Risk for Clinically Relevant Adverse Cardiac Events in Patients With Chest Pain at Hospital Admission

Michael B. Weinstock, MD; Scott Weingart, MD; Frank Orth, DO; Douglas VanFossen, MD; Colin Kaide, MD; Judy Anderson, MS, MAS; David H. Newman, MD

IMPORTANCE Patients with potentially ischemic chest pain are commonly admitted to the hospital or observed after a negative evaluation in the emergency department (ED) owing to concern about adverse events. Previous studies have looked at 30-day mortality, but no current large studies have examined the most important information regarding ED disposition: the short-term risk for a clinically relevant adverse cardiac event (including inpatient ST-segment elevation myocardial infarction, life-threatening arrhythmia, cardiac or respiratory arrest, or death).

OBJECTIVE To determine the incidence of clinically relevant adverse cardiac events in patients hospitalized for chest pain with 2 troponin-negative findings, nonconcerning initial ED vital signs, and nonischemic, interpretable electrocardiographic findings.

DESIGN, SETTING, AND PARTICIPANTS We conducted a blinded data review of 45,416 encounters obtained from a prospectively collected database enrolling adult patients admitted or observed with the following inclusion criteria: (1) primary presenting symptom of chest pain, chest tightness, chest burning, or chest pressure and (2) negative findings for serial biomarkers. Data were collected and analyzed from July 1, 2008, through June 30, 2013, from the EDs of 3 community teaching institutions with an aggregate census of more than 1 million visits. We analyzed data extracted by hypothesis-blinded abstractors.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of life-threatening arrhythmia, inpatient ST-segment elevation myocardial infarction, cardiac or respiratory arrest, or death during hospitalization.

RESULTS Of the 45,416 encounters, 11,230 met criteria for inclusion. Mean patient age was 58.0 years. Of the 11,230 encounters, 44.83% of patients arrived by ambulance and 55.00% of patients were women. Relevant history included hypertension in 46.00%, diabetes mellitus in 19.72%, and myocardial infarction in 13.16%. The primary end point occurred in 20 of the 11,230 patients (0.18% [95% CI, 0.11%-0.27%]). After excluding patients with abnormal vital signs, electrocardiographic ischemia, left bundle branch block, or a pacemaker rhythm, we identified a primary end point event in 4 of 7266 patients (0.06% [95% CI, 0.02%-0.14%]). Of these events, 2 were noncardiac and 2 were possibly iatrogenic.

CONCLUSIONS AND RELEVANCE In adult patients with chest pain admitted with 2 negative findings for serial biomarkers, nonconcerning vital signs, and nonischemic electrocardiographic findings, short-term clinically relevant adverse cardiac events were rare and commonly iatrogenic, suggesting that routine inpatient admission may not be a beneficial strategy for this group.
ore than 7 million emergency department (ED) visits for chest pain occurred in the United States in 2010, representing 5.4% of ED visits nationally.¹ Admission or observation of such patients represented annual US charges of more than $11 billion for nonspecific chest pain in 2006.²⁻³ Most of the patients are eventually determined to have a noncardiac diagnosis, suggesting a very low short-term risk for serious adverse events.⁴⁻¹¹ Wide variability exists in the treatment and disposition of these patients, based in part on risk aversion by the patient and the health care professional.¹²

Hospital admission or extended observation after a negative ED evaluation is assumed to confer a safety benefit for patients with chest pain; however, this assumption remains untested. The potential for this benefit depends largely on the rate of treatable or avoidable adverse events during hospitalization. Previous studies have examined primarily rates of cardiac events rates at 30 days or longer, including adverse events after hospitalization and after outpatient follow-up. Moreover, ED-based randomized clinical trials of patients with chest pain that compare clinical pathways, testing options, and disposition decisions have been unable to identify outcome benefits with any approach during hospitalization or during follow-ups typically lasting 30 days or more.¹³⁻¹⁷

Importance
Inpatient admission or observation for the purpose of managing potential adverse events constitutes a considerable burden to the health system and the patient. In addition, the risks of hospital admission, including false-positive testing sequelae, hospital-acquired infections, venous thromboembolism, pneumonia, falls, and other iatrogenic events are considerable¹⁸ and typically greater than the 2% rate of adverse events at 30 days often cited as an upper boundary estimate for low-risk patients with chest pain. Reliable estimation of the incidence of such events in an admitted population with chest pain therefore has the potential to inform harm-benefit analyses for this group.

Goals
We aimed to quantify the incidence of short-term life-threatening events among patients with chest pain admitted to the hospital after the ED evaluation is negative for ischemia and includes negative serial biomarker findings, normal vital signs, and nonischemic electrocardiographic (ECG) findings. We hypothesized that the overall incidence of such events would be less than 1%.

Methods

Study Design
We conducted a multicenter study examining an existing database developed at 3 hospitals in the US Midwest with a combined annual ED census of approximately 230,000 patients. The study was approved by the Mount Carmel Institutional Review Board. Patient data were deidentified.

Data Collection
We analyzed data extracted from the medical records and initially reviewed by data abstractors from the quality and safety department of each institution. All data were collected before our study began and stored in a protected database consisting of data elements for accreditation by the Society of Cardiovascular Patient Care (formerly the Society of Chest Pain Centers).

Selection of Participants
Using the existing database, we selected adults (aged ≥18 years) who presented at a study ED with chest pain, chest tightness, chest burning, or chest pressure from July 1, 2008, through June 30, 2013. We further selected patients admitted to the hospital (admission or observation) who underwent serial troponin testing initiated in the ED. Patients were included only when subsequent troponin serum testing was performed 60 to 420 minutes after the initial sample for troponin testing was drawn (Figure) and the results of both assays were negative (as defined by the corresponding laboratory reference range).

To optimize capture of all major adverse events, we initially set data filters to cast a wide net for a diagnosis of any arrhythmia, pacemaker placement, death, cardiac arrest, respiratory arrest, or myocardial infarction (MI) (all outcomes prespecified in the initial collection protocol for this database), which localized 197 events.

Medical Record Review
Because data elements needed to identify some exclusion criteria were not tracked in the initially constructed database, we reviewed the medical records manually. For records in the wide-net group with arrhythmia, pacemaker placement, death, cardiac arrest, respiratory arrest, or MI, (n = 197) a trained, hypothesis-blind data abstractor extracted the final printed ECG reading and data concerning initial vital signs and critical care or coronary catheterization laboratory transfers, using a data form with predefined terminology.¹⁹ Medical records identified with the occurrence of arrhythmia or insertion of a pacemaker or defibrillator were reviewed again by a board-certified cardiologist-electrophysiologist, also blinded to the study hypothesis, for the presence or absence of any of the following 4 predefined findings: ventricular fibrillation, ventricular tachycardia (sustained and requiring treatment), symptomatic bradycardia or bradyasystole requiring emergent intervention, or any tachydysrhythmia treated with cardioversion.

From this wide-net group of 197 patients, we identified 20 patients with the primary end point of life-threatening arrhythmia, inpatient ST-segment elevation MI (STEMI), arrest, or death. We then excluded from the primary outcome those patients unlikely to have been sent home from the ED, including those with initial vital signs reflecting hypotension (systolic blood pressure <100 mm Hg), tachycardia (pulse >100 beats/min), tachypnea (respiratory rate >20 breaths/min), or hypoxemia (oxygen saturation level <95%) and those with ECG findings interpreted as showing ischemic changes or ECG findings uninterpretable for ischemia (pacemaker rhythm or left bundle branch block).

Of the total 11,230 patients, a random sample of 562 medical records (5.00%) was reviewed (1 record did not have an ECG printout, leaving 561) with 363 (64.7%) meeting criteria for inclusion (nonconcerning vital signs and no ischemia, pacemaker rhythm, or left bundle branch block on the ECG finding). With this estimate applied to the total, we were left with a final denominator of 7266 medical records (0.647 × 11,230) (Figure).
Outcome Measures
We predefined the following 4 outcomes as clinically relevant adverse cardiac events (CRACE): (1) life-threatening arrhythmia (ventricular fibrillation, sustained ventricular tachycardia requiring treatment, symptomatic bradycardia or bradyasystole requiring emergent intervention, and any tachydyssrhythmia treated with cardioversion); (2) inpatient STEMI; (3) cardiac or respiratory arrest; and (4) death.

Interrater Reliability and Excluded Patients
To test interrater reliability for inclusion criteria, we abstracted 20 of the 197 medical records (10.2%) with documentation of any arrhythmia, pacemaker placement, death, cardiac arrest, respiratory arrest, or MI. All records were found to have inclusion criteria without exclusions, indicating 100% interrater agreement.

Five patients in the initial database of 197 had no room-air oxygen saturation level recorded and were thus excluded from the dataset. In addition, 2 patients experienced major events during the ED evaluation, including one with heart block and severe bradycardia and another with transient cardiac arrest after intravenous administration of metoprolol tartrate. By consensus of the study investigators, these 2 cases were excluded from the final outcome group in keeping with the intention that patients with clear indications for inpatient admission be excluded. None of these 7 patients experienced an event consistent with the primary outcome.

Data Analysis
Data were analyzed from July 1, 2008, through June 30, 2013. We used simple descriptive statistics for the primary and any secondary outcomes, with 95% CIs for all proportions. No formal power analysis was performed, although we determined that, presuming a 0.5% potential rate of adverse events, 5000 or more patients would be needed to ensure a CI remaining less than 1%.

Results
Characteristics of Study Patients
From July 1, 2008, through June 30, 2013, 1 124 719 visits to the EDs of the 3 participating hospitals occurred. Of these visits, 45 416 adult patients presented with chest pain, chest tightness, chest burning, or chest pressure, of whom 22 457 (49.45%) were admitted to the hospital (to an inpatient unit or to an extended observation unit). In this group, the number of patients with 2 troponin-negative results of tests performed from 60 to 420 minutes apart totaled 11 230 (24.72%) (Table).

Primary Outcome Results
Events meeting criteria for the primary outcome of life-threatening arrhythmia, inpatient STEMI, cardiac or respiratory arrest, or death during hospitalization occurred in 20 of 11 230 patients (0.18% [95% CI, 0.11%-0.27%]) (Table). Of these 20 patients, we excluded those not likely to be sent home from the ED owing to abnormal vital signs or ischemic ECG findings or who were unable to undergo evaluation for ischemia. Exclusions included tachycardia (3 patients), hypotension (4 patients), tachypnea (1 patient), hypoxemia (3 patients), ische-
Clinical Relevance

Clinically Relevant Adverse Cardiac Events in Chest Pain

Table. Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 11,230)</th>
<th>With Adverse Events (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5058 (45.04%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Female</td>
<td>6172 (55.00%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>58 (14.4)</td>
<td>71 (12.7)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5163 (46.00%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2215 (19.72%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1478 (13.16%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>166 (1.48)</td>
<td>0</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>901 (8.02)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td><strong>Method of arrival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobby</td>
<td>6044 (53.82)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Ambulance</td>
<td>5035 (44.83)</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Undocumented</td>
<td>151 (1.34)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Type of patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>9016 (80.28)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>2214 (19.72)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td><strong>Adverse event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening arrhythmia</td>
<td>NA</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Inpatient STEMI</td>
<td>NA</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>NA</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>NA</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Death</td>
<td>NA</td>
<td>9 (45%)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; STEMI, ST-segment elevation myocardial infarction.

a Unless otherwise indicated, data are expressed as number (percentage) of patients.
b Some patients had more than 1 medical condition.
c Some patients had more than 1 event.

gastrointestinal tract bleeding secondary to warfarin coagulopathy, with secondary comorbidities of chronic obstructive pulmonary disease, pulmonary hypertension, and renal failure. He died in the hospital (primary outcome).

**Patient 2**
A man in his 60s had a history of hypertension, diabetes mellitus, and MI. The time from the first to the second troponin tests was 130 minutes, with the primary outcome of STEMI. He experienced chest tightness, dyspnea, and diaphoresis beginning 30 minutes before arrival in the ED where he was diagnosed as having chest pain. In the hospital, angiography demonstrated triple-vessel disease. In the recovery unit after diagnostic catheterization, the patient complained of chest pain rated as 6 on a scale of 1 to 10. The ECG finding revealed inferior STEMI, and a second catheterization showed 99% occlusion in the left anterior descending artery with an emergent intra-aortic balloon pump placement, followed by an emergent coronary artery bypass graft. The final diagnoses included coronary artery bypass graft, coronary artery disease, and MI, and the patient was discharged to a skilled nursing facility.

**Patient 3**
A man in his 40s had a history of hypertension and type 2 diabetes mellitus. The time from the first to the second troponin tests was 97 minutes, with the primary outcome of STEMI. He experienced chest stiffness beginning 2 hours before arrival in the ED, jaw radiation, and dyspnea; the ED admission diagnosis was chest pain. During hospitalization, he developed ST elevation and symptoms during a stress test. He underwent coronary catheterization and had a stent placed in the right coronary artery. He developed ventricular fibrillation after the procedure but underwent successful defibrillation. He was discharged home with the final diagnoses of chest pain, acute inferior MI, ventricular fibrillation, hypertension, stent placement in the right coronary artery, and type 2 diabetes mellitus.

**Patient 4**
A woman in her 60s had a history of hypertension, coronary artery disease, and a coronary artery bypass graft. The time from the first to the second troponin tests was 315 minutes, with the primary outcomes of life-threatening bradyarrhythmia and placement of a pacemaker. The patient had experienced squeezing chest discomfort intermittently for months before presentation to the ED and received an admission diagnosis of chest pain. During hospitalization she experienced a recurrence of pain, for which she received nitroglycerin, with immediate bradysystole cardiac arrest. Chest compressions were successful and a pacemaker was placed. After negative findings for biomarkers, negative provocative test results, and normal echocardiographic findings, the chest pain was deemed noncardiac. The final diagnoses included sinus node dysfunction with syncope, bradycardia, bradyarrhythmia, bradycardiac arrest, asystole secondary to nitroglycerin therapy, chronic hypertension with apparent paroxysmal elevation, atypical chest pain, and anxiety. She was discharged to home.

estimated percentage of these patients with important adverse events was 4 of 7266 (0.06% [95% CI, 0.02%-0.14%]). These 4 specific patient presentations are described below.

**Patient 1**
A man in his 80s had a history of coronary artery disease, percutaneous coronary intervention (stent), hypertension, diabetes mellitus, obesity, congestive heart failure, and chronic renal insufficiency. The time from the first to the second troponin tests was 386 minutes, with a primary outcome of death. Patient 1 had chest pain to the left arm immediately before arrival in the ED. His hemoglobin level was 9.1 g/dL (to convert to grams per liter, multiply by 10.0); creatinine level, 6.04 mg/dL (to convert to micromoles per liter, multiply by 88.4); and international normalized ratio, 5.5. His admission diagnoses included chest pain, congestive heart failure, atrial fibrillation, and acute renal failure. He developed fatal intracerebral hemorrhage believed to be secondary to warfarin sodium (Coumadin) coagulopathy, with a decrease in hemoglobin level to 7.7 g/dL. The final diagnosis was massive
Secondary Outcomes
We identified 62 of 11,230 patients with possible or definite MI (defined by final diagnosis or by an elevated level of troponin at the third or subsequent testing) (0.55% [95% CI, 0.42%-0.71%]). When those patients with abnormal initial vital signs in the ED and interpretable, nonischemic ECG findings were excluded, 28 patients remained. Using the 7266 records as an estimate of the number of patients with 2 troponin-negative test levels, nonischemic interpretable ECG findings, and nonconcerning vital signs, we determined that the estimated percentage of these patients with possible or definite MI was 0.39% (95% CI, 0.26%-0.56%). Of these 28 patients, none experienced a CRACE and 26 underwent cardiac catheterization at least 1 day after hospital admission. Interventions after angiography included percutaneous coronary intervention (n = 18), coronary artery bypass surgery (n = 4), and optimized medical management (n = 4).

Limitations
We attempted to minimize bias using design techniques that included hypothesis blinding and rigorous data collection; however, as a data and medical record review, our study was subject to all the inherent limitations of this design. Moreover, our database included only hospitalized patients with events occurring during hospitalization; therefore, among patients discharged rapidly from the inpatient environment, we are unable to report follow-up or outcome data. These results are also from a single city in the US Midwest and may not be easily generalized to other settings.

The primary outcome was based on an estimate of the final denominator (7266, estimated from a 5% sample of the 11,230 patients). This method limits our ability to determine the precise rate of CRACE, which may be slightly higher or lower. However, based on the large number of patients and the small numerator, such changes to the denominator would be unlikely to alter the rate of important events.

While suggesting that such events are rare, the small number of events in our final cohort also prevents meaningful analysis of risk factors that may be associated with adverse outcomes. A considerably larger database would be necessary to pinpoint patients with greater potential benefit from inpatient admission. In addition, 26 patients underwent invasive testing in our cohort, including 22 who underwent subsequent coronary revascularization interventions, raising the possibility that adverse outcomes may have been prevented by these interventions. Based on a lack of data demonstrating short-term benefits or substantial reductions in events with these procedures in patients with troponin-negative test results, however, this number is likely to approach zero.20-22 Finally, our study was not able to capture the incidence of iatrogenic harm owing to hospitalization; therefore we were not able to determine a true risk-benefit analysis of admission compared with expedited outpatient follow-up.

Discussion
In our 3-hospital system during a 5-year period, patients with a negative ED evaluation for chest pain of potentially coronary origin rarely had clinically relevant adverse cardiac events. We used conservative estimates wherever possible to maximize the chance of capturing such events. We identified only 4 adverse events in 7266 patients. Of these patients, 2 were ultimately deemed to have noncardiac chest pain and 2 had possible iatrogenic disease, including a periprocedural MI and STEMI during a stress test.

We chose a priori to exclude non-STEMI events from our primary outcome, instead reporting non-STEMI as a secondary outcome. Our study aimed to report clinically relevant end points, and for that reason an increase in the troponin level (non-STEMI), when occurring in the absence of morbidity, mortality, or a cardiac event such as a life-threatening arrhythmia, was not included in the primary end point. Although risk stratification in the ED may predict long-term cardiovascular outcomes,23 our goal was to determine the likelihood of an important, potentially treatable event occurring during the short-term period of hospitalization. Routine invasive intervention, a hospital-based therapy, does not appear to affect mortality in patients with a non-STEMI event and is associated with small, equivocal benefits on nonfatal MI.20-22 In contradistinction, acute intervention for STEMI is broadly accepted as conferring a mortality benefit and is thus an end point of unambiguous interest when determining the utility of hospitalization. In this respect, our findings appear to be consistent with a widely cited, commonly misquoted study in which the mortality rate for those discharged home with missed MI was statistically indistinguishable from the mortality rate among those with MI that was identified and treated.24

Our findings support the notion that adverse iatrogenic events as a result of admission may eclipse potential benefits in low-risk patients. Current estimates are that 1 in 164 hospitalized patients have a preventable adverse event that contributes to their death, with serious harm 10- to 20-fold more common.18 In our cohort, using the most conservative estimate, the risk of a CRACE after a negative result of ED evaluation was 1 in 1817, suggesting this rate to be a maximum potential rate of clinical benefit from hospitalization. With a more liberal interpretation, excluding a patient with chest pain who died as a result of gastrointestinal tract hemorrhage and a patient who received sublingual nitroglycerin on hospital day 3 for what turned out to be noncardiac chest pain, the maximum benefit was 1 per 3634 patients.

Our study does not demonstrate that patients derive no utility from further management or diagnostic workup after the ED evaluation. We believe that judicious follow-up is in the best interest of most such patients. However, our findings suggest that further evaluation may be best performed in the outpatient rather than the inpatient setting, and that this information should be integrated into shared decision-making discussions regarding potential admission. Moreover, in the context of established risks due to hospitalization, we believe that current recommendations to admit, observe, or perform provocative testing routinely on patients after an ED evaluation for chest pain has negative findings25 should be reconsidered.
Conclusions
The risk for clinically relevant adverse cardiac events in patients treated in the ED and subsequently admitted with chest pain and initial troponin-negative findings, nonconcerning vital signs, and interpretable nonischemic ECG findings is exceedingly low. These findings may inform physician and patient decisions about the utility and potential benefits of hospitalization compared with outpatient evaluation.

REFERENCES