among patients presenting with chest pain at the emergency department, the early diagnosis of acute coronary syndromes (ACS) is a major challenge for physicians. In 50–80% of the patients, the ECG is normal or non-diagnostic at presentation,1 which makes early differentiation from non-cardiac causes of chest pain difficult. Serial assessment of cardiac markers results in a high sensitivity to detect myocardial damage; however, the absence of evidence of myocardial damage does not exclude ACS. Therefore, novel early markers of ACS are needed. The main cause of ACS is atherosclerotic plaque disruption with superimposed arterial thrombus formation. Tissue factor induced thrombin generation has a pivotal role in this process.2 The purpose of this study was to evaluate the diagnostic value of coagulation markers (that is, markers of thrombin generation (prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin (TAT) complexes), soluble tissue factor, and tissue factor pathway inhibitor (TFPI) activity) and a fibrinolytic marker (plasminogen activator inhibitor (PAI)) for the early identification of ACS in patients presenting to the emergency department with chest pain and a normal or non-diagnostic ECG.

METHODS
We performed a nested case–control study within a cohort of patients with chest pain presenting to the emergency department with a normal or non-diagnostic ECG within six hours after symptoms onset. Patients were observed in the emergency department for ≤ 24 hours before discharge or hospital admission. Cardiac troponin T (cTnT) was assessed on admission and at 12 hours after onset of symptoms. The case group consisted of patients with ACS with recurrent chest pain, dynamic ST segment or T wave changes on the ECG during observation, and a negative serial cTnT (n = 33; group 1) and of patients with ACS with at least one positive cTnT (defined as a peak cTnT concentration ≥ 0.06 μg/l, n = 63; group 2). The control group (n = 62) comprised patients without a history of cardiovascular disease, who were considered to have chest pain of non-cardiac origin without known or suspected thromboembolic or infectious disease, or signs of inflammation, and who were event free during the subsequent six months of follow up.

Venous blood samples, for the measurement of haemostatic markers, were taken from each patient on admission to the emergency department. The haemostatic markers were compared between the control group and each ACS case group by Mann-Whitney U tests. Receiver operating characteristic (ROC) curves were constructed for the sensitivities and specificities of the haemostatic markers for the detection of ACS (that is, cTnT negative or positive ACS). Additional ROC curves were constructed specifically to detect cTnT positive ACS or cTnT negative ACS.

RESULTS
Plasma concentrations of F1+2 and TAT complexes were slightly higher in cTnT positive ACS patients than in controls (median (interquartile range (IQR)) concentrations of F1+2 0.9 (0.7–1.3) v 0.8 (0.6–1.1) nmol/l, respectively; median (IQR) concentrations of TAT 2.3 (1.0–7.6) v 1.0 (< 1.0–4.8) ng/ml, respectively). Plasma concentrations in the cTnT negative ACS case group were equal to those found in the control group.

There was no difference in tissue factor plasma concentrations and TFPI activity between the case groups and controls. Among the three study groups, median soluble tissue factor range was from 43.5–49.2 pg/ml, whereas TFPI activity ranged between 1105–1200 U/l.

Significantly higher PAI plasma concentrations were observed in the cTnT negative ACS patients than in controls (median (IQR) concentrations 72.3 (44.9–131.7) ng/ml v 44.2 (30.2–83.1) ng/ml, respectively, p = 0.014). The cTnT positive ACS patients also had higher PAI concentrations than controls; however, the difference did not reach significance (median (IQR) concentrations 57.8 (35.5–107.2) ng/ml v 44.2 (30.2–83.1) ng/ml, respectively, p = 0.1).

Table 1 shows the diagnostic utility of the haemostatic markers to detect patients with ACS or to identify a subgroup with cTnT positive ACS. The cut off values presented in this table correspond to the points of the ROC curves with the best balance between sensitivity and specificity. As table 1 shows, the positive (PPV) and negative predictive values (NPV) to identify patients with an ACS were comparable for all four markers. To detect patients with a cTnT positive ACS, F1+2 was more accurate than the other markers; however, its PPV and NPV were only 62% and 66%, respectively.

After exclusion of cTnT positive ACS cases, only TFPI and PAI had diagnostic value to detect cTnT negative ACS (area under the ROC curves 0.57 (95% confidence interval (CI)) 0.44 to 0.70) and of 0.65 (95% CI 0.54 to 0.77), respectively). At cut off values of TFPI > 1400 U/l and of PAI > 110 ng/ml, the sensitivity, specificity, PPV, and NPV to identify cTnT negative ACS were, for TFPI, 31% (95% CI 15% to 47%), 79% (95% CI 69% to 89%), 43% (95% CI 23% to 63%), and 69% (95% CI 58% to 80%), respectively, and for PAI, 34% (95% CI 15% to 53%).

Abbreviations: ACS, acute coronary syndromes; CI, confidence interval; cTnT, cardiac troponin T; F1+2, prothrombin fragment 1+2; IQR, interquartile range; PPV, negative predictive value; PAI, plasminogen activator inhibitor; PPV, positive predictive value; ROC, receiver operating characteristic; TAT, thrombin-antithrombin; TFPI, tissue factor pathway inhibitor
Patients with cTnT positive ACS previously demonstrated significantly increased coagulation activation than patients with cTnT negative unstable angina. However, we could not confirm this in our study population. We observed no differences in plasma concentrations of coagulation markers between patients with cTnT positive and with negative ACS. Despite evidence of myocardial necrosis, the extent of coagulation activation in the coronary arteries may be insufficiently reflected by systemic plasma concentrations in patients with a cTnT positive ACS and whose ECG does not show characteristic changes of myocardial ischaemia. Thus, in our study, which is limited by relatively small sample sizes, measurement of systemic plasma concentrations of haemostatic markers did not contribute to the triage of patients presenting with chest pain and a normal or non-diagnostic ECG to the emergency department.

### DISCUSSION

Patients with cTnT positive ACS previously demonstrated significantly increased coagulation activation than patients with cTnT negative unstable angina. However, we could not confirm this in our study population. We observed no differences in plasma concentrations of coagulation markers between patients with cTnT positive and with negative ACS. Despite evidence of myocardial necrosis, the extent of coagulation activation in the coronary arteries may be insufficiently reflected by systemic plasma concentrations in patients with a cTnT positive ACS and whose ECG does not show characteristic changes of myocardial ischaemia.

We observed increased plasma concentrations of PAI antigen in both ACS case groups compared with controls but this was only significant in patients with a cTnT negative ACS. Increased PAI plasma concentrations are associated with common risk factors for coronary artery disease such as hypertension and particularly diabetes. These two factors were more prevalent in both case groups, in particular in the cTnT negative ACS case group (data not shown), and this contributed to the enhanced PAI concentrations in these groups compared with controls.

The limited extent of coagulation activation in patients with cTnT positive ACS was reflected by the poor diagnostic performance of the haemostatic markers to identify these patients. Since these patients can be identified after serial measurement of cardiac serum markers, it remains a difficult task to detect patients with an ACS without evidence of myocardial damage and presenting with a non-diagnostic ECG. In the present study, after excluding the cTnT positive ACS cases from the analyses, only TFPI and PAI had diagnostic value to identify these patients.

<table>
<thead>
<tr>
<th>Haemostatic marker cut off</th>
<th>Area under the ROC curve</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detecting ACS at large</td>
<td></td>
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<tr>
<td>F1+2 &gt;1.1 mmol/l</td>
<td>0.53 (0.44 to 0.63)</td>
<td>31 [22 to 40]</td>
<td>80 [70 to 90]</td>
<td>71 [57 to 85]</td>
<td>42 [33 to 51]</td>
</tr>
<tr>
<td>TAT complexes &gt;6.0 ng/ml</td>
<td>0.52 (0.42 to 0.61)</td>
<td>27 [18 to 36]</td>
<td>80 [70 to 90]</td>
<td>68 [53 to 83]</td>
<td>40 [31 to 49]</td>
</tr>
<tr>
<td>TFPI activity &gt;1400 U/l</td>
<td>0.57 (0.48 to 0.66)</td>
<td>29 [20 to 38]</td>
<td>79 [69 to 89]</td>
<td>68 [54 to 82]</td>
<td>40 [33 to 51]</td>
</tr>
<tr>
<td>PAI &gt;110 ng/ml</td>
<td>0.61 (0.52 to 0.70)</td>
<td>28 [19 to 37]</td>
<td>85 [76 to 94]</td>
<td>75 [61 to 89]</td>
<td>43 [34 to 52]</td>
</tr>
<tr>
<td>Detecting cTnT positive ACS (case group 2)</td>
<td></td>
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<tr>
<td>F1+2 &gt;1.1 mmol/l</td>
<td>0.62 (0.53 to 0.71)</td>
<td>40 [28 to 52]</td>
<td>83 [75 to 91]</td>
<td>62 [47 to 77]</td>
<td>66 [57 to 75]</td>
</tr>
<tr>
<td>TAT complexes &gt;6.0 ng/ml</td>
<td>0.59 (0.50 to 0.68)</td>
<td>29 [18 to 40]</td>
<td>79 [71 to 87]</td>
<td>50 [34 to 66]</td>
<td>61 [52 to 70]</td>
</tr>
<tr>
<td>TFPI activity &gt;1400 U/l</td>
<td>0.55 (0.46 to 0.64)</td>
<td>28 [17 to 39]</td>
<td>76 [67 to 85]</td>
<td>44 [29 to 59]</td>
<td>60 [51 to 69]</td>
</tr>
<tr>
<td>PAI &gt;95 ng/ml</td>
<td>0.54 (0.45 to 0.63)</td>
<td>29 [18 to 40]</td>
<td>76 [67 to 85]</td>
<td>45 [30 to 60]</td>
<td>61 [52 to 70]</td>
</tr>
</tbody>
</table>

Data presented with 95% confidence intervals. cTnT, cardiac troponin T; F1+2, prothrombin fragment 1+2; NPV, negative predictive value; PAI, plasminogen activator inhibitor; PPV, positive predictive value; ROC, receiver operating characteristic; TAT, thrombin-antithrombin; TFPI, tissue factor pathway inhibitor.
The value of haemostatic markers in the triage of patients with chest pain presenting with a normal or non-diagnostic ECG

A H M Moons, P M van der Zee, R Bholasingh, A Sturk, C E Hack, J C M Meijers, O Kamp, J H Cornel, R J G Peters and R J de Winter

*Heart* 2005 91: 1215-1216
doi: 10.1136/hrt.2004.039644

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