

QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

Initial Clinical Results Using Intracardiac Electrogram Monitoring to Detect and Alert Patients During Coronary Plaque Rupture and Ischemia

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Objectives	We report the first clinical studies of intracardiac ST-segment monitoring in ambulatory humans to alert them to significant ST-segment shifts associated with thrombotic occlusion.
Background	Despite improvements in door-to-balloon times, delays in symptom-to-door times of 2 to 3 h remain. Early alerting of the presence of acute myocardial infarction could prompt patients to seek immediate medical evaluation.
Methods	Intracardiac monitoring was performed in 37 patients at high risk for acute coronary syndromes. The implanted monitor continuously evaluated the patients' ST segments sensed from a conventional pacemaker right ventricle apical lead, and alerted patients to detected ischemic events.
Results	During follow-up (median 1.52 years, range 126 to 974 days), 4 patients had ST-segment changes of ≥ 3 SDs of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 min (6, 18, 21, and 60 min, respectively). Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in 4 patients. There were 2 false-positive ischemia alarms related to arrhythmias, and 1 alarm due to a programming error that did not prompt cardiac catheterization.
Conclusions	Shifts exceeding 3 SD from a patient's daily intracardiac ST-segment range may be a sensitive/specific marker for thrombotic coronary occlusion. Patient alerting was associated with a median alert-to-door time of 19.5 min for patients at high risk of recurrent coronary syndromes who typically present with 2- to 3-h delays. (J Am Coll Cardiol 2010;56:1089-98) © 2010 by the American College of Cardiology Foundation

Acute myocardial infarction (MI) remains a leading cause of mortality in the Western world (1). Early detection of acute MI and prompt intervention may substantially improve clinical outcomes (2-7). Despite efforts to educate the public over the past decade, the mean time from MI symptom onset to arrival at a hospital for treatment has not changed, remaining at 2.5 to 3.0 h (6-10). There may, in fact, be no

reduction in pre-hospital delay between first and second (or subsequent) heart attacks, with a median of 2.4 h for both first and second MI (11,12). Because a large proportion of irreversible myocardial injury and fatal ventricular arrhythmias occurs in the first hour after coronary thrombosis, it may be difficult to further improve upon the prognosis of ST-segment elevation myocardial infarction (STEMI) pa-

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ischemia; he is also the CEO and founder of, owns stock in, receives an annual salary from, and has licensed patents to Angel Medical Systems. Dr. John is a co-investigator on a SBIR grant for developing a similar device that will use subcutaneous sensing of cardiac activity to detect ischemia; he also owns stock in Angel Medical Systems and receives an annual salary. Dr. Foster has stock in Angel Medical Systems. Dr. Kovach has served on the Speakers' Bureau of Medtronic Corporation and Lilly. Dr. Gibson has served as a consultant to (not in the past year) and received research grants from Angel Medical Systems. All other authors have reported that they have no relationships to disclose.

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Abbreviations and Acronyms

ECG = electrocardiogram

ICEG = intracardiac electrogram

LAD = left anterior descending artery

MI = myocardial infarction

STEMI = ST-segment elevation myocardial infarction

tients unless an earlier and reliable diagnosis can be made (6–14) that would, in turn, prompt patients to seek immediate care.

Although fixed coronary artery narrowing may result in ST-segment depression with elevated heart rates (demand-related ischemia), rapidly progressive ST-segment shifts within the “normal” heart rate range (supply-related ischemia) is a highly specific, and early, marker of

thrombotic (or vasospastic) coronary artery occlusion. Such ST-segment changes often precede, and may occur in the absence of, clinical symptoms. Continuous monitoring of a patient’s electrogram ST-segment may allow an implanted device to detect acute closure of a coronary artery. If the implanted device then alerted the patient, that could lead to a reduction in symptom-to-door time and thereby potentially improve clinical outcomes.

The current study reports the first in-humans clinical experience with intracardiac ischemia monitoring, combining 2 phase 1 studies: the Cardiosaver study (conducted in Brazil) and the DETECT (Angel Medical Systems DETECT Feasibility) study, a Food and Drug Administration investigational device exemption study (conducted in the U.S.).

Methods

Subjects. Two phase 1 clinical studies, Cardiosaver (n = 20) and DETECT (n = 17), assessed device safety and feasibility. Patient demographic data are summarized in Table 1.

Ischemia monitoring system components. The AngelMed Guardian implantable ischemia detection system (Angel Medical Systems, Shrewsbury, New Jersey) is designed to provide early detection and patient alerting for ischemic events in ambulatory patients. An implantable device monitors the intracardiac electrogram (ICEG) signal, acquired at 200 Hz using a band-pass of 0.25 Hz (2-pole) to 48 Hz (5-pole), from the tip of a steroid-eluting pacemaker lead placed at the right ventricle apex. Using a can-to-tip vector, the implantable device monitors the ST-segment of the sensed ICEG to detect and alert patients to excessive ST-segment shift events. The algorithm computes the ST-segment shift of each beat compared with average baseline ST-segment levels sampled across the prior 24 h, and normalizes this as a percent of the baseline average R-wave height to derive a measure referred to as ST-shift%. Both positive and negative ischemia detection thresholds are defined for ST-shift%. The implantable and external components of the system (Fig. 1) provide ischemia detection and alerting, as has previously been described in detail (15,16).

Study protocol. The Cardiosaver and DETECT study protocols are described in Table 2. All patients participated only after reviewing and signing informed consent, as per Brazilian and U.S. (Food and Drug Administration) guidelines, and local approval from institutional review boards.

Patients returned within 2 weeks after surgical implantation to undergo a stress test used to program heart rate ranges and respective ischemia detection thresholds at levels that would not trigger an alert based upon the patient’s normal intrinsic ischemic burden. A “normal” heart rate range was set for each patient by their physician, as was a maximum heart rate above which an alarm was defined. The range between normal and maximum was divided into 4 elevated heart rate ranges. The DETECT study utilized an automated threshold feature built into the programmer. The feature calculates ischemia detection thresholds using an initial period of up to 2 weeks of data and suggests positive/negative thresholds for different heart rate ranges. Thresholds are set for each heart rate range using a mean ± a variance estimate. The variance was 3 SD of measured ST-segment levels compared to isoelectric (ST-segment deviation) that occurred during this initial period (in the normal heart rate range). The Cardiosaver study initially set ischemia thresholds based upon clinical judgment, but as the study progressed, the automatically chosen thresholds were adopted.

After device programming, patients underwent training to experience and distinguish between the 2 types of alarms (“Emergency” and “See Doctor”). Patients were then discharged. Patients were required to return: 1) at 1 month, at 3 months, and then at 6-month follow-up intervals during which data were downloaded and reviewed to ensure proper monitor operation and to confirm that ischemia detection parameters did not require adjustment; 2) if they had symptoms they thought were consistent with a cardiac problem, even if the device was not alerting; and 3) because of an Emergency or See Doctor alarm, according to the study protocols.

Patient alerting and response protocol. The Guardian system provides 2 types of patient alerting across 3 sensory

Table 1 Demographic Data

	Cardiosaver	DETECT
Mean age, yrs	60 (49–70)	60 (42–71)
Female	3/20 (15%)	5/17 (29%)
Smoking	13/20 (65%)	11/17 (65%)
Diabetes mellitus	5/20 (25%)	7/17 (41%)
Previous MI	9/20 (45%)	13/17 (76%)
STEMI		7 (41%)
NSTEMI		6 (35%)
Previous PCI/CABG	5/20 (25%)	17/17 (100%)
Mean coronary artery diameter stenosis	71.4%	NA

CABG = coronary artery bypass graft surgery; DETECT = Angel Medical Systems DETECT Feasibility study; MI = myocardial infarction; NA = not available; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

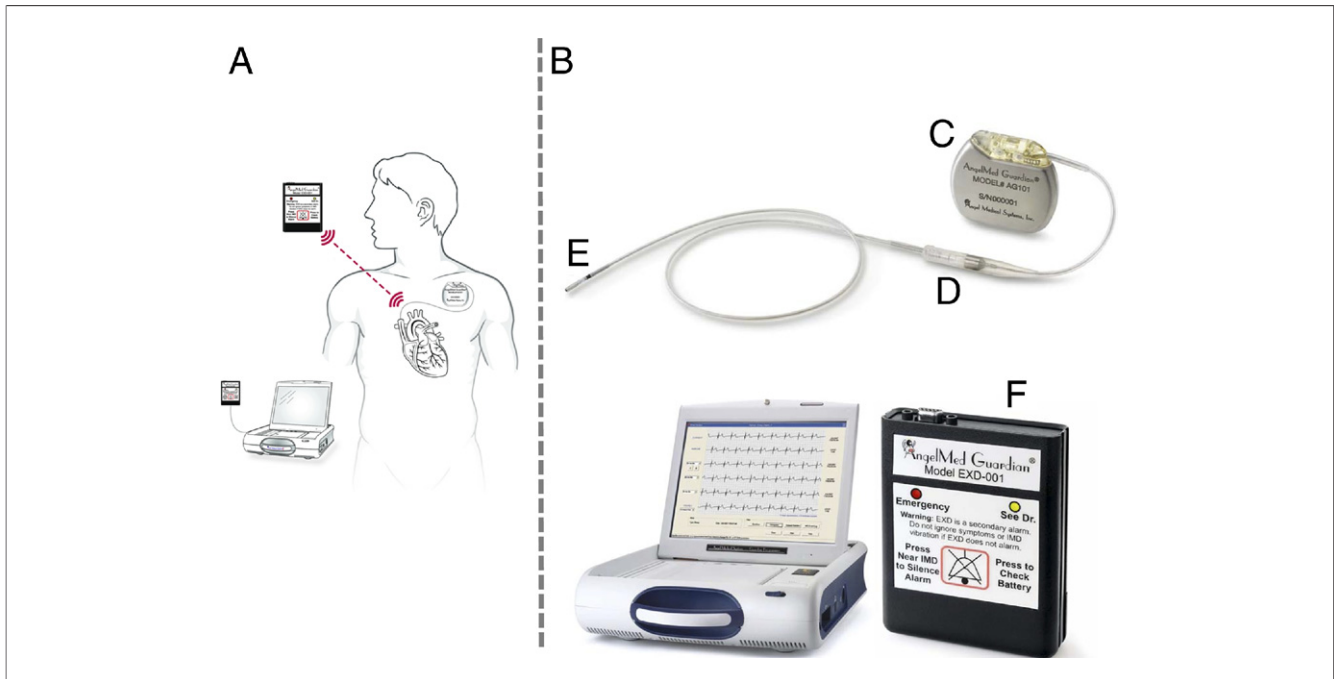


Figure 1 Guardian System

(A) Schematic of the components of the ischemia detection system. The implanted monitoring device (IMD) communicates with the external device (EXD) via telemetry. The EXD can be connected to the programmer by a cable to provide programming and data uploading from the IMD. (B) Photographs of the Guardian components. The monitor (C), resembling a VVI pacemaker, is attached to the lead adapter (D) and a standard bipolar, active-fixation, right ventricular lead (E). The IMD emits distinct patterns of vibratory alarms, and the EXD (F) provides sonic and visual notification, with a red light for Emergency alarms and a yellow light for See Doctor alarms. Two highly distinguishable patterns, which conform to international medical equipment alarm standards, differentiated the 2 types of patient alarms. Patients halt the alert by placing the EXD on their chest and pressing the EXD's "alarm silence" button.

modalities (Fig. 1). After detection of excessive ST-segment shift (ST-shift) over 1.5 min, when the patient's heart rate is not elevated, the system provides an Emergency alarm

indicating that thrombosis may be present. Patients were instructed to seek help immediately if the Emergency alarm occurred. For non-life-threatening detections, the monitor

Table 2 Protocols for Cardiosaver and DETECT Phase I Studies

Cardiosaver Study (São Paulo, Brazil)	DETECT Study (U.S.)
Locations patients recruited/implanted Dante Pazzanese Institute of Cardiology, São Paulo, Brazil	Locations patients recruited/implanted Borgess Heart Institute, Kalamazoo, Michigan Virtua Hospital, Marlton, New Jersey Baptist Hospital West, Knoxville, Tennessee
Primary objective To evaluate the ability of the Guardian ischemia detection system to measure intracardiac ST-segment shifts associated with subendocardial ischemia during a stress test and transmural ischemia during 3-min coronary occlusion in PCI (balloon and stent placement)	Primary objective To evaluate the safety of the Guardian ischemia detection system and to evaluate algorithm for suggesting appropriate ST-segment shift detection thresholds
Study population: 20 enrolled, 20 implanted CAD patients, stable angina (CCS) Age ≥40 and <70 yrs >1.5-mm ST-segment depression on stress test Stenosis in native coronaries, PCI indicated Implant suitability	Study population: 20 enrolled, 17 implanted Post-MI patients with other risk factors TIMI flow grade 3 or worse Implant suitability
Procedures 1. System implant (pacemaker lead in the RV) 2. Stress test (pre-PCI) 3. PCI after injury current dissipates (~1–2 weeks) 4. Balloon inflation for 3 min 5. Standard stent placement 6. Patient training on the alarm recognition 7. Discharge and follow-up	Procedures 1. System implant (pacemaker lead in the RV) 2. Wait until injury current dissipates (~1–2 weeks) 3. Stress test to get data at elevated heart rates 4. Device programming using automatic and statistically based thresholds 5. Patient training on the alarm recognition 6. Discharge and follow-up

CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; RV = right ventricle; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

issued a See Doctor alarm. See Doctor alarms could be triggered by excessive ST-shift concurrent with an elevated heart rate, by the detection of additional conditions related to device operation, and by status-checks that the ischemia detection algorithm performed. All patients were trained to respond to See Doctor alarms by immediately calling their doctor to schedule an appointment within 1 to 2 days.

Data. The results are from the Cardiosaver study (active May 2006 to November 2007) and the DETECT study (active June 2007 to present) and include all study period data collected through January 1, 2009. The ICG data were uploaded from implantable monitor’s memory during scheduled patient visits and visits made in response to alarms. The implantable monitor normally stores selected electrogram data strips from the preceding 24 h. After an Emergency alarm, strips for up to 8 h after the alarm are also stored. More than 58 patient-years of aggregate monitoring produced >350,000 10-s electrogram strips, which were uploaded into the study database.

Emergency alarm event types. Ischemic events were classified into 3 types. Type 1 events comprise alarms triggered by persistent excessive ST-shift% detected during, or after, an elevated heart-rate (demand-related ischemia, typically seen in abnormal 12-lead exercise stress test data). Type 2 events comprise false-positive alarms that were unrelated to a verifiable ischemic condition. Type 3 events comprise alarms triggered by excessive ST-shifts detected at normal heart rates (supply-related ischemia) without associated elevated heart rate consistent with coronary thrombosis.

Results

The 37 patients were monitored for a total of 58.2 patient-years (mean follow-up 1.53 ± 0.54 years; median follow-up 1.52 years). The range of follow-up was from 126 to 974 days. The implant success rate was 37 of 37 (100%). One device replacement was required because of vibration alarm motor failure. No other device-related failures or complications occurred during the study period.

Four patients had type 1 events, with positive ST-shift alarms at an elevated heart rate ($n = 1$), and negative ST-shifts at a nonelevated heart rate, after a period of elevated heart rate ($n = 3$). Three patients had type 2 events, including false positive ST-segment shift detections caused by an intermittent ventricular dysrhythmia, which required device reprogramming ($n = 2$) and a false positive occurring just after improper programming of the device thresholds before the patient left the hospital ($n = 1$). Four patients had type 3 events, which included excessive ST-shifts at normal heart rates, unrelated to any episode of elevated heart rate (Figs. 3 to 7).

Heart rate-related ST-shift alarms (type 1 events). Figure 2A shows the plot of ST-shift% versus heart rate (beats/min), illustrating an example of a type 1 event. As the heart rate elevates (red), there is ST-shift (depression). Figures 2B and 2C show the ICEGs at baseline and during demand ischemia related to an obstructive lesion of the right coronary artery revealed in that patient. The figure shows that ST-shift levels remained depressed for up to 5 min after the patient’s heart rate recovered to normal levels. Three other patients had heart rate-related ST-shift alerts. These demand-

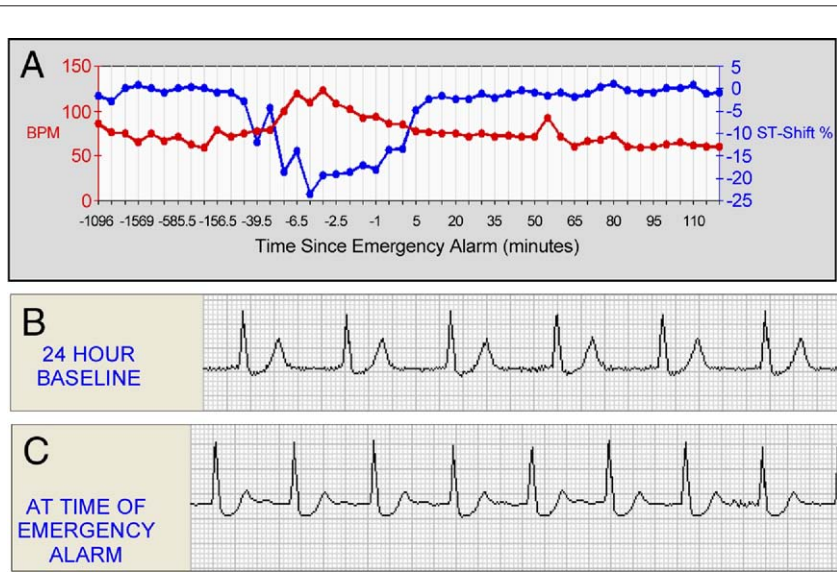


Figure 2 Heart Rate Related ST-Segment Shift% Alarms

(A) Heart rate (beats/min [BPM]) (red) versus ST-segment shift percent (ST-shift%) (blue) over time. Time is represented in minutes across a period of about 20 h (log scale). Time zero is when the alarm occurred. The lower 2 plots are electrogram strips from the patient’s baseline (B) and at the time of the alarm (C) showing substantial ST-segment depression.

related ST-shifts in the 3 other patients were all associated with hemodynamically significant new coronary obstructive lesions from either atherosclerotic progression or in-stent restenosis.

False positive ST-shift detections (type 2 events). Two false positive alarms occurred as the result of ventricular dysrhythmias. These caused the R-wave identification of the monitoring algorithm to measure the beats incorrectly, leading to a false Emergency alarm. The R-wave identification algorithm parameters were manually adjusted, and no additional false positive alarms occurred in these 2 patients. A third false positive was due to a programming error.

Excessive ST-shifts at normal heart rates (type 3 events). Case studies are presented for 7 true positive Emergency alarm events that occurred in 4 patients during the study period. Cases 1 and 2 are from the Cardiosaver study, and cases 3 and 4 are from the DETECT study.

CASE 1: LCX RUPTURED PLAQUE. The patient is a postmenopausal woman with prior MI, diabetes mellitus, hypertension, and hyperlipidemia who presented with unstable angina due to a 70% stenosis of the right coronary artery. The ischemia monitor was implanted during that hospitalization with right coronary artery stenting 1 week later, as per protocol. Six months later, she presented 1 h after an Emergency alarm that occurred in the setting of chest pain lasting 10 to 20 min. Her troponin and 12-lead electrocardiogram (ECG) were normal. The ICEG data (Figs. 3A to 3D) demonstrated a 15- to 20-min episode of significant positive ST-shift, which coincided with the alarm (12:20 PM) and her symptoms, which resolved by the time of hospital arrival. Treatment included intravenous unfractionated heparin and clopidogrel. Eleven hours after admission, she had a recurrent episode of chest pain greater than that during the first event, and a second Emergency alarm occurred. Of note, the simultaneous 12-lead

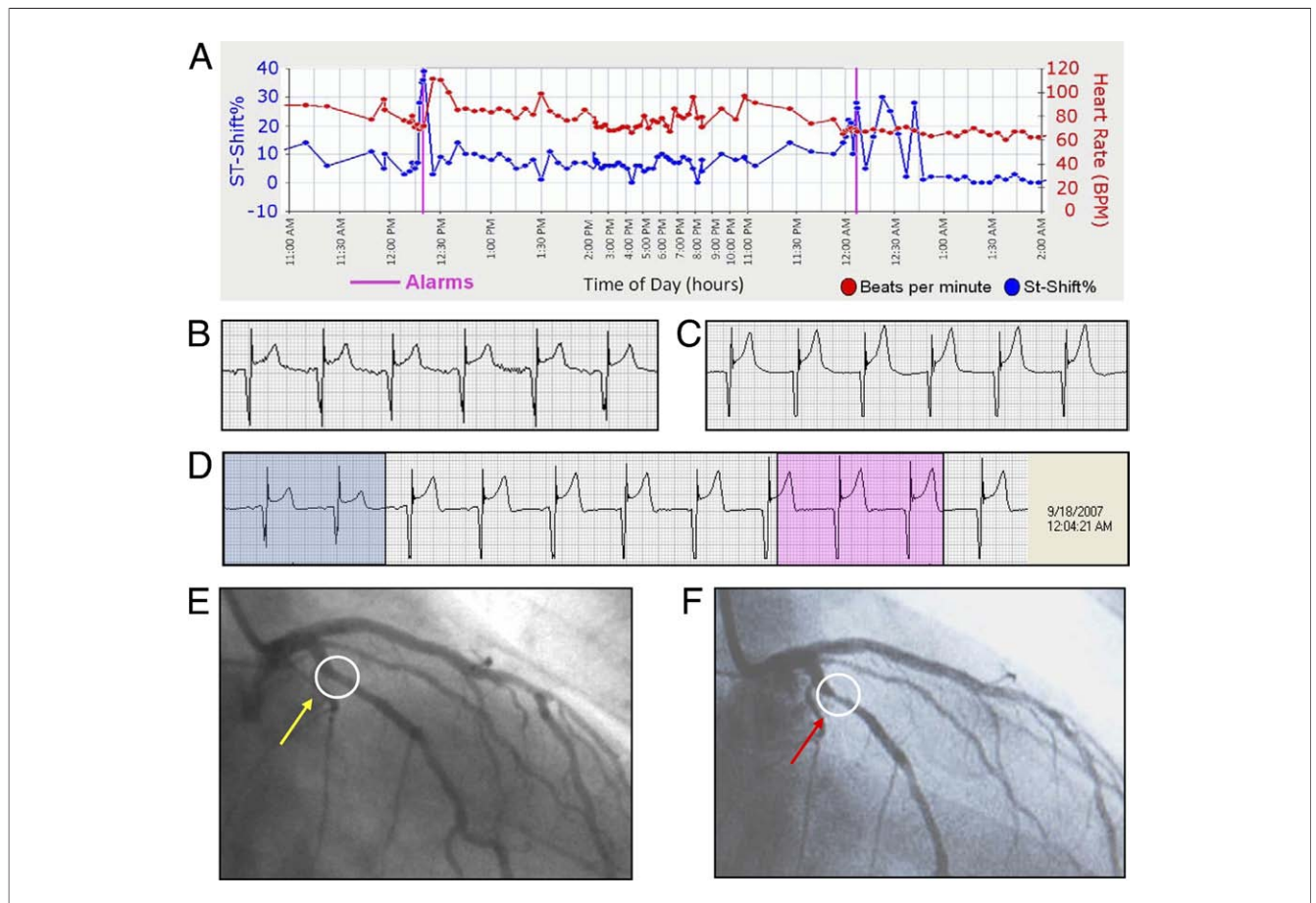


Figure 3 Case 1: Heart Rate Versus ST-Segment Shift Over Time

(A) Heart rate (beats/min [BPM]) (red) versus ST-segment shift percent (ST-shift%) (blue) over time. Pink lines denote ST-segment shifts that triggered the 2 Emergency alarms. (B) The baseline intracardiac electrogram (ICEG) tracings from the day before the alarm are shown. (C) The ICEG tracings at ~12:20 PM, during the first Emergency alarm, are shown, demonstrating significant T-wave peaking and ST-segment elevation compared with baseline. Peak ST-shift% was 39%, at normal heart rate, with threshold set at $\pm 25\%$. (D) The rapid, beat-to-beat elevation of ST-segment and T-wave peaking during the second Emergency alarm (ST-shift% = 30%) is shown. The shaded boxes highlight the rapid evolution of the ST-shift from a waveform similar to B (blue shadowing) to substantial ST-segment changes (pink shadowing) over a series of 7 to 10 beats. (E) The baseline angiogram of the left circumflex lesion (yellow arrow) is shown. (F) The pronounced progression of the proximal left circumflex lesion is shown at the time of admission for recurrent ischemic alarm events. Intravascular ultrasonography demonstrated a ruptured plaque at the site of the red arrow.

surface ECG showed little change from baseline, and the troponin remained within normal limits. This second event prompted cardiac angiography, which demonstrated a large increase in the severity of a lesion in the proximal portion of the left circumflex, compared with prior angiography (Figs. 3E and 3F). Intravascular ultrasonography confirmed the presence of a ruptured plaque. Four days after the second alarm, the patient underwent successful bypass surgery.

CASE 2: RCA RUPTURED PLAQUE. The second patient is a 65-year-old man with hypertension and dyslipidemia who presented with new-onset angina (Canadian Cardiovascular Society Angina score of II) due to a 70% mid-left anterior descending artery (LAD) lesion, associated with a positive exercise test (2- to 3-mm ST-segment depression at peak exercise). The patient underwent elective stent placement in the LAD 1 week after device implantation. Eighteen

months later, the Emergency alarm was triggered while he was picking up medication at the hospital, and was due to a significant positive ST-shift% (~65%), which persisted at >30% for >30 min and was accompanied by minimal symptoms. The patient was admitted, and aspirin and intravenous unfractionated heparin were administered. Nine hours later, a second Emergency alarm occurred because of recurrent ST-segment elevation (peak ST-shift exceeding 35%), which resolved over the next 2 h (Fig. 4, top panel) in the absence of symptoms. The next morning, the patient underwent angiography (Fig. 4C), which demonstrated a severe, eccentric lesion with a ruptured plaque (Figs. 4D and 4E) in the distal portion of a dominant right coronary artery.

CASE 3: LAD RUPTURED PLAQUE. This patient is a 65-year-old man with renal insufficiency, hypertension, dyslipidemia, and an MI 8 years before enrollment. Approximately 1

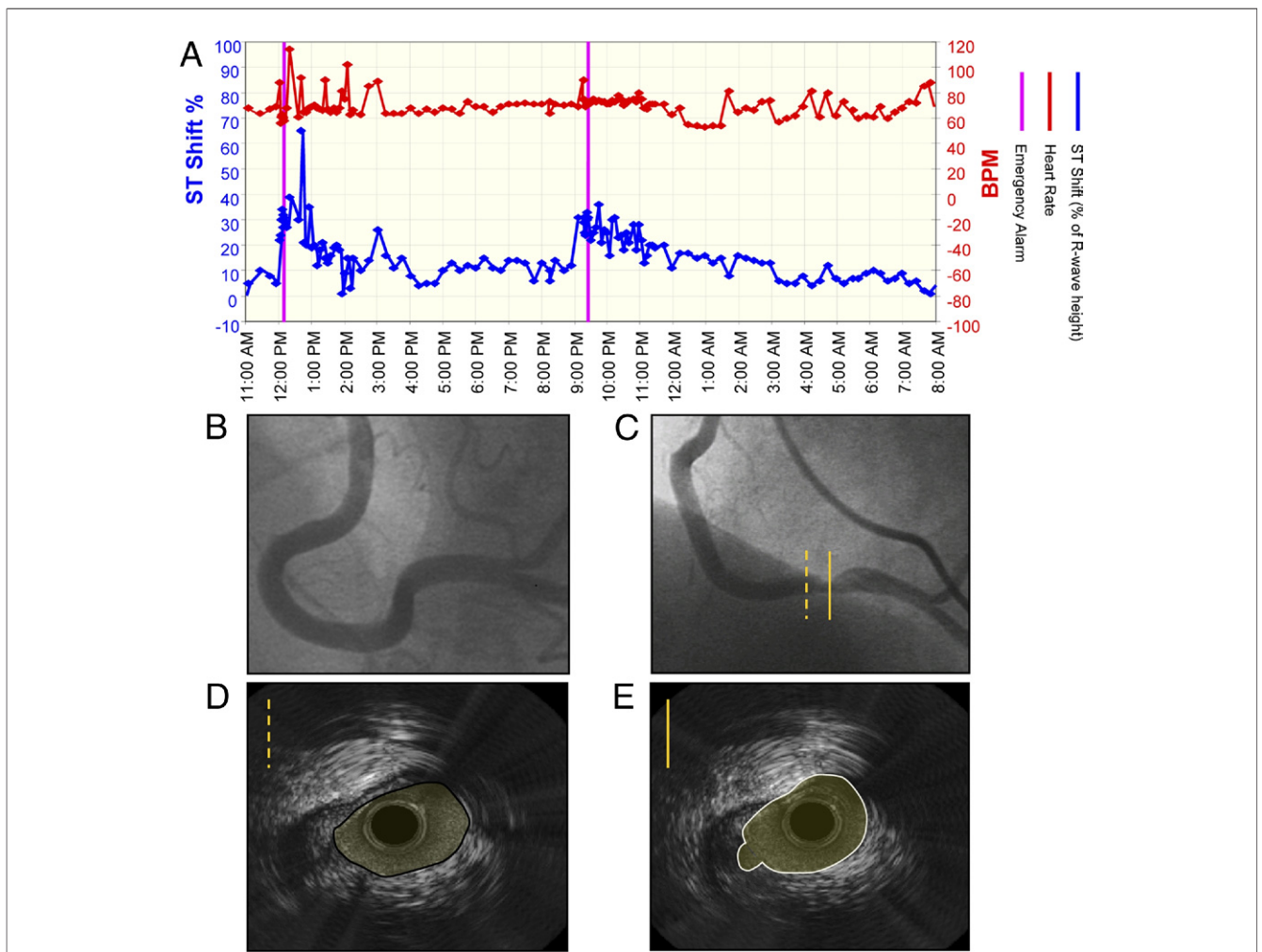


Figure 4 Case 2: Heart Rate Versus ST-Segment Shift Over Time

(A) Heart rate (beats/min [BPM]) (red line) versus ST-segment shift percent (ST-shift%) (blue line) over time is shown. Two Emergency alarms occurred, as denoted by pink lines. (B) The baseline angiogram of the right coronary artery (May 2006) and (C) the subsequent angiographic findings at the time of Emergency alarms (November 2007) are shown. (D, E) Lesion progression, with intravascular ultrasonography evidence of plaque rupture, is evident. Dashed and solid lines denote the location of intravascular ultrasonography sections shown in C and D.

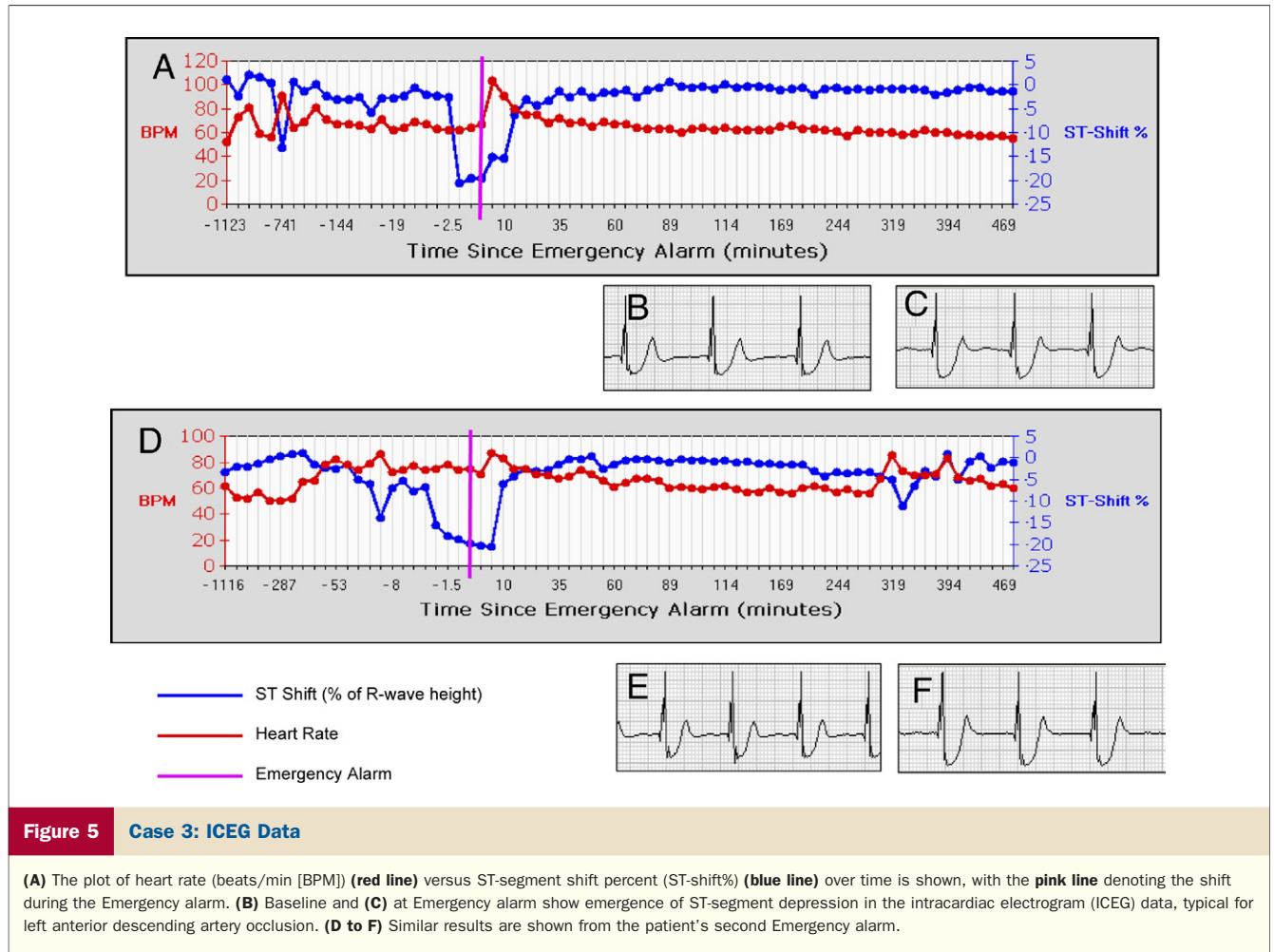


Figure 5 Case 3: ICEG Data

(A) The plot of heart rate (beats/min [BPM]) (red line) versus ST-segment shift percent (ST-shift%) (blue line) over time is shown, with the pink line denoting the shift during the Emergency alarm. (B) Baseline and (C) at Emergency alarm show emergence of ST-segment depression in the intracardiac electrogram (ICEG) data, typical for left anterior descending artery occlusion. (D to F) Similar results are shown from the patient's second Emergency alarm.

month before study enrollment and implantation, he presented with unstable angina (Canadian Cardiovascular Society Angina score of IV). Approximately 1 month after implantation, he had an Emergency alarm triggered by an ST-segment shift of -24% (Figs. 5A to 5C [-18% was detection threshold]) while watching the Super Bowl. The surface 12-lead ECG in the emergency room was inconclusive, but troponin I levels were elevated, and a nuclear stress test detected anterior ischemia. Angiography revealed a 70% stenosis in the mid-portion of the LAD that was treated with primary stenting. A second Emergency alarm was triggered 3 weeks later by a negative 24% ST-segment shift at a normal heart rate (Figs. 5D to 5F). The subject was immediately transported to the hospital. The 12-lead surface ECGs and cardiac enzymes were inconclusive. Angiography demonstrated a 70% stenosis in the LAD distal to the (patent) first stent. Intravascular ultrasonography confirmed that this distal lesion contained a ruptured plaque. The patient was treated with a coronary stent, with the possibility that the distal lesion, and not the originally stented lesion, may have been the culprit lesion that triggered both ischemic events. Since stenting of the second lesion, the patient has had no recurrent ischemic events.

CASE 4, STEMI. This patient is a 60-year-old woman with coronary artery disease, hypertension, dyslipidemia, and a long history of smoking. Nine months after implantation, the patient had severe chest pain. Nineteen minutes after the onset of her chest discomfort, she received the Emergency alarm. A 12-lead ECG performed by paramedics in the ambulance was mildly abnormal, with ST-segment abnormalities in the inferior leads and clear T-wave changes in the pre-cordial leads (Fig. 6A). The 12-lead ECG in the emergency room demonstrated ST-segment depression in the anterior precordium consistent with a posterior MI, as shown in Figure 6B. The Emergency alarm was triggered by a positive 17% ST-segment shift (11% was ischemia threshold) at a normal heart rate. The ST-shift% versus heart rate plot and the ICEG tracings are shown in Figures 7A, 7B, and 7C. The total creatinine kinase and troponin levels were elevated shortly after arrival at the hospital. The patient was taken emergently for coronary angiography. A new subtotal occlusion of the proximal left circumflex was found (Figs. 7D and 7E). She underwent stenting (Fig. 7F), and was discharged without complications or further alarms.

Behavioral results. Each of the 4 case study patients responded quickly to the Emergency alarm, regardless of

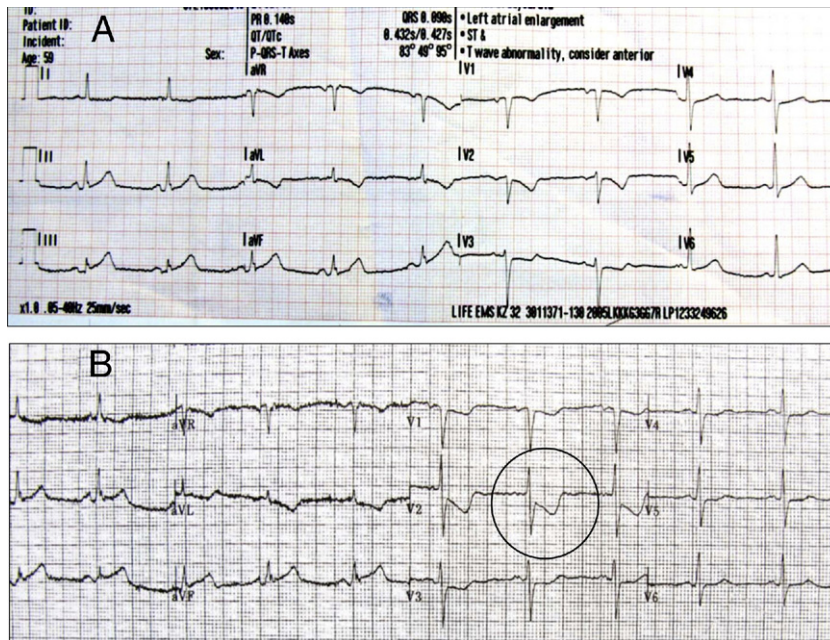


Figure 6 Case 4: Surface 12-Lead ECG

(A) The 12-lead electrocardiogram (ECG) at ambulance arrival (7:00 AM) is shown. (B) The evolution to “true posterior” ST-segment elevation myocardial infarction (circled beat in lead V₂) is shown at 7:20 AM, during hospital arrival.

concurrent subjective symptoms. Cases 1, 2, 3, and 4 had alarm-to-door times of 60, 6, 18, and 21 min, respectively (mean 26.5 min, median 19.5 min).

Discussion

This study demonstrates the safety and feasibility of ICEG monitoring to detect and alert patients to ischemic events associated with documented plaque rupture and/or thrombotic occlusion (supply-related ischemia at normal heart rate). Alarms also occurred at elevated heart rates in response to disease progression in fixed obstructive lesions, such as is observed during abnormal (12-lead) stress test (demand-related ischemia). The discrete shifts in the ST-segment that triggered Emergency alarms were large and exceeded the small day-to-day variation in ST-segment shifts ($< \pm 10\%$ in the normal heart rate range) by 3 SD for at least 1.5 min.

Four patients had 7 ST-segment shift detections in the setting of a normal heart rate triggering Emergency alarms associated with STEMI, a severe coronary lesion, and/or with intravascular ultrasonography evidence of plaque rupture. The mean alarm-to-door time of 26.5 min (median 19.5 min) is approximately 2 h faster than the 144-min symptom-to-door time observed in general STEMI patient populations (12). Seeking medical care 2 h earlier, during the beginning of acute MI, may be associated with significant improvements in clinical outcomes, including reductions in the development of heart failure and mortality.

Several potential explanations exist for the observation that some Emergency alarms occurred in the absence of troponin elevation, surface ECG changes, and/or symptoms (e.g., Case 3) although plaque rupture or thrombus was documented on intravascular ultrasound. The ICEG may be more sensitive than 12-lead surface ECGs, particularly for detection of injury involving the posterior aspect of the left ventricle. Indeed, in Cases 1 and 4, the surface 12-lead ECG was insensitive to left circumflex coronary artery occlusion. This finding is consistent with prior demonstrations that the ICEG is more sensitive than surface ECG to balloon occlusion during angioplasty (13,14,17–19). Further, the real-time quantification available from a self-normative implanted monitor increases sensitivity compared with that of traditional ECG. In some patients, the ICEG recordings may have reflected transient coronary occlusion and/or cyclic flow variations in the early period after plaque rupture and before formation of a stable occlusive clot (20–24).

Patients may not sense chest pain, despite ischemia, possibly as a result of a defective anginal warning system. For example, in the Framingham experience, 1 in 4 new Q-wave MIs were silent (25). Given the mild nature of symptoms, some patients (e.g., Case 2) may not have sought medical attention in the absence of device alarming. Intracardiac electrogram data may not only prompt the patient to seek medical attention earlier, but because it is more sensitive than the surface ECG, a more definitive pre-

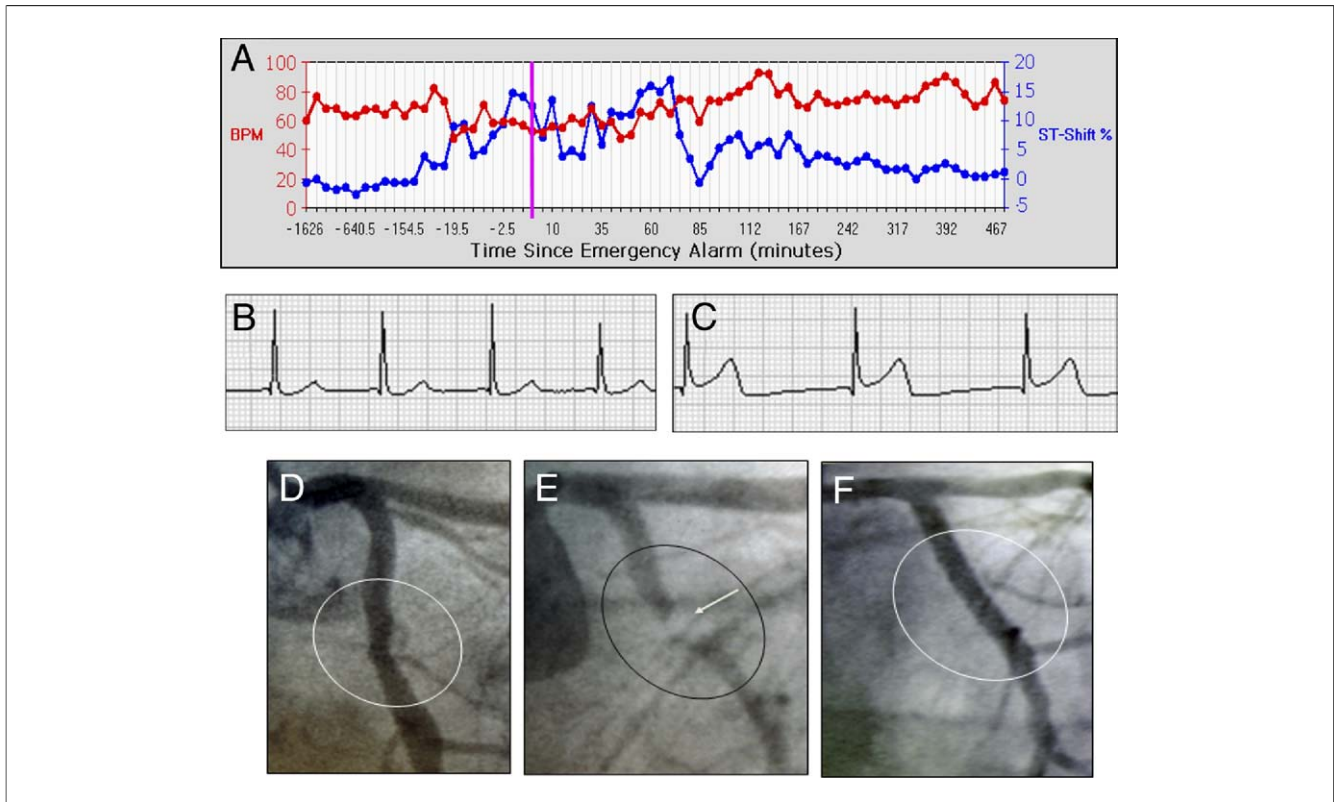


Figure 7 Case 4: ICEG Data and Angiographic Findings

(A) Heart rate (beats/min [BPM]) (red line) versus ST-segment percent (ST-shift%) (blue line) is shown over time, with the pink line denoting the change that prompted the Emergency alarm. (B) The baseline intracardiac electrogram (ICEG) is shown. (C) The ST-segment elevation that triggered the Emergency alarm is shown. The ST-segment elevation persisted until successful stenting of the subtotally occluded left circumflex. Of note, the alarming ST-segment shift in the ICEG was evident >30 min before 12-lead electrocardiographic findings were diagnostic for ST-segment elevation myocardial infarction (Fig. 6B). (D, E) Prior angiograms of the left circumflex coronary artery (October 2007) and at the time of Emergency alarm (July 2008), respectively, are shown. Marked lesion progression to subtotal occlusion is evident at follow-up (white arrow). (F) The result after stent placement.

hospital diagnosis may further reduce door-to-balloon times by improving triage decisions in the emergency room (26).

Three false positive events comprise the only false positive alarms during 58 patient-years of monitoring. These false positive detections, which appear to be secondary arrhythmias, permitted early adjustments in the monitoring algorithm. After these adjustments, no additional false positives occurred. No false negative alarms occurred during the study period: there were no undetected STEMI, cardiac deaths, or Q-wave MIs in any of the cohort during the follow-up. No clinically significant, unanticipated adverse device-related events occurred in any patient. The monitor's safety profile is anticipated to be similar to the safety of a single-chamber pacemaker.

Study limitations. The number of Emergency alarms reported here is consistent with the 5% to 10% risk of acute MI in this population. The number of cases here is too small to evaluate the clinical impact of early detection of ST-segment shifts. In this study, the Emergency alarms were not intended to trigger immediate trips to the catheterization laboratory. However, emergency alerting was subsequently associated with thrombotic occlusion or ruptured

plaque. None of the false positive patients underwent cardiac catheterization. Whether patients should proceed to the cardiac catheterization laboratory earlier is not addressed in the present study. These issues are now being addressed in the ALERTS (AngelMed Early Recognition and Treatment of STEMI) study, a phase II randomized clinical trial of 1,000 patients. It is possible that "silent" ischemic events occurred that did not trigger an Emergency alarm and for which the patient did not experience symptoms and seek hospitalization. In the ALERTS trial, the development of new Q waves in the absence of symptoms will be evaluated. Early alerting and treatment of patients in the early phase of an acute coronary syndrome may minimize or prevent the progression to a higher-risk, more established acute coronary syndrome or acute MI. Paradoxically, this scenario may obscure the ability to demonstrate that MIs were detected early if they were, in fact, prevented. This issue will be addressed by the control group in the ALERTS trial. There were no control patients in the present study. The expected rate of resource consumption will also be addressed by the control group in the ongoing randomized ALERTS trial who will not receive Emergency alarms.

Conclusions

This study represents 58.2 patient-years of monitoring and >18 million monitored electrogram segments in a population at high risk for recurrent thrombotic events. Long-term intracardiac ST-segment deviation appears relatively stable in the absence of substantial coronary artery occlusions. A shift of 3 SD from a patient's normal daily ST-segment range on ambulatory intracardiac monitoring may be a sensitive/specific marker for plaque rupture and/or thrombotic coronary occlusion. Early warning was associated with a median alert-to-door time of 19.5 min for patients at high risk of recurrent coronary syndromes, who typically present with delays of 2 to 3 h.

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Key Words: electrogram ■ ischemia monitoring ■ myocardial infarction ■ vulnerable plaque.