Efficacy of Coronary Revascularization in Patients With Acute Chest Pain Managed in a Chest Pain Unit

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OBJECTIVE: To investigate the safety of discharge of patients deemed at low risk of cardiac events after evaluation in a chest pain unit and to determine the prognostic effect of revascularization of patients deemed at high risk.

PATIENTS AND METHODS: The study population consisted of 1088 patients presenting at the emergency department from January 15, 2001, to September 1, 2006, with chest pain but without ischemia on electrocardiography or troponin elevation. Patients were managed by a chest pain unit protocol that included early exercise testing. Three groups of patients were distinguished: (1) those discharged after exercise testing (424 [39%]); (2) those in whom unstable angina was ruled out after in-hospital evaluation (208 [19%]); and (3) those in whom unstable angina was confirmed or not ruled out (456 [42%]). Of the 456 patients in group 3, 183 (40%) were revascularized at the index episode. The primary end point was the occurrence of myocardial infarction or death within 1 year. Adjustments were made for patient characteristics and a propensity score for revascularization (c statistic 0.83).

RESULTS: Groups 1 and 2 showed lower rates of the primary end point than group 3 (group 1: 7 [1.7%]; group 2: 1 [0.5%]; group 3: 62 [13.6%]; P=.001). In group 3, revascularization at the index episode did not reduce the primary end point in the univariate (22 [12%] vs 29 [11%]; P=.80) and multivariate (hazard ratio, 1.4; 95% confidence interval, 0.7-2.5; P=.40) analyses. In-hospital revascularization decreased the need for postdischarge revascularization (hazard ratio, 0.3; 95% confidence interval, 0.1-0.7; P=.01).

CONCLUSION: Chest pain unit protocols are associated with safe patient discharge. Although early revascularizations may decrease the need for postdischarge revascularizations, they may not improve 1-year outcomes by reducing the number of myocardial infarctions or deaths.


CI = confidence interval; HR = hazard ratio

Making decisions for the care of patients presenting at the emergency department with chest pain of uncertain origin is challenging.1 Physicians risk incorrectly discharging patients with acute coronary syndrome or inappropriately hospitalizing patients without ischemic heart disease. The cardiac troponins, which are markers of acute myocardial infarction, permit diagnosis with high sensitivity and specificity.2 In addition, the implementation of chest pain unit protocols incorporating early exercise testing allows the evaluation of patients with non–diagnostic findings on electrocardiography and normal troponin levels.3 Noninvasive imaging techniques complete the triage process in instances in which patients are unable to exercise.4,6

This exhaustive evaluation reveals a number of patients with significant coronary artery stenosis despite the absence of evidence of ischemia on initial electrocardiography and normal levels of troponin markers. In these cases, unstable angina is usually diagnosed, which is then treated with a revascularization procedure. The outcome of prompt revascularization in such patients is uncertain. Subgroup analysis in acute coronary syndrome trials has not shown a benefit of invasive management in patients without ST-segment deviation or troponin elevation.7,8 These trials involved a broad spectrum of patients, including those with non–ST-segment elevation acute myocardial infarction, and did not represent the chest pain unit population.

The current study examined a series of consecutive patients presenting at an emergency department with chest pain without ST-segment deviation or troponin elevation. The patients were managed by a chest pain unit protocol. The aim of the study was to investigate the safety of the decision to discharge patients deemed at low risk of cardiac events and to determine the effect of early revascularization on the prognosis of patients deemed to have unstable angina or to be at high risk of cardiac events at the index episode.

PATIENTS AND METHODS

The study group included 1088 consecutive patients presenting at the emergency department from January 15, 2001, to September 1, 2006, with chest pain considered by the cardiologist on duty to be of possible coronary origin. A noncardiologist assessed the eligibility of patients for the...
study by determining whether their chest pain was of coronary origin, and a cardiologist performed a second evaluation and confirmed the diagnosis. The exclusion criteria were ST-segment deviation of 1 mm or greater on initial electrocardiography, troponin I elevation at any determination, or known prior nonischemic heart disease (valvular heart disease or cardiomyopathy). Troponin I was measured at admission and at 12 hours from the onset of chest pain. Two different troponin I assays were used: the Immulite assay (Diagnostic Products Corporation, Los Angeles, CA) until October 1, 2003, and, after that date, the Dimension assay (Dade Behring, Newark, DE). Positive and negative values for myocardial infarction were assigned according to the minimal troponin threshold measured with a coefficient of variation less than 10% in each assay, as indicated by the manufacturer. The precision of the troponin threshold measurements was confirmed by our laboratory. For commercially available troponin assays, the less than 10% imprecision cutoff value has been recommended for clinical purposes.9

**MANAGEMENT**

All patients were evaluated by a chest pain unit protocol, which included a clinical history and early (<24 h after admission) exercise testing in patients able to exercise.10-13 A complete clinical history was recorded, including symptoms at presentation, coronary risk factors, history of ischemic heart disease, and extracardiac vascular disease (peripheral arterial disease, prior stroke, or renal failure defined by a creatinine level ≥1.4 mg/dL [to convert to µmol/L, multiply by 88.4] at admission). Data on the characteristics of chest pain at presentation were collected using a predefined questionnaire introduced by Geleijnse et al,14 which evaluates pain location, radiation, characteristics, severity, influences, associated symptoms, and history of exertional angina. Points were assigned according to the presence or absence of these diagnostic features. Typical chest pain was defined by a total score of 10 points or greater.

A symptom-limited Bruce protocol was used in the exercise test. Patients who were unable to exercise or who had positive findings on the exercise test were hospitalized for further evaluation, whereas patients with negative findings on the exercise test were discharged. If the exercise test was inconclusive, the final decision to hospitalize or discharge the patient was at the discretion of the attending physician.

**STUDY GROUPS**

The patient population was divided into 3 groups: group 1 (424 [39%]) included patients discharged after the exercise test; group 2 (208 [19%]), those initially hospitalized but in whom unstable angina was ruled out after further evaluation; and group 3 (456 [42%]), those in whom unstable angina was confirmed or could not be ruled out after hospitalization at the index episode. In group 3, revascularization at the index hospitalization was performed in the case of substantial coronary artery stenosis that was deemed amenable to revascularization.

Figure 1 summarizes in-hospital management and study groups. Group 1 patients were discharged early: 392 (92%) after negative findings on an exercise test and 32 (8%) after an inconclusive exercise test. However, 664 (61%) of the study patients were hospitalized: 134 (20%) after positive findings on an exercise test, 97 (15%) after an inconclusive test, and 433 (65%) who were unable to exercise. In patients who were unable to exercise, the extent of the in-hospital evaluation was determined by the treating cardiologist, who had the options of cardiac magnetic resonance imaging with dipyridamole, coronary angiography, or medical treatment without further study.15

Among hospitalized patients, group 2 patients had no evidence of unstable angina (208 patients [31%]), as determined by normal findings on cardiac magnetic resonance imaging with dipyridamole in 94 patients (45%) and by normal findings on coronary angiography in 114 patients (55%). Group 3 comprised the remaining 456 patients, in whom unstable angina was diagnosed or could not be eliminated as the diagnosis. Of the 292 patients (64%) in group 3 who underwent coronary angiography that revealed substantial coronary artery stenosis, 190 (65%) were revascularized (134 underwent coronary angioplasty and 56 had bypass surgery). The remaining 164 patients (36%) in group 3 were conservatively managed.

**END POINTS**

The primary end point was acute myocardial infarction or all-cause mortality at 1-year follow-up. The secondary end point was postdischarge revascularization. An acute myocardial infarction was defined as a new episode of chest pain with increased troponin I levels. Acute myocardial infarction was also diagnosed if creatine kinase MB mass increased to 3 times or more the upper limit of normal after coronary angioplasty or to 5 times or more the upper limit of normal after coronary bypass surgery.

**STATISTICAL ANALYSES**

Differences in baseline characteristics and outcomes were compared among the 3 study groups using the $\chi^2$ test. A specific analysis was undertaken to assess the protective effects of revascularization at the index episode on outcomes in group 3. Because of the differences in the baseline characteristics between patients with and without revascularization, a propensity score method was applied. Baseline variables associated with revascularization ($P<.25$) were identified by univariate analysis. These variables were used
in a logistic regression model to calculate the probability that each patient would require revascularization. This probability constituted the propensity score. Patient outcomes were distributed among quartiles of the propensity score.

Variables that may predict outcomes were investigated in group 3. The association between revascularization at the index episode and patient outcome was analyzed by univariate analysis using the \( \chi^2 \) test. In addition, crude estimates were calculated as hazard ratios (HRs) with their respective 95% confidence intervals (CIs) using a univariate Cox regression analysis. A multivariate Cox regression analysis was performed, which included the baseline clinical predictive variables \((P<.20)\) in the univariate analysis as well as revascularization and the propensity score. The proportional hazards assumption was also evaluated. This test provided evidence that the variable in-hospital revascularization did not fulfill the proportionality assumption, thereby accounting for the accumulation of periprocedural myocardial infarctions at the index episode in revascularized patients. Therefore, in addition to the multivariate Cox model, a parametric proportional hazards model with Gompertz distribution was used in the analysis.

Parametric survival analysis with accelerated failure time parameterization is an alternative to the Cox model for the analysis of time-to-event data while permitting relaxation of the proportionality assumption. Differences between groups are expressed as a direct effect of time. This is in contrast to the Cox proportional hazards model, which models group differences in terms of the risk of the event of interest at any given time. Under the accelerated failure time parameterization, the effect of the exposure and covariables is assumed to act additively on the log time scale. In this case, the coefficient of the exposure variable represents the (adjusted) difference in the median survival times on the log scale between the 2 levels of the variable; the exponentiated value is the ratio of the medians on the time scale itself. We found that the Gompertz distribution fits the trajectory of the instantaneous hazard across time for our data. Because the Gompertz distribution does not have an accelerated failure time parameterization, the results are presented as HRs.
Baseline characteristics of patients from groups 1, 2, and 3 are presented in Table 1. As expected, group 3 showed the highest-risk profile. A complete follow-up examination was obtained in 1055 (97%) of the patients; 33 patients (3%) were not followed up for a full year but did not die. These patients were considered at risk until the date of final contact.

At which point they were censored. During follow-up, patients from group 3 presented the highest rate of myocardial infarction or death (62 [13.6%] for group 3 vs 7 [1.7%] for group 1 and 1 [0.5%] for group 2; \( P = .001 \)) and the highest rate of postdischarge revascularization (32 [7%] for group 3 vs 8 [1.9%] for group 1 and 2 [1%] for group 2; \( P = .001 \)).

**Revascularization at the Index Episode**

Unstable evolution occurred shortly after hospitalization but before revascularization could be carried out in 11 patients from group 3 (3 who died and 8 who experienced a nonfatal myocardial infarction). These patients were excluded from the analysis of the prognostic influence of revascularization. Of the remaining 445 patients, 146 (33%) had a positive finding on an exercise stress test, 39 (9%) had an inconclusive exercise stress test, and 137 (31%) underwent primary angiography. At the index episode, 183 patients (41%) were revascularized and 79 (43%) of these patients had positive findings on a noninvasive test, 20 (11%) had an inconclusive noninvasive test, and 84 (46%) underwent direct angiography.

Differences in baseline characteristics between patients with and without revascularization are summarized in Table 2. Nonrevascularized patients showed a poor risk profile and tended to be older men with a higher frequency of a Killip class greater than 1 at admission and women with extracardiac disease or prior myocardial infarction, coronary artery stenosis, or coronary bypass surgery. In addition, these patients underwent exercise testing (63 [24%] vs 77 [42%]; \( P = .001 \)), cardiac magnetic resonance imaging (24 [9%] vs 30 [10%]; \( P = .001 \)), and coronary angiography (100 [38%] vs 133 [45%]; \( P = .001 \)) less frequently than the other patients. At discharge, nonrevascularized patients received aspirin, clopidogrel, statin, or \( \beta \)-blocker treatment less frequently than did the other patients.

A propensity score for revascularization was constructed that included the following baseline variables in the univariate analysis: 2 or more episodes of pain in the past 24 hours, Killip class greater than 1, older age, male sex, smoking, hypertension, diabetes, prior myocardial infarction, prior coronary artery stenosis, prior coronary bypass surgery, extracardiac disease, left bundle branch block, and any complementary study performed (noninvasive stress test or coronary angiography). The \( c \) statistic (0.83) of the propensity score was adequate. No patient with a propensity score in the lowest quartile was revascularized, whereas 74% of the patients in the highest quartile were revascularized (\( P = .001 \)).

**Effect of Revascularization on Prognosis**

Despite the poor baseline risk profile of nonrevascularized patients, univariate analysis showed no differences in the primary end point between patients with and those without...
revascularization (22 [12%] vs 29 [11%]; HR, 1.2; 95% CI, 0.7-2.0; P = .60) in the univariate analysis. Neither were there differences in the individual end points: mortality (7 [3.8%] vs 15 [5.7%]; HR, 0.7; 95% CI, 0.3-1.7; P = .40) and acute myocardial infarction (17 [9.3%] vs 19 [7.3%]; HR, 1.3; 95% CI, 0.7-2.6; P = .40). The event rate did not differ between patients with and without positive findings on a noninvasive test (12 [8%] vs 39 [13%]; HR, 0.6; 95% CI, 0.3-1.2; P = .20).

In the revascularized subgroup, 4 intervention-related deaths occurred (all at the index episode) vs 1 death in the nonrevascularized subgroup (at the follow-up). Procedure-related nonfatal myocardial infarctions occurred in 15 patients (8%) of the revascularized subgroup at the index episode and in 1 patient of the nonrevascularized subgroup at the follow-up. Mean ± SD creatine kinase-MB levels were 61.5±42.0 ng/mL (range, 19.5-184.0 ng/mL).

By Cox regression analysis, myocardial infarction or death at 1 year was associated with 2 or more episodes of pain in the past 24 hours (HR, 2.2; 95% CI, 1.2-3.9; P = .01), age older than 65 years (HR, 1.8; 95% CI, 0.9-3.5; P = .10), diabetes (HR, 2.0; 95% CI, 1.1-3.4; P = .02), prior coronary bypass surgery (HR, 1.9; 95% CI, 0.9-3.9; P = .06), extracardiac disease (HR, 1.6; 95% CI, 0.9-6.2; P = .10), and left bundle branch block (HR, 2.4; 95% CI, 1.0-6.2; P = .06). In-hospital revascularization (HR, 1.4; 95% CI, 0.7-2.5; P = .40) and the propensity score (P = .80) were not associated with the primary end point. The parametric proportional hazard model with Gompertz distribution also showed the lack of a significant association between in-hospital revascularization and outcome (HR, 1.7; 95% CI, 0.80-3.5; P = .20).

As depicted in the Kaplan-Meier curves adjusted by the covariate clinical factors independently associated with the outcome, the time course of events was different in patients with and without revascularization (Figure 2). Revascularized patients showed an initial increase of the primary end point during hospitalization that depended on revascularization, with only a few events after discharge. In nonrevascularized patients, a progressive increase in the primary end point was observed throughout the follow-up period. After 1 year, there were no significant differences between revascularized and nonrevascularized patients. If periprocedural myocardial infarctions are excluded, then in-hospital revascularization reduces the primary end point (HR, 0.3; 95% CI, 0.1-0.9; P = .03).

Revascularization at the index episode was associated with a lesser frequency of postdischarge revascularization by univariate (6 [3.3%] vs 26 [9.9%]; P = .01) and multivariate (HR, 0.3; 95% CI, 0.1-0.7; P = .01) analysis. The propensity score was unrelated to this event (P = .50).

**DISCUSSION**

Our findings show that a chest pain unit protocol that ensures a safe patient discharge is associated with either

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**TABLE 2. Characteristics of Group 3 Patients With and Without Revascularization**

<table>
<thead>
<tr>
<th></th>
<th>Revascularization (n=262)</th>
<th>Without Revascularization (n=183)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical chest painb</td>
<td>193 (74)</td>
<td>131 (72)</td>
<td>.70</td>
</tr>
<tr>
<td>≥2 episodes of pain in past 24 h</td>
<td>116 (44)</td>
<td>111 (61)</td>
<td>.001</td>
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<tr>
<td>Killip class &gt;1</td>
<td>21 (8)</td>
<td>4 (2)</td>
<td>.01</td>
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<td>Coronary risk factors</td>
<td></td>
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<tr>
<td>Age (y), mean ± SD</td>
<td>69±11</td>
<td>65±10</td>
<td>.001</td>
</tr>
<tr>
<td>Men</td>
<td>177 (68)</td>
<td>144 (79)</td>
<td>.01</td>
</tr>
<tr>
<td>Current smokers</td>
<td>42 (16)</td>
<td>48 (26)</td>
<td>.01</td>
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<tr>
<td>Hypertension</td>
<td>179 (68)</td>
<td>113 (62)</td>
<td>.20</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>135 (52)</td>
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<td>.50</td>
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<td>Diabetes mellitus</td>
<td>79 (30)</td>
<td>68 (37)</td>
<td>.20</td>
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<tr>
<td>Family history</td>
<td>27 (10)</td>
<td>18 (10)</td>
<td>&gt;.99</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>104 (40)</td>
<td>57 (31)</td>
<td>.07</td>
</tr>
<tr>
<td>Prior coronary artery stenosis ≥50%</td>
<td>107 (41)</td>
<td>52 (28)</td>
<td>.01</td>
</tr>
<tr>
<td>Use of aspirin</td>
<td>159 (61)</td>
<td>104 (57)</td>
<td>.40</td>
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<tr>
<td>History of heart failure</td>
<td>11 (4)</td>
<td>7 (4)</td>
<td>&gt;.99</td>
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<td>Prior coronary angioplasty</td>
<td>36 (14)</td>
<td>31 (17)</td>
<td>.40</td>
</tr>
<tr>
<td>Prior coronary bypass surgery</td>
<td>38 (15)</td>
<td>10 (6)</td>
<td>.01</td>
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<tr>
<td>Extracardiac disease</td>
<td>78 (30)</td>
<td>40 (22)</td>
<td>.06</td>
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<td>Electrocardiographic findings</td>
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<tr>
<td>Left bundle branch block</td>
<td>14 (5)</td>
<td>4 (2)</td>
<td>.10</td>
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<tr>
<td>T-wave inversion (≥1 mm)</td>
<td>36 (14)</td>
<td>26 (14)</td>
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<td>Treatment at discharge</td>
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<td>Aspirin</td>
<td>225 (86)</td>
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<td>Clopidogrel</td>
<td>24 (9)</td>
<td>126 (69)</td>
<td>.001</td>
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<tr>
<td>Statins</td>
<td>157 (60)</td>
<td>133 (73)</td>
<td>.01</td>
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<tr>
<td>β-Blockers</td>
<td>148 (57)</td>
<td>146 (80)</td>
<td>.001</td>
</tr>
</tbody>
</table>

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*a Data are given as number (percentage) of patients, unless otherwise indicated.
* Total score ≥10 points on the questionnaire developed by Geleijnse et al.14
* Peripheral arterial disease or prior stroke or a creatinine level ≥1.4 mg/dL (to convert creatinine values to µmol/L, multiply by 88.4) at admission.

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**FIGURE 2. Adjusted Kaplan-Meier curves depicting the time course of events in patients with and without revascularization.**

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early patient discharge after negative findings on an exercise test or a late discharge after further in-hospital explorations to rule out unstable angina. However, the performance of noninvasive tests and coronary angiography prompted a number of revascularizations that did not improve the prognosis in terms of myocardial infarction or death, although they decreased the occurrence of postdischarge revascularization procedures.

This systematic study of patients in chest pain units revealed a number of angiographic candidates for revascularization. It is unclear if revascularization provides any benefit to the patient. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial showed that coronary angioplasty is not superior to medical treatment in stable patients. Although randomized trials on non-ST-segment elevation acute coronary syndromes have shown that an invasive approach improves patient prognosis, the subgroup of patients without ST-segment deviation or troponin elevation, such as those found in the chest pain unit, do not receive any benefit. However, these trials, which involved a high proportion of patients with acute myocardial infarction, are not a proper comparison for patients in a chest pain unit population. In the current study of patients in a chest pain unit, revascularization was not associated with a better outcome such as lower rates of myocardial infarction or death; however, the need for postdischarge revascularization procedures was reduced.

A number of revascularized patients experienced peri-procedural myocardial infarctions. The meaning of peri-procedural infarctions and the exact threshold of myocardial necrosis that is clinically relevant remain a matter of debate. Risk of myocardial necrosis related to the revascularization procedure must be considered when deciding to perform revascularization in a low-risk population such as patients in a chest pain unit. Although peri-procedural infarctions might be considered a benign phenomenon, some studies indicate that any increase in necrosis markers has prognostic value. The threshold for creatine kinase-MB elevation used in the current study (>3 times the upper limit of normal after angioplasty and >5 times the upper limit of normal after surgery) is accepted as clinically relevant.

Troponin markers have improved the sensitivity of the diagnosis of acute myocardial infarction. Implementation of chest pain unit protocols leads to detailed study and medical observation in all patients and reduces the number of inappropriate discharges. In the current study, patients discharged early after negative findings on an exercise test and those who were found not to have unstable angina after in-hospital evaluation had an excellent prognosis. However, this screening method requires many resources. In many instances, it is difficult to promptly implement an exercise testing program that provides access to patients 24 hours daily 7 days per week, and noninvasive imaging and coronary angiography require that patients be hospitalized. Simple clinical risk scores and biomarkers that are easy to measure (such as N-terminal pro-brain natriuretic peptide levels) have prognostic value, although they may not have been prospectively evaluated for decision making. Clinical risk scores and biomarkers better predict events such as myocardial infarction or death than revascularization, a procedure that is chosen using the results of noninvasive tests or angiography. According to our results, however, early revascularization did not affect the occurrence of myocardial infarction or death. Therefore, simpler and faster risk stratification using clinical data and conceivably biomarkers could be used as an initial management strategy. Further studies could be postponed in lower-risk patients. This approach would allow a complete diagnosis, and the decision to proceed with revascularization could be made in an ambulatory setting.

Because this was a retrospective cohort study and revascularization was not randomized, differences in baseline characteristics could have influenced the results. A propensity score for revascularization with a c statistic of 0.83 was used to minimize potential bias, and multivariate analysis for outcomes was performed, including baseline characteristics and the propensity score.

CONCLUSION

Early revascularizations associated with chest pain unit protocols may not improve 1-year outcomes (myocardial infarction or death), although they decrease the need for postdischarge revascularization procedures. Further studies are warranted to define both the subgroup of patients who require intense study and revascularization at the index episode and the subgroup of patients whose evaluation could be deferred after simple clinical risk stratification and medical treatment. Therefore, a chest pain unit protocol should be flexible and allow consideration of different approaches to treatment depending on the baseline risks of the patients analyzed.

REFERENCES
CORONARY REVASCULARIZATION IN PATIENTS WITH ACUTE CHEST PAIN


