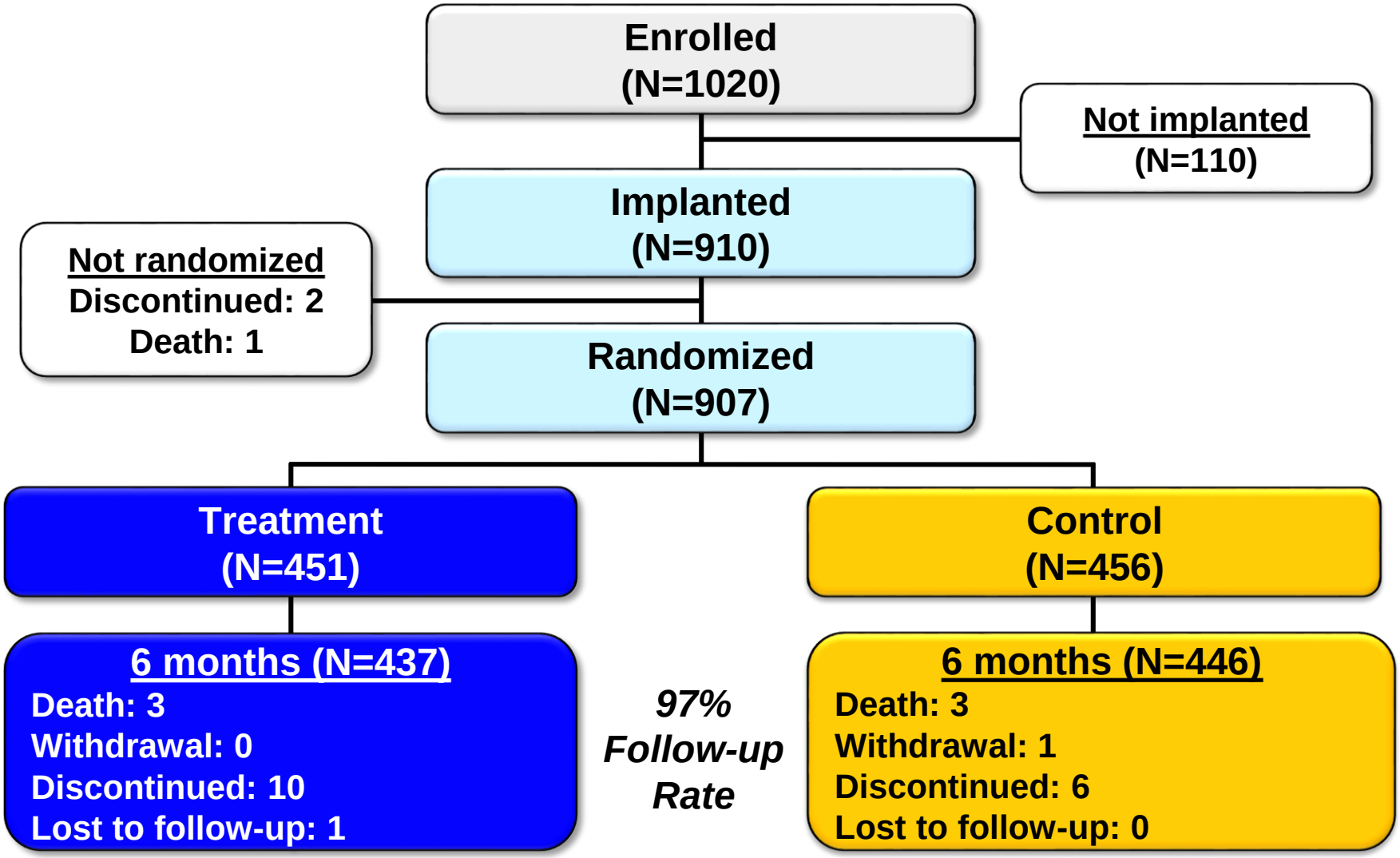
Follow-up Schedule During Randomized Period

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

Guardian Feature	Treatment	Control
Detection	**ON**	**ON**
Alerting	**ON**	**OFF**

- Follow-up visits: 1, 3, and 6 months
- ECGs at pre-implant, randomization, and every follow-up visit

High Rate of Patient Follow-up



Baseline Demographic Characteristics Were Well Balanced Between Groups

Characteristic	Treatment Group (N=451)	Control Group (N=456)
Age (years), Mean±SD	59±11	60±10
Sex (Female)	30%	34%
Ejection fraction (%), Mean±SD	54±9	54±9
Diabetes	46%	49%
History of reperfusion/revascularization	98%	97%
History of renal insufficiency	16%	18%
Previous STEMI	24%	25%
Previous NSTEMI	28%	28%
History of unstable angina	44%	44%
Angina frequency: 3-6 times/month	26%	22%
Angina frequency: >6 times/month	24%	27%
TIMI risk score, Mean±SD	3.7±1.0	3.6±1.0

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

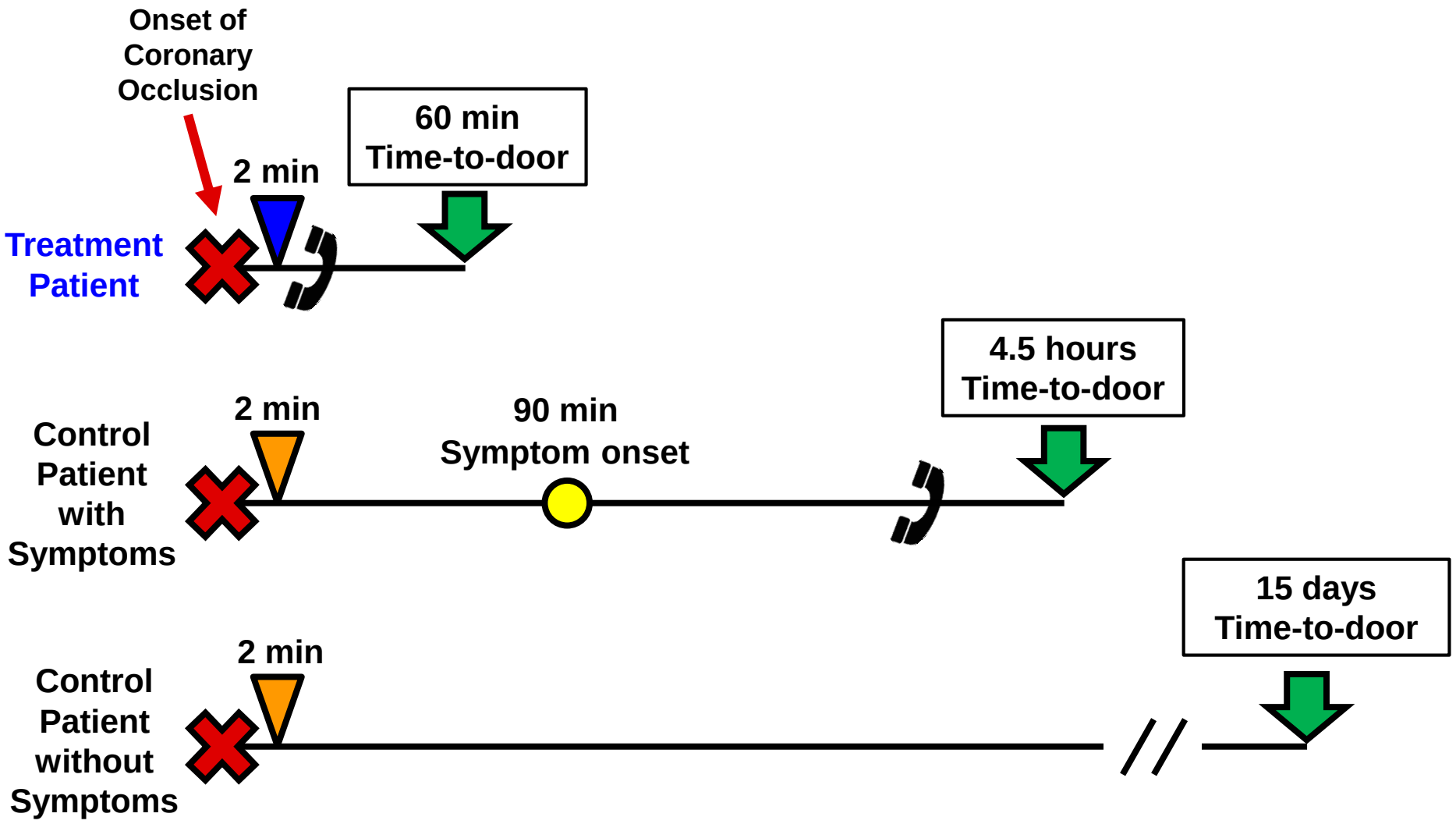
- Used to determine time-to-door endpoints in ALERTS
- Adjudicated by independent AGEA committee
- If occlusion had multiple detections, first detection used for analysis

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

1 Marijon et al. 2013 AHA Session. Now published as: Marijon et al. *Ann Intern Med* 2016;164:23-9.

Example Calculations of Time from Occlusion-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]

1 Mendis et al (World Health Organization Writing Group). *Int J Epidemiol* 2011;40:139-46.
2 ACCF/AHA. *Circulation* 2011;123:2022-60.

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

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

* 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

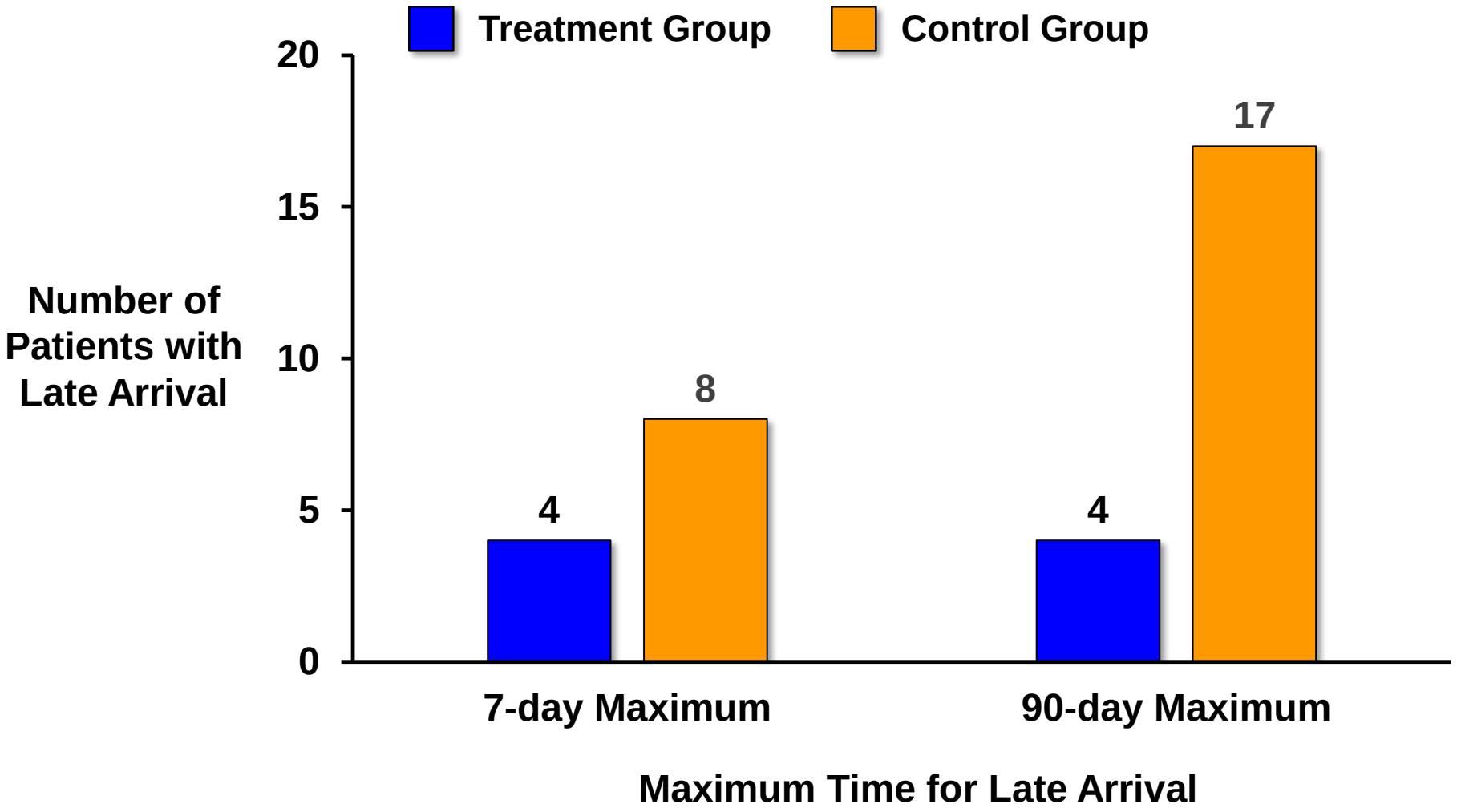
	Primary Safety Endpoint (N=910)
Event-free patients	880
Patients with system-related complications	30
% Event-free	96.7%
Posterior probability	> 0.9999

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



Assessment of New Q-waves

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

Baseline at Randomization	New Q-waves Present		
	1 Month Visit	3 Month Visit	6 Month Visit
-	X	X	X
-	-	X	X
-	-	-	X

- Single baseline serial over-read process showed: 10 Treatment vs. 14 Control new Q-waves
  - Consistent with ACC/ESC definition

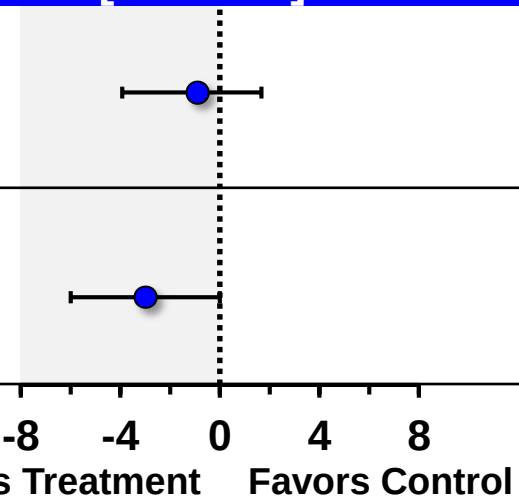
Few Cardiac or Unknown Deaths; All Had Prior Guardian Detections

- 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

Maximum Time for Late Arrivals	Treatment (N=423) n (%)	Control (N=428) n (%)	Treatment Difference [95% CrI]	Posterior Probability
7 Days	16 (3.8%)	21 (4.9%)		0.786
90 Days	16 (3.8%)	29 (6.8%)		0.974



Threshold for statistical significance = 0.983

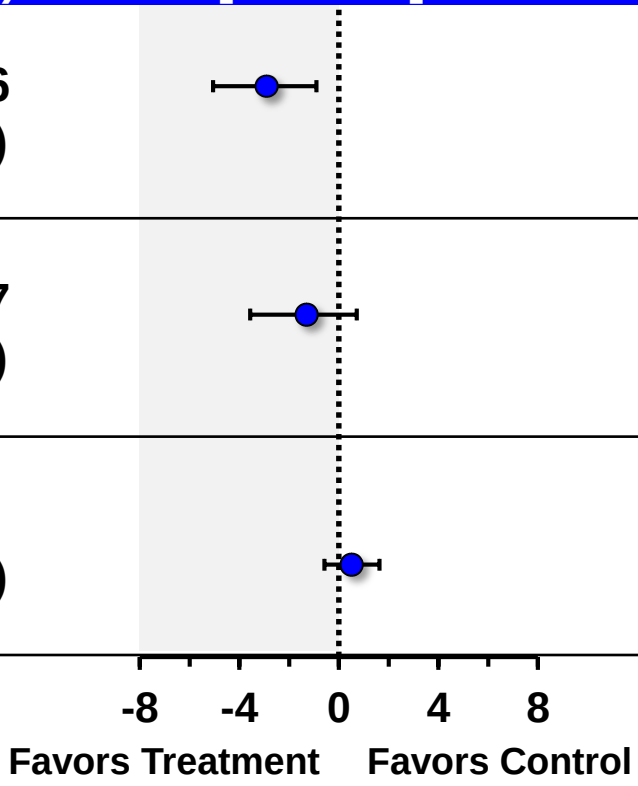
ALERTS Secondary Efficacy Endpoints

Secondary Endpoint	Assessment
Cardiac or unexplained death	All patients
New Q-waves	All patients
Late arrival (>2 hrs) for confirmed events	All patients
Average time from occlusion-to-door	All confirmed events
New Q-waves	Silent MI Risk Subgroup*
New Q-waves or late arrival	Silent MI Risk Subgroup*

*Silent MI Risk Subgroup: diabetics, women >65 years, prior silent MI

Secondary Endpoints: Components of the Composite Primary Efficacy Endpoint

	Treatment n/N (%)	Control n/N (%)	Treatment Difference [95% CrI]	Posterior Probability
Late arrival for confirmed event (90-day max)	4/439 (0.9%)	17/446 (3.8%)		0.9978
New Q-waves (single baseline)	10/420 (2.4%)	14/427 (3.3%)		0.7783
Cardiac or unexplained death	3/441 (0.7%)	1/447 (0.2%)		0.1830



Threshold for statistical significance = 0.975.

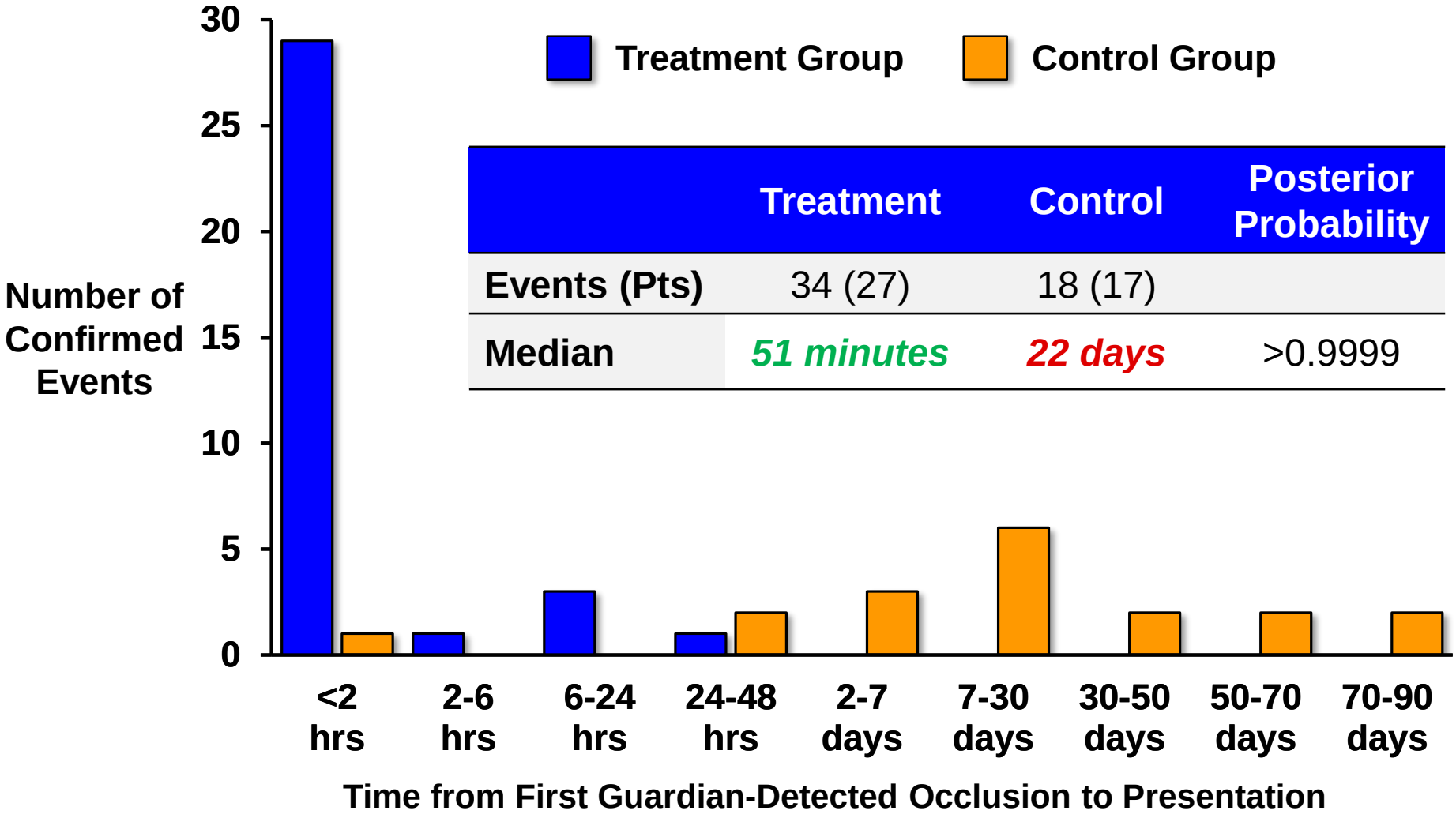
Confirmatory Positive Tests by Group

# of Tests	Tests Confirming Event				Treatment (N=34)	Control (N=18)
	Enzymes	ECG	Angio	Stress test		
4	✓	✓	✓	✓	1	0
3	✓	✓	✓		1	2
		✓	✓	✓	3	1
2	✓	✓			6	0
	✓		✓		4	2
		✓	✓		5	1
		✓		✓	1	1
			✓	✓	3	0
1	✓				3	4
		✓			3	5
			✓		2	1
				✓	2	1

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

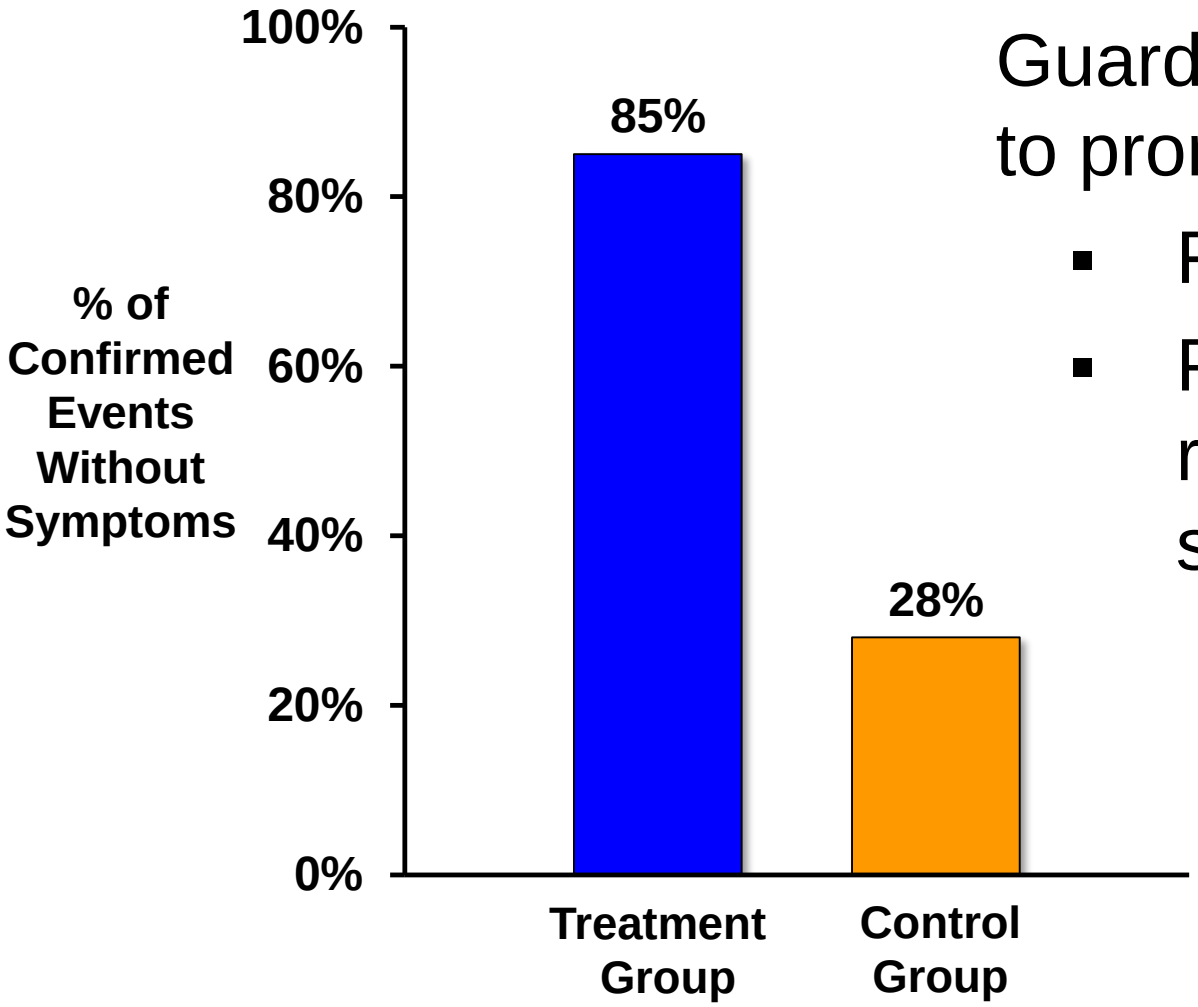


	Treatment	Control	Posterior Probability
Events (Pts)	34 (27)	18 (17)	
Median	*51 minutes*	*22 days*	>0.9999

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

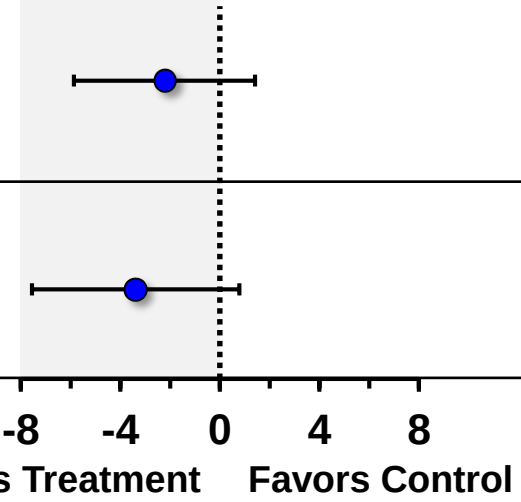


Guardian was able to prompt patients:

- For silent events
- Prior to onset of recognized symptoms

Secondary Endpoints in Silent MI Risk Subgroup

	Treatment (N=222) n (%)	Control (N=243) n (%)	Treatment Difference [95% CrI]	Posterior Probability
New Q-waves	6 (2.7%)	12 (4.9%)		0.8867
New Q-waves or Late arrival for confirmed event	8 (3.6%)	17 (7.0%)		0.9446



- 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

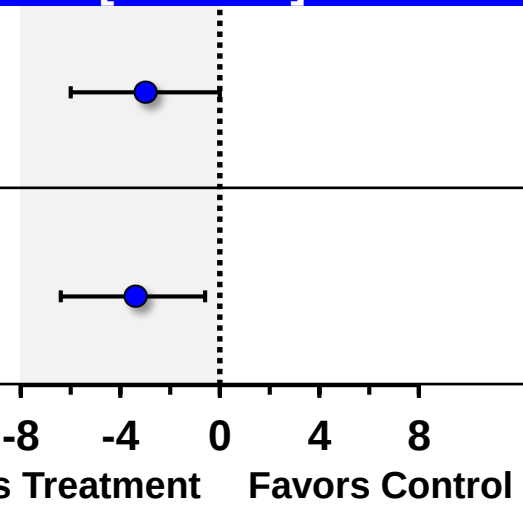
- Issue: pre-existing Q-waves missed at randomization
  - Some Q-waves didn't appear on randomization ECG, but were present at pre-implant ECG
  - Fixed by dual baseline (required absence of Q-waves at screening and randomization)

Pre-Implant Baseline	Randomization Baseline	1 Month Visit	3 Month Visit	6 Month Visit
X	-	X	X	X
-	-	X	X	X
-	-	-	X	X
-	-	-	-	X

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

ECG Baseline	Treatment (N=423) n (%)	Control (N=428) n (%)	Treatment Difference [95% CrI]	Posterior Probability
Single	16 (3.8%)	29 (6.8%)		0.9740
Dual	13 (3.1%)	28 (6.5%)		0.9908



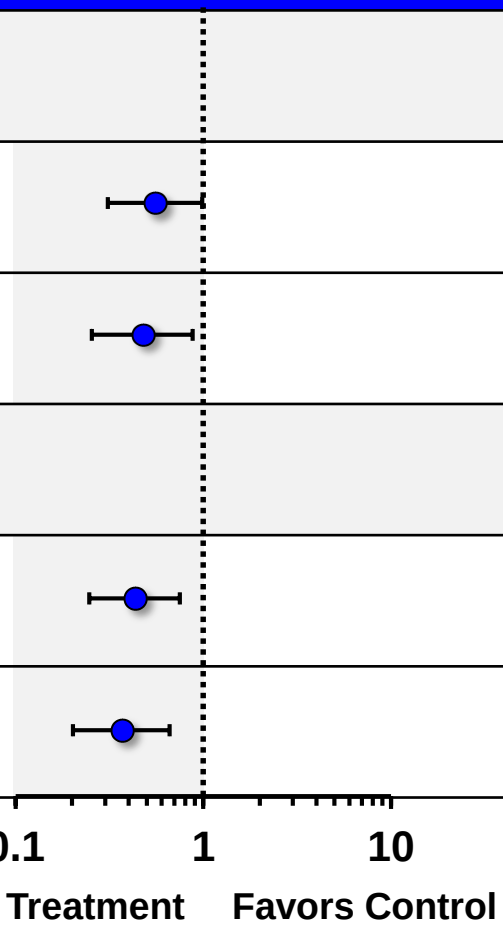
90-day maximum for late arrivals.
Threshold for statistical significance = 0.983

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

Analysis ECG Baseline	Treatment Events	Control Events	Rate Ratio [95% CrI]	Posterior Probability
Endpoint-based analysis				
Single	18	32		0.9779
Dual	15	31		0.9918
Detection-based analysis				
Single	18	41		0.9989
Dual	15	40		0.9997



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

Device Performance

Diagnostic Accuracy of Emergency Alarms

Cardiac Catheterizations

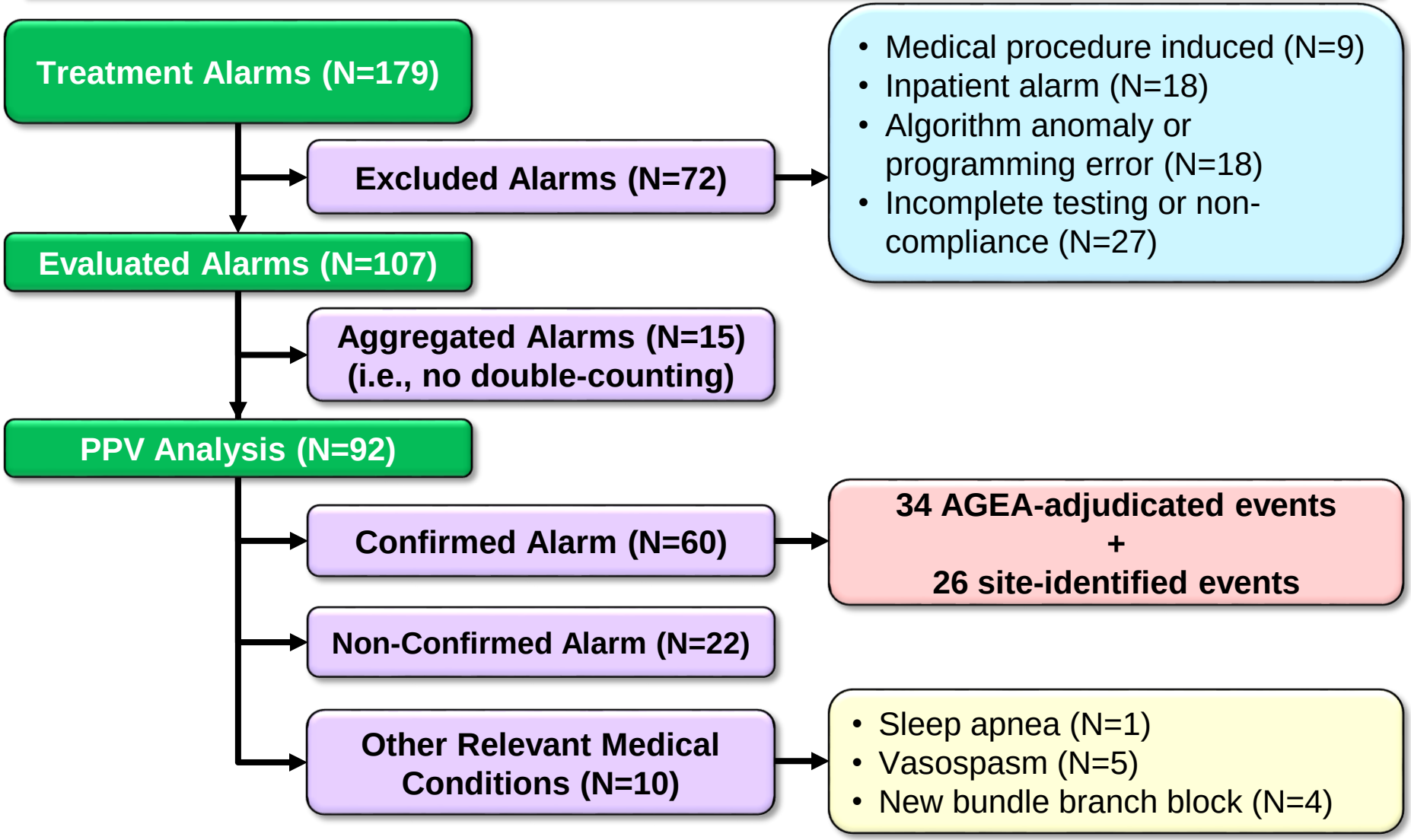
STEMIs and Plaque Ruptures

Patient Acceptance

Treatment 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
- PPV = CPA / (CPA + NCPA)

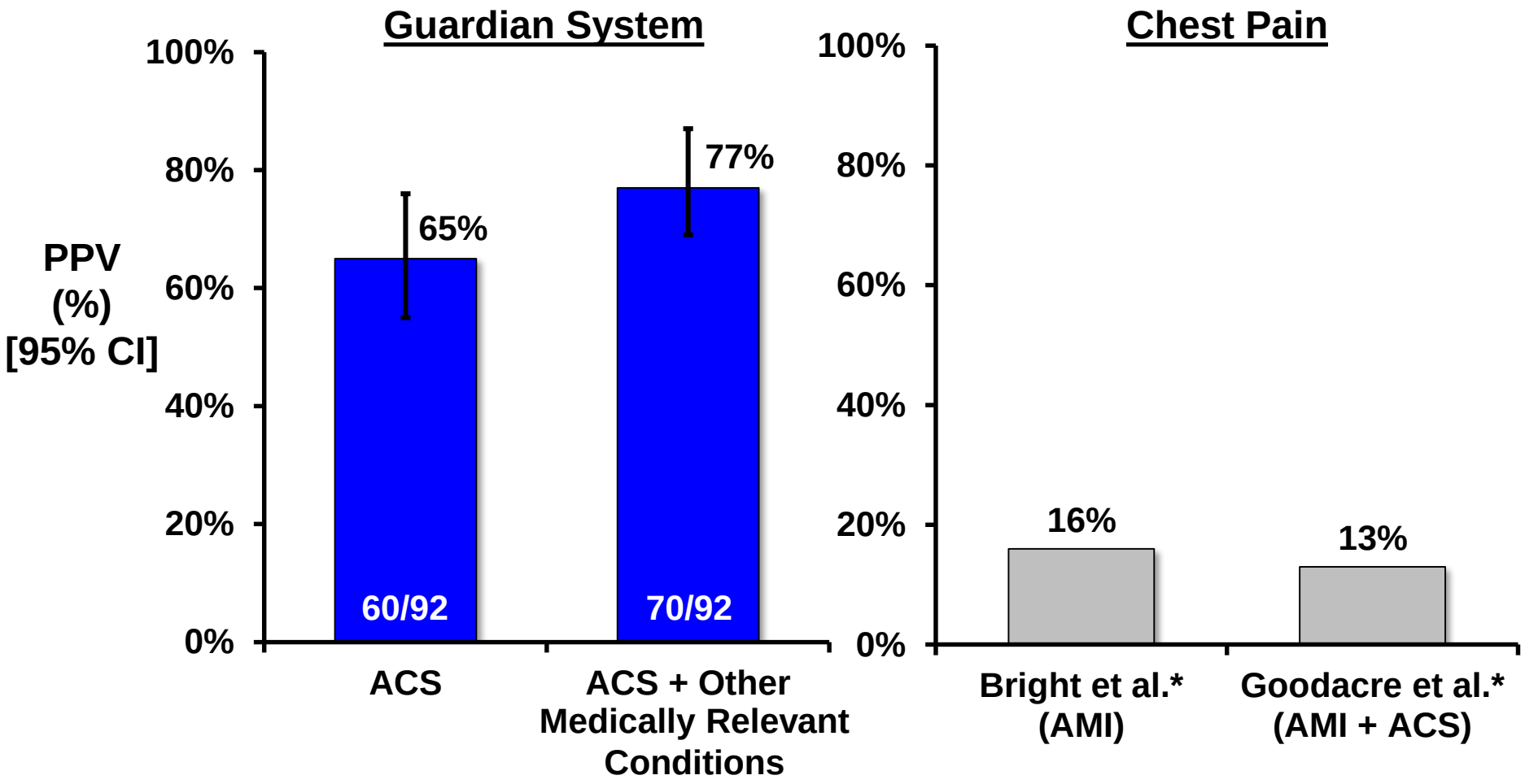
Summary of All Emergency Alarms in ALERTS Treatment Patients



Rationale for Exclusion of Alarms from PPV Analysis

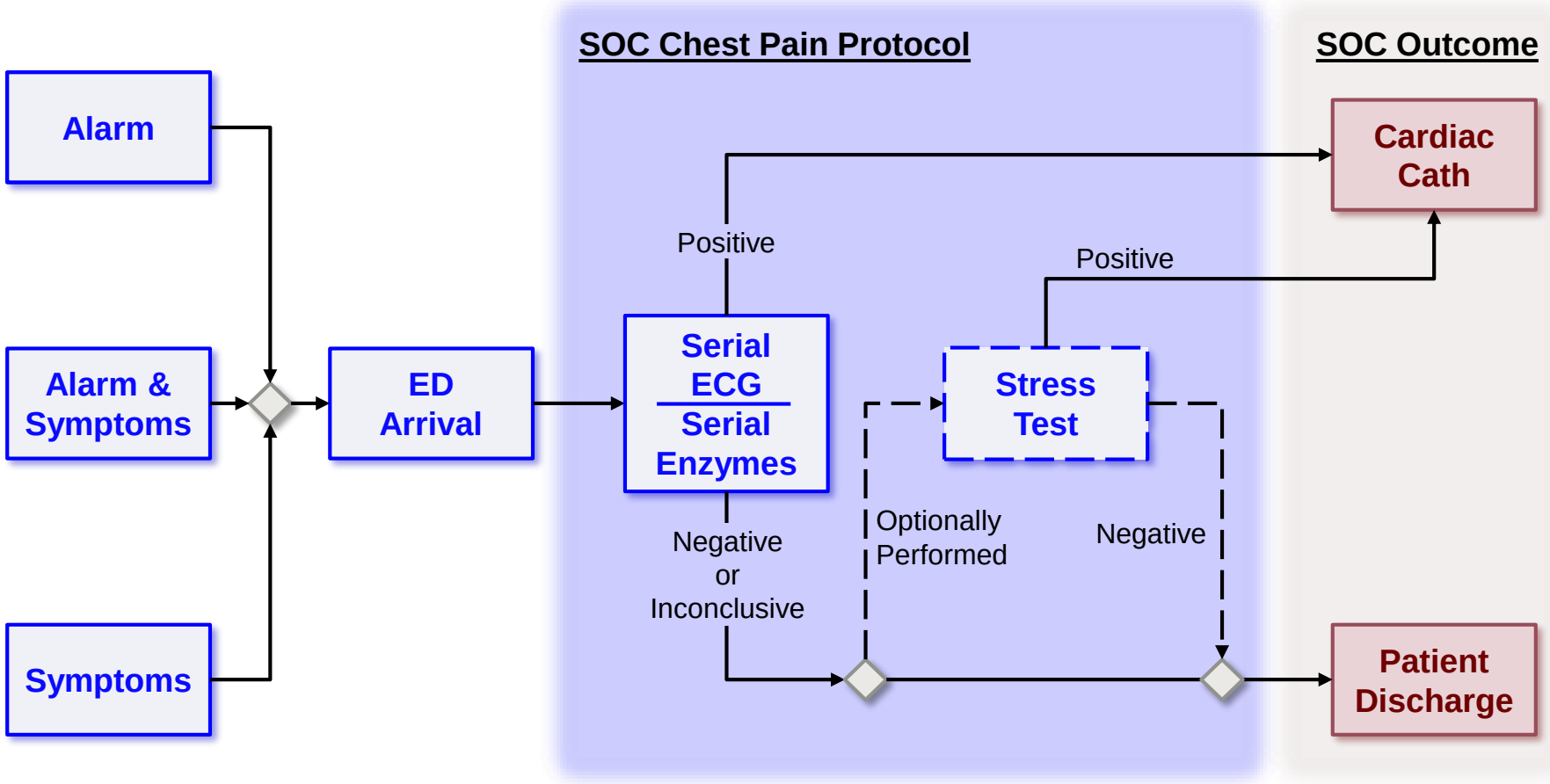
Excluded Alarms (N=72)	N Alarms Excluded
Medical procedure induced • Cardiac cath / PCI / CABG	**9**
Inpatient alarm • Patient was already in hospital	**18**
Programming error (n=17) / algorithm anomaly (n=1) • Corrected early in the study	**18**
Incomplete testing (n=8) or non-compliance (n=19) • Patient did not undergo timely protocol-specified standard of care tests	**27**

PPV of Emergency Alarms for ACS Events Is Higher Than Chest Pain

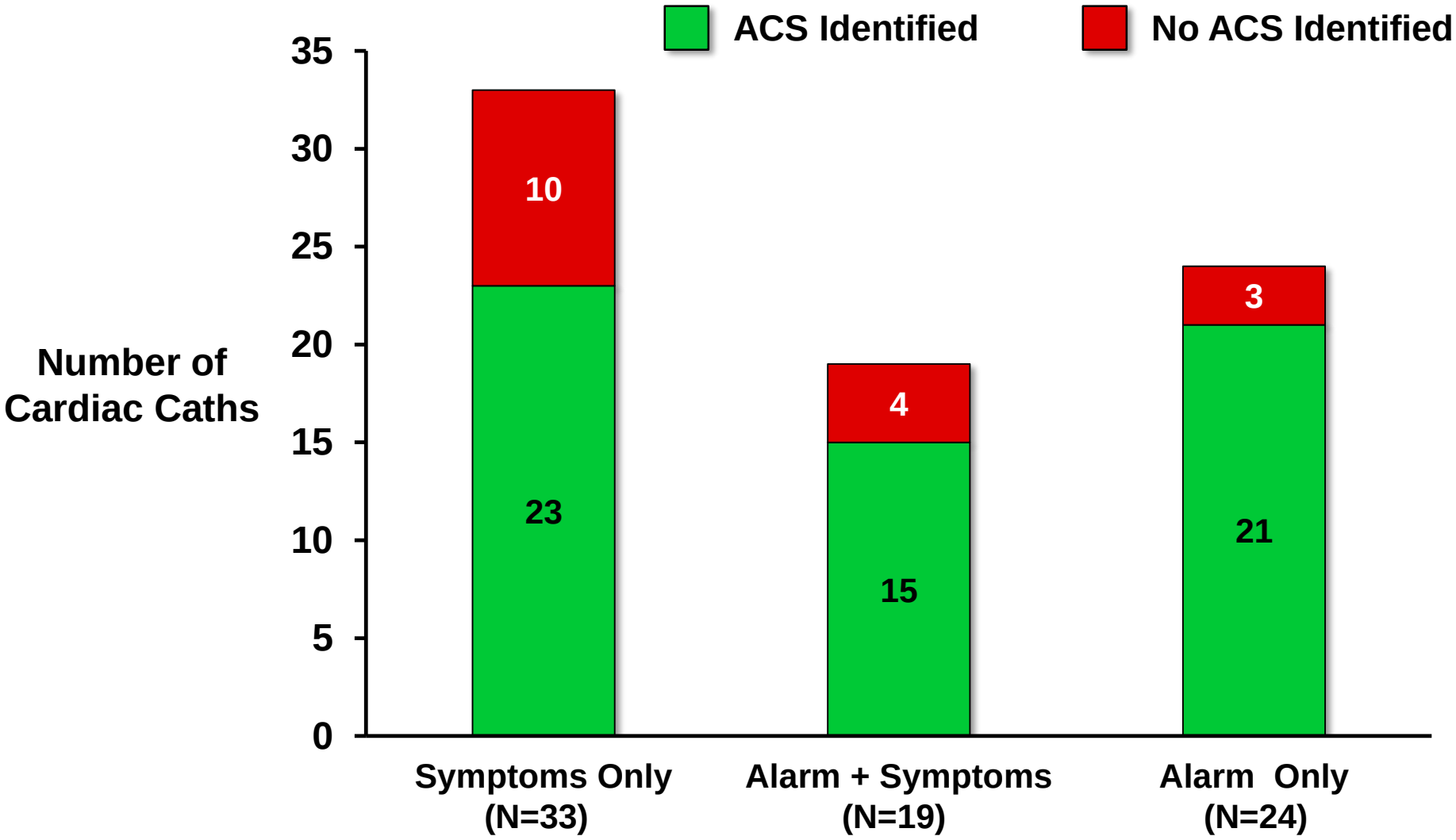


* Bright and Pocock. *Can J Emerg Med* 2002;4:212-4.
** Goodacre et al. *Acad Emerg Med* 2002;9:203-8.

ALERTS Emergency Department Standard of Care Diagnostic Flow



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



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

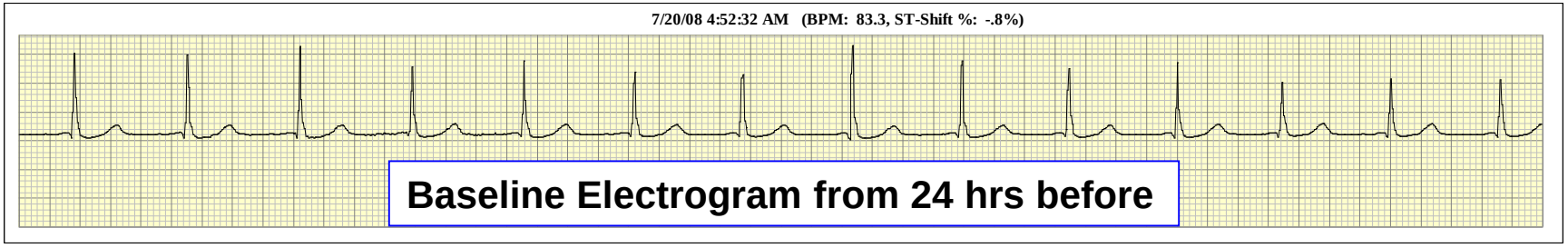
- New registry study
  - Prospective, event-driven
  - Number of events required for registry closure to be discussed with FDA
  - Planned collaboration with ACC's NCDR ACTION Registry
    - Allows for nested design and comparison to a control group without the Guardian

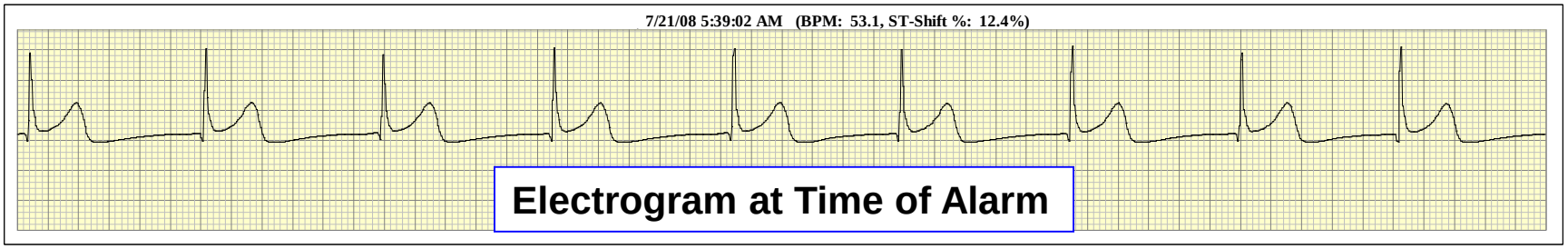
Proposed Post-Market Registry Endpoints

- 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

Guardian Will Provide Physicians Considerable Diagnostic Information

- When commercially available, Guardian will provide valuable ECG diagnostic information
  - Electrograms from last 24 hours





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

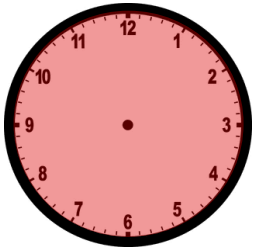
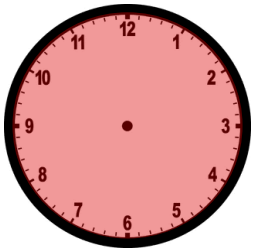
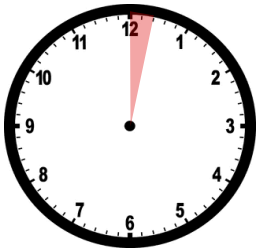
- Alerts patients to acute coronary occlusions persistent for 2 minutes
- First technology to provide objective signal of coronary occlusion to high-risk patients

- 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

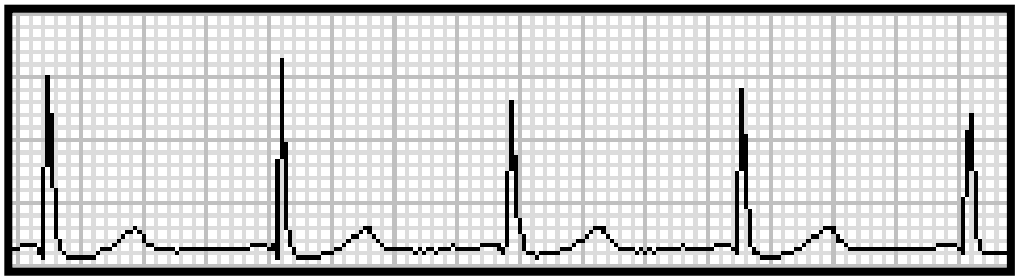
Old Paradigm *"Reactive"*	New Paradigm *"Proactive"*
  **Best Case Scenario**	
2 hours of symptoms	**2 minutes of occlusion**
Requires chest pain or atypical symptoms	**Independent of symptoms**
Sustained total occlusion of vessel	**First occurrence of vessel occlusion**
Treatment of MI	**Prevention of MI**

Example of Coronary Occlusion Detection with the Guardian System

Patient at home

6:40 am

Guardian Baseline Electrogram



Emergency Alarm Electrogram

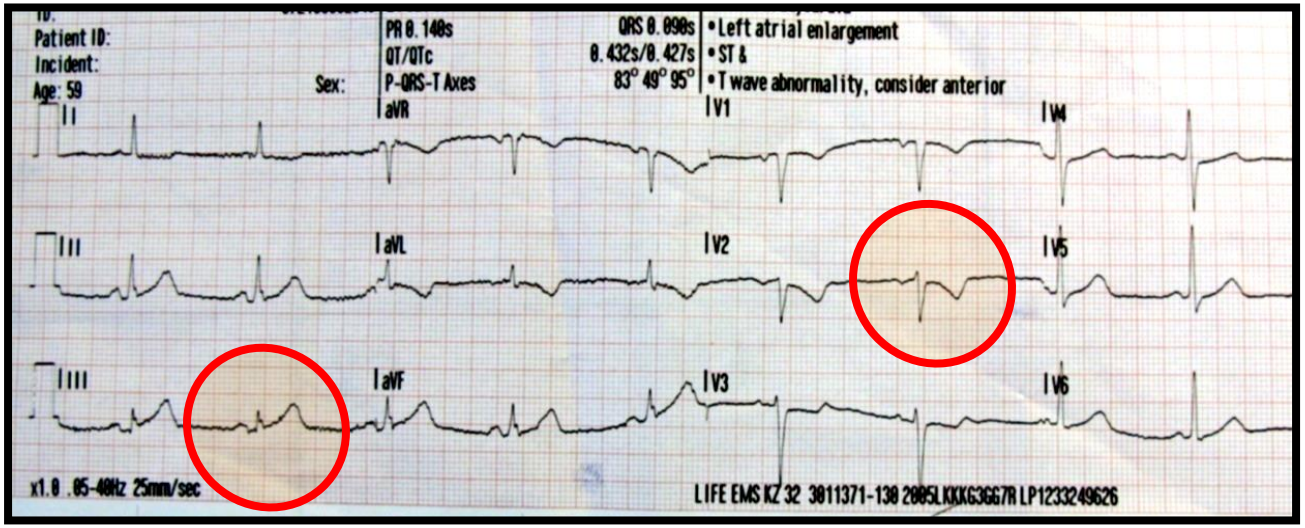
Fischell et al. *J Am Coll Cardiol* 2010;56:1089-98.

Example of Coronary Occlusion Detection with the Guardian System

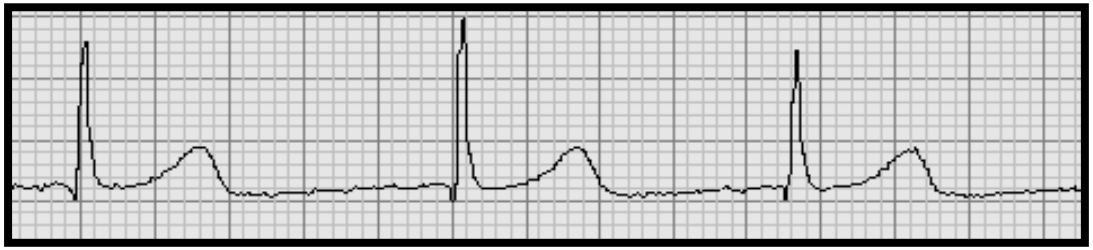
Patient in ambulance

7:00 am

External Surface ECG



Guardian Electrogram



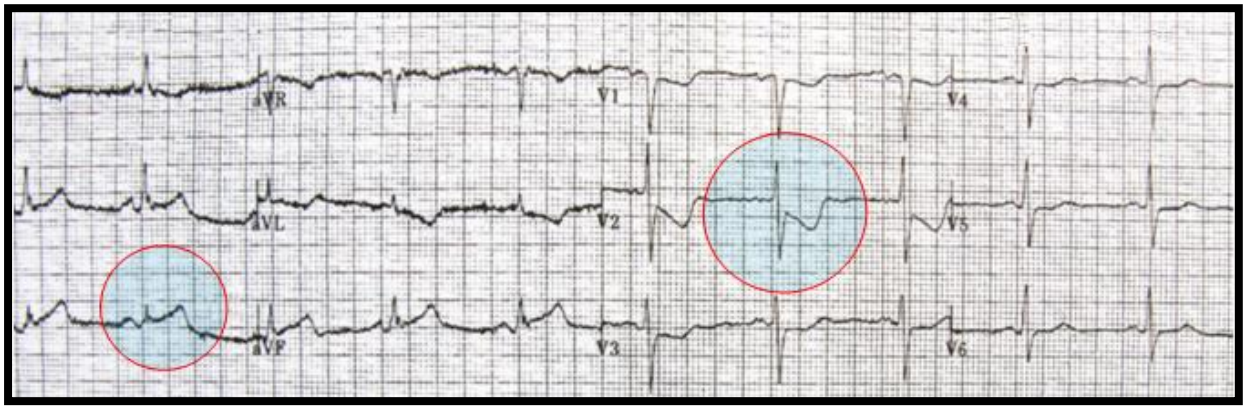
Fischell et al. *J Am Coll Cardiol* 2010;56:1089-98.

Example of Coronary Occlusion Detection with the Guardian System

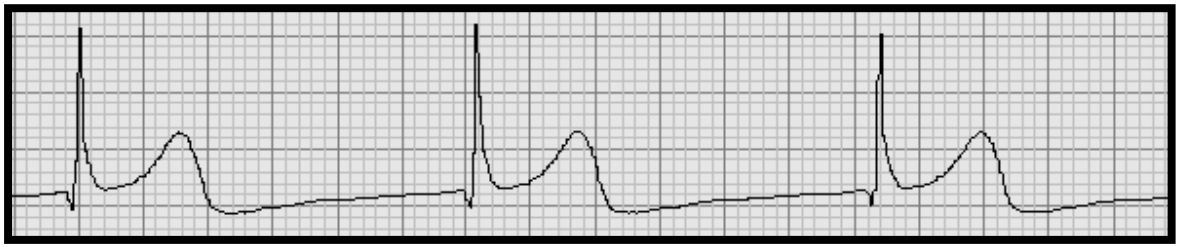
Patient in emergency department

7:30 am

External Surface ECG



Guardian Electrogram



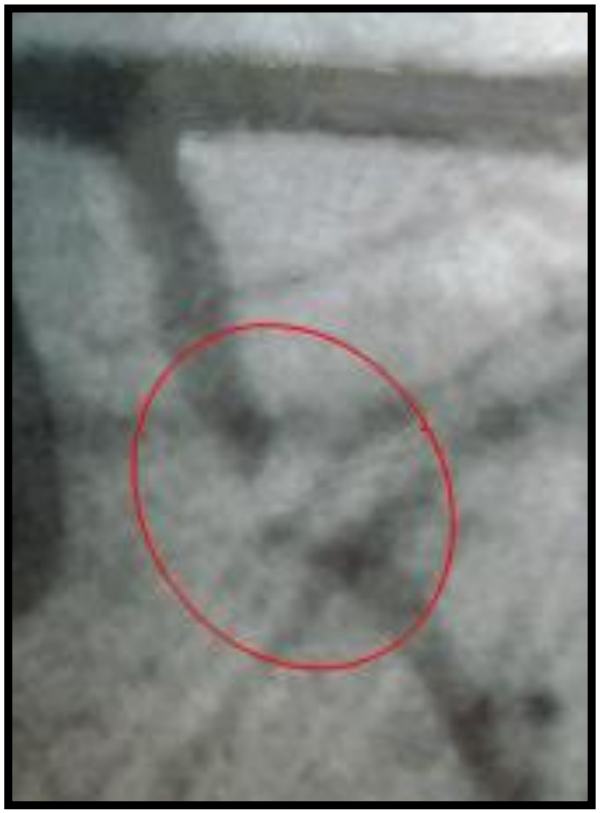
Fischell et al. *J Am Coll Cardiol* 2010;56:1089-98.

Example of Coronary Occlusion Detection with the Guardian System

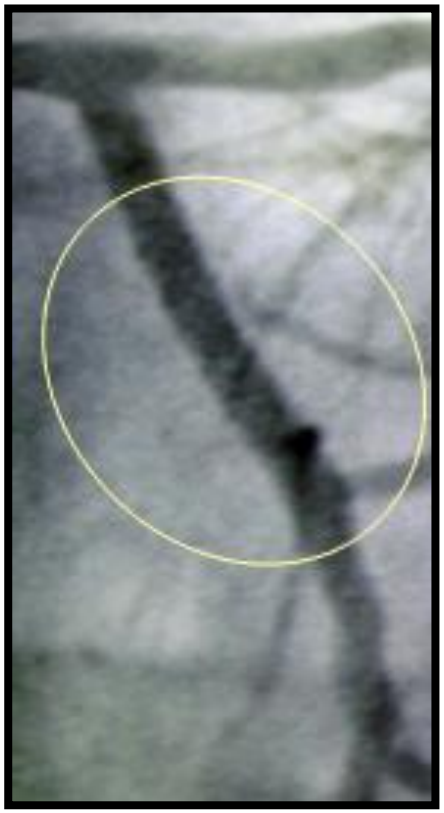
Patient in cath lab

8:30 am

LCX – Occlusion



After Stent



Total time from occlusion to treatment in under 2 hours

Fischell et al. *J Am Coll Cardiol* 2010;56:1089-98.

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