Incremental Diagnostic and Prognostic Value of Contemporary Stress Echocardiography in a Chest Pain Unit Mortality and Morbidity Outcomes From a Real-World Setting

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Background—Clinical assessment often cannot reliably or rapidly risk stratify patients hospitalized with suspected acute coronary syndrome. The real-world clinical value of stress echocardiography (SE) in these patients is unknown. Thus, we undertook this study to assess the feasibility, safety, ability for early triaging, and prediction of hard events of SE incorporated into a chest pain unit for patients admitted with acute chest pain, nondiagnostic ECG, and negative 12-hour troponin.

Methods and Results—Accordingly, 839 consecutive patients who underwent clinical, ECG, and SE assessments within 24 hours of admission were assessed for feasibility, safety, impact on triaging and discharge, and 30-day readmission rate and were followed up for hard events (all-cause mortality and acute myocardial infarction). Of the 839 patients, 811 (96.7%) had diagnostic SE results. Median time to SE and median length of stay for normal SE patients (77%) were both 1 day. The 30-day readmission rate was 0.5%. During long-term follow-up of 27±11 months, 39 hard events (30 deaths and 9 acute myocardial infarctions) occurred. Kaplan-Meier estimates of hard events were 0.5% versus 6.6% in the normal versus abnormal SE groups, respectively, in the first year of follow-up (15 events in the first year). Among all prognostic variables, only abnormal SE (hazard ratio, 4.08; 95% confidence interval, 2.15–7.72; P<0.001) and advancing age (hazard ratio, 1.78; 95% confidence interval, 1.39–2.37; P<0.001) predicted hard events in multivariable regression analysis.

Conclusions—SE incorporated into a chest pain unit has excellent feasibility and provides rapid assessment and discharge with accurate risk stratification of patients with suspected acute coronary syndrome but nondiagnostic ECG and negative 12-hour troponin. (Circ Cardiovasc Imaging. 2013;6:202-209.)

Key Words: acute coronary syndrome ■ chest pain ■ prognosis ■ stress echocardiography

P

atients presenting to the emergency department (ED) with chest pain represent a significant healthcare burden; the estimated annual cost to the US economy is $10 to $12 billion.1 A large proportion of ED admissions are patients with suspected acute coronary syndrome (ACS) but with a nondiagnostic ECG and a normal 12-hour troponin, although fewer than half are subsequently diagnosed with ACS.2 A retrospective study found that the mean cost per patient was $3200, with 73% of cost attributable to admission time.3

Stress echocardiography (SE) is a safe, rapid, and reliable investigation that does not involve exposure to ionizing radiation, can be performed at the bedside, and can risk stratify such patients.4 Our group previously reported the results of a prospective, randomized study that showed that SE was superior to exercise ECG for risk stratification and cost to diagnosis of coronary artery disease (CAD) and that a larger number of patients were safely discharged compared with exercise ECG.5

However, no studies to date have evaluated the clinical impact of incorporating SE, performed early for the assessment of both short- and long-term prediction of hard events (all-cause mortality and acute myocardial infarction [AMI]), into a real-world chest pain unit (CPU). Accordingly, we assessed the feasibility, safety, impact on patient triaging and discharge times, and, most importantly, the accuracy of SE in risk stratification for prediction of hard events in consecutive patients who underwent SE in our CPU.
Methods
ED patients with ≥2 cardiac risk factors (known diabetes mellitus, known hypertension, age >55 years [men] or >65 years [women], known hyperlipidemia [patient on lipid-lowering therapy], smoker, family history of premature CAD [first-degree relative who suffered from AMI or stroke at, <55 years for men or <65 years for women], previous AMI, or percutaneous coronary intervention) and with suspected ACS but nondiagnostic ECG were admitted to our CPU. Patients with negative 12-hour troponin subsequently underwent SE within 24 hours of admission if admitted Monday through Friday. Patients admitted over the weekend underwent SE the following Monday morning. Consecutive SE patients admitted to our CPU from April 2007 to June 2009 were followed up retrospectively for hard events. Study approval was obtained from our local ethics committee.

Initial Clinical Evaluation
History of chest pain, cardiovascular risk factor profile, physical examination findings, and 7-point Thrombolysis in Myocardial Infarction (TIMI) risk score were documented during admission assessment. Resting 12-lead ECGs were classified as ischemic (ST-segment deviation of ≥2 mm from baseline, new-onset left bundle-branch block, or new-onset anterior T-wave inversion) or nonischemic. Routine blood tests (including troponin I) were performed ≥ED patients with chest pain at 30 days after discharge from the ED admissions and within 12 hours after the onset of pain. Suspected ACS but nondiagnostic ECG were admitted to our CPU. Patients with negative 12-hour troponin subsequently underwent SE within 24 hours of admission if admitted Monday through Friday. Patients admitted over the weekend underwent SE the following Monday morning. Consecutive SE patients admitted to our CPU from April 2007 to June 2009 were followed up retrospectively for hard events. Study approval was obtained from our local ethics committee.

Stress Echocardiography
Treadmill exercise was the preferred stress modality, during which 12-lead ECGs were classified as ischemic (ST-segment elevation, or extensive wall motion abnormality), achievement of peak dose (40 μg/kg per minute of dobutamine plus 1.2 μg atropine), or occurrence of intolerable side effects. Rest and stress images were displayed side by side for ease of comparison. Stress echocardiograms were reported as normal (no wall thickening abnormality at rest or stress), abnormal ischemic ( inducible wall thickening abnormality >1 segment at peak stress or presence of biphasic response in patients with resting wall thickening abnormalities during low and high doses of dobutamine), or abnormal nonischemic (which included patients with resting wall thickening abnormality ≥1 segment with no change during stress and patients diagnosed with prognostically significant valvular heart disease [eg, moderate or severe aortic stenosis or mitral regurgitation]) or structural heart defects (eg, hypertrophic cardiomyopathy). Significant ECG changes were not taken as a criterion for test positivity in the absence of new wall thickening abnormalities. SE was considered inconclusive when terminated before any end point was achieved or when images were uninterpretable.

Management After SE
Patients with a normal SE were discharged. Patients with abnormal SE were kept in hospital and managed by the admitting cardiologist, who was responsible for decisions on coronary angiography and revascularization (based on clinical and SE findings). At angiography, significant CAD was defined as ≥50% narrowing in ≥1 of the 3 epicardial coronary arteries or their major branches.

Follow-up
We identified patients from hospital records and our SE database. The hospital death register and the hospital national mortality and general practitioner databases were searched to obtain information on the occurrence and timing of mortality and AMI. Patients were also directly contacted if necessary so that AMI treated at another hospital was not overlooked. AMI was diagnosed when patients were hospitalized with acute chest pain with elevated troponin ( >0.03 μg/L) with or without ischemic ECG changes and without a plausible alternative explanation (eg, rapid tachyarrhythmia, severe sepsis, or renal failure). We also determined the rate of readmission with chest pain at 30 days after discharge from the ED admissions database.

Statistical Analysis
Categorical variables are expressed as percentages and continuous variables as mean±SD. Categorical variables were compared by use of the χ2 test. Cox regression analysis was performed to assess

<table>
<thead>
<tr>
<th>Table 1. Demographics of the Study Population (n=802)</th>
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<tr>
<td><strong>Patient Characteristic</strong></td>
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<tr>
<td>Mean ± SD age, y</td>
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<tr>
<td>Male sex</td>
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<td>Family history of premature CAD</td>
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<td>Median (IQR) TIMI risk score</td>
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<td>TIMI risk group</td>
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<tr>
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<tr>
<td>Mean±SD resting WMSI</td>
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<tr>
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<td>RWMA at rest only</td>
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</table>

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention; RWMA, regional wall motion abnormality; TIMI, Thrombolysis in Myocardial Infarction; and WMSI, wall motion score index.
Results

Patient Demographics and Characteristics

Between April 2007 and June 2009, 849 consecutive patients were admitted to our CPU with suspected ACS (Table 1). Figure 1 illustrates that of these 849 patients, 802 were ultimately available for follow-up after patient self-discharge (10 patients), inconclusive SE studies (28 patients), and loss to follow-up (9 patients).

Stress Echocardiography

Approximately 78% (627 of 802) of patients underwent dobutamine SE, and 77% (618 of 802) of SE tests were normal. Of the 802 patients, 98 patients (12%) had inducible ischemia (18 of 98 were biphasic responses during viability SE protocol), whereas 86 patients (11%) had resting abnormalities but no ischemia. There were 11 patients (1.4%) with significant valvular heart disease or cardiomyopathy. Ultrasound contrast was used in 414 cases (51.6%). There were no major complications during any SE test; specifically, no patients developed chest pain with ST-segment elevation, ventricular arrhythmias, or AMI. Of the 28 inconclusive tests, 11 were not conclusive because of failure to achieve target heart rate, 6 because of intolerable side effects from dobutamine, 6 (0.7%) because of poor image quality, and 5 for other (technical) reasons. Thus, 99.3% of SE studies had diagnostic image quality.

Follow-up Results

Of the 802 patients, 654 (82%) were admitted between Monday and Friday and 148 (18%) were admitted over the weekend. Median time to SE was 1 day for weekday patients and 2 days for weekend admissions. Median length of stay for normal SE patients was also 1 day for weekday admissions and 2 days for weekend admissions. Over a follow-up period of 27±11 months, 9 of 811 patients (1.1%) were lost to follow-up. There were 39 hard events (4.8%; 30 deaths and 9 AMIs). At least 1-year follow-up was obtained in 781 of 802 patients (97%), during which there were 15 hard events (1.9%; 10 deaths and 5 AMIs).

The cumulative Kaplan-Meier estimates of mortality in the first, second, and third years of follow-up were 0.3%, 1.7%, and 4.5%, respectively, for those with normal SE compared with 4.5%, 6.6%, and 15.8%, respectively, for patients with abnormal SE (Table 2). Both death and AMI were most likely to occur in the first year after SE, and event rates progressively decreased with time thereafter. Approximately 40% of events occurred in the first year of follow-up, of which abnormal SE predicted 80% of the deaths (8 of 10) and 80% of the hard events (4 of 5). Twelve of 15 patients with ischemic SE predicted 50% of the events. A normal SE carried a 99.7% event-free survival for death and 99.5% event-free survival for all hard events in the first year of follow-up, and these event rates increased 15-fold and 13-fold, respectively, if SE was abnormal. Over the long-term follow-up period of 27±11 months, a normal SE carried an annual mortality rate of 1.02% and a hard event rate of 1.24%.

Rates of Readmission

Only 4 patients (0.5%) were readmitted with chest pain within 30 days of discharge: 2 in the normal SE group (2 of 618 [0.3%]) and 2 in the abnormal SE group (2 of 184 [1.1%]). At 30 days after SE, there were no deaths in the normal SE group and 1 death in the abnormal SE group.

Predictors of Hard Events

Univariable Cox regression analysis revealed that age, absence of a family history of premature CAD, abnormal
resting WMSI, and abnormal SE result were significantly associated both with time to any hard event (death and AMI; Table 3). A history of previous percutaneous coronary intervention was also a univariable predictor of hard events. Multivariable analysis revealed that abnormal SE was the strongest predictor of death ($P<0.001$; hazard ratio [HR], 3.97; 95% confidence interval [CI], 1.87–8.40) and all hard events ($P<0.001$; HR, 4.10; 95% CI, 2.16–7.76), whereas advancing age also retained statistical significance. The results for family history of premature CAD seemed counterintuitive, with those with a family history at a lesser risk of an event. As a result, this variable was omitted from the multivariable analysis. Resting WMSI and TIMI score were not predictors of outcome. Abnormal SE carried a 4-fold increased risk of mortality compared with a normal SE result throughout follow-up. When the 11 patients with structural heart disease were either excluded from the analysis or included in the normal SE group, abnormal SE continued to be the strongest predictor of hard events ($P=0.005$; HR, 3.59; 95% CI, 1.54–8.37; and $P=0.008$; HR, 2.89; 95% CI, 1.28–6.52, respectively).

Figure 2. Kaplan-Meier survival estimate of time to any hard event in the first 365 days for patients with normal and abnormal stress echocardiography results.

Figure 3. Kaplan-Meier survival estimate of time to any hard event for patients with normal and abnormal stress echocardiography results over a 27±11-month period.
revealed that both abnormal–ischemia SE (HR, 3.26; 95% CI, 1.43–7.25; \( P = 0.005 \)) and abnormal–fixed wall motion abnormality SE (HR, 3.56; 95% CI, 1.53–8.30; \( P = 0.003 \)) SE were predictors of hard events. There was no significant difference in outcome between the 2 abnormal SE groups (\( P = 0.84 \)). Advancing age (HR, 1.63; 95% CI, 1.24–2.19; \( P = 0.002 \)) also retained statistical significance.

**Coronary Angiography and Revascularization Within the First 6 Months After Admission**

Of the 98 patients with inducible ischemia during SE, 82 (84%) underwent angiography and 57 patients (70%) had significant CAD, of whom 11 had 3-vessel disease, 11 had 2-vessel disease, and 35 had single-vessel disease. In addition, all 30 patients who underwent revascularization had an abnormal SE, of whom 28 of 30 (93%) had inducible ischemia. Of the 618 patients with a normal SE, only 1 patient (0.2%) underwent revascularization (after an AMI).

**Incremental Prognostic Value of SE**

Sequential Cox regression models were fitted to investigate the incremental predictive power of SE over clinical and ECG variables and resting left ventricular function. The initial model of clinical variables yielded a global \( \chi^2 \) value of 27.1, although addition of resting left ventricular function data—normal or abnormal—into this model increased the global \( \chi^2 \) significantly to 44.2 (\( P < 0.001 \)). However, addition of SE data significantly further improved the power of the model to predict outcome, increasing the global \( \chi^2 \) to 52.1 (\( P < 0.001 \)).

**Discussion**

This is the first large study to demonstrate the clinical value of weekday SE, incorporated into a CPU in a real-world setting with multiple SE operators, in terms of feasibility, safety, early triaging and rapidity of discharge, and prediction of early and late hard events in patients with \( \geq 2 \) cardiac risk factors with suspected ACS but nondiagnostic ECG and negative 12-hour troponin. SE predicted hard events, including all-cause mortality, independently and incrementally beyond that predicted by conventional clinical risk factors (including the TIMI risk score) and resting left ventricular function.

The creation of our institute’s CPU was approved 5 years ago after our group’s randomized studies that demonstrated the clinical and economic effectiveness of using SE as the first-line investigation (compared with exercise ECG testing) in this acute patient cohort. The primary objectives of the CPU were to facilitate rapid patient triage so that patients presenting with cardiac chest pain and ischemic ECG changes or positive troponin were identified and managed promptly as per standard ACS protocols and to enable early inpatient risk stratification for patients without ischemic ECG changes and with negative cardiac biomarkers. Consequently, since 2007, all patients admitted to our CPU with a negative 12-hour troponin have undergone SE, which was undertaken at a median time of 1 day from initial ED presentation for weekday admissions. The median time to discharge for normal SE patients (77%) was also 1 day for weekday admissions because results were available soon after test completion and thus patients were discharged immediately thereafter and with an extremely low 30-day readmission rate of only 0.5%. Patients with abnormal SE were kept in hospital and managed by the admitting cardiologist, with decisions on coronary angiography and revascularization determined on clinical grounds (including SE results).

Most of the patients belonged to the intermediate TIMI risk group with an overall hard event rate of 1.9% and all-cause mortality rate of 1.3% in the first year, during which a normal SE result predicted a hard event rate of only 0.5% and an all-cause mortality rate of 0.3%, both 4-fold reductions compared with the respective event rates in the whole population. On the contrary, an abnormal SE result predicted a hard event rate of 6.6% (≈13-fold increase) and all-cause mortality rate of 4.5% (a 15-fold increase) compared with normal SE. This pattern continued throughout the follow-up period of 27 months, so a normal SE was associated with an annualized all-cause mortality rate of ≈1% and an overall annualized hard event rate of ≈1.2%, both of which are consistent with several previous studies using pharmacological SE.

In keeping with other studies in this patient population, the TIMI risk score was not a predictor of hard events. A meta-regression analysis of 10 prospective studies of acute chest pain admissions, with a total of 17265 patients, concluded that although the TIMI score is an effective risk stratification tool, it should not be used as the sole means of determining patient disposition.

**Clinical Implications**

This study demonstrates the excellent feasibility and safety of SE in a real-world CPU setting. Approximately 97% of patients had conclusive SE results, and diagnostic SE images were obtained in >99% of patients, probably because contrast agents were used whenever image quality was deemed suboptimal. The use of contrast agents was 52% in this study. This finding is very important because inconclusive or indeterminate tests result in additional investigations and prolonged time in hospital, both of which increase cost. In terms of safety, although 25% of patients had abnormal SE, including inducible ischemia in >50%, no patients developed serious side effects.

Our results showed that both inducible ischemia and fixed wall motion abnormality predicted outcome. A significant proportion of patients with inducible ischemia underwent revascularization (or have medical therapy increased), which would be expected to improve outcome by reducing or abolishing myocardial ischemia. However, patients with a fixed wall motion abnormality only, consistent with prior infarction, required monitoring. Our data indicate that such patients should not be discharged without plans for further follow-up and optimal medical therapy.

Our results also show that SE appropriately influences the use of coronary angiography and subsequent revascularization. Only 1 of 618 patients (0.2%) with a normal SE required revascularization with an excellent outcome.
Comparison of SE With Other Imaging Techniques

Computed tomography coronary angiography is a rapidly advancing technique. Improvements in scanner technology have dramatically reduced both scan acquisition time and radiation dose to the patient. Studies have demonstrated excellent negative predictive value and favorable prognostic value during a 12-month follow-up. However, there are certain disadvantages of CT coronary angiography. The rate of inconclusive studies, which often results in additional testing and thus prolongs admission time and increases costs, is between 13% and 16% compared with only 3.3% with SE in this study. Exposure to ionizing radiation remains a concern; state-of-the-art scanners, with the lowest radiation doses, are limited to larger centers, and even dual-source CT, a relatively newer technological advancement, can result in high radiation doses. Therefore, nonionizing radiation technologies may be more suitable in younger and female patients. Furthermore, recent CT studies have excluded patients with known CAD or prior revascularization and patients in atrial fibrillation, those unable to hold their breath for >10 seconds, and those with contraindications to β-blockers and renal failure. Therefore, the wider application of CT coronary angiography to all comers in the ED is questionable.

Several studies have evaluated single-photon emission computed tomography (SPECT) in this setting. Rest-only and stress-only SPECT protocols have been validated for the detection of ACS. However, the main limitations of SPECT remain exposure to ionizing radiation, ready availability, and rapid reporting and disposal of patients. Adenosine cardiac magnetic resonance has been used for imaging patients with acute chest pain. Although equivalence to dobutamine SE and favorable prognosis up to 1 year for those discharged with a normal cardiac magnetic resonance scan have been demonstrated, there are few data on hard cardiac events. Furthermore, access to cardiac magnetic resonance remains limited; it carries high initial cost and is precluded in those with claustrophobia or implanted ferromagnetic objects. Finally, assessment of myocardial perfusion with ultrasound, myocardial contrast echocardiography, has been shown to provide incremental prognostic value over wall motion assessment in this patient cohort. However, the clinical value of myocardial contrast echocardiography over wall motion assessment needs to be tested in a real-world setting similar to our present study.

Study Limitations

This is a retrospective study. Nine patients were lost to follow-up. It is possible that some of these patients had adverse cardiac events that would influence the analysis. However, none of these 9 patients were in the highest TIMI risk group (TIMI score, 5–7), and 7 of 9 had normal SE results. It is therefore highly unlikely that events in these 9 patients would alter our results. We did not compare SE

Comparison With Previous Studies

Several studies previously reported the benefit of discharge SE in low-risk acute chest pain patients (Table 1 in the online-only Data Supplement). However, our study results are unique in several ways. First, our patient cohort is the largest to date. Second, this study reported outcome based on hard events only and has the largest number of hard events (n=39), whereas all prior studies reported outcomes driven by soft events (eg, rehospitalization and revascularization). Third, our study has the longest follow-up period (>2 years). Fourth, this study used both exercise and dobutamine stress techniques as opposed to just pharmacological SE, as often seen in past studies.
directly against another imaging technique; thus, we cannot conclude that SE is superior to other noninvasive forms of risk stratification. However, our previous randomized trial has established the superiority of SE over exercise ECG testing, which remains the test of choice in many centers worldwide. The aim of this study was not to perform another comparison of techniques but to assess the impact of SE in the real-world setting of a routine clinical CPU. Further (multicenter) studies comparing SE against CT coronary angiography, cardiac magnetic resonance, and SPECT will help to determine the most cost-effective means of investigating this acute patient population.

Analysis of all SE studies was performed by a single expert reader, which could be perceived as a limitation. However, we believe it is a strength rather than a weakness because, in routine clinical practice, all such tests would indeed be performed by a staff physician and interpreted with the assistance of an expert. However, although it would be anticipated that similar results could be obtained in other centers because use of contrast agents improves image quality (which translates into improved diagnostic yield), we acknowledge that a multicenter study validating these results outside our institution is also desirable.

Conclusions

The incorporation of SE, performed with either physiological or pharmacological stress by multiple operators, into a real-world CPU has excellent feasibility and safety, provides rapid assessment for early triaging and successful discharge of patients, and is accurate in the prediction of hard events, including all-cause mortality, over both short- and long-term follow-up in patients admitted with suspected ACS but nondiagnostic ECG and negative cardiac biomarkers.

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Disclosures

Dr Senior has previously received consultancy fees from Lantheus Medical Imaging. The other authors have no conflicts to report.

References


The initial clinical assessment of patients presenting to the emergency department with acute chest pain is often inconclusive, and patients frequently require admission for further investigation. Several noninvasive imaging modalities are available to enhance this risk stratification process. The aim of such a strategy is to swiftly and safely differentiate low-risk patients who can be discharged home from high-risk patients who require hospitalization for further management. Therefore, such an investigative technique should ideally be widely available, safe, low cost, free from ionizing radiation, feasible, and accurate. The present study has shown that stress echocardiography (SE), incorporated into a chest pain unit in a busy general hospital, has excellent feasibility and safety and provides rapid assessment and patient discharge with accurate risk stratification, including prediction of all-cause mortality, of patients with suspected acute coronary syndrome but nondiagnostic ECG and negative 12-hour troponin. Both pharmacological and physiological stress protocols were used, and ultrasound contrast agents were used in approximately half of all studies because they improve endocardial border definition and thus the accuracy of the test. Patients with a normal SE had extremely low readmission and hard event rates during a 2-year follow-up compared with patients with an abnormal SE. SE was the strongest predictor of event-free survival, and importantly, the Thrombolysis in Myocardial Infarction risk score was not a predictor of outcome in this large study. Given the low cost, lack of radiation exposure, accessibility, portability, and diagnostic accuracy of SE, we believe that these results support more widespread use of SE for the acute assessment of such patients.
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SUPPLEMENTAL MATERIAL
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<td>163</td>
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Legend – Table of past studies utilising SE for evaluation of patients admitted with acute chest pain (N/A = data not available)
Supplemental References


