Acute Ischemic Heart Disease

Randomized comparison between clinical evaluation plus N-terminal pro–B-type natriuretic peptide versus exercise testing for decision making in acute chest pain of uncertain origin

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Background Exercise testing constitutes the usual tool for decision making in chest pain units. This policy implies logistical constrains. Our aim was to evaluate a new strategy, combining a clinical risk score and N-terminal pro–B-type natriuretic peptide (NT-proBNP), in patients presenting to the emergency department with chest pain, without ischemic electrocardiogram changes or troponin elevation.

Methods A total of 320 patients were randomized to either usual management, involving exercise testing, or a new strategy combining a clinical risk score and NT-proBNP without exercise testing. In the usual management, discharge decision was guided by the result of exercise test. In the new strategy, those patients with low clinical risk score and NT-proBNP were directly discharged. The primary outcome was hospitalization at the index episode. Secondary outcomes were cardiac events at 1 year.

Results A total of 110 patients (69%) were hospitalized using usual management in comparison with 90 (56%) in the new strategy (P = .03). There were no differences in death or myocardial infarction (n = 11, 6.9% vs n = 6, 3.8%, P = .3) or cardiac events (n = 38, 24% vs n = 28, 18%, P = .2). Revascularizations at the index episode were more frequent under usual management (18% vs 8%, P = .01), although the new strategy was associated with higher rate of planned postdischarge revascularizations (0.6% vs 5%, P = .04).

Conclusions A strategy combining clinical history and NT-proBNP is simpler and reduced initial emergency hospitalizations in patients with chest pain, in comparison with the usual strategy involving exercise testing. Larger studies to assess its impact on long-term hard end points are needed. (ClinicalTrials.gov NCT00493844) (Am Heart J 2010;159:176-82.)

Decision making in patients presenting to emergency department with chest pain, nonischemic electrocardiogram, and normal troponin is challenging. This constitutes a low-risk population as a whole but contains some patients with high-risk unstable angina. Therefore, they deserve a careful evaluation, and the result of noninvasive tests usually guides discharge or hospitalization decision. Exercise testing is the most widespread tool, although inability to exercise and inconclusive or false-positive results are limitations inherent to exercise testing. Stress echocardiography, stress myocardial perfusion single-photon emission computed tomography, and multislice coronary computed tomography are promising alternatives.

However, postponing the decision to discharge or hospitalize a patient until noninvasive tests can be performed present logistical constraints. Noninvasive tests are often not available on a 24-hour/7-day a week basis and, in many hospitals, are not readily available in the chest pain unit. In part due to these logistical constrains, some patients with unstable angina are still inappropriately discharged. Therefore, simpler as well as safe tools would be of value.

Recently, we have demonstrated that N-terminal pro–B-type natriuretic peptide (NT-proBNP) provides additional prognostic information to a clinical risk score in patients
A number of clinical variables were recorded at admission including symptoms at presentation, coronary risk factors, history of ischemic heart disease, and prior vascular disease (peripheral artery disease or stroke). The characteristics of chest pain at presentation were collected using a predefined questionnaire introduced by Geleijnse et al., evaluating pain location, radiation, character, severity, influences, associated symptoms, and history of exertional angina. A number of points were assigned according to the presence or absence of these characteristics. The clinical risk score was calculated including the following variables: pain score $\geq$ 10 points (1 point), $\geq$ 2 pain episodes in the last 24 hours (1 point), age $\geq$ 67 years (1 point), insulin-treated diabetes (2 points), and prior percutaneous coronary intervention (1 point). High risk was defined by a risk score $\geq$ 3 points. The TIMI risk score was also calculated.

**Randomization**

Patients were randomized to either the usual management or the new strategy. Patients were assigned to their groups by central telephone using a randomization list that was concealed until interventions were assigned. Figure 1 shows the study design. The usual management involved a chest pain unit protocol using early (<24 hours) exercise testing. Consequently, hospitalization decision was guided by the exercise test. Patients were hospitalized in the case of a positive result, inconclusive result with $<$ 7 metabolic equivalents, or contraindication to exercise (physical inability or abnormal repolarization changes in the baseline electrocardiogram), whereas they were discharged in the case of a negative result or inconclusive result with $>$ 7 metabolic equivalents without ischemia induction. The new strategy combined the clinical risk score along with NT-proBNP levels, without exercise testing. Patients with clinical risk score $\geq$ 3 points as well as those patients with a risk score $<$ 3 points but with NT-proBNP $>$ 110 ng/L were directly hospitalized. On the other hand, patients with both clinical risk score $<$ 3 points and NT-proBNP $<$ 110 ng/L were directly discharged. All discharged patients were reevaluated 1 week later in an ambulatory setting in both groups. The management of hospitalized patients was at the criterion of the attending physician by using noninvasive imaging stress tests (technetium 99m-labeled tetrofosmin exercise or dipyridamole stress-rest single-photon emission computed tomography, or dipyridamole cardiac magnetic resonance), coronary angiogram, or medical treatment without further study. The institutional volume of coronary angioplasty and coronary bypass surgery was 600 and 250 procedures per year, respectively. The Ethical Committee of Clinical Research from the participant hospitals approved the study, and all patients gave informed consent.

**NT-proBNP testing**

NT-proBNP was measured by a commercially available immunoassay (Dade Behring, Newark, DE). NT-proBNP was determined using the blood sample drawn at 8 to 12 hours from pain onset for troponin testing and after confirming a negative troponin result. The 110 ng/L decision cutoff was chosen because it demonstrated to be of predictive value in a previous pilot series of patients with chest pain of possible coronary origin.
End points

The primary outcome was the hospitalization on the day of the index episode. Secondary end points were all-cause mortality or myocardial infarction and the composite end point of death, myocardial infarction, revascularization, or readmission by unstable angina at 1 year. An acute myocardial infarction was defined as a new episode of chest pain with increased troponin I. Acute myocardial infarction was also defined if creatine kinase MB mass increased to $\geq 3$ times the upper limit of normal after coronary angioplasty or to $\geq 5$ times the upper limit of normal after coronary bypass surgery. Readmission due to unstable angina was defined by a new episode of chest pain requiring hospitalization with concomitant electrocardiographic changes indicating acute ischemia or a coronary angiogram showing a significant coronary stenosis, without troponin elevation.

A diagnosis of unstable angina in the hospitalized patients at the index episode was deemed to be ruled out in the case of a normal noninvasive stress test or coronary angiogram. For patients who did not undergo a noninvasive stress test or angiogram, unstable angina was considered ruled out in the absence of cardiac events during the follow-up.

Statistical analysis

Categorical variables were compared using the $\chi^2$ test, whereas comparison of continuous variables was made by the unpaired $t$ test. Cox regression analysis and Kaplan-Meier curves were made to compare end points between both arms of the study.

The sample size was calculated for the primary outcome. In a previous study on patients with chest pain of possible coronary origin managed with early exercise testing, the hospitalization rate at the index episode was 66%. Therefore, a sample size of 300 patients was needed to investigate whether the new strategy could reduce the hospitalization rate in 25%, with 80% statistical power and 5% $\alpha$ value.

This work was supported by a grant HERACLES (Instituto de Salud Carlos III), Dr Juan Sanchis, Vicent Bodí, Julio Núñez, and Angel Llácer were also supported by a grant FIS PI070640 (Instituto de Salud Carlos III), and Dr Xavier Bosch was also supported by a grant FIS PI0500120 (Instituto de Salud Carlos III). The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the article and its final contents.

Results

Patient population

Of 320 patients enrolled, 160 were randomized to each arm of the study. Table I shows the characteristics of the population. Half of patients had demonstrated cardiovascular disease and one third coronary artery disease. In addition, the chest pain was typical (pain score $\geq 10$ points) in more than a half of patients and 42% had $\geq 2$ episodes before admission. The risk scores were similar in both groups.

The number of patients with contraindication to exercise testing was evaluated. There were no differences. In the usual management group, 32 patients had physical inability to exercise and 20 showed abnormalities in the baseline electrocardiogram. The corresponding rates in the new strategy subgroup were 33 and 16 patients.

Hospitalization on the day of the index episode

The new strategy significantly reduced the number of hospitalizations on the day of the index episode. A total of 90 patients (56%) were hospitalized using the new strategy in comparison with 110 (69%) under the usual management (odds ratio 0.6, 95% CI 0.4-0.9, $P = .05$) (Figure 2). In the new strategy, the reasons for hospitalization were high clinical risk (score $\geq 3$ points) but high NT-proBNP in 50 patients.

In 128 (65%) of the hospitalized patients, the diagnosis of unstable angina was ruled out, with no differences between the usual and new strategies ($n = 66, 60\%$ vs $n = 62, 69\%, P = .30$).

### Table I. Baseline characteristics of the population

<table>
<thead>
<tr>
<th>Risk score (points)</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score</td>
<td>1.9 ± 1.2</td>
<td>1.8 ± 1.2</td>
<td>.25</td>
</tr>
<tr>
<td>Pain score &gt;10 points</td>
<td>95 (59%)</td>
<td>91 (57%)</td>
<td>.73</td>
</tr>
<tr>
<td>TIMI risk score (points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (0-2)</td>
<td>98 (61%)</td>
<td>98 (61%)</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate risk (3-4)</td>
<td>62 (39%)</td>
<td>58 (36%)</td>
<td>.70</td>
</tr>
<tr>
<td>High risk (5-7)</td>
<td>4 (2%)</td>
<td>0</td>
<td>.20</td>
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</table>

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>64 ± 12</td>
<td>63 ± 13</td>
<td>.69</td>
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<table>
<thead>
<tr>
<th>Men</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>113 (71%)</td>
<td>103 (64%)</td>
<td>.28</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Current smokers</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (21%)</td>
<td>47 (29%)</td>
<td>.09</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>102 (64%)</td>
<td>93 (58%)</td>
<td>.36</td>
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<table>
<thead>
<tr>
<th>Hypercholesterolemia</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>97 (61%)</td>
<td>89 (56%)</td>
<td>.43</td>
<td></td>
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<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>46 (29%)</td>
<td>40 (25%)</td>
<td>.53</td>
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<table>
<thead>
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<th>Insulin-treated diabetes</th>
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<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (9%)</td>
<td>12 (8%)</td>
<td>.84</td>
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<table>
<thead>
<tr>
<th>Family history</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (7%)</td>
<td>14 (9%)</td>
<td>.68</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior myocardial infarction</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 (28%)</td>
<td>49 (31%)</td>
<td>.71</td>
<td></td>
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</tbody>
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<table>
<thead>
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<th>Prior coronary stenosis ≥50%</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (33%)</td>
<td>55 (34%)</td>
<td>.91</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior coronary angioplasty</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 (26%)</td>
<td>39 (24%)</td>
<td>.90</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Prior coronary bypass surgery</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (6%)</td>
<td>14 (9%)</td>
<td>.39</td>
<td></td>
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<table>
<thead>
<tr>
<th>Peripheral artery disease</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (9%)</td>
<td>6 (4%)</td>
<td>.07</td>
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<table>
<thead>
<tr>
<th>Prior stroke</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (7%)</td>
<td>8 (5%)</td>
<td>.64</td>
<td></td>
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<table>
<thead>
<tr>
<th>Contraindication to exercise</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 (33%)</td>
<td>49 (31%)</td>
<td>.81</td>
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<table>
<thead>
<tr>
<th>Aspirin at discharge</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>109 (68%)</td>
<td>100 (63%)</td>
<td>.35</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clopidogrel at discharge</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 (31%)</td>
<td>36 (23%)</td>
<td>.13</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-Blockers at discharge</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>83 (52%)</td>
<td>67 (42%)</td>
<td>.09</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Statins at discharge</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 (63%)</td>
<td>98 (61%)</td>
<td>.90</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiotensin-converting enzyme inhibitors at discharge</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 (51%)</td>
<td>75 (47%)</td>
<td>.58</td>
<td></td>
</tr>
</tbody>
</table>
Follow-up

All patients completed the follow-up. The treatment prescribed at discharge was the same in both arms of the study (Table I). A total of 3 patients (0.9%) died, 16 (5%) had an acute myocardial infarction, 11 (3.4%) were readmitted because of unstable angina, and 53 (17%) were revascularized. All deaths occurred after discharge, whereas 2 infarctions occurred during hospitalization at the index episode and 14 after discharge. The rates of death or myocardial infarction and the composite end point were 17 (5.3%) and 66 (21%), respectively.

Table II shows the individual events in each study group. There were no differences in death or myocardial infarction or the composite end point between the usual and new management strategies (Figure 3).

Revascularizations at the index episode were more frequent under the usual management (n = 29, 18.1% vs n = 13, 8.1%, P = .01). In contrast, the new strategy was associated with more planned postdischarge revascularizations (n = 8, 5% vs n = 1, 0.6%, P = .04) indicated in the ambulatory setting. As a whole, the total rate of revascularizations tended to be higher with

![Table II. Outcomes](Image)

<table>
<thead>
<tr>
<th>Event</th>
<th>Usual management (n = 160)</th>
<th>New strategy (n = 160)</th>
<th>P (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.6%)</td>
<td>2 (1.3%)</td>
<td>1</td>
</tr>
<tr>
<td>In-hospital AMI</td>
<td>2 (1.3%)</td>
<td>0</td>
<td>.5</td>
</tr>
<tr>
<td>Postdischarge AMI</td>
<td>9 (5.6%)</td>
<td>5 (3.1%)</td>
<td>.4</td>
</tr>
<tr>
<td>Total AMI</td>
<td>11 (6.9%)</td>
<td>5 (3.1%)</td>
<td>.2</td>
</tr>
<tr>
<td>Readmission by UA</td>
<td>5 (3.1%)</td>
<td>6 (3.8%)</td>
<td>1</td>
</tr>
<tr>
<td>Rev</td>
<td>32 (20%)</td>
<td>21 (13.1%)</td>
<td>.2</td>
</tr>
<tr>
<td>Index episode Rev</td>
<td>29 (18.1%)</td>
<td>13 (8.1%)</td>
<td>.01</td>
</tr>
<tr>
<td>Urgent postdischarge Rev *</td>
<td>4 (2.5%)</td>
<td>2 (1.3%)</td>
<td>.7</td>
</tr>
<tr>
<td>Planned postdischarge Rev †</td>
<td>1 (0.6%)</td>
<td>8 (5%)</td>
<td>.04</td>
</tr>
</tbody>
</table>

AMI, Acute myocardial infarction; UA, unstable angina; Rev, revascularization. * Revascularization during readmission by AMI or UA. † Revascularization planned in ambulatory setting.

![Figure 2](Image)

Number of patients discharged and hospitalized at the index episode, in both arms of the study.

![Figure 3](Image)

Survival Kaplan-Meier curves comparing death or myocardial infarction and the composite end point (death or myocardial infarction or readmission by unstable angina) in both arms of the study. (n = 38, 24% vs n = 28, 18%, HR = 1.5, 95% CI 0.8 to 2.5, P = .2) between the usual and new management strategies (Figure 3).
the usual management (n = 32, 20% vs n = 21, 13.1%, HR = 1.6, 95% CI 0.9-2.7, P = .2). A total of 4 infarctions were related with revascularization procedures: 3 under usual management and 1 in the new strategy (9% and 5% of the revascularization procedures performed, respectively).

Patients discharged without hospitalization at the index episode

A total of 50 patients under the usual management and 70 with the new strategy were discharged without hospitalization. There were no differences in the TIMI risk score between the study groups (1.4 ± 1.1 vs 1.3 ± 1.0 points, P = .5). During follow-up, no early discharged patient died and 5 had an acute myocardial infarction (3 with usual management and 2 with the new strategy).

In patients early discharged with the new strategy, the distribution among TIMI risk score categories were 59 patients of low risk (0-1 points) and 11 of intermediate risk (3-4 points). A total of 9 patients managed using the new strategy underwent postdischarge elective coronary angiogram: 2 of them showed a normal angiogram, whereas the remaining 7 were revascularized. An additional patient was revascularized after readmission for acute myocardial infarction. The number of planned revascularizations was higher with the new strategy (n = 7, 10% vs 0, P = .04). These revascularizations were indicated in the ambulatory setting and performed in the first month after the index episode in all but one patient, who was revascularized in the second month.

Discussion

Main findings

The present study shows that a strategy combining clinical history and NT-proBNP, without exercise testing, reduced initial emergency hospitalizations in patients with chest pain of uncertain origin in comparison with the usual strategy involving exercise testing. The reduction of hospitalizations during the index episode did not increase events during follow-up. However, there were several patients who received revascularization that was indicated during their ambulatory follow-up visit. Therefore, reevaluation in the ambulatory setting seems to be advisable. It must be pointed out that the sample size was calculated based on hospitalization rates and not on hard events, such as death or myocardial infarction. Consequently, a possible deleterious effect of inappropriate discharging due to the new approach cannot be excluded. Larger studies would be needed before this approach could be recommended for routine clinical implementation.

Limitations of exercise test in chest pain units

Exercise testing constitutes the usual tool for decision making in chest pain units.2-7 In this sense, its contribution for decreasing both inappropriate hospitalizations and discharges is well recognized. There are, however, important limitations as follows: (1) logistical constrains because exercise testing is not usually available on a 24 h/d, 7 d/wk basis. Therefore, patients have to wait a certain time for the test and (2) inability to exercise, mainly not only because of physical incapacity but also because of alterations in the baseline electrocardiogram. We have found around 30% of patients with inability to exercise in both groups. Studies on chest pain units tend to be highly selective, including only low-risk patients with ability to exercise. Therefore, the proportion of patients who are unable to exercise is not well known. According to our previous data in a consecutive series without exclusions, this proportion is around 40% of the patients with chest pain of uncertain origin.16 In this setting, a simpler alternative tool to exercise testing seems to be justified.

Limitations of clinical history

As we have previously shown, high-risk patients can be identified by the clinical history.1 Furthermore, the long-term prognosis of these patients is similar to that of patients with positive troponin.13 However, a major issue remains to be the correct discrimination of low-risk patients for early discharge. In chest pain series, despite using models including a high number of clinical variables, the clinical history lacked enough accuracy to predict short-term events, mainly revascularizations elicited by the result of exercise testing.10 Although the prognostic benefit of these revascularizations in chest pain unit populations is not fully clear,17 the fact is that the clinical history, as a stand-alone tool, is not reliable in physicians’ decision making.

NT-proBNP

Coronary ischemia induces changes in the processes of ventricular relaxation and contractility that trigger the release of natriuretic peptides. In addition, such a release can occur after brief periods of ischemia without concomitant changes in left ventricular diastolic pressure, suggesting a direct primary effect of ischemia.18,19 In the clinical setting, the prognostic value of NT-proBNP has been demonstrated in the whole spectrum of acute coronary syndromes, including those with normal troponin.20-25 In chest pain units, however, it has hardly been studied. In a pilot study, NT-proBNP provided additional prognostic information over the clinical history.11 A cutoff value of 110 ng/L was selected as the median value of the population. This cutoff value is very close to 125 ng/L recommended by the manufacturer and used in stable diabetic patients to predict cardiovascular events.26

Unstable angina was ruled out in 65% of patients hospitalized at the index episode. These hospitalizations could be considered as unnecessary. There were no
differences between both management groups in their discrimination capacity. Conceivably, a high NT-proBNP cutoff value could have avoided some hospitalizations, but safety concerns led us to choose a conservative decision cutoff. On the other hand, it can be argued that the number of late planned revascularizations neutralize the initial benefit in hospitalizations. However, a planned revascularization can be better logistically managed than an emergency admission by the health system organization. Furthermore, the total rate of revascularizations tended to be higher with exercise testing management as a consequence of a more invasive approach linked to the performance of the stress test. Whether these revascularizations have a prognostic impact in low-risk patients, such as chest pain unit patients, is a matter of controversy.¹⁷

Conclusions
In patients presenting to the emergency department with chest pain of uncertain origin, decision making based on a simple strategy combining clinical assessment and NT-proBNP decreases emergency hospitalizations. The implementation of this strategy in the emergency departments could simplify the assessment of chest pain, but larger studies to assess its impact on long-term hard end points are needed.

Limitations
The results of the present study were limited by the weakness of the primary end point. This end point was selected given the practical limitations to the population size for a clinical end point. Therefore, studies sized for clinical end points are needed to confirm the promising results of the present pilot study.

References
