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Implantable Cardiac Alert System for Early Recognition of ST-Segment Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND Symptoms remain a poor prompt for acute coronary syndromes (ACS). Timely restoration of perfusion in ST-segment elevation myocardial infarction is associated with improved left ventricular function and survival.

OBJECTIVES This report details the results of ALERTS (AngelMed for Early Recognition and Treatment of STEMI), a multicenter, randomized trial of an implantable cardiac monitor that alerts patients with rapidly progressive ST-segment deviation.

METHODS High-risk ACS subjects (N = 907) were randomized to a control (alarms deactivated) or treatment group for 6 months, after which alarms were activated in all subjects. The primary safety endpoint was absence of system-related complications (>90%). The composite primary efficacy endpoint was cardiac/unexplained death, new Q-wave myocardial infarction, or detection to presentation time >2 h.

RESULTS Safety was met with 96.7% freedom from system-related complications (n = 30). The efficacy endpoint for a confirmed occlusive event within 7 days was not significantly reduced in the treatment compared with control group (16 of 423 [3.8%] vs. 21 of 428 [4.9%], posterior probability = 0.786). Within a 90-day window, alarms significantly decreased detection to arrival time at a medical facility (51 min vs. 30.6 h; Pr [pt < pc] >0.999). In an expanded analysis using data after the randomized period, positive predictive value was higher (25.8% vs. 18.2%) and false positive rate significantly lower in the ALARMS ON group (0.164 vs. 0.678 false positives per patient-year; p < 0.001).

CONCLUSIONS The implantable cardiac system detects early ST-segment deviation and alerts patients of a potential occlusive event. Although the trial did not meet its pre-specified primary efficacy endpoint, results suggest that the device may be beneficial among high-risk subjects in potentially identifying asymptomatic events. (AngelMed for Early Recognition and Treatment of STEMI [ALERTS]; NCT00781118) (J Am Coll Cardiol 2019;73:1919–27)

Improvements in total ischemic time (symptom-to-door + door-to-balloon or door-to-needle times) in the setting of ST-segment elevation myocardial infarction (STEMI) are associated with improved survival (1-6). Despite the well-recognized time dependency of myocardial salvage in STEMI (7), improvements in door-to-balloon time from 90 to 75 min have not improved survival (8). Additional improvements in survival are likely dependent on decreasing symptom-to-door time (9). The lengthy

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ECG = electrocardiogram

EXD = external alarm device

IMD = implantable monitoring device

LVEF = left ventricular ejection fraction

MI = myocardial infarction

PPV = positive predictive value

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

duration from symptom onset to hospital presentation may be attributed to several factors, including delayed recognition of myocardial infarction (MI) symptoms and the presence of atypical symptoms (3,10–12). More importantly, patients may not even experience symptoms, as 25% to 30% of MIs are silent (13–18).

Rapidly progressive ST-segment changes in the absence of an increased heart rate represent supply-related ischemia and are an early marker of acute coronary artery occlusion (19). ST-segment changes associated with MI commonly precede symptom onset and may occur among asymptomatic patients. Interest in an implantable monitoring device (IMD) that alerts patients of rapid, progressive ST-segment changes emerged in an attempt to augment symptoms as a prompt for patient presentation, alert silent acute coronary syndrome (ACS), and reduce pre-hospital delays through the early recognition of STEMI (20–22).

The AngelMed Guardian system (Angel Medical Systems, Eatontown, New Jersey) is a cardiac monitoring and alerting system designed for the early detection of intracardiac ST-segment changes among patients who are at high risk for ACS/MI (23). The system consists of an IMD with vibrational alerting that continuously monitors the heart and an external medical device (EXD) with additional auditory and visual alerting. ALERTS (AngeLmed Early Recognition and Treatment of STEMI) is a randomized, prospective clinical trial that evaluates the safety and efficacy of the system in the early detection and alerting of rapidly progressive ST-segment shifts potentially indicative of ACS events.

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METHODS

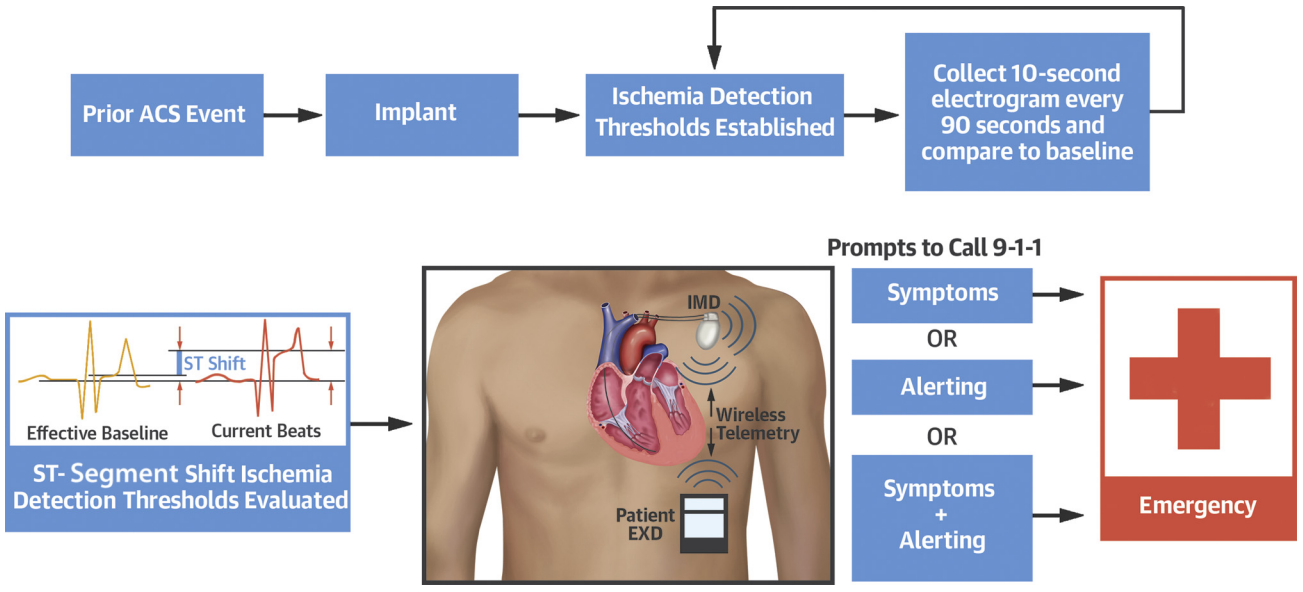
The ALERTS trial design has been previously published (24). The study was approved by national and institutional regulatory authorities and ethics committees (25). All participants provided written informed consent prior to participation.

STUDY POPULATION. Patients age >21 years presenting within 6 months of a high-risk ACS or multivessel coronary artery bypass graft surgery were screened. At least 1 additional criterion was required for enrollment: diabetes mellitus, renal insufficiency (creatinine >1.2 mg/dl or creatinine clearance <50 ml/min), or a TIMI (Thrombolysis In Myocardial Infarction) risk score ≥3. Major exclusion criteria included atrial fibrillation, bundle branch block, left ventricular hypertrophy, history of prior hemorrhagic stroke or transient ischemic attack in the past 6 months, inability to respond to alarms properly, localized scar tissue and high thresholds at the lead implantation site, and presence of an implantable cardioverter-defibrillator or pacemaker.

STUDY PROTOCOL. All subjects received the implantable system. At 7 to 14 days after implantation, subjects were randomized in a 1:1 fashion to either the treatment group with the alerts activated (treatment), or the control group in whom alerts were disabled (control). The Guardian system consists of a high-fidelity IMD, which is implanted under the skin in the left pectoral region and connected to a right ventricular apical pacemaker lead. The system captures and stores electrogram data and detects rapidly progressive ST-segment shifts relative to the subject's self-referenced 24-h averaged baseline. Upon detection, the device alerts subjects to seek medical attention through a vibratory alarm felt within the chest and with a visual and auditory alarm transmitted wirelessly to an EXD resembling a pager (**Central Illustration**). Electrogram data are saved by the IMD from up to 24 h before and 8 h after a triggered alarm and can be retrieved for review. IMDs in the control group detected events and collected cardiac data even while the alerting feature was disabled. Subjects were not blinded to their group status. All subjects received education regarding the importance of minimizing symptom-to-door time in the presence of chest pain or ischemic equivalents, regardless of alarm status. Following randomization, subjects returned for follow-up visits at 1, 3, and 6 months, and every 6 months thereafter. Control subjects had the alerting feature activated and were given an EXD after their 6-month follow-up visit. Upon study completion, subjects had the option of removing the IMD, removing the IMD and lead, or leaving the system fully implanted.

Late arrival was defined as detection-to-door time of >2 h for a confirmed occlusive event. Among the control group, the device was interrogated for event detection during pre-scheduled study visits or spontaneous visits, and detection-to-door times were calculated during the 7 days prior to hospital presentation (referred to as a 7-day "look-back" period). The pre-specified "look-back" window was set at 7 days, but exploratory analyses based on additional look-back windows were pre-specified in the statistical analysis plan (30, 50, 70, and 90 days). The 90-day interval was selected to detect silent ACS events as it reflected the longest interval of time that

CENTRAL ILLUSTRATION **Implantable Cardiac Medical Device That Continuously Monitors the Heart**



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The patient is alerted via vibrations through the implantable cardiac medical device and via auditory and visual alerts with the external medical device if ST-segment shifts exceeding a threshold are detected. ACS = acute coronary syndrome; EXD = external alarm device; IMD = implantable monitoring device.

could elapse between scheduled visits and device interrogation. All adverse events were adjudicated, and safety reviews were performed by an independent data and safety monitoring board throughout the course of the trial.

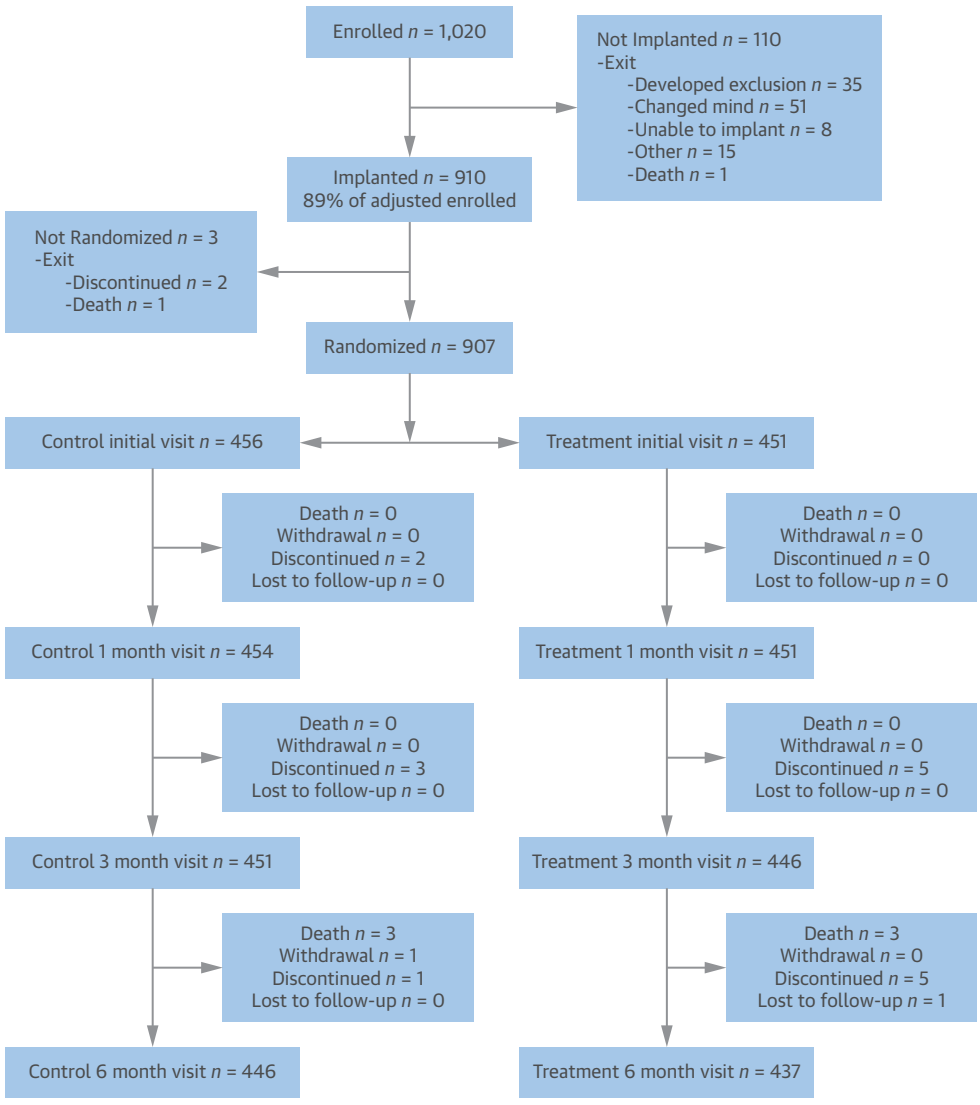
ENDPOINTS. The primary safety endpoint was the absence of system-related complications that required a system revision or invasive intervention to resolve in at least 90% of subjects through the 6-month follow-up. The primary efficacy endpoint for the randomized period was a composite endpoint of: 1) cardiac or unexplained death; 2) new Q-wave MI; or 3) detection-to-presentation time >2 h for a documented coronary occlusion event. Cardiac death was defined as a death directly related to the electrical or mechanical dysfunction of the heart.

Electrocardiogram (ECG) tracings were obtained prior to implantation; at randomization; at 1, 3, and 6 months; and at every emergency presentation, and were analyzed by a blinded, independent ECG core laboratory at Duke Clinical Research Institute. New Q-wave MI was defined as the appearance of new pathological Q-wave(s) at 6 months in a distribution of cardiac leads in which no pathologic Q-wave(s) were present at baseline, specified as the pre-implantation ECG. However, during the first adaptive look of the trial and following partial unblinding (statistician only), it became apparent that Q-waves could be transient and appear or disappear between the ECG obtained before implantation and at randomization. An exploratory dual baseline Q-wave analysis using both the ECG at pre-implantation and randomization was conducted to reduce noise and improve the quality and accuracy of the analysis. Both the single baseline ECG analysis and the exploratory "dual baseline ECG" analysis required that the presence of new Q waves be persistent across subsequent ECGs (Online Tables 1A and 1B).

An occlusive coronary event was confirmed by the presence of a new Q-wave or ST-segment elevation via 12-lead ECG, elevated enzymes/biomarkers, a positive stress test, or by angiography as assessed by an independent angiographic core laboratory (PERFUSE Core Lab, Beth Israel Deaconess Medical Center, Harvard Medical School). The criteria of 1-mm depth or width was used to define a pathological Q-wave. Confirmation of an occlusive coronary event is described in further detail in the Online Appendix.

Secondary efficacy endpoints included the individual components of the primary composite endpoint, as well as time from detection to presentation, incidence of any MI (Q-wave plus non-Q-wave MI), and incidence of new plaque rupture or significant disease progression as determined by the

FIGURE 1 CONSORT Diagram



The ALERTS trial enrolled 1,020 subjects. Of those, 910 were implanted with the system and 907 were randomized, with 456 in the control group and 451 in the treatment group.

angiographic core laboratory. Exploratory outcomes included assessment of left ventricular ejection fraction (LVEF) at discharge following a confirmed occlusive event.

Additional expanded analyses examining device accuracy not pre-specified in the original protocol were performed in all subjects, including data from after the 6-month randomization period, during which all subjects, including control subjects, had alerting turned on (ALARMS ON) (Online Figure 1). An independent clinical events committee adjudicated all emergency room visits and determined whether an occlusive event occurred. A coprimary endpoint including superiority for positive predictive value (PPV) and noninferiority for false positive rate (FPR) was pre-specified prior to analysis. Further information regarding the development and implementation of the expanded analyses can be found in the Online Appendix.

STATISTICAL ANALYSIS. Reinfarction or sudden death was estimated to be between 4.80% and 5.61% in the control group. However, no rate of new Q-wave

MI was available in the published data. Due to this uncertainty of the event rate in the control group, as well as uncertainty regarding treatment effect, a Bayesian adaptive design that allowed for sample size adjustment during the course of the trial was used. Sample size checks were planned after the first 600 subjects were randomized, with subsequent analyses every 300 subjects. Subject enrollment was halted after randomization of 900 subjects. Therefore, an alpha penalty of 0.25 was taken for the interim look at event rates after 600 subjects, which required the posterior probability for statistical significance for the primary, secondary, and safety endpoints to be >0.975. A second statistical analysis plan using frequentist statistics was developed for the expanded analyses. Fisher exact test and a generalized linear model was used to compare PPV and FPR, respectively. All analyses were completed by the independent study statisticians.

RESULTS

BASELINE CHARACTERISTICS. A total of 1,020 subjects were enrolled in the ALERTS trial, and 910 systems were successfully implanted. Of those, 907 subjects were randomized (Figure 1). The 2 arms were well-matched with respect to baseline characteristics and intensity of angina at baseline (Table 1). The mean duration of follow-up through the entire study was 3.05 years.

SAFETY. The primary safety endpoint was met with 96.7% freedom (posterior probability >0.999). In total, 31 system-related complications in 30 (3.3%) subjects were reported (Table 2). Infections were the predominant cause of complications and were observed in 1.2% (11 of 910) of subjects. In total, 20 subjects had the implantable system removed, 11 (1.2%) for infection, 3 (0.3%) for persistent pain at the incision site, 2 (0.2%) for erosion, 2 (0.2%) for device malfunction, 1 (0.1%) for perforation, and 1 (0.1%) for cosmetic issues. There was no permanent morbidity or disability from any system-related complications.

EFFICACY. The occurrence of an ACS event was low. The incidence of the primary composite endpoint did not differ between strategies when the pre-specified single baseline ECG and 7-day look back period was applied (21 of 428 or 4.9% in control vs. 16 of 423 or 3.8% in treatment; posterior probability = 0.786). No significant reductions using the additional look-back windows were observed, but the difference trended toward significance at 90 days (6.8% vs. 3.8%; Pr [pt < pc] = 0.974). In a non-pre-specified analysis using dual baseline ECGs for assessment, there was a significant reduction in the primary composite endpoint for the 50-day, 70-day, and 90-day look-back windows (Table 3). A breakdown of each component of the primary efficacy outcome using the dual baseline analysis can be found in Online Table 2.

Using the pre-specified 7-day look back window, the median time from Guardian detection to arrival at a medical facility was 51 min for treatment subjects and 30.6 h for control subjects (Pr [pt < pc] >0.999). Using the 90-day look back, the median time-to-door arrival in the treatment group remained the same, but

TABLE 1 Demographics and Intensity of Angina at Baseline

	Control Group (n = 456)	Treatment Group (n = 451)	% Difference (Treatment − Control) 95% BCI
Demographics			
Age, yrs	59.5 ± 10.2	59.4 ± 10.5	−1.4 to 1.3
Female	154 (33.8)	137 (30.4)	−9.4 to 2.7
Caucasian	391 (85.7)	391 (86.7)	−3.7 to 5.5
Body mass index, kg/m^2	31.7 ± 6.5	31.9 ± 11.8	−1.0 to 1.5
Presentation of index ACS			
STEMI	113 (24.8)	109 (24.2)	−6.2 to 5.0
NSTEMI	127 (27.9)	126 (27.9)	−5.7 to 5.9
Unstable angina	199 (43.6)	199 (44.1)	−6.0 to 6.9
Other*	15 (3.3)	15 (3.3)	−2.4 to 2.4
Unknown	2 (0.4)	2 (0.4)	−1.1 to 1.1
Diabetes	224 (49.1)	206 (45.7)	−9.9 to 3.0
Dyslipidemia requiring medication	421 (92.3)	416 (92.2)	−3.6 to 3.4
Hypertension requiring medication	426 (93.4)	414 (91.8)	−5.1 to 1.8
Currently smoking	121 (26.5)	117 (25.9)	−6.3 to 5.1
History of heart failure	60 (13.3)	79 (17.5)	−0.5 to 8.9
LVEF, %	53.9 ± 8.8	54.1 ± 9.4	−1.1 to 1.4
History of renal insufficiency	75 (16.4)	83 (18.4)	−3.0 to 6.9
History of reperfusion/ revascularization	444 (97.4)	442 (98.0)	−1.4 to 2.7
History of silent MI	28 (6.2)	25 (5.5)	−3.7 to 2.5
History of silent ischemic changes			
Yes	34 (7.5)	28 (6.2)	−4.6 to 2.1
No	309 (67.8)	338 (74.9)	1.3 to 13.0
Unknown	133 (41.5)	85 (18.8)	−11.2 to −0.5
TIMI risk score	3.623 ± 0.968	3.706 ± 1.023	−0.048 to 0.213
Intensity of angina at baseline			
Angina in previous 6 months	400 (87.7)	395 (87.6)	−4.4 to 4.1
Average frequency of angina			
>10 times/month	63 (15.8)	58 (14.7)	−6.0 to 3.9
6–10 times/month	44 (11.0)	37 (9.4)	−5.9 to 2.6
3–6 times/month	87 (21.8)	101 (25.6)	−2.1 to 9.7
<3 times/month	205 (51.4)	198 (50.3)	−8.0 to 5.8
Angina status (most recent episode as of pre-procedure examination)			
Stable	233 (58.5)	228 (58.6)	−6.8 to 6.9
Unstable	165 (41.5)	161 (41.4)	−6.9 to 6.8

Values are mean ± SD or n (%), unless otherwise indicated. Analyses were based on all available data. *Other includes subjects that had a CABG as their qualifying event.

ACS = acute coronary syndrome; BCI = Bayesian credible interval; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 2 Adjudicated Adverse Events Among Subjects With Successful Implantation

	Pooled Treatment Groups (n = 910)	
	Events	%
Cardiac perforation	2	0.2
Erosion	3	0.3
Infection	11	1.2
Lead migration/dislodgment	4	0.4
Device malfunction	2	0.2
Lead malfunction	1	0.1
Loss of sensing due to dislodgement or malfunction of lead	2	0.2
Pain at or near the pocket site	5	0.6
Visible bump where implanted in the chest	1	0.1

All 11 subjects who developed infections had the device removed. Additionally, 3 subjects with persistent pain at the incision site, 2 with erosion, 2 with device malfunction, 1 with perforation, and 1 with cosmetic issues had the device removed.

the control group median time-to-door arrival increased to 22 days (Pr [pt < pc] >0.999). Subject arrival within 2 h of a detected and confirmed coronary occlusion occurred in 85% (29 of 34) of the treatment group compared with only 5% of the control group, with the majority of patients in the control arm presenting after 7 days (Online Figure 2). A table of the positive tests used to confirm all the coronary occlusive events at the end of the randomization period can be found in Online Table 3.

Despite a numerical reduction in new Q-wave MI using single and dual baseline ECGs at any of the pre-specified look-back windows, the posterior probability of superiority did not reach statistical significance (Online Table 4). Results were consistent among a subset of patients at higher risk for a silent MI (Online Table 5). Hypothesis testing regarding cardiovascular or unexplained death was not undertaken as a separate endpoint due to the small number of deaths in the study (0.6%), with only 4 identified as cardiac in nature (Online Table 6).

LVEF was assessed among subjects with a confirmed occlusive event (64 events among 51 subjects). Mean LVEF in the treatment subjects was significantly greater than that in the control subjects (53.3 ± 10.3% vs. 44.8 ± 14.6%; Pr [pt < pc] >0.991). Among patients with a documented LVEF >40% prior to study initiation, the proportion of patients with an LVEF ≤40% at discharge was significantly lower among patients in the treatment group versus the control group (4% [1 of 25] vs. 35.7% [5 of 14]; Pr [pt < pc] = 0.994).

EXPANDED ANALYSES. Through the entire follow-up period, including data from subjects in the control arm who had alarms activated after the 6-month follow-up, PPV in the ALARMS ON group for alerts with or without symptoms was 25.8% (89 true positives of 345 ER visits due to alarms) compared with a PPV of 18.2% for symptoms (33 true positives of 181 ER visits due to symptoms) in the ALARMS OFF group (control subjects in the initial 6 month period) (Online Table 7). A total of 42 silent MIs were detected in the ALARMS ON group (PPV of 20.0%) that would not have otherwise been detected in the ALARMS OFF group (**Table 4**). Further, the FPR was significantly lower in the ALARMS ON (with or without symptoms) versus the ALARMS OFF group (0.164 false positives vs. 0.678 false positives per patient-year; p < 0.001) (Online Table 7). Of note, the overall false positive rate for all ALARMS ON emergency visits (including alarm only, symptoms only, and alarm with symptoms) was 0.499 per patient-year (p < 0.001), demonstrating a 26% reduction compared with ALARMS OFF. Positive predictive value during the randomized period can be found in Online Table 8.

System alerts occurred for 108 events in 79 (8.7%) subjects who sought medical attention resulting in the diagnosis of events not related to ACS. The majority of the events were due to changes in the subject's heart rate or rhythm (Online Table 9). Further, the need for therapeutic devices such as pacemakers and implantable cardioverter-defibrillators was also identified in approximately 5% of subjects.

TABLE 3 Primary Composite Efficacy Endpoint With Multiple Look-Back Windows By Single Baseline ECG and Dual Baseline ECG

Look-Back Window	Control Group (n = 428)	Treatment Group (n = 423)	% Difference (Treatment-Control) 95% BCI	Posterior Prob Pr ($R_T < R_C$ | Data)
Single baseline ECG				
7-day	21 (4.9)	16 (3.8)	−3.93 to 1.67	0.786
30-day	25 (5.8)	16 (3.8)	−5.02 to 0.84	0.918
50-day	27 (6.3)	16 (3.8)	−5.55 to 0.43	0.953
70-day	28 (6.5)	16 (3.8)	−5.82 to 0.24	0.964
90-day	29 (6.8)	16 (3.8)	−6.06 to 0.03	0.974
Dual baseline ECG				
7-day	20 (4.7)	13 (3.1)	−4.28 to 1.02	0.883
30-day	24 (5.6)	13 (3.1)	−5.36 to 0.23	0.964
50-day	26 (6.1)	13 (3.1)	−5.89 to −0.18	0.981
70-day	27 (6.3)	13 (3.1)	−6.16 to −0.38	0.987
90-day	28 (6.5)	13 (3.1)	−6.43 to −0.60	0.991

Values are n (%) unless otherwise indicated. Subjects with their device removed or with electrocardiograms (ECGs) missing, uninterpretable, or outside of the window were excluded from the analysis.

BCI = Bayesian credible interval.

DISCUSSION

The primary efficacy endpoint of cardiac or unexplained death, new Q-wave MI, and detection-to-presentation time >2 h following a confirmed

occlusive event within 7 days was numerically, but not statistically reduced among patients in the ALARMS ON treatment group. When the observation window was extended to 50, 70, and 90 days in a prespecified analysis to include the majority of confirmed occlusive events in the control group, and an exploratory dual baseline ECG analysis was used to reduce noise, a significant reduction in the primary endpoint was observed. Further, in the expanded analysis, the ALARMS ON PPV was higher than the ALARMS OFF PPV (25.8% vs. 18.2%), accompanied by a significant FPR reduction through the entire study.

The 51-min detection-to-door delay among treatment subjects is consistent with the data from the Cardiosaver and DETECT phase I clinical studies (20,21) where the detections-to-door median time was 48 min. The delayed detection-to-door time of >30 h among control subjects was long, given that historically, the symptom-to-door time is typically approximately 3 h (26). There are often cyclic flow variations, with the artery transiently closing and opening before permanent occlusion in STEMI (27-31). The difference between the 2 arms may be explained at least in part by the ability of the implantable ECG in the treatment group to detect these transient occlusions, which may not cause prolonged chest pain that would lead a control group patient to seek medical care. Further, control group subjects may have experienced atypical symptoms or no symptoms, which could delay detection until the subsequent scheduled follow-up visit.

No prompt is currently available for patients experiencing an asymptomatic ACS event. Aggressive follow-up via device interrogation was needed among the control group to capture all silent MIs, which typically account for approximately 30% of all MIs and are historically associated with increased rates of morbidity and mortality (13,16,32). The rate of silent MI is even higher among certain populations, such as women, diabetic patients, and older patients (14,15). In this study, 42 silent ACS events were detected by an alert only (PPV of 20.0%). Further, alarming was associated with a reduction in the rate of new onset of LV dysfunction (LVEF <40%, an incidence of 33.3% vs. 4.0%) at discharge following a confirmed occlusive event. Although the duration of follow-up in this study was limited, a reduction in post-MI LV dysfunction of this magnitude may be associated with improved long-term outcomes (26,33-35).

This is the first system to alert high-risk ACS subjects of a potential coronary occlusive event. The system did not appear to cause excess utilization of resources or expose subjects to unneeded risk, as the FPR was reduced in subjects presenting due to alarms (with or without symptoms) compared with subjects presenting with symptoms alone. Further, the system did not appear to cause subjects to ignore symptoms in the absence of a confirmatory alarm, as 625 symptom-only presentations in ALARMS ON subjects were observed. Therefore, the Guardian system may be useful in clinical practice in detecting potential coronary occlusive events and in reducing time to treatment among ACS subjects deemed to be at high risk for a recurrent event.

TABLE 4 Positive Predictive Values in the Expanded Analysis

	ALARMS OFF	ALARMS ON			
	Symptoms Only	Alert Only	Symptoms Only	Alert With Symptoms	Alert With or Without Symptoms
Emergency visits	181	210	625	135	345
True positive	33	42	104	47	89
False positive	148	168	521	88	256
PPV, %	18.2	20.0	16.6	34.8	25.8

Values are n.
PPV = positive predictive value.

STUDY LIMITATIONS. A major limitation of the randomized trial was the unanticipated low event rate. Additionally, no difference in hard clinical outcomes was observed between the treatment and control group, such as cardiovascular or unexplained death. However, this lack of effect on hard outcomes may be attributed, at least in part, to these extremely low event rates. Another limitation was the unexpected variation in the primary endpoint including the discrepancies in ECG tracings and the extended time between event detection and presentation. Notably, due to this variation, the primary efficacy endpoint was only met using the dual baseline ECG analysis and extending the look-back window to at least 50 days. However, the large delay between event detection and presentation further highlights the need for a device such as the Guardian system, and all pre-specified results demonstrated a trend in favor of the system.

It should also be noted that this discrepancy in ECG tracings contributed, in part, to the early termination of the study despite interim analyses suggesting that enrollment should continue, which is a protocol violation. Although this violation could affect the randomized trial, the expanded analyses were

developed and conducted after early termination, and are therefore not affected. Additionally, post hoc analyses, as well as a lack of adjustment for multiplicity, leaves the analyses more vulnerable to type I error. Finally, the criteria for a confirmed occlusive event may vary in importance and seriousness to both clinicians and patients. However, taken together, the original results with the expanded analysis show a consistent benefit of the system in the detection of events.

CONCLUSIONS

Overall, the implantable cardiac system was safe, and the rate of complications was low. However, the ALERTS trial failed to meet the pre-specified primary efficacy endpoint of the randomized trial. Nonetheless, in an expanded analysis including data both during and after the randomized portion of the trial, the PPV was higher and the FPR was lower among the ALARMS ON group. These findings suggest the system may be beneficial in the identification of symptomatic and asymptomatic occlusive coronary events among high-risk ACS subjects.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Use of an implanted electrocardiographic monitoring device in high-risk patients can detect ACS early after onset without burdening the health care system with a large proportion of false alerts or exposing patients to unnecessary medical procedures.

TRANSLATIONAL OUTLOOK: Greater experience with this technology could facilitate systematic methods to translate early detection of acute ischemic events into improvement in left ventricular function and long-term clinical outcomes.

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KEY WORDS acute coronary syndrome, implantable monitoring device, ST-segment elevation myocardial infarction, symptom-to-door time

APPENDIX For supplemental information including figures and tables, please see the online version of this paper.