Beyond diagnostic accuracy. Applying and extending methods for diagnostic test research
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Citation for published version (APA):

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The added value of pre-discharge Dobutamine Stress Echocardiography in the long-term risk stratification of chest pain patients

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Abstract
Background - Dobutamine stress echocardiography (DSE) has been proposed as a risk stratification tool in patients with chest complaints with a normal or non-diagnostic electrocardiogram on presentation at the emergency room.
Objective - To evaluate the added value of DSE in the long-term risk assessment relative to physicians' risk estimates.
Methods - Chest pain patients with a normal or non-diagnostic ECG presenting at the emergency room were included after ruling out acute coronary syndrome. At admission and at discharge attending physicians estimated patient-specific probabilities of a cardiac event in the next 6 months of which the calibration was evaluated. A pre-discharge DSE was performed, of which the results were not disclosed to the physicians. The DSE likelihood ratios were used to transform physicians' discharge estimates (pre-test probabilities) into post-test probabilities. The main outcome measure used was the area under the receiver operating characteristic (ROC) curve to compare pretest probabilities with posttest probabilities.
Results - The 6-month cardiac event rate in the 398 included patients was 7.5%. DSE likelihood ratios were 7.8 (95% CI: 4.2 to 14) for a positive and 0.63 (0.47 to 1.8) for a negative result. Physicians' probabilities were well calibrated. The area under the ROC curve did not significantly improve by including the DSE results.
Conclusion - Due to the low event rate and an undiscriminating negative likelihood ratio the DSE has limited additional value in the long term risk stratification of chest pain patients, with a possible exception for patients judged to be at intermediate risk.
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Introduction
Patients presenting with chest pain at the emergency department constitute a heterogeneous population as to the cause of their symptoms. Diagnosis varies from atypical chest pain to acute myocardial infarction. The short-term risk stratification aims at identification of urgent conditions requiring immediate treatment: acute coronary syndromes. These patients will be admitted and further management will be relatively straightforward.

The majority of chest pain patients presenting at the emergency room, however, do not have an acute coronary syndrome, but nevertheless are at increased risk of subsequent cardiac events. Reported long-term cardiac rates in these patient groups vary from 6 to 12%. These disturbingly high risks require further investigations in these patients, aimed at more accurate risk assessment, identifying patients with an acceptably low risk of a cardiac event, whom can be safely discharged without follow-up.

Several objective diagnostic tools are available for long-term risk assessment. An abnormal exercise test is an indicator of poor prognosis, but the value of this test is limited, especially in patients with an non-interpretable electrocardiogram (LVH, BBB, pacemaker, medication). An exercise test is often impracticable due to concomitant conditions such as peripheral artery disease, obstructive pulmonary disease, and neurological or muscular-skeletal disorders. Vasodilator stress testing with either dipyridamole or adenosine in conjunction with thallium/MIBI perfusion imaging or echocardiogram may have better accuracy, but is relatively laborious and may not be readily available for patients presenting at the emergency room.

An attractive alternative is the dobutamine stress echocardiography (DSE). The diagnostic and prognostic value of DSE has been demonstrated in patients with known or suspected coronary artery disease, post myocardial infarction, and prior to non-cardiac vascular surgery. Pre-discharge dobutamine stress echocardiography has been shown to carry independent prognostic value in low risk, troponin negative chest pain patients.

Despite this well-demonstrated association between the results of pre-discharge dobutamine stress echocardiography and cardiac events, one can question whether such a test is indicated in all patients. Patients presenting at the emergency room do not form a homogeneous population, due to variability in complaints, history and presentation, which leads to differences in the degree of suspicion with respect to future events.

For this purpose we evaluated the added value of DSE in the long-term risk stratification of patients with chest complaints with an inconclusive electrocardiogram and ruled out acute coronary syndrome. The added value is defined relative to the
degree of suspicion expressed by the physician, based on information available, expressed in a subjective probability. Our aim was to identify patients at low risk for a cardiac event after discharge from the emergency room, after they had been admitted with typical chest pain. The reference standard was the blindly assessed occurrence of a cardiac event within 6 months after admission.

**Patients and Methods**

**Patients**

Data were obtained as part of a prospective study that was performed from July 1997 to April 2000 at the cardiac emergency room of three Dutch hospitals. Consecutive patients with typical chest pain within 6 hours of onset, with a normal or non-diagnostic electrocardiogram where included if they were at least 18 years and had given written informed consent. Acute myocardial infarction (AMI) and unstable angina pectoris were ruled out in a standard protocol of 12 hour observation. AMI was defined by a rise of CKMB levels of twice the upper limit of normal or more. Unstable angina was defined as repetitive episodes of chest pain accompanied by ECG changes despite optimal oral medication and/or requiring i.v. medication. Excluded were patients with ventricular tachycardia, chronic atrial fibrillation, conduction disturbances, severe uncontrolled hypertension (systolic > 180 mmHg or diastolic > 120 mmHg despite therapy), overt heart failure requiring CCU admission, congenital heart disease, idiopathic of hypertrophic cardiomyopathy, resuscitation, known or suspected thrombotic, inflammatory, or neoplastic conditions likely to be associated with an acute phase response and pregnancy.

**Diagnostic procedures**

Attending physicians were residents in training for cardiology, supervised by qualified cardiologists. At admission, after history, physical examination and 12 lead electrocardiogram, the attending physician estimated the probability that the patient would suffer a cardiac event within the next 6 months. This probability was marked on a double logistic probability scale. At discharge, 12 hours after onset of pain, the attending physician provided a new estimate for the probability that the patient would suffer a cardiac event in the 6 months to come. Between the first and second probability estimate the following diagnostic information had become available: results of blood tests (CK-MB, BSE, kidney function, glucose, cholesterol) any recurrent or resistant pain episodes and additional ECG's.

All patients underwent Dobutamine Stress Echocardiography (DSE) within 24 hour after admission according a standard protocol. The physician reading the
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DSE did not receive any additional patient information or test result. The DSE results were not revealed to any of the attending physicians during admission or follow-up.

Follow-up data on cardiac events were collected at 4 weeks after discharge, at 3 months and at 6 months. A cardiac event was defined as cardiac death (defined by either clinical assessment, cardiac iso-enzymes, 12 lead ECG, or autopsy), non-fatal AMI (WHO criteria), hospital admission for unstable angina and coronary revascularization procedure (PTCA or CABG), and development of new arrhythmia.

Analysis

Calibration graphs were drawn from the physicians probability estimates assessed at admission and discharge. If estimated probabilities are well calibrated they will equal the observed cardiac event rate. To assess calibration, the probability estimates were ranked and assigned to four groups, based on quartiles. Then the average probability as assigned by the physicians in each of the four groups was plotted against the proportion of patients with a cardiac event.

The result from follow-up (the reference standard) and DSE were organized in a 2x2 contingency table. Subsequently the likelihood ratio of a positive DSE (LR+) and negative DSE (LR-) with their 95% confidence intervals were estimated. The LR of a test result indicates the relative frequency of that test result in patients with a cardiac event during the 6 month follow-up period relative to the frequency of that same result in those without a cardiac event.

To evaluate the additional value of the DSE we used the likelihood ratios to estimate patient-specific post-test probabilities of a cardiac event occurring in the 6 months, using Bayes' Theorem. The probability estimate at discharge was used as the pre-test probability. Subsequently, a ROC curves was constructed using these post-test probability estimates and compared with the ROC curves of the physicians estimates at admission and discharge. Areas under the ROC curve were compared using the method of Hanley and McNeill. ROC curves can be estimated from the sensitivity (y-axes) and 1-specificity (x-axes) at each possible probability cut-off. The area under the ROC curve (AUC), a measure of discriminating performance, is 1 for perfect tests and 0.5 for tests that do not discriminate at all. The statistical software package SPSS version 11 was used for computations.

Results

A total of 611 patients were admitted, of which 203 were excluded (figure 1). Probability estimates were missing for 10 patients, so all analyses are based on 398 patients. The baseline characteristics of the 408 included patients and the 398
patients are shown in table 1. During the 6 month follow-up period, 30 patients (7.5%) had at least one cardiac event. Table 2 provides details on the clinical outcomes.

Table 1 Clinical and demographical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Included patients</th>
<th>Patients eligible for analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=408</td>
<td>n=396</td>
</tr>
<tr>
<td>Males</td>
<td>237 (58%)</td>
<td>231 (58%)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>57 (12)</td>
<td>57 (12)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>85 (21%)</td>
<td>81 (20%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>40 (9.8%)</td>
<td>40 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>157 (38%)</td>
<td>157 (39%)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>111 (27%)</td>
<td>109 (27%)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>54 (13%)</td>
<td>51 (13%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>129 (32%)</td>
<td>126 (32%)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>62 (15%)</td>
<td>59 (15%)</td>
</tr>
<tr>
<td>Statine</td>
<td>67 (16%)</td>
<td>63 (16%)</td>
</tr>
<tr>
<td>Ace-inhibitor</td>
<td>46 (13%)</td>
<td>46 (12%)</td>
</tr>
</tbody>
</table>

*) History of coronary artery disease defined as, prior acute myocardial infarction, PTCA, CABG, or coronary artery disease documented on coronary angiograms.

** Figure 1 Flow of patients
* ) Excluded Patients: Acute coronary syndrome n=91; Other diagnoses n=32; Withdrawal n=51; Poor echo image n=23; Abnormality on the resting echocardiogram n=6.
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Table 2 The specific clinical outcomes of the 30 patients with events in the 6 months follow-up per DSE result. (n=398)

<table>
<thead>
<tr>
<th></th>
<th>Positive DSE</th>
<th>Negative DSE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=12</td>
<td>n=18</td>
<td>N=30</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Non-fatal AMI</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Rehosp-UA*</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>PTCA</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>CABG</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>


The probability estimates at admission showed substantial variability, with a median value of 30% and an inter-quartile range from 10% to 50%. The mean of the physicians’ probability estimates at admission was 34%, considerably higher than the 7.5% event rate. The calibration for the probability estimate at admission (figure 2) revealed a substantial overestimation of the risk of a cardiac event: for all 4 quartiles the actual event rate was lower than the estimated risk. Probability estimates were lower when patients were discharged from the hospital but still showed variability, with a median 10% (IQR: 5% to 30%). The mean was 21%, still higher than the observed event rate of 7.5%. The adjustment to lower probability estimates at discharge is seen in the calibration graph (figure 2). It shows a consistent overestimation of the event rate in all groups. The average probability in the highest quartile was 57%, versus an observed event rate of 24%.

![Figure 2](image-url)
The DSE test was positive in 31 patients, of which 12 developed a cardiac event and negative in 367 patients, of which 349 did not develop a cardiac event. The likelihood ratio of the positive and negative DSE test result were, respectively, 7.8 (95% CI: 4.2 to 14) and 0.63 (0.47 to 1.8), see table 3.

Table 3  Measures of performance of the DSE in predicting a cardiac event (n=398, event rate 7.5%)

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>40</td>
<td>22 to 58</td>
</tr>
<tr>
<td>Specificity</td>
<td>95</td>
<td>93 to 97</td>
</tr>
<tr>
<td>Likelihood ratio pos.</td>
<td>7.8</td>
<td>4.2 to 14</td>
</tr>
<tr>
<td>Likelihood ratio neg.</td>
<td>0.63</td>
<td>0.47 to 1.8</td>
</tr>
</tbody>
</table>

The performance of the physicians in identifying patients at high risk for a cardiac event in the 6 months can be assessed by inspection of the receiver operating characteristic (ROC) curves (figure 3), and the area under them (AUC). The AUC of the physicians’ probability estimates at admission was 0.76 (95% CI: 0.68 to 0.84), not statistically significant better than the AUC of 0.83 (95% CI: 0.77 to 0.90) at discharge (p=0.07). The AUC for the post-test probabilities after the DSE (AUC=0.87, 95% CI: 0.81 to 0.93) was not significantly better compared to the physicians’ probabilities at discharge (p=0.11). (see figure 3).

![Figure 3](image)

We looked at the value of the DSE test in specific subgroups of patients (table 4). The group of patients in the lowest quartile, with an estimated probability at discharge of 0 to 5%, had a zero event rate. Even after a positive DSE, the risk of
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an event will be extremely low. In this low risk group (145/408 patients), the DSE has no additional value in risk assessment. The upper quartile consists of 87 patients, with an estimated probability of 31 to 100%. After a negative DSE the probability of an event is still 16%. In this subgroup at high risk the DSE has limited additional value in risk assessment either: all patients remain at elevated risk, even after a negative DSE result. In the remaining group, the two intermediate quartiles consisting of 166 patients with an estimated probability between 6% and 30%, the cardiac event rate is 5.4%. In this subgroup (166/408), the event rate for patients with a positive test result is 25%, whereas the event rate for a negative test is 3.9%, much lower than the overall event rate of 7.5%.

Table 4 Subgroups of patients, based on the probability estimate at discharge and the event rate per group.

<table>
<thead>
<tr>
<th>Estimated probability range</th>
<th>Cardiac Event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSE +</td>
</tr>
<tr>
<td>Low risk 0 to 5%</td>
<td>0%</td>
</tr>
<tr>
<td>Intermediate risk 6 to 30%</td>
<td>25%</td>
</tr>
<tr>
<td>High risk 31 to 100%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Discussion

We evaluated the added value of the pre-discharge DSE in the long-term risk stratification of chest pain patients with non-diagnostic or normal ECG and with ruled out acute coronary syndrome at the emergency room. In this population the overall event rate in the follow-up was 7.5%. The calibration of the physicians in estimating the probability of an event was modest, with overestimated cardiac event rates. This tendency to overestimate is typical for physicians in general. In contrast, the discriminating performance of the physicians can be considered as good, with an AUC of 0.83. The area under the curve of the post-DSE probabilities only showed a minor improvement relative to the AUC of the physicians, indicating a modest added value of the DSE. It seems that only in a subgroup of patients at intermediate estimated risk, consisting of less than half of the patients in the study group, the DSE is able to differentiate between clinical relevant high risk and low risk patients.

One potential limitation of this study is the absence of post-test probabilities as estimated by the physicians themselves, incorporating the results of the DSE. A direct comparison of such a post-test probability estimate with the probability estimate at discharge was thus not possible. This was inherent in the study design,
which called for a total blind evaluation of the DSE, to prevent that a positive test result would be incorporated in the decision to perform an intervention defined as one of the endpoints. Instead we calculated posttest probabilities using Bayes Theorem, using a single set of likelihood ratios for all patients, based on the observed event rates.

A number of other studies have looked at stress echocardiography in admitted chest pain patients with negative or non-diagnostic electrocardiograms, reporting promising results of the DSE.\textsuperscript{12,10} We are not aware of literature on the added value of DSE in these particular patients.

We've previously published results of the prognostic value of the DSE in predicting a cardiac event in this study population.\textsuperscript{3} By means of multivariable logistic regression, the DSE was found to carry independent prognostic value, with an odds ratio of 10.7 in troponin negative patients. Despite the statistically significant association, the present study shows that the added clinical value may be limited to patients in whom the attending physician attributes an intermediate risk of subsequent cardiac events.

The less than perfect sensitivity and high specificity of the DSE result in a poorly informative likelihood ratio of a negative test result. In other words, a negative DSE test is unable to exclude future events.\textsuperscript{11} In this study, 92% of the patients had a negative DSE test. In addition the event rate was rather low, 7.5%. Tests in general tend to perform poorly in populations with a low event rate.\textsuperscript{12}

We sought to identify subgroups in which the DSE may have additional discriminating value. We found that patients at low risk (0 to 5%), as estimated by the physician at discharge, can be discharged safely without performing a DSE test. The test will most likely be negative, and the event rate after a positive test result is still very low. Alternatively, in the patients where the physicians assigned a high probability to (30% or more), the probability of an cardiac event is elevated, even after a negative DSE result. Only in an intermediate group (estimates risks of 6-30%) the DSE can be used to distinguish patients at relatively low risk from patients at high risk, although the event rate will still be nonzero, even after a negative result. Naturally, it may be important to use a test to lower the risk from 7.5% to 3.9%.

Despite a well-established prognostic association the, added value of the pre-discharge DSE is modest in the risk stratification of patients with chest pain and a non-diagnostic electrocardiogram, as physicians perform rather well in the risk stratification of these patients. Other tools will be needed to improve risk assessment further.
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References