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Implanted Monitor Alerting to Reduce Treatment Delay in Patients With Acute Coronary Syndrome Events

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ABSTRACT

BACKGROUND Increased pre-hospital delay during acute coronary syndrome (ACS) events contributes to worse outcome.

OBJECTIVES The purpose of this study was to assess the effectiveness of an implanted cardiac monitor with real-time alarms for abnormal ST-segment shifts to reduce pre-hospital delay during ACS events.

METHODS In the ALERTS (AngeLmed Early Recognition and Treatment of STEMI) pivotal study, subjects at high risk for recurrent ACS events (n = 907) were randomized to control (Alarms OFF) or treatment groups for 6 months, after which alarms were activated in all subjects (Alarms ON). Emergency department (ED) visits with standard-of-care cardiac test results were independently adjudicated as true- or false-positive ACS events. Alarm-to-door (A2D) and symptom-to-door (S2D) times were calculated for true-positive ACS ED visits triggered by 3 possible prompts: alarm only, alarms + symptoms, or symptoms only.

RESULTS The Alarms ON group showed reduced delays, with 55% (95% confidence interval [CI]: 46% to 63%) of ED visits for ACS events <2 h compared with 10% (95% CI: 2% to 27%) in the Alarms OFF group ($p < 0.0001$). Results were similar when restricted to myocardial infarction (MI) events. Median pre-hospital delay for MI was 12.7 h for Alarms OFF and 1.6 h in Alarms ON subjects ($p < 0.0089$). Median A2D delay was 1.4 h for asymptomatic MI. Median S2D delay for symptoms-only MI (no alarm) in Alarms ON was 4.3 h.

CONCLUSIONS Intracardiac monitoring with real-time alarms for ST-segment shift that exceeds a subject's self-normative ischemia threshold level significantly reduced the proportion of pre-hospital delays >2 h for ACS events, including asymptomatic MI, compared with symptoms-only ED visits in Alarms OFF. (AngeLmed for Early Recognition and Treatment of STEMI [ALERTS]; NCT00781118) (J Am Coll Cardiol 2019;74:2047–55) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CEC = Clinical Events Committee

ED = emergency department

iEGM = intracardiac electrogram

NSTEMI = non-ST-segment elevation myocardial infarction

STEMI = ST-segment elevation myocardial infarction

UA = unstable angina

In patients with acute coronary syndromes (ACS), namely ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), timely presentation to a medical facility improves the potential for early diagnosis, risk stratification, and implementation of well-documented clinical management strategies focused on improving clinical outcome. This is particularly important in patients presenting with STEMI, and formed the basis for the National Quality Initiative "Door to Balloon" time (1). Timely presentation depends on several factors, including both presence and recognition of symptoms, attribution of those symptoms to a potential cardiac source, patient's decision to act, and then transport to a medical facility (2,3). It is well-established that ACS symptoms are highly variable, if they occur at all, creating barriers to timeliness in patients taking action (4), and the ongoing dilemma of morbidity and mortality from asymptomatic myocardial infarctions (MIs). Strategies to reduce pre-hospital delay times have been challenging. One recent approach has been the development of an implantable cardiac monitor with real-time alarm capability triggered by acute quantitative intracardiac electrocardiographic changes. The device is designed to provide a more accurate real-time detection of ACS event onset and alert patients, either as an adjunct to symptom recognition or in the absence of clinical symptoms. When compared with patient-recognized symptoms alone (i.e., the current standard of care [SOC]), this technology showed early promise of both increased positive predictive value (PPV) for ACS events and decreased time from onset of an ACS event to presentation for medical care (5,6). A unique advantage of this intracardiac electrogram (iEGM)-based system is that it can identify ACS events and prompt the patient to seek medical attention even in the absence of symptoms.

The design considerations and results of the U.S. Food and Drug Administration-approved ALERTS (AngeLmed Early Recognition and Treatment of STEMI) randomized, prospective phase III trial, which evaluated the safety and efficacy of an intracardiac monitoring and alerting system known as the AngelMed Guardian system (Angel Medical Systems, Eatontown, New Jersey), have been previously reported (7,8). This paper provides previously unreported results from the ALERTS trial that focus on pre-hospital delays. These delays occurred in adjudicated ACS events after symptoms and/or a Guardian alarm (due to abnormal ST-segment iEGM shift events) prompted subjects to seek medical care.

METHODS

The technology used in the ALERTS trial has been described previously (5). Briefly, the system includes an implantable cardiac monitoring device attached to a standard IS-1 active-fixation pacemaker lead (used for sensing alone) that is implanted in the apex of the right ventricle. "ST-segment shifts" from each patient's reference ST-segment levels were identified using machine learning techniques to statistically compare the ST-segment deviation of a sample iEGM of the patient to that patient's 24-h composite baseline ST-segment deviation for a normal heart rate. The implanted monitor has a vibrational alarm system that is programmed to alert the patient to sustained (>2 min) ST-segment shifts occurring in beats within the patient's normal (resting) heart rate range. The system also includes an external personal device that provides additional auditory and visual alarms to augment patient notification (9).

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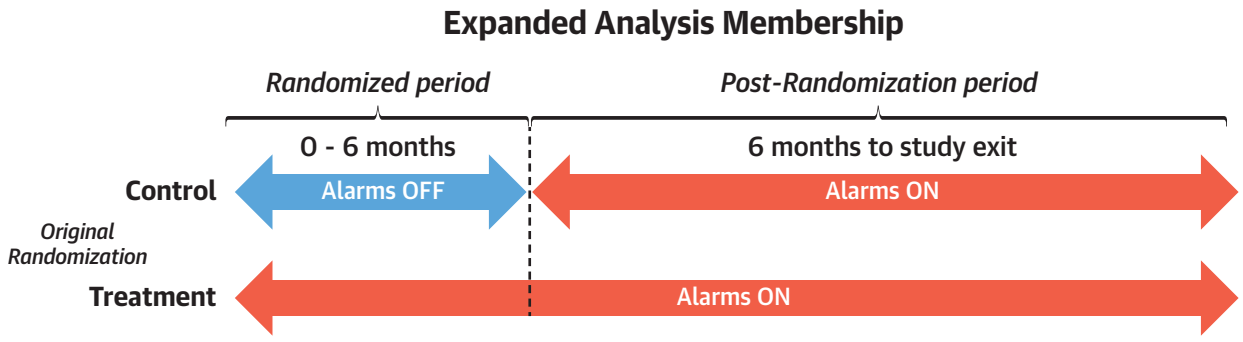
ALERTS enrolled 1,020 high-risk coronary artery disease (CAD) subjects, 907 of whom had a successful implantation of the monitor and were randomized in a 1:1 fashion to either the treatment group, in whom alarms were activated, or the control group, in whom alarms were disabled, and this was known to the subject to emulate the SOC. The ALERTS patient demographics have been described in detail previously (7,10). The randomized portion of the trial lasted for 6 months, with follow-up including device interrogation in all subjects at 1, 3, and 6 months. In treatment group subjects, detection of excessive ST-segment shifts at a normal heart rate range resulted in real-time "emergency" alarms, for which patients were instructed to call 911. In the control group subjects, excessive ST-segment shifts were identified and stored, but no patient alarm occurred (8,11).

The expanded analysis (11), conducted on independently adjudicated endpoints in cooperation with the U.S. Food and Drug Administration, defined 2 coprimary efficacy endpoints: superiority of PPV and noninferiority of false positive rate for emergency department (ED) visits prompted by alarms compared to symptoms-only. As shown in **Figure 1**, the expanded analysis endpoints were assessed by comparing ED visits for an Alarms OFF group (control subjects during the randomized 6-month period) to

FIGURE 1 Study Design



The original PMA ALERTS analysis included a randomized period of 0 to 6 months and compared control patients (alarms off) with treatment patients (alarms activated). The expanded analyses compared patients in the Alarms OFF period (who sought emergency room only due to symptoms) to patients in the Alarms ON (which included both control patients in post-randomization period and treatment patients where both had alerting turned on). Alarms ON sought the emergency room due to prompts, which included either alarms (with or without symptoms) or symptoms. The expanded analysis duration for the Alarms ON period lasted until the date the electronic case report forms database was locked, April 15, 2014. Data from the expanded analysis involved a pre-specified assessment of a coprimary endpoint including positive predictive value and false positive rate, as well as secondary endpoints of time to door reported here. Adapted with permission of the Online Figure S1 of Gibson et al. (8).

ED visits of an Alarms ON group (including both the treatment subjects during the first 6 months and all implanted patients beyond 6 months with alarms activated). Alarms OFF subjects thus represent the "current standard-of-care" reference group who relied upon symptoms alone to prompt presentation. The Alarms ON subjects were prompted either by an alarm (only), an alarm + symptoms, or symptoms (only). The expanded analysis adjudicated ED visits into either true or false-positive ACS events based on independent review of cardiac test data (electrocardiogram, enzymes, catheterization, stress test) as available through SOC management, as has previously been reported (8). The expanded analysis also included pre-specified secondary endpoints that reported the mean, median, and distributions of the pre-hospital delays for all ED visits adjudicated as true-positive ACS events and for the subcategories of STEMI, MI (STEMI and NSTEMI), and UA. Unless identified as pre-specified coprimary endpoints, the statistical comparisons reported herein are exploratory. Fisher exact tests are used to assess proportions, and Wilcoxon 2-sample tests are used to assess differences between medians.

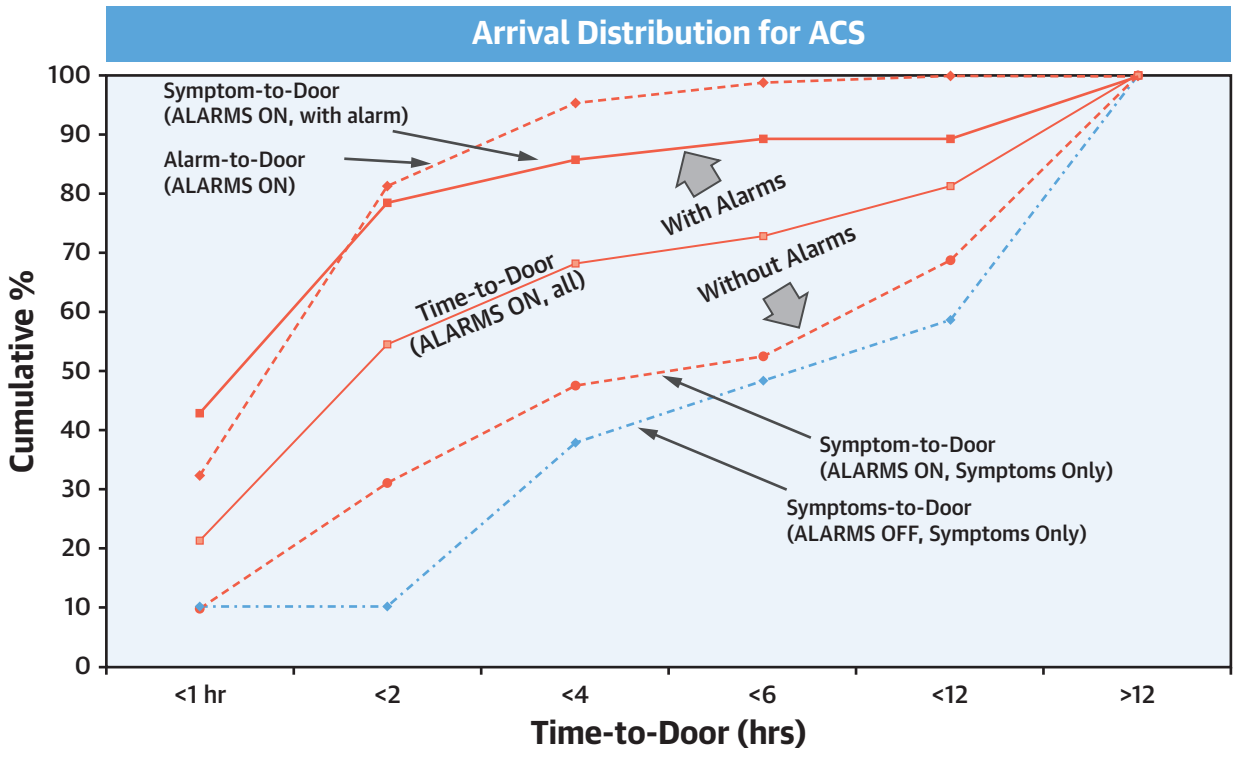
This paper reports, for the first time, to the best of our knowledge, on the time-to-door results of the expanded analysis (secondary endpoints 2, 3, 4, and 5, as amended) which relied upon the following nomenclature. For all presentations, the time between symptom onset and ED arrival was defined as symptom-to-door (S2D) time. "Symptom-only" ED visits occurred in both Alarms OFF and also in Alarms ON subjects. The latter were instructed not to ignore symptoms they believed could be warning them about an ACS event, even when these occurred in the absence of an alarm. In Alarms ON subjects, patients were instructed to call 911 due to cardiac symptoms (even in the absence of an alarm), or an alarm, even in the absence of cardiac symptoms. For all presentations prompted by an alarm, the time interval between the alarm and presentation at the ED is termed "alarm-to-door" (A2D) time. A2D time is a novel measure that is only possible due to the ability of the implantable monitor to detect ST-segment shift events. Last, "Alarm-only" ED visits occurred when symptoms were absent/silent at the time of the alarm and did not contribute to the patient's decision to call 911 or otherwise "move toward" the ED.

RESULTS

ACS EVENTS AND MEDIAN ARRIVAL TIMES. The ALERTS trial subjects presented to the ED and had SOC cardiac tests performed on 1,151 occasions. There were 181 ED visits during a 218.15 implant-year interval for Alarms OFF and 970 ED visits (345 with alarms + 625 symptoms only) during a 1,557.64 implant-year interval for Alarms ON. The annual rate for Clinical Events Committee (CEC)-adjudicated ACS events was 0.151 (33 of 218.15) in the Alarms OFF group and 0.124 (193 of 1,557.64) in the Alarms ON group.

In the Alarms OFF group, of the 181 ED visits, the CEC adjudicated 33 (18%) as ACS events (MI = 22

FIGURE 2 **Arrival Distribution for All ACS Events**



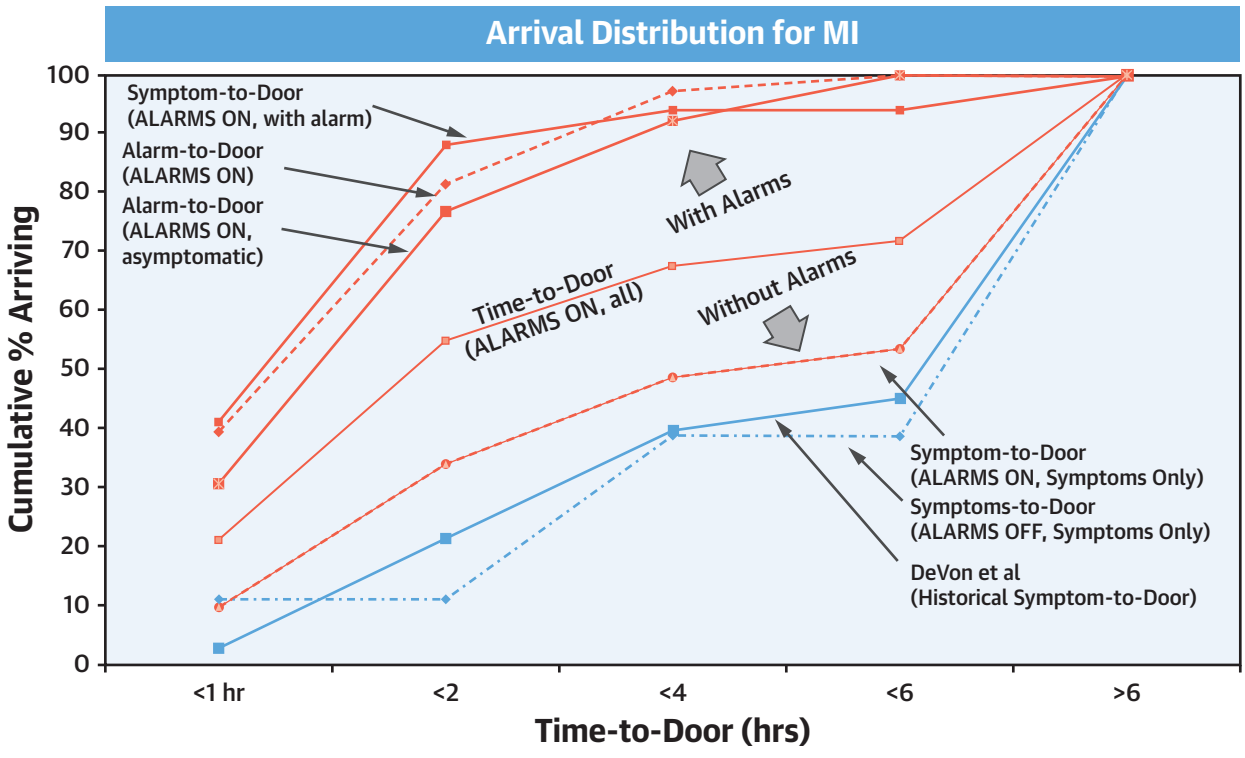
Symptom-to-door times (Alarms ON, with alarm, n = 28; Alarms ON, symptoms only, n = 80; Alarms OFF, symptoms only, n = 29) and alarm-to-door times (Alarms ON, with or without symptoms, n = 86). The "Time-to-Door" Alarms ON curve shows the overall benefit of being in the Alarms ON group and combines the 3 possible types of presentation (symptom-to-door times [for symptoms-only], symptom-to-door times [for symptoms with alarm], and alarm-to-door times [for alarm-only presentations]). Adapted from Table 15 Guardian System ACS Detection Results, Amendment to PMA 150009. ACS = acute coronary syndromes.

[67%]; UA = 11 [33%]), with the remaining visits adjudicated as due to either stable CAD or indeterminate etiology. The median S2D time for Alarms OFF ACS events was 8.0 h (95% confidence interval [CI]: 3.2 to 47.5 h).

In Alarms ON subjects, of the 970 ED visits, the CEC adjudicated 193 (20%) as ACS events, with the remainder classified as stable CAD, indeterminate events, and/or a false-positive alarm. Of the 193 ACS events, 89 events (46%) were prompted by alarms (with or without symptoms; MI = 40 [45%]; UA = 49 [55%]). The remaining 104 visits (54%) were prompted by symptoms only (MI = 60 [58%]; UA = 44 [42%]). An overall median arrival time of 1.7 h was found for the Alarms ON group composite including all 3 prompt types for ED arrival (alarms only, alarms + symptoms, or symptoms only), which was significantly shorter than the 8.0 h delay of the Alarms OFF group ($p < 0.0001$). For the individual prompt types, the median Alarms ON pre-hospital delays prompted by alarms only (i.e., clinically silent), alarms + symptoms, and symptoms only were 1.4, 1.0, and of 4.6 h, respectively. These were all less than the 8.0-h median delay of the Alarms OFF group, although the reduction for symptoms-only delay did not reach statistical significance ($p < 0.0001$, $p < 0.0001$, and $p = 0.2237$, respectively).

TIME-TO-DOOR DISTRIBUTIONS. Figure 2 shows the S2D distribution of ED visits for ACS events in the Alarms OFF group and the arrival distribution in the Alarms ON group (across the 3 prompt types). The lower 2 curves represent the S2D times for ACS event presentation due to symptoms-only. The upper 2 curves represent the distributions when alarms (with or without symptoms) occurred and reflect S2D times (median 1.0-h delay) and A2D times (median 1.3-h

FIGURE 3 Arrival Distribution for MI Events



Symptom-to-door times (Alarms ON, with alarm, n = 17; Alarms ON, symptoms only, n = 41; Alarms OFF, symptoms only, n = 18) and alarm-to-door time (Alarms ON, with or without symptoms, n = 38; Asymptomatic [silent myocardial infarction (MI)], n = 13). The time-to-door Alarms ON curve shows the overall benefit of being in the Alarms ON group and combines the 3 possible types of presentation (symptom-to-door times [for symptoms-only], symptom-to-door times [with alarm], and alarm-to-door times [alarm-only presentations]). Adapted from Table 14 Guardian System MI Detection Results, Amendment to PMA 150009. The figure also shows data from DeVon et al. (12) as a historical reference (n = 243). Reader note: there is an x-axis change to 6 h to allow comparison with the DeVon historical data, as DeVon et al. (12) did not break out 6 to 12 h.

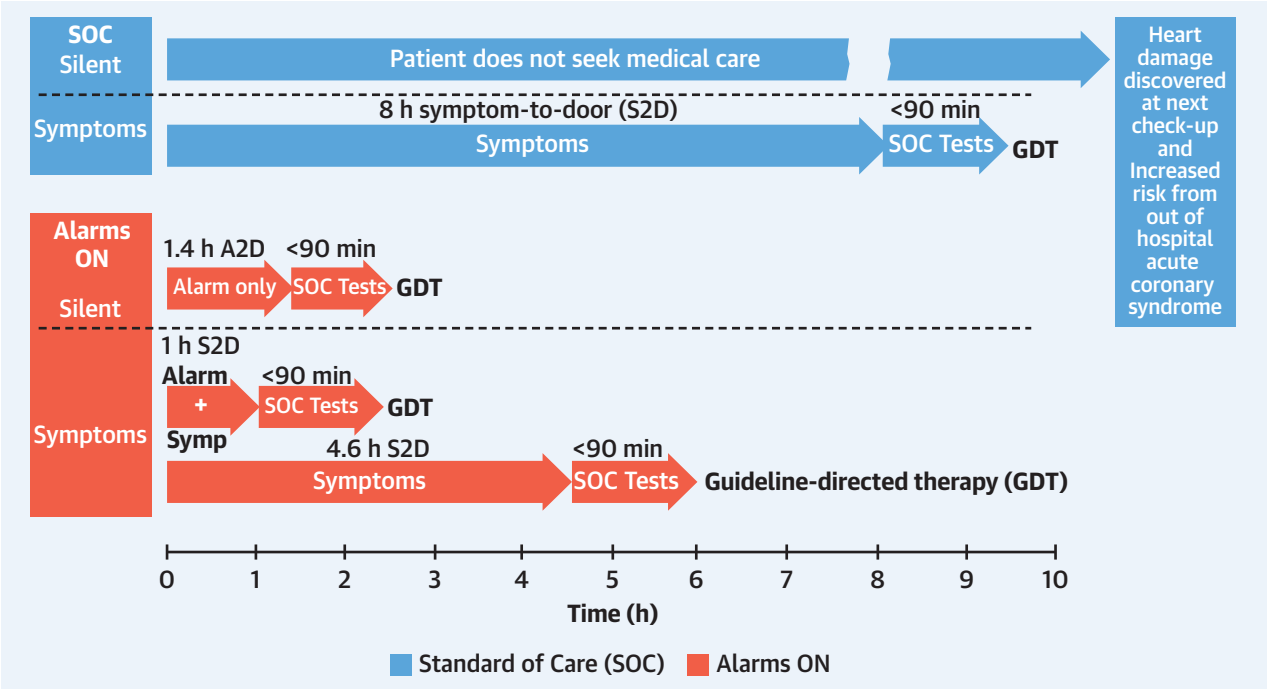
delay). When both symptoms and alarms were present, alarms preceded symptoms 52% of the time, and lagged symptoms 48% of the time. The middle curve reflects the delay for the Alarms ON group across all 3 possible prompts for ED visits (symptoms only, alarms only, or both). In the Alarms OFF group, 10% (95% CI: 2% to 27%) arrived in ≤2 h, while 55% (95% CI: 46% to 63%) of the Alarms ON "all" group arrived at the ED ≤2 h, which increased to 81% when restricted to visits having an alarm (with or without symptoms). The A2D curve includes alarms with and without symptoms (i.e., asymptomatic) and shows a similar rate (i.e., 81%) for ED presentations ≤2 h after the alarm occurred.

Figure 3 shows the arrival-time distributions of Figure 2, when limited to MI. It also plots 2 additional distributions: the A2D for asymptomatic MI, and a historical MI presentation distribution derived from DeVon et al. (12). For MI subjects presenting with both alarms and symptoms, the median S2D time was 1.0 h, with 88% presenting ≤2 h. When only an alarm occurred, 77% presented ≤2 h and the arrival distribution was similar (i.e., the top 3 curves of the graph are similar). The STEMI subset of alarmed events had a median S2D time of 45 min.

Median pre-hospital delay for MI was 12.7 h (95% CI: 3.0 to 53.8 h) for Alarms OFF (symptoms only) and 1.6 h (across all prompt types, 95% CI: 5.55 to 36.50 h) in Alarms ON subjects ($p < 0.0089$). Median A2D delay was 1.4 h for MI without symptoms (i.e., silent MI). Median S2D delay for symptoms-only MI in Alarms ON was 4.3 h.

The top 2 curves of Figure 3 show the pre-hospital delay distributions of S2D (median 1.0) and A2D (median 1.3) for presentations having both alarms and symptoms. The 2 curves are similar and reflect that these alarms and symptoms occurred at similar times, with an alarm preceding the

CENTRAL ILLUSTRATION **Patient Journey for True-Positive Acute Coronary Syndrome Events: Standard of Care Versus Alarms ON**



Holmes, Jr., D.R. et al. J Am Coll Cardiol. 2019;74(16):2047–55.

In standard of care (SOC), pre-hospital median delay was 8 h, and for silent acute coronary syndrome, events may only be discovered upon next routine doctor visit. The Alarms ON patients showed shorter median pre-hospital delays and were alerted by the implantable cardiac device and by auditory and visual alarms of an external pager-sized device when ST-segment shifts exceed a threshold, by symptoms, or both. After arrival, SOC testing and guideline-directed therapy occurs, with the goal being that intervention occurs within 90 min of presentation, when warranted. A2D = alarm-to-door; symp = symptoms.

symptoms about one-half of the time (44%), and vice versa.

DISCUSSION

In patients with ACS, reduction in pre-hospital delays is important in providing in-hospital medical monitoring of the patient and improving outcome by facilitating prompt application of guideline-directed therapy. This is of particular importance in patients presenting with STEMI, in whom there is a clear correlation of door-to-balloon time and outcome (13) and an even closer correlation of symptom-onset to balloon-reperfusion time. Despite the emphasis by professional societies on patient education to recognize symptoms early and report urgently for medical evaluation and treatment, delays remain unchanged in contemporary care even in patients who have experienced a previous MI. These efforts also fail to address patients having asymptomatic ischemia and infarction. Finally, the emphasis on early recognition of symptoms is confounded by the large percentage of nonischemic chest pain presentations to EDs annually (Central Illustration).

Pre-hospital delays include several components, most prominently patient recognition of symptoms as cardiac in etiology. This component is of particular importance in population segments such as older or diabetic patients who may have more atypical or milder symptom clusters (14-16). Another important component is patient attribution of sufficient importance of the specific symptom to actually seek immediate care. The Guardian System was designed as a unique, quantitative electrophysiological-based solution to address both components that underly patient-related delay.

The results reported here support the ability of real-time cardiac monitoring, with patient-level alarms for excessive ST-segment shifts, to reduce pre-hospital delays for adjudicated ACS events. Patient-related

pre-hospital delays assessed across all prompts for ED arrival were significantly reduced in the "Alarms ON" group compared with the "Alarms OFF" group, whose dependence on recognition of ischemic symptoms reflect contemporary clinical care. The cumulative percentage of all ED visits for ACS events within 2 h significantly increased from 10% with Alarms OFF to 55% with Alarms ON. When ED visits included an alarm, approximately 79% of ACS events and 88% of MIs had S2D times ≤2 h. In Alarms ON subjects, 77% of arrivals were ≤2 h from alarm time for MIs where symptoms did not serve as a prompt to call 911 (silent MI). As reported previously (8), the PPV of the alarms (with or without symptoms) was 25.8%, which was higher than the PPV for symptoms 18.2%. Providing a more reliable prompt that also decreases pre-hospital delay is an important benefit, and may be even more so in a high-risk coronary population who have already had a first event, with increased risk of subsequent events (17,18). The creation of additional rules to this nascent technology might allow further improvements in performance for future versions of the algorithm. For example, early in the ALERTS study, an algorithm improvement was made to address post-exercise "recovery events" where heart rate recovers faster than the demand-related ischemia.

In this Alarms OFF group, the median S2D time was 8 h; when the alarm was present, the median time was markedly less and ranged between 1.4 (alarm only) and 1.0 h (alarm and symptoms); and for symptoms-only, the median was 4.6 h. In the absence of an alarm, Alarms ON subjects did not ignore or delay presentation due to symptoms-only: S2D median symptom-only delays for Alarms ON were not longer than for Alarms OFF.

The delays due to symptoms only for both Alarms ON and OFF patients may be larger than what might be expected from some prior reports (19) of pre-hospital delays due to several factors. The Guardian population was selected to be high-risk with a unique demographic profile with characteristics such as diabetes (e.g., 47% diabetic), which have been shown to be correlated with longer delays (20). Additionally, S2D studies on national registries may use artificial cut-offs of 12 or 24 h and restrict symptom onset definitions in various manners that influence time-to-door intervals toward shorter estimates (21–23). The cutoffs and definitions, while relevant to the topic under study (e.g., thrombolytic efficacy) may cause the often-reported median times in the 2- to 3-h range to be artificially low. Longer delay distributions have been reported on other trials of ACS patients using various definitions for symptom onset (9,24–26). In ALERTS, ~20% (Alarms ON) and 40% (Alarms OFF) of ED arrivals were >12 h, and a proportion of these would be "invisible" in other studies that constrain their definition of symptom onset. In **Figure 3**, the shape of the symptoms-only ALERTS distributions for Alarms OFF is similar to the distributions of data published previously by DeVon et al. (12) having a median of 9.5 h (women) and 6 h (men). DeVon et al. (12) may serve well for comparison, because the study reported on MI with S2D arrival times that included, and even exceeded, 96 h.

The ACS events shown in **Figure 2** include UA events that did not transition to NSTEMI or STEMI after arrival at the ED. It may be argued that a benefit from shorter pre-hospital delay is not clear for UA visits. While of interest for all ACS presentations, the reduction of patient-related pre-hospital delays may have the most profound impact with very early detection of STEMI. However, ACS events are dynamic and often progressive. A designation of STEMI, NSTEMI, or UA reflects instantaneous status at a particular point in time. This status is determined by a combination of factors including time course, stability of coronary occlusion, and site of occlusion: even for a fully occluded artery, the surface recordings may not show STEMI if external electrodes are not in appropriate locations, or when obscured by presence of bundle branch block or factors such as obesity. These status labels are relevant to the perspective of treatment, with a STEMI providing a clear incentive for rapid intervention to avoid ischemic-necrosis. However, a continuous ST-segment detection and alerting intracardiac monitor moves the emphasis from treatment of STEMI to management of a progressive ischemic event that may transition into and out of STEMI status. Early patient arrival allows for early medical monitoring and management within a hospital setting while also permitting timely treatment, when indicated. Further, very early medical intervention, such as aspirin and heparin, if provided in the ambulance may allow for clot dissipation when it is a cluster of platelets before formation of an occlusive thrombus (e.g., the MI may be aborted in this setting). The MITI (Myocardial Infarction Triage and Intervention) trial and other published data suggest that potential benefit of earlier arrival for ACS might be useful (27–30). Early arrival may increase the benefit of quicker door-to-intervention, which may be masked when pre-hospital delay is too large (31,32).

The ALERTS trial was designed to show a reduction in S2D, rather than symptom-to-*treatment*. The Guardian alarm does not prescribe what additional testing or therapies should be applied as best

practice. After arrival at an ED, a combination of SOC testing, patient history, comorbidities, and symptoms (if present) must determine the appropriate treatment pathway. ALERTS subjects did not undergo invasive intervention after arrival unless both SOC test results and the patient-specific medical picture determined that this was clinically indicated. In the commercial setting, the full clinical scenario should similarly determine what occurs for each patient.

The A2D times reported here for asymptomatic MI are a novel measurement that has previously not been possible. Others have found that 78% of individuals with myocardial scarring were unaware of the damage, which was only detected upon review of cardiac magnetic resonance imaging (33). Accordingly, the detection of such events may be delayed for weeks, months, or even years. In ALERTS, even in the case of silent MI, 77% of subjects had pre-hospital A2D delays of ≤2 h. The clinical significance of A2D time may be distinct from S2D time. Enzyme biochemical time-course modeling has suggested occlusion onset may often precede symptom-onset by several hours (34). The results reported for **Figure 2** indicate that symptoms occurred prior to alarms, with about the same likelihood as the reverse scenario. The interplay between sensitivity of anginal warning symptoms, collateral flow, and functional flow reserve (yielding a net ischemic burden of an occlusion that is enough to trigger an abnormal ST-segment shift alarm) determines whether the alarm occurs prior to the onset of symptoms or vice versa.

STUDY LIMITATIONS. Future work is needed to better understand the sources of false-positive and false-negative iEGM monitoring scenarios. Although this paper presents compelling data on reduction in pre-hospital delay, assessment of the resulting clinical benefit will require further assessment in post-market studies.

CONCLUSIONS

Implantation of a device for intracardiac ST-segment monitoring and alerting in subjects who are at high risk for recurrent ACS resulted in a statistically significant decrease in median pre-hospital delay compared with current SOC, as reflected by subjects who relied upon symptoms only. Reduced delay facilitates opportunities to provide earlier diagnosis and care using guideline-directed therapy, and thus, has the potential to improve clinical outcome. With iEGM-driven alarms, silent MI median arrival time was ≤2 h for events that may otherwise go undetected until the next hospital visit.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: An implantable cardiac monitor that alerts patients with CAD to rapidly progressive, abnormal ST-segment deviation can reduce delayed arrival in the ED for management of acute MI.

TRANSLATIONAL OUTLOOK: Further studies of this technology are needed to identify patients at risk of coronary events in whom reducing pre-hospital delay improves long-term clinical outcomes.

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