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# C-reactive protein improves risk prediction in patients with acute coronary syndromes

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**Aims** Elevated C-reactive protein level is a risk marker in patients with acute coronary syndromes (ACSs), but current risk score systems do not consider this factor. We studied the incremental predictive value of adding C-reactive protein to the Global Registry of Acute Coronary Events (GRACE) risk score.

**Methods and results** Characteristics, treatments and 30-day mortality were recorded for 1408/1901 consecutive ACS patients. Changes in global model fit, discrimination, calibration, and reclassification were evaluated upon addition of C-reactive protein to the GRACE risk score. High-C-reactive protein patients (C-reactive protein >22 mg/L, 4th quartile of C-reactive protein) were older, had more comorbidities and worse haemodynamic conditions, received less recommended treatment, and had a four-fold higher 30 day mortality. Multivariable analysis demonstrated high-C-reactive protein as an important and independent predictor of mortality. Addition of high-C-reactive protein in the GRACE model modestly improved global fit, discriminatory capacity (c-statistic from 0.795 to 0.823), and calibration. Patients were divided into four groups according to GRACE risk score prediction: <1, 1 to <5, 5 to <10, and ≥10%. The model with high-C-reactive protein allowed adequate reclassification in 12.2%.

**Conclusion** Elevated C-reactive protein level is a modest but independent predictive factor of 30-day mortality in ACS patients, even after adjustment for co-morbidities, haemodynamic conditions, and treatment. Combined with the GRACE risk score, C-reactive protein information improves risk classification.

**Keywords** C reactive protein • Acute coronary syndromes • Risk prediction

## Introduction

C-reactive protein, which plays an important role in the immune response, is implicated in the development and complications of atherosclerosis. Elevated C-reactive protein level is a strong predictor of clinical events in healthy people,[1] diabetic patients,[2] patients with mild or elevated cholesterol levels,[3,4] and patients with acute coronary syndrome (ACS).[5–7] For cardiovascular risk prediction, the usual threshold value of C-reactive protein is 2 mg/L,[1–3,8] whereas in patients admitted for ACS, a higher cut-off level, above 10 mg/L,[6,7,9,10] has been used to identify patients at higher risk for death. In the management of patients with ACS, risk stratification is an important step, and guidelines recommend the use of established and validated risk scoring systems,[11,12] such as the Global Registry of Acute Coronary Events (GRACE) risk score.[13] The biological variables included in the currently used risk scores are limited to serum creatinine and troponin, and the C-reactive protein level is not considered. So far, little is known regarding the addition of C-reactive protein information in currently used risk scoring systems. The aim of this study was to determine the incremental prognostic value of the C-reactive protein on top of the GRACE risk score on 30 day mortality in patients admitted for ACS.

## Methods

### Population

The study population was part of the 'Registre Franc Comtois des Syndromes Coronariens Aigus', an ongoing prospective ACS registry that

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includes all patients admitted for ACS in any of the 10 cardiology centres in the region of Franche-Comté, a region in Eastern France with a population of 1.2 million inhabitants. All patients gave informed consent. A dedicated team of data managers was available to assist with the completion of the data.

## Definitions and data collection

Serum was collected for C-reactive protein level assessment from all patients at admission, after the first fasting night, using a commercially available kit (a highly sensitive latex-based immunoassay, BN Dade Behring; Siemens Diag). Baseline C-reactive protein values were available for 74% of all patients admitted; the high-level C-reactive protein (high-C-reactive protein) group was defined as patients with a C-reactive protein level above the third quartile of the C-reactive protein distribution. The variables for estimation of the GRACE risk score of in-hospital mortality (age, heart rate, systolic blood pressure, Killip class, cardiac arrest at admission, troponin release, ST segment deviation, and serum creatinine) were prospectively recorded, as well as demographic data, previous medication and diseases, clinical presentation, and treatment administered during hospitalization (antiplatelet agents, anticoagulants, angiotensin converting enzyme inhibitors, beta-blockers, reperfusion, coronary angiography, and statins). In-hospital mortality was recorded and survivors were contacted at 1 month by telephone or a scheduled consultation to assess survival (all causes of death were considered), recurrent myocardial infarction, or stroke.

## Statistical methods

Categorical variables were presented as number of cases (percentage), continuous variables as mean (standard deviation) when normally distributed, and as median (interquartiles) when non-normally distributed. One month survival and recurrent myocardial infarction probabilities were presented by cumulative event curves, stratified on high-C-reactive protein.

Association between variables and mortality was assessed using a multivariable logistic regression: variable candidates for the multivariable model were determined by univariate relation with mortality ($P < 0.10$ by Wald chi-square test) and only those with $P < 0.05$ were retained in the final model: age, serum creatinine, systolic blood pressure and heart rate at admission, use of beta-blocker, ace inhibitors, invasive procedures, and C-reactive protein.

To assess the incremental value of adding C-reactive protein information to the GRACE score model, we compared the changes in appropriateness when high-C-reactive protein was added. As recommended by Cook,[14] we used several different approaches: (i) the relation between the GRACE risk score and C-reactive protein, assessed by the Pearson correlation, after Log transformation of the C-reactive protein value (ii) changes in measure of global fit by the Bayes information criterion (BIC) (a likelihood-based measure that adds a penalty for model complexity and is related to the posterior probability) and in the Akaike information criterion (AIC); lower values of BIC and AIC indicate better fit, (iii) changes in indices of calibration (Hosmer–Lemeshow *P*-value), changes in indices of discrimination by the c-statistics (comparison using a bootstrapping approach[15]), (iv) graphic comparison of the observed prevalence of mortality for each decile in the whole population, and (v) estimation of the rate and appropriateness of patients reclassification after transformation of the predicted mortality given by both models (GRACE score and GRACE score with high-C-reactive protein) into four risk categories: $<1$, 1 to $<5$, 5 to $<10$, and $\geq 10\%$ 30 day mortality. Reclassification was considered as appropriate or inappropriate when the 'new' risk prediction corresponded or did not correspond to the actual mortality category. All tests were two-sided, and a *P*-value $< 0.05$ was considered significant. Analyses were performed using SAS software, version 9 (SAS Institute Inc.).

# Results

Over a period of 18 months (June 2006 to December 2007), 1901 patients were admitted with a final diagnosis of ACS. Of these patients, C-reactive protein level data were available for 1684 patients, and 1501 had complete data, including a 30 day clinical follow-up; the flow chart of data from this population is presented in *Figure 1*. Baseline characteristics of the study population were compared with those of the non-study population (*Tables 1* and *2*). In the whole population, the C-reactive protein value was not normally distributed; the median value was 6.4 mg/L (2.4; 22) and 395 patients with C-reactive protein $>22$ mg/L composed the high-C-reactive protein group. In this group, the median value of C-reactive protein was 66 mg/L (38; 120).

## Baseline characteristics, risk score, and acute management

Non-study and study patients had comparable characteristics, except for a lower risk profile at admission, a lower rate of use of oral antiplatelet agents, and a higher rate of use of early invasive strategy with GPIIb–IIIa receptor inhibitors in the non-study group (*Tables 1* and *2*). In the study population, patients in the high-C-reactive protein group were, on average, 6 years older and had more previous co-morbidities and more cardiovascular risk factors, and more frequently had a history of diabetes and renal dysfunction compared with patients in the lower quartiles. In addition, these patients more often presented haemodynamic instability at admission: lower systolic blood pressure, higher heart rate, and higher GRACE risk score (*Tables 1* and *2*). During hospitalization, high-C-reactive protein patients received aspirin, clopidogrel, beta-blockers, ACEI, or statins less frequently than other patients. Among patients with ST segment elevation myocardial infarction (STEMI), those from the high-C-reactive protein group were less often submitted to reperfusion; among patients with non-STEMI, the high-C-reactive protein group was associated with reduced use of early invasive strategy with glycoprotein IIb/IIIa inhibitors (*Table 2*).

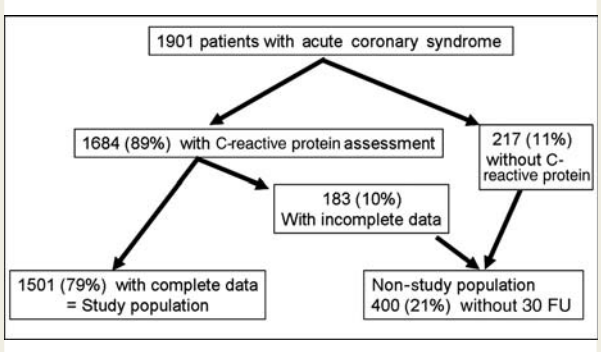


**Figure 1** Flow chart of data from the study population.

**Table 1 Comparison of clinical characteristics according to study and non-study patients and (in the study population) according to C-reactive protein quartile**

| Variables | Non-study population | Study population | *P*-value | First to third C-reactive protein quartile | Highest C-reactive protein quartile | *P*-value |
|---|---|---|---|---|---|---|
| *n* | 400 | 1501 | | 1106 | 395 | |
| STEMI | 184 (46) | 708 (47) | 0.10 | 532 (48) | 176 (45) | 0.001 |
| NSTEMI | 184 (46) | 679 (45) | | 481 (43) | 198 (50) | |
| UA | 32 (8) | 113 (7) | | 93 (8) | 20 (5) | |
| Male | 268 (67) | 1023 (68) | 0.54 | 767 (69) | 265 (67) | 0.24 |
| Age[a] | 68 (15) | 69 (15) | 0.30 | 68 (15) | 73 (13) | 0.001 |
| Diabetes | 88 (22) | 361 (24) | 0.33 | 217 (20) | 143 (36) | 0.001 |
| HBP | 228 (57) | 842 (56) | 0.5 | 590 (53) | 249 (63) | 0.002 |
| HCT | 176 (44) | 707 (47) | 0.62 | 534 (48) | 170 (43) | 0.07 |
| Current smoker | 100 (25) | 391 (26) | 0.62 | 316 (29) | 78 (20) | 0.002 |
| Previous MI | 64 (16) | 255 (17) | 0.64 | 189 (17) | 80 (20) | 0.15 |
| Previous angioplasty | 48 (12) | 180 (12) | 0.85 | 142 (13) | 42 (10) | 0.29 |
| Previous CABG | 12 (3) | 60 (4) | 0.38 | 54 (5) | 177 (4) | 0.66 |
| Stroke | 32 (8) | 90 (6) | 0.10 | 44 (4) | 33 (8) | 0.001 |
| Per. vessel disease | 48 (12) | 165 (11) | 0.4 | 114 (10) | 57 (14) | 0.02 |
| GFR group | | | | | | |
| >60 mL/min/1.73 $m^2$ | 156 (39) | 556 (37) | 0.12 | 471 (42) | 104 (26) | 0.001 |
| 30–60 mL/min/1.73 $m^2$ | 155 (39) | 662 (44) | | 485 (44) | 172 (44) | |
| <30 mL/min/1.73 $m^2$ | 88 (22) | 286 (19) | | 150 (14) | 119 (30) | |
| Fasting glucose (mmol/L)[a] | 7.04 (4.3) | 7.2 (4.2) | 0.55 | 7.08 (4.2) | 7.52 (4.1) | 0.001 |
| BNP level (pg/L)[b] | 654 (200; 1990) | 800 (305; 1700) | 0.82 | 203 (77; 507) | 770 (260; 1835) | 0.001 |
| Serum creatinine (mmol/L)[a] | 115 (86) | 114 (95) | 0.75 | 105 (66) | 136 (96) | 0.001 |

Values expressed as *n* (%), *P*-values from Chi-square test.
[a]Mean (SD), *P*-value from *t*-test.
[b]Median (interquartiles).
STEMI, ST elevation myocardial infarction; HBP, high blood pressure; HCT, hypercholesterolaemia, CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; Per., peripheral; BNP, b-type natriuretic peptide; Hs-C-reactive protein, high sensitive C-reactive protein.

The 30 day mortality was significantly higher in the high-C-reactive protein group (17.7 vs. 4.9%, $P < 0.001$). *Figure 2* presents the Kaplan–Meier survival probability curves at 1 month according to high-C-reactive protein.

## Logistic models on mortality with and without high-C-reactive protein

By multivariable analysis, high-C-reactive protein was found to be an independent predictor of 30 day mortality (*Table 3*). Logistic regression analysis showed that this relationship persisted after adjustments for age, co-morbidities, condition at admission, and treatments used. When combined in a prediction model based on the variables used for the GRACE risk score, high-C-reactive protein remained an independent predictor of mortality, and regardless of the model, the odds ratio associated with high-C-reactive protein was 3.33 (1.82; 5.88) for 30 day mortality (*Table 3*). The addition of high-C-reactive protein improved the global model fit, with a lower BIC and AIC, better discriminatory capacity with a significant increase in c-statistic value, and better calibration of the models with a higher *P*-value of Hosmer–Lemeshow test (*Table 3*). *Figure 3* presents the weak linear correlation between the GRACE score and the C-reactive protein level with a coefficient of determination of 4.8%. *Figure 4* displays the plot of observed vs. predicted 30 day mortality (by deciles risk estimation) of the GRACE score alone and when high-C-reactive protein was combined with the GRACE score.

If both models were able to identify extremely high-risk patients, the risk estimation was more linear with the model combining GRACE score and high-C-reactive protein. The incremental prognostic value of high-C-reactive protein in addition to the GRACE risk score is illustrated by *Figure 5*: half of deaths and myocardial infarctions occurred in patients with high-C-reactive protein and

**Table 2 Comparison of clinical characteristics, treatments, and outcomes according to study and non-study patients and (in the study population) according to C-reactive protein quartile (first to third vs. fourth)**

| Variables | Non-study population | Study population | *P*-value | First to third C-reactive protein quartile | Highest C-reactive protein quartile | *P*-value |
|---|---|---|---|---|---|---|
| *n* | 400 | 1501 | | 1106 | 395 | |
| Troponin T (μg/L)[a] | | | | | | |
| At 4 h | 2.8 (0.4; 11) | 3.3 (0.6; 12) | 0.5 | 0.5 (0.1; 3) | 3.1 (0.6; 11) | 0.24 |
| At 24 h | 6.3 (1.7; 25) | 7.8 (1.9; 24) | 0.42 | 5.3 (0.7; 32) | 7.6 (1.8; 24) | 0.16 |
| Heart rate[a] | 76 (18) | 79 (20) | 0.05 | 77 (19) | 85 (22) | 0.001 |
| Admission systolic blood pressure (mmHg)[a] | 134 (26) | 132 (30) | 0.1 | 136 (30) | 126 (27) | 0.002 |
| LVEF (angiography)[a] | 0.60 (13) | 0.57 (13) | 0.01 | 0.56 (0.14) | 0.48 (0.13) | 0.001 |
| GRACE score[a] | 139 (33) | 147 (39) | 0.001 | 139 (37) | 168 (39) | 0.001 |
| Aspirin | 376 (94) | 1474 (98) | 0.001 | 1090 (99) | 384 (97) | 0.008 |
| Clopidogrel | 368 (92) | 1415 (94) | 0.01 | 1059 (96) | 366 (93) | 0.015 |
| Aspirine+Clopidprel | 364 (91) | 1400 (93) | 0.03 | 1047 (95) | 358 (91) | 0.004 |
| ACEI or ARB | 344 (86) | 1290 (86) | 0.91 | 979 (89) | 309 (78) | 0.001 |
| Statins | 372 (97) | 1440 (96) | 0.54 | 1068 (97) | 369 (94) | 0.002 |
| Beta-blockers | 276 (69) | 1023 (68) | 0.5 | 813 (73) | 221 (56) | 0.001 |
| Coronary angiography | 336 (84) | 1294 (86) | 0.29 | 922 (92) | 253 (73) | 0.001 |
| Reperfusion (STEMI) | 148 (81) | 584 (82) | 0.65 | 428/532 (80) | 93/176 (53) | 0.001 |
| Thrombolysis | 44 (24) | 217 (31) | 0.09 | 166 (31) | 26 (14) | 0.001 |
| Primary PCI | 101 (55) | 367 (52) | 0.52 | 262 (49) | 67 (37) | 0.001 |
| Early invasive strategy+GPIIb/IIIa (NSTEMI) | 120 (56) | 372 (47) | 0.02 | 235/481 (49) | 78/198 (39) | 0.001 |
| 30 day mortality | | | | 66 (6.0) | 78 (19.8) | 0.001 |
| 30 day recurrent myocardial infarction | | | | 5 (0.5) | 7 (2.1) | 0.01 |
| 30 day combined endpoint | | | | 69 (6.5) | 83 (20.9) | <0.001 |

Same abbreviations as in *Table 1*.
[a]Mean (SD), *P*-value from *t*-test.
LVEF, left ventricular ejection fraction; GRACE, Global Registry of Acute Coronary Events; ACEI, angiotensin converting enzyme inhibitor.

the presence of elevated C-reactive protein level indicated a higher risk independently of the GRACE risk score.

## Risk reclassification

The population was divided into four groups of different risk level according to the GRACE risk score: <1, 1 to <5, 5 to <10, and ≥10%. The average predicted mortality in these groups was 0.5, 2.2, 7.7, and 26.4%, respectively. The addition of high-C-reactive protein in the model allowed a reclassification in different risk categories (*Table 4*). The observed 30 day mortality in these groups was compared with the two predictive models: the reclassification was appropriate (i.e. closer to the actual mortality) in 12.2% of the whole population and inappropriate in 5%.

# Discussion

Our data confirm that elevated C-reactive protein level assessed at admission in patients with ACS is a marker for risk and an independent predictor of 30 day mortality. Moreover, this information, combined with the GRACE risk score, improved the discriminatory capacity of the model and allowed a reclassification in different risk categories (higher or lower risk) in a substantial proportion of patients.

Links between elevated C-reactive protein and plaque inflammation,[16] increased thrombosis,[17] decrease in nitric oxide synthesis,[18] expression of adhesion molecules, alteration of complement function,[19] and inhibition of the physiologic fibrinolysis[17,18] have been extensively studied. The clinical translation of these patho-physiologic effects have been observed in randomized clinical trials, such as the 'Fragmin during Instability in Coronary Artery Disease' (FRISC)[7] and the 'Thrombosis in Myocardial Infarction' (TIMI) 11[10] studies, in which patients with high C-reactive protein levels had the worst clinical outcomes. Indeed, elevated levels of both troponin and C-reactive protein identified patients at higher risk for short-term mortality, with a threshold value for C-reactive protein as low as 2 mg/L.

In our study, the high-C-reactive protein group was defined by a C-reactive protein level above 22 mg/L. This threshold was defined by the fourth quartile of the distribution in our population. Such high cut-off values of C-reactive protein, above 10 mg/L, have

been used in the setting of ACSs.[6,7,9,10,20] In most of the cases, such as in our study, high levels of C-reactive protein were defined according to the quartiles of the C-reactive protein distribution; however, in a sub-study of the 'Chimeric c7E3 antiplatelet therapy in unstable angina refractory to standard treatment' (CAPTURE) study, the threshold value of C-reactive protein for mortality was determined by a receiver operating characteristic curve analysis at 10 mg/L. In this study, a C-reactive protein level

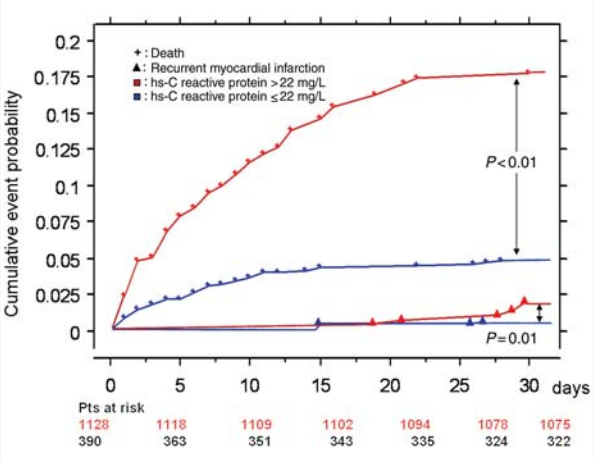


**Figure 2** Kaplan–Meier cumulative event curves of death and recurrent myocardial infarction according to the presence of high-C-reactive protein at admission.

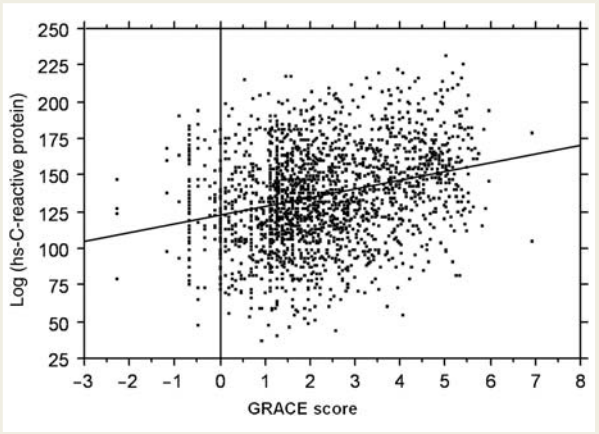


**Figure 3** Correlation between log C-reactive protein level and the GRACE risk score.

**Table 3 Model fit, discrimination, and reclassification indices when high-C-reactive protein is added in a model with GRACE risk score (top) and in a multivariable model (bottom)**

| | Without high-C-reactive protein, odds ratio (95% CI) | With high-C-reactive protein, odds ratio (95% CI) |
|---|---|---|
| Model with GRACE risk score (per 10% increase in score) | | |
| GRACE score | 1.47 (1.38; 1.58) | 1.44 (1.34; 1.54) |
| high-C-reactive protein[a] | | 2.38 (1.61; 3.45) |
| Measures of fit | | |
| Bayes information criterion | 1869 | 1857 |
| Akaike information criterion | 1872 | 1862 |
| c-statistic | 0.795* | 0.823* |
| *P* (Hosmer–Lemeshow) | 0.42 | 0.54 |
| Multivariable model | | |
| Age (per year) | 1.03 (1.01; 1.05) | 1.02 (1.01; 1.04) |
| Peripheral artery serum disease | 1.75 (0.84; 3.44) | 1.85 (0.90; 1.41) |
| Admission, heart rate (per b.p.m.) | 1.01 (1.00; 1.02) | 1.01 (0.99; 1.02) |
| Admission, systolic blood pressure (per mmHg) | 0.98 (0.97; 0.99) | 0.98 (0.97; 0.99) |
| Serum creatinine level (per mmol/L) | 1.003 (1.001; 1.005) | 1.003 (1.002; 1.005) |
| ACEI (or ARB) use | 0.44 (0.23; 0.86) | 0.48 (0.25; 0.92) |
| Beta-blocker use | 0.34 (0.18; 0.63) | 0.39 (0.21; 0.74) |
| high-C-reactive protein[a] | | 3.33 (1.82; 5.88) |
| Measures of fit | | |
| Bayes information criterion | 1863 | 1853 |
| Akaike information criterion | 1881 | 1874 |
| c-statistic | 0.859** | 0.875** |
| *P* (Hosmer–Lemeshow) | 0.42 | 0.54 |

[a]High-C-reactive protein: serum C-reactive protein level >22 mg/L (fourth quartile of C-reactive protein).
Difference in c-statistic with a bootstrapping approach: *$P = 0.02$, **$P = 0.05$.

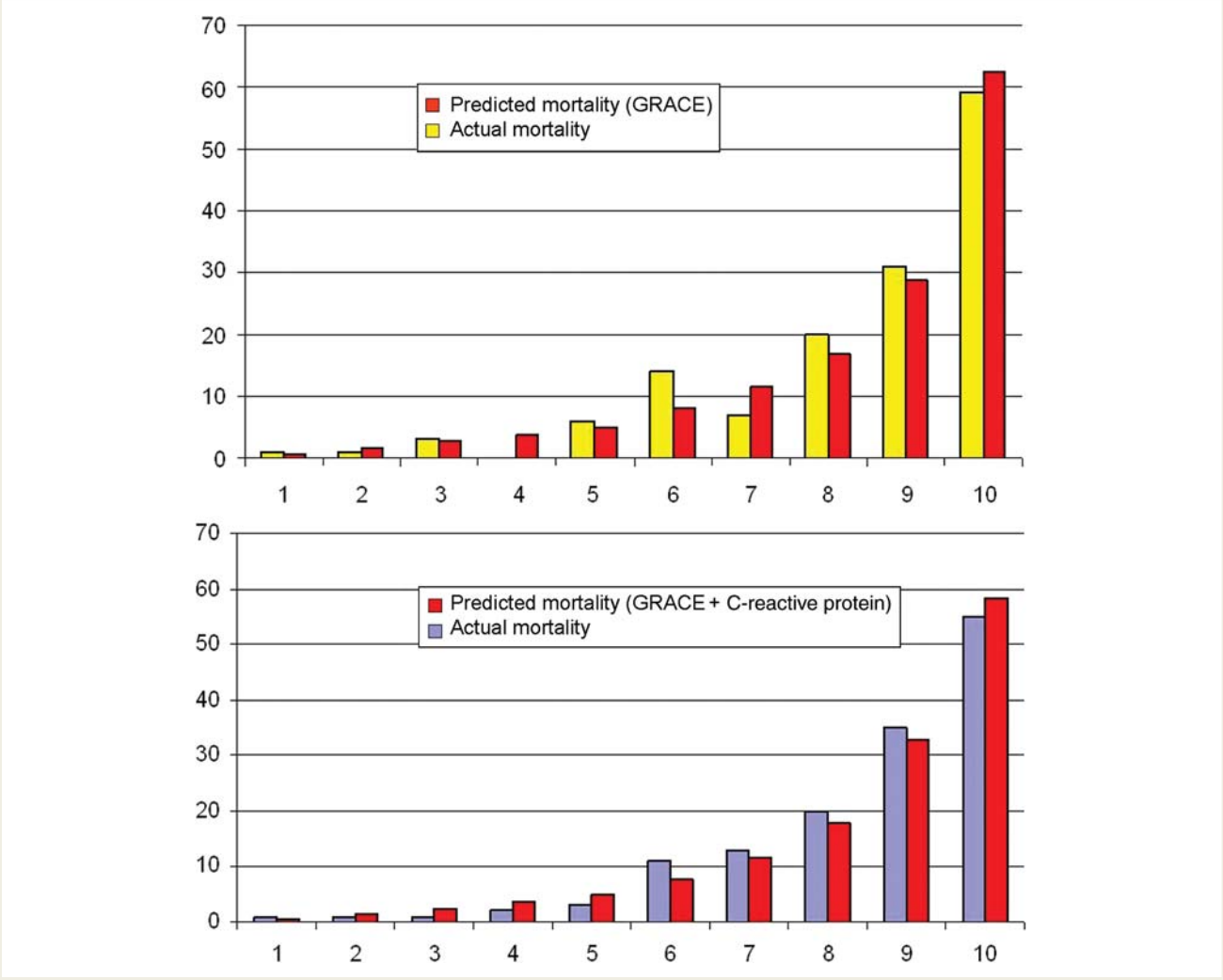


**Figure 4** Actual and estimated mortality by deciles of risk estimation: above, from a model with the GRACE risk score alone and from a model with the GRACE risk score and the high-C-reactive protein.

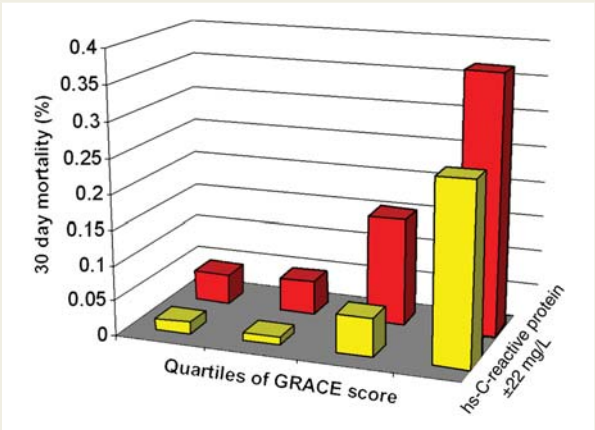


**Figure 5** Thirty day mortality rate according to the quartiles of GRACE risk score and to the high-C-reactive protein.

>10 mg/L was an independent predictor of death or myocardial infarction, even after an adjustment for variables such as gender, age, cardiovascular risk factors, ST segment depression, and troponin release.[6] Interestingly, in this study, one-fifth of the population had a C-reactive protein >22.5 mg/L, and this quintile had the highest mortality rate, comparable to that observed in our population.

Our results confirm that the 25% of patients with C-reactive protein >22 mg/L were also those at higher risk; this group presented with older age, more co-morbidities, more previous diseases, and worse haemodynamic condition at admission, and, moreover, these patients less frequently received treatments recommended according to guidelines. The multivariable analysis showed that, despite these confounding factors, high-C-reactive protein level was an independent and important prognostic factor for mortality with an odds ratio of 3.3 after adjustment. These results suggest that such a high-C-reactive protein level represents more a factor for worse prognosis than a simple bystander of higher risk or lower treatment.

**Table 4 Risk reclassification comparing a model with the GRACE risk score only, with a model using the GRACE risk sore, and the presence of elevated C-reactive protein**

| | GRACE model without C-reactive protein | | | |
|---|---|---|---|---|
| **GRACE model with C-reactive protein** | **0 to <1% (*n* = 204)** | **1 to <5% (*n* = 585)** | **5 to <10% (*n* = 222)** | **≥10% (*n* = 397)** |
| 0 to <1% (*n* = 222) | 185 | 37 | 0 | 0 |
| Actual death rate (%) | 0.5 | 0 | 0 | 0 |
| 1 to <5% (*n* = 578) | 19 | 507 | 52 | 0 |
| Actual death rate (%) | 0 | 1.4 | 9.4 | 0 |
| 5 to <10% (*n* = 236) | 0 | 41 | 136 | 59 |
| Actual death rate (%) | 0 | 9.8 | 5.9 | 9.8 |
| ≥10% (*n* = 372) | 0 | 0 | 34 | 338 |
| Actual death rate (%) | 0 | 0 | 11.4 | 29.4 |
| Reclassified/categories[a] | 19/204 (9.3) | 78/585 (13.3) | 87/222 (39.2) | 59 (14.9) |
| Reclassified/all patients | 1.3% | 5.5% | 6.2% | 4.2% |
| Appropriately, *n* (%) | 0 (0) | 78 (5.5) | 35 (2.5) | 59 (4.2) |
| Inappropriately, *n* (%) | 19 (1.3) | 0 | 52 (3.7%) | 0 |

[a]Categories: groups of predicted mortality according to the GRACE risk score.

The second finding of our study was the ability of C-reactive protein information to improve the prognostic value of the GRACE risk score. Addition of C-reactive protein information to established risk scoring systems has already been studied in stable patients[8] and in patients with ACS,[6,21] but no studies have assessed its inclusion with the GRACE risk score. We selected the GRACE risk score, as this score system is widely used, relatively simple to assess, assessable at admission, effective in risk estimation of mortality, and is recommended for patients with ACS.[11,12] The weak correlation between the GRACE risk score and the C-reactive protein level suggest that C-reactive protein brings an independent information on top of the GRACE score. The modest changes in overall model fit (BIC and AIC) in indices of discrimination (c-statistics) and in indices of calibration (Hosmer–Lemeshow chi-square statistics) explain why the addition of the C-reactive protein information could improve the risk stratification based on the GRACE score. The risk reclassification after introduction of high-C-reactive protein showed that a substantial proportion of patients was better categorized, and the reclassification was considered adequate in 12.2% of the population. Although statistically significant, the improvement of risk classification allowed by the addition of C-reactive protein remains modest and at the cost of an increase in the complexity of the score.

Moreover, the combination of high GRACE risk score and high C-reactive protein level might focus physicians' attention to the importance of prompt initiation or high doses of statins in order to achieve low LDL cholesterol and low C-reactive protein level, as supported by the results of randomized studies[22] and recommended by guidelines.[11,12,23]

## Limitations

This study has several inherent limitations associated with cohort studies. During the study period, 21% of the patients had missing data and composed the non-study population. Despite clinical characteristics and treatment being comparable in the study and non-study patients, we cannot exclude a selection bias. The GRACE risk score was designed to estimate the risk of in-hospital mortality or congestive heart failure, and not 1 month or 30 day mortality. The addition of a variable in any risk scoring system such as the GRACE score increases the difficulty of assessment and may discourage physicians to use the system.

# Conclusions

Our data confirm that high-C-reactive protein is a modest but independent predictive factor of mortality, even after adjustment for co-morbidities, haemodynamic conditions, and treatment used. For risk stratification at admission of patients with ACS, the integration of the C-reactive protein with the GRACE risk score would allow improved risk classification.

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**Conflict of interest:** none declared.

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